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SUMMARY DANMAP 2022

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

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1. Introduction

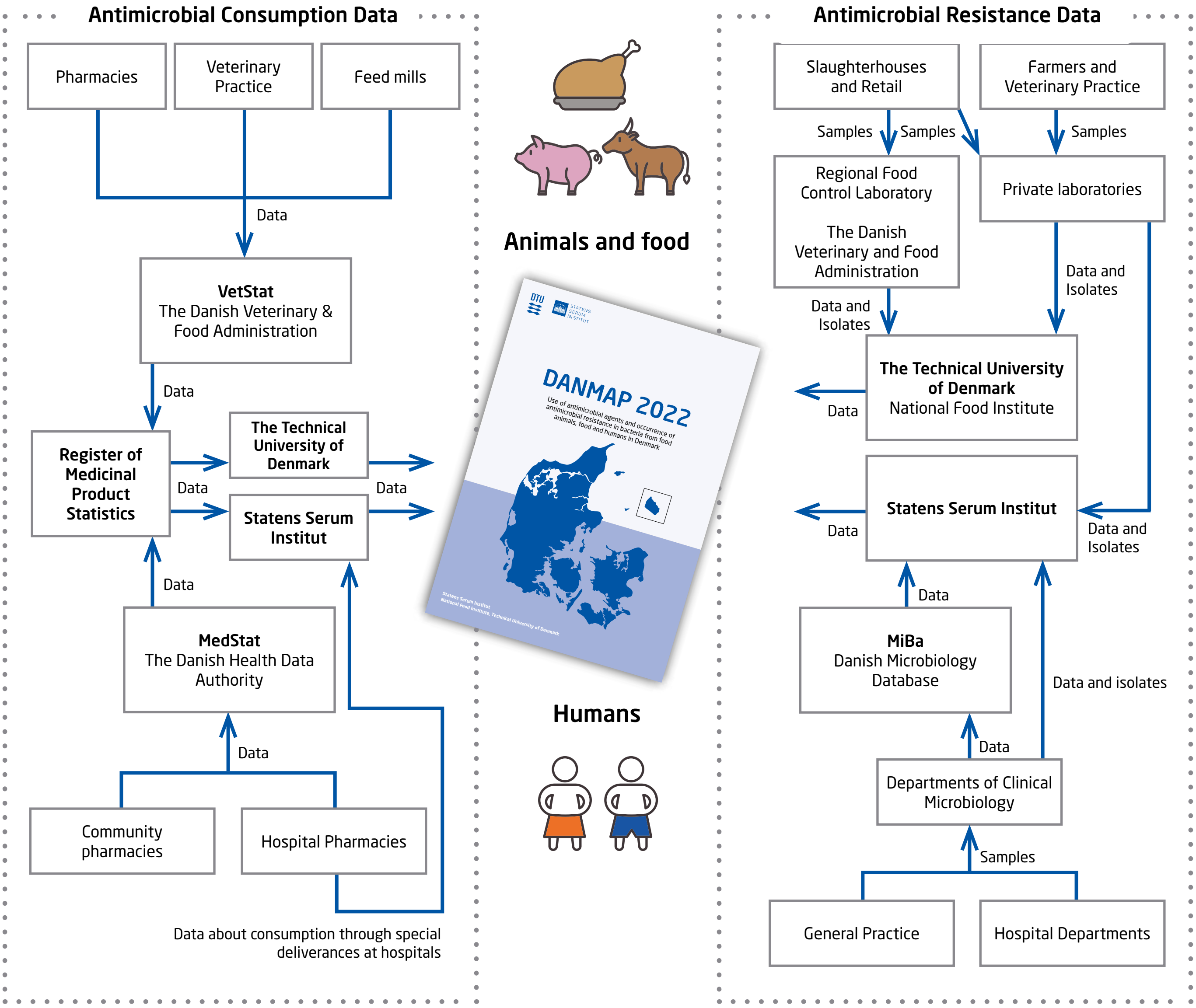
The Danish integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) is a governmentally financed surveillance programme that collects and presents antimicrobial use (AMU) and antimicrobial resistance (AMR) data in humans and animals in Denmark. The programme was established in 1995 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 summary report 2022 complements the more comprehensive DANMAP report 2022. 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 2022 and former reports.

Figure 1.1 Organisation of DANMAP 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. In the following sections, antimicrobial consumption data are presented at national level as well as at different animal species levels.

Metrics for measuring antimicrobial consumption in animals

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

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 active compound. 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).

Since 2001, all medicines prescribed for use in animals have been recorded in the national database, VetStat, the database collecting consumption data on veterinary prescription medicines in Denmark.

Since the days when DANMAP was established, many initiatives have been taken to reduce antimicrobial consumption in both animals and humans (Chapter 9. Timeline). These include discontinued use of antimicrobial agents for growth promotion, voluntary bans on the use of cephalosporins in pig and cattle production, regulatory legislation regarding therapeutic use and the Yellow Card Initiative. The initiatives have all had a marked effect on the antimicrobial consumption in animals, especially the consumption in pigs. Figure 2.1 shows the overall antimicrobial consumption in animals, along with recent important initiatives.

In addition, over time, antimicrobial consumption in animals has been affected, not only by the risk management measures established to reduce use, but also by changes in animal production, foremost increases in pig production.

The Yellow Card Initiative

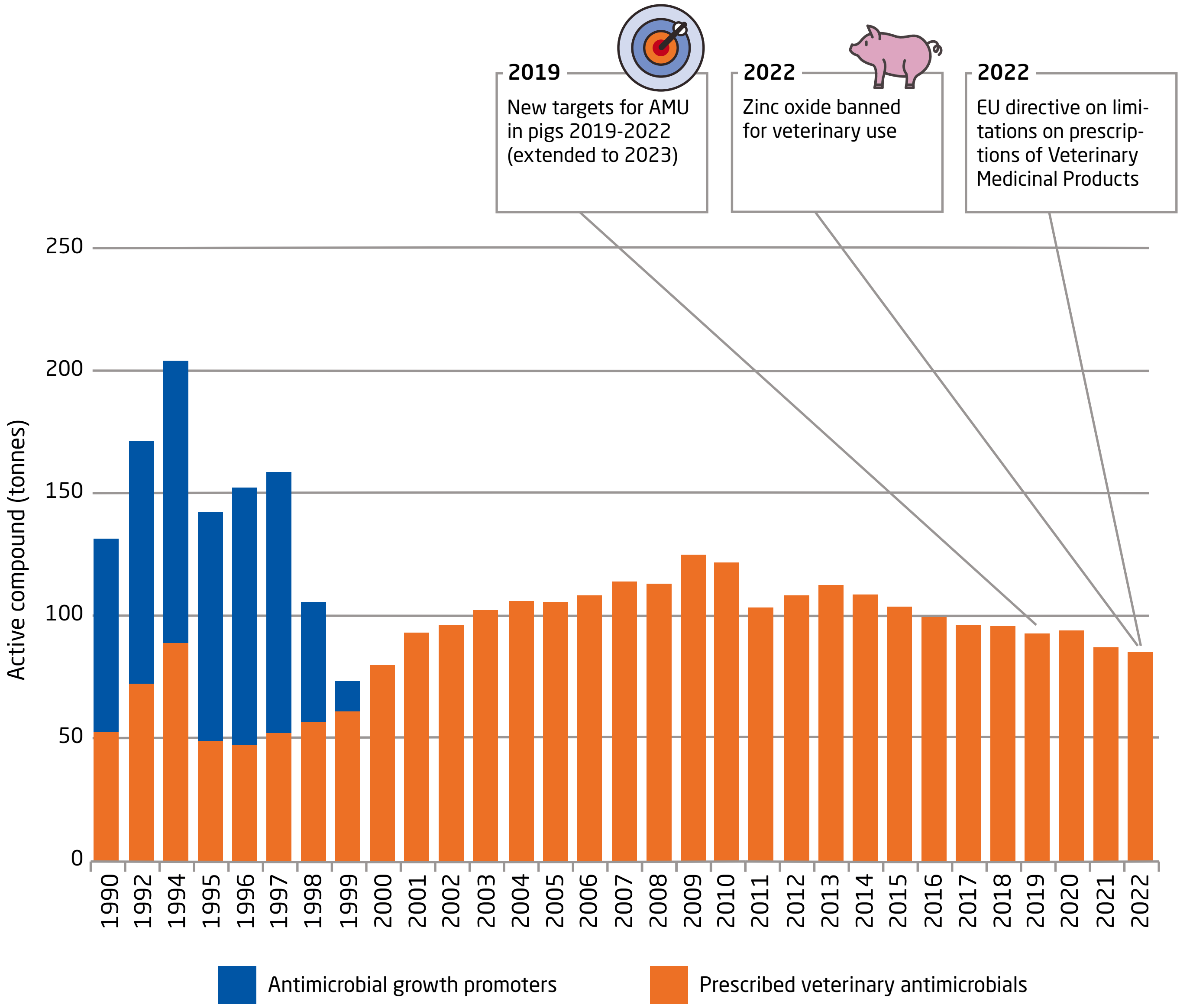
In 2010, the Danish Veterinary and Food Administration (DVFA) introduced the Yellow Card initiative to reduce the use of antimicrobials in Danish pigs. The initiative targets farms with high consumption of antimicrobials and works as an incentive for pig producers to contribute to the goal of reducing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

The initiative is based on monitoring AMU on detailed levels on each farm. If the average antimicrobial consumption in a holding, within a nine-month period, exceeds the given threshold levels, (which is an individual threshold level based on the production size of the holding) the DVFA may issue an order or injunction (a yellow card) compelling the owner of the holding to reduce the antimicrobial 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 the 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.

Figure 2.1 Antimicrobial consumption in animals and recent important initiatives to reduce antimicrobial use in animals, Denmark, 1990-2022



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 resistance. A former One Health AMR strategy from 2010 had established a cross-sectoral coordination mechanism, the National Antibiotic Council (discontinued in 2019), 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 consumption by setting several different goals.

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

Together with the One Health strategy, the Danish Veterinary and Food Administration launched an Action Plan against antimicrobial resistance in animals and food in 2017. The aim of the Action Plan was to implement the One Health strategy within the veterinary and food production sectors, particularly including measurable goals to reduce veterinary antimicrobial consumption. A second Action Plan was launched in 2021, which continued former visions and goals from the first Action Plan and set new goals.

Goals of the Action Plans against antimicrobial resistance in animals and food

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.

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.

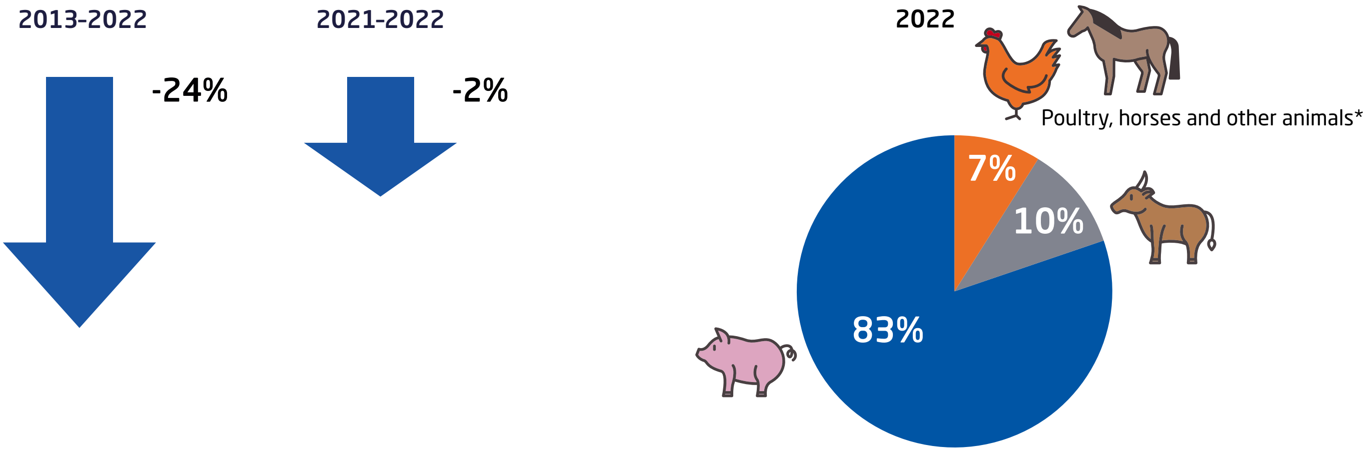
Overall antimicrobial consumption in animals

In 2022, the total consumption of antimicrobials in animals amounted to 86.2 tonnes of active compounds (Figure 2.1). The consumption in animals accounted for approximately two thirds of all antimicrobials prescribed in the human and animal sectors in Denmark.

Since 2013, the overall usage of active compounds of antimicrobials in animals has decreased every year, except in 2020 (Figure 2.1). The total consumption was 27.4 tonnes (24%) lower in 2022 compared to 2013, and 1.9 tonnes (2%) lower than in 2021 (Figure 2.2). Part of this reduction can be explained by the lower consumption in cattle, pigs, and companion animals (Figure 2.3).

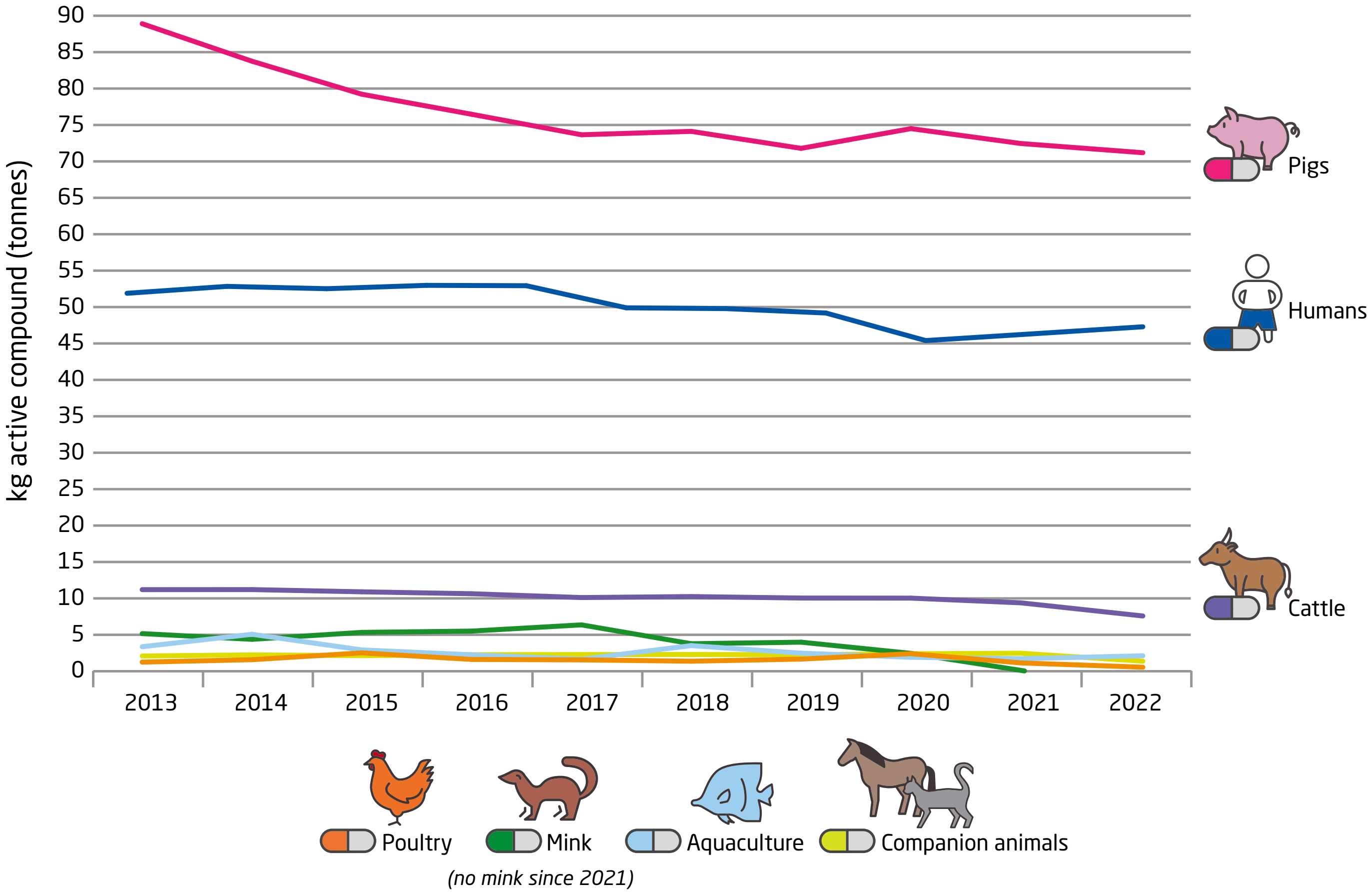
The pig sector is the main driver of veterinary antimicrobial consumption in Denmark. Therefore, any major changes in usage patterns in the pig sector will also have a major impact on the overall antimicrobial consumption in animals. In 2022, approximately 83% of veterinary prescribed antimicrobials were used for pigs, amounting to 71.4 tonnes of active compounds (Figure 2.2).

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



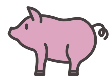
* Other animals include aquaculture and pets

Figure 2.3 Total antimicrobial consumption of active compounds (kg) by animal species and humans, Denmark, 2013-2022



Small amounts of kg active compound were used by unspecified animal species in 2022

Antimicrobial consumption in pigs



Animal definitions

Sow: Any breeding female pig on a farm.

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

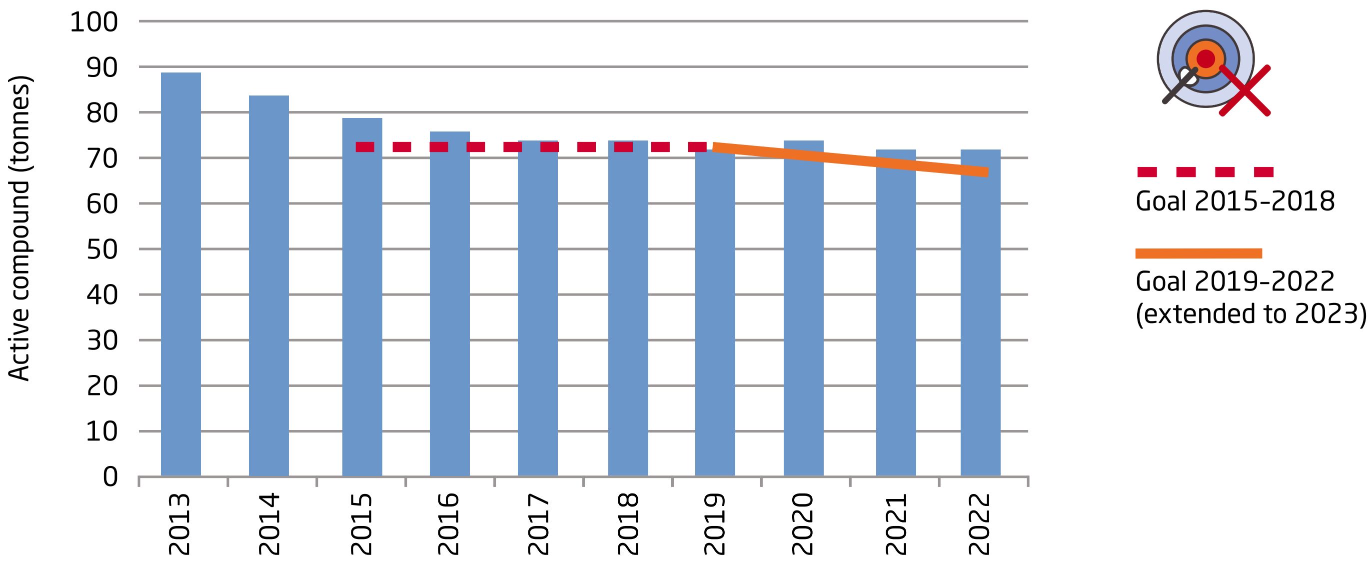
Weaner: A pig of 7-30 kg live weight after it has been weaned (dry diet and water only).

Finisher: A pig of 30-100 kg live weight, after the weaner stage until time of slaughter.

Changes in antimicrobial consumption for pigs driven by the Yellow Card initiatives
Several initiatives have aimed at reducing tetracycline usage, since this may select for livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA). Similarly, other initiatives have aimed at phasing out critically important antimicrobials such as fluoroquinolones, cephalosporins and colistin. For a more historical view of the changes in AMU in the different age groups of pigs, please refer to DANMAP 2022.

The overall consumption of antimicrobials in pigs decreased from 2021 to 2022 by 989 kg of active compounds (Figure 2.3 and 2.4). Although the consumption of antimicrobials has decreased during the period from 2019 to 2022, Goal 1: To achieve a reduction of 2 per cent per year (2019-2022) in the use of antimicrobials in pigs has not been fulfilled (Figure 2.4).

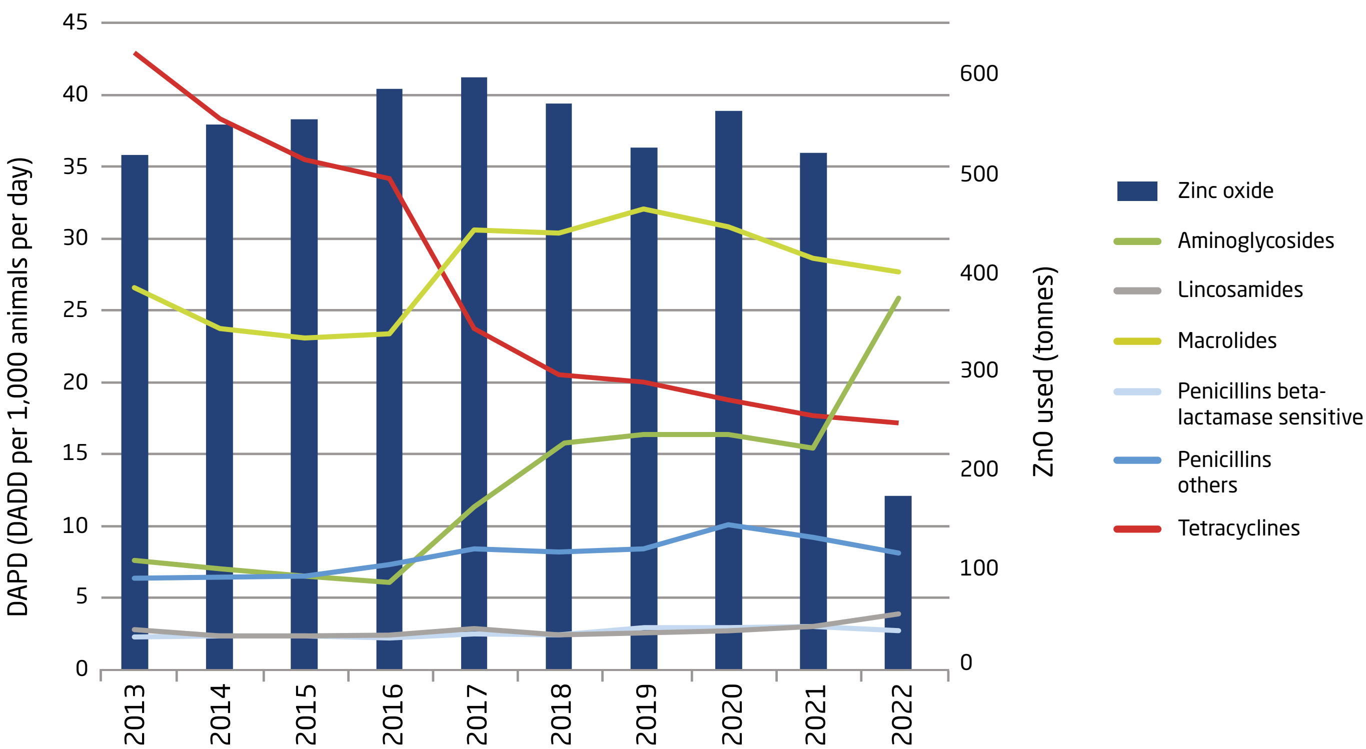
Figure 2.4 Antimicrobial consumption in pigs and goals of the National Action Plans against antmicrobial resistance, Denmark, 2013-2022



Measured in treatment proportion (DAPD), which includes adjustments for changes in production, an estimated 2.7% (26.8 DAPD) of all pigs received treatment with an antimicrobial per day in 2022. In 2010, when the Yellow Card initiative was introduced, approximately 3.6% of all pigs received treatment per day. The treatment proportion is much higher in weaners than in the other age groups. Thus, on a given day in 2022, approximately 1-2% of the sows and piglets and finishers and 9.8% of the weaners received treatment with an antimicrobial.

For weaners, the DAPD increased by 7.6% from 2021 to 2022 (Figure 2.5). The increase was primarily driven by increased consumption of aminoglycosides – specifically, neomycin. This coincides with the EU-wide withdrawal of medical zinc oxide in pigs by the European Commission, effective from June 2022. Medical zinc oxide was commonly prescribed to newly weaned pigs to prevent or treat diarrhea.

Figure 2.5 Antimicrobial (DAPD) and zinc oxide (kg) consumption in weaners, Denmark, 2013-2022



Antimicrobial consumption in other animals

In 2022, a total of 8,177.9 kg was prescribed for **cattle** (Figure 2.3), of which approximately 68% was used for treating cattle older than 12 months, including 450.8 kg used for intramammary treatment. An overall decreasing trend has been observed over the last decade and in 2022 the use in cattle was 27.2% lower than in 2013 and 13% lower than in 2021. No fluoroquinolones or 3rd or 4th generation cephalosporins were registered for use in cattle.

Antimicrobial consumption in Danish **poultry** is generally low. The statistics will be markedly affected by disease outbreaks in just a few farms. In 2022, usage increased by 4.4% compared to the usage in 2021 (Figure 2.3). For the past decade, cephalosporins have not been used in the poultry industry, and the use of fluoroquinolones has been close to zero.

Antimicrobial consumption in **aquaculture** varies considerably with water temperatures, because bacterial diseases are more likely to occur when temperatures are high. The AMU in 2022 was 2,451.8 kg, which was 36.4% higher than in 2021 (Figure 2.3). Mainly three compounds are used to treat bacterial infections in aquaculture: 79.2% of sulfonamides and trimethoprim, 14.9% of \`other quinolones´ (oxolinic acid), and 5.9% of amphenicols (florfenicol).

Data on antimicrobial consumption in **companion animals** is less detailed than for the food-producing animals because registering of species is not mandatory. The consumption for companion animals was estimated to be 2,143.3 kg in 2022, which was the same as in 2013 and 14.9% lower than in 2021. More than half of all cephalosporins, all 3rd and 4th generation cephalosporins, as well as close to all fluoroquinolones prescribed for veterinary use, were prescribed for companion animals.

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 health care sector level, 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

Total consumption of antimicrobials in Denmark

Major part of antimicrobial consumption is prescribed in primary health care

Total antimicrobial consumption in Denmark in 2022 was 15.50 DID, of which 87% was prescribed in primary healthcare. 15% of sales in primary care were based on prescriptions issued by hospital doctors, presumably upon discharge from the hospital (Figure 3.1).

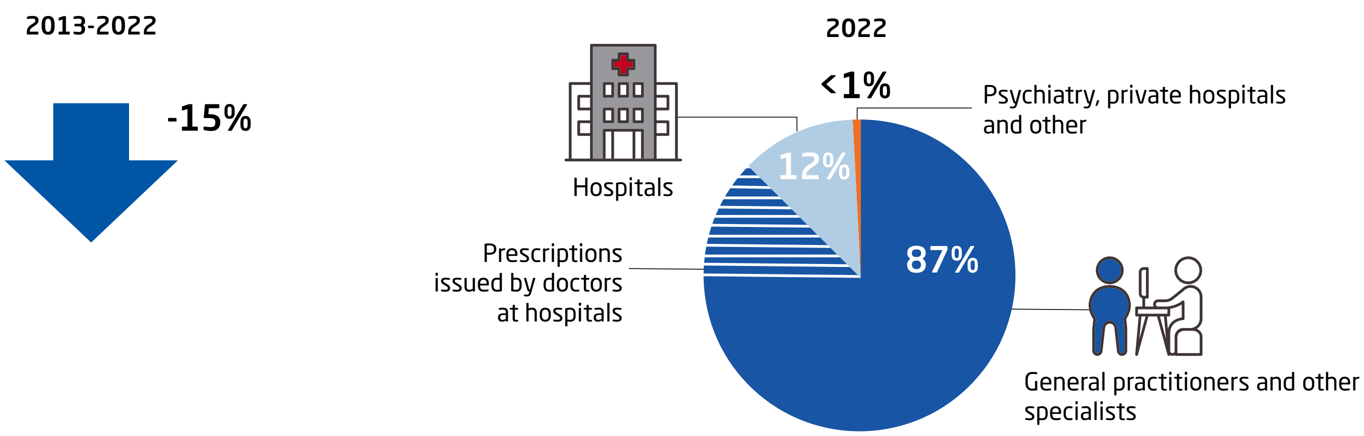
Decreased consumption of antimicrobials by 15% over the past decade

Over the past decade, total antimicrobial consumption in Denmark decreased by 15% (Figure 3.1). However, consumption has increased since the COVID-19 related drop in 2020 and 2021. Thus, antimicrobial consumption in 2022 was close to 2019 (15.77 DID).

Increased antimicrobial consumption at hospitals

In contrast to the overall antimicrobial consumption in Denmark, antimicrobial consumption at hospitals has increased by 24% over the past decade, when standardised by changes in hospital activity over the years (128 DBD in 2022 versus 104 DBD in 2013).

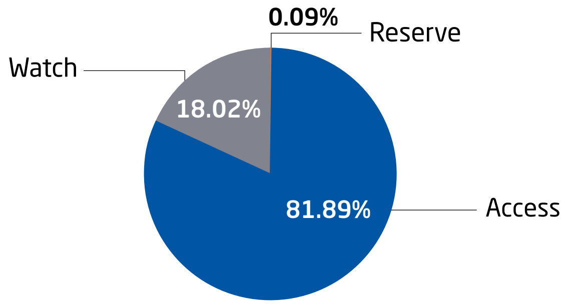
Figure 3.1 Change in total antimicrobial consumption and distribution by healthcare providers, Denmark, 2013-2022



AWaRe classification of antimicrobials in Denmark, 2022

The World Health Organization (WHO) has developed the AWaRe classification system as a tool to assist antibiotic stewardship and to reduce antimicrobial resistance. Antibiotics are classified into three groups to emphasise the importance of their appropriate use:

- **Access:** Antibiotics used to treat common susceptible pathogens with lower resistance potential than antibiotics in the other groups. 60% of total antimicrobial consumption should consist of Access agents.
- **Watch:** Antibiotics that have higher resistance potential, including most of the highest priority agents. These antibiotics should be prioritised as key targets of stewardship programs and monitoring.
- **Reserve:** Antibiotics reserved for treatment of confirmed or suspected infections due to multi-drugresistant organisms. These antibiotics should be considered as "last resort" options.



WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, 2017.
Geneva: World Health Organization; updated 2023 (WHO-MHP-HPS-EML-2023.04)

Antimicrobial consumption in primary health

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

The total antimicrobial consumption in primary health care was 424 prescriptions per 1,000 inhabitants in 2022, a 25% reduction from the 565 prescriptions per 1,000 inhabitants in 2013 (Table 3.1). Compared to 2021, consumption has increased by 7%, however the level is still 5% lower than in 2019 (445 prescriptions per 1,000 inhabitants).

Table 3.1 Consumption of antimicrobial agents in primary health care, prescriptions per 1,000 inhabitants per day, Denmark, 2013-2022

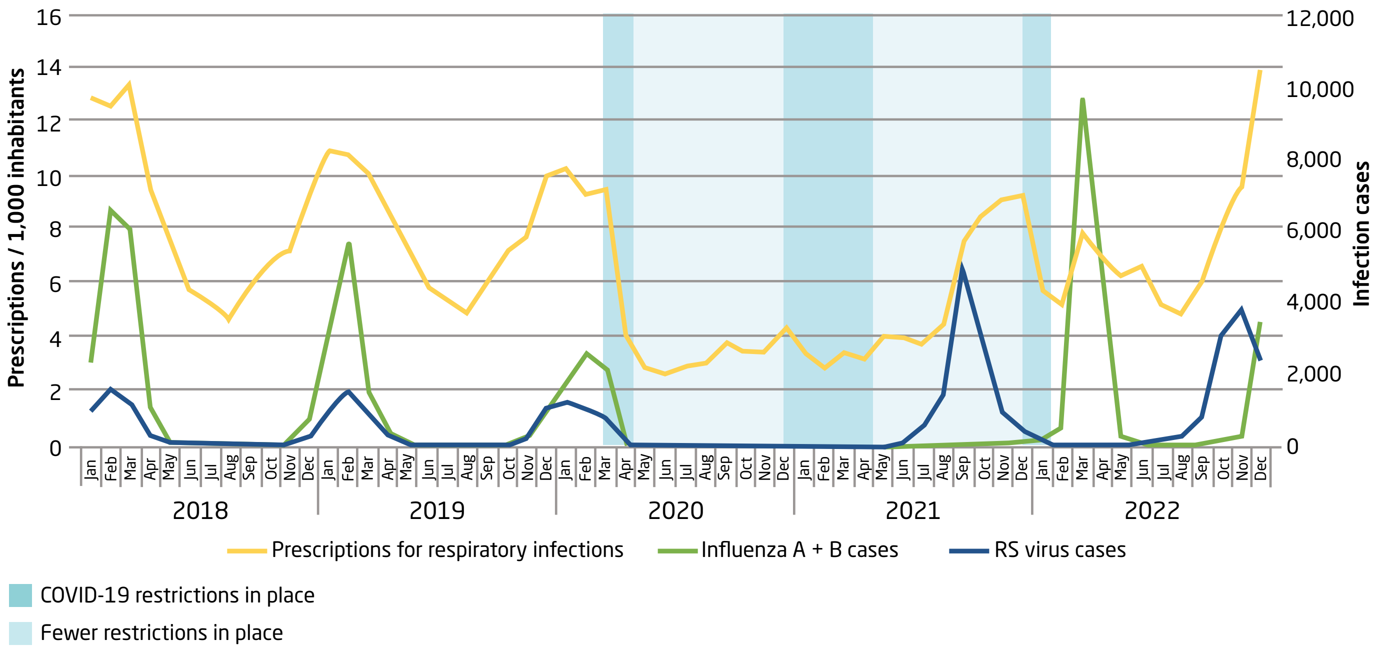
ATC group	Therapeutic group	Year									
		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	22.89	20.00	17.90	17.18	15.89	14.63	15.11	20.19	18.25	18.71
J01CA	Penicillins with extended spectrum	114.30	113.83	113.53	113.16	114.37	114.31	112.19	105.93	107.97	112.19
J01CE	Beta-lactamase sensitive penicillins	180.54	170.70	163.09	157.13	148.52	136.81	128.77	104.07	107.28	122.88
J01CF	Beta-lactamase resistant penicillins	41.25	41.04	40.81	41.87	41.87	43.35	43.16	42.87	43.17	45.66
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	28.01	29.02	30.73	31.13	27.09	23.71	23.07	19.14	20.36	23.45
J01E	Sulphonamides and trimethoprim	43.53	41.51	38.39	36.41	34.29	31.74	28.14	25.59	23.07	21.26
J01FA	Macrolides	74.51	68.01	68.00	68.85	60.00	52.64	50.71	33.66	33.80	36.94
J01MA	Fluoroquinolones	20.65	19.67	19.50	18.74	17.37	15.97	13.99	12.07	11.41	11.96
J01X	Other antibacterials (methenamine >99%)	17.41	16.73	16.28	15.82	10.18	6.76	10.29	10.62	10.70	10.72
P01AB01	Metronidazole	19.26	19.06	19.15	18.63	17.26	16.31	15.78	15.62	16.00	16.17
J01 and P01AB01	Antibacterial agents for systemic use	565.26	542.53	530.56	522.19	490.08	459.39	444.53	393.34	395.76	423.71

Antimicrobial consumption for respiratory infections

Consumption of antimicrobials prescribed for respiratory tract infections dropped sharply from April 2020 to July 2021 with the emergence of COVID-19 (Figure 3.2). This coincided with a sharp decrease in the number of laboratory confirmed influenza and Res-piratory Syncytial Virus (RSV) infections. The decrease in the spread of respiratory infections was most likely caused by the societal restriction implemented in March 2020 due to the COVID-19 pandemic.

From August 2021, the consumption increased to levels similar to the corresponding pre-pandemic months in 2019, which again coincided with the RSV summer epidemic in 2021. In 2022, the usual winter peak in antimicrobial consumption reached a higher level than observed in 2018-2019. This was probably due to an early RSV epidemic in the autumn 2022 that overlapped with an early influenza season.

Figure 3.2 Monthly consumption of systemic antimicrobials for the treatment of respiratory tract infections in primary health care, prescriptions per 1,000 inhabitants, and monthly number of laboratory confirmed influenza A and B as well as Respiratory Syncytial Virus (RSV), Denmark, 2018-2022

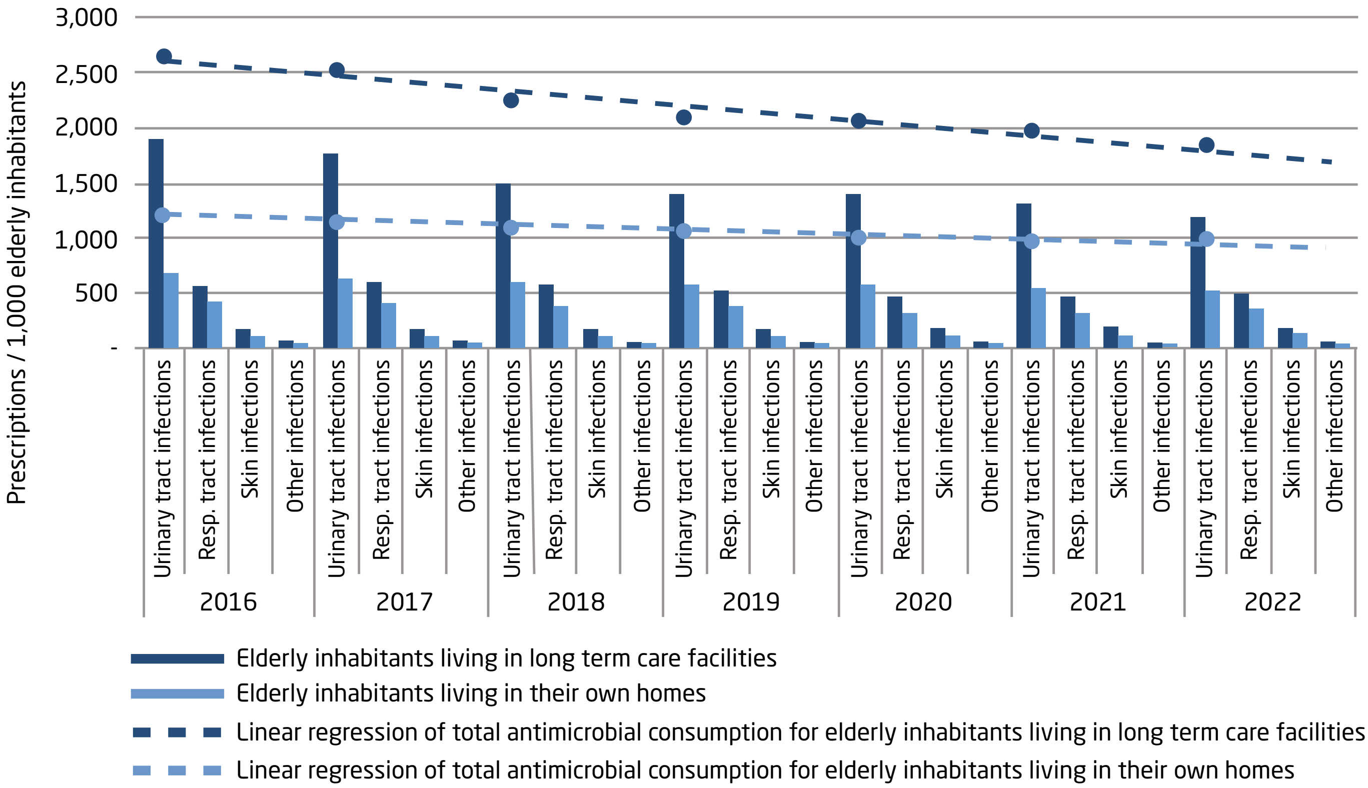


Antimicrobial consumption in elderly residents living in care homes is higher than in elderly residents living in their own homes

Elderly inhabitants living at care homes in 2022 received 88% more antimicrobials than elderly inhabitants living in their own homes (Figure 3.3). Urinary tract infections were the main cause of the observed difference in the treatment frequency.

The differences are observed despite a 30% decrease in the antimicrobial consumption for elderly inhabitants living at long term care facilities from 2016 to 2022 (from 2,636 prescriptions/1,000 inhabitants to 1,833 prescriptions/1,000 inhabitants). In the same period, consumption of antimicrobials for elderly living in their own homes decreased by 18% (from 1,195 prescrip-tions/1,000 inhabitants to 976 prescriptions/1,000 inhabitants).

Figure 3.3 Consumption of antimicrobials in primary health care for elderly inhabitants living in long term care facilities and for elderly inhabitants living in their own homes, Denmark, 2016-2022



Antimicrobial consumption at somatic hospitals

Change in use of antimicrobial groups

The 24% 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 (96% increase from 2013 to 2022) (Figure 3.4). At the same time the consumption of antimicrobials of special critical interest (cephalosporins, fluoroquinolones and carbapenems) decreased by 22% (Table 3.2).

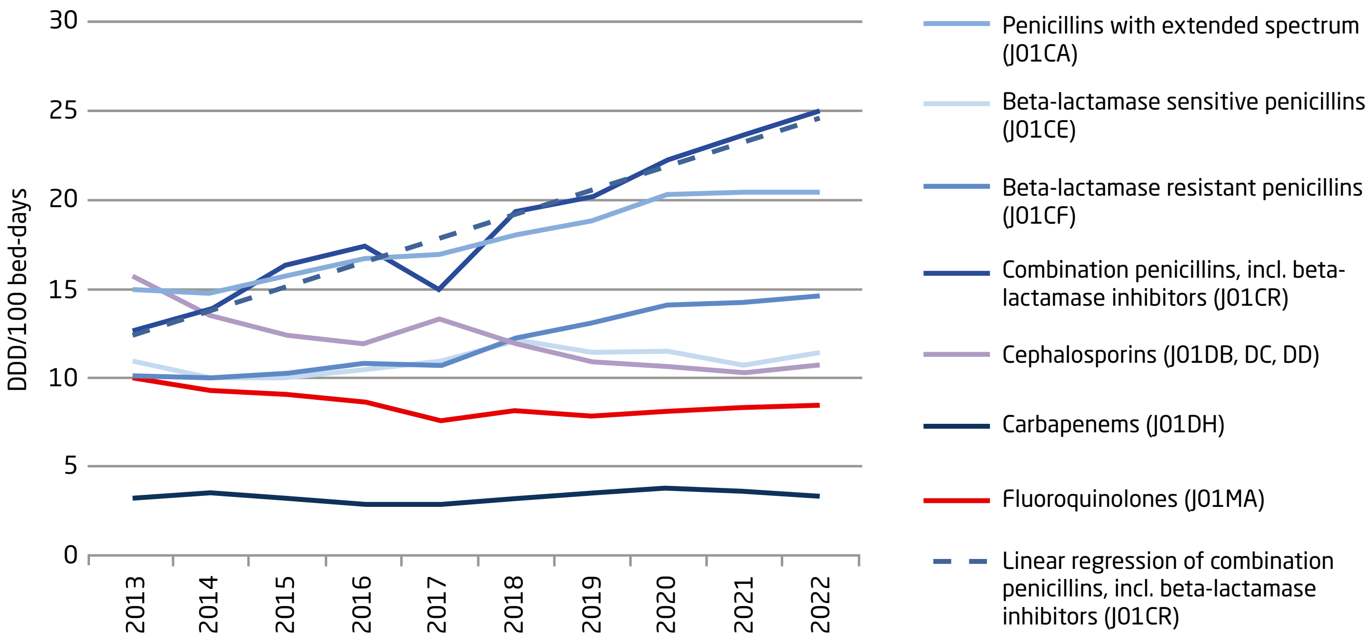
Somatic hospitals - definition

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, 2013-2022

Therapeutic group	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Combinations of penicillins, including beta-lactamase inhibitors (J01CR)	12.71	13.81	16.21	17.43	14.91	19.29	20.15	22.23	23.63	24.97
Penicillins with extended spectrum (J01CA)	15.00	14.72	15.63	16.76	16.89	18.01	18.73	20.33	20.49	20.48
Beta-lactamase sensitive penicillins (J01CE)	10.95	10.07	10.05	10.62	10.89	12.18	11.42	11.51	10.73	11.46
Beta-lactamase resistant penicillins (J01CF)	10.22	10.05	10.26	10.82	10.70	12.25	13.08	14.09	14.15	14.66
Cephalosporins (J01DB, DC, DD)	15.68	13.44	12.41	11.93	13.26	11.99	10.88	10.73	10.24	10.68
Fluoroquinolones (J01MA)	10.04	9.33	9.18	8.67	7.70	8.20	7.90	8.12	8.37	8.51
Macrolides (J01FA)	3.81	3.94	4.81	5.44	6.10	7.34	7.84	7.07	5.64	5.75
Carbapenems (J01DH)	3.25	3.57	3.22	3.12	3.07	3.28	3.46	3.76	3.61	3.52
Aminoglycosides (J01GB)	2.51	2.21	2.39	2.26	2.38	2.51	2.84	2.95	2.79	2.75
Others (A07AA09, P01AB01, J01AA, J01DF, J01E, J01FF, J01X)	19.35	18.49	19.01	20.69	19.62	22.29	23.53	24.25	24.63	25.12
Total antimicrobial consumption (J01, A07AA09, P01AB01)	103.51	99.64	103.16	107.74	105.52	117.34	119.82	125.03	124.29	127.89

Figure 3.4 Antimicrobial consumption at somatic hospitals by antimicrobial group, DDD per 100 bed-days, Denmark, 2013-2022



4. Resistance in zoonotic bacteria

Surveillance of antimicrobial resistance (AMR) in the zoonotic bacteria *Campylobacter* and *Salmonella* from healthy food-producing animals, from fresh meat, and from human clinical cases has been part of the DANMAP programme since 1995. Monitoring results for occurrence of resistance in *Campylobacter* and *Salmonella* can be accessed and interactively visualized in DANMAP *explorer*, available at www.DANMAP.org.

In Denmark, antimicrobials are only recommended for the treatment of *Campylobacter* or *Salmonella* human infections in cases of diarrhea of prolonged duration or in severely ill patients. If treatment is required, azithromycin (macrolide) is recommended to treat campylobacteriosis and less severe cases of salmonellosis in hospital patients, and fluoroquinolones may also be used in recurrent or prolonged infections. 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 primarily limited to tetracyclines.

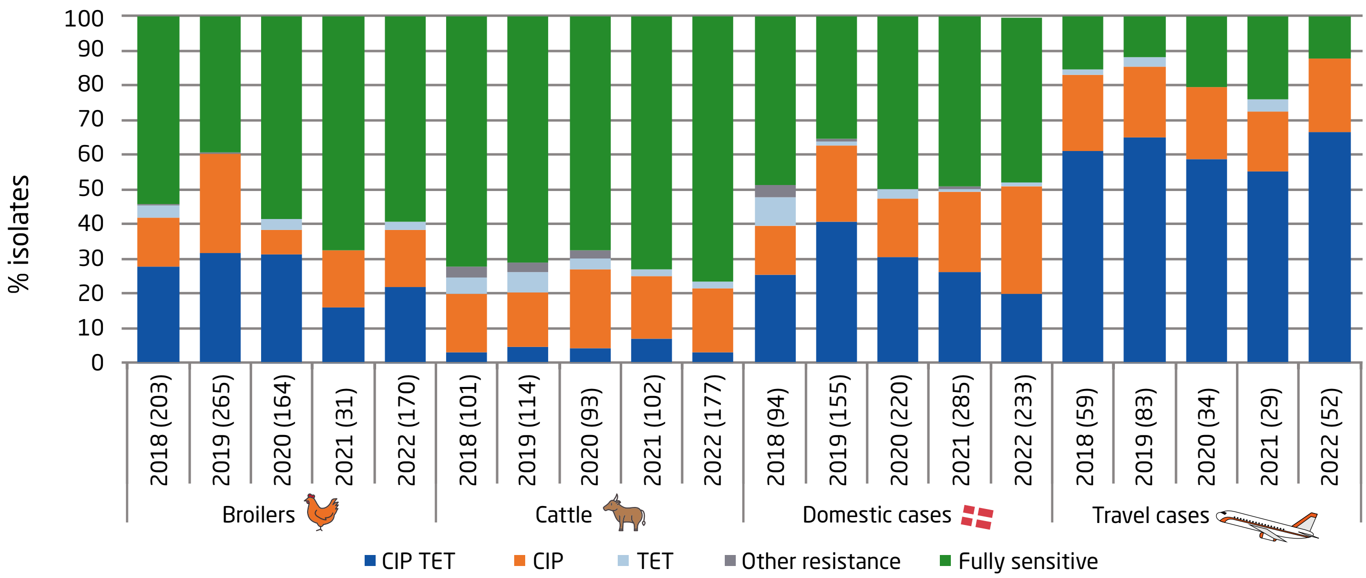
Resistance in *Campylobacter jejuni* and *Campylobacter coli*: increase in *C. jejuni* from broilers; decrease in *C. jejuni* from cattle; higher occurrence in *C. coli* than in *C. jejuni*

Campylobacter spp. are commonly associated with gastrointestinal intestinal disease in humans in Denmark. *Campylobacter jejuni* is the dominating human pathogen followed by *C. coli*. Both species are ubiquitous in food-producing animals, however *C. jejuni* is most common in broilers and cattle, while *C. coli* is most common in pigs. In addition to *C. jejuni*, the monitoring of resistance in *C. coli* in food-producing animals has been mandatory in the EU since 2021. In 2022, *C. coli* was monitored in broilers.

As in previous years, the resistance levels in *C. jejuni* from humans were higher than in isolates from broilers and cattle. Among the human infections the resistance levels were higher in isolates from travel-associated cases compared to the domestically-acquired infections. Compared to 2021, the percentage of fully-susceptible *C. jejuni* decreased by 9% in 2022 among isolates from broilers (59%), and increased by 3% among isolates from cattle (76%) (Figure 4.1).

Ciprofloxacin and tetracycline resistance in *C. jejuni* are common, whereas resistance is rarely observed for chloramphenicol, erythromycin and gentamicin. Accordingly, macrolide (erythromycin) resistance in *C. jejuni* remained very low in human isolates and was not detected in isolates from cattle and broilers (Table 4.1).

Figure 4.1 Distribution (%) of AMR profiles among *Campylobacter jejuni* from broilers, cattle and human cases, Denmark, 2018-2022



An isolate is categorised as domestically-acquired if the patient did not travel outside Denmark one week prior to the onset of disease

Fluoroquinolone (ciprofloxacin) resistance remained common in *C. jejuni* isolates from humans (58%), and in comparison to 2021, it decreased by 3% in isolates from cattle (22%) and increased by 6% in isolates from broilers (38%) (note that the number of isolates was comparably lower in 2021) (Table 4.1). The level of tetracycline resistance in *C. jejuni* isolates from humans was 29% and 24% and 5% in broilers and cattle, respectively. Accordingly, compared to the previous year, the percentage of isolates with combined resistance to ciprofloxacin and tetracycline increased in broilers and decreased in cattle by magnitudes similar to the above mentioned (Figure 4.1).

Campylobacter coli from broilers were commonly resistant to ciprofloxacin (39%) and tetracycline (45%). Resistance to erythromycin, chloramphenicol or gentamicin were not observed. The percentage of fully-sensitive *C. coli* in broilers (38%) was lower than the percentage observed in *C. jejuni* (Table 4.1).

The monitoring of carbapenem resistance in *Campylobacter* in food-producing animals and their meat started at EU-level in 2021, by including the antimicrobial ertapenem in the test panel. In 2022, ertapenem resistance was detected in 2% of the *C. jejuni* isolates and in 23% of the *C. coli* isolates from broilers. Among *C. jejuni* from human infections, 1% and 12% of the isolates from domestically-acquired and travel-associated infections, respectively, were resistant to ertapenem (Table 4.1).

Table 4.1 Resistance (%) in *Campylobacter jejuni* isolates from broilers, cattle and human cases, Denmark, 2022

	Broilers	Cattle	Human		
	Danish	Danish	Domestically acquired	Travel abroad reported	Total
Antimicrobial agent	%	%	%	%	%
Chloramphenicol	0	0	0	0	0
Ciprofloxacin	38	22	51	88	58
Ertapenem	2	0	1	12	3
Erythromycin	0	0	0	0	0
Gentamicin	0	0	0	0	0
Tetracycline	24	5	21	67	29
Fully sensitive (%)	59	76	48	12	41
Number of isolates	170	102	233	52	285

An isolate is categorised as domestically-acquired if the patient did not travel outside Denmark one week prior to the onset of disease. An isolate is considered fully sensitive if susceptible to all antimicrobial agents included in the test panel

Resistance in *Salmonella* Typhimurium: lower multidrug-resistance in Danish pork

DANMAP focuses on phenotypic resistance in *Salmonella* Typhimurium and the related monophasic variants, as these serotypes are present in clinical human isolates and in isolates from food-producing animals, especially in pigs. Clonal dissemination plays an important role for the occurrence of antimicrobial resistance among *S.* Typhimurium. The global dissemination of genomic islands conferring resistance to ampicillin, sulfamethoxazole and tetracycline (the ASuT multidrug-resistance profile) among *S.* Typhimurium and, in particular, its monophasic variants, continues to contribute to a high level of multidrug-resistance (resistance to three or more antimicrobial classes) among isolates from animals and humans.

As in most previous years, ASuT resistance represented the majority of multidrug-resistance profiles among all isolates, and was relatively higher among Danish pork isolates than among human isolates from domestically-acquired infections. Accordingly, the occurrence of fully sensitive isolates was lower in domestic pork than in human cases (Figure 4.2). For human isolates the majority of the AsuT profiles relates to the monophasic variants.

Macrolides may be used for treatment of human *Salmonella* infections in Denmark, and macrolide resistance is monitored using azithromycin. Resistance to azithromycin in *S.* Typhimurium remained low as in previous years in isolates from human infections (1%) and from Danish pork (4%) (Table 4.2).

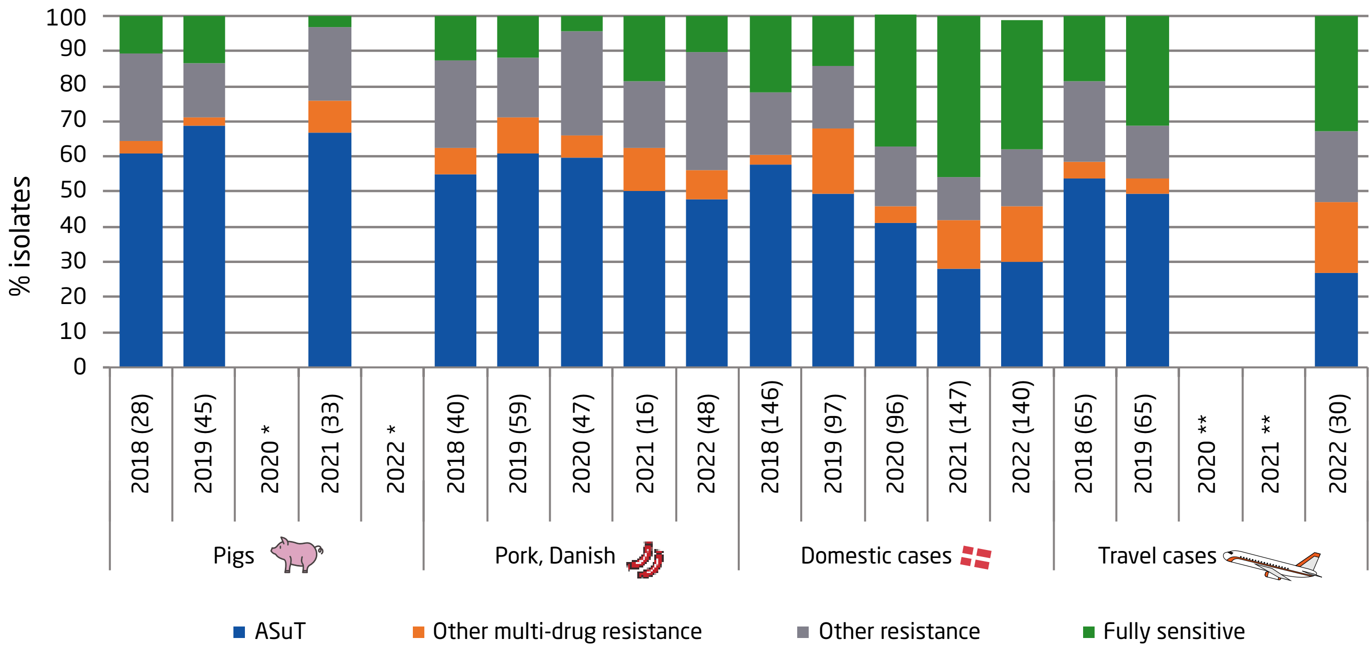
Fluoroquinolones may be used in combination therapy for the treatment of prolonged or recurrent human salmonellosis, and fluoroquinolone resistance is monitored using ciprofloxacin. Historically, ciprofloxacin resistance has predominantly been observed in isolates from travel-associated cases, and in 2022 ciprofloxacin resistance was observed in 4% of the isolates from domestically-acquired infections and in 20% of the isolates from travel-associated cases, while it remained absent among isolates from Danish pork (Table 4.2).

The recommended treatment of complicated *Salmonella* infections in hospitalized patients is intravenous ceftriaxone (a 3rd generation cephalosporin). Resistance to the critically important 3rd generation cephalosporins and carbapenems are rare in *S.* Typhimurium. In 2022, 3rd generation cephalosporin resistance (cefotaxime and ceftazidime) was observed in 1% of the human isolates, and no meropenem resistance was observed. As in the previous years, none of the *S.* Typhimurium isolates from domestic pork were resistant to 3rd generation cephalosporins or to meropenem (Table 4.2).

The levels of gentamicin resistance have been low and stable over the last years, and in 2022, 1% of the human isolates were resistant towards gentamicin. Notably, after a decrease in 2020 and 2021 in the occurrence of resistance to gentamicin in isolates from pork, in 2022 it increased to a level (8%) similar to 2019 (Table 4.2).

Resistance to tigecycline, colistin and amikacin in *S.* Typhimurium is rare in Denmark. In 2022, 1% of the human isolates were recorded as colistin resistant, and as in the previous years, no colistin resistance was found among pork isolates. Resistance towards tigecycline was observed in 1% of the human isolates and in 2% of the pork isolates. Resistance to amikacin was observed in 3% of the human isolates and all isolates from pork were amikacin-sensitive (Table 4.2).

Figure 4.2 Distribution (%) of AMR profiles among *Salmonella* Typhimurium from pigs, pork and human cases, Denmark, 2018-2022



* No data available
** Distribution not shown due to low number of isolates (<15)

Table 4.2 Resistance (%) in *Salmonella* Typhimurium isolates from domestic pork and humans, Denmark, 2022

	Pork	Human					
	Danish	Domestically acquired	Travel abroad reported	Unknown origin	Total	*S.* Typhimurium diphasic	*S.* Typhimurium monophasic
Antimicrobial agent	%	%	%	%	%	%	%
Amikacin	0	2	7	0	3	1	4
Ampicillin	79	51	53	35	50	15	86
Azithromycin	4	0	3	0	1	1	0
Cefotaxime	0	1	3	0	1	0	2
Ceftazidime	0	1	3	0	1	0	2
Chloramphenicol	13	6	13	5	7	10	4
Ciprofloxacin	0	4	20	0	6	8	3
Colistin	0	1	7	0	2	2	1
Gentamicin	8	1	3	0	1	0	2
Meropenem	0	0	0	0	0	0	0
Nalidixic acid	0	4	13	0	5	6	3
Sulfamethoxazole	81	54	47	35	51	19	84
Tetracycline	56	55	50	25	51	15	88
Tigecycline	2	1	0	0	1	2	0
Trimethoprim	25	11	7	5	9	4	15
Fully sensitive (%)	10	37	33	65	39	74	4
Number of isolates	48	140	30	20	190	96	94

Includes isolates verified as monophasic variants of *S*. Typhimurium with antigenic formula 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

5. Resistance in indicator bacteria

Escherichia coli and Enterococci (*E. faecalis* and *E. faecium*) are included in the DANMAP programme to monitor the 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.

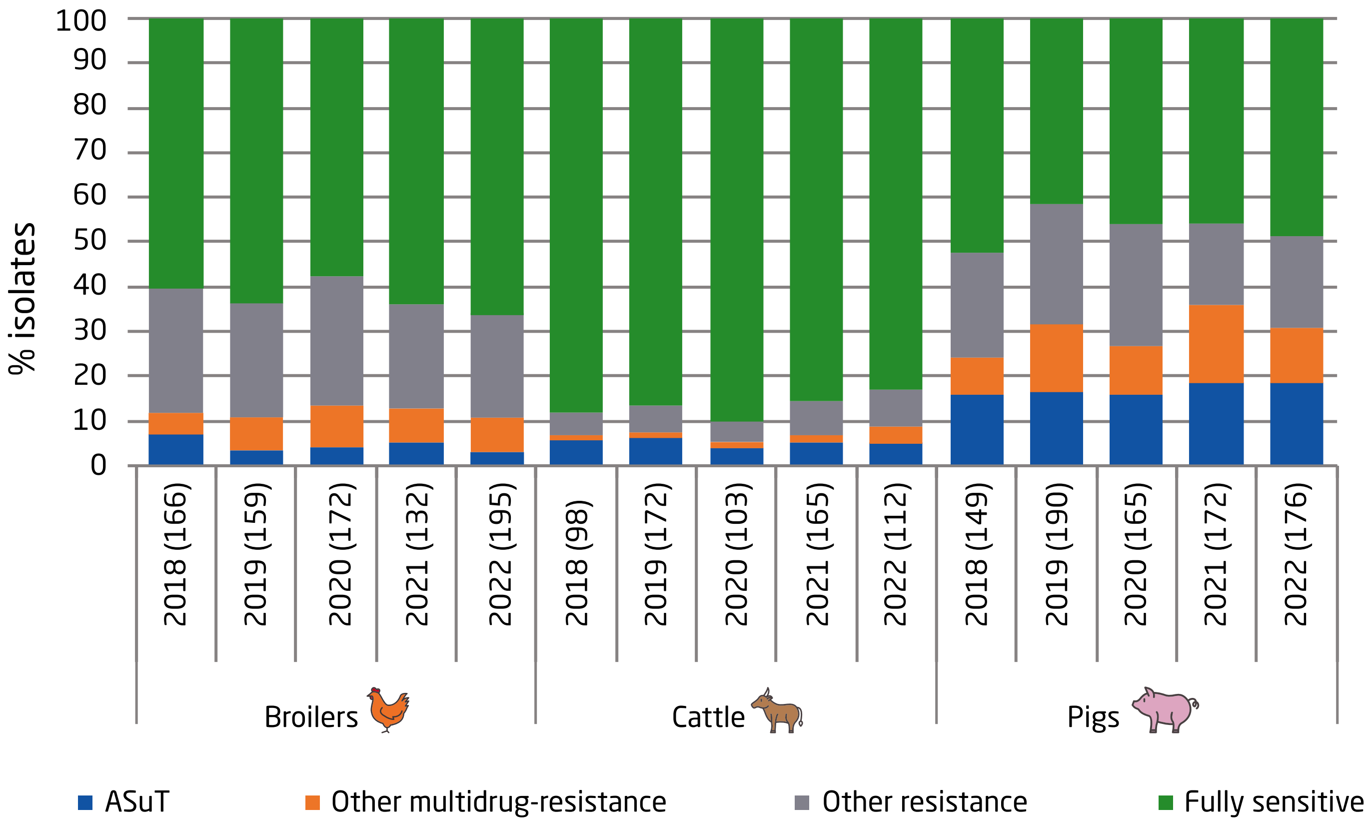
E. coli exhibiting resistance to 3rd generation cephalosporins via production of beta-lactamases, including extended-spectrum β-lactamases (ESBLs) and cephalosporinases (AmpC), are spreading fast in both humans and production animals worldwide. Carbapenemase-producing Enterobacteriaceae (CPE) are a great 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 the EU. β-lactamase- and CP-producing *E. coli* are monitored in DANMAP, both in healthy animals at slaughter and in fresh meat of domestic- and imported origin, via antimicrobial susceptibility testing and whole genome sequencing.

Monitoring results for occurrence of resistance in indicator *E. coli*, indicator Enterococci and β-lactamase-producing *E. coli* can be accessed and interactively visualized in DANMAP *explorer*, available at www.DANMAP.org .

Resistance in indicator *E. coli* – lower full-sensitivity in cattle; higher full-sensitivity in broilers; increase in ciprofloxacin resistance in broilers

Although no significant trend has been detected in the prevalence of fully sensitive indicator *E. coli* from Danish food-producing animals over the last five monitoring years, since 2020 the occurrence of fully sensitive *E. coli* has increased in broilers (67% in 2022) and decreased in cattle (84% in 2022) (Figure 5.1).

Figure 5.1 Distribution (%) of fully-sensitive, resistant and multidrug-resistant *Escherichia coli* isolates from broilers, cattle and pigs, Denmark, 2018-2022



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 three or more antimicrobial classes included in the test panel. ASuT are the multidrug-resistant isolates resistant to ampicillin, sulfamethoxazole and tetracycline, which may also be resistant to other antimicrobials

Compared to the previous year, in 2022 the relative occurrence of multidrug-resistant indicator *E. coli* decreased in broilers and pigs and increased in cattle. Combined resistance to ampicillin, sulfamethoxazole and tetracycline (ASuT) continued to be the most common multidrug-resistance profile in all monitored animal populations, however the occurrence of other multidrug-resistance profiles has increased in isolates from broilers and decreased in isolates from cattle in the past 5 years (Figure 5.1).

Regarding resistance to critically important antimicrobials, as in previous years, no colistin, meropenem or tigecycline resistance were detected in indicator *E. coli*. Resistance to ciprofloxacin continued to be low among isolates from cattle and pigs, while it increased in isolates from broilers, reaching the maximum level of the last ten years (18%). Compared to 2021, in 2022 azithromycin resistance was again detected in few isolates from pigs (3%), and the occurrence of chloramphenicol resistance decreased (8%) (Table 5.1).

Table 5.1 Resistance (%) in *Escherichia coli* isolates from broilers, cattle and pigs, Denmark, 2022

	Broilers	Cattle	Pigs
	Danish	Danish	Danish
Antimicrobial agent	%	%	%
Amikacin	0	0	0
Ampicillin	9	5	35
Azithromycin	0	0	3
Cefotaxime	0	0	0
Ceftazidime	0	0	0
Chloramphenicol	<1	7	8
Ciprofloxacin	18	0	<1
Colistin	0	0	0
Gentamicin	3	0	0
Meropenem	0	0	0
Nalidixic acid	18	0	0
Sulfamethoxazole	14	10	42
Tetracycline	5	13	28
Tigecycline	0	0	0
Trimethoprim	5	3	31
Fully sensitive (%)	67	84	49
Number of isolates	195	112	176

An isolate is considered fully-sensitive if susceptible to all antimicrobial agents included in the test panel

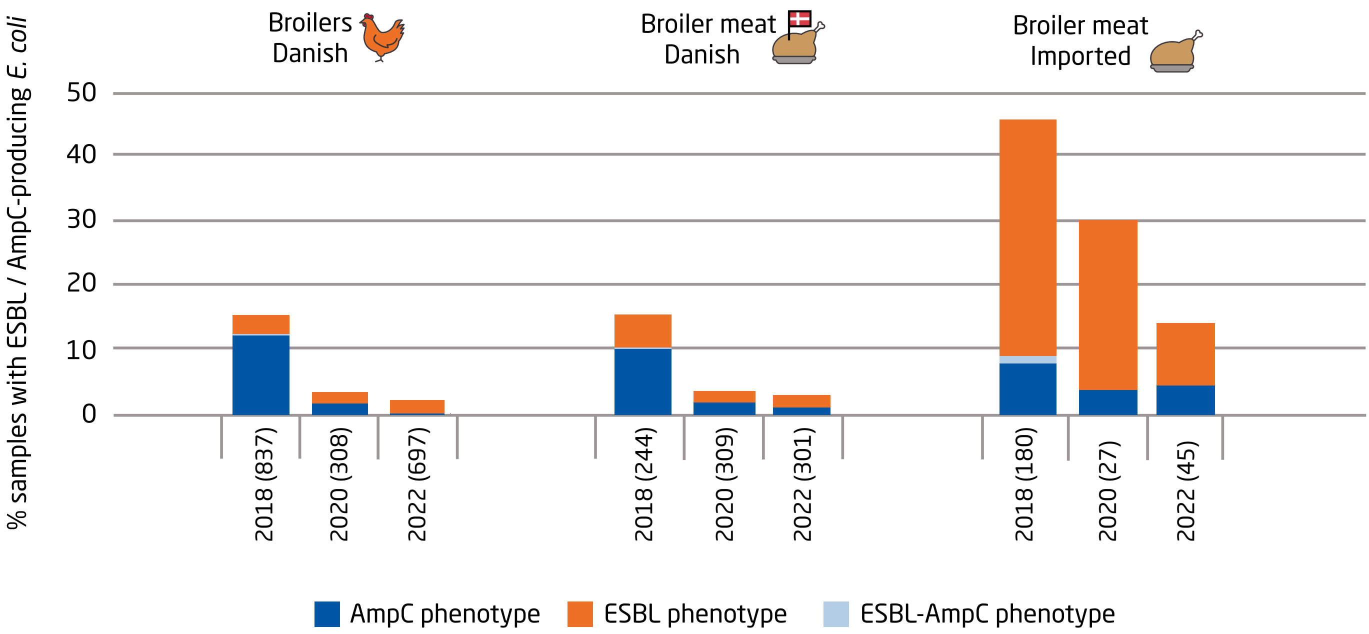
Occurrence of β-lactamase-producing *E. coli* - decreasing trend in broilers and broiler meat; high in imported turkey meat

The occurrence of *E. coli* producing beta-lactamases continued the decreasing trend observed since 2018 in broilers and broiler meat. In 2022, the occurrence in imported turkey meat was 52%. All except one of the monitored turkey meat samples originated from a single EU country. As in previous years, no samples were found positive for carbapenemase-producing *E. coli* (Figure 5.2).

The phenotypic and genotypic resistance profiles of β-lactamase-producing *E. coli* were mostly in concordance, however whole genome sequencing revealed occurrence of both ESBL- and AmpC encoding genes in five isolates, while susceptibility testing showed an AmpC-producing phenotype.

For all AmpC genotypes, resistance was conferred by upregulated AmpC promotor C-42T mutations. Among the ESBL genotypes, 14 different ESBL-encoding genes were detected, with most variation among isolates from imported turkey meat, of which 46% had more than one ESBL encoding gene. 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 broilers and broiler meat recovered by selective enrichment, Denmark, 2018-2022

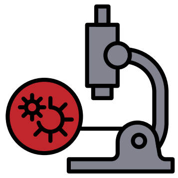


Number of samples tested per year is presented in parentheses. Classification of ESBL and/or AmpC phenotypes based on antimicrobial susceptibility testing

Table 5.2 Number of ESBL and/or AmpC enzymes detected in β-lactamase-producing *E. coli* isolates from animals and meat recovered by selective enrichment, Denmark, 2022

	Broilers	Broiler meat		Turkey meat
	Danish	Danish	Import	Import
CTX-M-1	2	1		3
CTX-M-14				2
CTX-M-15				28
CTX-M-27				6
CTX-M-32				2
CTX-M-55			2	5
CTX-M-65			1	1
OXA-1				2
SHV-12		1		6
TEM-135				3
TEM-176				1
TEM-1B	3	1	4	21
TEM-1D				1
TEM-52B	1	2		
CMY-2	1	1	2	
Chromossomal AmpC (C-42T)	3	1		3
Number of AmpC genotypes	1	1	1	3
Number of ESBL genotypes (two or more enzymes)	3 (0)	4 (0)	4 (2)	54 (25*)
Number of AmpC+ESBL genotypes	3	1	1	0
Not available	2	0	0	2
Number (%) positive samples	9 (1%)	6 (2%)	6 (13%)	59 (52%)
Number of tested samples	697	307	45	113

Number (%) positive samples are isolates recovered by selective enrichment methods for specific monitoring of ESBL/AmpC producing *E. coli*. ESBL/AmpC enzymes were determined by whole genome sequencing of the recovered isolates. Not available refers to isolates without WGS results.
* Two of the 25 isolates from turkey meat with more than one ESBL enzyme had three different enzymes.



Extended-spectrum beta-lactamases (ESBL) and Cephalosporinases (AmpC)

Gram-negative bacteria, such as *E. coli*, resistant to β-lactam antibiotic(s) most commonly produce one or more β-lactamase enzymes, which hydrolyze the given antibiotic(s).

β-lactamases can be classified according to different structural and functional classification systems. The functional classification has the advantage to relate the enzymes to their ability to hydrolyze specific β-lactam classes, and to identify the possibility of their inactivation with β-lactamase inhibitor substances, thus supporting antimicrobial therapy choices in clinical practice.

According to their functional classification, β-lactamases can be classified in three major groups, and several subgroups. In DANMAP, *E. coli* is monitored for ESBL and AmpC enzymes.

AmpC enzymes - group 1 cephalosporinases
AmpCs are active on cephalosporins and cephamycins, and usually resistant to inhibition by clavulanic acid. In large amounts, especially against low amounts of β-lactams, AmpCs can also provide resistance to carbapenems. These enzymes are encoded on the chromosomes of many *Enterobacteriaceae*, however, plasmid-mediated AmpCs also occur for example in the families CMY or DHA, although less commonly than plasmid-mediated ESBLs. Group 1 includes subgroup 1e, which encompasses AmpC variants with greater activity against ceftazidime (a 3rd generation cephalosporin), also called extended-spectrum AmpCs.

ESBL enzymes - group 2 serine β-lactamases
Group 2 is the largest functional group of β-lactamases, and it includes 12 subgroups. Subgroup 2b β-lactamases hydrolyze penicillins and early-generation cephalosporins, and are strongly inhibited by clavulanic acid and tazobactam. They include the most common plasmid-mediated β-lactamases in the TEM and SHV families. Subgroup 2be comprises the ESBLs. ESBLs have the activity of enzymes of subgroup 2b, and additionally hydrolyze one or more 3rd generation cephalosporins. They include mostly enzymes of the families TEM, SHV, and the more rapidly proliferating CTX-M enzymes.

Enterococci in broilers – lower resistance levels compared to previous monitoring year

In 2022, 39% of *E. faecalis* and 52% of *E. faecium* isolated from broilers were fully sensitive. None of the enterococci isolates showed resistance to ampicillin, chloramphenicol, daptomycin, gentamicin, linezolid, teicoplanin, tigecycline or vancomycin. Combined resistance to tetracycline and erythromycin was the most common resistance profile in *E. faecalis*, whereas *E. faecium* were most commonly resistant only to quinupristin-dalfopristin. Compared to 2020, the occurrence of resistance to tetracycline or erythromycin remained the same in *E. faecium* and fluctuated in *E. faecalis*.

Table 5.3 Resistance (%) in Enterococci isolates from broilers, Denmark, 2022

Antimicrobial agent	*Enterococcus faecalis*	*Enterococcus faecium*
	%	%
Ampicillin	0	0
Chloramphenicol	0	0
Ciprofloxacin	0	3
Daptomycin	0	0
Erythromycin	43	9
Gentamicin	0	0
Linezolid	0	0
Quinupristin/dalfopristin	-	43
Teicoplanin	0	0
Tetracycline	50	12
Tigecycline	0	0
Vancomycin	0	0
Fully sensitive (%)	39	52
Number of isolates	28	305

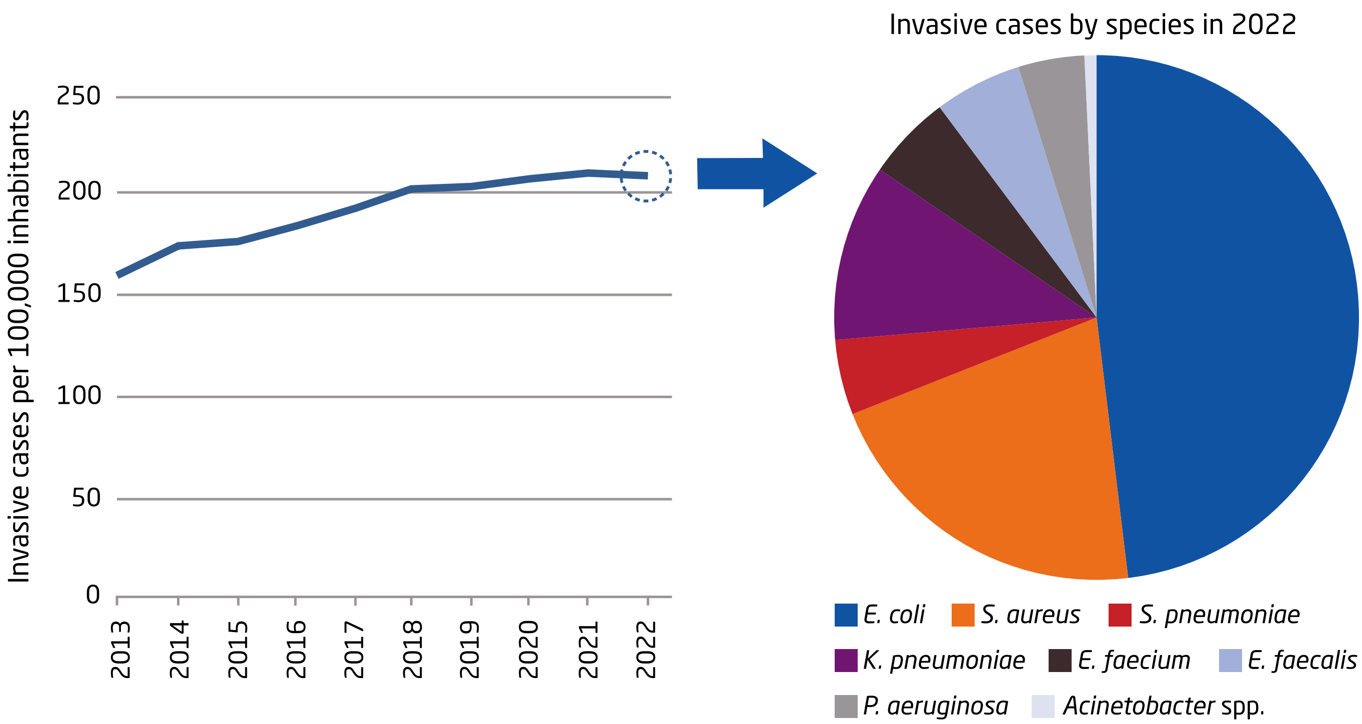
6. Resistance in human pathogens

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 (NRLs) at Statens Serum Institut (SSI). Data for DANMAP is either extracted from the Danish Microbiological database (MiBa) or collected from the registers at the NRL.

Stabilisation in the number of invasive infections by bacterial species monitored in Denmark

Escherichia coli remains the most frequent cause of invasive infections (5,905 in 2022) with a 49% increase in the number of invasive isolates over the last decade. *Staphylococcus aureus* bacteraemia accounted for 2,589 patient cases (1,685 in 2013, 54% increase), followed by *Klebsiella pneumonia* with 1,346 patient cases (875 in 2013, 54% 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. However, comparing to 2021, the total number seems to have stabilized with 12,147 cases in 2021 and 12,169 in 2022. 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 2022, a total of 3,343 patients per 100,000 inhabitants had at least one blood culture taken compared to 2,412 patients per 100,000 inhabitants in 2013, an increase of 39%. Simultaneously, the number of positive blood cultures from bacterial species under surveillance in DANMAP increased markedly, by 36%, Figure 6.1.

Figure 6.1 Number of monitored invasive cases, Denmark, 2013-2022



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. However, increases in resistance towards multiple antibiotics were observed from 2021 to 2022. For *K. pneumoniae* similar trends were observed, the decreases in resistance to cephalosporins, fluoroquinolones and gentamicin being even more notable.

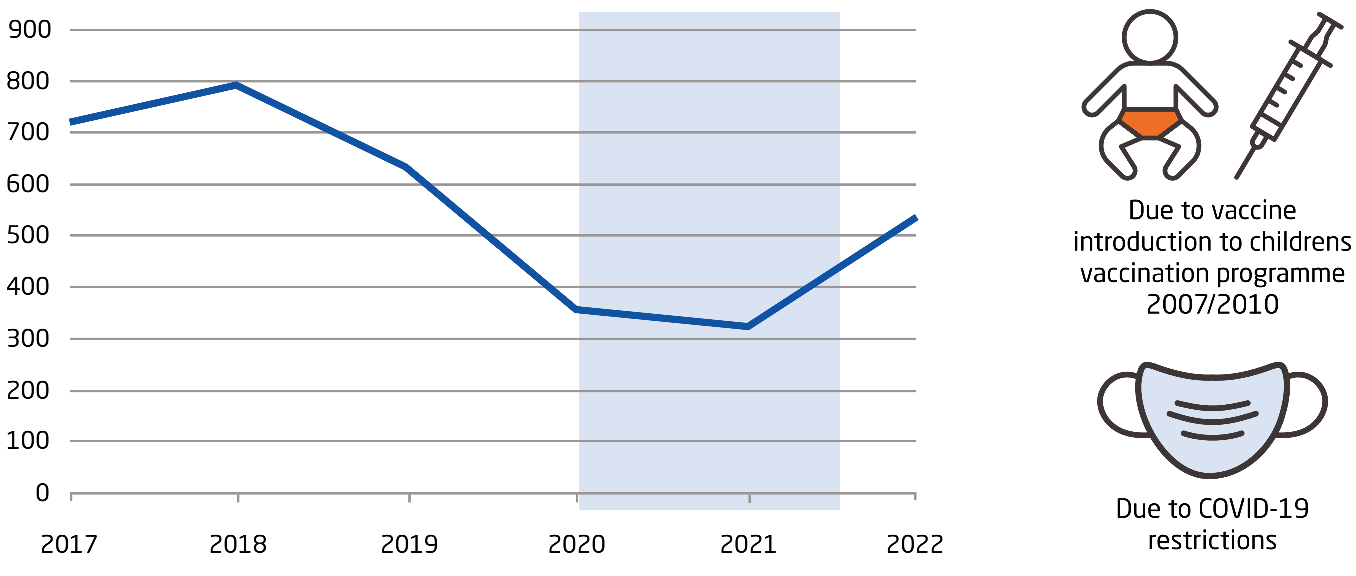
Table 6.1 Resistance (%) in *E. coli* and *K. pneumoniae* from urine and blood cultures, 2022

	E. coli		*K. pneumoniae*	
	Urines from praxis	Invasive	Urines from praxis	Invasive
Ampicillin	35	43	100	100
Mecillinam	4.3	8.8	7.9	8.7
Trimethoprim	20	-	12.3	-
Amoxicillin/clavulanic acid	-	34.4	-	14
Piperacillin-tazobactam	-	6.3	-	9.2
Cefuroxim	-	9.9	-	7.7
3rd gen. cephalosporins	4.8	6.2	3.4	4.8
Ciprofloxacin	6.9	11	5.1	7.4
Carbapenem	-	0.0	-	0.4

Invasive pneumococcal infections resurging after COVID-19 restrictions end

Invasive pneumococcal disease (IPD) 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. During the COVID-19 pandemic and the associated restrictions, a marked decrease in IPD followed. However, since the lifting of restrictions there has been a resurgence of cases. Resistance to penicillin and erythromycin has slowly increased over the past 25 years, but fluctuates with the circulating serotypes.

Figure 6.2 Invasive infections caused by *S. pneumoniae*, Denmark, 2017-2022. The light blue area denotes the period with intermittent COVID-19 restrictions



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

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. While a marked decrease in the number of ESBL and/or AmpC positive invasive *E. coli* isolates was observed from 2020 to 2021 (from 352 to 254 isolates, respectively), the number has since increased again to 336 isolates in 2022. CTX-M-15 remains the most common ESBL-gene present in 52% of cases.

Increasing numbers of CPO isolates associated with travel and of unknown origin

Carbapenemase-producing organisms (CPO) have been notifiable since 2018. A substantial increase in patients with CPO related to outbreaks in Danish hospitals was observed from 2019 to 2021 with 42 and 97 isolates, respectively (Figure 6.3a), but now remains stable. In 2022, there were 17 registered on-going outbreaks. Acting in accordance with the CPO guidelines is of the utmost importance 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.

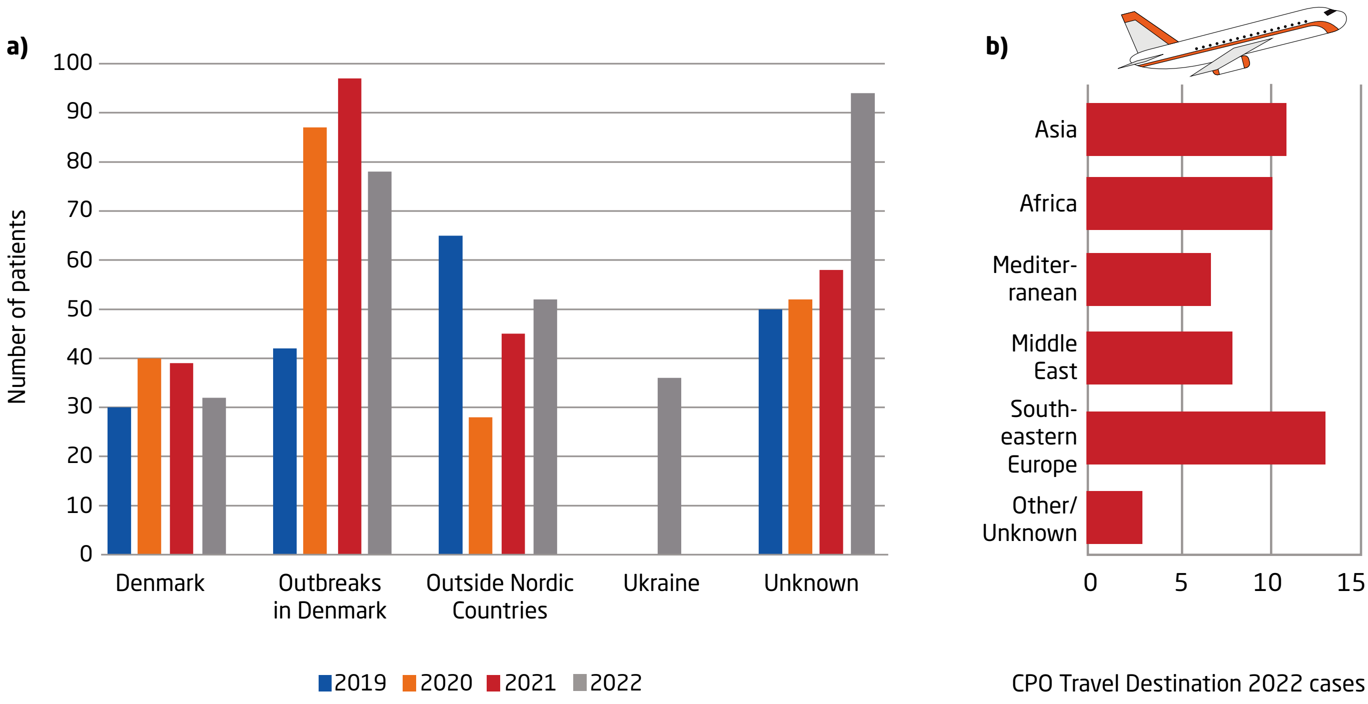
Detection of CPO was made notifiable in Denmark in September 2018.

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*

In 2022, 52 persons with CPO had been travelling compared to 45 in 2021 and 28 in 2020. The regions where the patients had travelled to in 2022 can be seen in Figure 6.3b. The largest increase in the specified origin was seen for unknown origin, which is now the largest category with 94 people.

Figure 6.3 a) Classification of CPO cases from 2019 through 2022 b) World regions where the patients with travel related cases have travelled



The number of vancomycin-resistant and vancomycin-variable enterococci (VRE/VVE) continues to increase

Voluntary submission of VRE from the DCMs to the SSI reference laboratory has been on-going since 2005. In 2022, 845 VRE/VVE isolates were detected in Denmark - a 14% increase compared to the 742 isolates found in 2021. This is a worrying development after the stable numbers found in 2021. The increasing numbers warrant 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 2022 (5 and 15 isolates, respectively), but are still an increase from 2021 (LRE: 1, LVRE: 14). 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 increase in the number of bacteraemia cases in 2022

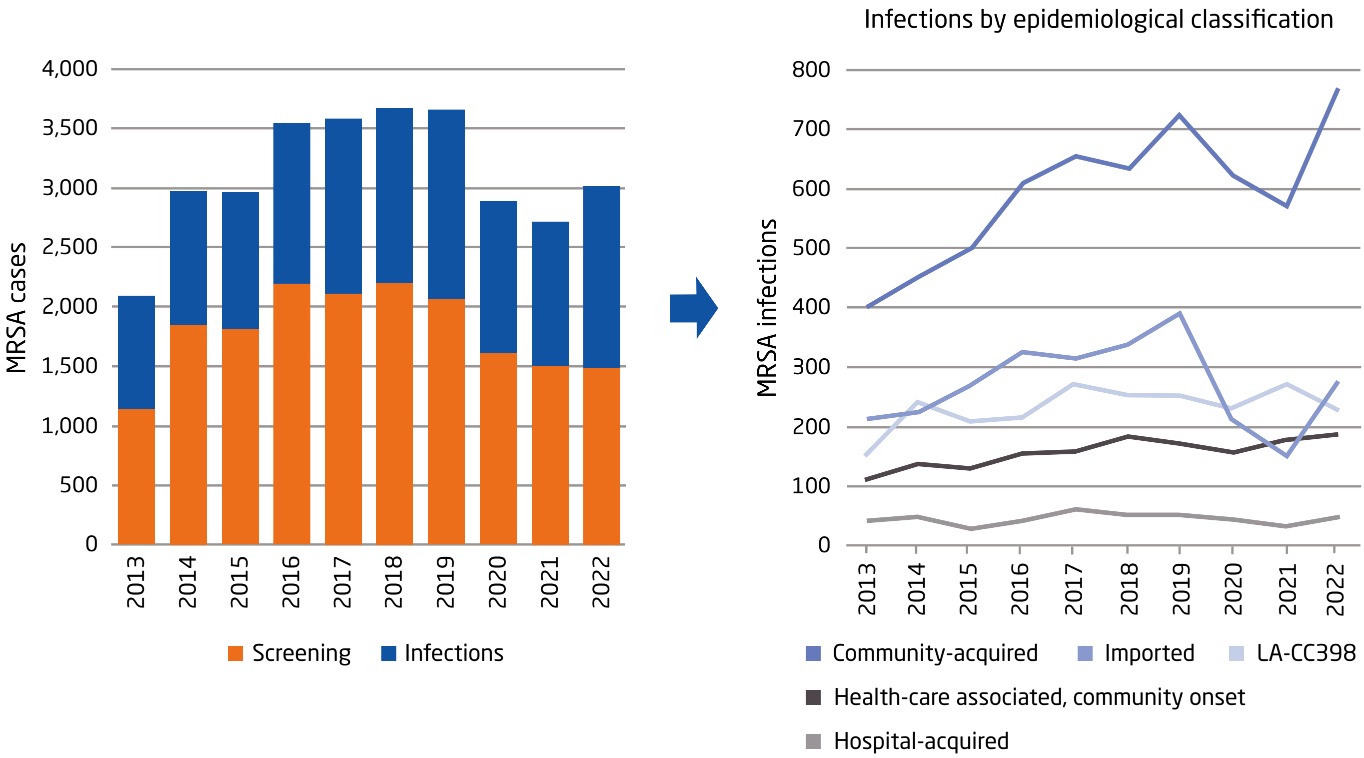
Since 1957 isolates from invasive infections with *Staphylococcus aureus* have on a voluntary basis been referred to the reference laboratories at Statens Serum Institut. Since 2006, the isolation of methicillin resistant *S. aureus* (MRSA) from either infected or non-infected (colonized) persons has 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 2022, the number of invasive *S. aureus* isolates from blood remained stable increasing by 3% from 2,511 cases in 2021 to 2,578 cases in 2022. Fifty of the bacteraemia cases were caused by methicillin-resistant (MRSA) out of which seven were LA-MRSA.

Surveillance of all MRSA cases, e.g. infected and colonized persons, showed an increase of 10% in 2022 (2,996 cases) compared to 2021 (2,712 cases) and a 43% increase compared to 2013 (2,091 cases), Figure 6.4. LA-MRSA constituted 28% 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 increased compared to 2021 and 2020 with 39 outbreaks in 2022 involving 143 patients (30 outbreaks in 2021, 31 in 2020; 109 patients in 2021, 130 in 2020).

Figure 6.4 Number of MRSA under surveillance (screen and infections), Denmark, 2013-2022



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 2022, SSI's reference laboratory confirmed 1,841 unique cases of gonorrhea compared to 1,408 in 2021. 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 40% 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. Resistance in animal pathogens

Increased frequency of neomycin resistance in clinical *Escherichia coli* isolates from pigs

Surveillance of antimicrobial resistance in 2022 focused on pathogenic bacteria from pigs and included results obtained through antimicrobial susceptibility (AST) testing and/or whole genome sequencing (WGS) of isolates belonging to *Actinobacillus pleuropneumoniae* (AST and WGS), *Bordetella bronchiseptica* (AST and WGS), *Clostridium perfringens* (WGS), *Erysipelothrix rhusiopathiae* (WGS), haemolytic and non-haemolytic *Escherichia coli* (AST and WGS), *Glaesserella parasuis* (WGS), *Klebsiella pneumoniae* (AST and WGS), *Salmonella enterica* (AST and WGS), *Staphylococcus hyicus* (AST and WGS) and *Streptococcus suis* (AST and WGS).

AST showed that most pathogenic bacteria from pigs displayed similar frequencies of phenotypic resistance as in previous years.

A notable exception was the increased frequency of neomycin resistance in haemolytic haemolytic *E. coli*, from 6.9% in 2016 to 43.2% in 2022. This is concerning because it is one of only a few drugs recommended in Denmark as first choice for treating *E. coli*-associated post-weaning diarrhea (Figure 7.1). The rapid increase in neomycin resistance might, at least in part, be due to increased use of neomycin in weaners (Figure 7.2).

WGS demonstrated that resistance towards antimicrobial agents considered critically important for human medicine remained at a low level.

The observed concordance between AST results and WGS-based detection of resistance genes and point mutations was 99.7% for *A. pleuropneumoniae*, 64.5% for *B. bronchiseptica*, 92.8% for haemolytic *E. coli*, 93.9% for non-haemolytic *E. coli*, 61.7% for *K. pneumoniae*, 95.7% for *S. enterica*, 92.6% for *S. hyicus* and 94.0% for *S. suis*.

Figure 7.1 Neomycin resistance among haemolytic *Escherichia coli* isolates from pigs, Denmark, 2016-2022

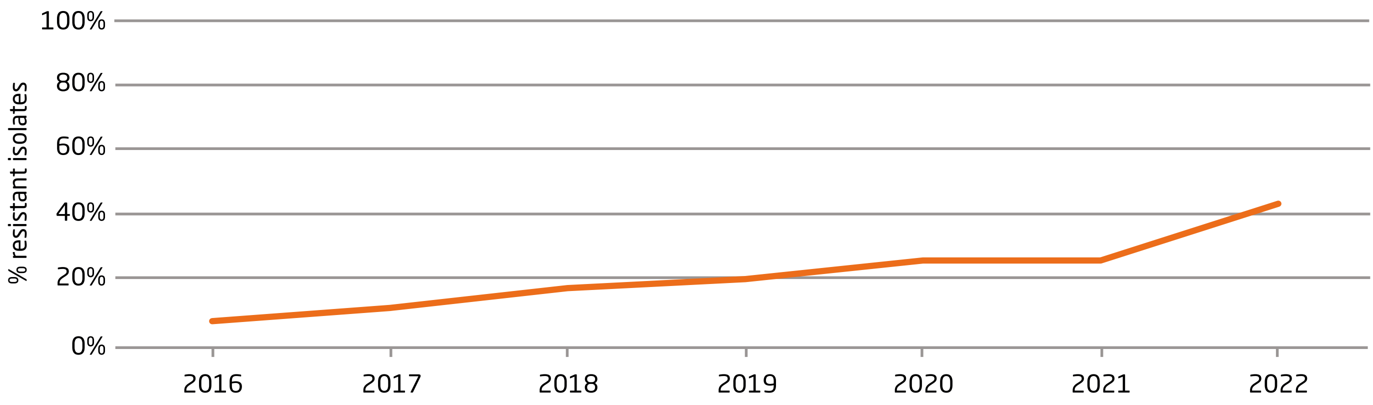
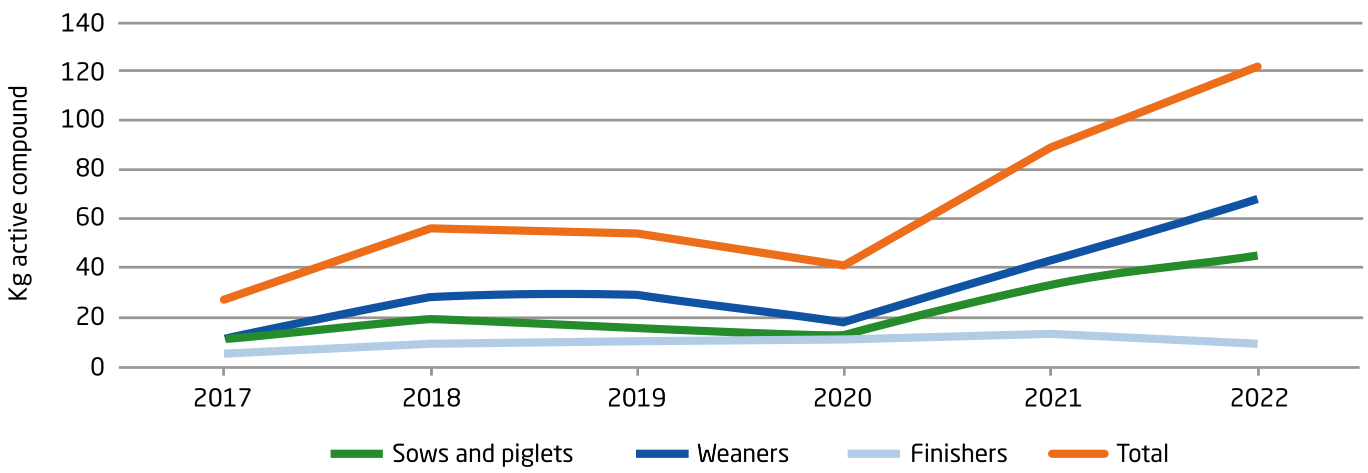


Figure 7.2 Neomycin use in the total pig population and in each age group, Denmark, 2017-2022

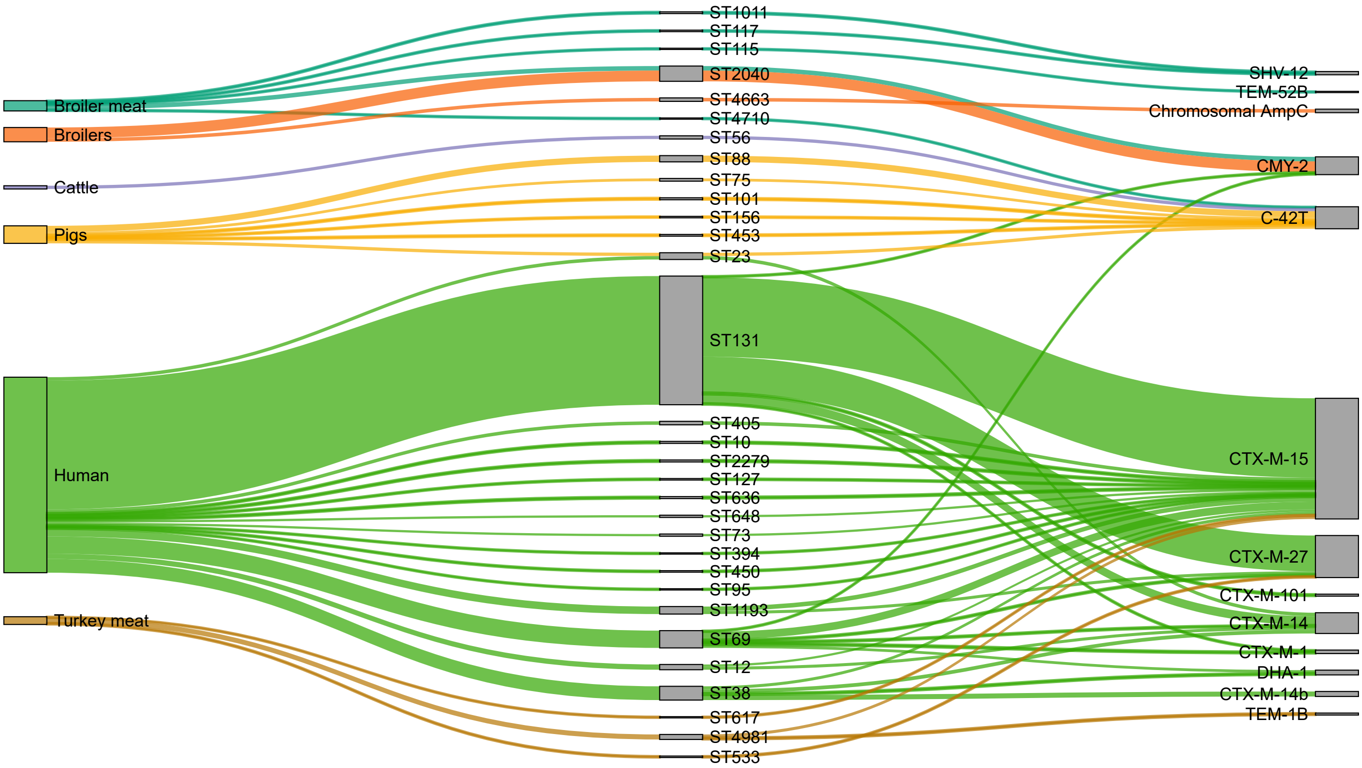


8. One Health AMR

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 simple analysis was performed.

The analysis involved *E. coli* ESBL/AmpC isolates from human blood stream infections, food-producing animals and meat. A total of 1,649 isolates from 2018 through 2022 were included with 1,057 from humans, 294 from meat and 298 from animals. Sequence types (ST) and ESBL genes were compared using a Sankey diagram (Figure 8.1). 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. Interestingly, the ESBL-genes found in turkey meat were of the CTX-M-15 and CTX-M-27-kind that were otherwise only found in humans. However, the STs were different from the STs identified in human isolates. This still warrants further investigation as it is possible that horizontal gene transfer events took place.

Figure 8.1 A Sankey diagram showing the source, MLST and ESBL/AmpC gene of the included isolates. Flows of a minimum of five are shown



9. 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

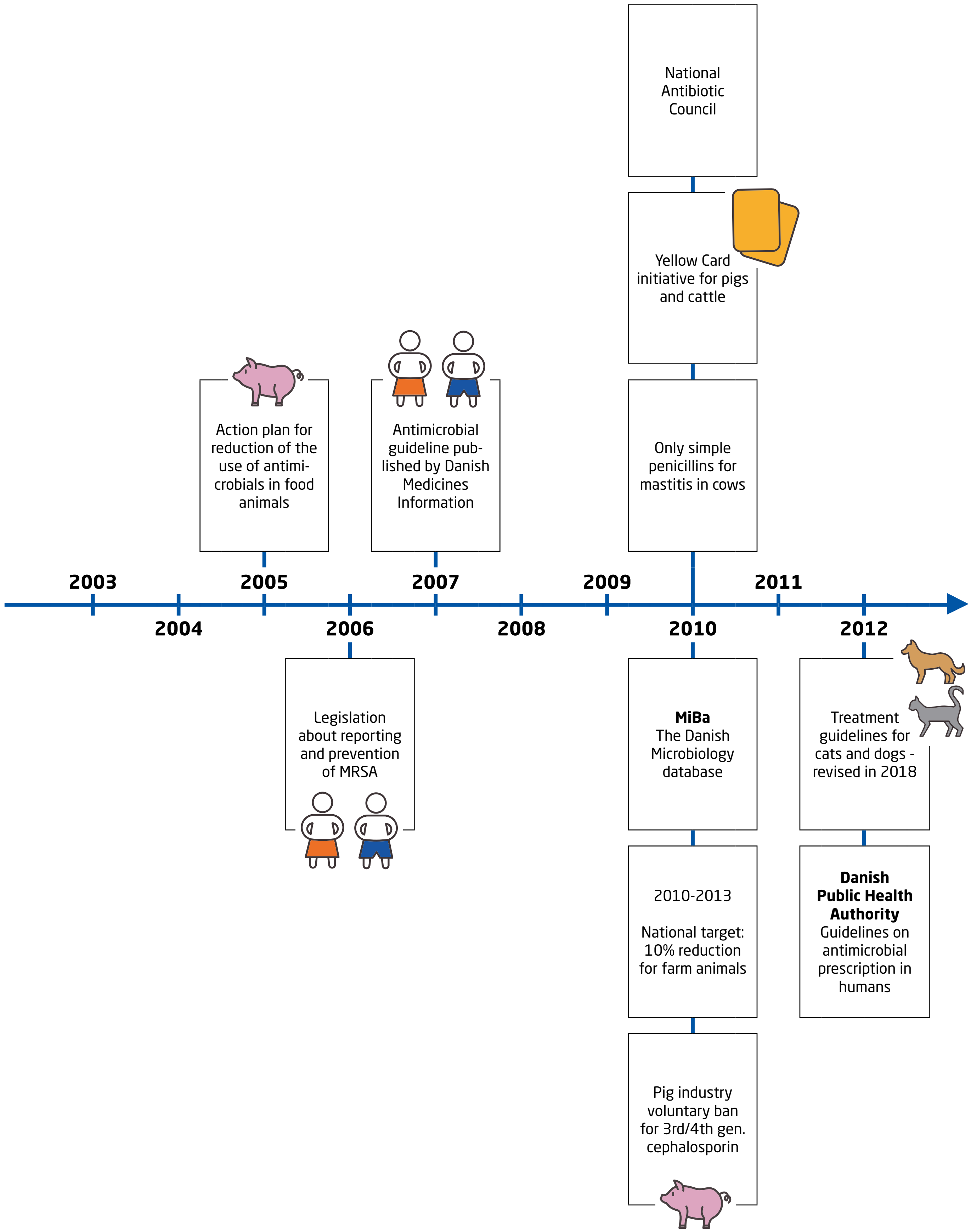
Regulation on stop for antimicrobial growth promotors

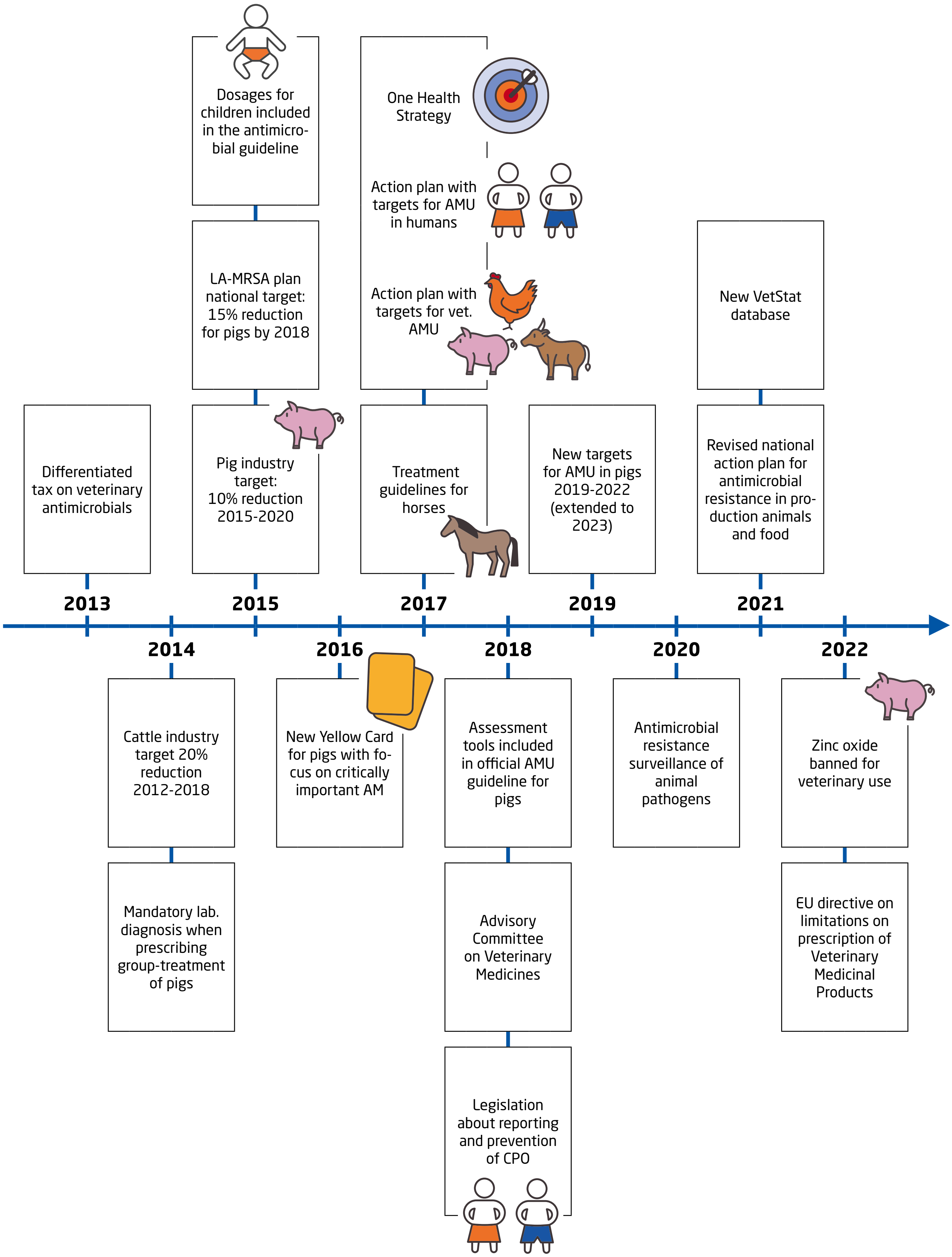
2001

2002

Restrictions on fluoroquinolones for food animals

* Veterinary Advisory Service contracts


National Antibiotic 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 pub-lished by Danish Medicines 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
Danish Public Health Authority Guidelines on 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
Pig industry target: 10% reduction 2015-2020
LA-MRSA plan national target: 15% reduction for pigs by 2018
Dosages for children included in the antimicro-bial guideline
2016
New Yellow Card for pigs with fo-cus on critically important AM
2017
Treatment guidelines for horses
One Health Strategy
Action plan with targets for AMU in humans
Action plan with targets for vet. AMU
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 (extended to 2023)
2020
Antimicrobial resistance surveillance of animal pathogens
2021
Revised national action plan for antimicrobial resistance in pro-duction animals and food
New VetStat database
2022
Zinc oxide banned for veterinary use
EU directive on limitations on prescription of Veterinary Medicinal Products

10. 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
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

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