5

ANTIMICROBIAL CONSUMPTION IN HUMANS

5. Antimicrobial consumption in humans

Highlights

Total antimicrobial consumption in Denmark was 15.50 DID in 2022, 15% lower than 10 years ago in 2013 (18.44 DID) and minus 1.7% compared to consumption in 2019 (15.70 DID), underlining that consumption has resurged since the COVID-19 related marked decreases in 2020 and 2021.

In primary health care, total antimicrobial consumption was 13.59 DID in 2022, 1.3% lower than the 13.77 DID in 2019 and 16% lower than in 2013 (16.19 DID). Penicillins constituted 73% of the consumption and penicillins with extended spectrum and beta-lactamase sensitive penicillins were the two most used groups of antimicrobials (accounting for 24% each of total consumption in primary health care).

Antimicrobials prescribed for respiratory tract infections dropped sharply with the emergence of COVID-19 in 2020. The implemented societal restrictions prevented also the spread of viral respiratory infections. In 2022, the usual winter peak in antimicrobial consumption reached a higher level than observed in 2018-2019. This was probably due to a surge in respiratory infections altogether, including an early RSV epidemic in the autumn that overlapped with an early influenza season.

Antimicrobials prescribed to children also demonstrated marked decreases during the pandemic, regaining higher levels in 2022 but maintaining an observed downward trend for the past decade. Among the 0-4 year olds, consumption in 2022 was 188 treated patients per 1000 inhabitants, a 36% decrease compared to 358 treated patients per 1000 inhabitants in 2013. For the 5-9 year olds, 122 patients per 1000 inhabitants were treated in 2022 compared to 195 patients per 1000 inhabitants in 2013 (-37%).

Elderly inhabitants living at care homes during 2022 received 88% more antimicrobials than elderly inhabitants living in their own homes (1,833 prescriptions per 1000 inhabitants at long term care facilities compared to 976 prescriptions per 1000 inhabitants in their own homes). Urinary tract infections were the main cause of the observed difference in the treatment frequency. However, consumption for elderly inhabitants living at care homes has decreased by 30% from 2016 to 2022, while consumption for elderly living in their own homes has decreased by 18%.

Consumption in hospital care measured in DID (i.e. not accounting for hospital activity) was 1.86 DID in 2022, 4% lower than both in 2019 (1.93 DID) and in 2013 (1.90 DID). When measuring in DDD per 100 bed-days (DBD), the consumption in 2022 (127.89 DBD) was 7% higher than in 2019 (119.82 DBD) and 24% higher than in 2013 (103.51 DBD).

Product shortages are of increasing concern in antimicrobial supply. In 2022, penicillin/beta-lactamase inhibitor combinations decreased sharply in July and August 2022 due to product shortages. However, prescribers had access to the antimicrobials via special deliveries, why the overall consumption level was not affected.

5.1 Introduction

In Denmark, antimicrobials are available by prescription from medical doctors, veterinarians or dentists. Sale is restricted to licensed pharmacies who have exclusive right to sell prescription-only medicines, and no over-the-counter sale takes place. All consumption of medicinal products for humans is recorded through the Register of Medicinal Product Statistics at the Danish Health Data Authority (Figure 2.1). This includes sales data from all public and private healthcare providers. Antimicrobial sales data have been submitted from the primary care sector since 1994 and from the hospital sector since 1997.

Registration of medicines consumption in the primary care sector covers sales from pharmacies to individuals and private clinics. Sales data contain an identifier of the prescriber and the patient's age, gender and address in addition to information about the ATC code, formulation, package size and number of packages sold. Since 2004, the Register of Medicinal Product Statistics also receives information on the indication for prescribing. This allows a very detailed and near-complete surveillance of all systemic antimicrobials used in Denmark in the primary health care.

For the hospital sector, antimicrobial consumption data from all public somatic hospitals with acute care function (referred to as somatic hospitals) are included in the report. Data from psychiatric hospitals, private hospitals and hospices are excluded, since they only account for a minor share of the consumption and no reliable denominator for measuring antimicrobial consumption in these facilities is available.

In this chapter, the term 'antimicrobials' covers all systemic antibacterial agents for human use listed in the Anatomical Therapeutic Chemical (ATC) Classification under the code J01. In addition, since 2014 metronidazole (ATC code P01AB01) and for hospitals vancomycin (ATC code A07AA09) have been included. Consumption of tuberculostica, antifungal drugs and antivirals are not included in this chapter.

Changes in consumption of antimicrobials often mirror initiatives promoting prudent use of antibiotics and changes in health care organization. In 2012, the National Antibiotic Council was established following decisions on a national AMR strategy from 2010. The task of the National Antibiotic Council was to propose, promote and oversee actions for better management and prevention of antimicrobial resistance including fostering research in the area. In the following years, many different initiatives regarding prudent use of antibiotics were undertaken with particular focus on better diagnostics guiding antibiotic prescribing by general practisioners and working with antibiotic stewardship at hospitals. The former led to the establishment of the Danish Research Center for General Medicine while the latter was supported by the establishment of a network based on experiences from the Learning and Quality Teams at the bigger regional hospitals.

As many other European countries Denmark has also worked with annual antibiotic awareness campaigns since 2013, - except for in the pandemic years 2020-2022 - many of which can be found at www.antibiotikaellerej.dk.

Reorganization of the Danish healthcare system has led to functions being reassigned from hospital ambulatory care to smaller health units, rehabilitation centers and general practitioners. The resulting changes in activity across the healthcare sector may affect the consumption of antimicrobials. Finally, the COVID-19 pandemic and other infection waves had impact on activity in society, the healthcare system, and thus the spread and treatment of infectious diseases. These changes need to be considered when interpreting antimicrobial consumption surveillance data.

5.2 Total antimicrobial consumption in the Danish healthcare system

During the first five years of surveillance from 1996 to 2000, the consumption of systemic antimicrobials in Denmark showed no significant changes and consumption was estimated to be at 13 to 14 Defined Daily Doses per 1,000 inhabitants per day (DID). These first five years of reporting are not fully comparable to later years due to changes in reporting and in data systems. Between 2001 and 2011, consumption of antimicrobials increased steadily and peaked at a total of 18.95 DID in 2011 (not shown). From 2011 to 2021, consumption has decreased markedly (Figure 5.1).

In 2022, total consumption of antimicrobials was 15.50 DID (including all public and private healthcare facilities), which is 5% higher than the consumption in 2021 (14.72 DID) and 15% lower than the consumption 10 years ago in 2013 (18.14 DID) (Figure 5.1). In 2022, the primary care sector accounted for 13.59 DID (88%), the somatic hospital sector for 1.86 DID, whereas psychiatry, private hospitals and unspecified use accounted for 0.06 DID (not shown). The total consumption in 2021 corresponded to 48,215 kg active compound consumed.

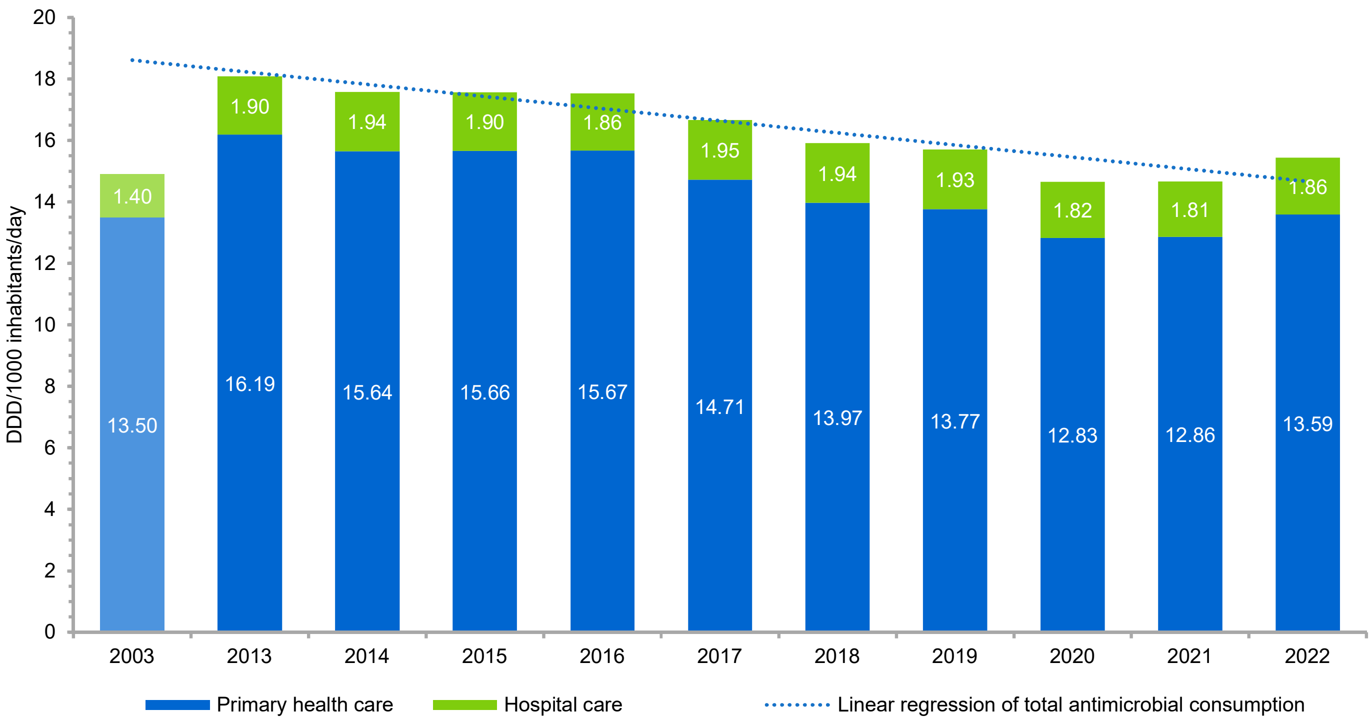
The decrease in total antimicrobial consumption since 2013 in Denmark has mainly been driven by reduced prescribing in primary health care. Measured in DID and not adjusted for hospital activity, antimicrobial consumption at hospitals fluctuated over the years; moving between the lowest levels of 1,86 DID in 2016 to highest levels of 1,95 DID in 2017. The notably lower levels of 1,82 DID in 2020 and 1,81 DID in 2021 are considered exceptions due to the COVID-19 pandemic. The hospital share of the total antimicrobial consumption increased from 10% in 2013 to 12% in 2022.

The main antimicrobial drug classes and their consumption in primary health care and at somatic hospitals are presented in Figure 5.2. Most notable are high use of beta-lactams in both health care sectors and low to none use of cephalosporins/aminoglycosides and of carbapenems in primary health care.

Consumption of antimicrobials in primary health care and somatic hospitals in the five Danish health regions is presented in Figure 5.3. The consumption decreased in all five regions in the primary sector since 2017. In 2022, the consumption was higher than in 2021 in all regions (4-6% increase). Region Zealand showed the highest total consumptions of 16.13 DID in 2022, whereas Central Region of Denmark had the lowest total consumption of 13.85 DID.

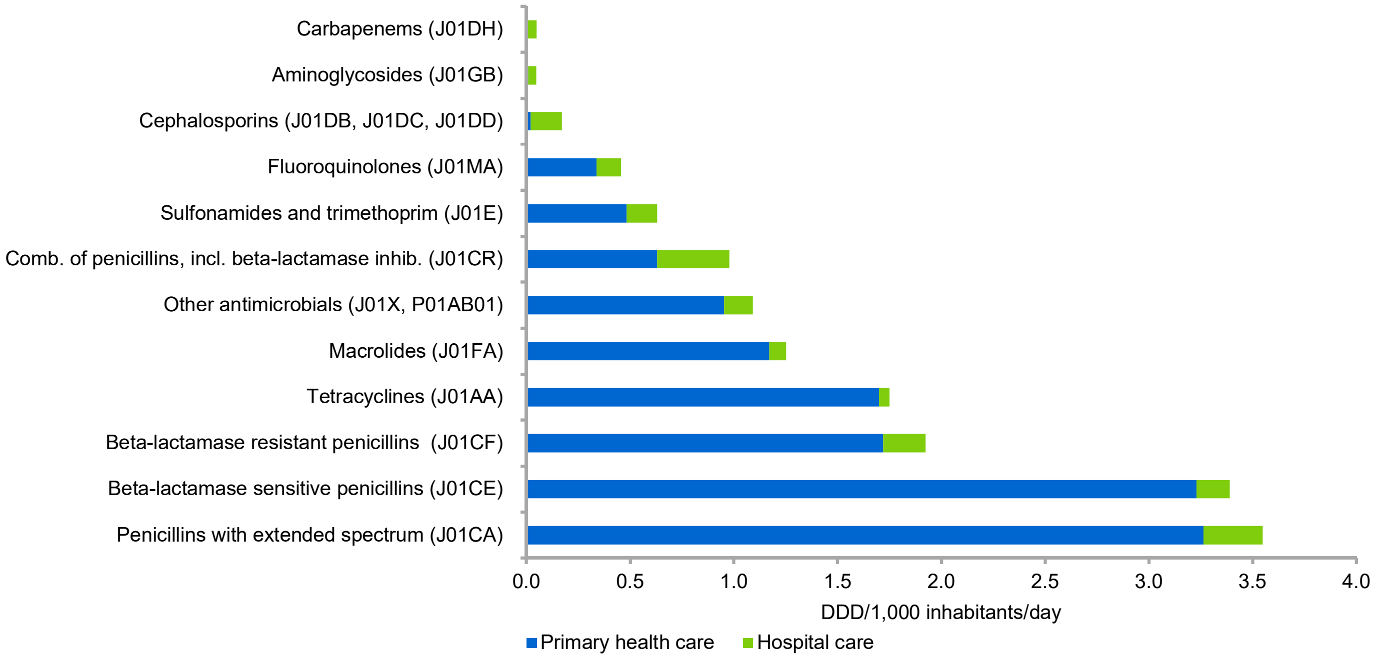
Figure 5.1 Total consumption of systemic antimicrobial agents in humans, DDD per 1,000 inhabitants per day, Denmark, 2003 and 2013-2022

DANMAP 2022



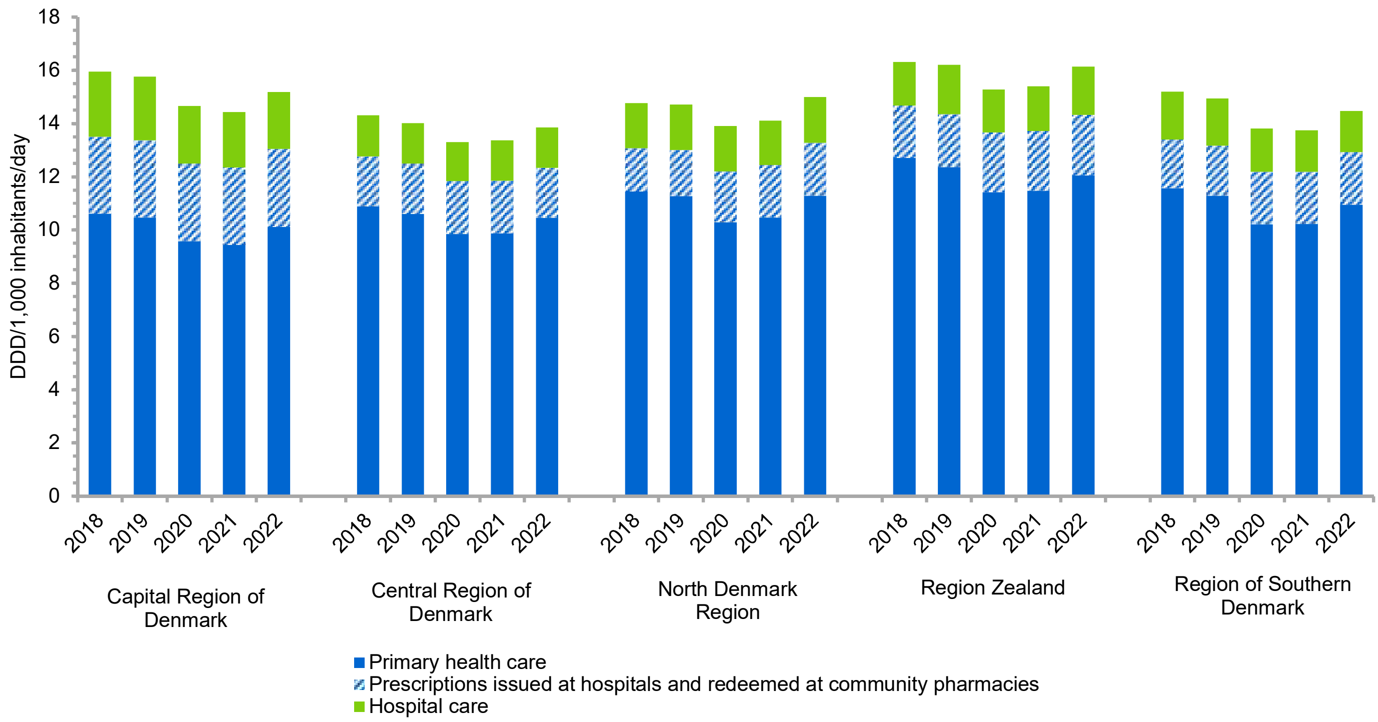
Data: Total sale of antimicrobials in Denmark
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.2 Distribution of main antimicrobial classes used for humans in primary and hospital care, DDD per 1,000 inhabitants per day, Denmark, 2022
DANMAP 2022



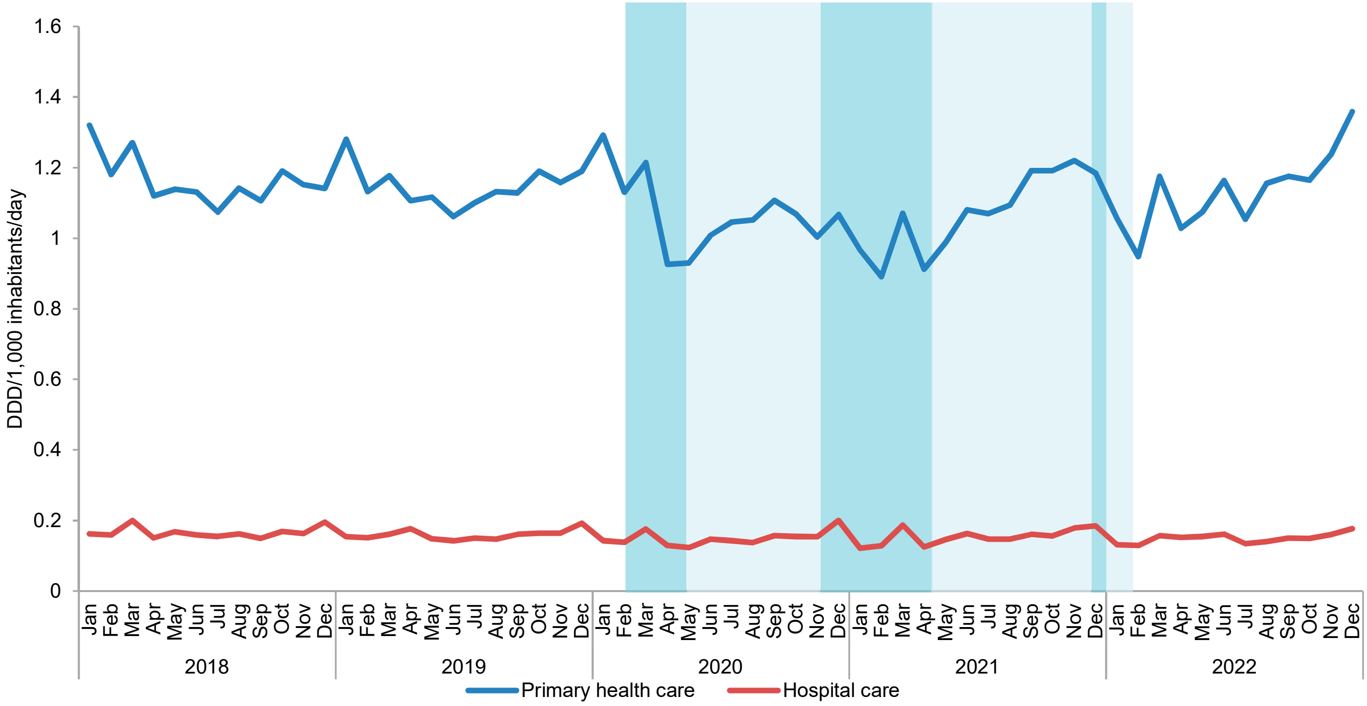
Data: Registered sale of antimicrobials to individuals and antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.3 Consumption of systemic antimicrobial agents in primary health care and at somatic hospitals, DDD per 1,000 inhabitants per day, by Danish region, 2018-2022
DANMAP 2022



Data: Registered sale of antimicrobials to individuals and antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.4 Total consumption of systemic antimicrobial agents in humans per month in primary health care and at hospitals, DDD per 1,000 inhabitants per day, Denmark, 2018-2022 DANMAP 2022



COVID-19 restrictions in place
Fewer restrictions in place
Data: Total sale of antimicrobials in Denmark
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Monthly consumption data from 2018 to 2022 show the effect of the COVID-19 pandemic on antimicrobial consumption through changed healthcare delivery, infection rates and social life (Figure 5.4): Total antimicrobial consumption in primary care measured in DID was lower from April 2020 until May 2021 when compared to previous years but increased with the lifting of restrictions in the summer of 2021. Towards the end of 2022, antimicrobial consumption peaked at 1,36 DID in primary health care, which can be associated to increased treatment of sore throat and upper respiratory infection.

Detailed analysis of antimicrobial consumption data from primary health care and hospital care can be found in Section 5.3 and Section 5.4. For information on population size and hospital activity, see Figure 2.2 and Table 2.1 in Chapter 2 'Introduction'. A comparison of antimicrobial consumption in the human and the animal sector is shown in Figure 4.1 in Chapter 4 'Antimicrobial consumption in animals'.

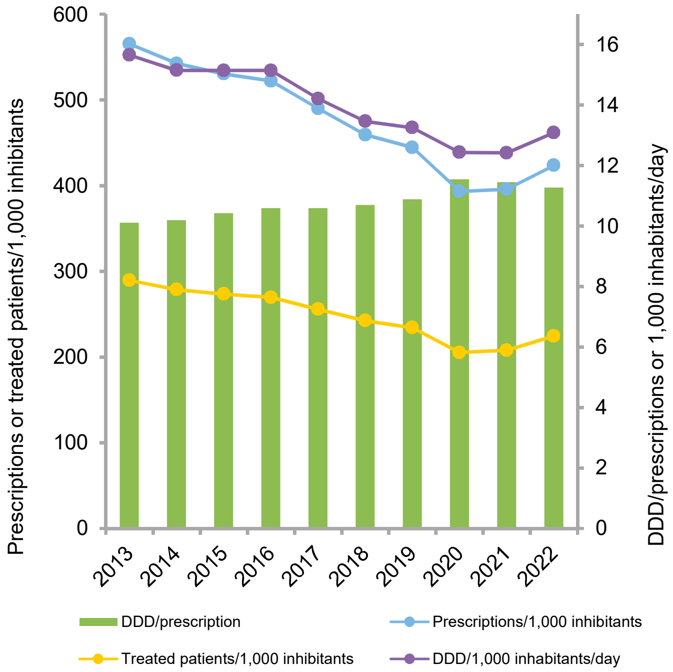
5.3 Antimicrobial consumption in primary health care

In the following sections, the consumption of antimicrobials in primary health care is described by the units DDD per 1,000 inhabitants per day, number of prescriptions per 1,000 inhabitants and number of treated patients per 1,000 inhabitants. The estimates are thus based on sales to individuals and do not include the approximately 4% of antimicrobials, mainly penicillins, sold to clinics and doctors on call. The antimicrobial consumption in 2022 is mainly compared to 2013 (10-year trend) and to 2019 to avoid the unusual COVID-19 years of 2020 and 2021.

5.3.1 Overall antimicrobial consumption in primary health care

Comparison of consumption trends over time by different indicators showed decreased consumption from 2013-2020, no change from 2020-2021 and increased consumption from 2021-2022 (Figure 5.5). In 2022, the average DDD/prescription was 11.3, 4% higher than in 2019 (10.9 DDD/prescription) and 12% higher than 2013 (10.1 DDD per prescription). The total number of prescriptions was 424 per 1,000 inhabitants in 2022, a 25% reduction from the 565 prescriptions per 1,000 inhabitants in 2013.

Figure 5.5 Consumption of systemic antimicrobial agents in primary health care, Denmark, 2013-2022 DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

In 2022 the total number of patients treated was 225 per 1,000 inhabitants (Table 5.3). In comparison, the number was 290 treated patients per 1,000 inhabitants in 2013. Thus, the number of treated patients and prescriptions has decreased over the decade, probably due to raising awareness among prescribers and the public. However, doses per prescription have increased, partly due to switch to antibiotics that contribute with more DDDs per treatment, e.g. the switch to pivmecillinam as drug of choice in the treatment of urinary tract infections and the switch to tetracycline as drug of choice in the treatment of chlamydia.

5.3.2 Consumption of antimicrobial groups

In compliance with treatment guideline, beta-lactamase sensitive penicillins were the most used antimicrobials in primary health care in Denmark for decades. However, this changed in 2020 where the consumption decreased 17% compared to 2019 due to COVID-19 restrictions. Since then, in 2020 and 2021 penicillins with extended spectrum were the most used antimicrobials. In 2022, beta-lactamase sensitive penicillins and penicillins with extended spectrum accounted both for 24% of total consumption in primary health care. Altogether the four penicillin groups (penicillins with extended spectrum; beta-lactamase sensitive penicillins; beta-lactamase resistant penicillins; combinations of penicillins, including beta-lactamase inhibitors) accounted for 8.84 DID (65%) of antimicrobials consumed in primary health care in 2022. Tetracyclines accounted for 1.70 DID (13%) and macrolides for 1.17 DID (9%). Fluoroquinolones accounted for 0.34 DID (2.5%), which is 8% lower than in 2019 (0.37 DID).

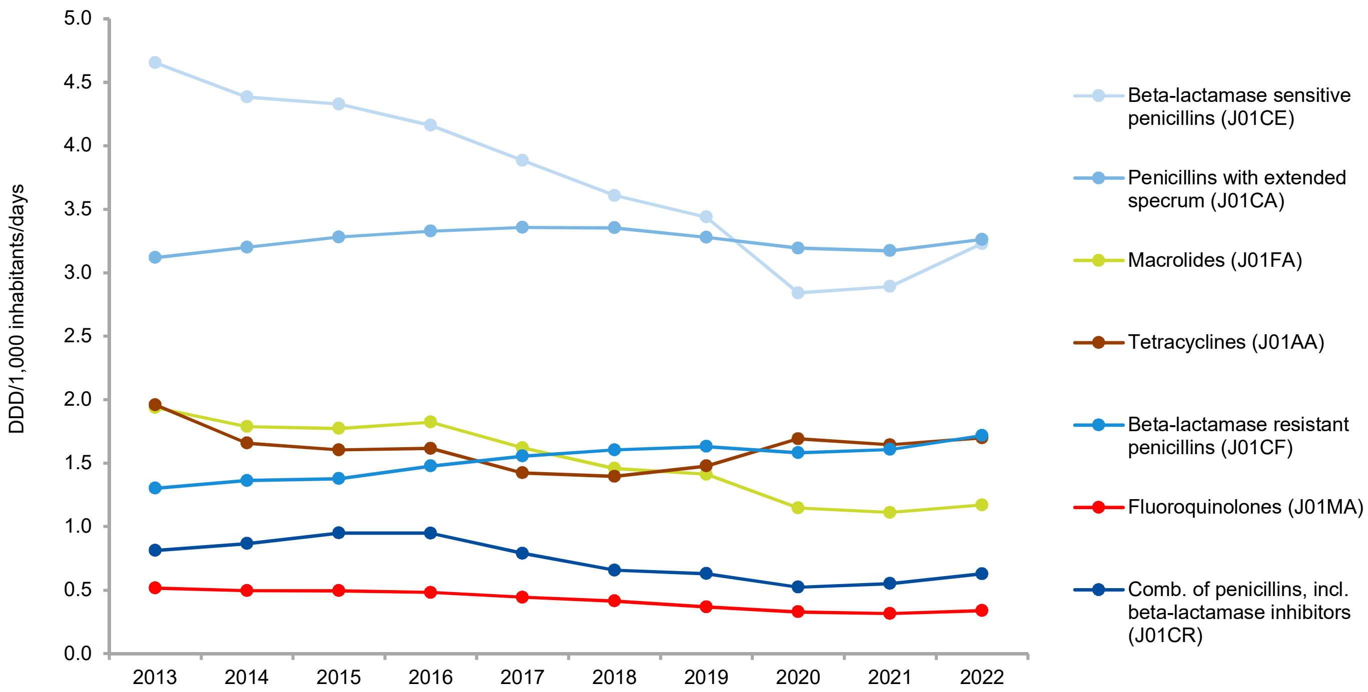
In 2013, the four groups of penicillins accounted for 9.89 DID, corresponding to 61% of the total consumption. Beta-lactamase sensitive penicillins accounted for 29%, penicillins with extended spectrum for 19%, beta-lactamase resistant penicillins for 8%, and combinations of penicillins, including beta-lactamase inhibitors accounted for 5%. Macrolides accounted for 12%. Other beta-lactams such as cephalosporins, monobactams and carbapenems were either used at extremely low level or restricted to hospital use only. For most other antimicrobial groups, the proportion of total consumption did not change notably.

Penicillins

From 2013 to 2022, consumption of beta-lactamase sensitive penicillins decreased by 31% (from 4.65 DID in 2013), while beta-lactamase resistant penicillins increased by 32% (1.30 DID in 2013) (Figure 5.6). Consumption of penicillins with extended spectrum increased during the first years of the decade, but has since levelled off. Combination penicillins increased continuously from their introduction to the Danish market in 2009 until 2015 (0.95 DID), showed no changes in 2016 and since then declined until 2020. In 2021 and 2022, the consumption increased again and was in 2022 at the same level as in 2019 (0.63 DID).

The increases described for the penicillins with extended spectrum are primarily due to increases in the consumption of pivmecillinam, which accounted for 75% of this antimicrobial class in 2022 (not shown). Over the decade pivmecillinam increased by 15% from 2.13 DID in 2013 to 2.45 DID in 2022. In the same time period pivampicillin decreased by 74% from 0.25 DID to 0.07 DID and amoxicillin increased by 4% from 0.72 DID to 0.74 DID (not shown). Consumption of amoxicillin fluctuated within the decade, decreasing from 2011 to 2016 (0.61 DID), increasing from 2016-2019 by 12%, decreasing from 2019-2020 by 11% and increasing from 2020-2022 by 21% (not shown). Increases in the use of pivmecillinam were related to changed recommendations for the treatment of urinary tract infections, while the decreased use of pivampicillin followed increased resistance towards ampicillin in *E. coli* (see Section 8.2.1.) and use of amoxicillin followed recommendations on a more prudent use in children.

Figure 5.6 Consumption of leading antimicrobial groups for systemic use in primary health care, DDD per 1,000 inhabitants per day, Denmark, 2013-2022
DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.1 Consumption of antimicrobial agents for systemic use in primary health care, DDD per 1,000 inhabitants per day, Denmark, 2003 and 2013-2022
DANMAP 2022

ATC group	Therapeutic group	Year										
		2003	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	1.08	1.96	1.66	1.60	1.62	1.42	1.40	1.48	1.69	1.64	1.70
J01CA	Penicillins with extended spectrum	2.18	3.12	3.20	3.28	3.33	3.36	3.35	3.28	3.19	3.17	3.26
J01CE	Beta-lactamase sensitive penicillins	5.12	4.65	4.38	4.33	4.16	3.88	3.61	3.44	2.84	2.89	3.23
J01CF	Beta-lactamase resistant penicillins	0.86	1.30	1.36	1.38	1.48	1.56	1.60	1.63	1.58	1.61	1.72
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.03	0.81	0.87	0.95	0.95	0.79	0.66	0.63	0.52	0.55	0.63
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	0.02
J01EA	Trimethoprim and derivates	0.38	0.53	0.55	0.56	0.56	0.56	0.53	0.45	0.43	0.42	0.39
J01EB	Short-acting sulfonamides	0.36	0.22	0.21	0.18	0.16	0.15	0.14	0.13	0.11	0.09	0.09
J01EE	Combination of sulfonamides and trimethoprim, including derivates	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01
J01FA	Macrolides	2.15	1.94	1.79	1.77	1.82	1.62	1.46	1.41	1.15	1.11	1.17
J01FF	Lincosamides	0.01	0.05	0.05	0.05	0.06	0.06	0.06	0.06	0.07	0.07	0.07
J01GB	Aminoglycosides	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluroquinolones	0.24	0.52	0.50	0.49	0.48	0.44	0.41	0.37	0.33	0.32	0.34
J01XC	Steroid antibacterials (combination fusidic acid)	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00
J01XE	Nitrofuran derivates (nitrofurantoin)	0.42	0.49	0.48	0.45	0.43	0.26	0.15	0.27	0.27	0.28	0.27
J01XX	Other antibacterials (metheamine >99%)	0.32	0.24	0.24	0.25	0.27	0.28	0.29	0.32	0.34	0.39	0.42
J01XD and P01AB01	Nitroimidazole derivates (metronidazole)	0.18	0.28	0.28	0.28	0.28	0.25	0.24	0.24	0.23	0.24	0.24
J01 and P01AB01	Antibacterial agents for systemic use (total)	13.43	16.19	15.64	15.66	15.67	14.71	13.97	13.77	12.83	12.86	13.59

Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.2 Number of prescriptions per 1,000 inhabitants for leading antimicrobial agents in primary health care, Denmark, 2003 and 2013-2022
DANMAP 2022

ATC group	Therapeutic group	Year										
		2003	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	18.58	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	98.79	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	226.86	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	37.47	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 betalctamase inhibitors	1.64	28.01	29.02	30.73	31.13	27.09	23.71	23.07	19.14	20.36	23.45
J01E	Sulphonamides and trimethoprim	53.98	43.53	41.51	38.39	36.41	34.29	31.74	28.14	25.59	23.07	21.26
J01FA	Macrolides	87.58	74.51	68.01	68.00	68.85	60.00	52.64	50.71	33.66	33.80	36.94
J01MA	Fluoroquinolones	11.70	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%)	13.95	17.41	16.73	16.28	15.82	10.18	6.76	10.29	10.62	10.70	10.72
P01AB01	Nitroimidazole derivatives (metronidazole)	13.93	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 (total)	565.60	565.26	542.53	530.56	522.19	490.08	459.39	444.53	393.34	395.76	423.71

Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.3 Number of treated patients per 1,000 inhabitants for leading antimicrobial agents in primary health care, Denmark, 2003 and 2013-2022
DANMAP 2022

ATC group	Therapeutic group	Year										
		2003	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	11.35	13.86	12.20	11.32	11.04	10.35	9.69	10.10	14.43	12.99	13.64
J01CA	Penicillins with extended spectrum	68.76	76.10	75.32	74.87	74.05	74.04	73.56	71.97	67.14	68.60	71.45
J01CE	Beta-lactamase sensitive penicillins	172.55	142.19	134.79	130.06	125.69	119.32	110.90	104.70	84.93	87.69	100.09
J01CF	Beta-lactamase resistant penicillins	26.38	29.07	29.24	28.85	29.70	29.96	31.10	31.06	30.52	30.89	32.93
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	1.10	19.71	20.52	22.03	22.17	19.89	17.73	17.33	14.43	15.50	17.90
J01E	Sulphonamides and trimethoprim	36.46	26.16	24.65	22.45	21.17	19.87	18.42	16.63	15.04	13.66	12.67
J01FA	Macrolides	64.13	56.16	51.38	51.75	53.21	46.01	40.11	38.45	25.13	24.97	27.16
J01MA	Fluoroquinolones	8.89	16.04	15.30	15.04	14.37	13.36	12.26	10.74	9.01	8.52	9.10
J01X	Other antibacterials (methenamine >99%)	6.95	7.48	7.16	7.35	7.47	5.01	3.62	5.66	5.80	5.95	5.91
P01AB01	Nitroimidazole derivatives (metronidazole)	11.94	16.51	16.31	16.47	16.03	14.84	14.05	13.57	13.36	13.77	13.94
J01 and P01AB01	Antibacterial agents for systemic use (total)	305.03	289.54	278.62	273.49	269.72	255.72	242.55	234.34	205.27	207.85	224.57

Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2022 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Tetracyclines and macrolides

In 2022, tetracycline consumption in primary health care was 1.70 DID, corresponding to 13% of the total consumption, whereas macrolides accounted for 1.17 DID (9%) (Figure 5.6). During the last decade, the consumption of tetracyclines decreased from 1.96 DID in 2013 (13%). Compared to 2019, the consumption of tetracyclines was 15% higher in 2022. Macrolides decreased from 1.94 DID in 2013 (-40%) and from 1.41 DID in 2019 (-17%).

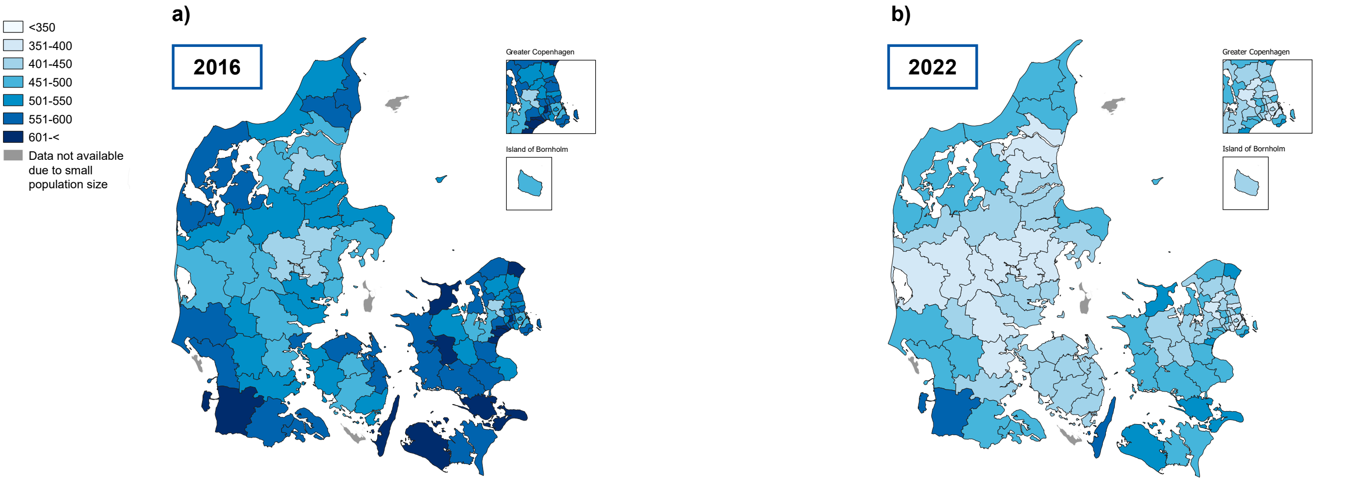
These changes in tetracycline and macrolide consumption may reflect compliance with the new guideline for chlamydia treatment issued by the Danish Dermatological Society in 2019. The guideline recommends doxycycline as first-line treatment instead of the previously recommended azithromycin. The treatment recommendation was changed due to concerns in Denmark about increasing azithromycin-resistance in *Mycoplasma genitalium*, a frequent co-infection in patients with chlamydial infections.

5.3.3 Antimicrobial consumption by prescriber

Interregional differences in the levels of prescribing have been described in DANMAP since 2017 (Table 5.4). In general, the Danish population is relatively homogenous and health care is of standardized quality, which, combined with several initiatives to educate GPs in appropriate prescribing, diminishes potential differences in prescribing trends. However, observed variations in prescribing may owe to differences in population density (distance to nearest general practitioner), differences in age and comorbidity of the population (younger populations in bigger cities and in the capital region) as well as behavioral differences between urban and rural populations.

Figure 5.7 shows the number of prescriptions per 1,000 inhabitants at municipality level in 2016 and 2022, respectively. In 2022, the consumption ranged from 351 to 582 prescriptions per 1,000 inhabitants. In 2016, the range was 434-727 prescriptions per 1,000 inhabitants. Of note is that prescribers in all municipalities reduced their prescribing activities in the shown period. Demographic differences might impact the range of prescribing. Distribution of elderly inhabitants above 60 years in the municipalities follows almost the distribution of prescriptions per 1,000 inhabitants with higher prescription rates in municipalities with bigger population of elderly inhabitants above 60 years (data not shown).

Figure 5.7 Number of prescriptions from primary health care per 1,000 inhabitants in Danish municipalities in a) 2016 and b) 2022
DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.4 Consumption of antimicrobial agents for systemic use in primary health care at regional level, Denmark, 2018-2022 DANMAP 2022

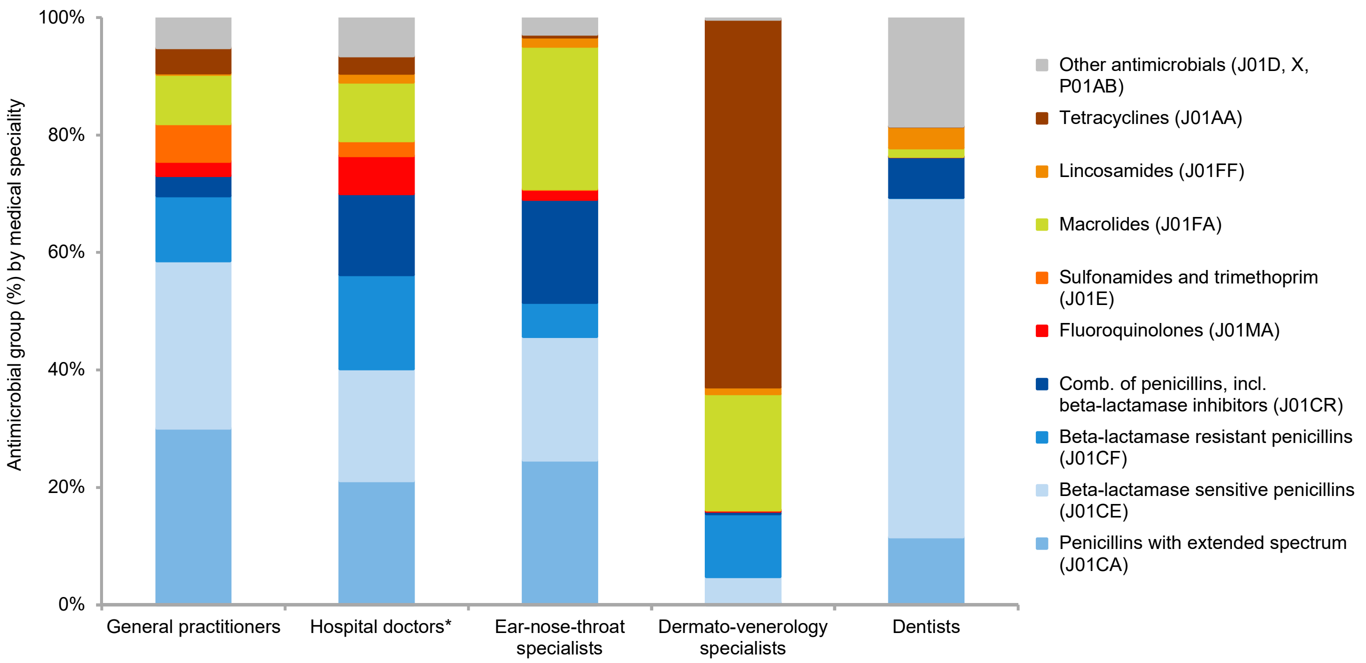
Region	Indicator	Year				
		2018	2019	2020	2021	2022
Capital Region	DDD/1,000 inhabitants/day	13.49	13.37	12.49	12.34	13.05
	Prescriptions/1,000 inhabitants	453	441	382	378	410
Region Zealand	DDD/1,000 inhabitants/day	14.68	14.36	13.66	13.72	14.32
	Prescriptions/1,000 inhabitants	501	482	436	440	466
Region of Southern Denmark	DDD/1,000 inhabitants/day	13.39	13.16	12.17	12.18	12.92
	Prescriptions/1,000 inhabitants	470	455	401	405	434
Central Denmark Region	DDD/1,000 inhabitants/day	12.76	12.49	11.84	11.84	12.33
	Prescriptions/1,000 inhabitants	431	417	374	380	402
North Denmark Region	DDD/1,000 inhabitants/day	13.07	13.00	12.21	12.43	13.28
	Prescriptions/1,000 inhabitants	452	436	390	400	432
Denmark (total)	DDD/1,000 inhabitants/day	13.46	13.25	12.43	12.42	13.08
	Prescriptions/1,000 inhabitants	459	445	393	396	424

Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Prescribing trends in primary health care also clearly differ by prescriber's specialty. Table 5.5 shows an overview of number of prescriptions issued by different specialists, including hospital doctors issuing prescriptions for patients at hospitals, which then are redeemed at a community pharmacy. Compared to 2019, the number of prescriptions per 1,000 inhabitants in 2022 was 8% lower for general practitioners and 15% lower for dermato-venerology-specialists. On the other hand, the number of prescriptions per 1,000 inhabitants was 20% higher for dentists in 2022 compared to 2019. For other specialties, minor changes were observed (<5%). Numbers of DDD per prescription also differ by prescriber's specialty (Table 5.5). Dermato-venerology-specialists prescribed the highest number of DDDs per prescription in 2022 (35 DDD/prescription, 12% higher than 2018). Number of DDDs/prescription increased by 5% and 8% for general practitioners and hospital doctors since 2018. These changes can among other be due to changes in treatment guidelines recommending antimicrobials that contribute with more DDDs per treated infection.

Figure 5.8 shows the main antimicrobial groups prescribed by medical specialty in primary health care in 2022. Also here, prescriptions from "hospital doctors" cover prescriptions issued to patients in ambulatory care and upon discharge from hospital and redeemed at the community pharmacy. In 2022, 63% of antimicrobial prescriptions from dermato-venerology-specialists were tetracyclines, which are indicated for treatment of severe acne and sexually transmitted chlamydia/mycoplasma infections. Majority of prescriptions by dentists were narrow-spectrum beta-lactamase sensitive penicillins (58%) reflecting adherence to the recommended first-line treatment for common dental infections in primary health care.

Figure 5.8 Antimicrobial groups prescribed by main medical specialities, primary health care, Denmark, 2022 DANMAP 2022



* Hospital doctors issuing prescriptions for patients in ambulatory care or upon discharge from hospital
Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.5 Number of prescriptions per 1,000 inhabitants by main medical specialities, Denmark, 2018-2022 DANMAP 2022

Prescriber		Year				
		2018	2019	2020	2021	2022
General practitioners	Prescriptions per 1,000 inhabitants	341.8	327.1	280.4	279.0	300.9
	DDD per prescription	10.3	10.4	11.1	11.0	10.8
Hospital doctors*	Prescriptions per 1,000 inhabitants	63.0	63.2	64.6	63.5	62.0
	DDD per prescription	12.6	12.8	13.1	13.2	13.6
Ear-nose-throat specialists	Prescriptions per 1,000 inhabitants	8.4	7.8	6.1	6.9	8.1
	DDD per prescription	8.1	8.1	8.9	8.3	8.1
Dermato-venerology specialists	Prescriptions per 1,000 inhabitants	5.2	5.4	5.3	5.0	4.6
	DDD per prescription	31.3	33.4	33.9	35.5	35.0
Dentists	Prescriptions per 1,000 inhabitants	27.8	28.8	25.6	28.9	34.4
	DDD per prescription	7.8	7.9	7.9	7.7	7.7

* Hospital doctors issuing prescriptions for patients in ambulatory care or upon discharge from hospital, redeemed at community pharmacies
Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2022 edition of the Anatomical Therapeutic Chemical (ATC) classification system

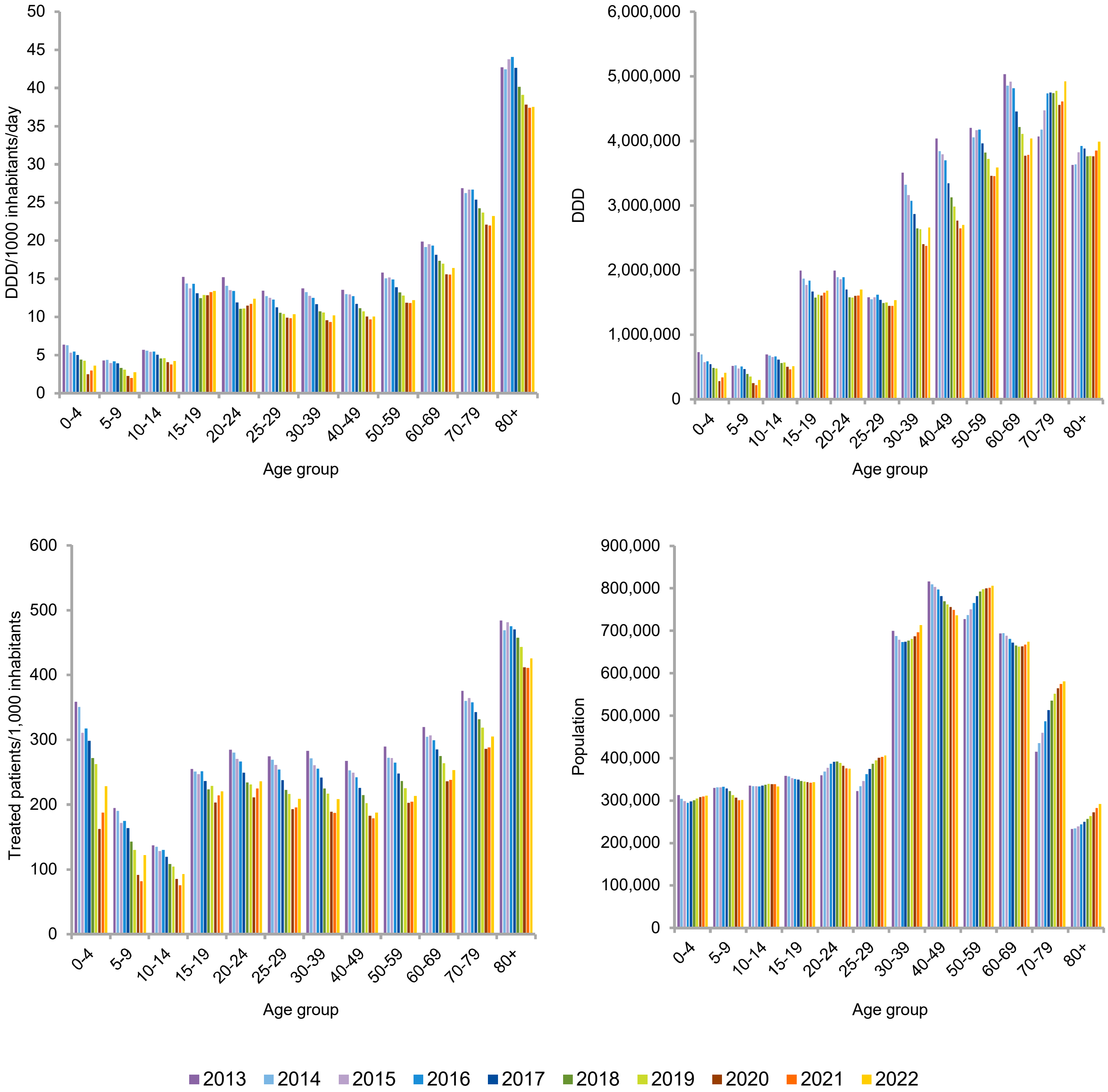
General practitioners have access to their own prescribing data through ordiprax+, an online dashboard with personal log-in which visualises prescribing data and enables comparisons with other practices on regional level (DANMAP 2020 Textbox 5.2).

5.3.4 Antimicrobial consumption by patient case mix

Antimicrobial consumption is highly affected by patient case mix. The need for antimicrobials is different throughout life and for the two genders. Antimicrobial consumption is also affected by other sociodemographic factors (Textbox 5.2).

Figure 5.9a-c presents consumption of antimicrobials by age group based on different denominators: Figure 5.9a presents consumption in DDD per 1,000 inhabitants per day, Figure 5.9b in crude DDD, i.e. not corrected for population size. Figure 5.9c presents the number of patients treated per 1,000 inhabitants. Figure 5.10d presents population size by age group. All figures show data from 2013 to 2022. Children and adolescents are presented in five-year age groups, while adults are clustered in 10-year age groups.

Figure 5.9 Consumption of systemic antimicrobial agents in primary health care by age group, measured in a) DDD per 1,000 inhabitants per day, b) DDD, c) treated patients per 1,000 inhabitants and d) population size, Denmark, 2013-2022 DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and Statistics Denmark

In 2022, 225 patients per 1,000 inhabitants were treated with antimicrobials, receiving 424 prescriptions per 1,000 inhabitants. In 2019, the corresponding numbers were approximately 4% higher, 234 treated patients and 445 prescriptions per 1,000 inhabitants. Since 2013, the consumption decreased from 290 treated patients per 1,000 inhabitants and 565 prescriptions per 1,000 inhabitants (reduction by 22% and 25% from 2013 to 2022, respectively).

Estimates of antimicrobial consumption for children using DDD need to be interpreted with caution since the DDD is defined as "maintenance dose per day for its main indication in adults". The maintenance dose per day for children may differ from the one for adults due to different pharmacodynamics and –kinetics. Furthermore, infants and young children in the same age group might be treated with different doses based on body weight. Therefore, other units of measurement might be more suitable to monitor consumption in children, e.g. number of treated patients per 1,000 inhabitants and number of prescriptions per 1,000 inhabitants.

Consumption in the 0-4 year olds. Consumption of antimicrobial agents in the youngest age group decreased by 36% from 2013 (358 treated patients per 1,000 inhabitants) to 2022 (229 treated patients per 1,000 inhabitants). After the significant decrease observed from 2019 to 2020 (-38%), the consumption remained 13% lower in 2022 than in 2019 (262 treated patients per 1,000 inhabitants) (Figure 5.11a). The antimicrobials used also changed during the last decade, but penicillins with extended spectrum and beta-lactamase sensitive penicillins remained the main antimicrobial agents used to treat children between 0-4 years in 2022 (117 and 119 patients per 1,000 inhabitants, respectively) (Figure 5.10a).

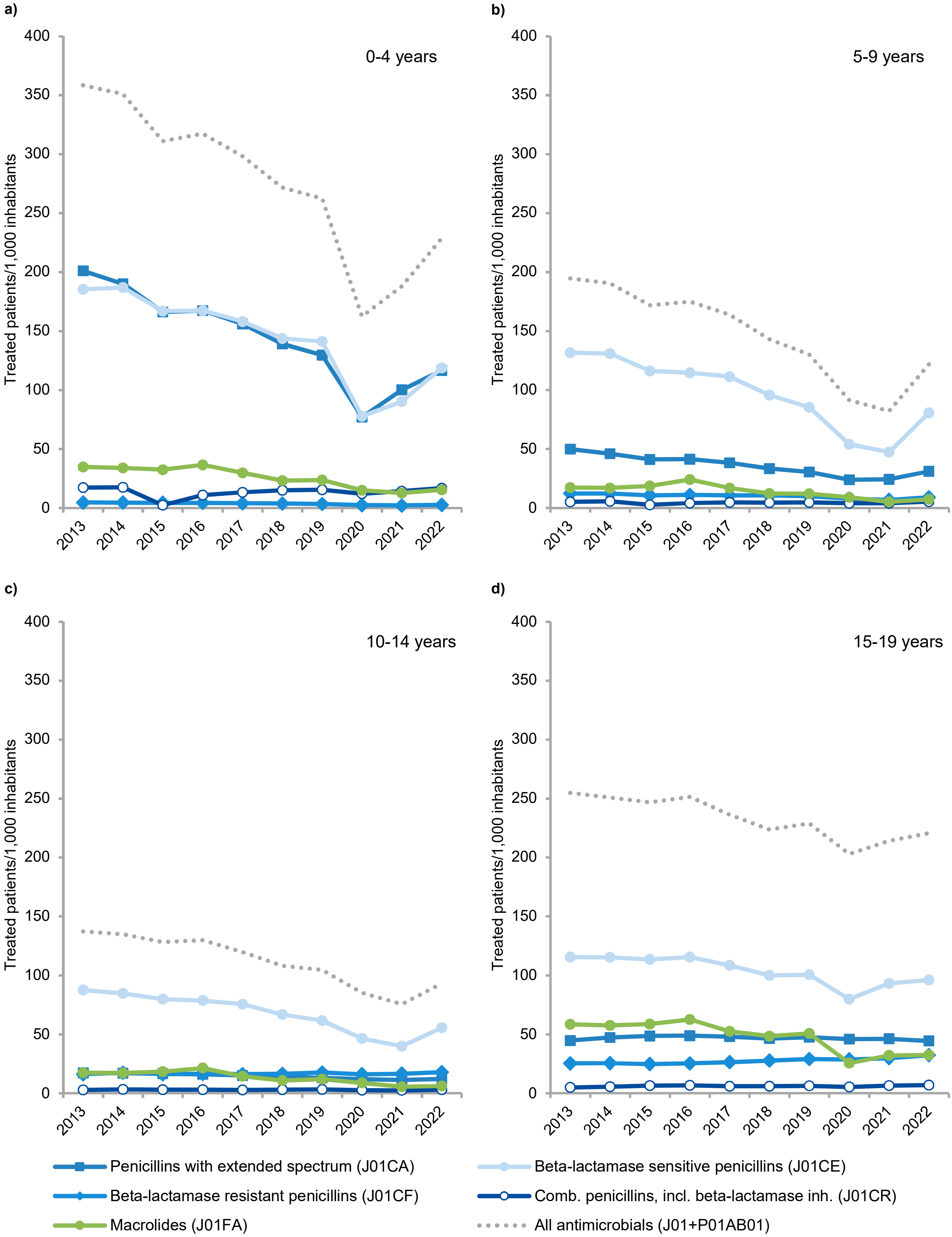
Consumption in the 5-9 year olds. In 2022, 122 patients per 1,000 inhabitants of 5-9 years were treated with antimicrobial agents (Figure 5.9c). This is 37% lower than 2013 (195 patients per 1,000 inhabitants) and 6% lower than 2019 (130 patients per 1,000 inhabitants). The distribution of the antimicrobials used to treat 5-9 year olds did not change markedly over the last decade (Figure 5.10b), and beta-lactamase sensitive penicillins remained the main antimicrobial agent used (81 patients per 1,000 inhabitants, 66% of total consumption in 2022).

Consumption in the 10-14 year olds. In 2022, the total consumption of antimicrobial agents (93 patients per 1,000 inhabitants) was 32% lower than a decade ago (137 patients per 1,000 inhabitants) and 11% lower than 2019 (105 patients per 1,000 inhabitants) (Figure 5.10c). Consumption data shows the lowest level of consumption in 2021 (76 patients per 1,000 inhabitants). Hereafter the consumption increased 23% to the level observed in 2022. Beta-lactamase sensitive penicillins remained the main antimicrobial agent (60%) even with continuous reduction in consumption the last decade (Figure 5.10c).

Consumption in the 15-19 year olds. Consumption of antimicrobial agents in older teenagers was 13% lower in 2022 than in 2013 and 4% lower than in 2019 (Figure 5.9a-c). In 2022, 221 patients per 1,000 inhabitants were treated with antimicrobial agents, whereas 229 patients per 1,000 inhabitants were treated in 2019. The observed decrease the last decade, was driven by a 44% reduction of macrolides and a 17% reduction of beta-lactamase sensitive penicillins (Figure 5.10d).

Macrolides play an important role in the treatment of bacterial respiratory tract infections in children and adolescents. Macrolides were also used as first-line treatment for chlamydia infections until the change in guidance (already described in DANMAP2020) which may be the reason for the relatively high consumption of macrolides in the 15-19 year olds. However, penicillins are the most used antimicrobial agents for children and adolescents, constituting between 44% and 66% of all antimicrobials prescribed depending on age group (Figure 5.10).

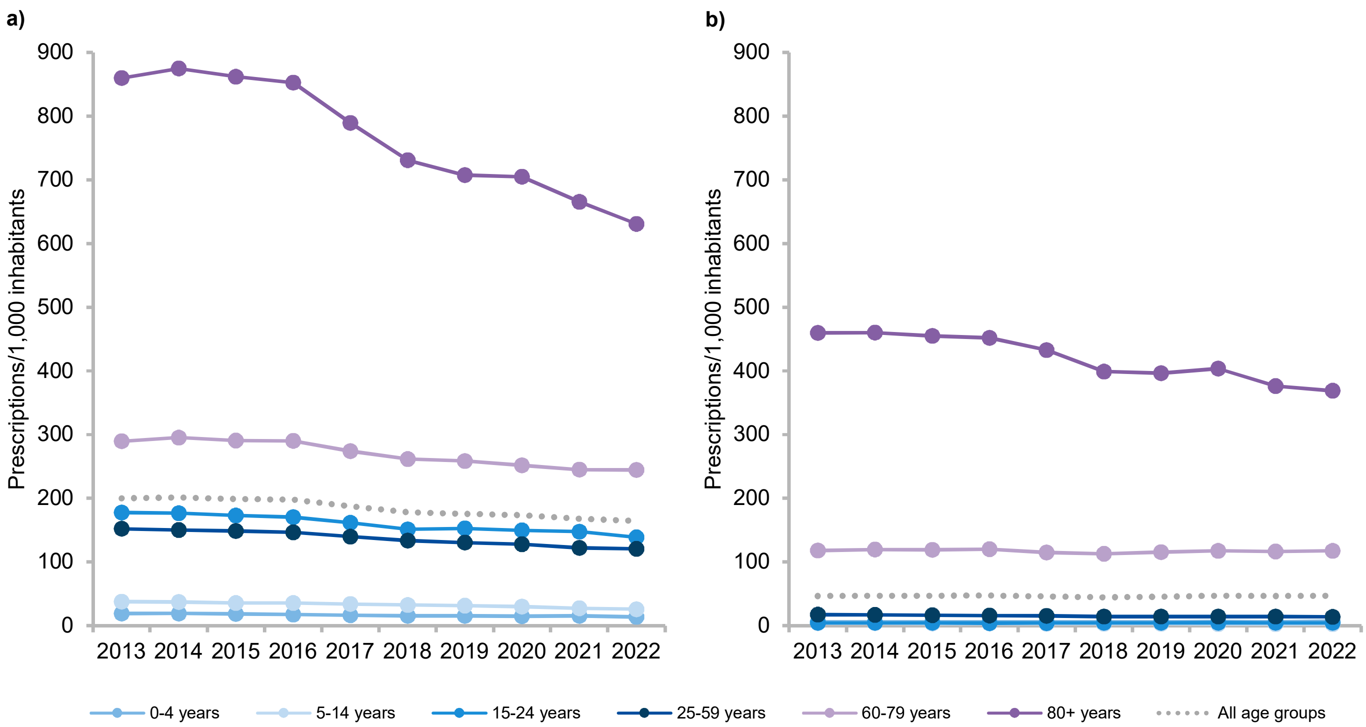
Figure 5.10 Consumption of five main antimicrobial agents for children/adolescents by age group, a) 0-4 years, b) 5-9 years, c) 10-14 years and d) 15-19 years, Denmark, 2013-2022
DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Differences in antimicrobial consumption between genders are well known. From 2013 to 2022, the number of treated females (all age groups) decreased by 22% from 339 to 265 per 1,000 inhabitants per year and the number of treated males decreased by 23% from 240 to 183 per 1,000 inhabitants per year. In general, females receive more treatment – a trend driven by higher incidence of urinary tract infections and different healthcare-seeking behavior. Thus, the consumption of pivmecillinam, sulfonamides, trimethoprim and nitrofurantoin, all indicated for treatment of urinary tract infections, is approximately three times higher for females than for males (Figure 5.11). The reduction in consumption of these antimicrobials was primary driven by fewer prescriptions for elderly women (80+ years), who are the most frequently treated (631 prescriptions per 1,000 females above 80 years). Also for antimicrobials used to treat respiratory tract infections (penicillins and macrolides) the differences in consumption between genders are substantial (Figure 5.12). These differences may be due to different healthcare seeking behavior more than higher incidence of infection.

Figure 5.11 Consumption of antimicrobials primarily used for treatment of urinary tract infections* in primary health care for a) females and b) males, prescriptions per 1,000 inhabitants, Denmark, 2013-2022 DANMAP 2022



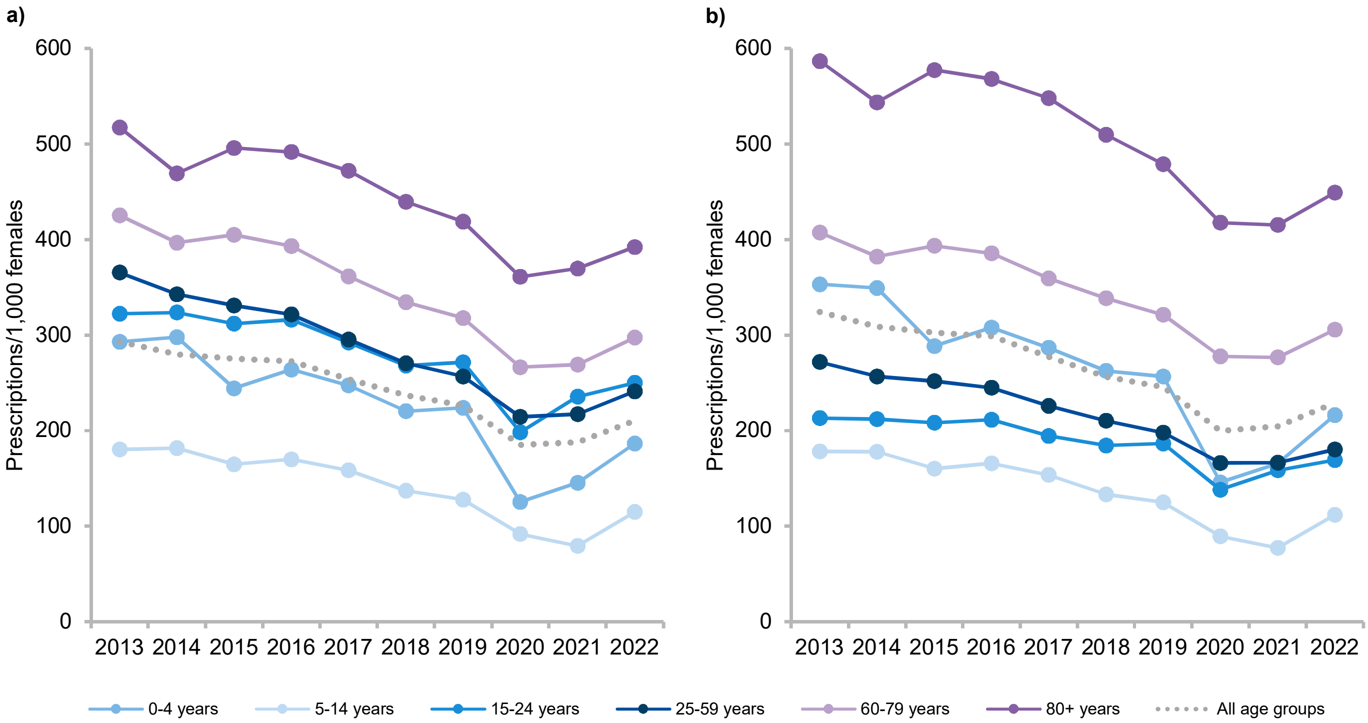
* Pivmecillinam, sulfonamides, trimethoprim and nitrofurantoin
Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.3.5 Antimicrobial consumption for treatment of respiratory tract infections

One of the main indications provided by prescribers in primary health care for treatment with antimicrobials is upper and/or lower respiratory tract infections. In 2020, consumption of antimicrobials prescribed for treatment of respiratory tract infections started slightly lower compared to previous years, and in addition was followed by a sharp drop in consumption from April 2020 to July 2021. This coincided with a sharp decrease in number of laboratory confirmed influenza and RSV infections, most likely due to the societal restriction implemented in March 2020 due to the COVID-19 pandemic (Figure 5.13). However, from August 2021 the consumption went back to levels similar to the corresponding pre-pandemic months in 2019, again coinciding with the Respiratory Syncytial Virus (RSV) summer epidemic in 2021. In 2022, the winter peak in antimicrobial consumption reached a higher level than observed in 2018-2019. This coincided with an early RSV and influenza season as well as an outbreak of Group A streptococci, as also observed in other European countries.

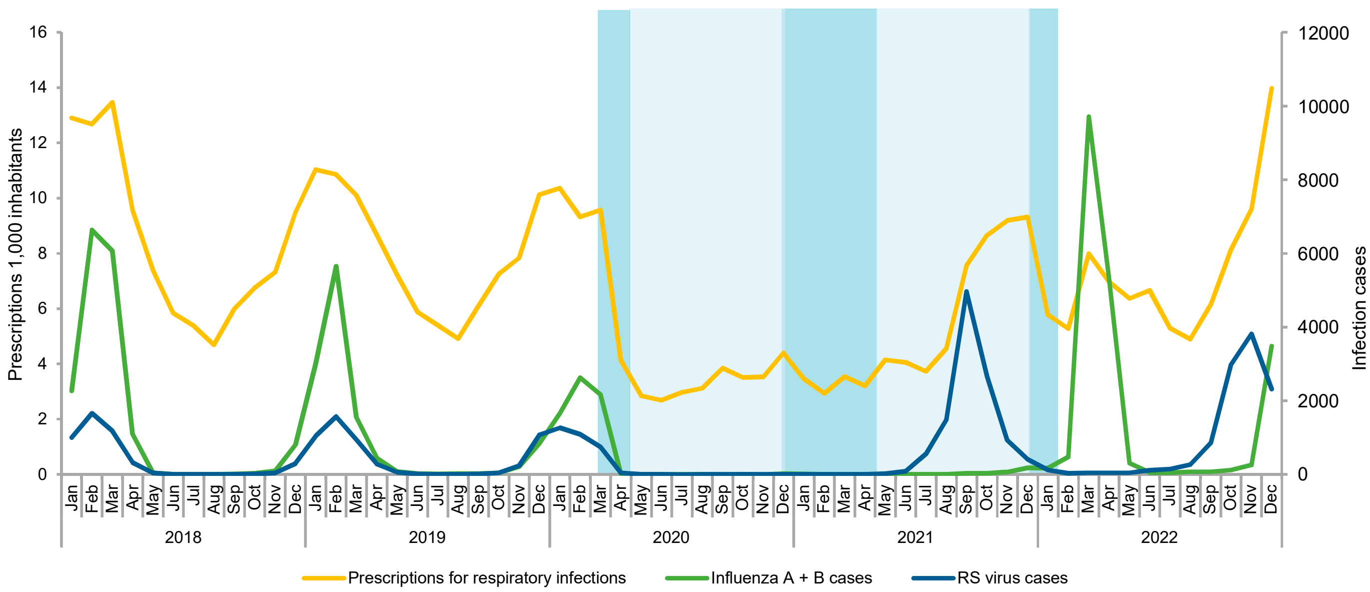
Figure 5.13 shows the first influenza A, influenza B and RSV positive PCR test per person per season for 2018 to 2022. The influenza season starts in week 40 and ends in week 39 in the following year. The RSV season starts in week 21 and ends in week 20 in the following year. Laboratory confirmed infections could originate from both primary health care and hospital care.

Figure 5.12 Consumption of antimicrobials primarily used for respiratory infections* in primary health care for a) females and b) males, prescriptions per 1,000 inhabitants, Denmark, 2013-2022 DANMAP 2022



* Penicillins (beta-lactamase sensitive, beta-lactamase resistant and combination penicillins) and macrolides
Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics and 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.13 Monthly consumption of systemic antimicrobials for treatment of respiratory tract infections in primary health care, prescriptions per 1,000 inhabitants, and monthly number of individuals with laboratory confirmed influenza A and/or B and RSV, Denmark, 2018-2022 DANMAP 2022



COVID-19 restrictions in place
Fewer restrictions in place
Data: Registered sale of antimicrobials to individuals and lalboratory confirmed Invluenza A, B and Respiratory Syncytial Virus (RSV)
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and Danish Microbiology Database (MiBa)

5.3.6 Antimicrobial consumption for elderly inhabitants

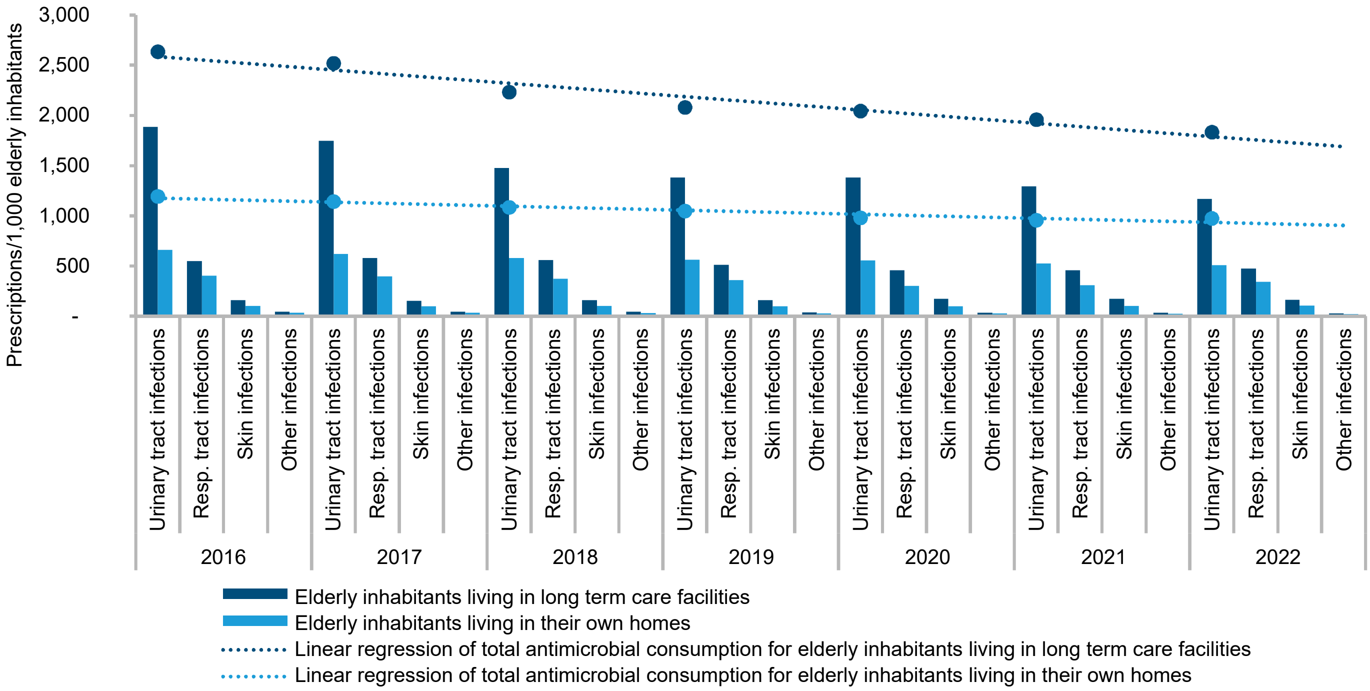
One of the recent surveillance approaches added to the DANMAP program is surveillance of antimicrobial consumption in elderly inhabitants aged 65 years and above. Close surveillance of antimicrobial consumption in this population is necessary as it is one of the most fragile populations in society. Surveillance contributes to high quality treatment of infections and thereby prevents emergence of antimicrobial resistant pathogens.

The surveillance is based on the Danish Care Home Register and Danish Civil Registry. By combining these registries, it is possible to divide elderly inhabitants into two populations; elderly inhabitants living in their own homes and elderly inhabitants living at long term care facilities. For more details, see Chapter 10.

Figure 5.14 shows antimicrobial consumption for elderly inhabitants aged 65 years and above. Elderly inhabitants living at care homes received 88% more antimicrobials than elderly inhabitants living in their own homes in 2022. The figure also compares treatment of specific infections in the two populations as it is well known that treatment of urinary tract infections is the main cause of the difference observed in the treatment frequency of the two populations of elderly inhabitants.

These differences in treatment of elderly inhabitants are observed despite a continuous decrease in the antimicrobial consumption for elderly inhabitants living at long term care facilities (Figure 5.14). From 2016 to 2022, the consumption of antimicrobials decreased by 30% (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 prescriptions/1,000 inhabitants to 976 prescriptions/1,000 inhabitants).

Figure 5.14 Consumption of antimicrobials (J01 and P01AB01) 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 DANMAP 2022



Data: Registered sale of antimicrobials to individuals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system, Care Home Register and Danish Civil Registry

5.4 Antimicrobial consumption at hospitals

Sales of systemic antimicrobials (ATC code J01, P01AB01 and A07AA09) from Danish hospital pharmacies to hospitals in 2022, excluding private hospitals and psychiatric departments (approximately 2-3% of the total hospital consumption), are shown in Table 5.6. Antimicrobial consumption data are presented as DDD per 100 occupied bed-days (DBD) to account for hospital activity. Information on consumption at patient level is currently not available to DANMAP for the hospital sector. This information is expected to become available to DANMAP through the "Hospital Medicine Register" in coming years. The antimicrobial consumption in 2022 is mainly compared to 2013 (10-year trend) and to 2019 to avoid the unusual COVID-19 years of 2020 and 2021.

Changes in hospital activity, for example due to earlier discharge of patients, i.e. decreased numbers of bed-days, and increasing ambulatory care functions in the community as well as in care homes, need to be considered when interpreting antimicrobial consumption trends in hospitals (see Table 2.1 in Chapter 2 'Introduction').

5.4.1 Antimicrobial consumption at public somatic hospitals accounting for hospital activity

In 2022, the consumption of antimicrobial agents at somatic hospitals was 127.89 DBD. This is 7% higher than in 2019 (119.82 DBD) and 24% higher than a decade ago (103.51 DBD in 2013) (Table 5.6).

Table 5.6 Consumption of antimicrobial agents for systemic use in somatic hospitals, DDD per 100 bed-days, Denmark, 2013-2022

DANMAP 2022

ATC group	Therapeutic group	Year									
		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	1.71	1.78	2.00	2.43	2.19	2.78	3.67	3.13	3.25	3.52
J01CA	Penicillins with extended spectrum	15.00	14.72	15.63	16.76	16.89	18.01	18.73	20.33	20.49	20.48
J01CE	Beta-lactamase sensitive penicillins	10.95	10.07	10.05	10.62	10.89	12.18	11.42	11.51	10.73	11.46
J01CF	Beta-lactamase resistant penicillins	10.22	10.05	10.26	10.82	10.70	12.25	13.08	14.09	14.15	14.66
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	12.71	13.81	16.21	17.43	14.91	19.29	20.15	22.23	23.63	24.97
J01DB	First-generation cephalosporins	0.13	0.07	0.05	0.05	0.04	0.04	0.03	0.04	0.03	0.03
J01DC	Second-generation cephalosporins	14.29	12.29	11.21	10.69	11.80	10.54	9.46	9.31	8.83	9.12
J01DD	Third-generation cephalosporins	1.26	1.08	1.15	1.19	1.42	1.41	1.39	1.38	1.38	1.52
J01DF	Monobactams	0.17	0.07	0.03	0.01	0.01	0.01	0.01	0.01	0.01	0.02
J01DH	Carbapenems	3.25	3.57	3.22	3.12	3.07	3.28	3.46	3.76	3.61	3.52
J01EA	Trimethoprim and derivatives	0.44	0.51	0.44	0.43	0.44	0.51	0.47	0.52	0.49	0.46
J01EB	Short-acting sulfonamides	0.19	0.15	0.13	0.12	0.11	0.12	0.10	0.07	0.07	0.06
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	5.12	5.23	5.77	6.21	5.98	7.02	7.77	8.42	9.28	9.58
J01FA	Macrolides	3.81	3.94	4.81	5.44	6.10	7.34	7.84	7.07	5.64	5.75
J01FF	Lincosamides	0.74	0.70	0.63	0.72	0.69	0.89	0.86	0.83	0.79	0.81
J01GB	Aminoglycosides	2.51	2.21	2.39	2.26	2.38	2.51	2.84	2.95	2.79	2.75
J01MA	Fluoroquinolones	10.04	9.33	9.18	8.67	7.70	8.20	7.90	8.12	8.37	8.51
J01XA	Glycopeptides	1.53	1.25	1.28	1.26	1.40	1.48	1.56	1.73	1.74	1.69
J01XB	Polymyxins	0.31	0.24	0.21	0.22	0.21	0.27	0.26	0.28	0.27	0.28
J01XC	Steroid antibacterials (fusidic acid)	0.26	0.25	0.18	0.13	0.07	0.07	0.07	0.06	0.07	0.05
J01XD	Imidazole derivatives	4.76	4.78	4.66	5.22	4.97	5.07	4.79	4.93	4.56	4.43
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.39	0.34	0.30	0.27	0.27	0.31	0.33	0.40	0.36	0.36
J01XX05	Methenamine	0.08	0.06	0.10	0.09	0.08	0.12	0.09	0.10	0.13	0.13
J01XX08	Linezolid	0.41	0.37	0.48	0.42	0.40	0.61	0.62	0.57	0.58	0.65
J01XX09	Daptomycin	0.03	0.06	0.04	0.06	0.09	0.17	0.08	0.11	0.14	0.13
P01AB01	Nitroimidazole derivatives (metronidazole)	2.61	2.14	2.22	2.52	2.18	2.28	2.23	2.30	2.22	2.17
A07AA09	Intestinal antiinfectives (vancomycin)	0.58	0.56	0.52	0.56	0.56	0.58	0.64	0.77	0.67	0.78
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin	103.51	99.64	103.16	107.74	105.52	117.34	119.82	125.03	124.29	127.89

Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

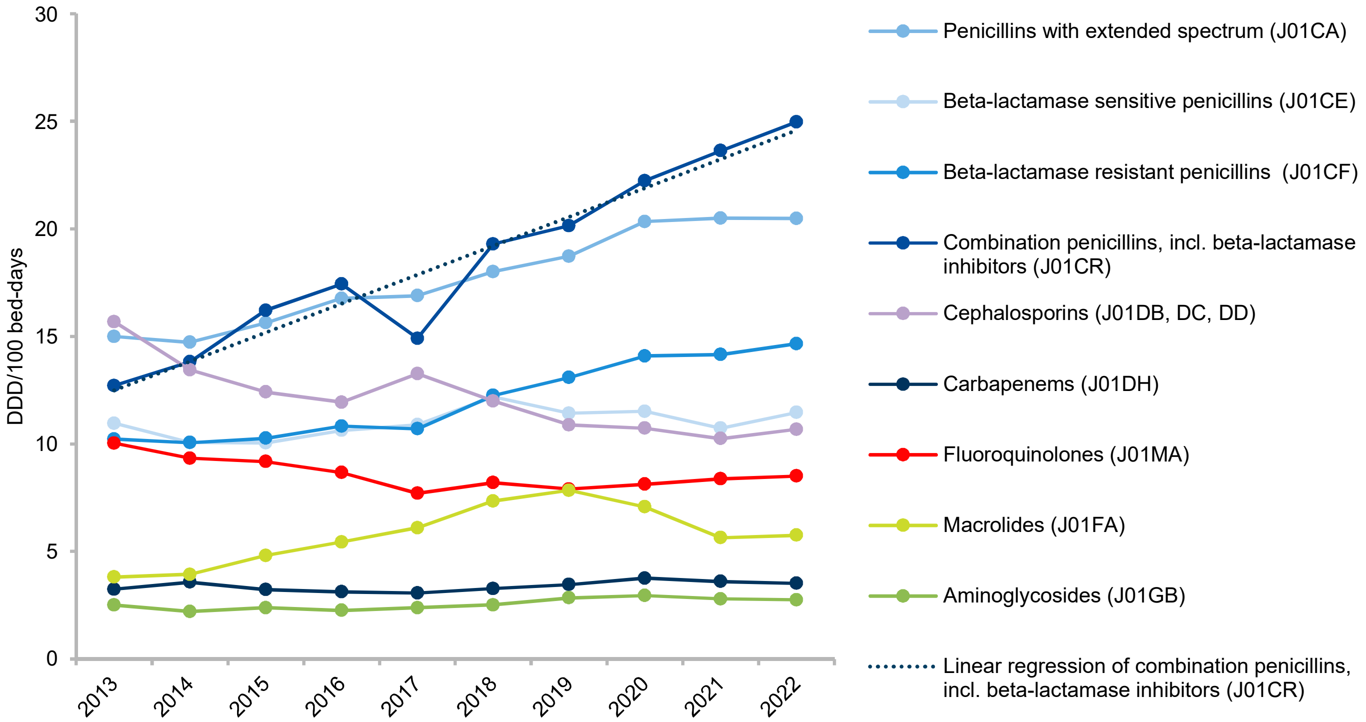
The four penicillin groups (penicillins with extended spectrum, beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins and combinations of penicillins, including beta-lactamase inhibitors) accounted for 71.56 DBD, corresponding to 56% of the total consumption of antimicrobials at somatic hospitals in Denmark in 2022. The consumption of combinations of penicillins, including beta-lactamase inhibitors, continued to increase (96% higher than in 2013 and 24% higher than in 2019) and accounted for 24.97 DBD, making it the largest group consumed in 2022 (20%). Penicillins with extended spectrum also increased markedly over the last decade (37% higher in 2022 compared to 2013) and were the second largest group consumed at Danish hospitals with 20.48 DBD (16%). Beta-lactamase sensitive penicillins accounted for 11.46 DBD (9%) and beta-lactamase resistant penicillins for 14.66 DBD (11%).

Tetracycline consumption increased during the past decade from 1.71 DBD in 2013 to 3.67 in 2019 but has fallen slightly since to 3.52 DBD in 2022. Consumption of combinations of sulfonamides and trimethoprim increased from 5.12 DBD in 2013 to 9.58 DBD in 2022, a total increase of 87% over the decade. Macrolide consumption continuously increased between 2013 and 2019 but has since decreased to 5.75 DBD in 2022. Consumption of carbapenems increased over the last decade from 3.25 DBD in 2013 to 3.52 DBD in 2022 (Table 5.6, Figures 5.15 and 5.16).

Linezolid consumption has increased to 0.65 DBD in 2022 which is the highest level observed the last decade. Over the past decade, the consumption of linezolid increased by 56% (0.41 DBD in 2013). Consumption of daptomycin peaked in 2018 (0.17 DBD), decreased in 2019 (0.08 DBD) and increased again up to 0.13 DBD in 2022 (Table 5.7). Although the overall consumption of both antimicrobials is low, these changes are of concern since both are reserved for treatment of serious infections caused by vancomycin-resistant enterococci (VRE) or methicillin-resistant *Staphylococcus aureus* (Section 8.3.3 and 8.3.4, Chapter 8 'Resistance in human pathogens').

The consumption of antimicrobials at hospitals can also be measured in relation to the number of patients being admitted, i.e. DDD per 100 admissions (DAD) (Table 5.7). Consumption estimated in DAD showed similar trends compared to trends measured in DBD between 2013 and 2022.

Figure 5.15 Consumption at somatic hospitals by leading groups of antimicrobial agents, DDD per 100 bed-days, Denmark, 2013-2022
DANMAP 2022



Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

Table 5.7 Consumption of antimicrobial agents for systemic use in somatic hospitals, DDD per 100 admissions, Denmark, 2013-2022

DANMAP 2022

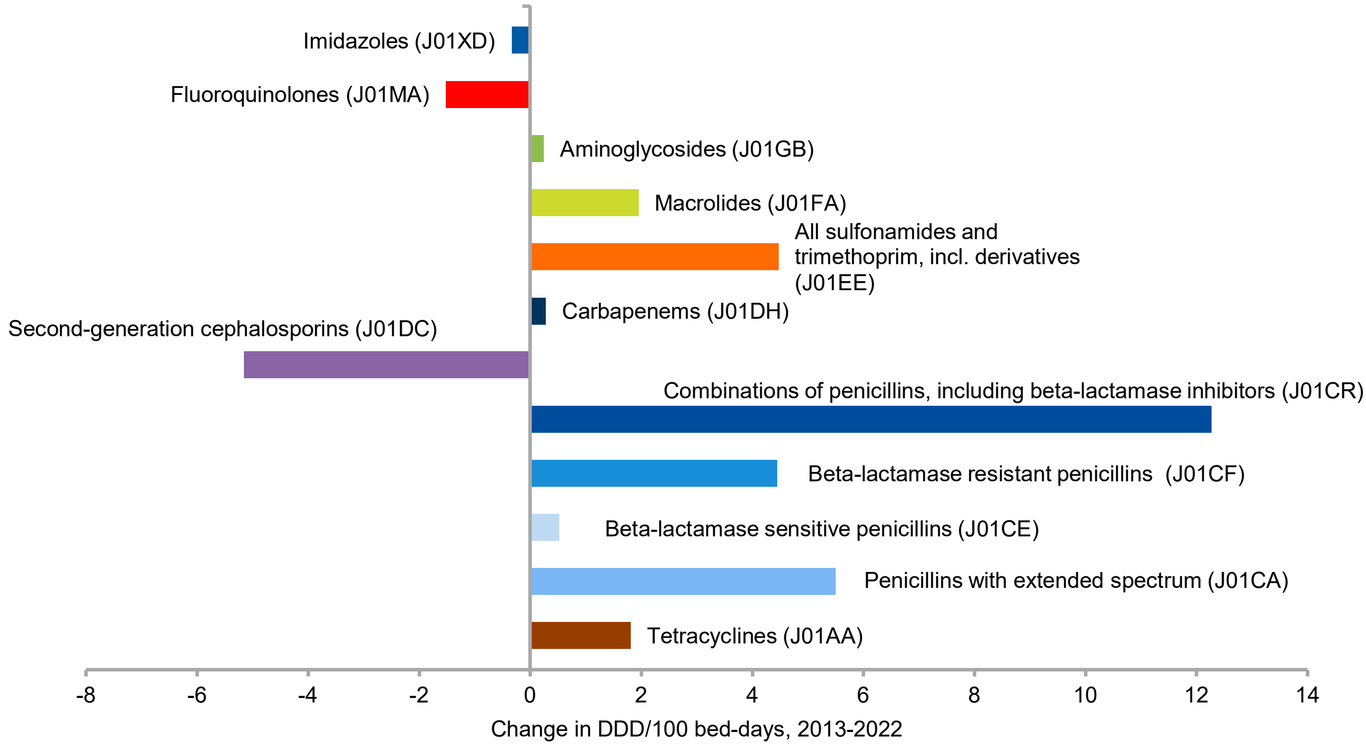
ATC group	Therapeutic group	Year									
		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetracyclines	8.28	9.01	9.87	11.36	10.97	12.54	16.22	13.43	13.91	14.93
J01CA	Penicillins with extended spectrum	72.52	74.28	76.91	78.38	84.75	81.27	82.82	87.14	87.84	86.89
J01CE	Beta-lactamase sensitive penicillins	52.97	50.83	49.44	49.68	54.67	54.99	50.52	49.35	45.99	48.64
J01CF	Beta-lactamase resistant penicillins	49.44	50.74	50.48	50.60	53.69	55.29	57.86	60.38	60.66	62.20
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	61.48	69.71	79.77	81.51	74.81	87.06	89.10	95.29	101.30	105.94
J01DB	First-generation cephalosporins	0.63	0.34	0.24	0.23	0.22	0.20	0.14	0.16	0.15	0.14
J01DC	Second-generation cephalosporins	69.13	62.04	55.18	50.00	59.20	47.59	41.86	39.91	37.85	38.71
J01DD	Third-generation cephalosporins	6.09	5.45	5.65	5.57	7.13	6.34	6.14	5.92	5.91	6.45
J01DF	Monobactams	0.80	0.35	0.15	0.06	0.04	0.03	0.05	0.04	0.03	0.06
J01DH	Carbapenems	15.69	18.03	15.85	14.61	15.41	14.79	15.29	16.11	15.45	14.93
J01EA	Trimethoprim and derivatives	2.13	2.55	2.16	2.03	2.22	2.31	2.06	2.23	2.09	1.94
J01EB	Short-acting sulfonamides	0.91	0.78	0.65	0.55	0.55	0.53	0.45	0.32	0.31	0.25
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	24.76	26.39	28.41	29.02	30.01	31.66	34.36	36.09	39.79	40.67
J01FA	Macrolides	18.42	19.87	23.68	25.44	30.60	33.13	34.68	30.31	24.17	24.41
J01FF	Lincosamides	3.60	3.53	3.10	3.38	3.46	4.03	3.82	3.57	3.39	3.45
J01GB	Aminoglycosides	12.12	11.15	11.75	10.55	11.96	11.34	12.58	12.63	11.98	11.67
J01MA	Fluoroquinolones	48.54	47.09	45.17	40.53	38.66	36.99	34.93	34.83	35.90	36.10
J01XA	Glycopeptides	7.40	6.29	6.29	5.88	7.03	6.70	6.88	7.42	7.46	7.19
J01XB	Polymyxins	1.51	1.22	1.05	1.05	1.03	1.20	1.14	1.18	1.17	1.19
J01XC	Steroid antibacterials (fusidic acid)	1.25	1.25	0.89	0.62	0.36	0.33	0.29	0.26	0.29	0.22
J01XD	Imidazole derivatives	23.04	24.14	22.95	24.43	24.93	22.88	21.18	21.14	19.56	18.79
J01XE	Nitrofuran derivatives (nitrofurantoin)	1.91	1.72	1.46	1.28	1.36	1.42	1.45	1.73	1.53	1.55
J01XX05	Methenamine	0.41	0.30	0.48	0.43	0.38	0.55	0.41	0.45	0.56	0.57
J01XX08	Linezolid	2.00	1.85	2.38	1.97	1.99	2.76	2.74	2.43	2.49	2.74
J01XX09	Daptomycin	0.13	0.30	0.21	0.27	0.44	0.75	0.33	0.48	0.61	0.54
P01AB01	Nitroimidazole derivatives (metronidazole)	12.65	10.78	10.92	11.80	10.92	10.28	9.88	9.87	9.51	9.19
A07AA09	Intestinal antiinfectives (vancomycin)	2.78	2.84	2.55	2.63	2.79	2.62	2.81	3.30	2.88	3.33
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin	500.61	502.82	507.66	503.83	529.58	529.58	529.99	535.97	532.78	542.67

Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2022 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

Monthly consumption of the main antimicrobial groups for treatment of critically ill patients at hospitals as well as the monthly number of bed-days from 2018 to 2022 are shown in Figures 5.17. Consumption of carbapenems (ertapenem, imipenem, meropenem) and penicillin/beta-lactamase inhibitor combinations (amoxicillin/clavulanic acid, piperacillin/tazobactam) per bed-day were high during the COVID-19-related lockdowns in Denmark in 2020 and 2021. This reflects most likely changes in hospital activity and in case mix in hospitals during these periods. In 2022, penicillin/beta-lactamase inhibitor combinations decreased sharply in July and August 2022 due to product shortages. However, prescribers had access to penicillin/beta-lactamase inhibitor combinations via special deliveries. Approximately 70,000 DDD penicillin/beta-lactamase inhibitor combinations were purchased through special delivery in 2022, whereas in 2019-2021 the number was approximately 4,000 DDD.

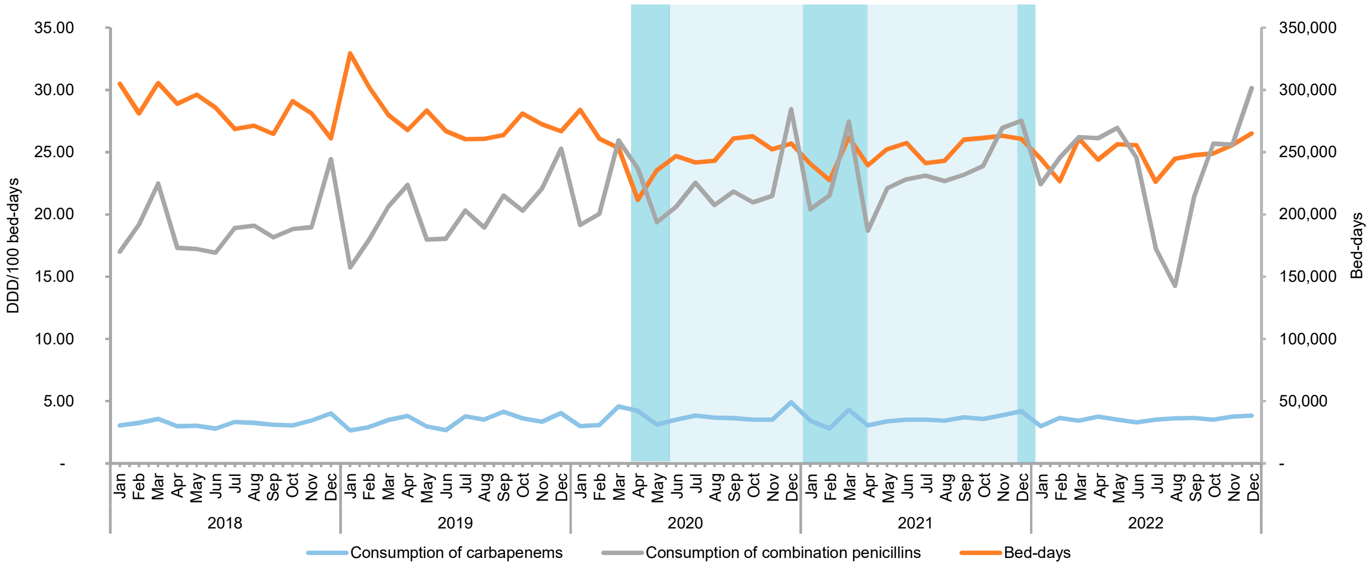
Piperacillin-tazobactam in combination with gentamicin is the recommended antibiotic treatment for septic patients with no known complications. From 2013 to 2022 piperacillin-tazobacam use increased from 6.55 DBD to 16.59 DBD (153%).

Figure 5.16 Changes in consumption of leading groups of antimicrobial agents at somatic hospitals, DDD per 100 bed-days, Denmark, 2013-2022
DANMAP 2022



Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

Figure 5.17 Consumption of key antimicrobials used for treatment of seriously ill patients in hospital, DDD per 100 bed-days, Denmark, 2018-2022
DANMAP 2022

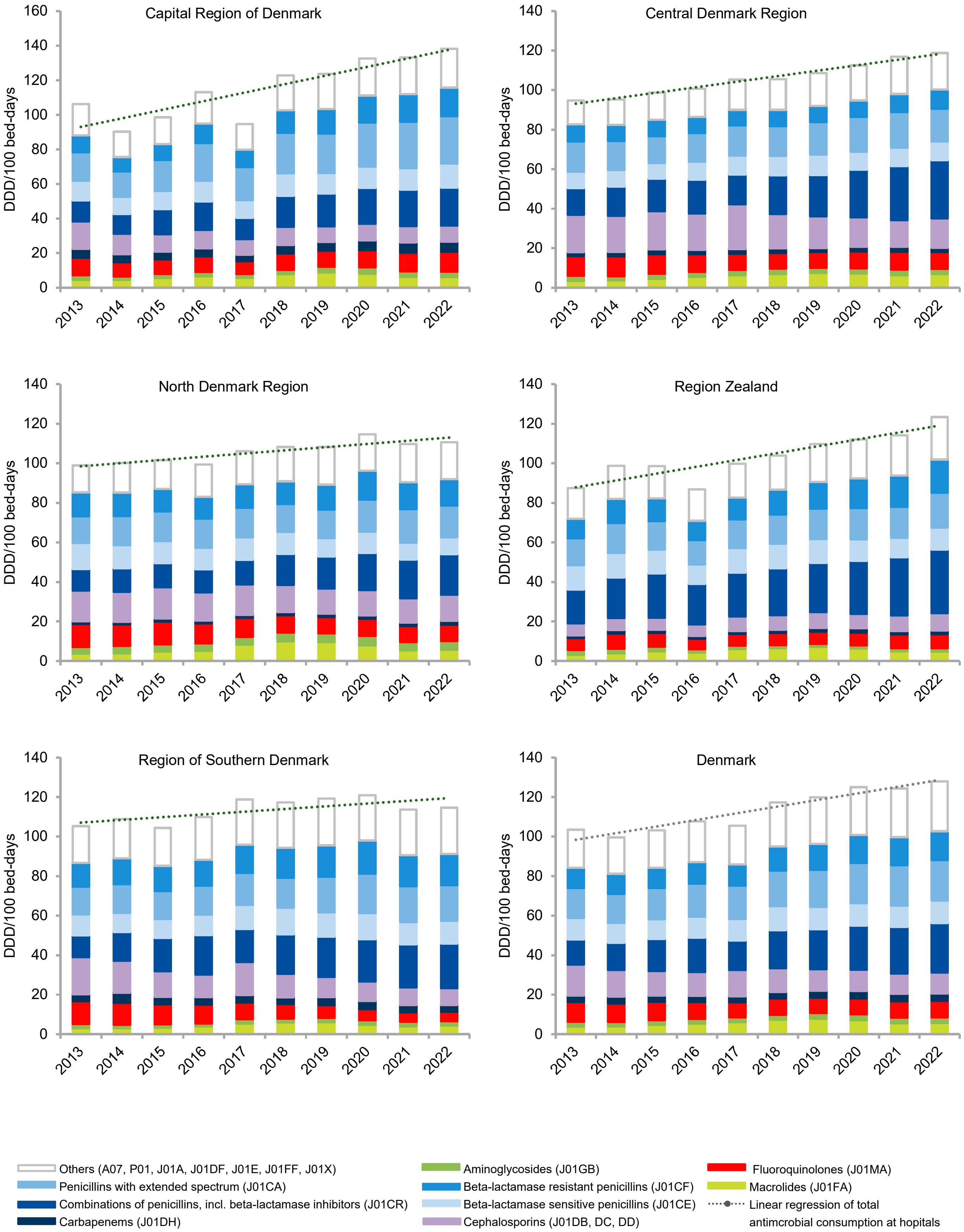


COVID-19 restrictions in place
Fewer restrictions in place
Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

5.4.2 Antimicrobial consumption at regional level at public somatic hospitals

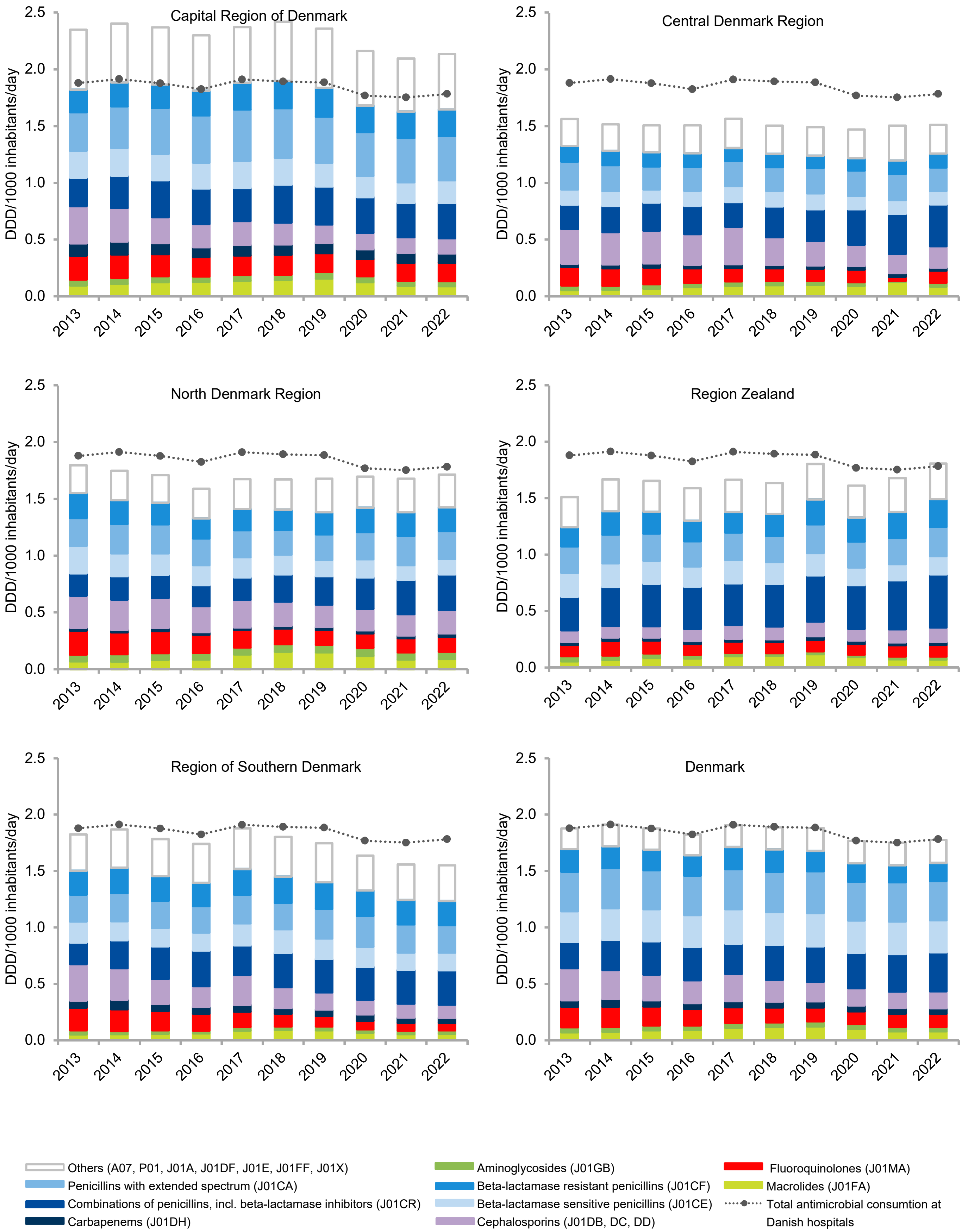
Trends in hospital consumption at regional level measured in DDD per 100 bed-days are presented in Figure 5.18. The Capital Region of Denmark shows the highest level of consumption when compared to the other regions in 2022. It is also notable that consumption increased for each region the last decade when measured in DBD (Figure 5.18) but remains almost unchanged over the same period when measured in DID (Figure 5.19). This reflects that hospital activity changes during the years and more antimicrobials were used in relation to hospital patients' bed-days.

Figure 5.18 Consumption of antimicrobial agents for systemic use at hospitals in the five health regions, DDD per 100 bed-days, Denmark, 2013-2022
DANMAP 2022



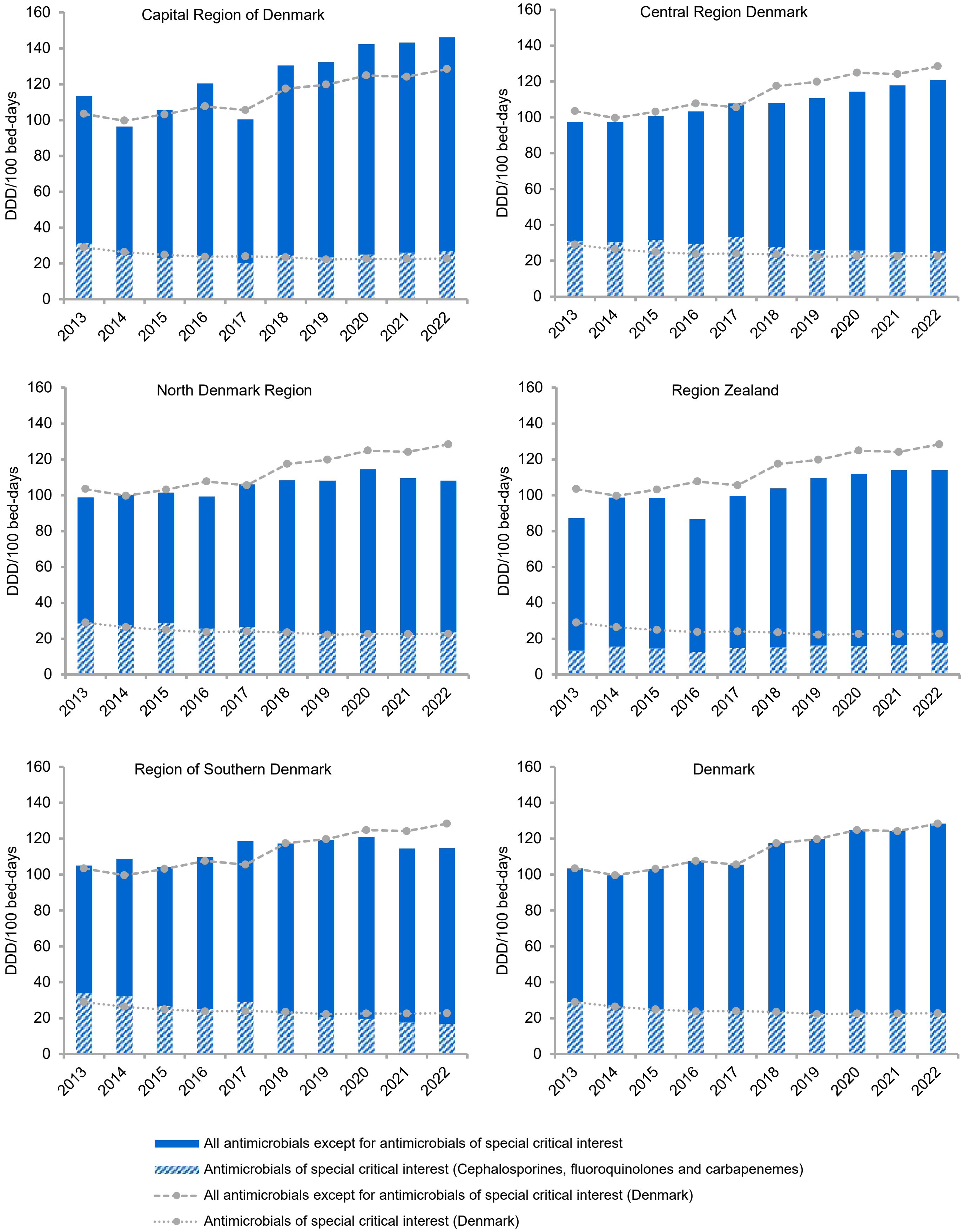
Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

Figure 5.19 Consumption of antimicrobial agents for systemic use at hospitals in the five health regions, DDD per 1,000 inhabitants per day, Denmark, 2013-2022
DANMAP 2022



Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

Figure 5.20 Consumption of antimicrobials of special critical interest (cephalosporins, fluoroquinolones and carbapenems) and all other antimicrobials in the five health regions, DDD per 100 bed-days, Denmark, 2013-2022 DANMAP 2022



Data: Antimicrobial consumption at somatic hospitals
Data source: Register of Medicinal Product Statistics, 2023 edition of the Anatomical Therapeutic Chemical (ATC) classification system and The National Patient Register

5.4.4 Changes in the consumption of antimicrobials of special critical interest

In Denmark, cephalosporins, fluoroquinolones and carbapenems have been defined as antimicrobials of special critical interest due to their resistance potential and their reserved use for treatment of severe infections. In 2022, the antimicrobials of special critical interest constituted 18% of the total consumption at somatic hospitals compared to 28% in 2013 (Table 5.6, Figure 5.20).

In 2022, cephalosporins accounted for 8.4%, fluoroquinolones for 6.7% and carbapenems for 2.8% of the total antimicrobial consumption in somatic hospitals in Denmark. The consumption trends for antimicrobials of special critical interest and all other antimicrobials are presented at regional and national level from 2013 to 2022 in Figure 5.20.

We would like to acknowledge Maja Laursen from the National Health Data Authority in Denmark for data on antimicrobial consumption and activity hospital care. We would also like to acknowledge all hospital pharmacies in Denmark for data on consumption of special delivery antimicrobials at the hospitals.

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Textbox 5.1

Comparison of antibiotic prescribing for elderly in long-term care facilities and elderly living at home

Background

Elderly people of 75 years and above are the age group that receive most antibiotics in Denmark. Urinary tract infection is the main indication. Antibiotic prescribing for this population was studied by comparing the use among elderly living in long-term care facilities and elderly living at home. Special attention was paid to the difference in prescribing antibiotics for urinary tract infection.

Methods

The study was observational and registry-based, and included all elderly Danish residents aged ≥ 75 years in 2016. Total antibiotic prescription rates were examined by including all antibacterial agents for systemic use (ATC J01). Prescription rates for urinary tract infection included pivmecillinam (ATC J01CA08), sulfamethizole (ATC J01EB02), trimethoprim (ATC J01EA01), nitrofurantoin (ATC J01XE01) and amoxicillin (ATC J01CA04). Antibiotic prescribing data were retrieved from the Danish National Prescription Database and residence status from the Nursing Home Register (AEPI-registry). Confounders were chosen a priori based on empirical evidence and on a directed acyclic graph. The chosen confounders were age, sex and comorbidity. Comorbidity was assessed via the Charlson Comorbidity Index[1] using data from the National Patient Register. Linear regression models were used to examine the difference in antibiotic prescription rates. The main outcomes were number of prescriptions per individual per year and DDD per individual per year.

Results

Out of the 416,627 elderly individuals aged ≥75 years included in the study population, 23,863 resided in a long-term care facility (5,7%) (Table 1). A slight difference in age between the two groups was noted, however this was insignificant. Regression models showed that elderly living in long-term care facilities received 1.7 [CI 1.7-1.7] prescriptions/individual/year more than elderly living at home. For urinary tract infection the difference between elderly living in long-term care facilities and elderly living at home was 1.2 [CI 1.2-1.3] prescriptions/individual/year (Table 2).

Table 1 Baseline characteristics of the study population aged ≥75 years according to residence status in 2016 DANMAP 2022

	Living in LTCF	Living at home
Individuals aged ≥75 years	23.863	392.764
Mean age (years ± SD)	86.2 ± 6.1	81.0 ± 5.1
Women (%)	72.4	57.3
Mean number of antibiotic prescriptions ± SD	2.9 ± 4.9	1.0 ± 2.1
Mean number of UTI antibiotic prescriptions ± SD	1.9 ± 4.3	0.4 ± 1.5
Mean number of antibiotic DDD ± SD	43.9 ± 118.7	11.3 ± 35.1
Mean number of UTI antibiotic DDD ± SD	29.7 ± 93.3	5.1 ± 25.3
Mean CCI ± SD	2.2 ± 2.1	1.8 ± 2.0

SD: standard deviation; UTI: urinary tract infection; DDD: defined daily dose; CCI: Charlson Comorbidity Index, LTCF: Long term care facility
Prescriptions/DDD are per individual per year
[1] Charlson Comorbidity Index is a weighted index that classifies individuals' prognostic comorbidity. The index takes the seriousness and the number of comorbid diseases into account

Table 2 Results of unadjusted and adjusted linear regression of antibiotic prescription rate comparing elderly living in LTCF to elderly living at home DANMAP 2022

	Crude parameter estimate [CI95%]	Adjusted* parameter estimate [CI95%]
Antibiotic prescriptions	2.0 [2.0-2.0]	1.7 [1.7-1.7]
UTI prescriptions	1.5 [1.4-1.5]	1.2 [1.2-1.3]
Antibiotic DDD	32.5 [32.2-32.9]	28.9 [28.5-29.3]
UTI antibiotic DDD	22.8 [22.5-23.1]	20.2 [20.0-20.5]

* Adjusted for age, sex and comorbidity, the latter assessed via the Charlson Comorbidity Index, LTCF: Long term care facility
Prescriptions/DDD are per individual per year

The unadjusted and adjusted analyses resulted in similar prescription rates, indicating that the relationship between long-term care facility residency status and prescription rate was not affected by the potential confounders: age, sex and comorbidity (Table 2).

Conclusion
A higher antibiotic prescription rate for elderly living in long-term care facilities could not be explained by higher morbidity in this group of elderly. The registry-based methodology limits the ability to assess the appropriateness of the antibiotic prescribing, why further investigation is needed to understand the underlying causes of the differences in prescription rates.

Link to published paper: https://pubmed.ncbi.nlm.nih.gov/35587537/.

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Textbox 5.2

Sociodemographic characterisation of antibiotic heavy users in the Danish elderly population

Background

Elderly people (≥65 years) have the highest use of antibiotics and studies have shown an overuse within this population (1-3). Sociodemographic inequality is a well-known problem in health care, but it is not known whether sociodemographic factors also influence antibiotic use among Danish elderly people. The aim of this study was to investigate whether sociodemographic factors were associated with an excess use of antibiotics (i.e., being an antibiotic heavy user) in general practice among elderly people in Denmark.

Methods

The study was based on national register data on antibiotic (ATC J01 and P01AB01) prescriptions redeemed by patients of 65 years or older in 2017. Only prescriptions issued by general practitioners were included. A linear regression model was applied to predict an individual's antibiotic use based on age, sex and morbidity level. Morbidity level was assessed by using data on hospitalization from the Danish National Patient Registry. Information on sociodemographic characteristics was collected from various registries, e.g. the educational registry.

A positive difference between the actual antibiotic use and the predicted antibiotic use was interpreted as excess use. Heavy users were defined as the 10% of the study population with the highest excess use. Stratified by sex, heavy users were compared to non-heavy users both in univariable and multivariable analyses using a logistic regression method. The relative importance of statistically significant sociodemographic factors was also examined.

Figure 1 Distribution of antibiotic excess use in the study population, Denmark, 2017 DANMAP 2022

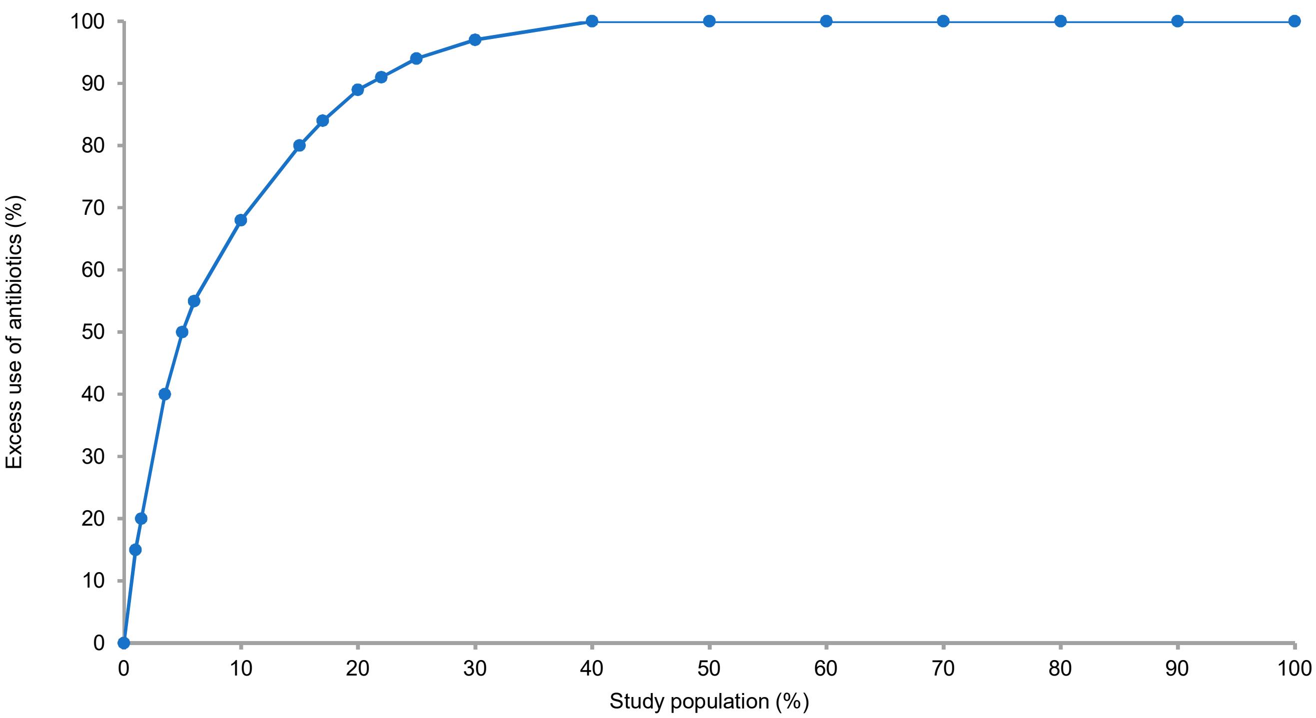
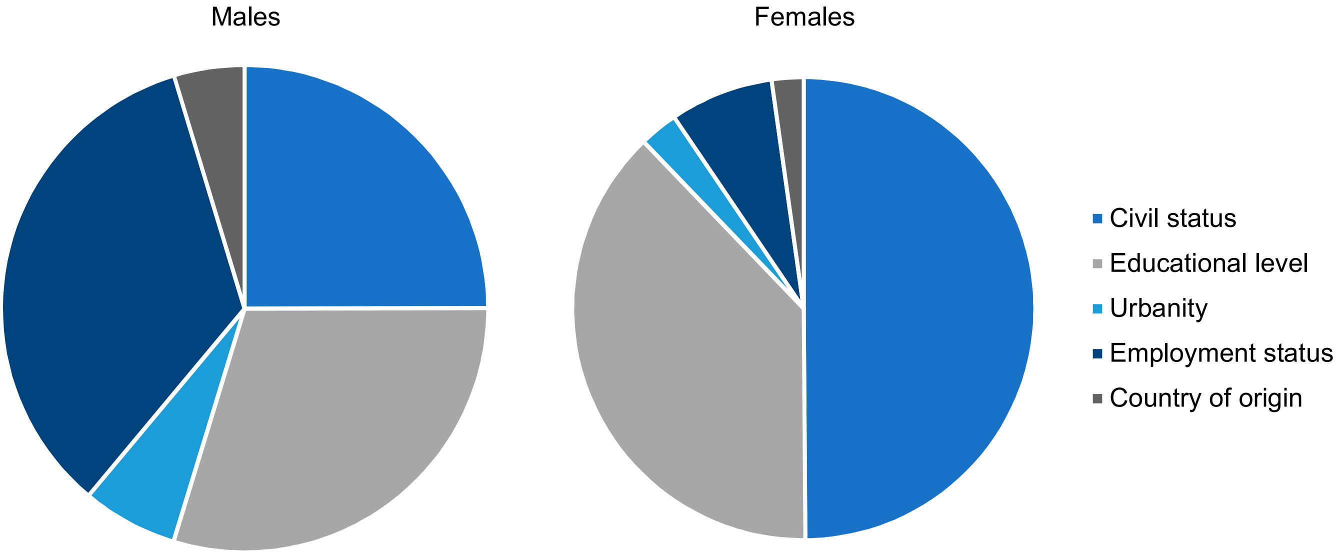


Figure 2 Distribution (%) of sociodemographic factors contributing to the explained variance of excess antibiotic use, Denmark, 2017
DANMAP 2022



Results

The study included 251,733 individuals, 95,544 males and 156,189 females, who redeemed one or more antibiotic prescriptions in 2017. The analyses showed that increasing educational level significantly lowered the risk of antibiotic heavy use. On the other hand, not being married (single, divorced and widowed) increased the risk of antibiotic heavy use, as did being born outside Scandinavia (Denmark, Norway and Sweden). The results were similar for both sexes. The linear regression model also showed that the defined 10% heavy users were responsible for 68% of all excess use of antibiotics in general practice in Denmark (Figure 1). The relative importance analysis showed that civil status and educational level contributed considerably to the explained variance for both sexes (Figure 2). For males, employment status was important as well.

Conclusion

The study showed that heavy users were responsible for about 2/3 of all excess antibiotic use among elderly people. Furthermore, an association between several sociodemographic characteristics and antibiotic heavy use was found. The relative importance analysis showed that for males and females, civil status and educational level were important, and for males, employment status was important as well. The study indicate that the risk of heavy use is substantially affected by socioeconomic characteristics and future interventions to reduce overuse of antibiotics among elderly should target individuals at highest risk.

Sociodemographic characterisation of antibiotic heavy users in the Danish elderly population. Jensen, Maria L V; Aabenhus, Rune M; Holzknecht, Barbara J; Bjerrum, Lars; Siersma, Volkert; Cordoba, Gloria; Jensen, Jette N. ISSN: 1403-4948, 1651-1905; DOI: 10.1177/14034948221119638; PMID: 36076357 Scandinavian journal of public health., 2022, p.14034948221119638.

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Textbox 5.3

Incidence of multiresistant bacteria and consumption of antimicrobial agents in Greenland

Background

Greenland has a population of 56.562 inhabitants (January 2022, StatBank Greenland) and Nuuk is the capital with 19.261 inhabitants (January 2022, StatBank Greenland). Greenland has its own Ministry of Health and the country is divided into five health regions. There are five smaller hospitals, one national hospital and 11 health care centres in the five health regions. The national and largest hospital Dronning Ingrids Hospital (182 beds), is situated in Nuuk. Around 15-16,000 persons are admitted to hospital once or several times a year. Patients with specific or serious diseases which cannot be treated at Dronning Ingrids Hospital (DHI) are transferred to Denmark or Iceland, e.g. haemodialysis, cancer treatment, brain surgery etc.

Resistant bacteria

From 2000 to 2022, 129 patients were diagnosed with methicillin-resistant *Staphylococcus aureus* (MRSA), 195 patients with extended spectrum beta-lactamase (ESBL)-producing *Enterobacterales*, four patients with vancomycin-resistant enterococci (VRE), and 217 patients with *Clostridium difficile* infection.

MRSA

In the latest years there has been a huge increase in incidence of MRSA with several large outbreaks throughout the country. The largest outbreak was seen during 2021 in Ilulissat involving 21 persons at two long term care facilities (LTCFs). Most of the affected persons were old residents, however two health care workers were also colonized. Several residents had chronic wounds which made treatment of carrier state impossible and this was a great challenge concerning prevention of further transmission in the LTCFs. The second largest outbreak involved 12 persons in Tasiilaq at the East coast of Greenland (described in details in DANMAP 2017). Most infections or colonizations with MRSA are seen in the community with transmission in families.

VRE

In spite of ongoing VRE outbreaks in Denmark, so far only four patients have been diagnosed with VRE in Greenland. Three patients were colonized with VRE in the rectum and one patient had pleurisy – in all four cases VRE occurred after hospitalization in Denmark. No transmission was seen in the wards.

CPO

In recent years, an increase in incidence of carbapenemase-producing organisms (CPO) in Denmark has been observed but until now, no CPO has been reported in Greenland.

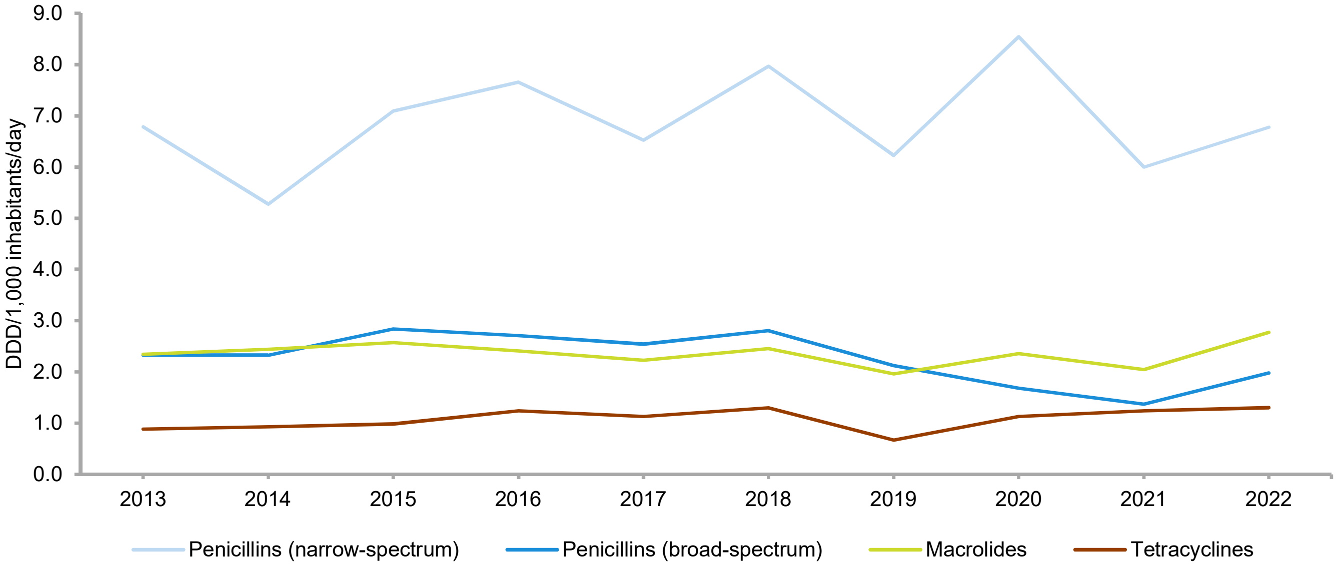
Other resistant bacteria

Most of the other resistant bacteria observed were imported from Denmark or abroad, but in some cases, especially in patients with ESBL-producing *Enterobacterales*, treatment with broad-spectrum antimicrobial agents in Greenland has probably selected for these bacteria. From 2012 to 2013, there were outbreaks with *C. difficile* type 027 in the hospitals, and transmission within the country occurred. But due to a great infection prevention and control effort from the hospital staff, these outbreaks were quickly stopped. Of the 23 new *C. difficile* patients in 2022, two of them were of the 027 type.

Consumption of antimicrobial agents

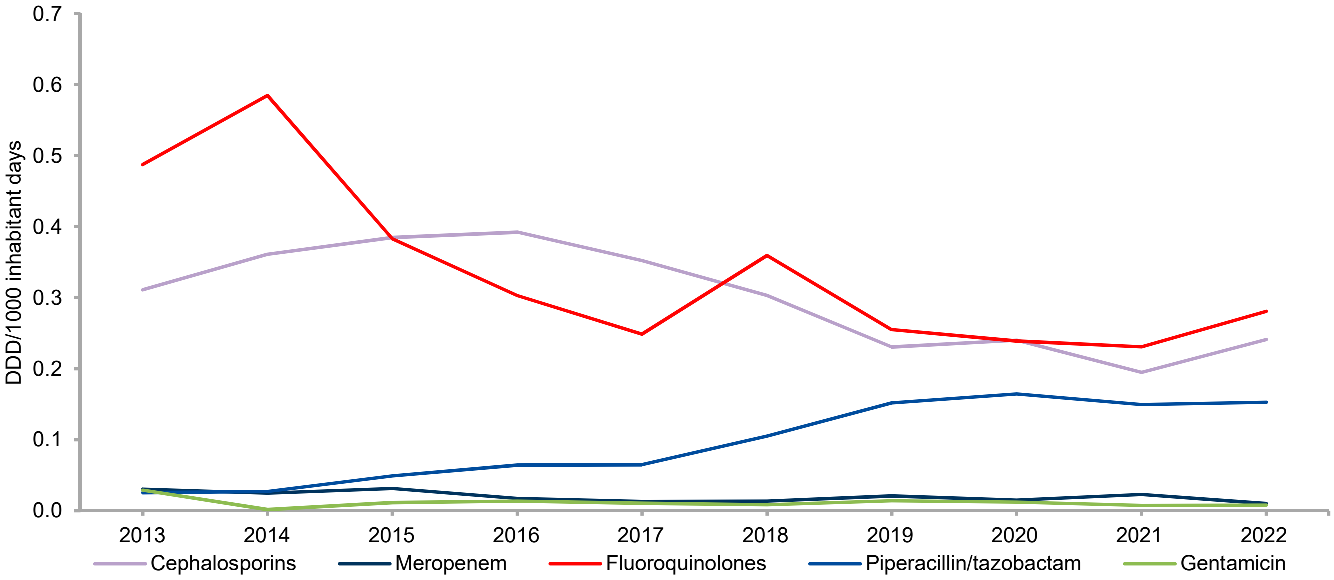
All antimicrobial agents in Greenland are purchased and distributed from the National Pharmacy. Figure 1a and b show the total purchase of selected antimicrobial agents in DDD per 1,000 inhabitants per day (DID) from 2013 to 2022. Throughout the last 10 years the largest consumption of antimicrobial agents is seen in the group of narrow-spectrum penicillins (with fluctuations from year to year). There has been a decline in broad-spectrum penicillins from 2018 to 2021 (50%) with an increase (43%) from 2021 to 2022. Macrolides have been quite stable throughout the years but an increase (40%) is seen from 2021 to 2022. A larger decrease in fluoroquinolones from 2014 to 2017 (60%) was alternated by some fluctuations/increases but in 2022 it is still half of the consumption in 2014. Cephalosporins have been decreasing since 2017 with a low and stable consumption since 2019. A remarkable increase has been seen since 2015 in piperacillin-tazobactam with an increase (50%) from to 2021 to 2022. Meropenem still has a low and stable consumption.

Figure 1a Consumption of narrow- and broad-spectrum penicillins, macrolides and tetracyclines in humans in Greenland, DDD/1,000 inhabitants/day, 2013–2022
DANMAP 2022



Narrow-spectrum penicillins include benzylpenicillin, phenoxymethylpenicillin and dicloxacillin and broad-spectrum penicillins include ampicillin, pivampicillin, amoxicillin and amoxicillin with enzyme inhibitor

Figure 1b Consumption of cephalosporins, meropenem, fluoroquinolones, piperacillin/tazobactam and gentamicin in humans in Greenland, DDD/1,000 inhabitants/day, 2013-2022
DANMAP 2022



continued ... Textbox 5.3

Conclusion

The consumption data for antimicrobial agents are based on purchases and fluctuations are therefore seen from year to year. It is however noteworthy that the increased focus on prescription of antibiotics in the recent years has resulted in remarkable decreases in purchases of cephalosporins, fluoroquinolones and meropenem, and continued increase in purchase of piperacillin-tazobactam.

Continued focus on the use of broad-spectrum antimicrobial agents, on the incidence of multiresistant bacteria, and on compliance to guidelines for infection prevention and control is still important in Greenland in the future.

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Textbox 5.4

Shortage of antibiotics at Community Pharmacies in Denmark

The Association of Danish Pharmacies is the employer and professional organization of community pharmacies in Denmark. The association's Executive Board has the overall responsibility for the association's activities covering member services and promoting community pharmacy professional health services as an integrated part of the health care sector.

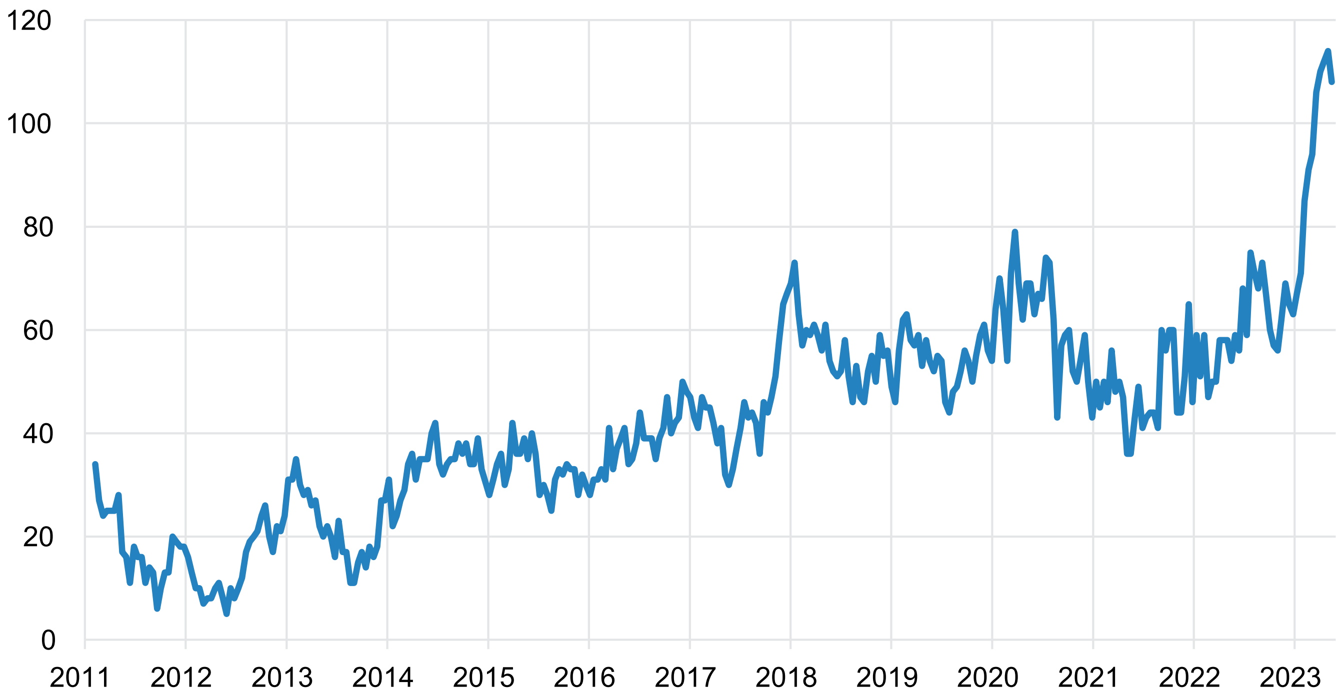
In Denmark, legislation obliges pharmacies to offer patients the cheapest, generic product of the prescribed medicine - also known as generic substitution. The legislation requires these substitutional products to have the same active component, formulation, strength, and same or smaller package size to ensure the same pharmaco-dynamics and -kinetics as the originally prescribed product. Antibiotics are allocated in dispensing group 'B' which means that package size is allowed to differ by up to 25% from the prescribed package size.

In case of supply shortages, the restrictions in the substitution legislation can be a challenge. If the pharmacy only can offer an alternative with different formulation, strength or larger package size, the patient will need a new prescription to get the medicine. The same applies in case of extreme price jumps of the prescribed medicine, where a cheaper alternative with a different formulation, strength or larger package size will demand a new prescription. In special circumstances and to limited degree the Danish Medicines Agency can authorize sale or dispensing of medicine, which is not on the market in Denmark. This 'compassionate use permit' requires an application from the prescriber and is given on an individual patient case and for a specified prescribed treatment only and cannot be extended to cover prolonged periods or several patients.

Increased shortages of antibiotics in Denmark

The number of antibiotics (J01) in shortage in Denmark almost doubled in the first half of 2023. As shown in Figure 1, the number of antibiotic packages in shortage at all pharmaceutical wholesalers in Denmark increased gradually from around 20-40 packages in 2011-2017 to around 60 packages in 2018-2022. In the first half of 2023 the number reached 110 antibiotic packages in shortage. However, most of the shortages did not reach the patients, as generic substitutes were available.

Figure 1 Number of antibiotic packages (J01) in shortage, Denmark, 2011-2023 DANMAP 2022

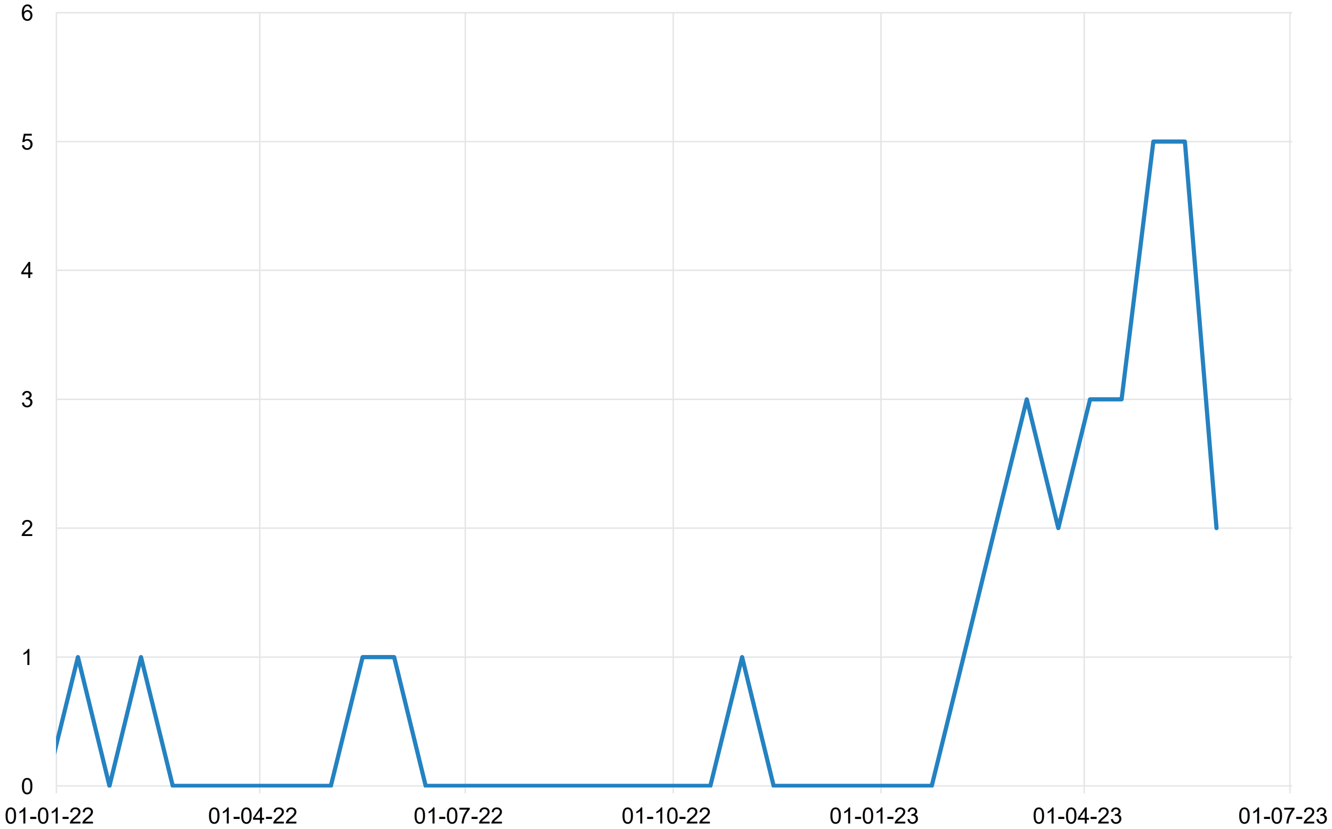


Source: The Danish Medicines Agency and the Association of Danish Pharmacies

continued ... Textbox 5.4

In 2022, shortages covered all packages in one generic substitution group only a few times and for limited time (Figure 2). However, in the first half of 2023 the shortages several times covered 2 to 5 entire generic substitution groups, making it increasingly burdensome for patients, doctors, and pharmacies to find an adequate treatment.

Figure 2 Number of entire generic substitution groups of antibiotics (J01) in shortage, Denmark, 2022-2023 DANMAP 2022



Source: The Danish Medicines Agency and the Association of Danish Pharmacies

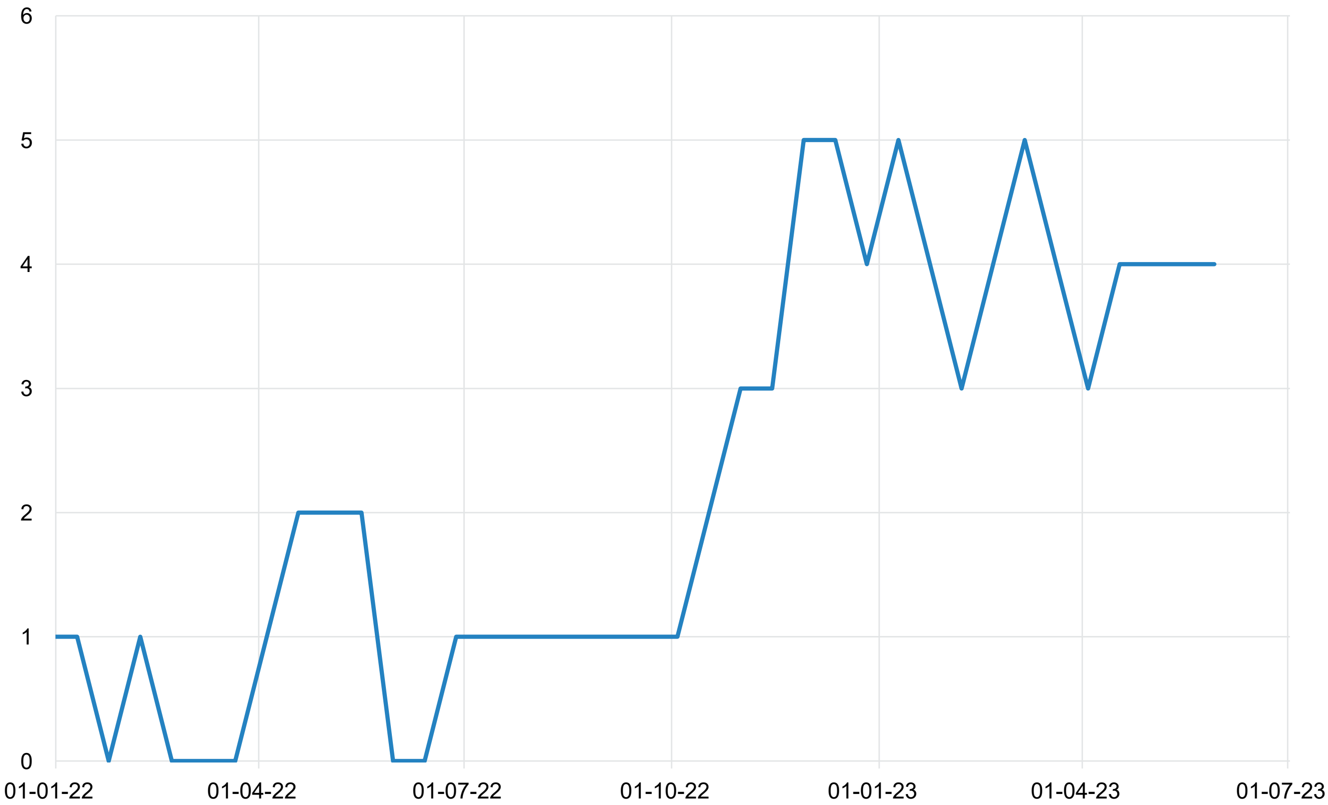
At the same time, the shortage of antibiotics with no marketed generic substitute increased from 0-2 packages in shortage in the first 3 quarters of 2022 to 3-5 packages in the 4th quarter of 2022 and in the first half of 2023 (Figure 3).

The Danish pharmacies have two main pharmaceutical supply wholesalers. If one wholesaler is out of stock, the pharmacy is required to order the medicine from the other wholesaler. If a pharmacy is out of stock of a certain medicine and the medicine is in shortage at both wholesalers, the pharmacy can check electronically if other pharmacies still have the medicine in stock and refer patients to these pharmacies. Furthermore, the pharmacy app 'Apoteket' refers patients to the nearest 25 pharmacies with the prescribed medicine in stock. It is not possible to trade pharmaceuticals between pharmacies.

Each day, pharmacies secure patients access to – and safe and efficient use of – the right pharmaceutical treatment. However, in recent years this access is increasingly challenged by medicine shortages. These are partly due to globalization and concentration of pharmaceutical production facilities and the aftermaths from the covid-19 pandemic and the Ukrainian war.

Due to the increase in medicine shortages, it is now possible for a regional administration to apply for compassionate use permits regarding certain pharmaceuticals for all doctors and other practitioners in the region. This reduces the administrative pressure on the medicines agency and speeds up the process of receiving such a permit, but it still takes time and the individual patient still needs a new prescription for the authorized medicine. Therefore, the compassionate use permit is not a quick-fix-solution for the patient in cases of supply shortages at the pharmacy.

Figure 3 Number of antibiotic packages (J01) in shortage where no generic substitute is marketed, Denmark, 2022-2023 DANMAP 2022



Note: Excl. injection and infusion medicine.
Source: The Danish Medicines Agency and the Association of Danish Pharmacies

Table 1 Examples of generic substitution groups of antibiotics (J01) in full shortage, Denmark, May 2023 DANMAP 2022

ATC Code	Pharmaceuticals	Strength	Package size
J01CA04	Amoxicillin	500 mg	10 tablets
J01CE02	Phenoxymethylpenicillin	50 mg/ml	200 ml
J01CR02	Amoxicillin & beta lactamase inhibitor	50 mg/ml + 12,5 mg/ml	100 ml
J01FA06	Roxithromycin	150 mg	20 tablets
J01FA06	Roxithromycin	300 mg	7 tablets

continued ... Textbox 5.4

Since 2019, pharmacies in the United Kingdom have been able to solve more medicine shortages by adhering to 'Serious Shortage Protocols' which contain information from the health authorities on authorized alternative pharmaceutical options when no generic product is available. The protocol allows the pharmacy to deviate from the standard rules and hand out a suitable alternative to the lacking drug in specific circumstances, for a specific period and in clearly defined clinical situations.

In Denmark, all pharmacies have a prescribing pharmacist, who is trained and authorized to re-prescribe certain pharmaceuticals. Expanded substitution through a Danish Serious Shortage Protocol in case of medicine shortages would result in:

- Better access to treatment
- Improved continuity in treatment
- Fewer contacts to the doctor for new prescriptions.

Thus, in the case where no generic substitute is available, a 'Serious Shortage Protocol´ could ease the burden for patients, doctors and pharmacies and increase timely access to adequate treatment.

Overall, most medicine shortages are solved swiftly by the pharmacies through generic substitution. But every single day pharmacies meet patients who cannot get their medicine due to medicine shortages. And pharmacy staff must be the 'bad guys' telling patients they cannot get the medicine from the shelf without a new prescription – even though the pharmacy staff would be able to help several of the patients and relieve doctors from the task of changing prescriptions, if legislation provided a wider range of substitution alternatives at pharmacies. This could relieve patients, practitioners and pharmacy staff from some of the burden of increasing medicine shortages.

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Textbox 5.5

Research Units for General Practice in Denmark

In Denmark, about 75% of antibiotics for human use are prescribed in general practice - mostly for infections related to the respiratory- and urinary tract systems. Also eye, skin, gastro-intestinal and sexually transmitted infections, among others, are treated with antibiotics in general practice.

Many patients present with viral, self-limiting infections; however, some do have serious, bacterial infections - in need of antibiotic treatment.

Research on antibiotic use

It can be challenging to find the "needle in the haystack" and no doubt both under- and overtreatment with antibiotics occur in general practice. For years, research on the management of infectious diseases and antibiotic use have been prioritised at the research units for general practice in Denmark. Professor Lars Bjerrum was one of the first researchers within general practice, to focus on rational use of antibiotics. In 2007, he coordinated a large European-funded project entitled the HAPPY AUDIT. The project used the Audit Project Odense method to collect data on the management of acute respiratory tract infections in six different European countries.

History of the research units

In Denmark, four research units for general practice exist. The first unit was established in Copenhagen in 1978; then Aarhus followed in 1992, Odense in 1993, and Aalborg in 2015. Recently, satellite research units in Esbjerg and Køge have been established. All units have an interdisciplinary academic environment. The research units are funded by the Danish Research Foundation of General Practice, established by the Danish Organisation of General Practitioners (PLO) and the Danish Regions. Most projects conducted at the research units are funded by external sources. All research units work closely with the universities - and joint organisations (center for general practice) have been established in some of the respective cities.

Research with and for general practice

The research units for general practice have a proud tradition for conducting projects in close collaboration with general practice. Often, projects are performed across the four research units, and sometimes including external partners, such as for example specialists in clinical microbiology or infectious diseases. Also, the Danish College of General Practice (DSAM) and the Danish Organisation for General Practice (PLO) are involved in some projects.

New projects in pipeline

The table below summarises ongoing/soon to start projects at the four research units for general practice in Denmark, focusing on management of infections and/or antibiotic use in general practice.

Project title	Aim	Research group
	Acute respiratory tract infections	
When are you cured? Defining a cut-off point using the Acute Respiratory Tract Infection Questionnaire	Define cut-off points to determine when patients can be considered cured from their acute respiratory tract infection.	Eskild Johansen Volkert Siersma Malene Plejdrup Hansen Rune Munck Aabenhus
The optimal antibiotic treatment duration for community-acquired pneumonia in adults diagnosed in general practice in Denmark: an open-label, pragmatic, randomised controlled trial.	Identify the optimal treatment duration with phenoxymethylpenicillin for community-acquired pneumonia in adult patients diagnosed in Danish general practice.	Eskild Johansen Henrik Nielsen David Gillespie Rune Aabenhus Malene Plejdrup Hansen
The effect of focused lung ultrasonography on antibiotic prescribing in patients with acute lower respiratory tract infections in Danish general practice – a pragmatic randomised controlled trial.	Determine if adding focused lung ultrasonography to usual care of patients presenting with symptoms of an acute lower respiratory tract infection in general practice reduces the general practitioner's antibiotic prescribing at index consultation.	Julie Jepsen Strøm Camilla Aakjær Martin Bach Jensen Janus Laust Thomsen Christian Borgbjerg Laursen Malene Plejdrup Hansen
Patient decision aids for acute respiratory tract infections; how to use in Danish general practice?	Investigate the feasibility of implementing the use of four patient decision aids for acute respiratory tract infections in Danish general practice.	Lotti Eggers-Kaas Anna Mygind Dorte Ejg Jarbøl Malene Plejdrup Hansen

continued ... Textbox 5.5

Project title	Aim	Research group
	Urinary tract infections	
Optimisation of antibiotic use in nursing homes through cross-sectorial collaboration: a registry study of safe and effective practice.	Investigate the long-term impacts of a complex intervention on patient safety, systemic antibiotic consumption, and health services usage among nursing home residents, and identify the nursing home and resident level factors that influence these impacts over the same period.	Sif Helene Arnold Anne Holm Maria Louise V. Mandrup Lars Bjerrum Jette Nygaard Jensen (Project group not fully established)
	Quality improvement	
Do quality clusters in general practice improve antibiotic prescribing?	Investigate whether engagement in quality clusters improves antibiotic prescribing in a general practice setting. High-quality register data on redeemed antibiotics prescriptions are linked with survey data on whether, when, and how the clusters engaged with antibiotics as a quality improvement topic.	Maria Bundgaard Dorte Ejg Jarbøl Eskild Klausen Fredslund Jens Søndergaard Marius Brostrøm Kousgaard Sonja Wehberg Line Bjørnskov Pedersen
	Point-of-care testing	
A cluster-randomised trial of point-of-care PCR diagnostics of respiratory tract infections in general practice.	The scientific evaluation of the study comprises 3 parts: 1. Effectiveness study 2. Economic evaluation 3. Process evaluation	Kirubakaran Balasubramaniam Jens Søndergaard Jesper Bo Nielsen Trine Thilsing Sonja Wehberg Dorte Jarbøl Jesper Hallas Tina Lein Rasmussen Line Planck Kongstad Rikke Sand Andersen Elisabeth Hvidt Line Simonsen And others
	Out-of-hours primary care	
Use of C-reactive protein testing and help-seeking behaviour in out-of-hours primary care.	Investigate whether patients contact out-of-hours primary care more frequently if they have previously encountered a general practitioner with high use of C-reactive protein testing.	Jesper Lykkegaard Jonas Kanstrup Olsen Malene Plejdrup Hansen Claus Høstrup Vestergaard Linda Huibers
Antibiotic use in out-of-hours primary care: the influence of video consultations.	Investigate how use of video consultations in Danish out-of-hours primary care influences the antibiotic prescribing pattern.	Mette Amalie Nebjerg Malene Plejdrup Hansen Linda Huibers (Project group not fully established)
	European-funded projects	
HAPPY PATIENT (2021-2023)	Evaluate the impact of a multifaceted intervention for rational use of antibiotics to treat community-acquired infections in four different settings; general practice, out-of-hours, nursing homes and pharmacies. More information available at: https://happypatient.eu/	Jesper Lykkegaard Jonas Kanstrup Olsen Anders Munck Jens Søndergaard Jette Nygaard Jensen Lars Bjerrum Malene Plejdrup Hansen (Only Danish partners mentioned)
IMAGINE (2023-2025)	Systematise and enhance efforts to prevent infections, mainly urinary tract infections, and reduce antibiotic inappropriateness by implementing a multifaceted intervention targeting healthcare professionals in nursing homes. More information available at: https://imagineproject.eu/	Jesper Lykkegaard Jonas Kanstrup Olsen Anders Munck Jens Søndergaard Jette Nygaard Jensen Anna Marie Theut Valeria Antsupova Athina Chalkidou Lars Bjerrum Malene Plejdrup Hansen (Only Danish partners mentioned)

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