5

ANTIMICROBIAL CONSUMPTION IN HUMANS

5. Antimicrobial consumption in humans

Highlights

Total consumption. In 2019, total consumption of antimicrobial agents in humans in Denmark was 15.76 defined daily doses per 1000 inhabitants per day (DID). Within the last decade the consumption decreased with altogether 13.9% (18.31 DID in 2010); since the highest peak of 18.95 DID in 2011 the decreases have been continuous. From 2018 to 2019 decreases were 1.3% (15.97 DID in 2018). Decreases owe to reduced consumption in the primary sector and were observed for all municipalities and within all medical specialties that prescribe in primary health care. In 2019, primary health care accounted for 87% of all prescribed antimicrobials.

Consumption in primary health care. In 2019, the consumption in primary health care was 13.76 DID, a 17% reduction since 2010 (16.56 DID) and a 1.5% reduction since 2018. Most marked decreases within the decade were observed from 2011 to 2012 and from 2016 to 2018 and were due to a reduced number of prescriptions issued, measurable in total reductions as well as in reduced numbers of patients treated. Decreases were observed within all age groups and for both genders. Due to changes in the health system over time, the proportion of antimicrobial agents prescribed by hospital doctors but redeemed at community pharmacies increased from constituting 13.1% of the consumption in primary health care in 2015 to constituting 16.7% in 2019 (measured in DID).

Consumption in hospital care. In 2019, the consumption of antimicrobials at Danish hospitals was 1.93 DID. This corresponds to 107 DDD per 100 occupied bed-days (DBD), a 49% increase since 2010 (71.6 DBD) and a 6.2% increase since 2018 (100.7 DBD). Measured in DDD per 100 admissions (DAD), the consumption in 2019 (306 DAD) was 21.0% higher than in 2010 (253 DAD) and 3.4% higher than in 2018 (296 DAD).

Consumption of penicillins. In 2019, penicillins accounted for 65% of the consumption in primary health care and 54% of the consumption in hospital care. However, due to shifting trends in the usage of different penicillin drug classes, the consumption of beta-lactamase sensitive penicillins decreased from constituting 53% of all penicillins in primary health care in 2010 to constituting 38% in 2019. In hospital care, the consumption of all penicillins increased over the last decade. Most marked increases were in the consumption of beta-lactamase resistant penicillins (+112%) and combination of penicillins incl. beta-lactamase inhibitors (+259%).

National Action Plan. In primary health care, the number of redeemed prescriptions decreased from 462 to 382 prescriptions per 1000 inhabitants per year from 2016 to 2019 (goal 1: 350 presc/1000 inh/year by 2020). However, the proportion of beta-lactamase sensitive penicillins remained unchanged at 31% of total consumption (goal 2: 36% by 2020). The consumption of antimicrobials of special critical interest at hospitals decreased by 7.4% (from 20.77 DBD in 2016 to 19.24 DBD in 2019), (goal 3: 10% reduction by 2020).

5.1 Introduction

In Denmark, all consumption of human medicine is recorded through the Register of Medicinal Product Statistics at the Danish Health Data Authority. This includes sales data from all public and private healthcare providers. Antimicrobial sales data have been submitted from the primary sector since 1994, whereas the hospital sector has submitted data since 1997.

In Denmark, only medical doctors, veterinarians and dentists can prescribe antibiotics and sale is through publicly registered and approved pharmacies. All Danish medical doctors and dentists have the right to prescribe freely what they find appropriate for their patients. There are no restrictions regarding specific antimicrobial classes but prescribing is guided by national and/or local guidelines on prudent use issued through different medical specialties and through recommendations issued by the Danish Health Authority. Recording of the consumption in the primary sector is based on total sales from pharmacies to individuals or private clinics. For all sales, data contains information on the ATC code, formulation, package size and number of packages sold. For sales to individuals, additional information is available from the prescription registry; this includes an identifier of the prescriber and information on the age, gender and address of the patient. Since 2004, it also includes the indication for prescribing the medication. No over-the-counter sale takes place. This enables an almost complete surveillance of all systemic antimicrobials used in Denmark in the primary sector.

For the hospital sector, primarily data from public somatic hospitals with acute care function (referred to as somatic hospitals) is included in the report. Data from psychiatric hospitals, private hospitals and hospices have been excluded, since consumption at these facilities is minor. Furthermore, no reliable denominator for measuring the consumption in these patient populations exists. Figure 5.1a is the only figure in the report, that presents complete Danish consumption, collating data from all healthcare providers, both public and private sectors. The recent upgrade of The National Patient Register, implemented during 2019, has had a major impact on the calculations of the consumption of antibiotics at hospitals, partly because data has been frozen. For more detailed information on data reporting and registration, including hospital activity and bed-day definitions, please see chapter 9.8, materials and methods.

A political plan for the Danish health system from 2018 focuses on enforcement of the primary sector by moving time consuming functions from hospital ambulatory care to smaller health units, rehabilitation centers and GPs in the municipalities. This demands a restructuring and strengthening of collaboration between all sectors. It may affect monitoring systems, since bed-days become more difficult to measure when it comes to describing the actual activity at different parts of the health sector. Boundaries between primary and hospital sector become more fluent and hospital activity becomes harder to determine. It also challenges the comparison of consumption over time.

In January 2019, the WHO Collaborating Centre for Drug Statistics Methodology in Oslo introduced new DDD values for some of the commonly used antimicrobials. These changes were implemented in last years report (DANMAP 2018) and all numbers in the figures and tables were updated 10 years back. Due to new DDD values, figures in the present report are thus comparable only to figures and numbers in DANMAP 2018.

In 2017, Danish adjusted DDDs (DaDDD) were developed for monitoring hospital consumption data. For the 2018 report, new values were also developed for the primary sector. In 2019, consumption in both DDD and DaDDD were applied in two figures, for the primary sector and the hospital sector, respectively (Figure 5.5 and Figure 5.14). For more information regarding DaDDD, see Table 9.5 and 9.6 in chapter 9.8, materials and methods.

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

5.2 Total consumption (all public healthcare systems in Denmark)

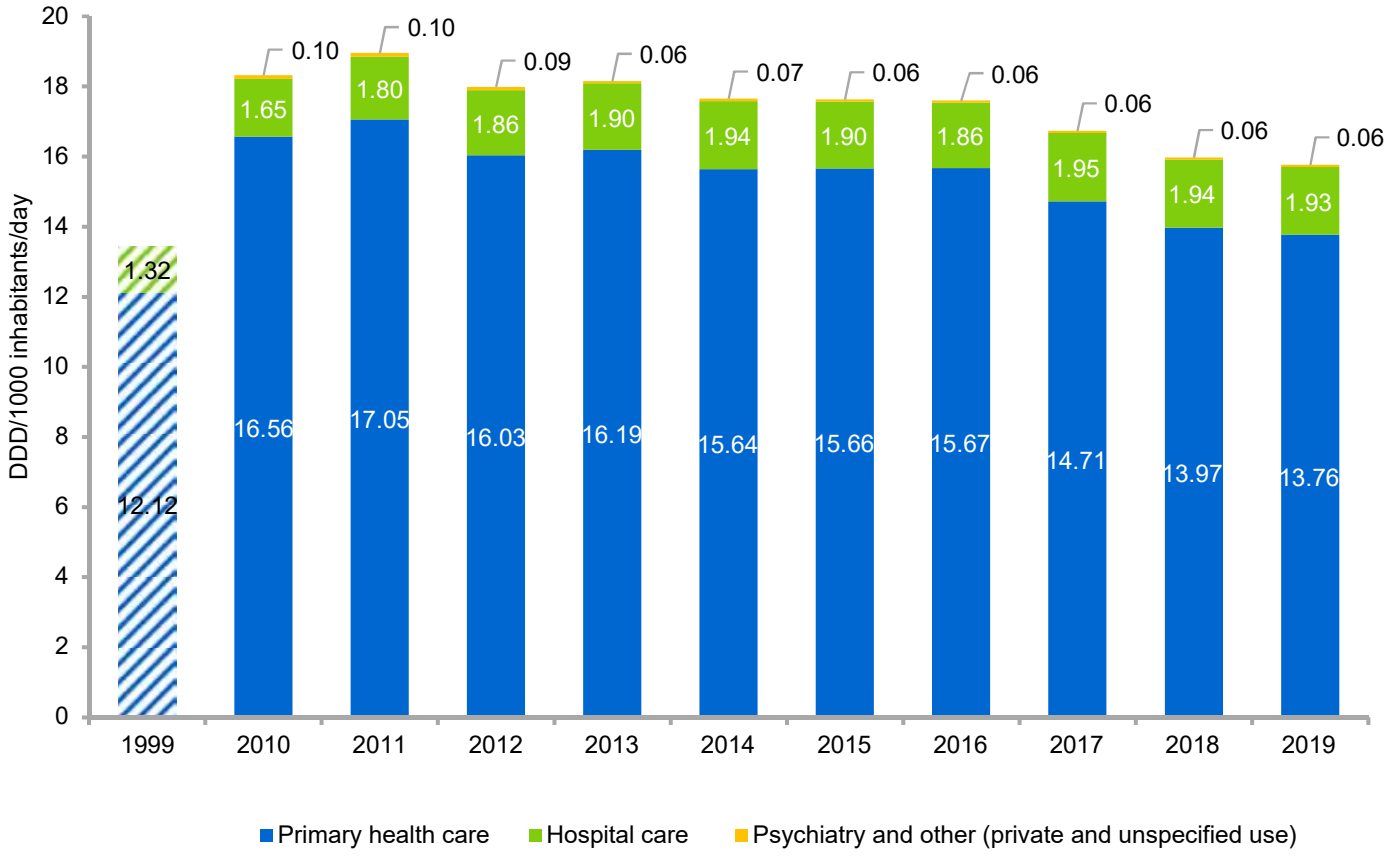
Historically, the consumption of antimicrobials in Denmark showed no significant trends during the first five years of systematic registration from 1996 to 2000, where consumption was estimated to be between 13.40 and 13.63 DDD per 1000 inhabitants per day (DID; based on former WHO DDD values and therefore not directly comparable to newer calculations). After these stabile years, steady increases were observed until 2011. Since then, the consumption has first levelled off and since decreased markedly.

In 2019, consumption of systemic used antimicrobials was 15.76 DID in total (all public and private healthcare systems), which is 1.3% less than the consumption in 2018 (15.97 DID) and 13.9% less than the consumption a decade ago in 2010 (18.31 DID), (Figure 5.1a). The primary sector accounted for 13.76 DID, the somatic hospital sector for 1.93 DID and psychiatry and private or unspecified use ("other") for 0.06 DID. The total consumption in 2019 corresponds to 49.183 kg active compound consumed (Table A5.1 in web annex).

Since 2011, a marked decrease was observed for the total consumption in Denmark. The decrease is driven by reduced prescribing in primary health care, which in 2019 accounted for 87% of all antimicrobials used in humans in Denmark. At hospitals, consumption did not change correspondingly, thus the proportion of antimicrobials used at hospitals has increased during the decade, (Figure 5.1b).

Figure 5.1a Total consumption of systematic antimicrobial agents in humans, DDD per 1000 inhabitants per day, Denmark

DANMAP 2019



Data for this figure is based on the total sales in Denmark
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

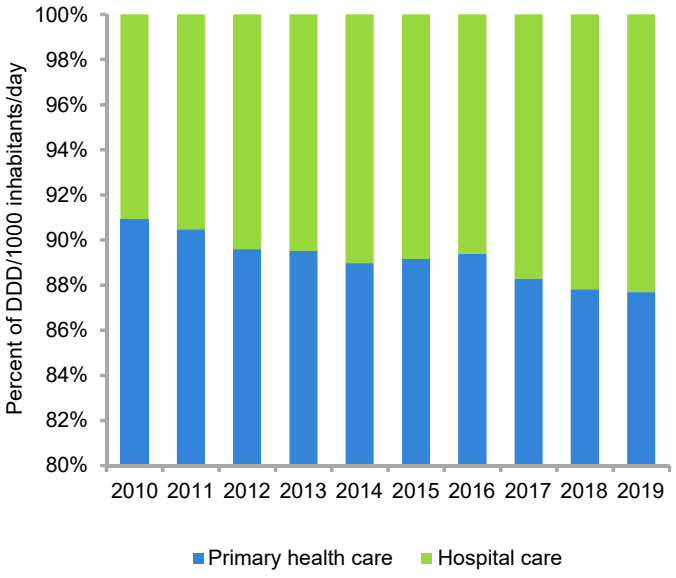
Consumption of the main antimicrobial drug classes by the primary sector and hospital sector, respectively, is presented in Figure 5.1c. Most notable are high use of beta-lactams in both health sectors and exclusive use of cephalosporines at hospitals.

Consumption of antimicrobials in primary care and somatic hospitals in the five regions is presented in Figure 5.2. Although consumption per inhabitant differs between the regions, for all five regions marked decreases were observed in the primary sector since 2016, more pronounced in the first years and less marked in 2019. The two neighbouring regions, the Capital Region and the Region Zealand showed highest total consumptions of 15.77 DID and 16.20 DID, respectively, the Capital Region due to a relatively high consumption at hospitals, and the Region Zealand due to a comparably high consumption in primary care. The Central and Northern Region had the lowest total consumption with 14.02 DID and 14.71 DID, respectively. They were similar in an overall low consumption in both primary and hospital care.

For more information on population size and hospital activity in the five health regions, see Figure 3.2 and Table 5.7.

Figure 5.1b Changes in distribution of total consumption of antimicrobials, % of DDD per 1000 inhabitants per day, Denmark

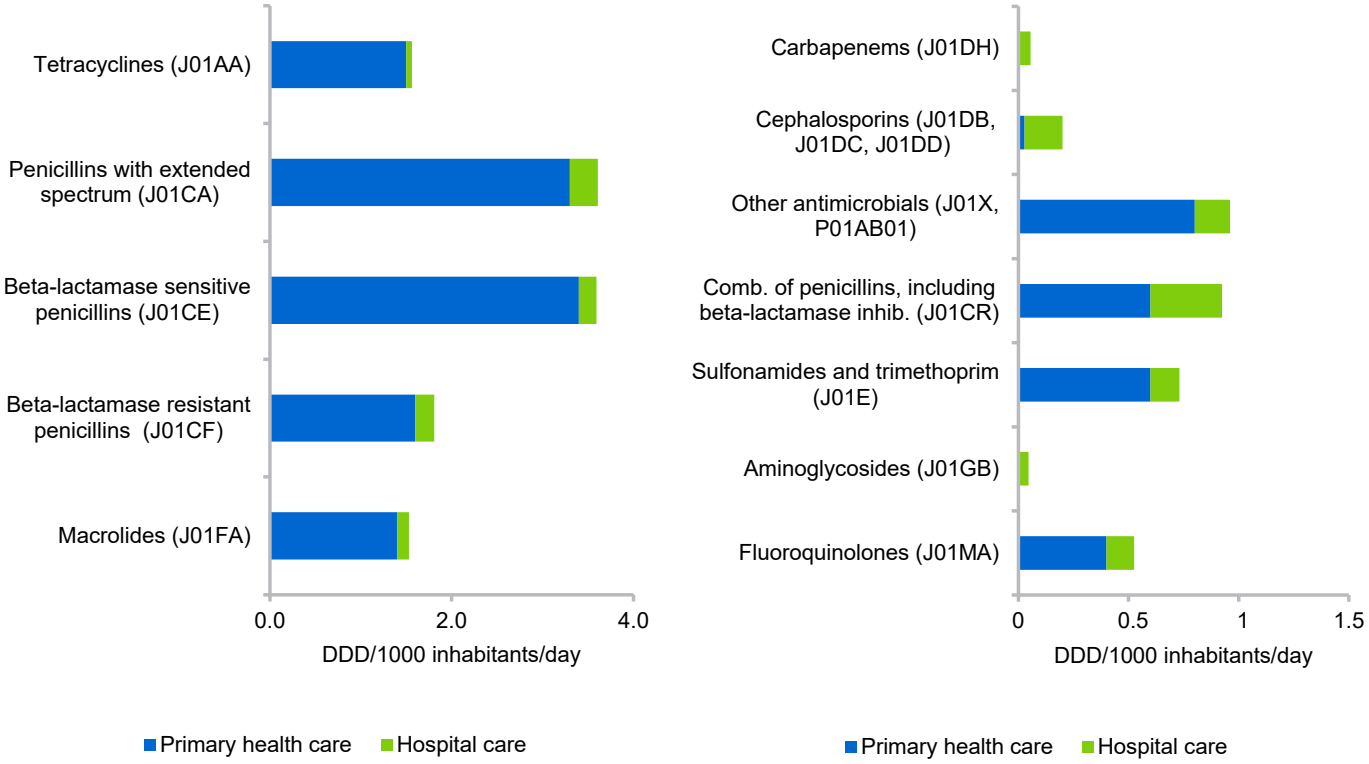
DANMAP 2019



Note: y-axis starts at 80%
Data for this figure is based on the total sales in Denmark
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.1c Distribution of main antimicrobial classes used for humans in primary and hospital care, DDD per 1000 inhabitants per day, Denmark

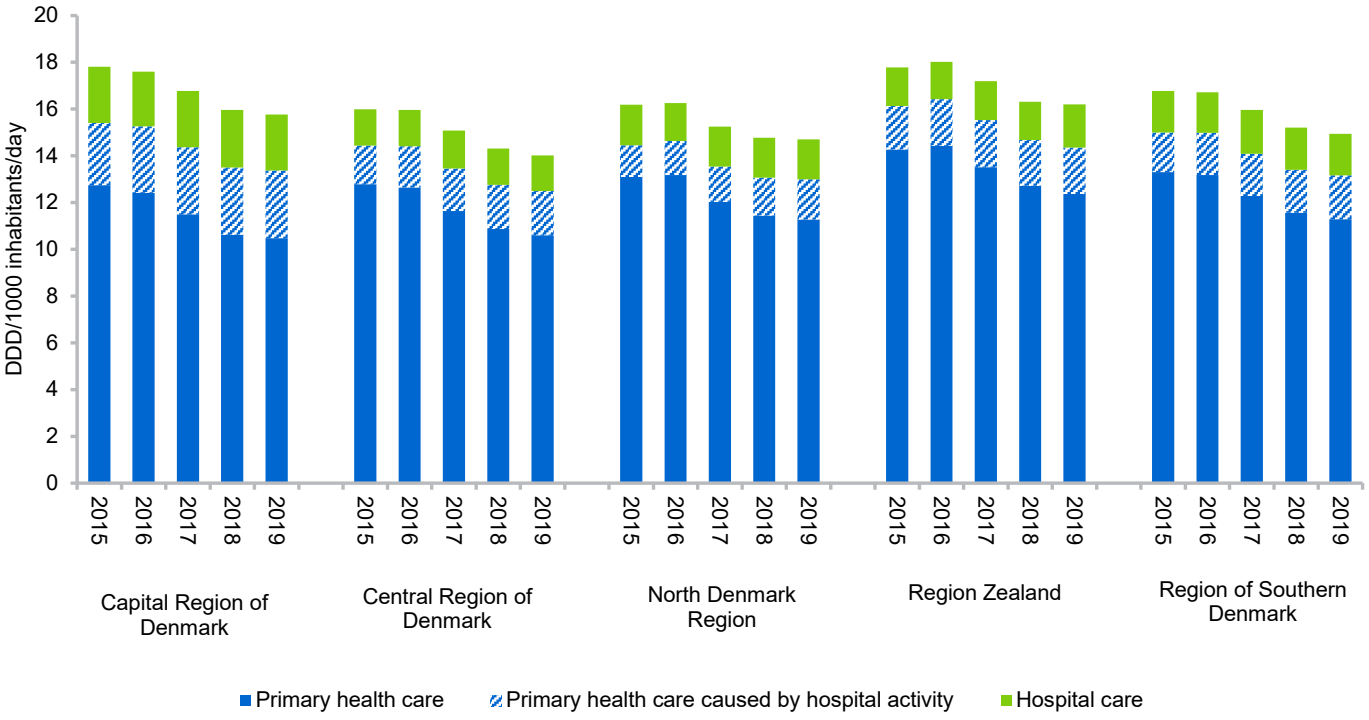
DANMAP 2019



Data used in this figure is based on registered sales to individuals and consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.2 Consumption of systemic antimicrobial agents in Danish regions (primary care and at somatic hospitals), DDD per 1000 inhabitants per day, Denmark

DANMAP 2019



Data used in this figure is based on registered sales to individuals and consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.3 Primary health care

5.3.1 Total consumption in primary health care in DID

In 2019, the consumption of antimicrobials in primary health care based on total sales from pharmacies was 13.76 DID, a decline of 1.5% from 2018 (13.97 DID), levelling off from the significant declines observed in previous years (-6.1% in 2017 and -5.1% in 2018). Compared to the peak of 17.05 DID in 2011, consumption in 2019 had changed by -19% (Figure 5.1a). Within the decade, decreases were overall 17% from 16.56 DID in 2010.

Beta-lactamase sensitive penicillins continued to be the biggest group consumed with 3.44 DID (accounting for 25% of the total consumption in primary care, Figure 5.3). Penicillins with extended spectrum accounted for 3.28 DID (24%), beta-lactamase resistant penicillins for 1.63 DID (12%), tetracyclines for 1.48 DID (11%) and macrolides for 1.41 DID (10%), (Figure 5.3 and Table 5.1). A decade ago, in 2010, beta-lactamase sensitive penicillins accounted for 32%, penicillins with extended spectrum for 18%, beta-lactamase resistant penicillins for only 7%, while macrolides accounted for 15% (not shown). For most other antimicrobial groups, their share of the total consumption did not change notably.

5.3.2 Trends in consumption of the leading antimicrobials in DID

Antimicrobial consumption in Denmark increased almost continuously from the beginning of registration in the 90ties until the peak of consumption measured for primary care in 2011. The decreases observed since 2011 were primarily driven by decreased consumption of beta-lactamase sensitive penicillins, the dominating antimicrobial class in Denmark, and macrolides, for many years the third biggest antimicrobial class in Denmark (Figure 5.4). Continued decreases since 2011 were also observed for fluoroquinolones. Simultaneously, the consumption of beta-lactamase resistant penicillins increased since 2010.

In 2019, beta-lactamase sensitive penicillins had decreased by -35% (from 5.29 DID in 2011), macrolides by -46% (from 2.60 DID in 2011) and fluoroquinolones by -35% (0.57 DID in 2011), while beta-lactamase resistant penicillins had increased by 39% (1.17 DID in 2010).

For the penicillins with extended spectrum consumption increased during the first years of the decade, from 3.02 DID in 2010 to 3.36 DID in 2017 (11%), but since then levelled off.

Combination penicillins increased continuously from their introduction to the Danish market in 2009 until 2015 (0.95 DID), showed no changes for 2016 and since declined, in 2019 accounting for 0.63 DID (-34% since 2015 and -4.2% from 0.66 DID in 2018).

Table 5.1 Consumption of antimicrobial agents for systemic use in primary health care (DDD per 1000 inhabitants per day), Denmark DANMAP 2019

ATC group	Therapeutic group	Year										
		2000	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01AA	Tetracyclines	0.99	1.70	1.74	1.76	1.96	1.66	1.60	1.62	1.42	1.40	1.48
J01CA	Penicillins with extended spectrum	1.98	3.02	3.11	3.03	3.12	3.20	3.28	3.33	3.36	3.35	3.28
J01CE	Beta-lactamase sensitive penicillins	4.76	5.26	5.29	4.68	4.65	4.38	4.33	4.16	3.88	3.61	3.44
J01CF	Beta-lactamase resistant penicillins	0.53	1.17	1.22	1.21	1.30	1.36	1.38	1.48	1.56	1.60	1.63
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.02	0.45	0.60	0.70	0.81	0.87	0.95	0.95	0.79	0.66	0.63
J01D	Cephalosporins and other betalactam antibiotics	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
J01EA	Trimethoprim and derivates	0.33	0.51	0.50	0.52	0.53	0.55	0.56	0.56	0.56	0.53	0.45
J01EB	Short-acting sulfonamides	0.37	0.26	0.24	0.22	0.22	0.21	0.18	0.16	0.15	0.14	0.13
J01EE	Combination of sulfonamides and trimethoprim, including derivates	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
J01FA	Macrolides	2.04	2.44	2.60	2.20	1.94	1.79	1.77	1.82	1.62	1.46	1.41
J01FF	Lincosamides	0.01	0.04	0.04	0.04	0.05	0.05	0.05	0.06	0.06	0.06	0.06
J01GB	Aminoglycosides	0.00	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluroquinolones	0.15	0.57	0.57	0.55	0.52	0.50	0.49	0.48	0.44	0.41	0.37
J01XC	Steroid antibacterials (combination fusidic acid)	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00	0.00
J01XE	Nitrofuran derivates (nitrofurantoin)	0.38	0.51	0.50	0.50	0.49	0.48	0.45	0.43	0.26	0.15	0.27
J01XX	Other antibacerials (metheamine >99%)	0.37	0.27	0.26	0.25	0.24	0.24	0.25	0.27	0.28	0.29	0.32
J01XD and P01AB01	Nitroimidazole derivates (metronidazole)	0.16	0.27	0.28	0.28	0.28	0.28	0.28	0.28	0.25	0.24	0.24
J01 and P01AB01	Antibacterial agents for systemic use (total)	12.18	16.56	17.05	16.03	16.19	15.64	15.66	15.67	14.71	13.97	13.76

ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Data used for this table is based on total sales in Denmark (individuals and clinics)

Fluoroquinolones represent the smallest antimicrobial drug class among the leading antimicrobial groups in Denmark. Together with the cephalosporines and carbapenems, they belong to the three antibiotic classes in focus in the guidelines on antibiotic use by the Danish Health Authorities from 2012 [www.sst.dk]. They are solely to be used for treatment of very few specific infections, where they are considered the drug of choice. They are also recommended in the case of infection with multidrug-resistant bacteria, where microbiological results point towards a fluoroquinolone to be the best or only choice. The decreasing trends observed for the consumption of fluoroquinolones during the decade follow the overall decreasing trends. Thus, in 2019, fluoroquinolones continued to account for approximately 3% of all antimicrobials consumed in primary care (Figure 5.3 and Figure 5.4). For more details about use of Fluoroquinolones in primary health care, see Figure A5.6 and A5.7 in web annex.

Changes in consumption within the last decade clearly follow different initiatives on a more prudent use of antibiotics, which have been implemented since 2011 due to concerns regarding the continuing increases over the former decades. Mentioned should be the establishment of the National Antibiotic Council in 2012, `happy audit´ and other initiatives on better diagnostics undertaken by general practitioners in recent years, evaluation and harmonization of antibiotic guidelines issued by the different medical associations as well as antibiotic campaigns aimed at the public launched since 2013.

Penicillins

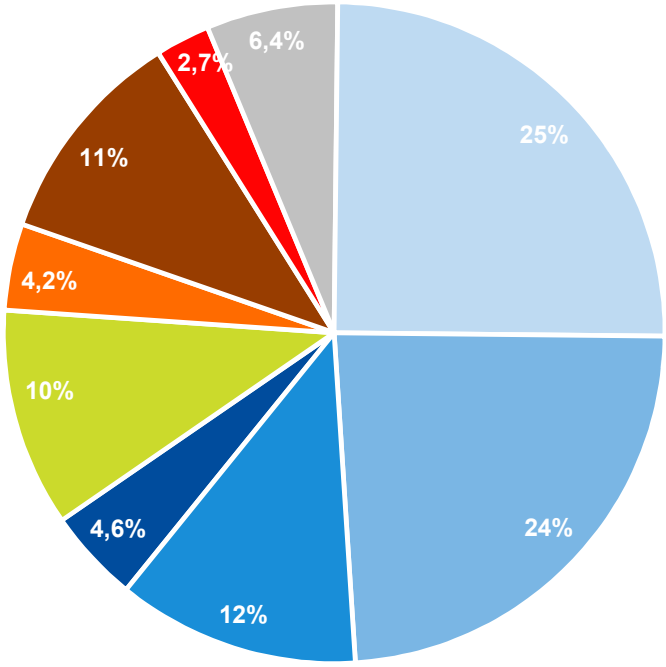
In Denmark, penicillins are the only beta-lactams used in primary health care; other beta-lactams such as cephalosporins, monobactams and carbapenems are solely used in hospital care and primarily at somatic hospitals with surgical or acute care functions.

In 2019, the four groups of penicillins accounted for altogether 8.98 DID, 65% of all antimicrobials consumed; a decade ago in 2010, they accounted for 9.91 DID, 60% of the total antimicrobials consumed that year. However, due to the described continuous decreases in the use of beta-lactamase sensitive penicillins and simultaneous increases in the penicillins with extended spectrum and the beta-lactamase resistant penicillins, in 2019 beta-lactamase sensitive penicillins constituted 38% of all penicillins used, while ten years back, in 2010, the share was 53% (Figure A5.5 in web annex).

The increases described for the penicillins with extended spectrum are primarily due to increases in the consumption of pivmecillinam, in 2019 accounting for approximately 75% of this antimicrobial class, (Figure 5.5a). Over the decade pivmecillinam increased with 45% from 1.67 DID in 2010 to 2.43 DID in 2019. Pivampicillin decreased simultaneously with 67% from 0.40 DID to 0.13 DID and amoxicillin decreased with 25% from 0.92 DID to 0.69 DID, respectively. Consumption of amoxicillin fluctuated within the decade, decreasing from 2009 to 2016 (0.61 DID) and increasing the recent two years, 9% (from 0.63 DID in 2017). Increases in the use of pivmecillinam were related to changed recommendations for the treatment of urinary tract infections (see 5.3.4), while the decreased use of pivampicillin followed increased resistance towards ampicillin in *E. coli* (see 8.2.1.) and use of amoxicillin followed recommendations regarding use of less antimicrobials in young children.

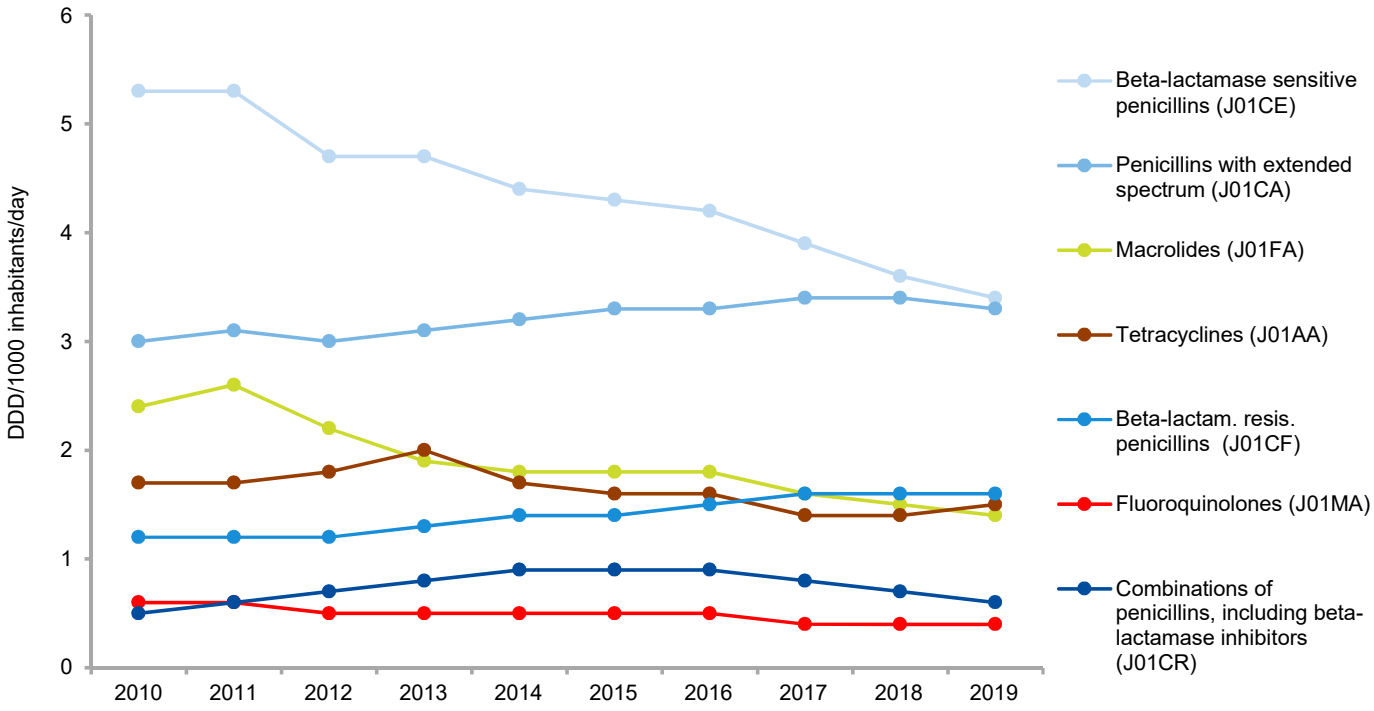
The increased consumption of beta-lactamase resistant penicillins was paralleled by an increased use at hospitals as well and followed the increased occurrence of staphylococcal infections observed in recent years (see section 8.1.3 and 8.3.8).

Figure 5.3 Distribution of antimicrobial groups within the total consumption in primary healthcare based on DDD, Denmark
DANMAP 2019



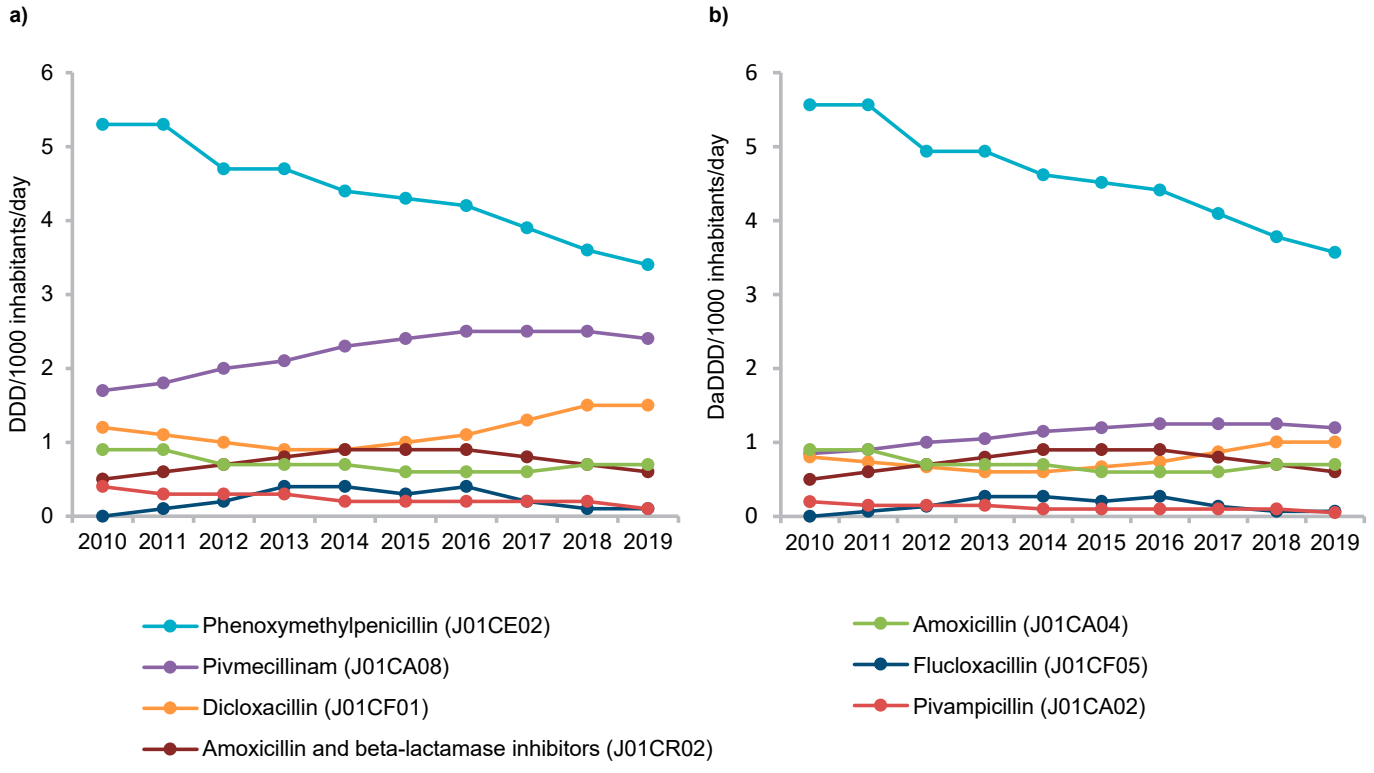
Data used for this figure is based on total sales in Denmark (individuals and clinics)
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.4 Consumption of leading antimicrobial groups for systemic use in primary health care, DDD per 1000 inhabitants per day, Denmark
DANMAP 2019



Data used for this figure is based on total sales in Denmark (individuals and clinics)
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.5 Consumption of main penicillins in the primary health care: a) DDD per 1000 inhabitants per day and b) DaDDD per 1000 inhabitants per day, Denmark
DANMAP 2019



Data used for this figure is based on total sales in Denmark (individuals and clinics)
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

The new WHO DDD values from January 2019 applied to amoxicillin and amoxicillin with clavulanic acid changed the records of these notably and their share of the total consumption, when calculated in DID. Since there were no changes in DDD values for the other main penicillins, their charts did not change correspondingly. This initiated the development of the Danish adjusted DDD (DaDDD) for all main penicillins, (Figure 5.5b), based on dosage recommendations from Danish treatment guidelines. Recommended dosages were then compared and adjusted in relation to the average doses actually given per treated patient, an information that was available through the data reported from the pharmacies each year. It is advisable to continue discussing the necessity of changing the DDD for the remaining penicillins not included in the revised DDD values, for a more true and fair reporting of antimicrobial consumption in the future. Consumption based on standard WHO DDD and DaDDD is presented in Figure 5.5a and b, respectively.

5.3.3 Measures at user level

In this and the following sections, the consumption of antimicrobials is described at user level by using either the number of prescriptions per 1000 inhabitants or the number of treated patients per 1000 inhabitants. The measures are thus based on all information available through the sales to individuals and do not include the approximately 4% of antibiotics, mainly penicillins, sold to clinics, dentists and doctors on call.

In 2019, the total number of prescriptions was 445 per 1000 inhabitants, a 3.2% reduction from the 459 prescriptions per 1000 inhabitants in 2018 and a 29% reduction compared to the 629 prescriptions per 1000 inhabitants in 2010 (Table 5.2). Decreases were observed for all antimicrobial drug classes apart from the tetracyclines and the group of "Other antibacterials", which increased from 2018 to 2019.

In 2019, the average number of prescriptions redeemed per patient was 1.90 and the total number of patients treated was 234 per 1000 inhabitants, (Table 5.3). In 2010, the number was 1.97 prescriptions per patient and 319 treated patients per 1000 inhabitants (not shown).

Trends in the number of prescriptions redeemed and the number of treated patients per 1000 inhabitants followed mainly the trends already described for the consumed DIDs. Within the last decade the most pronounced increase in the number of prescriptions per 1000 inhabitants was observed for the combination penicillins, including betalactamase inhibitors (40%). Most pronounced decreases in the number of prescriptions per 1000 inhabitants were observed for the folllowing: macrolides (-48%), beta-lactamase sensitive penicillins (-39%), sulphonamides and trimethoprim (-41%), tetracyclines (-33%) and fluoroquinolones (-41%), (Table 5.2).

Similar decreases were noted for the decade, when measured in the number of patients treated per 1000 inhabitants: macrolides (-47%), beta-lactamase sensitive penicillins (-36%), sulphonamides and trimethoprim (-43%), tetracyclines (-25%) and fluoroquinolones (-42%), (Table 5.3).

A comparison of the different indicators of consumption is presented in Figure 5.6. In 2019, the average DDD/prescription was 10.9, an increase of 2% compared to the 10.7 DDD/prescription in 2018, and an increase of 17% compared to the 9.3 in 2010.

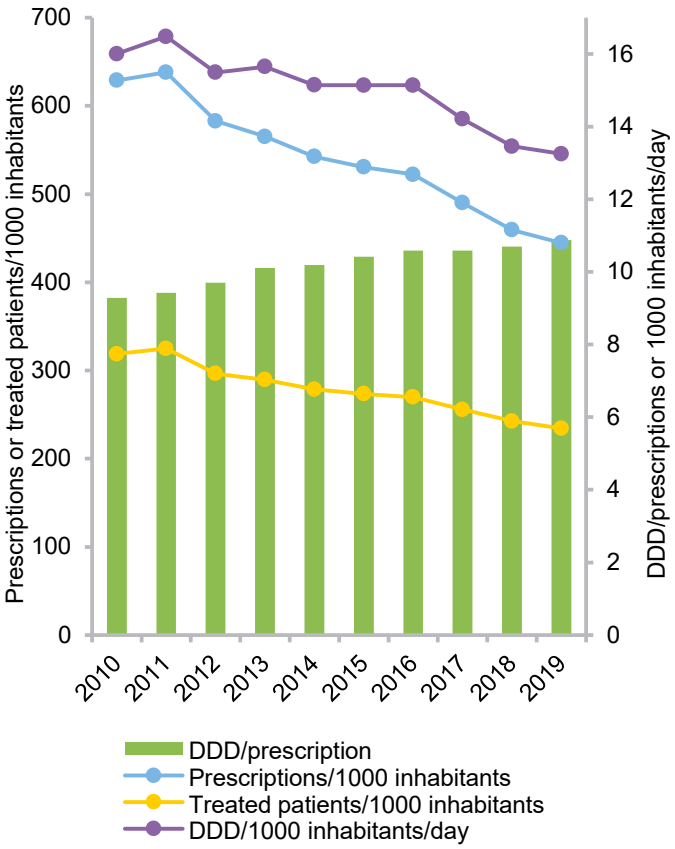
Table 5.2 Number of prescriptions per 1000 inhabitants for leading antimicrobial agents in primary health care, Denmark DANMAP 2019

ATC group	Therapeutic group	Year										
		2000	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01AA	Tetracyclines	19.37	22.49	22.70	22.56	22.89	20.00	17.90	17.18	15.89	14.63	15.11
J01CA	Penicillins with extended spectrum	93.45	127.23	125.17	115.91	114.30	113.83	113.53	113.16	114.37	114.31	112.19
J01CE	Beta-lactamase sensitive penicillins	222.09	212.19	213.32	186.91	180.55	170.70	163.09	157.13	148.52	136.81	128.77
J01CF	Beta-lactamase resistant penicillins	22.13	42.32	42.75	40.42	41.25	41.04	40.81	41.87	41.87	43.35	43.16
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.91	16.53	21.11	24.71	28.01	29.02	30.73	31.13	27.09	23.71	23.07
J01E	Sulphonamides and trimethoprim	53.20	47.35	45.05	43.86	43.53	41.51	38.39	36.41	34.29	31.74	28.14
J01FA	Macrolides	88.04	97.34	104.22	85.89	74.51	68.01	68.00	68.85	60.00	52.64	50.71
J01MA	Fluoroquinolones	8.89	23.69	23.15	22.14	20.65	19.67	19.50	18.74	17.37	15.97	13.99
J01X	Other antibacterials (methenamine >99%)	13.02	17.49	18.24	18.03	17.41	16.73	16.28	15.82	10.18	6.76	10.29
P01AB01	Nitroimidazole derivatives (metronidazole)	12.89	19.67	19.69	19.68	19.26	19.06	19.15	18.63	17.26	16.31	15.78
J01 and P01AB01	Antibacterial agents for systemic use (total)	534.87	628.78	638.08	582.80	565.26	542.53	530.56	522.19	490.08	459.39	444.54

ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Data used in this table is based on registered sales to individuals

Figure 5.6 Different indicators of antimicrobial consumption (J01 and P01AB01), in primary health care, Denmark

DANMAP 2019



Data used for this figure is based on registred sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.3.4 Prescribing activity in primary healthcare

Although Denmark has a very homogenous population with relatively small geographic and socioeconomic variations compared to other countries, considerable differences in the prescribing habits among medical doctors are frequently observed. In 2019, the Central Denmark Region had the lowest prescribing activity when compared to the other four regions, with 12.50 DID and 417 prescriptions per 1000 inhabitants per year, (Table 5.4). The Region Zealand had the highest prescribing activity with 14.36 DID and 482 prescriptions per 1000 inhabitants per year. For all regions, significant decreases in the DIDs and number of prescriptions redeemed were observed for the five years presented (on average 12% in DID and 16% in the number of prescriptions per 1000 inhabitants per year).

There may be several reasons to the differences in the number of prescriptions redeemed, e.g. variations in the density of the population and number of general practitioners as well as the proportion of elderly or chronically ill in a given geographic area. Due to differing organisation of general practitioners and clinical practices across the country, comparison of prescribing habits based on the individual clinical praxis is difficult. A clinical praxis can be based on a single physician but can also be a collaboration of up to seven physicians sharing facilities and staff. In addition, due to the lack of general practitioners in some areas, several new models of "health houses" served by physicians and other health staff are being established these years. General practitioners can follow their own prescription habits through the website www.ordiprax.dk, a closed IT system that collects all data on prescriptions and enables comparison with other praxis´ on a regional level.

Table 5.3 Number of treated patients per 1000 inhabitants for leading antimicrobial agents in primary health care, Denmark DANMAP 2019

ATC group	Therapeutic group	Year										
		2000	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01AA	Tetracyclines	12.04	13.44	13.66	13.53	13.86	12.20	11.32	11.04	10.35	9.69	10.10
J01CA	Penicillins with extended spectrum	65.78	85.04	84.19	77.31	76.10	75.32	74.87	74.05	74.04	73.56	71.97
J01CE	Beta-lactamase sensitive penicillins	169.32	162.81	164.34	145.53	142.19	134.79	130.06	125.69	119.32	110.90	104.70
J01CF	Beta-lactamase resistant penicillins	15.65	30.02	30.34	28.51	29.07	29.24	28.85	29.70	29.96	31.10	31.06
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.63	11.70	14.95	17.32	19.71	20.52	22.03	22.17	19.89	17.73	17.33
J01E	Sulphonamides and trimethoprim	36.51	29.31	27.63	26.48	26.16	24.65	22.45	21.17	19.87	18.42	16.63
J01FA	Macrolides	65.72	72.67	78.75	64.73	56.16	51.38	51.75	53.21	46.01	40.11	38.45
J01MA	Fluoroquinolones	7.00	18.45	18.10	17.25	16.04	15.30	15.04	14.37	13.36	12.26	10.74
J01X	Other antibacterials (methenamine >99%)	6.84	7.53	7.74	7.54	7.48	7.16	7.35	7.47	5.01	3.62	5.66
P01AB01	Nitroimidazole derivatives (metronidazole)	11.21	16.73	16.90	16.86	16.51	16.31	16.47	16.03	14.84	14.05	13.57
J01 and P01AB01	Antibacterial agents for systemic use (total)	295.78	318.69	324.91	296.40	289.54	278.62	273.49	269.72	255.72	242.55	234.34

ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Data used in this table is based on registered sales to individuals

Support of the general practitioners regarding their prescribing habits is in general provided through regional medicine consultants, who also have access to Ordiprax on clinic level, thus being able to monitor consumption and give individual advice. From 2018, the general practitioners in defined geographical areas have been joined in "quality clusters" for mutual support.

In Figure 5.7a and b, the number of prescriptions on municipality level are shown for years 2016 and 2019, respectively. For 2019, the numbers span from 366 to 603 prescriptions per 1000 inhabitants, most municipalities laying within the range of 400 to 500 prescriptions per 1000 inhabitants. Three years earlier, in 2016, the corresponding interval was 434-727 prescriptions per 1000 inhabitants. From the 98 municipalities in Denmark, four were excluded from the figure due to very small populations (typically islands).

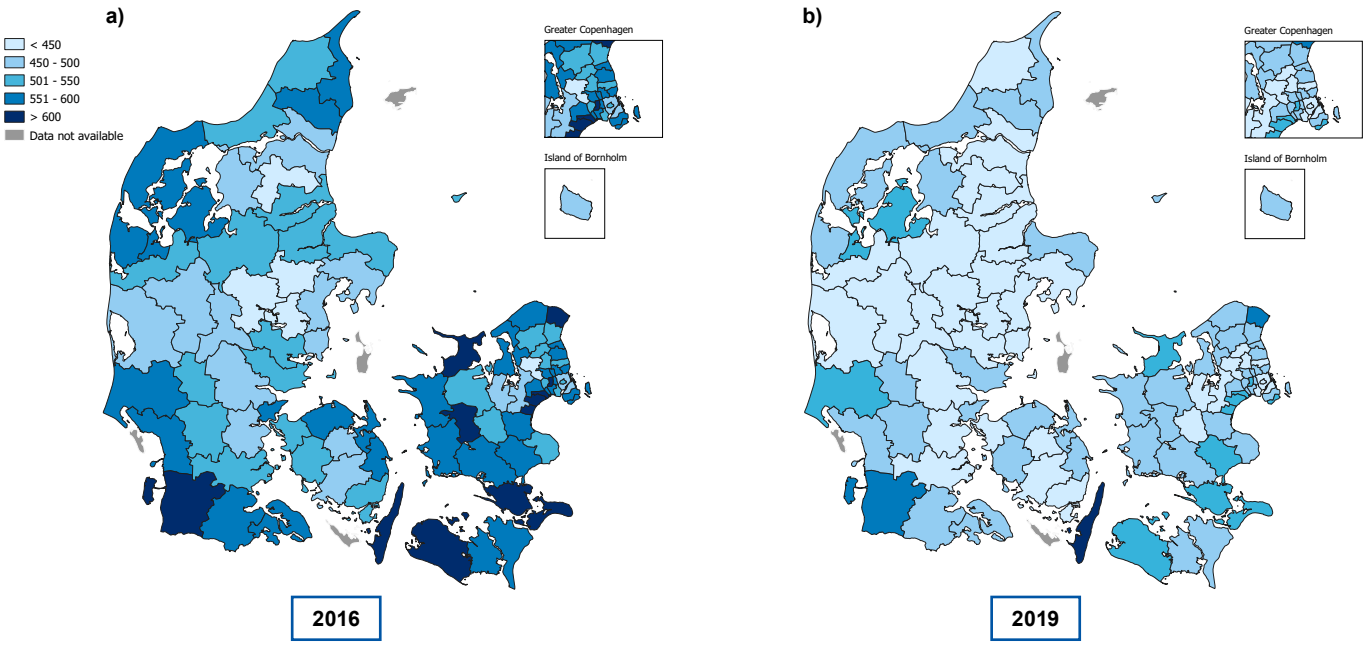
Prescribing habits of doctors with different specialties differ, e.g. in 2019, 63% of antimicrobial prescriptions from specialists in dermato-venerology were for tetracyclines, which is used to treat severe acne, while 58% of prescriptions issued by dentists were for beta-lactamase sensitive penicillins. An overview of the numbers of prescriptions issued by the different specialties can be found in Table 5.5 and Figure 5.8.

Table 5.4 Consumption of antimicrobial agents for systemic use in primary health care at regional level, Denmark DANMAP 2019

Region	Indicator	Year				
		2015	2016	2017	2018	2019
Capital Region	DDD/1000 inhabitants/day	15.40	15.26	14.36	13.50	13.38
	Prescriptions/1000 inhabitants	533.22	519.10	489.47	453.39	441.36
Region Zealand	DDD/1000 inhabitants/day	16.13	16.43	15.53	14.68	14.36
	Prescriptions/1000 inhabitants	575.14	574.86	539.02	501.32	481.81
Region of Southern Denmark	DDD/1000 inhabitants/day	14.99	14.98	14.09	13.40	13.16
	Prescriptions/1000 inhabitants	539.98	530.16	496.75	470.50	454.94
Central Denmark Region	DDD/1000 inhabitants/day	14.44	14.41	13.46	12.76	12.50
	Prescriptions/1000 inhabitants	494.17	487.24	458.31	430.90	417.31
North Denmark Region	DDD/1000 inhabitants/day	14.45	14.64	13.54	13.07	13.00
	Prescriptions/1000 inhabitants	510.13	509.05	472.15	451.55	435.96
Denmark (total)	DDD/1000 inhabitants/day	15.14	15.14	14.21	13.46	13.25
	Prescriptions/1000 inhabitants	530.56	522.19	490.08	459.39	444.54

Data used in this table is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.7 Number of prescriptions from primary healthcare per 1000 inhabitants in Danish municipalities in a) 2016 and b) 2019
DANMAP 2019



Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

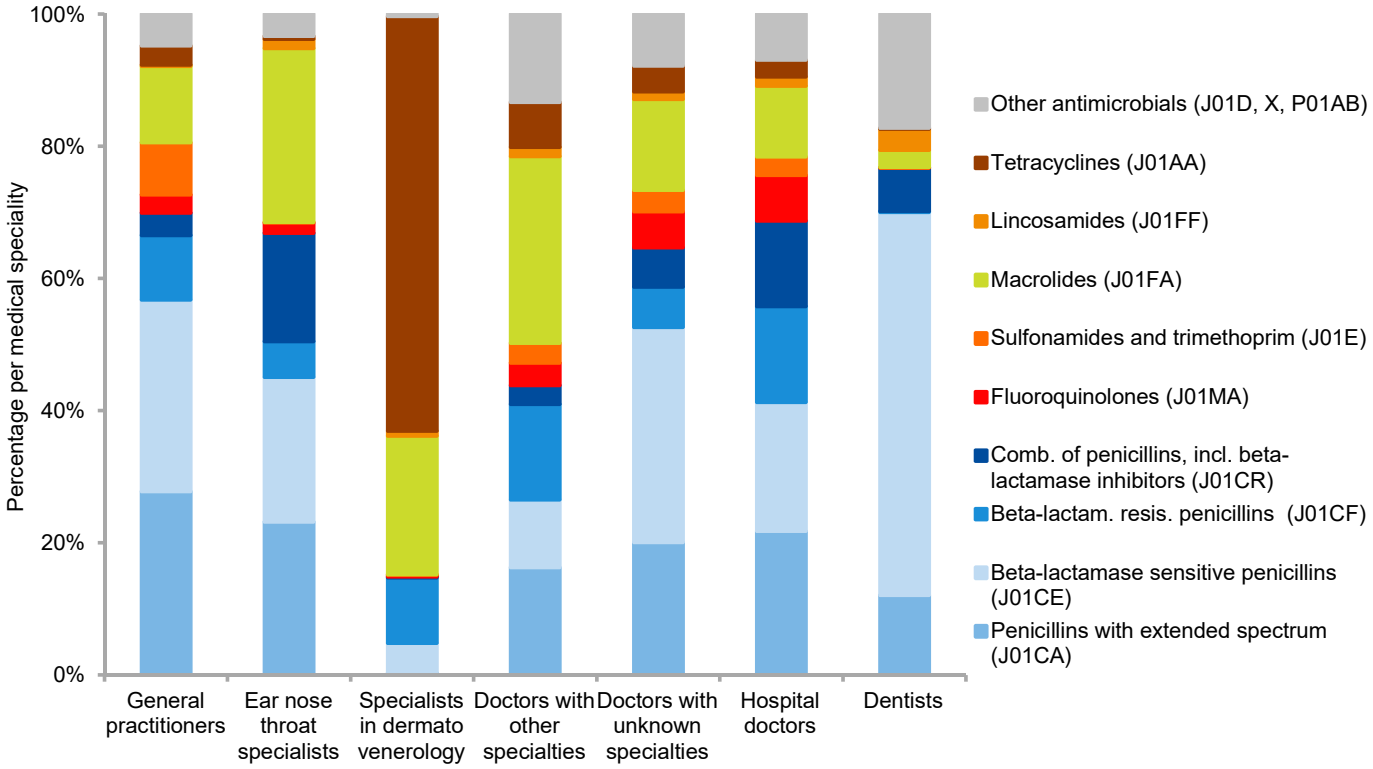
Consumption in primary sector includes prescriptions issued from hospital doctors upon discharge of a patient. In the past decade, the number of prescriptions issued through hospital doctors increased notably, probably due to changes in hospital work flow with shortening of bed-days and increasing activity in ambulatory care. In 2019, hospital doctors accounted for 63 prescriptions per 1000 inhabitants (14% of the antimicrobials sold at pharmacies), (Table 5.5). In 2008, it was 38 prescriptions per 1000 inhabitants (corresponding to 6% of sales), (not shown).

Table 5.5 Number of prescriptions per 1000 inhabitants for different doctor types DANMAP 2019

Doctor type	Year		
	2017	2018	2019
General practitioners	368.6	341.5	326.8
Ear nose throat specialists	8.9	8.4	7.8
Specialists in dermato venerology	5.9	5.2	5.4
Doctors with other specialties	4.3	4.2	4.2
Doctors with unknown specialties	10.9	9.7	8.7
Hospital doctors	62.6	62.8	63.0
Dentists	29.1	27.8	28.8

Data used for this table are based on registered sales to individuals

Figure 5.8 Prescribing habits presented as percentage of prescriptions by main medical specialties, primary sector, Denmark
DANMAP 2019



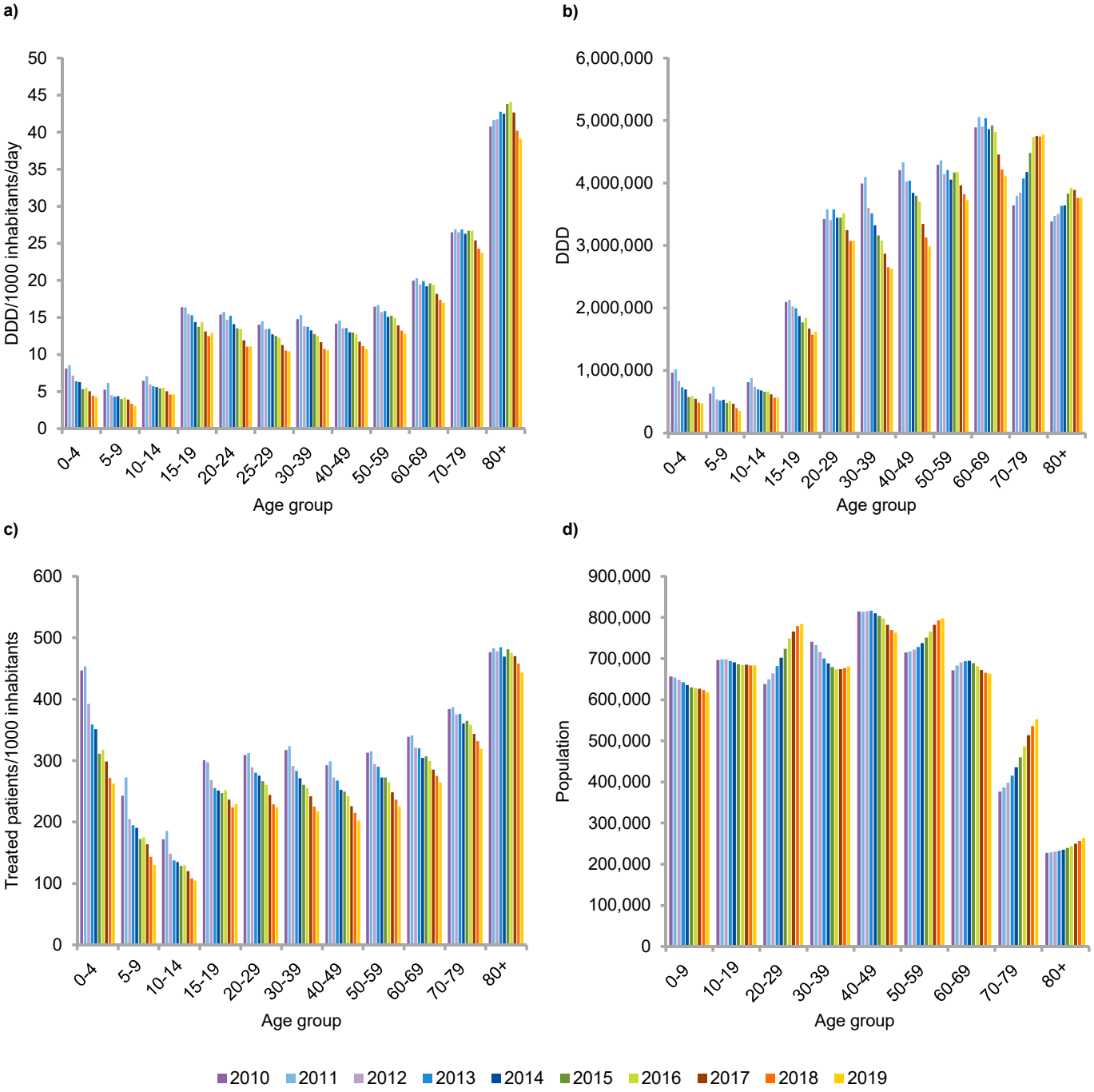
Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.3.5 Consumption by age group

Initiatives aiming at reducing overuse and misuse of antibiotics often focus on consumption in the youngest and the elderly. But inappropriate use is not restricted to overtreating children with fever conditions or elderly with unspecific urinary symptoms, also other age groups may be over- or undertreated.

Figure 5.9 presents consumption in the different age groups based on different denominators: Figure 5.9a presents consumption in DDD per 1000 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 1000 inhabitants and 5.6d presents the actual population sizes. All figures show data from 2010 to 2019. For children, WHO DDD values were used, although dosages given to children are based on body weight and therefore not directly comparable to adults. Children and adolescents are also presented in age groups of five years, while all others are clustered in 10-years age groups.

Figure 5.9a to d Consumption of antimicrobials and population per age group, DDD per 1000 inhabitants per day, DDD, number of treated patients per 1000 inhabitants and population size, clustered in five and ten years intervals DANMAP 2019



Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Population size in Figur 5.9d is based on data from Statistics Denmark at www.dst.dk

5.3.6 Consumption of antimicrobials in children

Measuring the consumption of antimicrobial agents in children in defined daily doses (DDD) is problematic, 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, in the youngest age groups children of the same age might be treated with different doses, since the dose is calculated based on body weight. Other parameters for measurement of consumption might be more suitable for children, e.g. number of treated patients per 1000 inhabitants and number of prescriptions per 1000 inhabitants. However, assuming that dosage regimens did not change considerably within the last decade, it is possible to compare the consumption in DDD within each age group over time.

In 2019, the overall consumption in children of 0-19 years was 181 treated patients per 1000 inhabitants receiving in total 287 prescriptions per 1000 inhabitants. Since 2010, the consumption decreased from 289 treated patients per 1000 inhabitants (-37%) and 510 prescriptions per 1000 inhabitants (-44%). In 2018, the corresponding numbers were 185 treated patients and 293 prescriptions per 1000 inhabitants (-2.4% and -1.9%, respectively).

Consumption in the 0-4 year olds. Consumption of antimicrobial agents in the youngest age group decreased with 41% from 2010 (447 treated patients per 1000 inhabitants) to 2019 (262 treated patients per 1000 inhabitants). Since 2018, the consumption decreased with 3.4% (272 treated patients per 1000 inhabitants), (Figure 5.10). On average, each treated patient received 2.00 prescriptions in 2010, which decreased to 1.66 prescriptions in 2019, (not shown). In 2019, the total consumption corresponded to 4.27 DID, 47% less than in 2010 (8.10 DID), (Figure 5.9a). The prescription tendency changed also during the last decade. In 2010, penicillins with extended spectrum were the main antimicrobial agents used to treat children between 0-4 years (274 patients per 1000 inhabitants, 61% of total consumption). In 2019, beta-lactamase sensitive penicillins were the most prescribed (141 patients per 1000 inhabitants, 54% of total consumption), (Figure 5.10).

Consumption in the 5-9 year olds. In 2019, 130 patients per 1000 inhabitants of 5-9 years were treated with antimicrobial agents, (Figure 5.9c). This is 46% lower than 2010 (243 patients per 1000 inhabitants) and 9.0% lower than 2018 (143 patients per 1000 inhabitants). On average, each treated patient received 1.53 prescriptions in 2010, which decreased to 1.43 prescriptions in 2019, (not shown). In 2019, the total consumption corresponded to 3.1 DID, 41% less than in 2010 (5.2 DID), (Figure 5.9a). The distribution of the antimicrobials used to treat the 5-9 year olds did not change markedly over the last decade, and beta-lactamase sensitive penicillins remained the main antimicrobial agent used (85 patients per 1000 inhabitants, 66% in 2019).

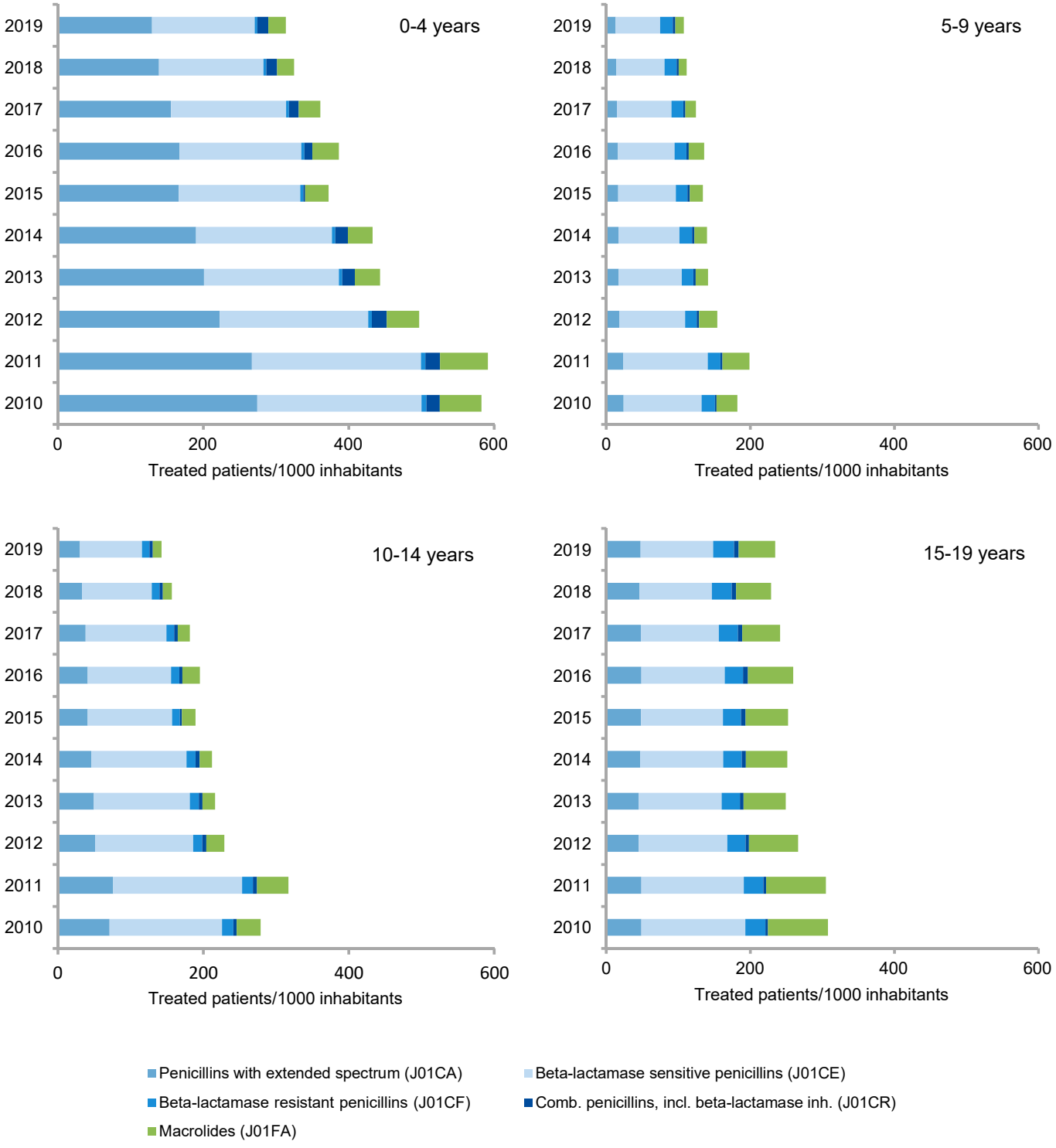
Consumption in the 10-14 year olds. In 2019, the total consumption of antimicrobial agents (105 patients per 1000 inhabitants) was 39% lower than a decade ago (172 patients per 1000 inhabitants) and 3.3% lower than 2018 (108 patients per 1000 inhabitants), (Figure 5.9c). On average, each treated patient received 1.49 prescriptions in 2010, which decreased to 1.44 prescriptions in 2019, (not shown). In 2019, the total consumption corresponded to 4.6 DID, 29% less than in 2010 (6.5 DID), (Figure 5.9a). The main change in the distribution of the consumption was increased share of beta-lactamase resistant penicillins (from 10.8% of total consumption in 2010 to 16.9% in 2019). Beta-lactamase sensitive penicillins remained the main antimicrobial agent (59% in 2019), (Figure 5.10).

Consumption in the 15-19 year olds. Consumption of antimicrobial agents in the oldest children increased in 2019 after several years with decreased consumption (Figure 5.9a-c). In 2019, 229 patients per 1000 inhabitants were treated with antimicrobial agents, 2.3% higher than in 2018 (224 patients per 1000 inhabitants). The increase was caused by increases in several main antimicrobial agents, (Figure 5.10): tetracyclines (+6.2%, not shown), beta-lactamase resistant penicillins (+5.2%), macrolides (+4.9%) and penicillins with extended spectrum (+2.9%). In 2019, the consumption corresponded to 382 prescriptions per 1000 inhabitants and 12.9 DID which is 2.7% and 3.5% higher than 2018, respectively.

Macrolides play an important role in the treatment of infections in children and the young, being the drug of choice for respiratory tract infections with *Mycoplasma pneumoniae* and in pertussis. Macrolides are also used in the adolescents for the treatment of sexually acquired infections, e.g. *Chlamydia*. This, combined with treatment of acute pharyngitis may be the reason for the relatively high consumption of macrolides in the 15-19 year olds, which in 2019 counted 51 patients per 1000 inhabitants. For the 0-4 year olds, the 5-9 year olds and the 10-14 year olds the corresponding numbers were 24, 12 and 12 patients per 1000 inhabitants per year, respectively, (Figure 5.10). However, as for the total population penicillins are the most used antimicrobial agents among children regardless of age (constituting between 44% and 66% per age group), Figure 5.10.

Comparison of consumption among girls and boys showed different tendencies in different age groups (not shown). The youngest boys (0-4 year olds) received 11% more prescriptions per 1000 inhabitants than the girls (457 versus 411). The opposite was observed among older children: girls aged 5-9 years received 24% more prescriptions per 1000 inhabitants than boys (207 versus 167), girls aged 10-14 years received 27% more prescriptions per 1000 inhabitants than boys (134 versus 169) and girls aged 15-19 years received 102% more prescriptions per 1000 inhabitants than boys (514 versus 255).

Figure 5.10 Consumption of five antimicrobial agents by children/adolecents age 0-19, Denmark DANMAP 2019



Data used in Figure 5.10a-c is based on registered sales to individuals
ATC numbers used in Figure 5.10a-b stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

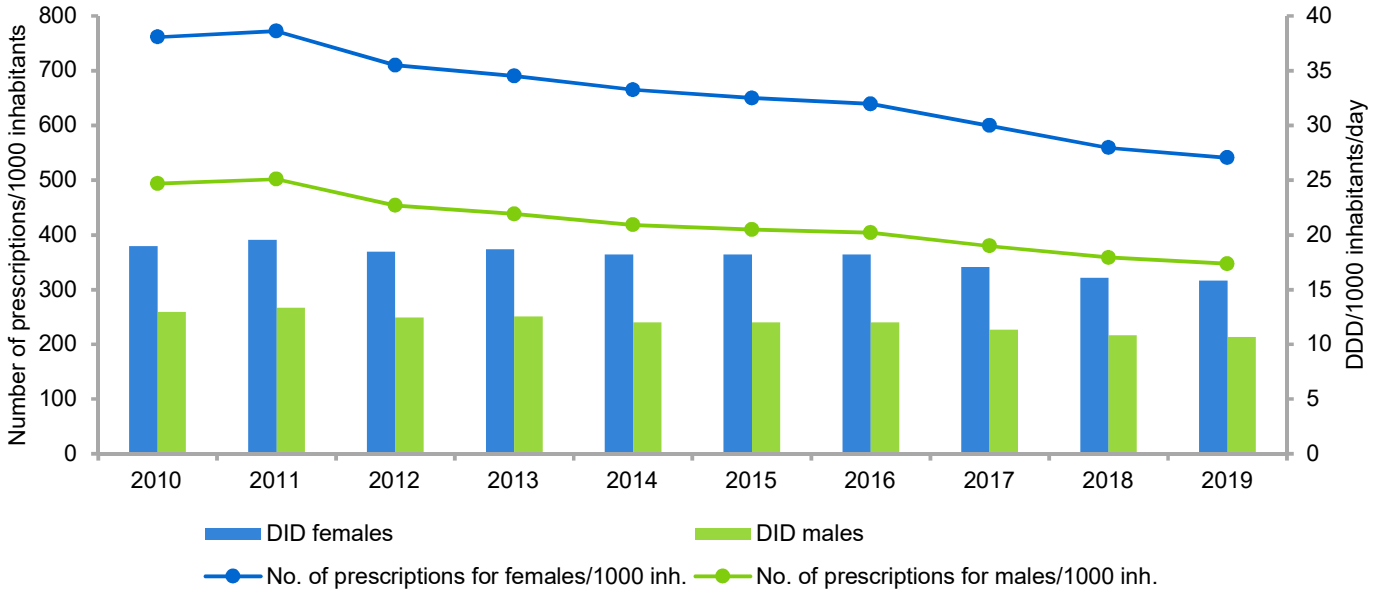
5.3.7 Consumption of antimicrobials according to gender

Differences between genders regarding consumption of antimicrobials are well known. In general, females receive more treatment – a trend driven by a much higher incidence of urinary tract infections in females. Thus, the consumption of pivmecillinam, sulphonamides, trimethoprim and nitrofurantoin is approximately three times higher for females than for males.

Also for beta-lactamase sensitive penicillins and macrolides the differences in consumption, especially when measured in DID, are substantial, (Figure 5.11a and b). From 2010 to 2019, the number of treated females (all age group) decreased from 369 to 277 per 1000 inhabitants (-25%) and the number of treated males per 1000 from 267 to 191 inhabitants (-28%).

Figure 5.11a Consumption of antimicrobial agents (J01 and P01AB01) per gender, prescriptions per 1000 inhabitants per year and DDD per 1000 inhabitants per day, Denmark

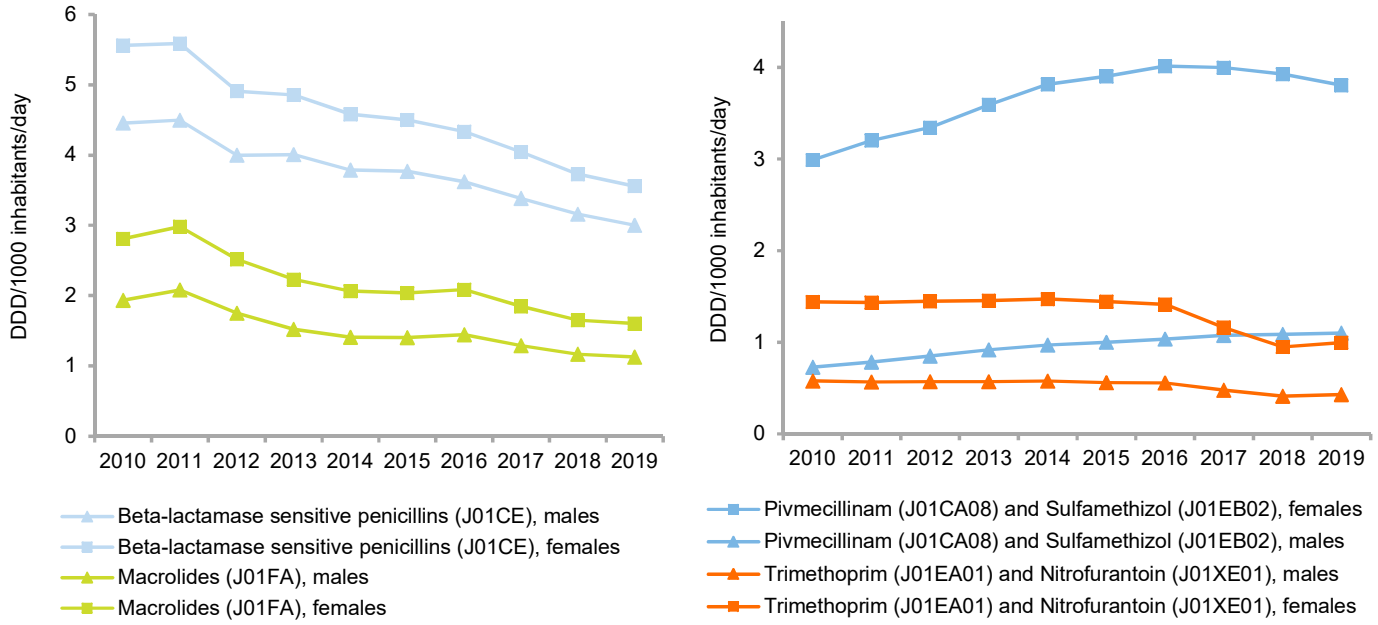
DANMAP 2019



Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.11b Consumption of most used antimicrobials for respiratory tract infections and urinary tract infections, DDD per 1000 inhabitants per day, Denmark

DANMAP 2019



Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

During the same period, the number of DDD per prescription increased for females from 9.1 to 10.7 (17%), and for males from 9.6 to 11.2 (17%). Altogether from 2010-2019, the consumption in females decreased from 19.0 DID to 15.8 DID (-17%), and in males from 13.0 DID to 10.7 DID (-18%).

Drugs for treatment of respiratory tract infections. For both females and males a decrease in the consumption of beta-lactamase sensitive penicillins and macrolides was observed over the last decade. From 2010 to 2019, for females, beta-lactamase sensitive penicillins decreased from 5.6 DID to 3.6 DID and macrolides from 2.8 DID to 1.6 DID, respectively. For males, the corresponding changes were from 4.5 DID to 3.0 DID and from 1.9 DID to 1.1 DID, respectively (Figure 5.11b).

Urinary drugs. Figure 5.11b presents the consumption of antimicrobial urinary drugs grouped into pivmecillinam and sulfamethizol (against acute infections) and trimethoprim and nitrofurantoin (more often used in the prevention of UTI in elderly or in recurring infections) for 2010 to 2019. Not presented are the shifting trends in use of the individual drug classes: In 2019, pivmecillinam accounted for 3.6 DID for females and 1.05 DID for males. In 2010, the corresponding numbers were 2.6 DID for females and 0.7 DID for males. For sulfamethizol consumption showed opposite trends: from 0.4 DID in 2010 to 0.2 DID in 2019 in females and from 0.06 DID to 0.05 DID in males, respectively.

Since 2017, consumption of all urinary drug classes has decreased. Most notable are the recent changes in consumption of nitrofurantoin: from a stabile 0.7 DID in women in the years 2009 to 2016, to 0.4 DID in 2017 and 0.2 DID in 2018. In men, the consumption of nitrofurantoin decreased from 0.3 DID in 2010 to 0.13 DID in 2019. In 2017, recommendations regarding the use of nitrofurantoin had been issued, advocating for caution in the use in elderly. Unexplained is the increase in women to 0.4 DID in 2019.

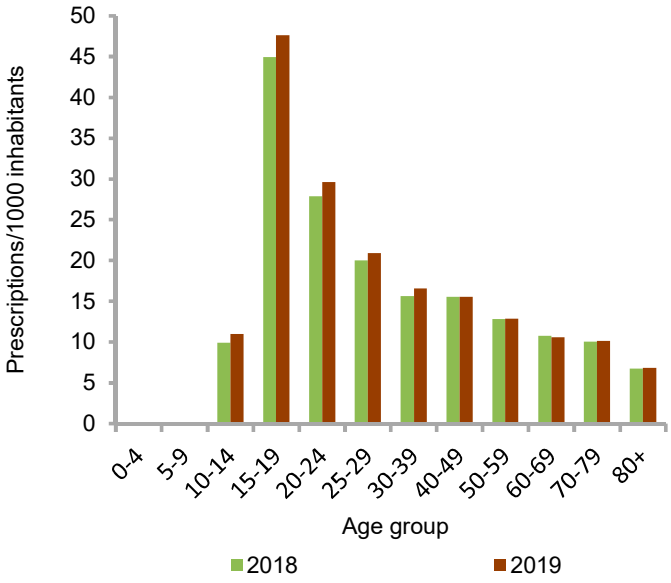
5.3.8 Tetracyclines

In 2019, tetracyclines accounted for 1.48 DID, corresponding to 11% of the total consumption in primary health care. During the last decade, the consumption has decreased by altogether 12.9% from 1.7 DID in 2010. In 2013, the consumption peaked unexpectedly at 1.96 DID. In 2019, the consumption increased again (5.8%), (Figure 5.4). Tetracyclines are used by all age groups above 12 years and by both genders (Figure 5.12).

Tetracyclines account for a considerable part of consumption of antimicrobials among adolescents due to the treatment of acne, (Table 5.6).Treatment lasts long (up to six months) and may even be repeated in a situation of relapse in patients, who may be suffering from the condition for years. Furthermore, within the same family/at the same family doctor, there may be tendency to treat younger siblings as well. There exist clear differences in prescription habits regarding boys and girls. Among girls, the treatment periods are longer and extend into the young adults of up to 24 years, while boys primarily are treated in shorter periods at the age of 15-19 years. In 2010, on average 37 boys aged 15-19 years were treated per 1000 inhabitants (2.1 treatments on average). For girls of the same age the corresponding number was 31 patients per 1000 inhabitants (1.9 treatments on average). In 2019, the number of 15-19 years old boys receiving treatment had declined to 27 treated patients (1.7 treatments) per 1000 inhabitants, while the number of 15-19 year old girls receiving treatment was 31 treated patients (1.6 treatments) per 1000 inhabitants.

In women (all ages) consumption decreased slightly from 1.8 DID in 2010 to 1.7 DID in 2019 and in men from 1.5 DID to 1.2 DID, respectively (not shown). Increases in the occurrence of sexually transmitted infections and changes in the treatment guidelines for these may be a challenge in future years, see chapter 8.3.9 on the occurrence of *N. gonorrhoea* in Denmark.

Figure 5.12 Consumption of tetracyclines in different age groups, prescriptions per 1000 inhabitants, Denmark DANMAP 2019



Data used for this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.6 Consumption of tetracyclines by clinical indication code DANMAP 2019

Indication written on the prescription	Year		
	2017	2018	2019
Against acne	50.7	54.9	55.6
Prevention of malaria	8.1	6.9	6.0
Against Borrelia infection	2.6	4.2	4.4
Against pelvic inflammatory disease	1.8	1.9	1.9
Against skin and soft tissue infection	1.2	1.5	1.6
Unspecified indications	35.6	30.6	30.4

Data used for this table is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.4 Hospital care

5.4.1 Introduction

Antimicrobial consumption at hospitals is reported to DANMAP once a year through the Register of Medicinal Product Statistics at the Danish Health Data Authority. Reporting is based on deliverances from the hospital pharmacies to the different clinical departments and includes all generic products that are supplied through general trade agreements between the regions and the company Amgros. For more information see chapter 9.8, material and methods.

DANMAP 2019 covers the total sales of systemic antimicrobials (ATC code J01 as well as ATC code P01AB01 and A07AA09) reported from all Danish hospital pharmacies. However, only Figure 5.1a on page 44 includes all consumption, (e.g. also including consumption at private hospitals and psychiatric departments), in 2019 accounting for approximately 2-3% of the total hospital consumption. In all other figures and calculations, only consumption at somatic hospitals with acute care functions is presented.

In DANMAP, data on hospital consumption is kept at a national or regional level. Data on hospital level can be supplied upon request.

Information on consumption at individual patient level is still lacking for the hospital sector. This information is expected to be available through the future national "Hospital Medicine Register", which is currently under development.

The consumption of antimicrobial agents in hospital care is presented as DDD per 100 occupied bed-days (DBD) and as DDD per 100 admissions (DAD) to account for hospital activity. Moreover, data are presented as DID to enable comparison with primary healthcare.

As mentioned, during the past decade the hospitalisation patterns in Denmark changed notably. The shortening of bed-days at hospitals and the increasing ambulatory care function, including increased surgical activity, causes increased pressure on the health system at municipality level, (Figure A5.3 and A5.4 in web annex). Therefore demands arise for more rehabilitation beds for patients dismissed from hospital, but not yet ready for continuing treatment at home.

The increasing number of invasive infections and infections at other sites also induces pressure into the system, increasing the demand for antibiotic treatment (see section 8.1 introduction and Figure 8.3). Since selection pressure for the emergence of antimicrobial resistance follows with increasing hospital activity, the selection pressure has increased considerably from 2010-2019, (Figure A5.3 in web annex).

Table 5.7 presents data on regional and national hospital activity together with information on the size of population for 2010 and 2019. Denmark has a very high bed occupancy rate and overcrowding happens relatively often, especially during winter time and in situations with influenza epidemics.

In 2019, the number of admissions at Danish somatic hospitals is estimated to be 1,364,804, while the number of bed-days is estimated to be 3,898,979. From 2010-2019, the number of bed-days decreased with altogether 16%, while the number of admissions increased with 3.9% and the Danish population with 4.9%. During the decade, activity in ambulatory care increased from 6,454,112 treated patients to 7,984,223 treated patients, (24%). On average, the number of bed-days decreased with an annual 2.0%, while the number of admissions on average increased with 0.8% per year, (Figure A5.3 in web annex).

On a regional level, the number of bed-days decreased in all regions from 2010-2019; Capital Region of Denmark and Region Zealand with -13%, Region of Southern Denmark with -17%, Central Denmark Region with -18% and North Denmark Region with -26%. The number admissions increased from 2010-2019 in Capital Region of Denmark (+5.7%), Region Zealand (+13.7%) and Central Denmark Region (+2.7%). The number of admissions decreased in Region of Southern Denmark and North Denmark Region with -0.8% and -6.7%, respectively.

Table 5.7 Activity at Danish hospitals DANMAP 2019

Region	Number of bed-days at somatic hospitals		Number of admission to somatic hospitals		Population	
	2010	2019*	2010	2019*	2010	2019
Capital Region of Denmark	1,649,961	1,438,898	450,289	475,758	1,680,271	1,835,562
Region Zealand	666,992	583,452	209,301	238,027	820,564	836,738
Region of Southern Denmark	901,209	749,208	258,459	256,324	1,200,277	1,223,348
Central Denmark Region	939,014	771,353	278,027	285,606	1,253,998	1,320,678
North Denmark Region	481,379	356,764	117,697	109,799	579,628	589,755
Denmark	4,638,555	3,898,979	1,313,773	1,364,804	5,534,738	5,806,081

* Data from 2019 are estimated by applying the 10 yr average increase/decrease observed for 2009-2018
Data used in this table is based on the activity at somatic hospitals

5.4.2 Public somatic hospitals - DDD per 100 occupied bed-days (DBD)

In 2019, the consumption of antimicrobial agents at somatic hospitals was 107 DBD, 6.2% higher than the observed 100.7 DBD in 2018 and 49% higher than the consumption measured a decade ago in 2010, (71.6 DBD). The consumption in 2019 was the highest measured this decade, (Table 5.8).

The four penicillin groups accounted for altogether 58.05 DBD, corresponding to 54% of the total somatic hospital consumption of antimicrobials (Figure 5.13, Table 5.8).

In 2019, combination penicillins accounted for 17.3 DBD, making it the largest group consumed in 2019 (16%). In 2017, a shortage of piperacillin with tazobactam had been responsible for a drop in consumption that year. In 2018, delivery had been reestablished, resulting in an increase in the consumption of combination penicillins of altogether 14% since 2016.

Penicillins with extended spectrum are the second largest group consumed at Danish hospitals. In 2019, they accounted for 16.0 DBD (15%) of the consumption in somatic hospitals, a 4.0% increase from 2018 (15.4 DBD). Beta-lactamase sensitive penicillins accounted for 9.75 DBD (9%) and beta-lactamase resistant penicillins for 14.99 DBD (14%), a 42% increase from 2018 (10.52 DBD).

Overall, the consumption of penicillins showed increasing trends for the decade. The combination penicillins increased steeply by 12.5 DBD (259%), the beta-lactamase resistant penicillins and penicillins with extended spectrum less markedly, but still continuously with 7.93 DBD (112%) and 4.54 DBD (40%), respectively, (Figure 5.14a and 5.15). These trends are comparable to the trends observed for the primary sector, apart from changes for 2017-2019, where consumption in the primary sector decreased notably for the combination penicillins.

Table 5.8 Consumption of antimicrobial agents for systemic use in somatic hospitals, DBD, Denmark DANMAP 2019

ATC group	Therapeutic group	Year									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01AA	Tetracyclines	1.01	1.09	1.55	1.48	1.65	1.82	2.09	2.05	2.38	3.28
J01CA	Penicillins with extended spectrum	11.45	11.35	12.47	12.88	13.62	14.14	14.50	15.81	15.37	15.99
J01CE	Beta-lactamase sensitive penicillins	8.25	9.03	9.32	9.41	9.32	9.09	9.19	10.20	10.40	9.75
J01CF	Beta-lactamase resistant penicillins	7.06	8.16	8.21	8.78	9.30	9.33	9.95	11.19	10.52	14.99
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	4.83	6.48	9.30	10.92	12.78	14.91	15.16	14.02	16.57	17.31
J01DB	1st generation cephalosporins	0.12	0.12	0.12	0.11	0.06	0.04	0.04	0.04	0.04	0.03
J01DC	2nd generation cephalosporins	11.15	14.34	13.36	12.28	11.37	10.14	9.25	11.04	9.00	8.08
J01DD	3rd generation cephalosporins	1.01	1.07	1.03	1.08	1.00	1.04	1.03	1.33	1.20	1.19
J01DF	Monobactams	0.04	0.14	0.15	0.14	0.06	0.03	0.01	0.01	0.01	0.01
J01DH	Carbapenems	1.65	2.38	2.58	2.79	3.30	2.98	2.72	2.91	2.83	2.99
J01EA	Trimethoprim and derivatives	0.32	0.31	0.36	0.38	0.47	0.40	0.37	0.41	0.44	0.40
J01EB	Short-acting sulfonamides	0.28	0.21	0.18	0.16	0.14	0.12	0.10	0.10	0.10	0.09
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	2.56	3.52	3.77	4.40	4.84	5.30	5.45	5.70	6.08	6.72
J01FA	Macrolides	3.17	3.26	3.38	3.27	3.64	4.35	4.70	5.71	6.27	6.70
J01FF	Lincosamides	0.43	0.48	0.61	0.64	0.65	0.57	0.63	0.65	0.76	0.74
J01GB	Aminoglycosides	1.71	2.02	2.10	2.15	2.04	2.22	1.98	2.27	2.20	2.67
J01MA	Fluoroquinolones	8.26	8.42	8.38	8.62	8.63	8.50	7.72	7.43	7.18	6.95
J01XA	Glycopeptides	0.98	1.22	1.25	1.31	1.15	1.16	1.09	1.31	1.27	1.33
J01XB	Polymyxins	0.24	0.22	0.22	0.27	0.22	0.19	0.19	0.19	0.23	0.22
J01XC	Steroid antibacterials (fusidic acid)	0.32	0.25	0.23	0.22	0.23	0.16	0.11	0.07	0.06	0.06
J01XD	Imidazole derivatives	3.51	3.71	3.92	4.09	4.42	4.22	4.52	4.65	4.33	4.09
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.27	0.29	0.33	0.34	0.32	0.27	0.24	0.25	0.27	0.28
J01XX05	Methenamine	0.07	0.09	0.08	0.07	0.06	0.09	0.08	0.07	0.10	0.08
J01XX08	Linezolid	0.20	0.29	0.31	0.36	0.34	0.44	0.36	0.37	0.52	0.53
J01XX09	Daptomycin	0.02	0.01	0.02	0.02	0.05	0.04	0.05	0.08	0.14	0.06
P01AB01	Nitroimidazole derivatives (metronidazole)	2.39	2.34	2.29	2.25	1.98	2.01	2.18	2.03	1.94	1.91
A07AA09	Intestinal antiinfectives (vancomycin)	0.25	0.40	0.47	0.49	0.52	0.47	0.49	0.52	0.50	0.54
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin (total)	71.56	81.20	85.98	88.92	92.16	94.03	94.22	100.39	100.71	106.98

Data used in this table is based consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Data from 2019 are estimated by applying the average decrease in bed-days observed in 2009-2018

The consumption of beta-lactamase sensitive penicillins increased with annual fluctuations, presenting fluctuations with decreases in 2014, 2015 and 2019. In 2019, the consumption of beta-lactamase sensitive penicillins was 9.75 DBD.

Notable trends for other antimicrobials for 2010 to 2019 were increases observed for tetracyclines, combinations of sulfonamides and trimethoprim and for macrolides. Although tetracyclines only account for a minor part of the antimicrobials consumed at hospitals, the drug class has been continuously increasing during the past decade; in 2010 they accounted for 1.01 DBD, while in 2019 the consumption had increased to 3.28 DBD. Consumption of combinations of sulfonamides and trimethoprim, increased from 2.56 DBD in 2010 to 6.72 DBD in 2019, a total increase of 163% for the decade. A rise in macrolides was observed from 3.17 DBD in 2010 to 6.70 DBD in 2019 (111%), (Table 5.8, Figure 5.14a and 5.15).

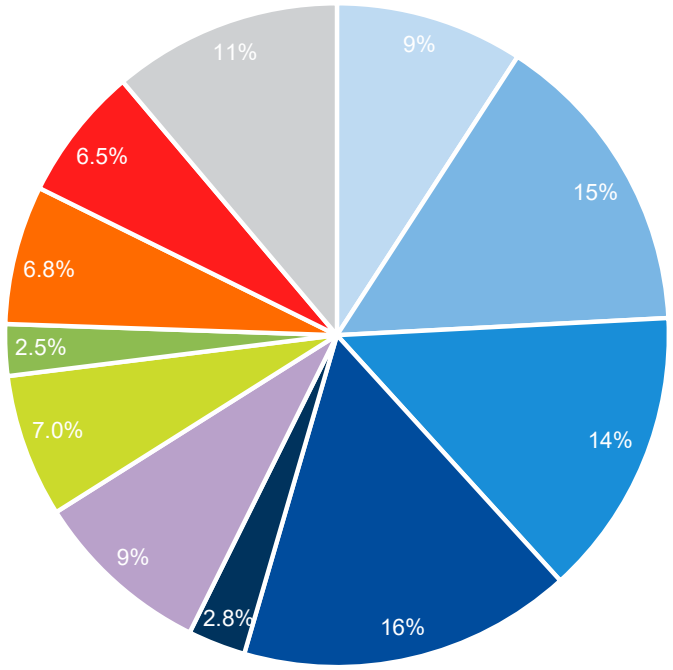
Finally, for linezolid the consumption peaked in 2019 at 0.53 DBD, whereas daptomycin decreased to 0.06 DBD after the observed peak in 2018 (0.14 DBD), (Table 5.8). Although the consumption of both is only minor, these changes are noteworthy: for Linezolid due to high risk of creating resistance, and for daptomycin due to its use in the treatment of invasive vancomycin resistant enterococci (VRE), the number of which has increased dramatically (see chapter 8.2.5 on invasive enterococci and 8.3.3 on VRE). The consumption of linezolid increased with 158% since 2010 (0.2 DBD) but no increase were observed for 2018-2019. The Capital Region of Denmark accounted for 73% of the consumption of linezolid.

Also for daptomycin the main use was in the Capital Region of Denmark (73%), which coincides with the Capital Region having the highest number of clinical cases of VRE in 2019, (section 8.3.3 and 8.3.4).

In 2019, the consumption of leading antimicrobials used in empirical treatment of main infections treated at hospitals continued its increases, a trend following the described increasing trends for the number of invasive isolates, (Figure 5.14a and Figure 8.1). In 2019, these leading antimicrobials constituted 86.7 DBD of the total consumption of 107 DBD (81%). In 2018, it was 81.6 DBD of a total of 100.7 DBD (81%).

Trends in the consumption at hospitals on regional level, measured in DDD per 1000 inhabitants per day and DDD per 100 bed-days, are presented in Figure 5.16, page 58 and 59.

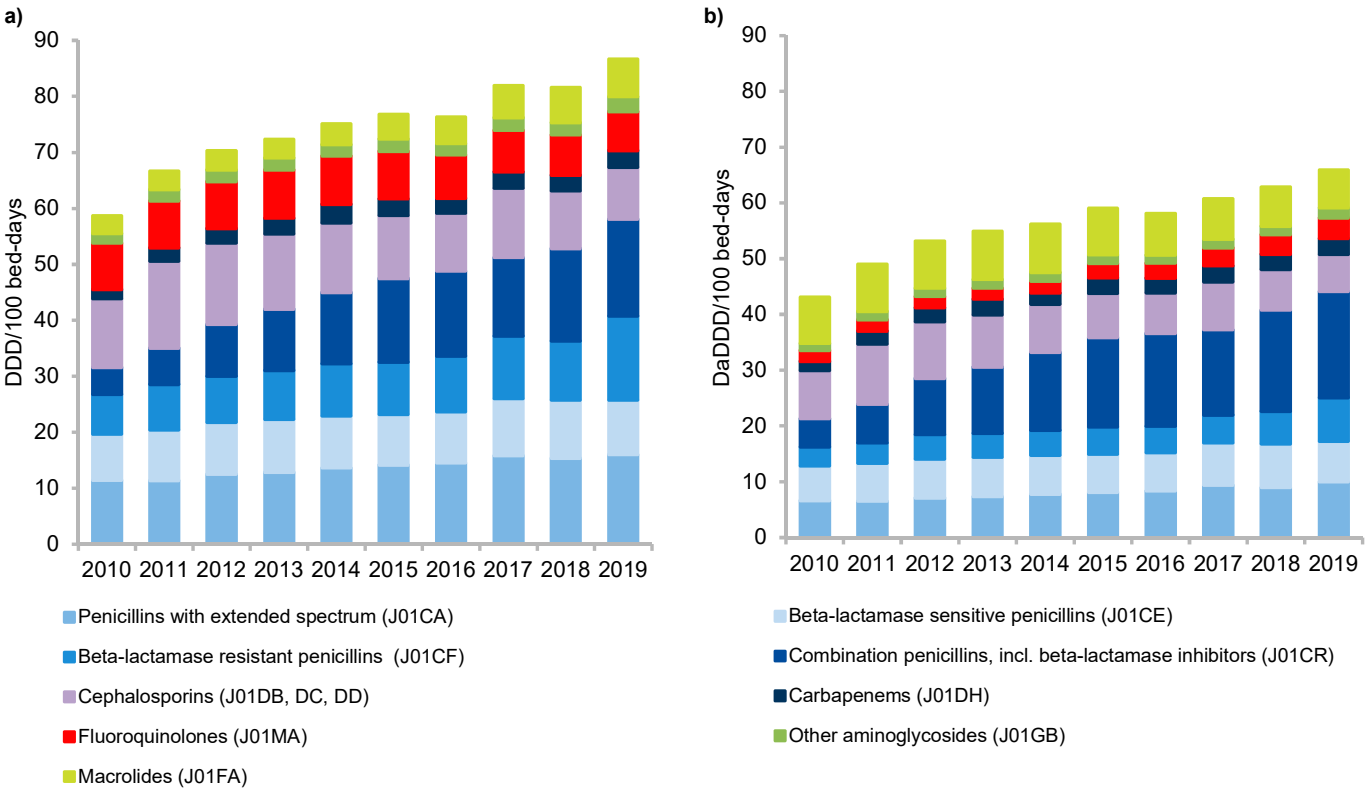
Figure 5.13 Distribution of drug groups within the total consumption of antimicrobial agents in somatic hospitals, in DDD, Denmark DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.14a and b Consumption at somatic hospitals by leading groups of antimicrobial agents (J01), DDD per 100 bed-days and DaDDD per 100 bed-days for comparison, Denmark

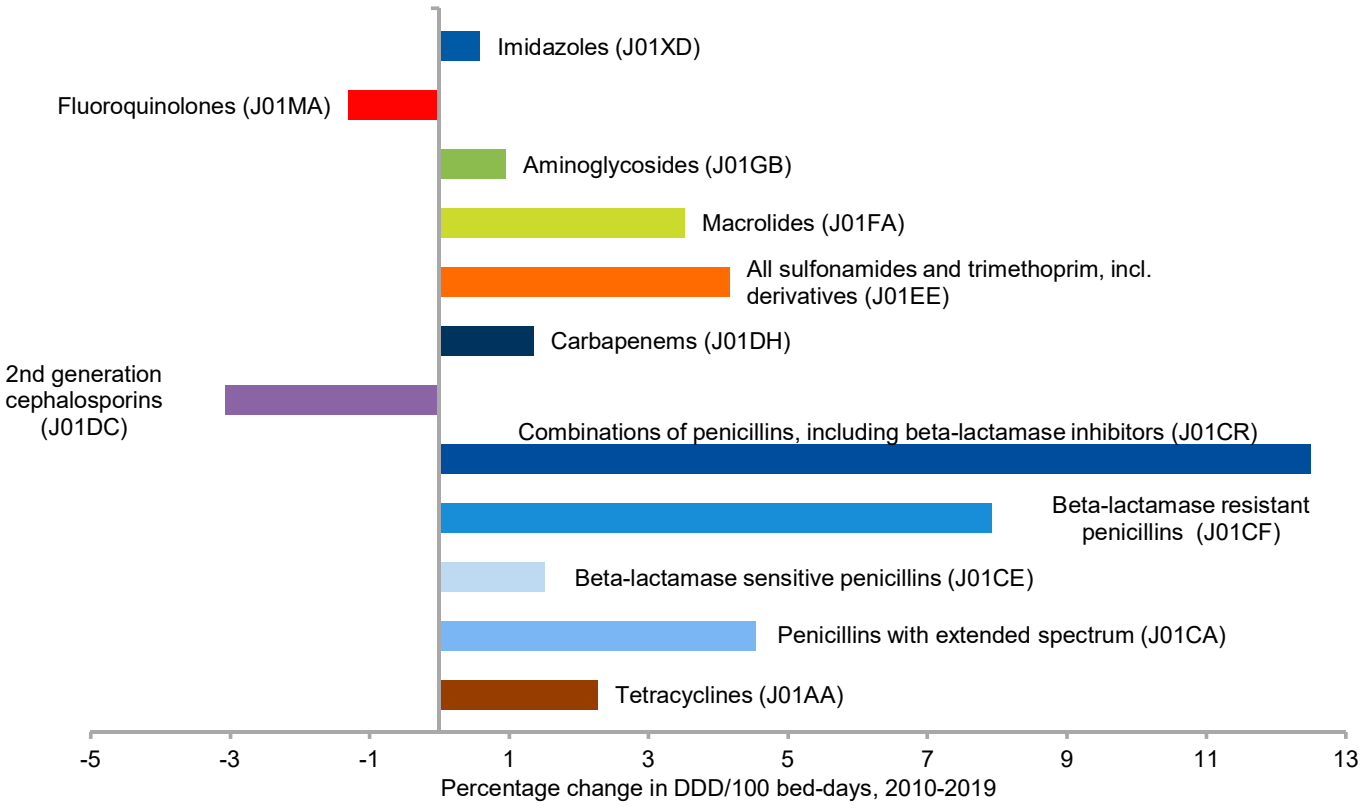
DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.15 Changes in the consumption of leading groups of antimicrobial agents at somatic hospitals, Denmark

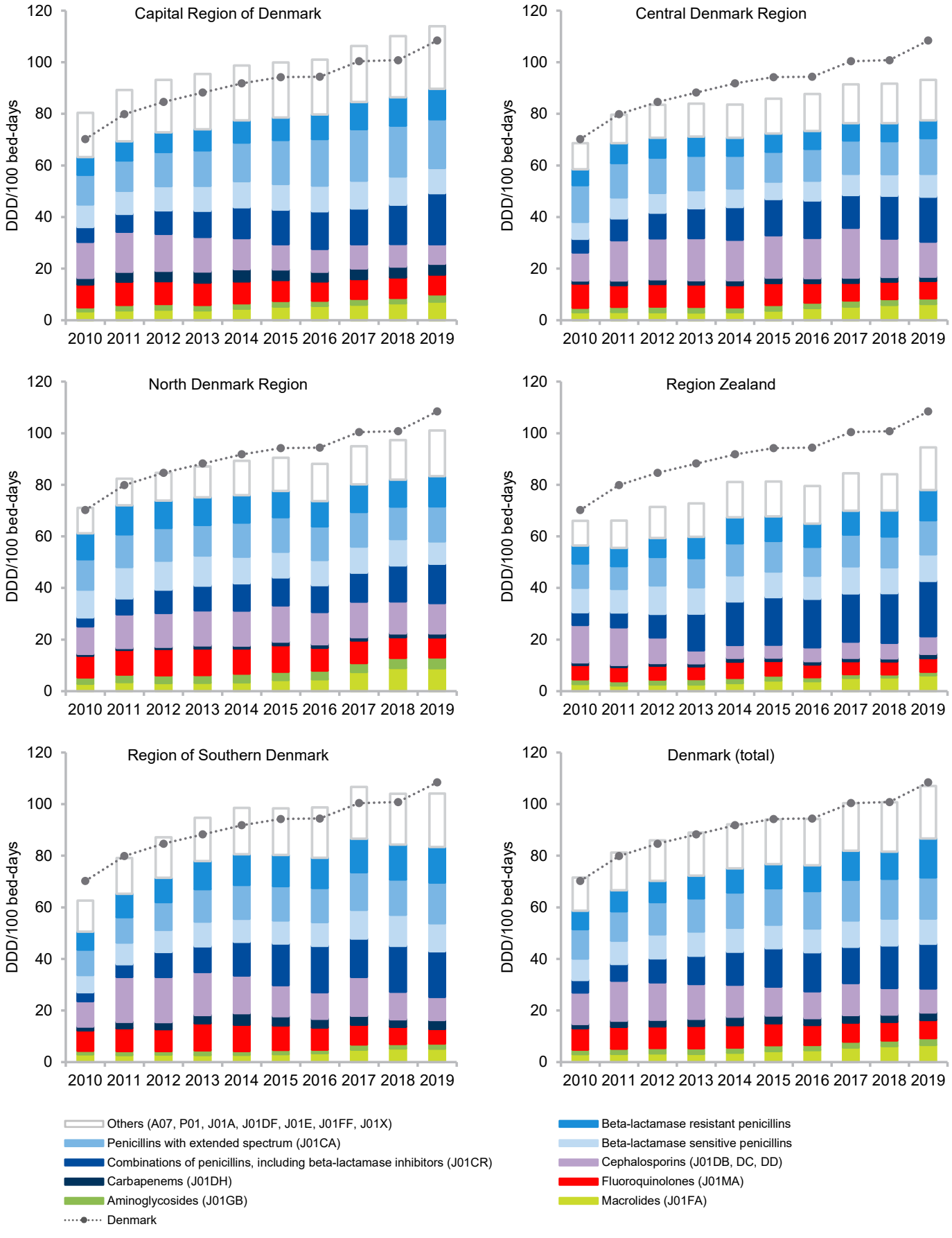
DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

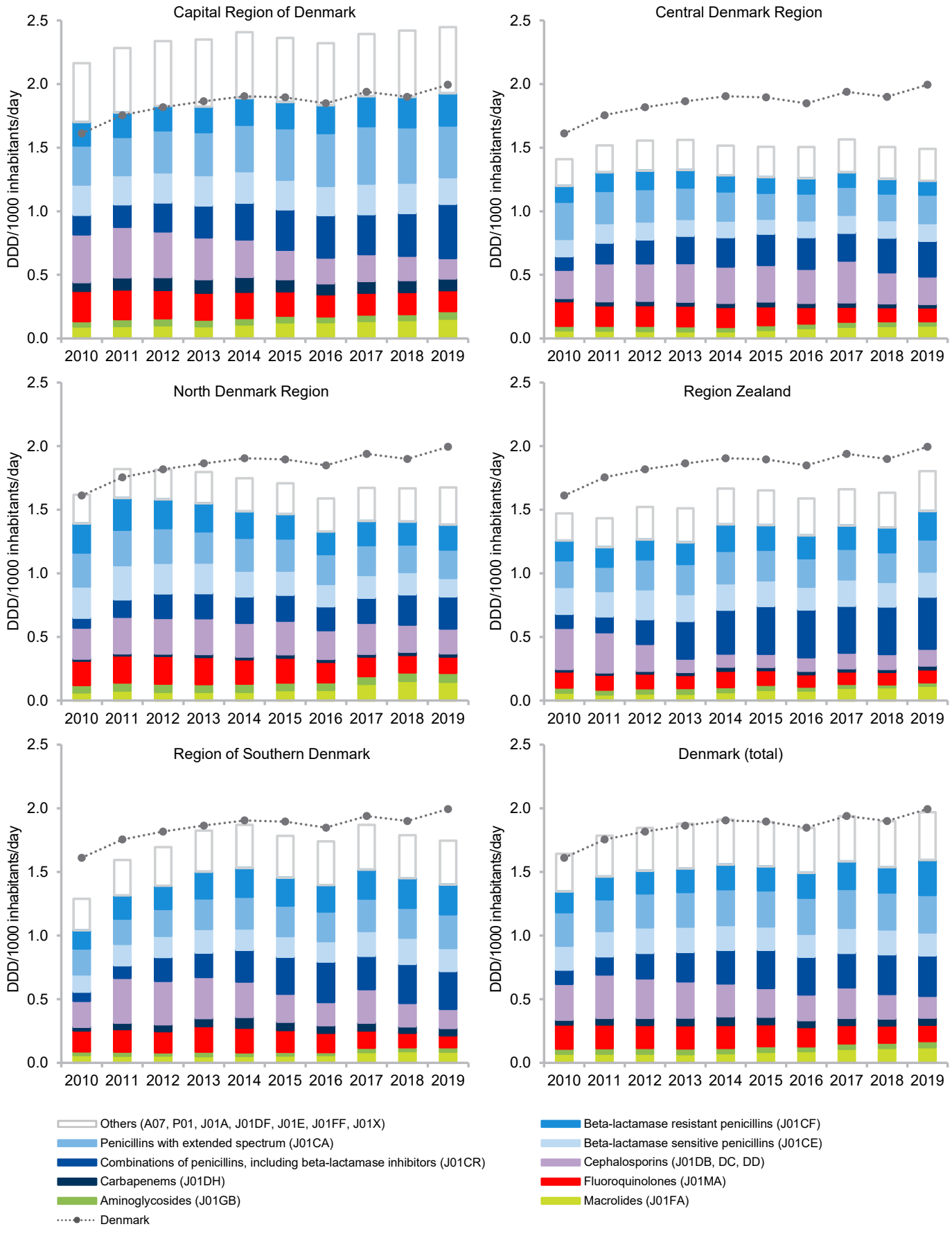
Figure 5.16a Consumption of antimicrobial agents for systemic use in the five health regions, DDD per 100 bed-days, Denmark

DANMAP 2019



Data used in this figure is based consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.16b Consumption of antimicrobial agents for systemic use in the five health regions, DDD per 1000 inhabitants per day, Denmark
DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

5.4.3 Other measures of consumption at somatic hospitals - DDD per 100 admissions (DAD)

The consumption of antimicrobials at hospitals can also be measured in relation to hospital activity calculated in number of patients "passing through", i.e. DDD per 100 admissions (DAD).

In 2019, the total consumption was 306 DAD, a 3.4% increase from the 296 DAD in 2018 and 21% increase from 253 DAD in 2010. The consumption measured in DDD per 100 admissions has increased since 2016, and in 2019 it reached the highest level ever measured, (Table 5.9). The trends in DDD per 100 admissions reflect for most antimicrobials the trends observed in DBD. However, the observed rates of increases were more marked, when measured in DDD per 100 bed-days than in DDD per 100 admissions for all antimicrobial classes, (Tables 5.8 and 5.9). This could be due to the change in hospital activity, as presented in Figure A5.3 in web annex.

At regional level, the hospital activity measured in admissions mirrors the density of the population, except for the Region of Southern Denmark and the North Denmark Region, where the population over the last decade has increased slightly, but the number of admissions at somatic hospitals has decreased, (Table 5.7). For all five Danish regions, the number of bed-days in somatic hospitals decreased from 2010-2019. Trends in consumption measured in DDD per 1000 inhabitants per day and DDD per 100 bed-days are presented in Figure 5.16a and b.

A comparison of the usage of antimicrobials for the treatment of animals and humans, respectively, measured in kg active substance is presented in Figure 4.1 and Table A5.1 in web annex. For comparison of consumption at hospitals with the consumption in the primary sector measured in DDD per 1000 inhabitants per day see Figure 5.4.

Table 5.9 Consumption of antimicrobial agents for systemic use in somatic hospitals, DDD per 100 admissions, Denmark DANMAP 2019

ATC group	Therapeutic group	Year									
		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
J01AA	Tetracyclines	3.55	3.69	5.07	4.74	5.11	5.52	6.21	6.01	6.98	9.37
J01CA	Penicillins with extended spectrum	40.42	38.47	40.70	41.41	42.29	43.00	43.14	46.44	45.14	45.68
J01CE	Beta-lactamase sensitive penicillins	29.10	30.59	30.41	30.25	28.93	27.64	27.34	29.96	30.55	27.86
J01CF	Beta-lactamase resistant penicillins	24.92	27.63	26.78	28.23	28.88	28.39	29.62	32.89	30.90	42.82
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	17.03	21.97	30.35	35.11	39.68	45.35	45.11	41.18	48.64	49.46
J01DB	1st generation cephalosporins	0.43	0.39	0.39	0.36	0.19	0.13	0.13	0.12	0.11	0.08
J01DC	2nd generation cephalosporins	39.36	48.57	43.58	39.48	35.32	30.85	27.52	32.44	26.43	23.09
J01DD	3rd generation cephalosporins	3.56	3.64	3.37	3.48	3.11	3.16	3.07	3.91	3.52	3.39
J01DF	Monobactams	0.13	0.49	0.47	0.46	0.20	0.08	0.03	0.02	0.02	0.03
J01DH	Carbapenems	5.81	8.06	8.40	8.96	10.26	9.05	8.09	8.54	8.30	8.55
J01EA	Trimethoprim and derivatives	1.14	1.05	1.18	1.22	1.45	1.21	1.11	1.22	1.28	1.13
J01EB	Short-acting sulfonamides	1.00	0.72	0.58	0.52	0.44	0.36	0.30	0.30	0.29	0.25
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	9.04	11.91	12.29	14.14	15.02	16.12	16.23	16.75	17.86	19.21
J01FA	Macrolides	11.19	11.03	11.04	10.52	11.31	13.24	14.00	16.77	18.40	19.13
J01FF	Lincosamides	1.52	1.62	1.97	2.05	2.01	1.74	1.86	1.90	2.24	2.11
J01GB	Aminoglycosides	6.04	6.85	6.87	6.92	6.35	6.75	5.90	6.66	6.47	7.63
J01MA	Fluoroquinolones	29.16	28.51	27.35	27.72	26.81	25.86	22.98	21.83	21.10	19.86
J01XA	Glycopeptides	3.45	4.12	4.09	4.22	3.58	3.52	3.23	3.85	3.72	3.80
J01XB	Polymyxins	0.84	0.76	0.73	0.86	0.69	0.59	0.58	0.57	0.67	0.63
J01XC	Steroid antibacterials (fusidic acid)	1.11	0.85	0.74	0.71	0.71	0.50	0.34	0.20	0.18	0.16
J01XD	Imidazole derivatives	12.40	12.56	12.79	13.15	13.74	12.83	13.44	13.66	12.71	11.68
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.97	0.97	1.06	1.09	0.98	0.82	0.71	0.74	0.79	0.80
J01XX05	Methenamine	0.26	0.31	0.26	0.23	0.17	0.27	0.24	0.21	0.31	0.22
J01XX08	Linezolid	0.72	0.99	1.01	1.14	1.05	1.33	1.08	1.09	1.53	1.51
J01XX09	Daptomycin	0.07	0.05	0.06	0.07	0.17	0.12	0.15	0.24	0.42	0.18
P01AB01	Nitroimidazole derivatives (metronidazole)	8.44	7.93	7.48	7.22	6.14	6.12	6.50	5.97	5.71	5.47
A07AA09	Intestinal antiinfectives (vancomycin)	0.89	1.36	1.52	1.59	1.62	1.43	1.45	1.53	1.45	1.55
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin (total)	252.59	275.09	280.56	285.88	286.22	285.98	280.35	294.97	295.72	305.65

Data used in this table is based consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Data from 2019 are estimated by applying the average decrease in bed-days observed in 2009-2018

5.4.4 Changes in the consumption of antimicrobials of critical interest

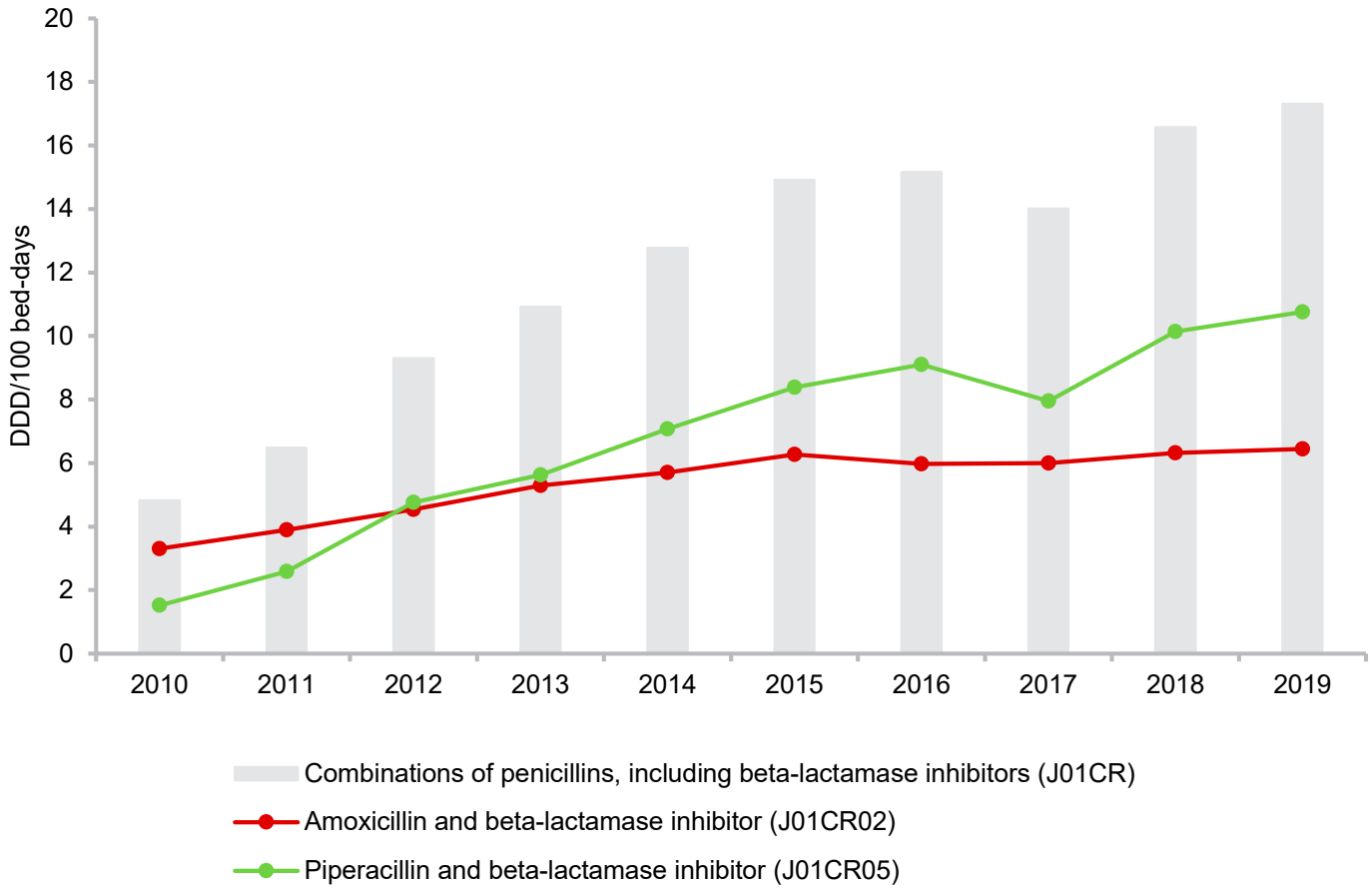
In Denmark, cephalosporins, fluoroquinolones and carbapenems have been collectively termed the antimicrobials of special critical interest due to their important role in the treatment of acutely ill patients suffering from severe infections. Their use is also correlated to a marked risk of resistance, which makes monitoring of the consumption of all three necessary.

For many years, 2nd generation cephalosporins were the main drug in the treatment of patients with sepsis. In an attempt to reduce the consumption of these, the use of piperacillin with tazobactam, a combination penicillin, was recommended as sepsis treatment at all major hospitals during the period of 2005 to 2008. Within recent years, the recommendations on empirical treament in patients with community-acquired sepsis have been further changed to the use of either beta-lactamase sensitive penicillins or penicillins with extended spectrum (in combination with gentamycin). Trends for the consumption of combination penicillins are shown in Figure 5.17. Due to a shortage of piperacillin with tazobactam in 2017, the overall consumption of the drug decreased markedly and was paralleled by a simultaneous increase in the consumption of cephalosporins. This becomes obvious in the regional monitoring of antimicrobials of critical interest for 2017, (Figure 5.17).

In 2019, the antimicrobials of special critical interest constituted altogether 18% of the total consumption at somatic hospitals, measured in DBD. In 2018, it was 20% and ten years ago, in 2010, it was 31%. The trends in the consumption for the five healthcare regions and the average national level during 2010 to 2019 are presented in Figure 5.18.

Cephalosporins accounted for altogether 9.29 DBD, 8.7% of the total consumption, a decrease of 25% from the 12.4 DBD in 2017, (Table 5.8). 2nd generation cephalosporins accounted for the biggest part, 8.08 DBD. Fluoroquinolones accounted for 6.95 DBD, a 3.3% reduction from 7.18 DBD in 2018. The consumption of fluoroquinolones peaked in 2015 and has since shown slight declines. Carbapenems accounted for 2.99 DBD in 2019, a 5.9% increase from 2.83 DBD in 2018.

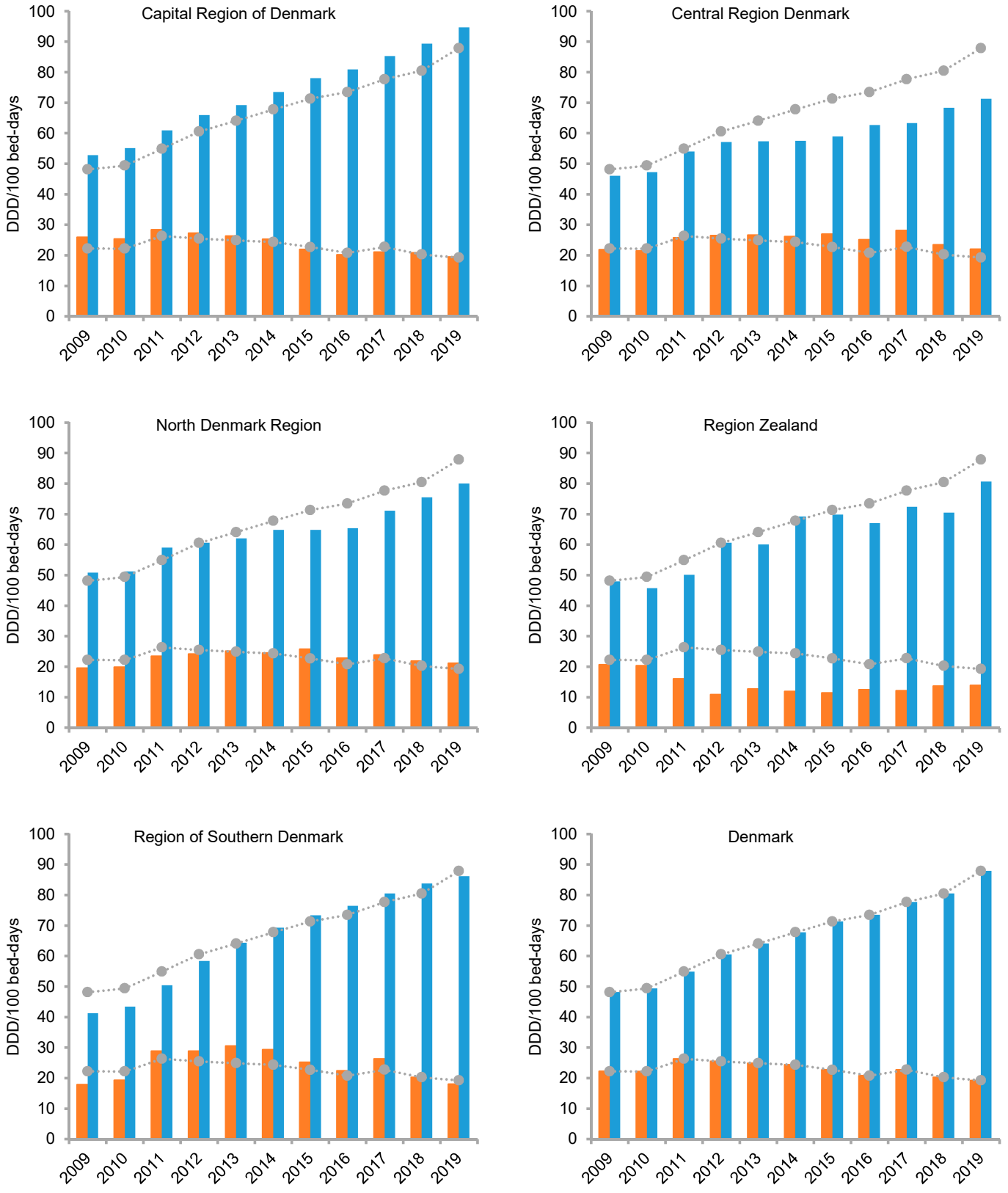
Figure 5.17 Consumption of combination penicillins at somatic hospitals, DDD per 100 bed-days, Denmark DANMAP 2019



Data used in this figure is based consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.18 Consumption of antimicrobials of special critical interest in the five health regions, DDD per 100 bed-days, Denmark

DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

The consumption of the three antimicrobial groups of critical interest will be monitored closely also in the future. This is due to local, regional and national initiatives. The most important one being the goals developed by working groups under the "National Quality and Learning Teams", an initiative spanning all Danish regions for 2017-2019. Their aim was applying principles of antibiotic stewardship to the main somatic hospitals, primarily focusing on emergency departments and medical departments with a relatively high number of acute patients. For the monitoring of these initiatives the Group developed Danish adjusted DDD for the main antimicrobial classes used at hospitals. When these are applied to the antimicrobial sales reported to DANMAP, the trends in consumption present as shown in Figure 5.14b. For more information on the working group, monitoring and results please see [www.kvalitetsteams.dk] (only available in Danish).

We would like to acknowledge Maja Laursen from the National Health Data Authority in Denmark for data on all antibiotic consumption from primary and hospital care and help in proof reading of this chapter.

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Textbox 5.1

National Action Plan on the reduction of antibiotics in humans, 2016-2020

The National Action Plan on the reduction of antibiotics in humans was issued in 2017 by the Danish Ministry of Health and supported by the National Antibiotic Council. Together with the National Action Plan, a One Health Strategy was published. Both are available at the Danish Ministry of Health's homepage at www.SUM.dk. The National Action Plan aims at fulfilling three measurable goals:

- The first goal targets an overall reduction in antimicrobial consumption in primary healthcare, from 462 redeemed prescriptions per 1000 inhabitants in 2016 to 350 redeemed prescriptions per 1000 inhabitants in 2020 (prescriptions issued through general practitioners, medical specialists and dentists)
- The second goal aims at increasing the share of beta-lactamase sensitive penicillins used in primary care to 36% by 2020, thus emphasizing the importance of beta-lactamase sensitive penicillins as the continued drug of choice in many common infections. Also this goal is directed at general practitioners, medical specialists and dentists
- The third goal aims at a 10% reduction in the consumption of the three antimicrobials of special critical interest (cephalosporins, fluoroquinolones and carbapenems) at hospitals from 2016 to 2020, measured in DBD.

The following results have been achieved from 2016-2019:

For goal one the number of prescriptions in primary healthcare (general practitioners, medical specialists and dentists) were reduced to 382 prescriptions per 1000 inhabitants in 2019. Figure 1 shows the number of prescriptions redeemed at pharmacies in Denmark from 2016-2019. Already in 2016, some of the general practioners prescribed less than 350 prescriptions per 1000 inhabitants (DANMAP 2017). By 2019, the percentage of general practioners reaching the goal had increased.

Figure 1 Prescribing trends in the primary sector, prescriptions per 1000 inhabitants, Denmark DANMAP 2019

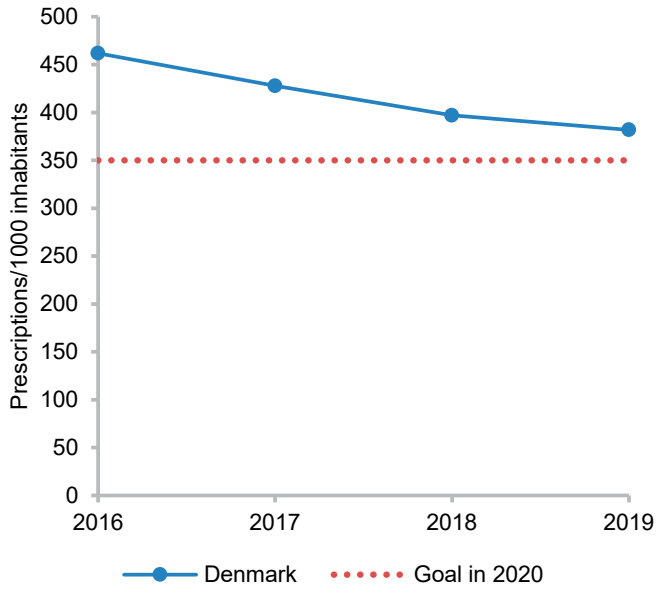
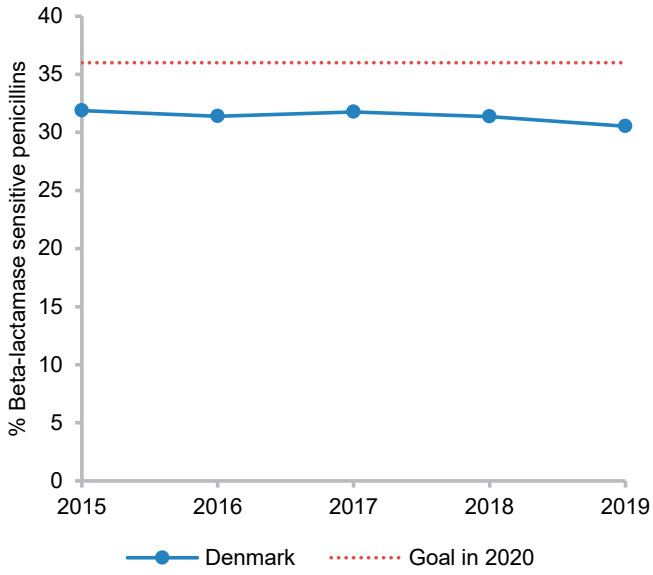


Figure 2 Share of beta-lactamase sensitive penicillins out of total consumption of antimicrobials, primary sector, % DANMAP 2019

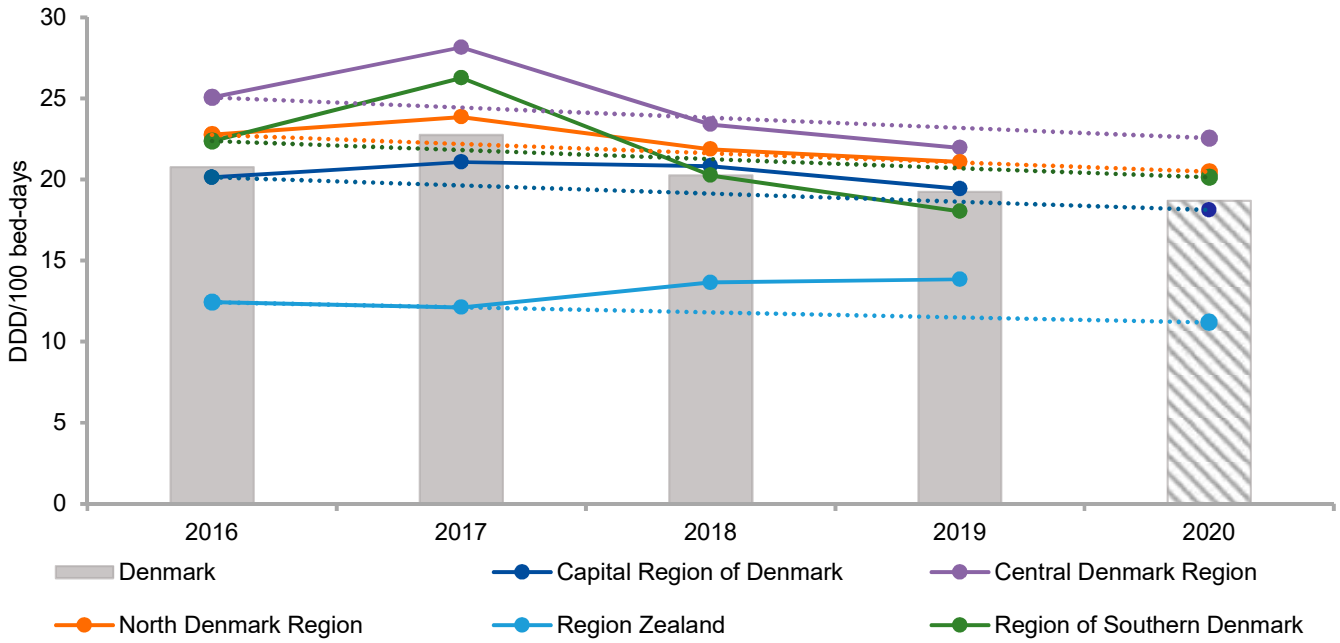


Data used in this figure is based on registered sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

For goal two, the proportion of beta-lactamase sensitive penicillin (based on number of prescriptions issued from general practitioners, medical specialists and dentists) remained unchanged (approximately 31%) on national level from 2016 to 2019 (Figure 2).

For goal three, the consumption of antimicrobials of special critical interest at hospitals decreased by 7.4% on national level (from 20.77 DBD in 2016 to 19.24 DBD in 2019), Figure 3. On regional level, the consumption decreased in the Capital Region of Denmark (-3.5%), Central Denmark Region (-12.4%), North Denmark Region (-7.3%) and Region of Southern Denmark (-19.4%). The consumption of antimicrobials of special critical interest increased in the Region Zealand with 11.4%; however, it remained lower than in the other regions.

Figure 3 Consumption of critically important antimicrobials on regional level incl. 10% reduction goal, DDD per 100 bed-days, Denmark
DANMAP 2019



Data used in this figure is based on consumption at somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

In 2017, goal three was challenged through shortages of piperacillin/tazobactam, which brought cephalosporins back as a first line treatment of septic patients. In 2018 and 2019, no difficulties in deliverance of critical important antimicrobials were reported, but for beta-lactams of different formulations it is anticipated to happen again.

The preliminary results from the initiatives based on the National Action Plan highlight the well-known fact that it is easier and faster to achieve overall reductions in consumption than to change habits towards a more prudent use; the latter takes more time and efforts.

Reducing the amount of antimicrobials consumed can only be achieved through parallel actions on the continued improvement of diagnostics and through infection control measures. The National Center for Infection Control (NCIC) at Statens Serum Institut supports many of the national antibiotic initiatives through recommendation guidelines aimed at hospitals and health care settings.

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