5

ANTIMICROBIAL CONSUMPTION IN HUMANS

5. Antimicrobial consumption in humans

Highlights

Total: In 2018, consumption of antimicrobials in humans for both primary sector and hospital sector combined was in total 15.95 defined daily doses per 1000 inhabitants per day (DID), lower than the consumption in 2017 (16.67 DID) and lower than a decade ago in 2009 (17.47 DID). The highest consumption ever reported in Denmark was in 2011 (18.91 DID). In 2018, the primary sector accounted for 13.98 DID, a decrease of -18% compared to the consumption in 2011 (17.06 DID), while the hospital sector accounted for 1.92 DID, an increase of 9% (1.76 DID in 2011).

Trends in consumption: Trends in antimicrobial consumption are driven by treatment of patients in the primary health sector, accounting for approximately 90% of all antimicrobials consumed. When measured in number of prescriptions redeemed per 1000 patients, 20 years ago (in 1999) the consumption was at a national average of 535 prescriptions per 1000 inhabitants per year, increasing until the first peak of 630 prescriptions per 1000 inhabitants per year in 2007 and the second, highest peak of 638 prescriptions per 1000 inhabitants per year in 2011. Since 2011, antimicrobial consumption in the primary health sector has decreased for all five health regions and in all municipalities. Marked decreases were observed since 2016, possibly related to the development and introduction of national goals for the reduced consumption of antimicrobials in humans as defined in the National action plan from the Danish Ministry of Health published July 2017.

Decreases in consumption in primary healthcare since 2011 were mainly observed for beta-lactamase sensitive penicillins and macrolides, the beta-lactamase sensitive penicillins decreasing from 5.29 DID to 3.61 DID and the macrolides from 2.44 DID to 1.46 DID during the years 2011 to 2018, respectively. Decreases were also observed for fluoroquinolones and tetracyclines,declining from 0.57 DID to 0.41 DID and from 1.74 DID to 1.40 DID, respectively for the same period. From 2011 to 2018, beta-lactamase resistant penicillins were the only antimicrobials with continued increased consumption observed, from 1.22 DID to 1.60 DID. Decreases were noted for both genders and all age groups, most pronounced among the youngest and less pronounced among the eldest above 80 years of age.

Simultaneously, the **consumption at hospitals increased** during the decade, from 70.35 DDD per 100 bed days (DBD) or 264.29 DDD per 100 admissions (DAD) in 2009 to 99.31 DBD or 291.63 DAD in 2018, respectively, corresponding to increases of 41% in DBD and 10% in DAD.

Consumption of the **antimicrobials of special critical interest** (cephalosporins, fluoroquinolones and carbapenems) in total at hospitals decreased in the beginning of the decade, from a combined 22.19 DBD in 2009 to 19.59 DBD in 2018. In 2018, they constituted altogether 20% of the antimicrobials consumed at hospitals, corresponding to 10.2 DBD for cephalosporins, 6.81 DBD for fluoroquinolones and 2.77 DBD for carbapenems, respectively. Consumption showed no notable changes between 2016 and 2018, despite a defined national goal of a 10% decrease from 2016 to 2020.

For DANMAP 2018, the new WHO DDD values were applied and all calculations and figures updated 10 years retrospectively. Due to changes in DDD values for several important antimicrobials, the numbers and figures in this report are not comparable to former reports.

5.1 Introduction

In Denmark, all consumption of human medicine including antimicrobials 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. The primary sector has submitted antimicrobial sales data since 1994, whereas the hospital sector has submitted data since 1997.

In Denmark only medical doctors, veterinarians and dentists can prescribe antibiotics and only publicly registered and approved pharmacies are allowed to sell. Recording of the consumption in the primary sector is based on the total sales from pharmacies to individuals and private clinics. For all sales, data contain 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 information on the prescriber and 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.

For the hospital sector, primarily data from public somatic hospitals with acute care function is included in the report – data from psychiatric hospitals, private hospitals and hospices has traditionally been excluded, since consumption at these facilities is only minor (0.5 DID in 2018) and no good denominator for measuring the consumption in these patient populations exists. But for Figure 5.1a (total consumption measured in defined daily doses (DDD) per 1000 inhabitants per day) all consumption data were included to give a complete picture on human antimicrobial consumption in Denmark.

For more detailed information on data reporting and registration, please see 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. The only other antimicrobials included are metronidazole (ATC code P01AB01) and vancomycin (ATC code A07AA09), since these contribute with valuable information regarding antibacterial treatments as well. Their consumption has been included in DANMAP since 2014. Tuberculostatica, antiviral and antifungal drugs are not included, but textbox 5.4 (page 74 to 78) deals with the consumption of antifungal compounds and resistance patterns in human invasive isolates of *Candida* and *Aspergillus*.

A major change in DANMAP 2018 is the correction for the new DDD values for some of the commonly used antimicrobials, changed by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo per January 2019. All numbers in the figures and tables were updated 10 years retrospectively with the new DDDs. Due to these changes, figures are no longer comparable between the present and former reports.

The most important changes in relation to the Danish patterns in consumption were the new DDD values for oral dosing of amoxicillin and amoxicillin with clavulanic acid and for parenteral dosing of meropenem, ciprofloxacin and colistin. Denmark has a strong tradition for using penicillins for the treatment of patients in both primary care and at hospitals. Over time, doses given per treatment have increased due to new knowledge in pharmacodynamics. Thus, for most penicillins the former WHO DDD values were no longer in correlation with actual recommendations on dosages, and the recent changes in the DDD were very welcome.

However, changes for the other groups of penicillins are still needed. In this report, for demonstration of differences and for use in National monitoring, Danish adjusted DDDs (DaDDD) were developed for both primary care data and hospital data and applied in two of the figures (Figure 5.4 and Figure 5.13, respectively). For more information regarding DaDDD, see Table 9.5 and 9.6 in chapter 9.8, materials and methods.

Further information and further numbers on the use of antimicrobials in Denmark can be found at www.medstat.dk and http://esundhed.dk/sundhedsregistre/LSR/ANT/Sider/ANT.aspx.

The Danish healthcare system has undergone significant changes since the DANMAP collaboration began in 1995. Most notable are the establishment of a more centralised hospital system, concentrating highly specialized functions in few tertiary care hospitals, paralleled by a reduction in the number of geographically more peripherally situated secondary care hospitals. Thus, during the last two decades the number of hospitals in Denmark offering 24 h acute care has diminished from 80 public somatic hospitals in 1995 to 41 in 2015. For 2020, it is expected that all acute care function can be merged further to 21 public hospitals.

Changes in organisation of hospital functions also happened to the overall organisation of surgical and medical treatment. Many surgical procedures are today performed in an ambulatory setting with only short time stay at the hospital. This also applies to internal medicine, where tasks have moved to ambulatory care or been outsourced to the general practitioner. A new political plan for the Danish Health system from 2018 focuses on enforcement of the primary sector by moving many functions from hospital ambulatory care back to 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 or less correct when it comes to describing the actual activity in the health care sector in total. Definitions of what is included in hospital activity become less clear and boundaries between primary and hospital sector become more fluent. It also challenges the comparison of consumption over time.

For DANMAP 2018, hospital consumption was measured in DDD per three different denominators: per 100 bed days, per 100 admissions and per 1000 inhabitants per region for more transparency and a clearer picture of the consumption in total.

Initiatives on the control and reduction of antimicrobials in the human health sector

The National Action Plan on the reduction of antibiotics in humans launched in July 2017 aims at fulfilling three measurable goals, two directed at the consumption in primary care and one focusing on hospital care. The first goal targets an overall reduction in antimicrobial consumption measured in the number of prescriptions redeemed at pharmacies in Denmark, from 462 prescriptions per 1000 inhabitants in 2016 to 350 prescriptions per 1000 inhabitants in 2020. In focus are general practitioners, medical specialists and dentists; prescriptions issued through hospital doctors are omitted from calculations, due to the assumption that these in most cases resemble continuation of a treatment begun at the hospital and thus should be counted there. The second goal aims at a more prudent choice of antimicrobials by focusing on an increase in 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% reduced consumption of the three antimicrobials of special critical interest (cephalosporins, fluoroquinolones and carbapenems) at hospitals from 2016 to 2020, measured in DBD. In 2017, this goal was challenged through shortages of piperacillin/tazobactam, which brought cephalosporins back as a first line treatment of septic patients. In 2018, no difficulties in deliverance of important antimicrobials were reported, but for beta-lactams of different formulations it is anticipated to happen again. During 2018, one and a half year into the plan, the following results had been achieved:

- For goal one the number of prescriptions from primary care (general practitioners, medical specialists and dentists) were reduced to 397 prescriptions per 1000 inhabitants per year

- For goal two, the proportion of beta-lactamase sensitive penicillin (based on number of prescriptions issued from general practitioners, medical specialists and dentists) had remained unchanged (31%) from 2016 to 2018

- At hospitals, the consumption of antimicrobials of special critical interest (cephalosporins, fluoroquinolones and carbapenems) had decreased by 2% (from 20.24 DBD in 2016 to 19.79 DBD in 2018)

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 taking more time and efforts.

The National Action Plan was issued by the Danish Ministry of Health and supported by the National antibiotic council representing all relevant health institutions, organisations and specialties working with AMR and treatment or control of infections in Denmark. Together with the National Action Plan, a One Health Strategy was published, building on the existing National Action Plan on the control of antimicrobial resistance from 2010. Both are available at the Danish Ministry of Health's homepage at www.SUM.dk.

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, (textbox 5.3, page 72)

5.2 Total consumption (Primary healthcare and Hospital care combined)

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 year (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.

For DANMAP 2018, calculations for figures were based on the new WHO DDD values, (Table 9.4 materials and methods) and data updated ten years back in time. Further back, data are not specified into the different drug classes and thus could not be updated.

The total consumption of systemic used antimicrobials in 2018 was 15.95 DID, which is 4.6% less than the consumption in 2017 (16.67 DID) and 9.5% less than the consumption a decade ago in 2009 (17.47 DID), (Figure 5.1a, total consumption of private and public health care, DID). The total consumption in 2018 corresponds to 49.786 kg active compound consumed (Table A5.1 in web annex).

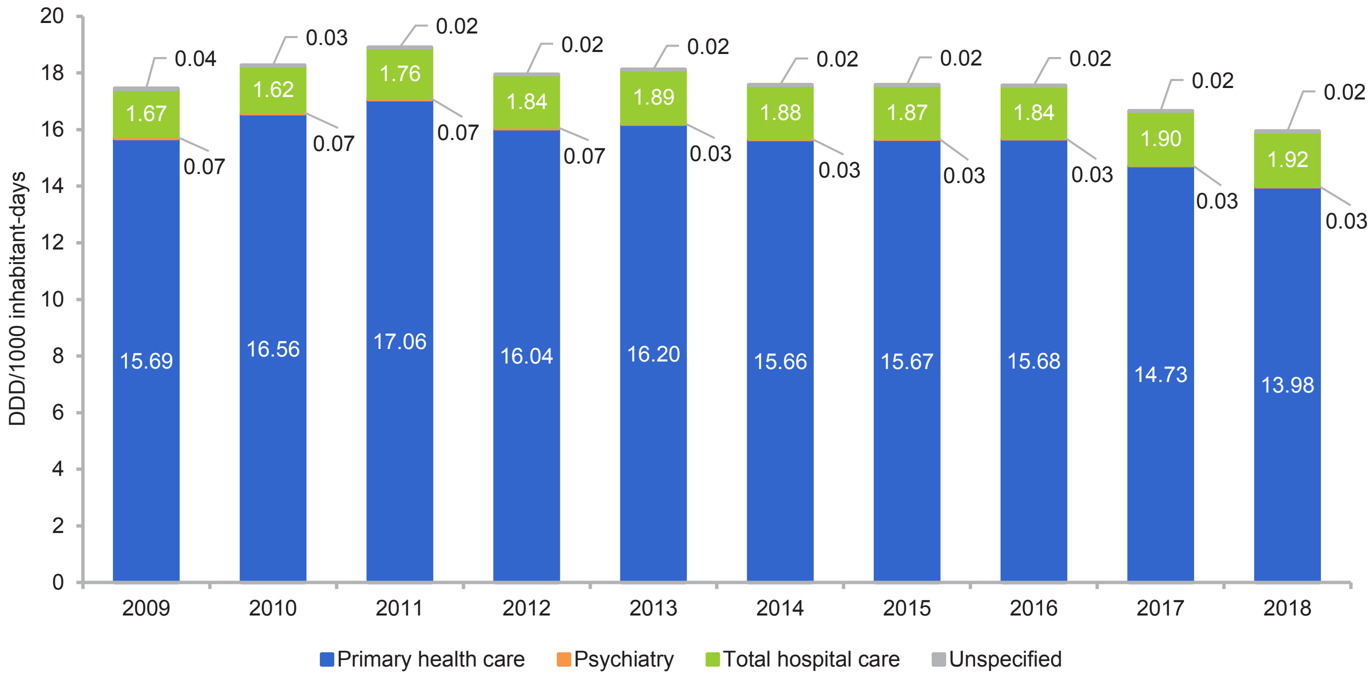
This is the second consecutive year with a marked decrease in the total consumption in Denmark. The decrease is driven by reduced prescribing in primary health care, which accounts for approximately 90% of all antimicrobials used in humans in Denmark.

Fig 5.1b presents consumption data from primary care and acute care hospitals divided into the five regions. Although consumption per inhabitant differs between the regions, for all five regions marked decreases were observed in the primary sector since 2016. The two neighbouring regions, the Capital region and the region of Zealand showed highest total consumptions of 15.89 DID and 16.32 DID, respectively; for the

Capital region due to a relatively high consumption at hospitals and for region Zealand due to a comparably high consumption in primary care. The Central and Northern Region had the lowest total consumption with 14.23 DID and 14.70 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.

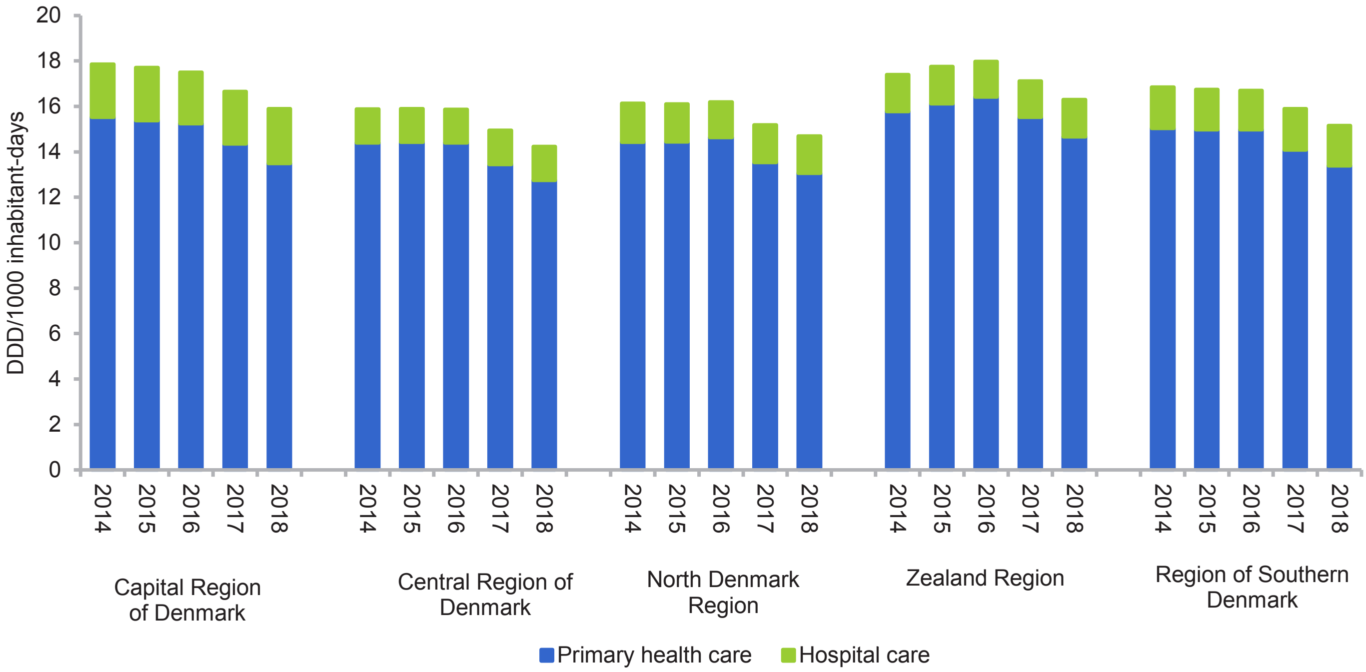
Figure 5.1c presents use of the main antimicrobial drug classes divided into primary care and hospital care, respectively.

Figure 5.1a Total consumption of all systemic antimicrobial agents used for humans, DID, Denmark DANMAP 2018



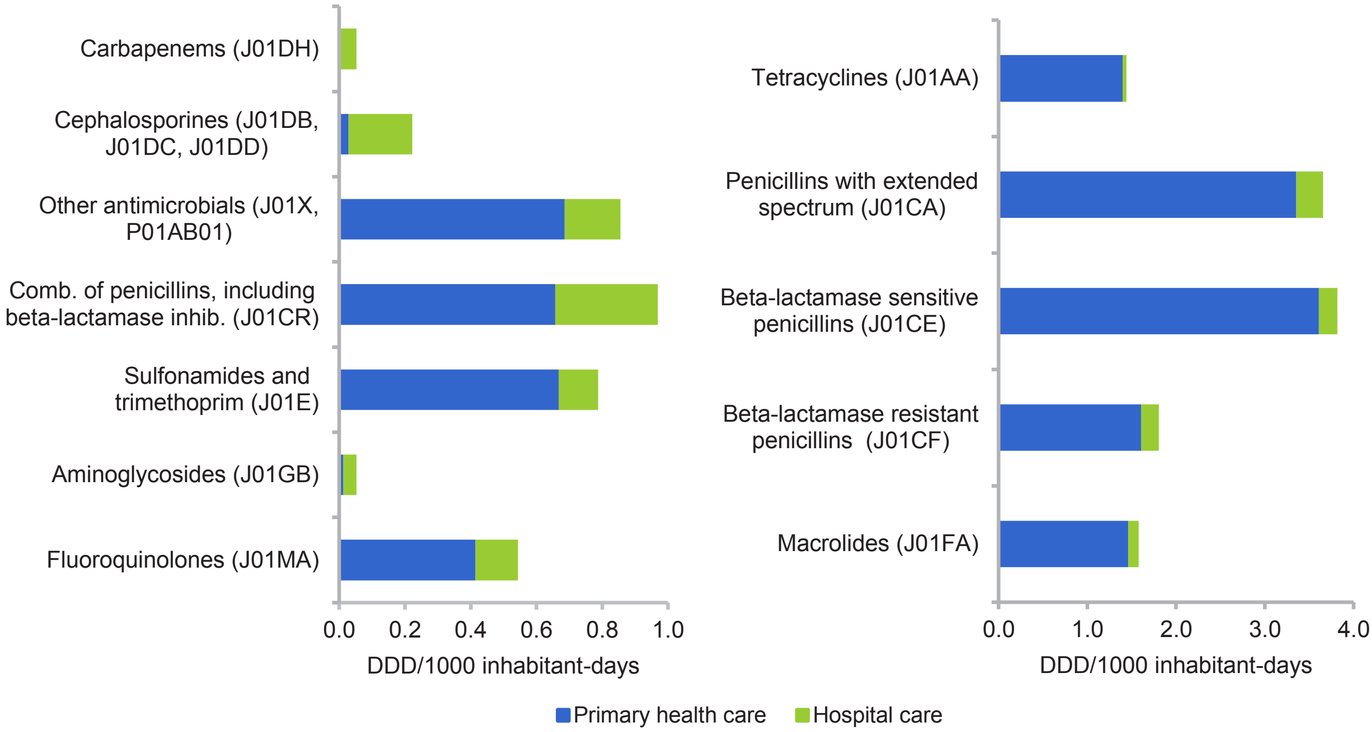
Data for this figure is based on the total sales in Denmark
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.1b Total consumption of systemic antimicrobial agents used in primary care and at acute care hospitals, divided in regions, DID, Denmark DANMAP 2018



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

Figure 5.1c Distribution of consumption of the main antimicrobial classes used for humans, DID, Denmark DANMAP 2018



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

Table 5.1 Consumption of antimicrobial agents for systemic use in primary health care (DID), Denmark DANMAP 2018

ATC group	Therapeutic group	Year									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
J01AA	Tetracyclines	1.62	1.70	1.74	1.76	1.96	1.66	1.60	1.62	1.42	1.40
J01CA	Penicillins with extended spectrum	2.88	3.02	3.11	3.03	3.12	3.20	3.28	3.33	3.36	3.35
J01CE	Beta-lactamase sensitive penicillins	5.13	5.26	5.29	4.68	4.65	4.38	4.33	4.16	3.88	3.61
J01CF	Beta-lactamase resistant penicillins	1.14	1.17	1.22	1.21	1.30	1.36	1.38	1.48	1.56	1.60
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.30	0.45	0.60	0.70	0.81	0.87	0.95	0.95	0.79	0.66
J01D	Cephalosporins and other betalactam antibiotics	0.04	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
J01EA	Trimethoprim and derivates	0.48	0.51	0.50	0.52	0.53	0.55	0.56	0.56	0.56	0.53
J01EB	Short-acting sulfonamides	0.27	0.26	0.24	0.22	0.22	0.21	0.18	0.16	0.15	0.14
J01EE	Combination of sulfonamides and trimethoprim, including derivates	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
J01FA	Macrolides	2.21	2.44	2.60	2.20	1.94	1.79	1.77	1.82	1.62	1.46
J01FF	Lincosamides	0.03	0.04	0.04	0.04	0.05	0.05	0.05	0.06	0.06	0.06
J01GB	Aminoglycosides	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluroquinolones	0.52	0.57	0.57	0.55	0.52	0.50	0.49	0.48	0.44	0.41
J01XC	Steroid antibacterials (combination fusidic acid)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.00
J01XE	Nitrofuran derivates (nitrofurantoin)	0.49	0.51	0.50	0.50	0.49	0.48	0.45	0.43	0.26	0.15
J01XX	Other antibacerials (metheamine >99%)	0.26	0.27	0.26	0.25	0.24	0.24	0.25	0.27	0.28	0.29
J01XD and P01AB01	Nitroimidazole derivates (metronidazole)	0.26	0.27	0.28	0.28	0.28	0.28	0.28	0.28	0.25	0.24
J01 and P01AB01	Antibacterial agents for systemic use (total)	15.69	16.56	17.05	16.03	16.19	15.64	15.66	15.67	14.71	13.97

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)

5.3 Primary healthcare

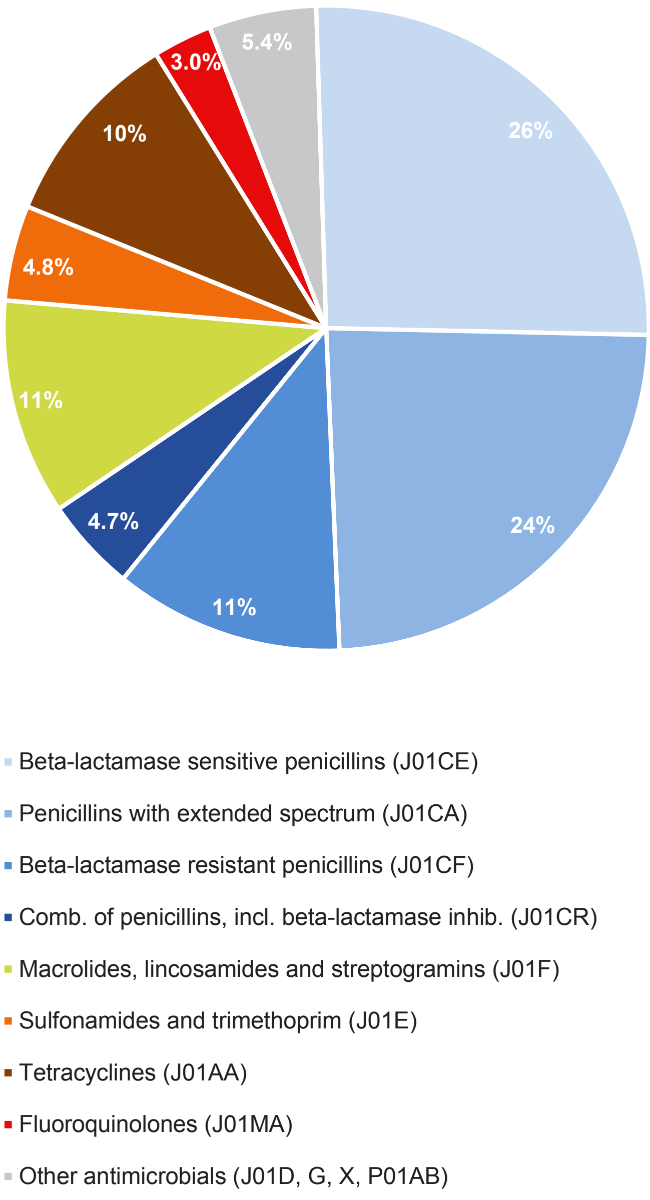
5.3.1 Total consumption in primary healthcare in DID

In 2018, the consumption of antimicrobials in primary healthcare based on total sales from pharmacies was 13.98 DID, a decline of 5.4% from 2017 (14.73 DID). This is the second year in a row with a significant decline since 2012 and a reduction of altogether 18% since the peak of 17.06 DID in 2011, (Figure 5.1a). Within the decade, the consumption has decreased overall 11% from 15.69 DID in 2009.

Beta-lactamase sensitive penicillins continued to be the biggest group consumed with 3.61 DID (accounting for 26% of the total consumption in primary care, Figure 5.2). They were followed closely by penicillins with extended spectrum with a consumption of 3.35 DID (corresponding to 24% of the total consumption). Beta-lactamase resistant penicillins surpassed macrolides in being the third biggest group consumed with 1.60 DID (accounting for 11% of the total consumption). Macrolides and tetracyclines were fourth and fifth biggest groups with 1.46 (11%) and 1.40 DID (10%), respectively, (Figure 5.2 and Table 5.1).

Figure 5.2 Distribution of the total consumption of antimicrobial agents in primary healthcare, based on DDD, Denmark

DANMAP 2018



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

5.3.2 Trends in consumption of the leading antimicrobials in DID

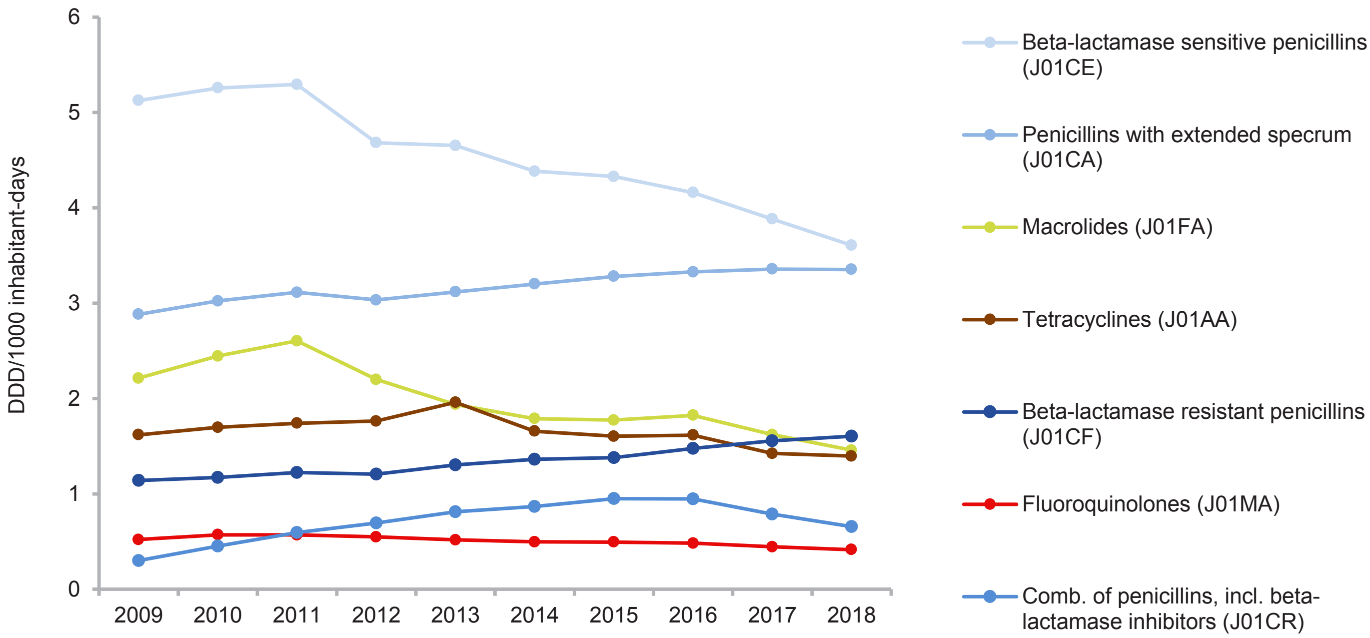
The decreases in consumption in primary health care observed since 2016 apply to seven of the nine main antimicrobial classes, (Figure 5.3). For the beta-lactamase sensitive penicillins, macrolides and fluoroquinolones this is a continuation of a decreasing trend observed since the peak of consumption in 2011. Within these seven years the consumption of beta-lactamase sensitive penicillins decreased from 5.29 DID in 2011 to 3.61 DID in 2018 (- 32%), while consumption of macrolides decreased from 2.60 DID to 1.46 DID, (-44%). From 2017 to 2018 alone, the corresponding decreases were 7.1% and 10%, respectively. Fluoroquinolones also decreased steadily from 0.57 DID in 2011 to 0.41 DID in 2018, (-28%), Table 5.1.

Fluoroquinolones represent the smallest drug class among the leading antimicrobials, for the last decade accounting for a stable 3% of the total consumption, when measured in DID, (Figure 5.2). In Denmark, fluoroquinolones are to be solely used for treatment of very few specific infections, where they are considered the drug of choice (e.g. exacerbation in a patient with chronic obstructive lung disease and known penicillin allergy). 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.

For all three drug classes (beta-lactamase sensitive penicillins, macrolides and fluoroquinolones) the decreases in consumption are paralleled by a corresponding decline in the number of treated patients and redeemed antimicrobial prescriptions, (Table 5.3 and 5.4). It also coincides with different initiatives on a more rational use of antibiotics in Denmark. Examples of these are the establishment of the National Antibiotic Council, 2012, recommendations regarding the use of antibiotics issued through the Danish Health Authority, also 2012, and `happy audit´ and other initiatives on better diagnostics undertaken by general practitioners in recent years. In addition, since 2012 antibiotic campaigns aimed at the public to create more knowledge and awareness regarding AMR were launched annually by the Ministry of Health.

The only antibiotics for which consumption showed continuing increasing trends during the decade (2009 to 2018), were the penicillins with extended spectrum and the beta-lactamase resistant penicillins. These increased from 2.88 DID to 3.35 DID (16%) and from 1.14 DID to 1.60 DID (33%), respectively.

Figure 5.3 Consumption of leading antimicrobial groups for systemic use in primary health care, DID, Denmark DANMAP 2018



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

Noteworthy for 2017 and 2018 were decreases in consumption for combination penicillins and tetracyclines. Combination penicillins had been steadily increasing since their introduction to the Danish marked in 2003, but decreased from 0.95 DID in 2015 and 2016 to 0.66 DID in 2018 (-31%). Tetracyclines presented with increases until the peak of 1.96 DID in 2013 but then levelled off and decreased from 1.62 DID in 2016 to 1.40 DID in 2018 (-14%), (Table 5.1).

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 2018, the four groups of penicillins accounted for 9.22 DID, 66% of all antimicrobials consumed; a decade ago in 2009, they accounted for altogether 9.45 DID, 60% of the total antimicrobials consumed that year. However, due to shifting trends in the usage of the different penicillin drug classes, the consumption of beta-lactamase sensitive penicillins in 2009 constituted 54% of all penicillins, while in 2018 they only constituted 39%, (not shown).

The increases described for the penicillins with extended spectrum are primarily due to increases in the consumption of pivmecillinam, in 2018 accounting for about 75% of this drug class, (Figure 5.4a). While pivmecillinam increased with 36% from 1.57 DID in 2009 to 2.47 DID in 2018, pivampicillin decreased simultaneously with 74% from 0.44 DID to 0.16 DID and amoxicillin with 26% from 0.85 DID to 0.67 DID. From 2017 to 2018, pivampicillin continued to decrease (-15%), while trends for pivmecillinam and amoxicillin reverted for the first time, pivmecillinam decreasing with 0.7% and amoxicillin increasing with 5.9%, respectively.

The increased consumption of beta-lactamase resistant penicillins (dicloxacillin and flucloxacillin) 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).

The new WHO DDD values from January 2019 apply to amoxicillin and amoxicillin with clavulanic acid, which 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, comparison of their use with other drug classes remained complicated, not reflecting the actual use of these. For comparison across drug classes, we therefore developed Danish adjusted DDD (DaDDD) for all main penicillins, (Figure 5.4b). The development was based on dosage recommendations from Danish treatment guidelines. These were then corrected for through comparison with the average doses actually given per treated patient, an information that was available through the elaborate data reported from the pharmacies each year. It is advisable to continue discussing the necessity of changes of the DDD also for these groups, for a more homonymous reporting of antimicrobial consumption in the future. Consumption measured in DID

Figure 5.4a Consumption of leading penicillins in the primary healh care, DID, Denmark DANMAP 2018

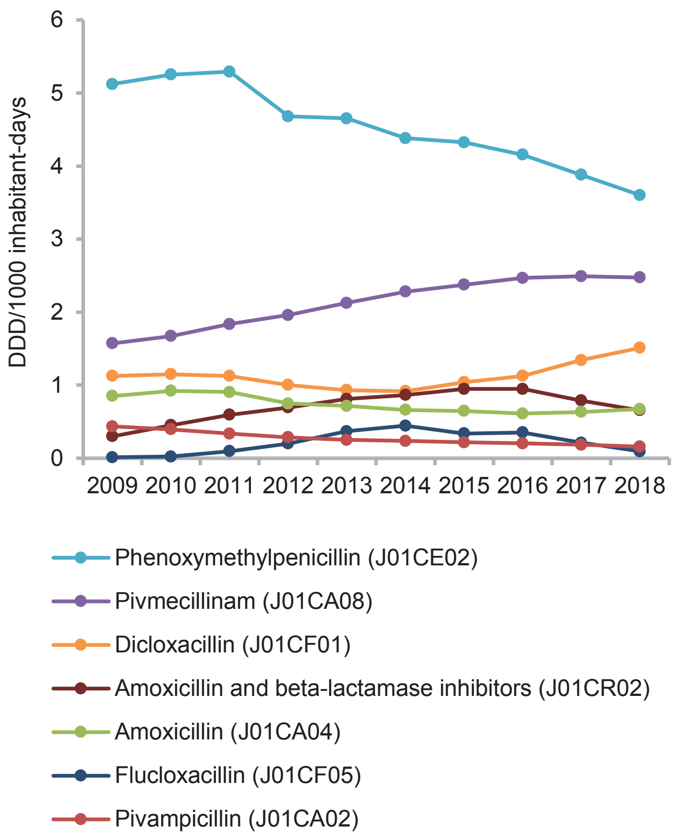
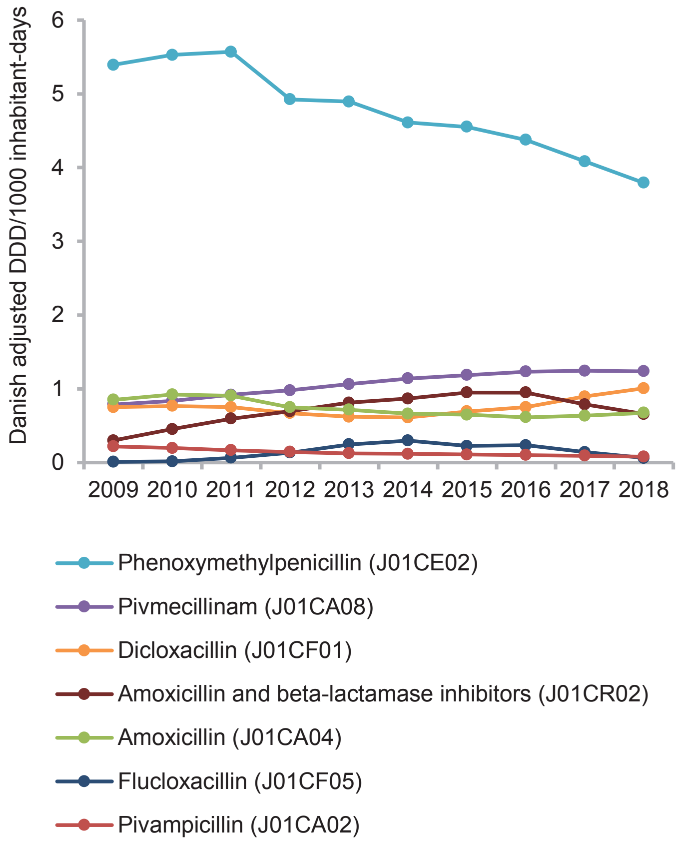


Figure 5.4b Consumpion of leading penicillins in the primary sector, Danish adjusted DaDDD, Denmark DANMAP 2018



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

based on standard WHO DDD and DaDDD is presented in Figure 5.4a and b, respectively, for a visual comparison.

5.3.3 Consumption by age group

Initiatives aiming at reducing overuse and misuse of antibiotics often focus on consumption in the youngest and the elderly, since these are prone to infections due to either an immature immune system or aging. But inappropriate use is not restricted to overtreating children with fever conditions or elderly with unspecific urinary symptoms, for which there is the tendency to misinterpret the situation as being a bacterial infection needing treatment.

Figure 5.5 presents conusmption in the different age groups based on different denominartors: Figure 5.5a presents consumption in DID, FIgure 5.5b in crude DDD, i.e. not corrected for population size, presenting the actual amount of antimicrobials consumed per age group. Figure 5.5c presents the number of patients treated and 5.5d the actual population sizes. All figures show data from 2009 to 2018. For children, WHO DDD values were used, although dosages given to children are based on bodyweight 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 groups.

5.3.4 Consumption of antimicrobials in children

The total consumption in children of all age groups continued the decreases observed for the last decade, regardless of the indicator used: In 2018, altogether 24.8 DID were consumed by children and young from 0 to 19 years. This corresponds to an average per age group of 6.2 DID, 187 treated patients per 1000 inhabitants (children) and 295 prescriptions redeemed per 1000 inhabitants (not shown). A decade ago, the corresponding numbers were: a total of 33.1 DID for all four age groups combined and corresponding averages of 8.3 DID, 271 treated patients and 462 prescriptions redeemed per 1000 children, (Figure 5.5a and 5.6).

As mentioned, measuring the consumption in children in defined daily doses is problematic, since the system of defined dailys doses was developed based on the "maintenance dose per day for its main indication in adults" (https://www.whocc.no/ddd/definition_and_general_considera/). For children, different pharmacodynamics and -kinetics apply and especially dosing in the younger classes is based on doses per bodyweight in kg. Still, assuming that dosage regimens did not vary considerably within the last decade, it is possible to compare the consumption in each age group with itself over time. Thus, the consumption of DIDs in the different age groups show a clear tendency to reductions for especially penicillins and macrolides, which decreased from an average of 2.9 DID and 1.3 DID in 2009 to 2.1 DID and 0.6 DID in 2018, respectively (data not shown). This trend can also be observed in the reduced number of treated patients, as presented for the main antimicrobials used in Figure 5.6.

From 2009 to 2018, the number of prescriptions redeemed for all young age groups (0-19 year olds) decreased from 462 to 295 prescriptions per 1000 inhabitants (-36%) and from 271 to 187 treated patients per 1000 inhabitants (-31%) for the decade, respectively. Differences in reduction varied

Figure 5.5a Consumption of all systemic antimicrobial agents in the primary sector in different age groups, DID, Denmark
DANMAP 2018

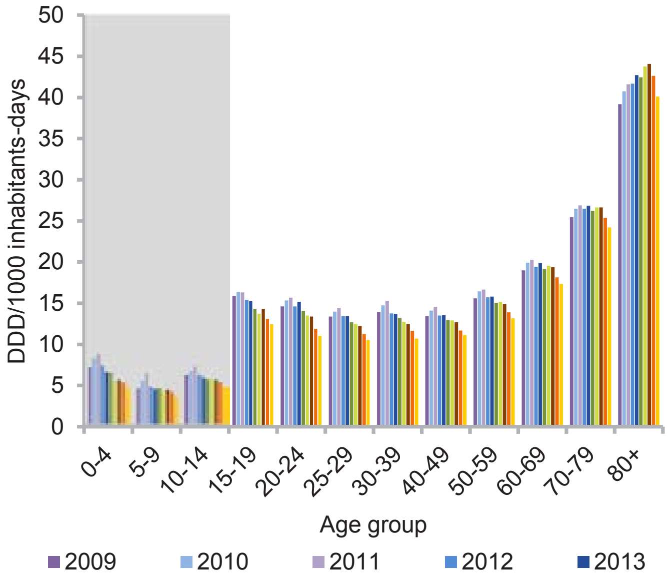


Figure 5.5b Consumption of all systemic antimicrobial agents in the primary sector in different age groups, DDD, Denmark
DANMAP 2018

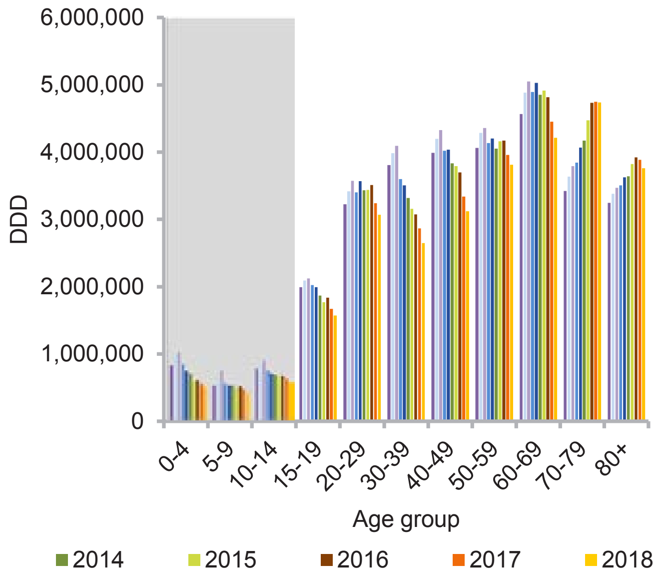


Figure 5.5c Treated patients per 1000 inhabitants in the primary sector in different age groups, Denmark
DANMAP 2018

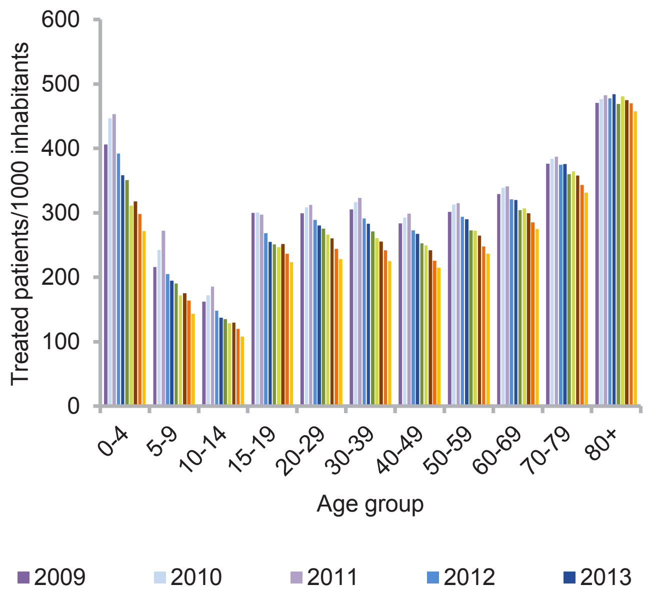
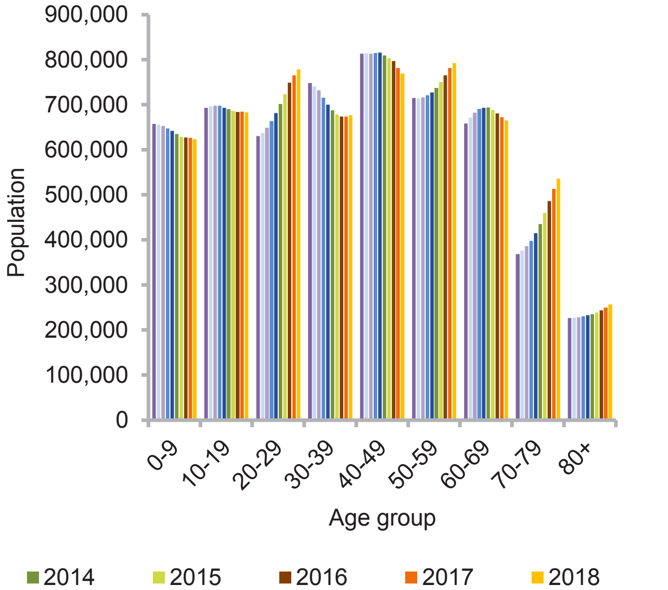


Figure 5.5d Population in different age groups, Denmark
DANMAP 2018

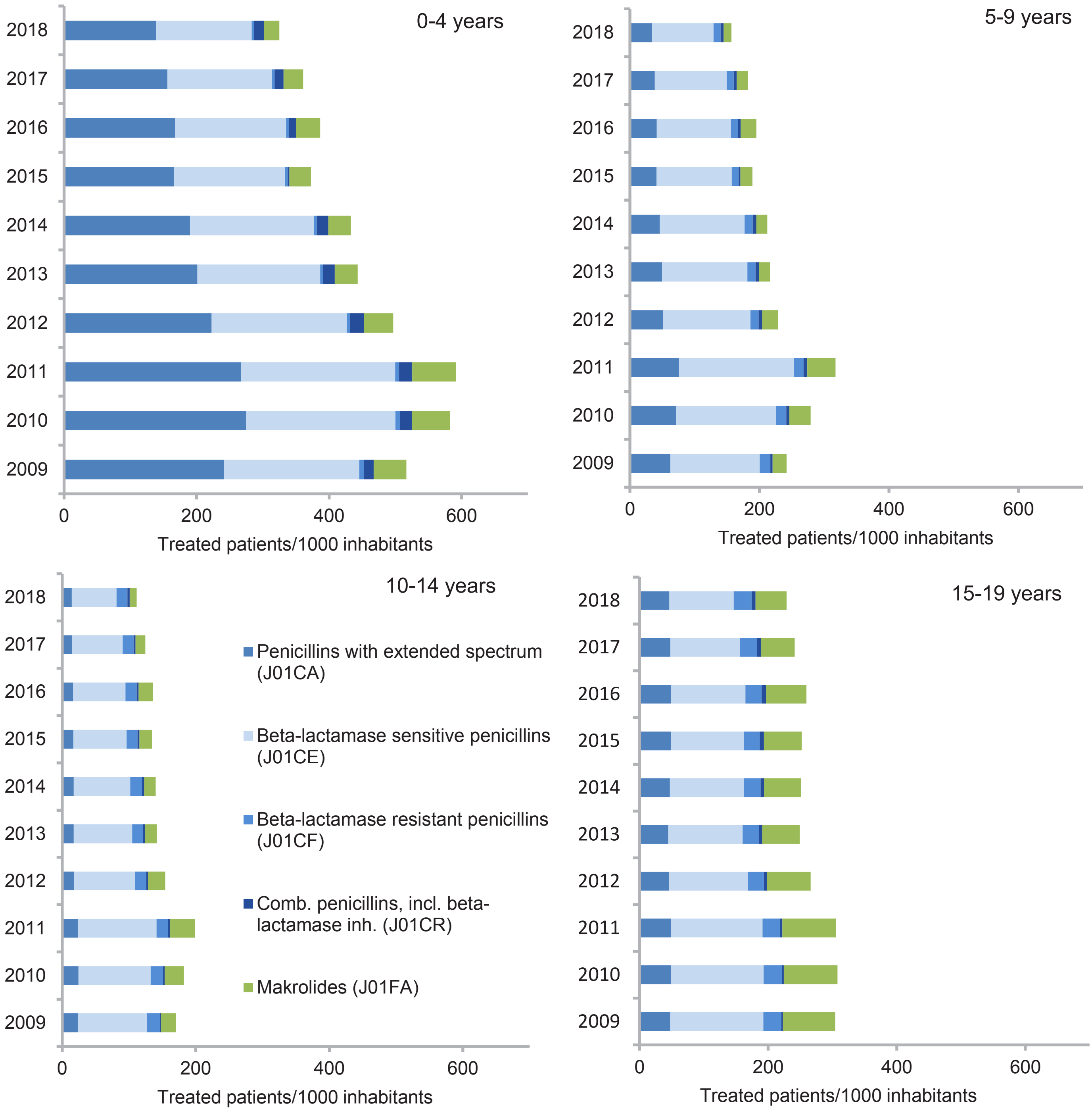


Data used in figure 5.5a-5.5c is based on registered sales to individuals
ATC numbers used in figure 5.5a-b stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system
Population size in Figur 5.d is based on data from Statistics Denmark at www.dst.dk

from a decrease of 41% in the number of prescriptions for the youngest (0-4 years old) to -30% for the oldest, (15-19 year olds). When measured in the number of treated patients, the decreases varied from -34% in the 5 to 9 years old to -26% in the adolescents (not shown).

In the youngest age group of 0 to 4 year olds, the boys received on average 10% more prescriptions than the girls – a trend that has been quite stabile. Thus in 2009, they received 813 versus 711 prescriptions per 1000 inhabitants (0-4 years old) and in 2018, 479 versus 420 prescriptions per 1000 inhabitants, respectively (not shown). For the 5 to 19 year olds, opposite trends with girls receiving approximately 30% more prescriptions on average were observed (not shown).

Figure 5.6 Consumption of five antimicrobial agents children/adolecents age 0-19, DID, Denmark DANMAP 2018



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

As for the general population, penicillins are the main antibiotics used in the treatment of bacterial infections in children. Beta-lactamase sensitive penicillins account for 30% to almost 50% of the consumption (depending on the indication) and the share of beta-lactamase sensitive penicillins compared to the other main antimicrobial classes used in children has increased in recent years. Thus, when measuring the number of treated patients per 1000 inhabitants from 2009 to 2018, the beta-lactamase sensitive penicillins decreased by 30 – 35% for all age groups (0 – 19 years old), while the beta-lactamase resistant penicillins, the penicillins with increased spectrum (primarily amoxicillin) and the macrolides decreased with 40 – 50%. Only for combination penicillins the number of treated patients increased over the decade, from 1% in the youngest to 139% in the adolescents.

Macrolides play an important role in the treatment of infections in children and the young. They are the drug of choice for respiratory tract infections with *Mycoplasma pneumoniae* and in pertussis, and in young school-aged children the consumption of macrolides will often mirror *Mycoplasma* epidemics, while consumption of macrolides in the youngest may to a certain extent mirror an epidemic with pertussis (but less pronounced due to generally fewer cases than with *Mycoplasma*). No epidemic occurred in the winter of 2016-2017 or 2017-2018. Macrolides are also used in the adolescents for the treatment of sexually acquired infections, e.g. *Chlamydia*. This (and acute pharyngitis) is probably the reason for the relatively high consumption of macrolides in the 15-19 year olds; 49 treated patients per 1000 inhabitants per year compared to 11 treated patients per 1000 for the 10-14 year olds, 12 treated patients per 1000 for the 5-9 year olds and 23 treated patients per 1000 for the 0-4 year olds for 2018, Figure 5.6).

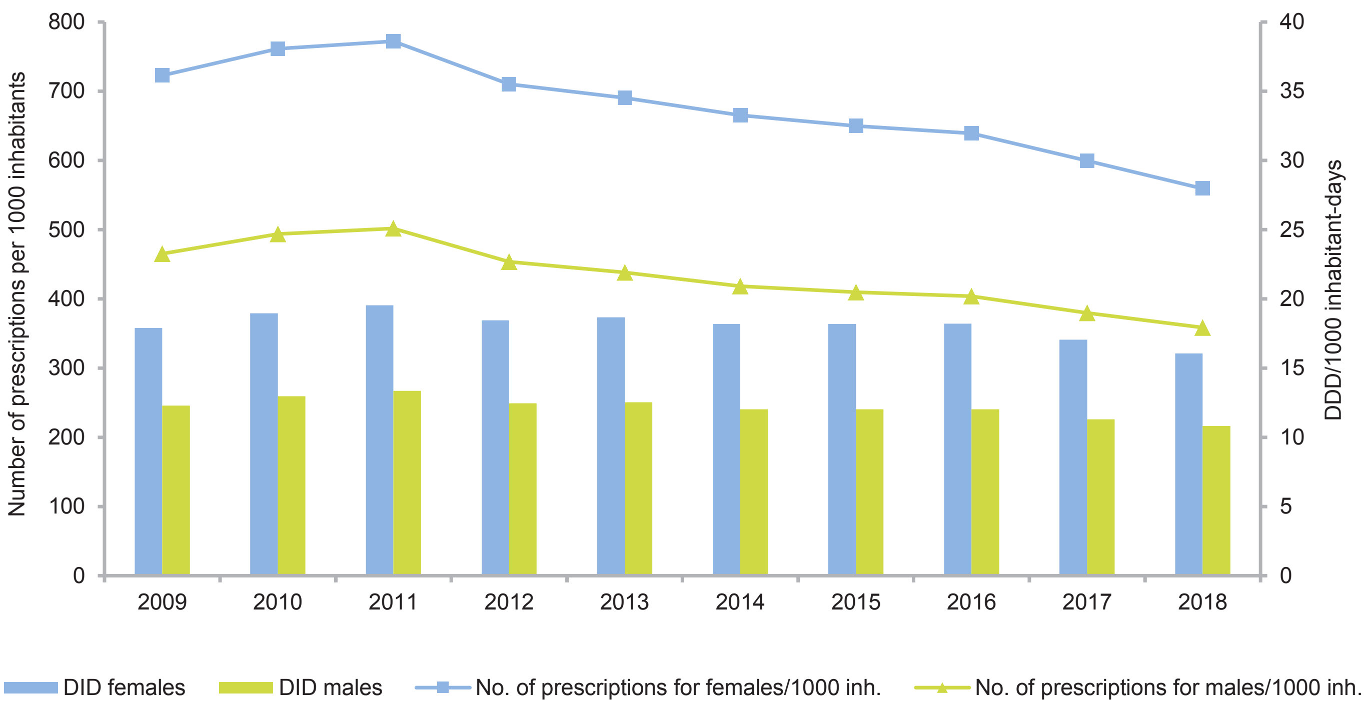
5.3.5 Consumption of antimicrobials according to gender

Differences between the genders regarding consumption of antimicrobials are well known, (Figure 5.7a). In general, women receive more treatment – a trend driven by a much higher incidence of urinary tract infections. Thus, the consumption of sulphonamides, trimethoprim and nitrofurantoin is three times higher for women than for men. Moreover, the consumption of pivmecillinam in women doubles the consumption in men. Also for beta-lactamase sensitive penicillins and macrolides the differences in consumption, especially when measured in DID, are substantial, (Figure 5.7b). For tetracyclines, there are less significant differences in gender and for the consumption of fluoroquinolones, no differences have been observed over the years, (not shown).

From 2009 to 2018, the number of treated women per 1000 inhabitants (all age groups) decreased from 356 to 287 (-19%) and the number of treated men per 1000 inhabitants from 256 to 198 (-23%). During the same period, the amount of DDD/prescription increased for women from 9.0 to 10.5 (17%), and for men from 9.6 to 11.0 (15%). Altogether the consumption in women decreased from 17.9 DID to 16.0 (-11%), and in men from 12.3 DID to 10.8 (- 12%).

Figure 5.7a Consumption of antimicrobial agents (J01 and P01) per gender, presc per 1000 inhabitans and DID, Denmark

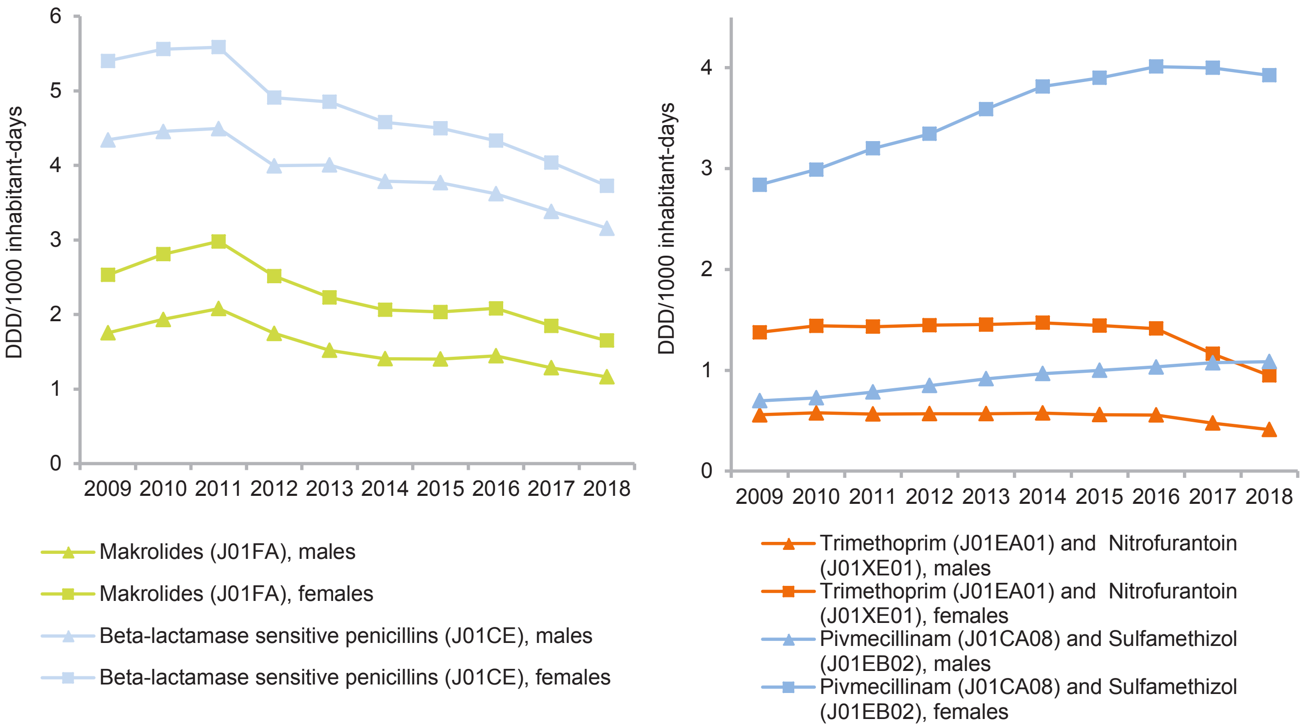
DANMAP 2018



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 5.7b Consumption of most used antimicrobials against respiratory infections and urinary tract infections, Denmark

DANMAP 2018



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

Drugs for the treatment of upper respiratory tract infections. For both women and men a decrease in the consumption of beta-lactamase sensitive penicillins and macrolides was observed. For women, the consumption decreased for the beta-lactamase sensitive penicillins from 5.4 DID in 2009 to 3.7 DID in 2018 and for the macrolides from 2.5 DID in 2009 to 1.6 DID in 2018. For men the changes were from 4.3 DID to 3.2 DID and from 1.8 DID to 1.2 DID, respectively, for the same decade, (Figure 5.7b).

Urinary drugs. From 2009 to 2017 the consumption of pivmecillinam in women increased continuously, from 2.4 DID to 3.8 DID and in men from 0.6 DID to 1.0 DID, while it remained almost unchanged in 2018 with 3.7 DID and 1.0 DID, respectively. In 2016, the national antibiotic campaign focused on reducing the amount of antimicrobials consumed in the treatment of UTIs in women using two different approaches: one broadcasting an educating movie on the social media targeted young women, the other directed at health personnel at nursing homes dealing with confused or dement elderly women with unspecific signs of UTI. In the beginning of 2017, recommendations regarding the use of nitrofurantoin were issued, advocating for caution in the use in elderly. This probably is the reason for the notable changes in the consumption of nitrofurantoin, from a stable 0.7 DID in women from 2009 to 2016 to 0.4 DID in 2017 and 0.2 DID in 2018. In men, the consumption increased from 0.2 DID in 2009 to 0.4 DID in 2017 and decreased to 0.1 DID in 2018. No significant changes were observed for pivmecillinam, sulfamethizol or trimethoprim for 2018, but the consumption seems to be levelling off since 2016. In Figure 5.7b the consumption of antimicrobial urinary drugs is 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).

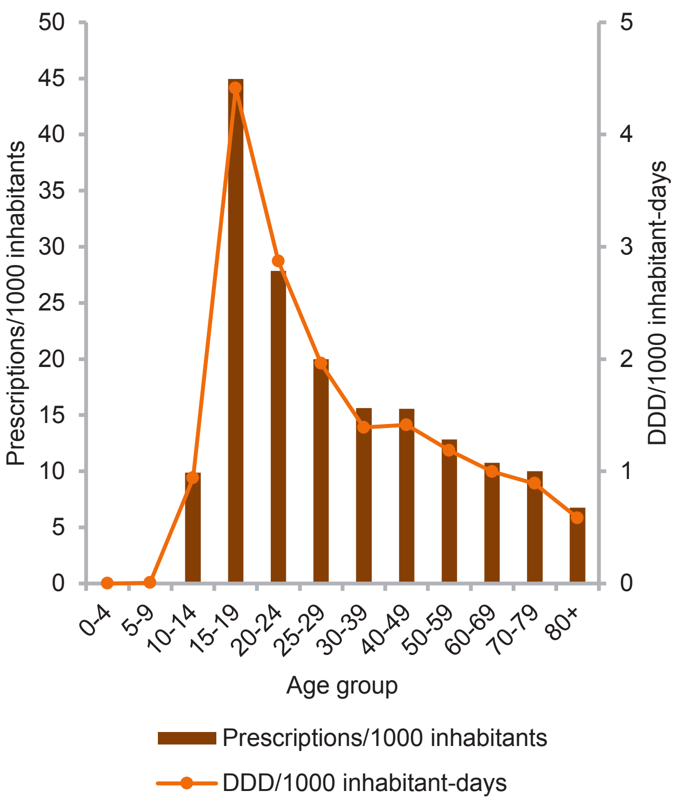
5.3.6 Tetracyclines

Tetracyclines are the fourth biggest group of antimicrobials consumed in Denmark. In 2018, they accounted for 1.40 DID, corresponding to 10% of the total consumption in primary health care. During the last decade, the consumption has decreased by 12.5% from 1.6 DID in 2009. In 2013, the consumption peaked unexpectedly at 1.96 DID but has since shown continuing decreases. Tetracyclines are used by all age groups above 12 years and by both genders, (Figure 5.8).

Tetracyclines account for a considerable part of the consumption of antimicrobials among adolescents due to the treatment of acne, (Table 5.2 on the distribution of indications among treated patients for 2016-2018). Treatment against acne 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 the tendency to treat younger siblings if a treatment course in an elder brother or sister has been of success. Both genders are affected, but there exist clear differences in prescription habits regarding boys and girls. Thus, among girls the treatment periods are longer and extend into the young adults of 20 to 24 years, while boys primarily are treated in shorter periods at the age of 15 to 19 years. In 2009, 15 to 19 year old boys received 76 prescriptions per 1000 inhabitants per year on average, whereas girls received 56, corresponding to 35 versus 30 patients treated per 1000 inhabitants. In 2018, the number of 15-19 year old boys receiving treatment had declined to 25 treated patients (corresponding to 42 prescriptions) per 1000 inhabitants, while the number of 15 -19 year old girls remained unchanged with 30 treated patients (but corresponding to 48 prescriptions redeemed) per 1000 inhabitants. Thus in 2018, girls received 1.6 prescriptions per patient on average while it was 1.9 in 2009.

While the number of DIDs consumed did not change much in women (primarily used by young women from 15 to 24 years) from 1.7 DID in 2009 to 1.6 DID in 2018, it decreased more in men (primarily used by boys from 15 to 19 years) – from 1.5 DID in 2009 to 1.1 DID in 2018 (not shown). Increases in the occurrence of sexually transmitted infections and changes in the treatment recommendations for these may be challenges in the future, see chapter on the occurrence of *N. gonorrhoea* in Denmark 8.3.9.

Figure 5.8 Consumption of tetracyclines in different age groups, presc per 1000 inh. and DID, 2018, Denmark
DANMAP 2018



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 5.2 Percentage of total consumtion of tetracyclines
DANMAP 2018

Indication given on the prescription	Year		
	2016	2017	2018
Against acne	44.9	50.7	54.9
Prevention of malaria	9.5	8.1	6.9
Against borrelia infection	2.0	2.6	4.1
Against pelvic inflammatory disease	1.3	1.8	1.9
Against skin and soft tissue infection	1.1	1.2	1.5
Unspecified indications	41.2	35.6	30.6

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

5.3.7 Measures at user level

In this and the following sections, the consumption of antibiotics is described at user level in 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 2018, the total number of prescriptions was 459 per 1000 inhabitants, a 6.3% reduction from the 490 prescriptions per 1000 inhabitants in 2017 and a 23% reduction compared to the 595 prescriptions per 1000 inhabitants in 2009 (Table 5.3). Decreases were observed for all antimicrobial drug classes apart from the penicillins with extended spectrum, which remained unchanged. In 2018, the average number of prescriptions redeemed per patient was 1.89. In 2009, the number was 1.94 (not shown). The number of treated patients in 2018 was 243 per 1000 inhabitants, a decrease of 21% compared to the 306 treated patients per 1000 inhabitants in 2009, (Table 5.4).

Trends in the number of prescriptions and treated patients for the different antimicrobial classes followed mainly the trends already described for the consumed DIDs. Most pronounced increases over the last decade in the number of prescriptions per 1000 inhabitants were seen for combination of penicillins, including betalactamase inhibitors (113%). Most pronounced decreases for the ten year period were in the number of prescriptions per 1000 inhabitants for the folllowing: macrolides (-40%), beta-lactamase sensitive penicillins (-34%), sulphonamides (-33%), tetracyclines (-32%) and fluoroquinolones (-26%), (Table 5.3).

Similar decreases were noted for the decade, when measured in the number of patients treated: macrolides (-38%), beta-lactamase sensitive penicillins (-30%), sulphonamides (-38%), tetracyclines (-26%) and fluoroquinolones (-27%), (Table 5.4).

A comparison of the different indicators of consumption is presented in Figure 5.9. In 2018, the average DDD/prescription remained with 10.7 at the same level as in 2017, an increase of 15% compared to the 9.3 DDD/prescription in 2009.

Table 5.3 Number of prescriptions per 1000 inhabitants for leading antimicrobial agents in primary healthcare, Denmark

DANMAP 2018

ATC group	Therapeutic group	Year									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
J01AA	Tetracyclines	21.62	22.49	22.70	22.56	22.89	20.00	17.90	17.18	15.89	14.63
J01CA	Penicillins with extended spectrum	119.28	127.23	125.17	115.91	114.30	113.83	113.53	113.16	114.37	114.31
J01CE	Beta-lactamase sensitive penicillins	205.85	212.19	213.32	186.91	180.55	170.70	163.09	157.13	148.52	136.81
J01CF	Beta-lactamase resistant penicillins	42.10	42.32	42.75	40.42	41.25	41.04	40.81	41.87	41.87	43.35
J01CR	Combinations of penicillins, including betalctamase inhibitors	11.15	16.53	21.11	24.71	28.01	29.02	30.73	31.13	27.09	23.71
J01E	Sulphonamides and trimethoprim	47.17	47.35	45.05	43.86	43.53	41.51	38.39	36.41	34.29	31.74
J01FA	Macrolides	87.24	97.34	104.22	85.89	74.51	68.01	68.00	68.85	60.00	52.64
J01MA	Fluoroquinolones	21.71	23.69	23.15	22.14	20.65	19.67	19.50	18.74	17.37	15.97
J01X	Other antibacterials (methenamine >99%)	17.93	17.49	18.24	18.03	17.41	16.73	16.28	15.82	10.18	6.76
P01AB01	Nitroimidazole derivatives (metronidazole)	19.02	19.67	19.69	19.68	19.26	19.06	19.15	18.63	17.26	16.31
J01 and P01AB01	Antibacterial agents for systemic use (total)	595.28	628.78	638.08	582.80	565.26	542.53	530.56	522.19	490.08	459.37

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

Table 5.4 Number of treated patients per 1000 inhabitants for leading antimicrobial agents in primary healthcare, Denmark

DANMAP 2018

ATC group	Therapeutic group	Year									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
J01AA	Tetracyclines	13.02	13.44	13.66	13.53	13.86	12.20	11.32	11.04	10.35	9.69
J01CA	Penicillins with extended spectrum	81.07	85.04	84.19	77.31	76.10	75.32	74.87	74.05	74.04	73.56
J01CE	Beta-lactamase sensitive penicillins	158.72	162.81	164.34	145.53	142.19	134.79	130.06	125.69	119.32	110.89
J01CF	Beta-lactamase resistant penicillins	29.87	30.02	30.34	28.51	29.07	29.24	28.85	29.70	29.96	31.09
J01CR	Combinations of penicillins, including betalctamase inhibitors	8.02	11.70	14.95	17.32	19.71	20.52	22.03	22.17	19.89	17.73
J01E	Sulphonamides and trimethoprim	29.51	29.31	27.63	26.48	26.16	24.65	22.45	21.17	19.87	18.42
J01FA	Macrolides	64.44	72.67	78.75	64.73	56.16	51.38	51.75	53.21	46.01	40.11
J01MA	Fluoroquinolones	16.87	18.45	18.10	17.25	16.04	15.30	15.04	14.37	13.36	12.26
J01X	Other antibacterials (methenamine >99%)	7.67	7.53	7.74	7.54	7.48	7.16	7.35	7.47	5.01	3.62
P01AB01	Nitroimidazole derivatives (metronidazole)	16.28	16.73	16.90	16.86	16.51	16.31	16.47	16.03	14.84	14.05
J01 and P01AB01	Antibacterial agents for systemic use (total)	306.41	318.69	324.91	296.40	289.54	278.62	273.49	269.72	255.72	242.55

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

5.3.8 Prescribing activity in primary healthcare

Although Denmark has a very homogenous population with relatively small geographic and socioeconomic variations, considerable differences in the prescribing habits among medical doctors are frequently observed. In 2018, the Central Denmark Region had the lowest prescribing activity when compared to the other four regions, with 12.7 DID and 431 prescriptions per 1000 inhabitants, respectively (Table 5.5). The Region of Zealand had the highest prescribing activity with 14.7 DID and 501 prescriptions per 1000 inhabitants. For all regions, significant decreases in the DIDs and number of prescriptions redeemed were observed for the five years presented (on average 10% in DID and 15% in the number of prescriptions per 1000 inhabitants).

There may be several reasons to the differences in the number of prescriptions redeemed, fx 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 working solo 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.

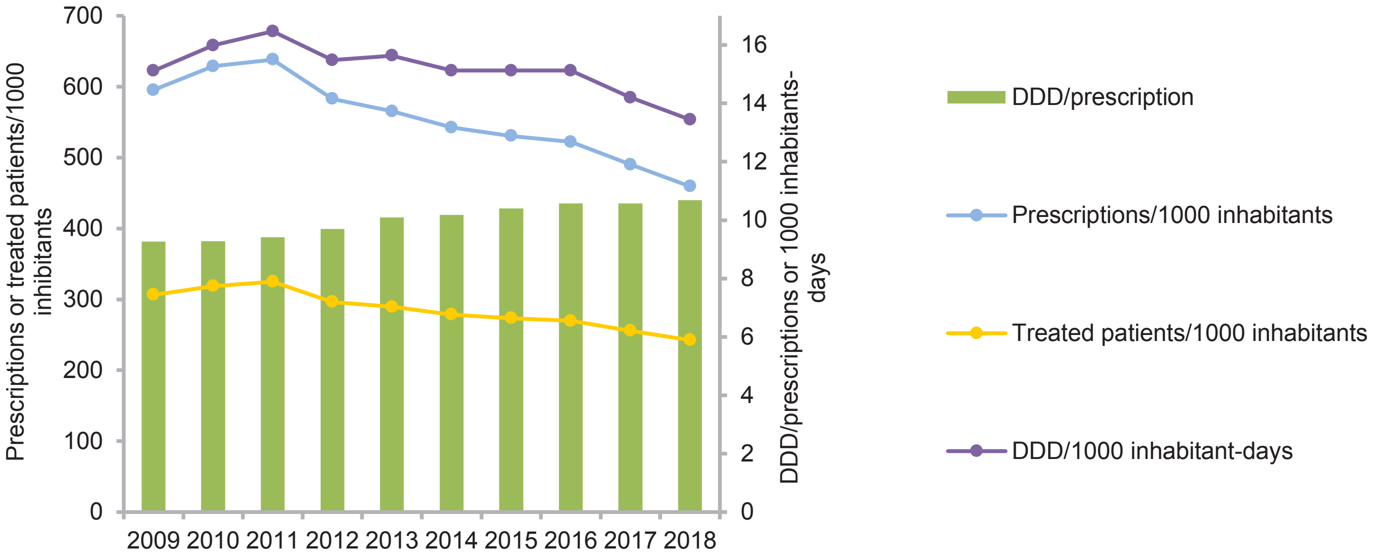
Support of the general practitioners regarding their prescribing habits is in general provided through regional medicine consultants, who also have access to Ordiprax on clinic level, thus being able to monitor consumption and give individual advice. From 2018, the general practitioners in defined geographical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

In Figure 5.10, the number of prescriptions on municipality level is shown, spanning from 368 to 614 prescriptions per 1000 inhabitants. In 2018, most municipalities lay within the range of 450 to 550 prescriptions per 1000 inhabitants. From the 98 municipalities in Denmark, four were excluded from the figure due to very small populations (typically islands).

As would be expected, prescribing habits of doctors with different specialties differ, fx are 60% of antimicrobial prescriptions from specialists in dermato-venerology for tetracyclines, which is used to treat severe acne, (Figure 5.11). Out of all prescriptions issued by dentists, 59% were for beta-lactamase sensitive penicillins, (see textbox 5.2). An overview of the numbers of prescriptions issued by the different specialties can be found in Table 5.6.

As mentioned in the introduction, consumption in the 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 2018, hospital doctors accounted for 62.8 prescriptions per 1000 inhabitants (14% of the antimicrobials sold at pharmacies), (Table 5.6). In 2008, it was 38 prescriptions per 1000 inhabitants (corresponding to 6% of sales), (not shown).

Figure 5.9 Different indicators of antimicrobial consumption (J01, P01AB1) in primary health care, Denmark DANMAP 2018



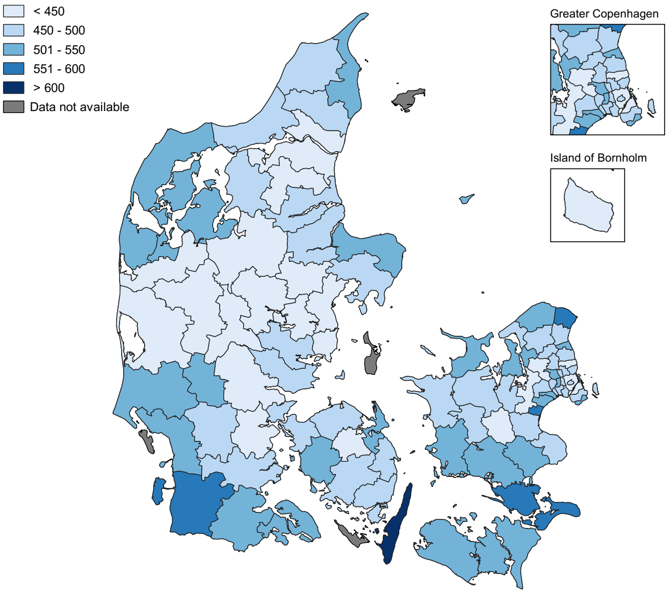
Data used for this figure is based on registred sales to individuals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 5.5 Consumption of antimicrobial agents for systemic use in primary health care at regional level, Denmark DANMAP 2018

Region	Indicator	Year 2014	2015	2016	2017	2018
Capital Region	DDD/1000 inhabitants/day	15.53	15.38	15.24	14.35	13.48
	Prescriptions/1000 inhabitants	549.13	533.22	519.10	489.50	453.55
Region Zealand	DDD/1000 inhabitants/day	15.78	16.12	16.42	15.52	14.67
	Prescriptions/1000 inhabitants	579.57	575.14	574.86	539.03	501.39
Region of Southern Denmark	DDD/1000 inhabitants/day	15.04	14.98	14.97	14.08	13.39
	Prescriptions/1000 inhabitants	556.21	539.98	530.16	496.77	470.58
Central Denmark Region	DDD/1000 inhabitants/day	14.40	14.43	14.39	13.45	12.74
	Prescriptions/1000 inhabitants	499.76	494.17	487.24	458.32	430.88
North Denmark Region	DDD/1000 inhabitants/day	14.42	14.44	14.63	13.53	13.06
	Prescriptions/1000 inhabitants	525.20	510.13	509.05	472.16	451.62
Denmark (total)	DDD/1000 inhabitants/day	15.12	15.12	15.13	14.19	13.44
	Prescriptions/1000 inhabitants	542.53	530.56	522.19	490.08	459.37

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 5.10 Number of prescriptions from primary healthcare /1000 inhabitants in Danish municipalities DANMAP 2018



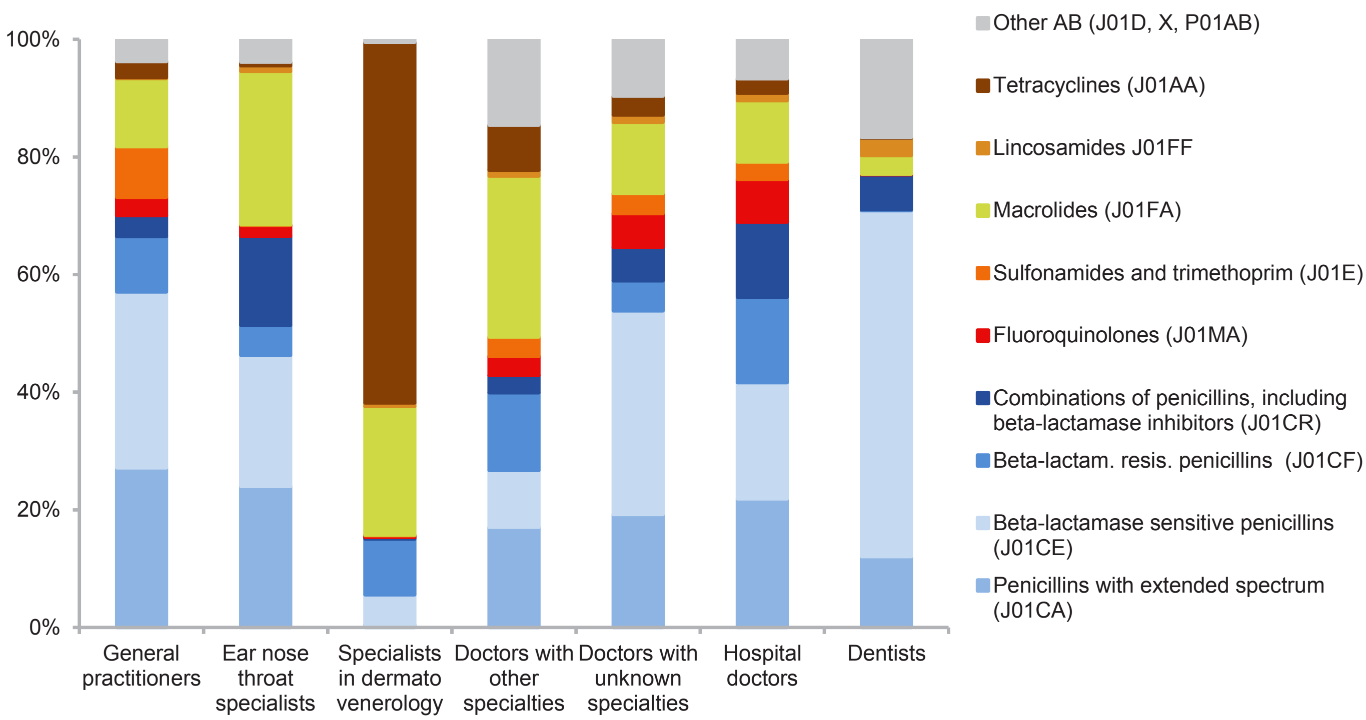
Data used for this figure is based on registered sales to individuals

Table 5.6 Number of prescriptions per 1000 inhabitants per prescribing specialty DANMAP 2018

Doctor type	Year 2016	2017	2018
General practitioners	390.7	368.6	341.5
Ear nose throat specialists	8.8	8.9	8.4
Specialists in dermato venerology	6.4	5.9	5.2
Doctors with other specialties	4.5	4.3	4.2
Doctors with unknown specialties	15.0	10.9	9.7
Hospital doctors	60.7	62.6	62.8
Dentists	36.5	29.1	27.8

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

Figure 5.11 Percentage of prescriptions issued through different medical specialties, primary sector, Denmark DANMAP 2018



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

5.4 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 2018 covers the total sales on systemic antimicrobials (all ATC code J01 as well as ATC code P01AB01 and A07AA09) reported from all Danish hospitals. However, only Figure 5.1a on page 45 includes all consumption, (e.g. also including consumption at private hospitals and psychiatric departments), in 2018 accounting for approximately 2-3% of the total hospital consumption. In all other figures and calculations, only consumption at public 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 health care. The consumption is measured at a national and regional level.

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 A5.2 and A5.3 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 2009 to 2018, (Figure A5.2 in web annex).

Table 5.7 presents data on regional and national hospital activity together with information on the size of population for 2009 and 2018. Denmark has a very high bed occupancy rate and overcrowding happens relatively often, especially during wintertime and in situations with influenza epidemics. In 2018, the number of admissions at somatic Danish hospitals was 1,354,248, while the number of bed-days was 3,976,635. Since 2009, the number of bed-days decreased with altogether 16%, while the number of admissions increased with 7.1% and the Danish population with 4.9%. During the decade, activity in ambulatory care increased from 6.454.112 patients treated to 7.984.223 patients treated, (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 A5.2 in web annex).

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

In 2018, the consumption of antimicrobial agents at somatic hospitals was 99.3 DBD, 3.5% higher than the observed 96.0 DBD in 2017 and 41% higher than the consumption measured a decade ago in 2009, (70.4 DBD). This is the highest consumption measured this decade, (Table 5.8).

The four penicillin groups accounted for altogether 52.4 DBD, corresponding to 53% of the total hospital consumption of antimicrobials (Figure 5.12, Table 5.8).

In 2018, combination penicillins accounted for 16.3 DBD, making it the largest group consumed in 2018 (16.4%). In 2017, a

Table 5.7 Activity at Danish hospitals DANMAP 2018

Region	Number of bed-days in somatic hospitals		Number of admission to somatic hospitals		Population	
	2009	2018	2009	2018	2009	2018
Capital Region of Denmark	1,692,035	1,462,332	430,967	470,971	1,662,285	1,822,659
Zealand Region	680,125	592,449	189,736	232,554	821,252	835,024
Region of Southern Denmark	940,141	766,345	257,156	256,374	1,199,667	1,220,763
Central Denmark Region	944,486	786,970	267,367	283,670	1,247,732	1,313,596
North Denmark Region	493,817	368,539	118,969	110,679	580,515	589,148
Denmark	4,750,604	3,976,635	1,264,195	1,354,248	5,511,451	5,781,190

Data used in this table is based on the activity at acute care public somatic hospitals

Table 5.8 Consumption of antimicrobial agents for systemic use in somatic hospitals, DBD, Denmark DANMAP 2018

ATC group	Therapeutic group	Year									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
J01AA	Tetracyclines	0.95	0.99	1.07	1.54	1.45	1.63	1.80	2.08	2.04	2.37
J01CA	Penicillins with extended spectrum	12.02	11.45	11.35	12.47	12.88	13.56	14.11	14.46	15.66	15.37
J01CE	Beta-lactamase sensitive penicillins	8.75	8.24	9.02	9.31	9.40	9.31	9.08	9.18	10.03	10.38
J01CF	Beta-lactamase resistant penicillins	6.69	6.88	7.69	7.96	8.69	8.96	9.22	8.75	8.81	10.39
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	3.83	4.83	6.48	9.30	10.92	12.76	14.40	15.00	13.48	16.26
J01DB	First-generation cephalosporins	0.12	0.12	0.12	0.12	0.11	0.06	0.04	0.04	0.04	0.04
J01DC	Second-generation cephalosporins	11.08	11.15	14.34	13.35	12.26	11.36	10.12	9.23	10.78	8.97
J01DD	Third-generation cephalosporins	1.17	1.01	1.07	1.03	1.08	1.00	1.04	1.03	1.33	1.20
J01DF	Monobactams	0.00	0.04	0.14	0.15	0.14	0.06	0.03	0.01	0.01	0.01
J01DH	Carbapenems	1.42	1.61	2.33	2.51	2.76	1.92	2.79	2.68	2.83	2.77
J01EA	Trimethoprim and derivatives	0.40	0.32	0.31	0.36	0.38	0.47	0.40	0.37	0.41	0.44
J01EB	Short-acting sulfonamides	0.36	0.28	0.21	0.18	0.16	0.14	0.12	0.10	0.10	0.10
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	2.22	1.86	2.91	3.26	4.28	4.68	5.06	5.20	5.40	5.80
J01FA	Macrolides	3.08	3.17	3.26	3.38	3.27	3.64	4.34	4.69	5.68	6.25
J01FF	Lincosamides	0.46	0.43	0.48	0.60	0.64	0.65	0.57	0.62	0.64	0.76
J01GB	Aminoglycosides	1.42	1.55	1.84	2.05	2.10	1.55	1.61	1.90	2.18	2.06
J01MA	Fluoroquinolones	8.40	8.24	8.39	8.37	8.60	8.51	8.09	7.26	6.98	6.81
J01XA	Glycopeptides	0.92	0.98	1.22	1.25	1.31	1.15	1.08	1.09	1.31	1.27
J01XB	Polymyxins	0.06	0.09	0.08	0.09	0.12	0.19	0.17	0.19	0.19	0.23
J01XC	Steroid antibacterials (fusidic acid)	0.29	0.32	0.25	0.23	0.22	0.23	0.16	0.11	0.07	0.06
J01XD	Imidazole derivatives	3.47	3.51	3.71	3.92	4.09	4.42	4.22	4.52	4.65	4.33
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.33	0.27	0.29	0.33	0.34	0.32	0.27	0.24	0.25	0.27
J01XX05	Methenamine	0.08	0.07	0.09	0.08	0.07	0.06	0.09	0.08	0.07	0.10
J01XX08	Linezolid	0.20	0.20	0.29	0.31	0.36	0.34	0.44	0.36	0.37	0.52
J01XX09	Daptomycin	0.02	0.02	0.01	0.02	0.02	0.03	0.04	0.05	0.08	0.14
P01AB01	Nitroimidazole derivatives (metronidazole)	2.43	2.39	2.34	2.29	2.25	1.98	2.01	2.18	2.03	1.94
A07AA09	Intestinal antiinfectives (vancomycin)	0.17	0.25	0.40	0.47	0.49	0.52	0.47	0.49	0.52	0.50
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin (total)	70.35	70.28	79.70	84.92	88.39	89.49	91.77	91.92	95.96	99.31

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

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 7.7% since 2016.

Penicillins with extended spectrum are the second largest group consumed at Danish hospitals. In 2018, they accounted for 15.4 DBD (15.5%) of the consumption in somatic hospital, a 1.9% decrease from 2017 (15.7 DBD), the first decrease for this group since 2011. Beta-lactamase sensitive penicillins accounted for 10.38 DBD (10%) and beta-lactamase resistant penicillins for 10.39 DBD (11%).

Overall, the consumption of penicillins showed increasing trends for the decade. The combination penicillins increased steeply by 12.4 DBD (325%), the penicillins with extended spectrum and beta-lactamase resistant penicillins less markedly, but still continuously with 3.34 DBD (28%) and 3.70 DBD (55%), respectively, (Figure 5.13a and 5.14). These trends are comparable to the trends observed for the primary sector, apart from changes for 2017 and 2018, where consumption in the primary sector decreased notably for the combination penicillins.

The consumption of beta-lactamase sensitive penicillins increased less continuously, presenting fluctuations with decreases for 2010 and 2014. In 2018, the consumption of beta-lactamase penicillins was 10.4 DBD.

Notable trends for other antimicrobials for 2009 to 2018 were increases observed for tetracyclines, for 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 2009 they accounted for 0.95 DBD, while in 2018 the consumption had increased to 2.37 DBD. Consumption of combinations of sulfonamides and trimethoprim, increased from 2.22 DBD in 2009 to 5.80 DBD in 2018, a total increase of 162% for the decade. A rise in macrolides was observed from 3.08 DBD in 2009 to 6.25 DBD in 2018 (103%), (Table 5.8, Figure 5.13a and 5.14).

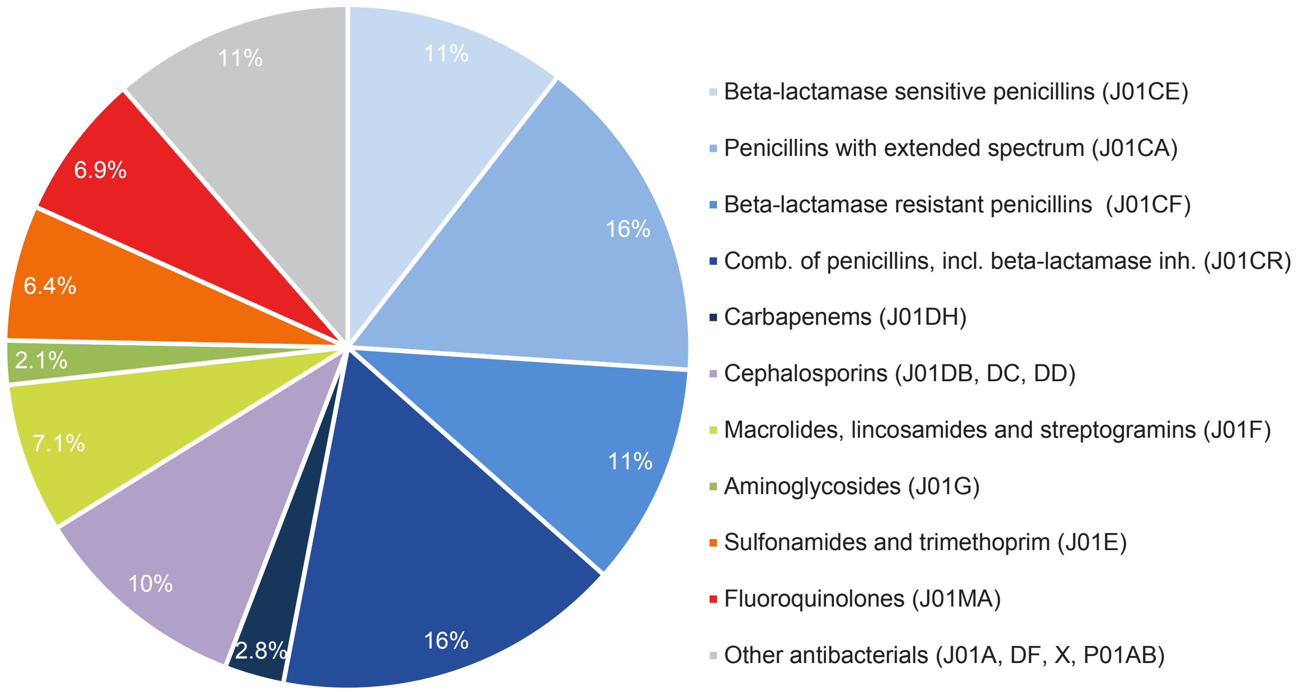
Finally, for linezolid and daptomycin the consumption peaked in 2018 at 0.52 and 0.14 DBD, respectively, (Table 5.8). Although the consumption of both is only minor, these changes are noteworthy: for Linezolid due to the high risk of creating resistance, for daptomycin due to its use in the treatment of invasive vancomycin resistant enterococci (VRE), the number of which is still low but has increased dramatically (see chapter 8.2.5 on invasive enterococci and 8.3.3 on VRE). The consumption of linezolid increased with 157% since 2009 (0.76 DBD) and with 41% since 2017 (1.09 DBD). The Capital Region of Denmark accounted for 71% of the consumption of linezolid.

The consumption of Daptomycin increased from 0.06 DBD in 2009. Also for daptomycin the main use was in the Capital region of Denmark (89%), which coincides with the Capital region having the highest number of clinical cases of VRE in 2018, (section 8.3.3 and 8.3.4).

In 2018, the consumption of first line antimicrobials used in empirical treatment for main infections treated at hospitals continued its increases, a trend following the described increasing trends for the number of invasive isolates, (Figure 5.13a and Figure 8.1). In 2018, these leading antimicrobials constituted 70.1 DBD of the total consumption of 99.3 DBD (71%). In 2017, it was 69.0 DBD of a total of 96.0 DBD (72%).

Trends in the consumption at hospitals on a regional level, measured in DID and DBD, are presented in Figure 5.15, page 62 and 63.

Figure 5.12 Distibution of the total consumption of antimicrobial agents in somatic hospitals, DDD, Denmark DANMAP 2018



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

Figure 5.13a consumption at acute care hospitals by leading groups of antimicrobial agents (J01), DBD, Denmark
DANMAP 2018

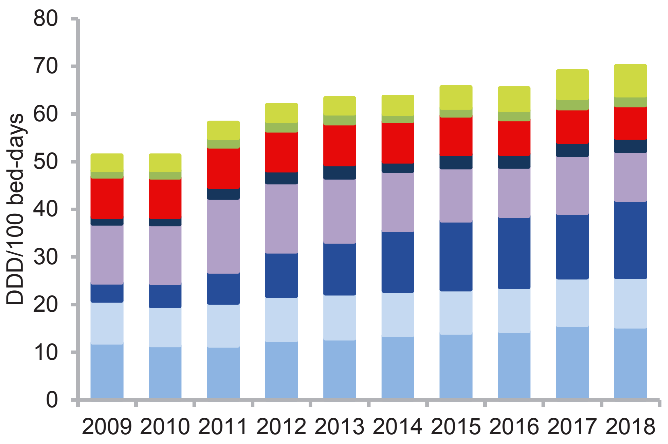
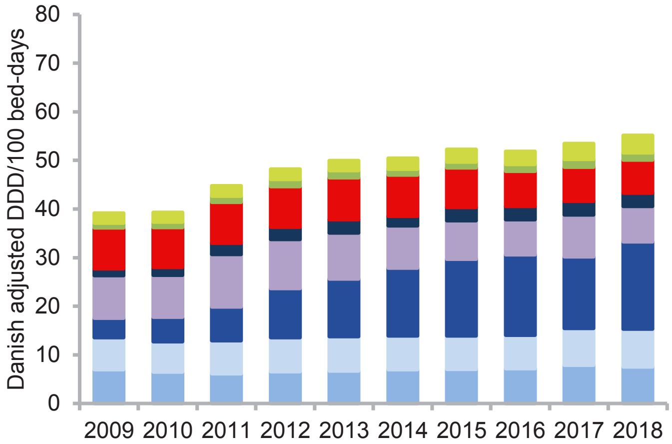
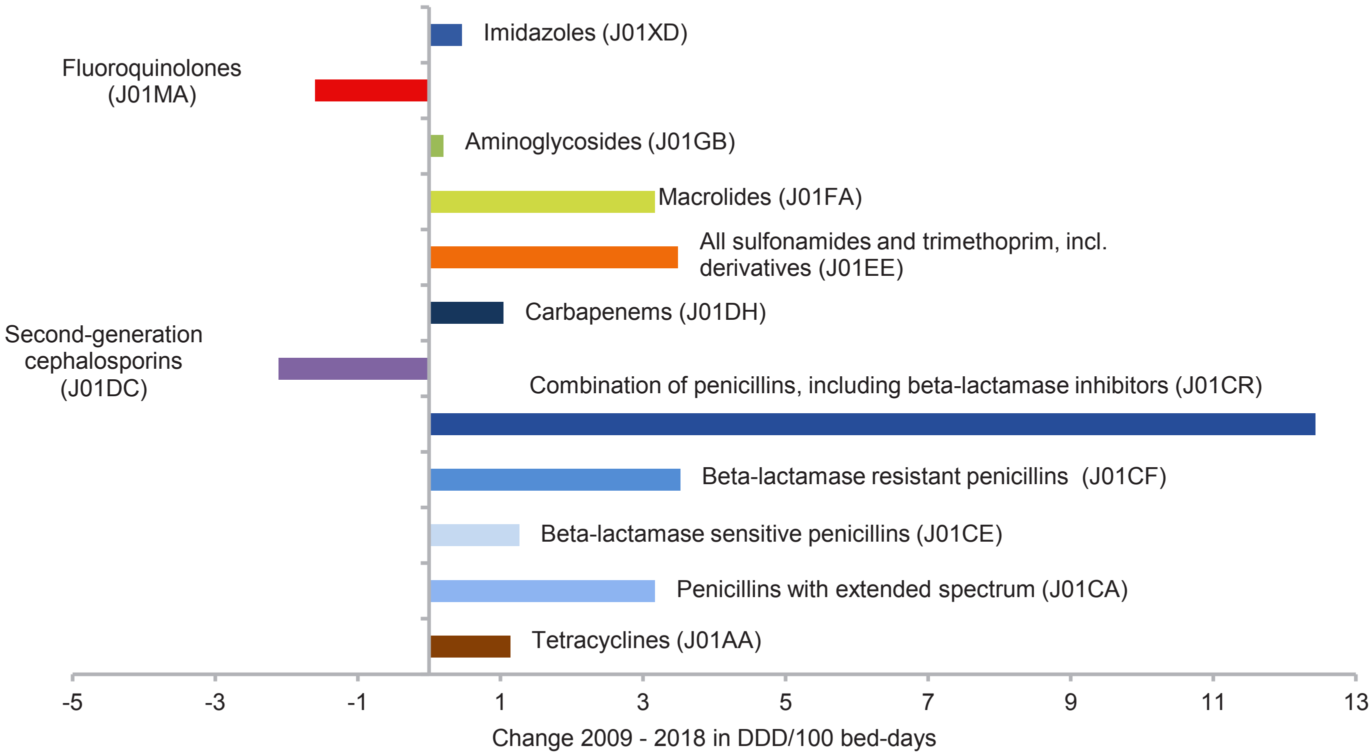


Figure 5.13b consumption at acute care hospitals by leading groups of antimicrobial agents (J01), meassured in DaDDD/100 bed-days, Denmark
DANMAP 2018



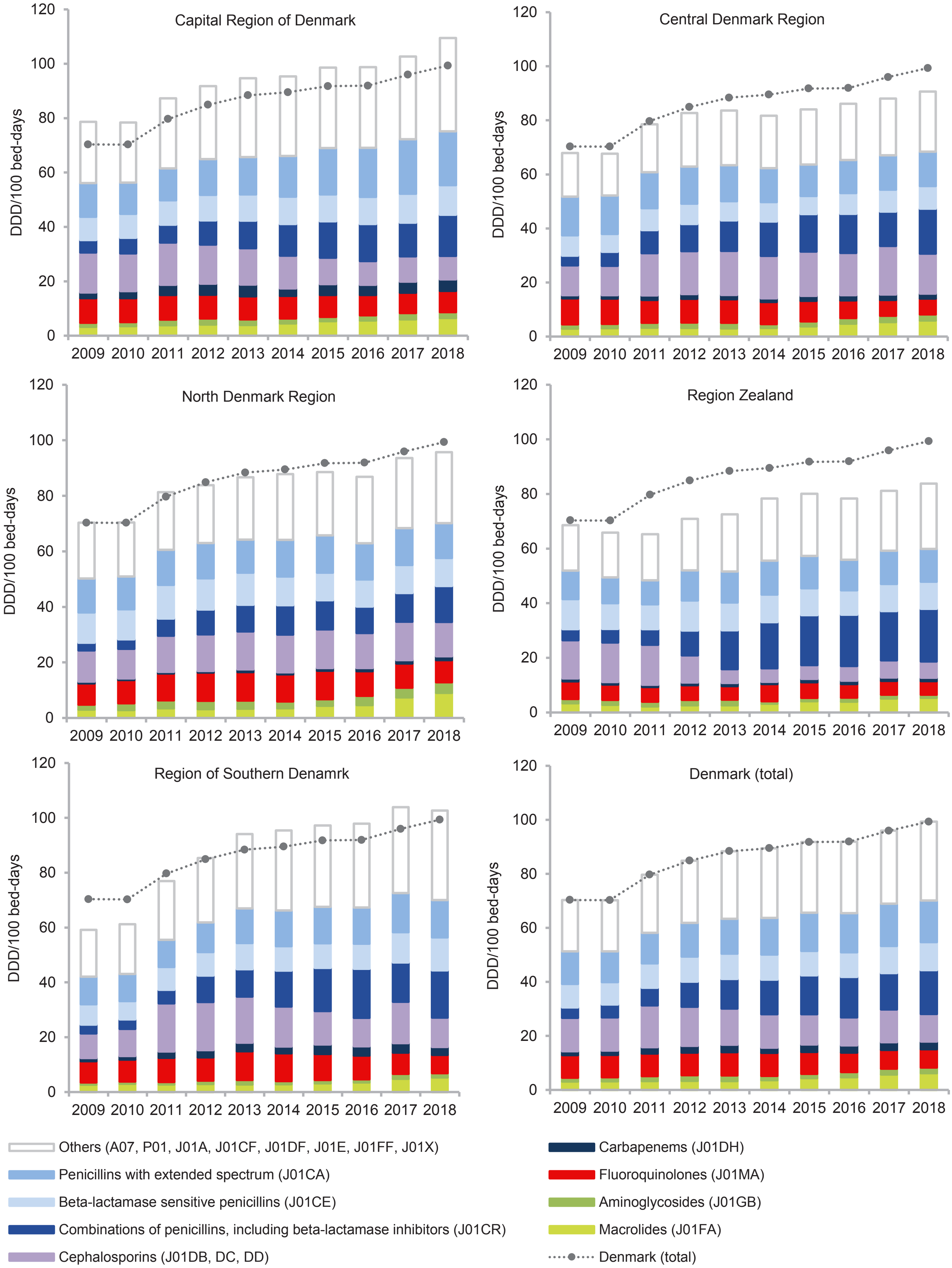
Data used in this figure is based on consumption at acute care public somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.14 Changes in the consumption by leading groups of antimicrobial agents in the hospital sector, DBD, Denmark
DANMAP 2018



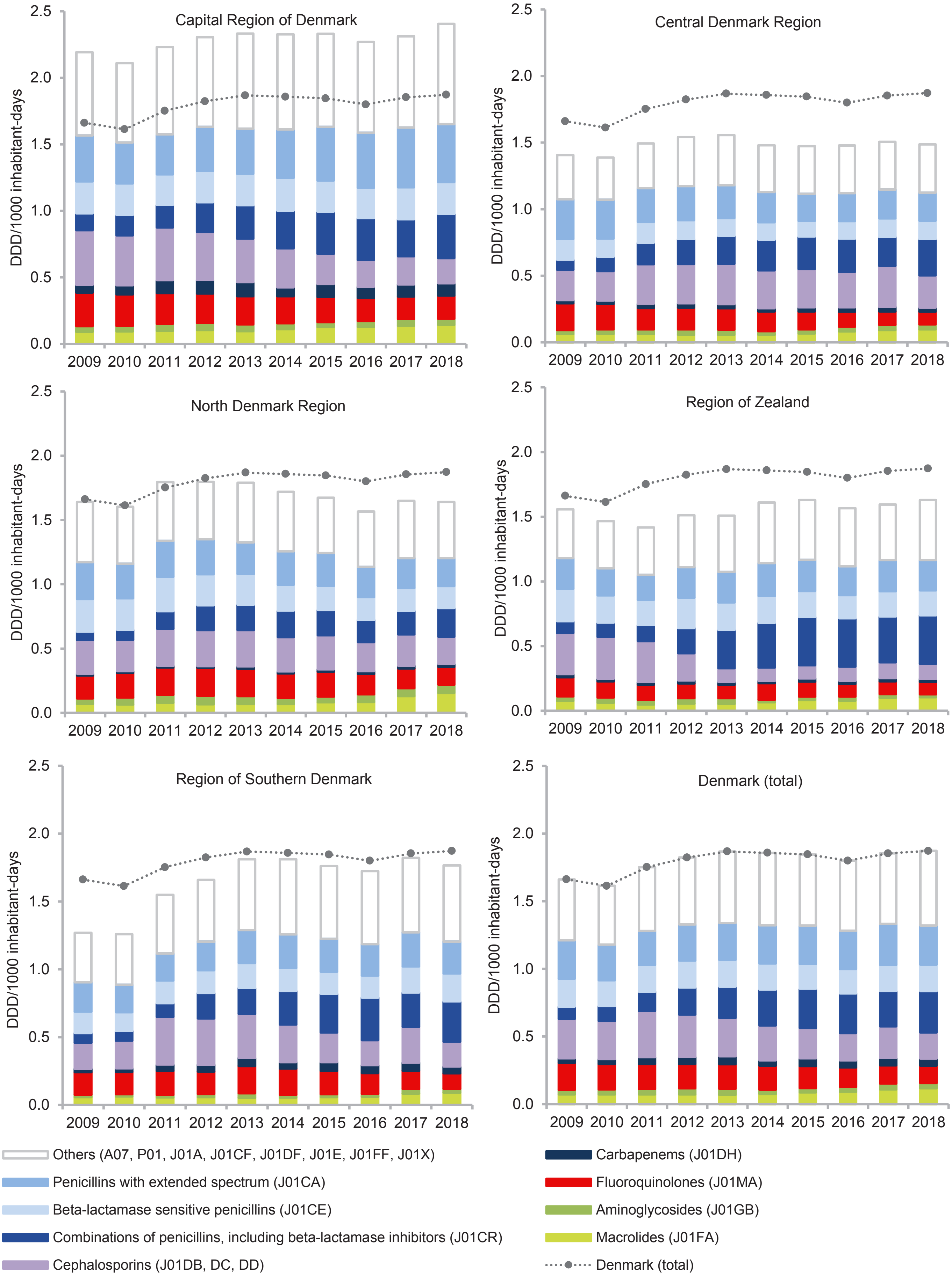
Data used in this figure is based consumption at acute care public somatic hospitals
ATC numbers stem from the 2019 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Figure 5.15a Consumption of antimicrobial agents for systemic use in the five health regions, DBD, Denmark DANMAP 2018



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

Figure 5.15b Consumption of antimicrobial agents for systemic use in the five health regions, DID, Denmark DANMAP 2018



Data used in this figure is based consumption at acute care public 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 2018, the total consumption was 292 DAD, a 3.4% increase from the 282 DAD in 2017 and 10% increase from 264 DAD in 2009. The consumption measured in DAD has increased since 2015, in 2018 it reached the highest level ever measured, (Table 5.9). The trends in DAD reflect for most antimicrobials the trends observed in DBD. However, the observed rates of increases were more marked, when measured in DBD than in DAD for all antimicrobial classes, (Tables 5.8 and 5.9). This could be due to the change in hospital activity, as presented in Figure A5.2 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 in somatic hospital has decreased, (Table 5.7). For all five Danish regions, the number of bed-days in somatic hospitals decreased from 2009 to 2018. Trends in consumption measured in DID and DBD are presented in Figure 5.15a 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 Table A5.1 in web annex. For comparison of consumption at hospitals with the consumption in the primary sector measured in DID see Table 5.1 on page 46.

Table 5.9 Consumption of antimicrobial agents for systemic use in somatic hospitals, DAD,Denmark DANMAP 2018

ATC group	Therapeutic group	Year									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
J01AA	Tetracyclines	3.56	3.50	3.64	5.02	4.68	5.06	5.46	6.19	5.99	6.95
J01CA	Penicillins with extended spectrum	45.16	40.42	38.45	40.69	41.40	42.11	42.91	43.02	46.01	45.12
J01CE	Beta-lactamase sensitive penicillins	32.88	29.09	30.57	30.39	30.22	28.91	27.61	27.31	29.48	30.47
J01CF	Beta-lactamase resistant penicillins	25.14	24.28	26.05	25.96	27.93	27.81	28.05	26.02	25.90	30.52
J01CR	Comb. of penicillins. incl. beta-lactamase inhibitors	14.38	17.03	21.97	30.35	35.11	39.63	43.81	44.62	39.61	47.74
J01DB	First-generation cephalosporins	0.45	0.43	0.39	0.39	0.36	0.19	0.13	0.13	0.12	0.11
J01DC	Second-generation cephalosporins	41.64	39.36	48.57	43.57	39.42	35.28	30.77	27.46	31.69	26.35
J01DD	Third-generation cephalosporins	4.40	3.56	3.64	3.37	3.48	3.10	3.16	3.07	3.91	3.52
J01DF	Monobactams	0.00	0.12	0.49	0.47	0.46	0.20	0.08	0.03	0.02	0.02
J01DH	Carbapenems	5.35	5.69	7.90	8.18	8.86	5.96	8.49	7.98	8.33	8.13
J01EA	Trimethoprim and derivatives	1.50	1.14	1.05	1.18	1.22	1.45	1.21	1.11	1.22	1.28
J01EB	Short-acting sulfonamides	1.36	1.00	0.72	0.58	0.52	0.44	0.36	0.30	0.30	0.29
J01EE	Comb. of sulfonamides and trimethoprim. incl. derivatives	8.33	6.56	9.85	10.62	13.75	14.53	15.40	15.48	15.85	17.03
J01FA	Macrolides	11.58	11.19	11.03	11.04	10.52	11.31	13.19	13.97	16.68	18.34
J01FF	Lincosamides	1.73	1.52	1.62	1.97	2.05	2.00	1.73	1.85	1.87	2.23
J01GB	Aminoglycosides	5.34	5.46	6.23	6.69	6.74	4.83	4.90	5.65	6.39	6.05
J01MA	Fluoroquinolones	31.57	29.07	28.43	27.31	27.63	26.43	24.61	21.60	20.52	20.00
J01XA	Glycopeptides	3.45	3.45	4.12	4.09	4.22	3.58	3.27	3.23	3.85	3.72
J01XB	Polymyxins	0.24	0.32	0.28	0.30	0.39	0.59	0.53	0.58	0.57	0.67
J01XC	Steroid antibacterials (fusidic acid)	1.08	1.11	0.85	0.74	0.71	0.71	0.50	0.34	0.20	0.18
J01XD	Imidazole derivatives	13.02	12.40	12.56	12.79	13.15	13.74	12.83	13.44	13.66	12.71
J01XE	Nitrofuran derivatives (nitrofurantoin)	1.24	0.97	0.97	1.06	1.09	0.98	0.82	0.71	0.74	0.79
J01XX05	Methenamine	0.28	0.26	0.31	0.26	0.23	0.17	0.27	0.24	0.21	0.31
J01XX08	Linezolid	0.76	0.72	0.99	1.01	1.14	1.05	1.33	1.08	1.09	1.53
J01XX09	Daptomycin	0.06	0.07	0.05	0.06	0.07	0.10	0.12	0.15	0.24	0.42
P01AB01	Nitroimidazole derivatives (metronidazole)	9.11	8.44	7.93	7.48	7.22	6.14	6.10	6.48	5.97	5.71
A07AA09	Intestinal antiinfectives (vancomycin)	0.65	0.89	1.36	1.52	1.59	1.62	1.43	1.45	1.53	1.45
J01, P01AB01, A07AA09	Antibacterial agents for systemic use, including metronidazole and vancomycin (total)	264.29	248.06	270.02	277.09	284.18	277.93	279.09	273.49	281.94	291.63

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

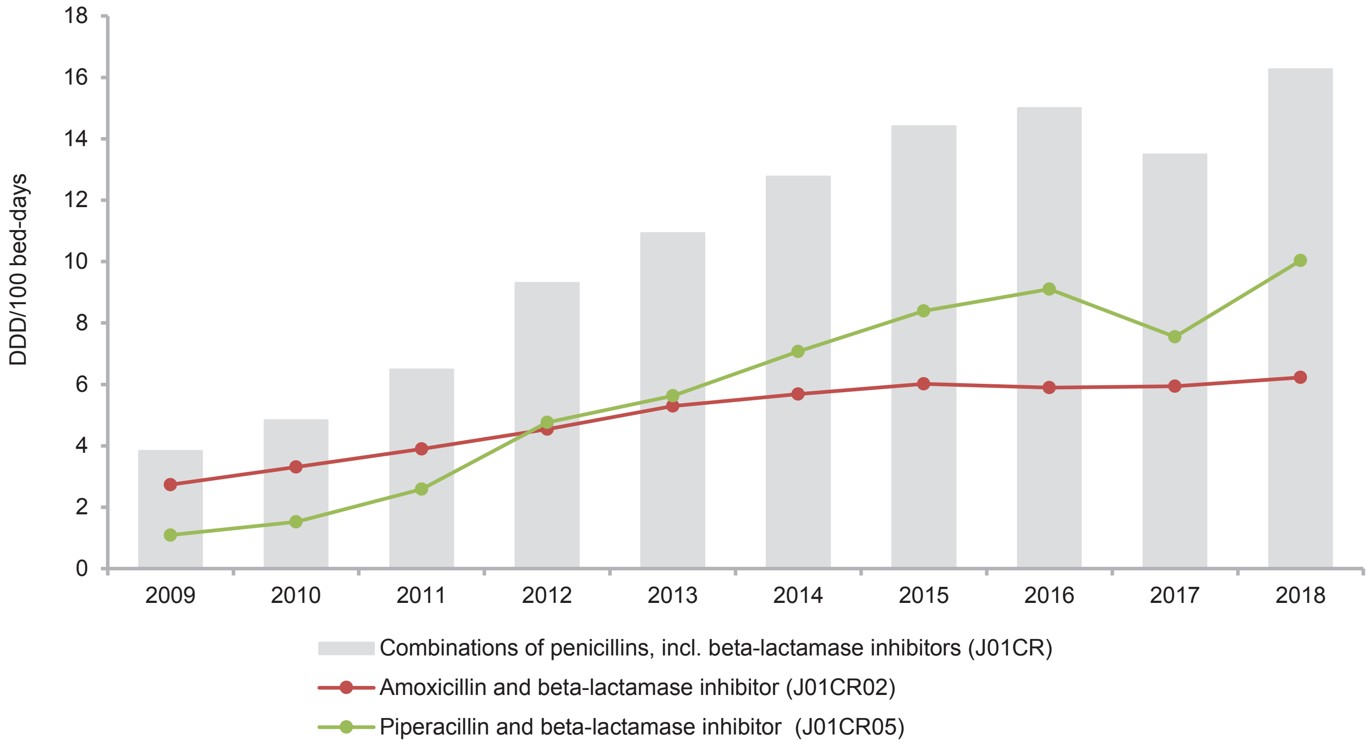
5.4.4 Changes in the consumption of antimicrobials of critical interest

In Denmark, cephalosporins, fluoroquinolones and carbapenems have been collectively termed the antimicrobials of special critical interest due to their important role as first line drugs in the treatment of acutely ill patients suffering from bloodstream infections. Their use is also correlated to a marked risk of resistance, which makes a monitoring of the consumption of all three necessary. For many years, 2nd gen 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 to 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 5.16. 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 the same year. This becomes obvious in the regional monitoring of the antimicrobials of critical interest for 2017, (Figure 5.17).

In 2018, the antimicrobials of special critical interest constituted together 20% of the total consumption at hospitals, measured in DBD. In 2017, it was 22% and ten years ago, in 2009, it was 32%. The trends in the consumption for the five healthcare regions and the average national level during 2009 to 2018 are presented in Figure 5.15 and as per cent of the consumption in DDD in Figure 5.17.

Cephalosporins accounted with altogether 10.2 DBD for 10% of the total consumption, a decrease of 16% from the 12.1 DBD in 2017, (Table 5.8). 2nd generation cephalosporins accounted for the biggest part, 8.97 DBD. Fluoroquinolones accounted for 6.81 DBD, a 2.5% reduction from 6.98 DBD in 2017. The consumption of fluoroquinolones peaked in the years of 2009 to 2013 and has since shown slight declines. Carbapenems accounted for 2.77 DBD in 2018, a 2.3% decrease from 2.83 DBD in 2017.

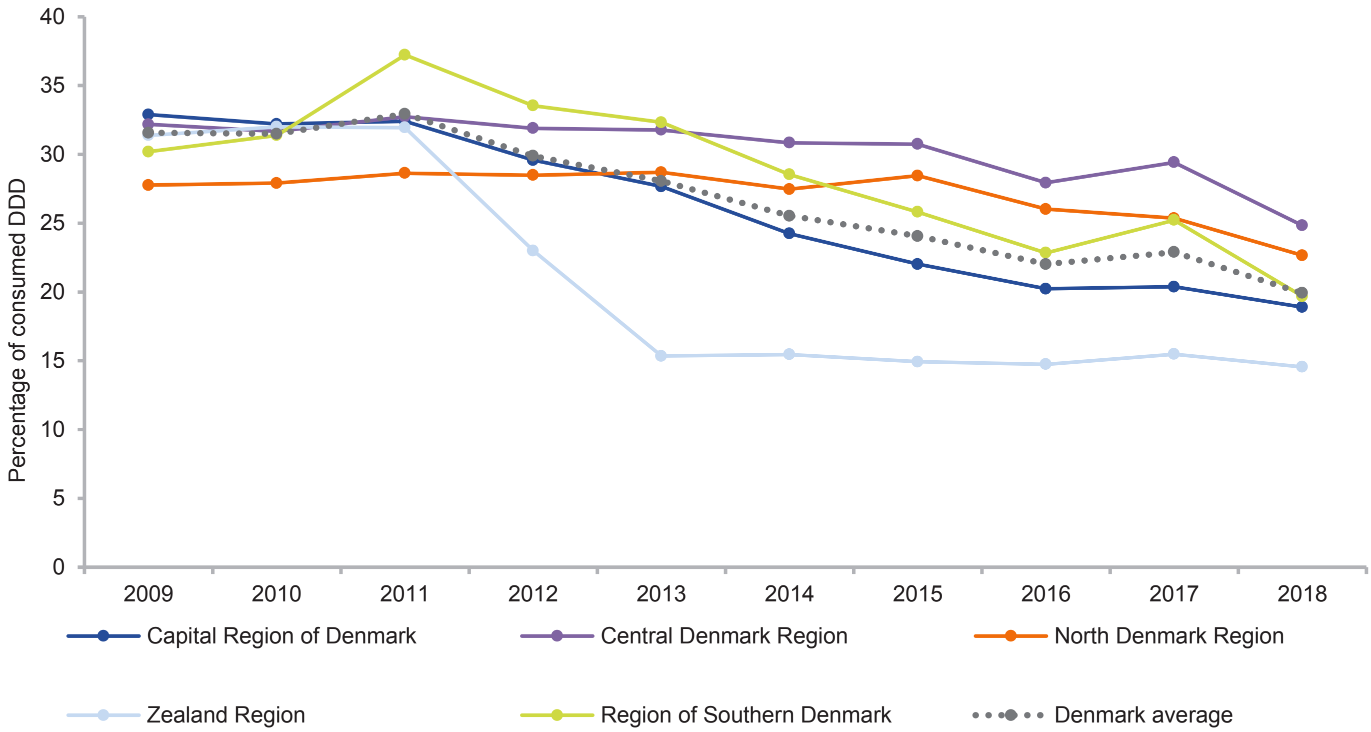
Figure 5.16 Consumption of combination penicillins in hospitals, DBD, Denmark DANMAP 2018



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

Figure 5.17 Percentage of the consumption of antimicrobials of special critical interest combined, divided into regional consumption, based on DDD, Denmark

DANMAP 2018



Data used in this figure is based consumption at acute care public 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 is applying principles of antibiotic stewardship to the main acute care 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 5.13b. For more information on the working group, monitoring and results please see https://kvalitetsteams.dk/laerings-og-kvalitetsteams/lkt-rationelt-antibiotikaforbrug-paa-hospitaler/links-og-materialer (only available in Danish).

The regional initiatives are supported by the implementation of the third measurable goal in the National Action Plan on antibiotics from 2017, aiming at a 10% reduction in the consumption of cephalosporins, fluoroquinolones and carbapenems from 2016 to 2020, when measured in DBD. For further information go to section 5.1, introduction to the human consumption. The mentioned shortages of piperacillin with tazobactam in 2017 may have caused reintroduction of cephalosporins in the treatment of acutely ill, septic patients at several hospitals. Therefore, extra attention will be paid to the consumption of cephalosporins also during next year.

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.

Karoline Skjold Selle Pedersen and Ute Wolff Sönksen
For further information: Ute Wolff Sönksen, uws@ssi.dk

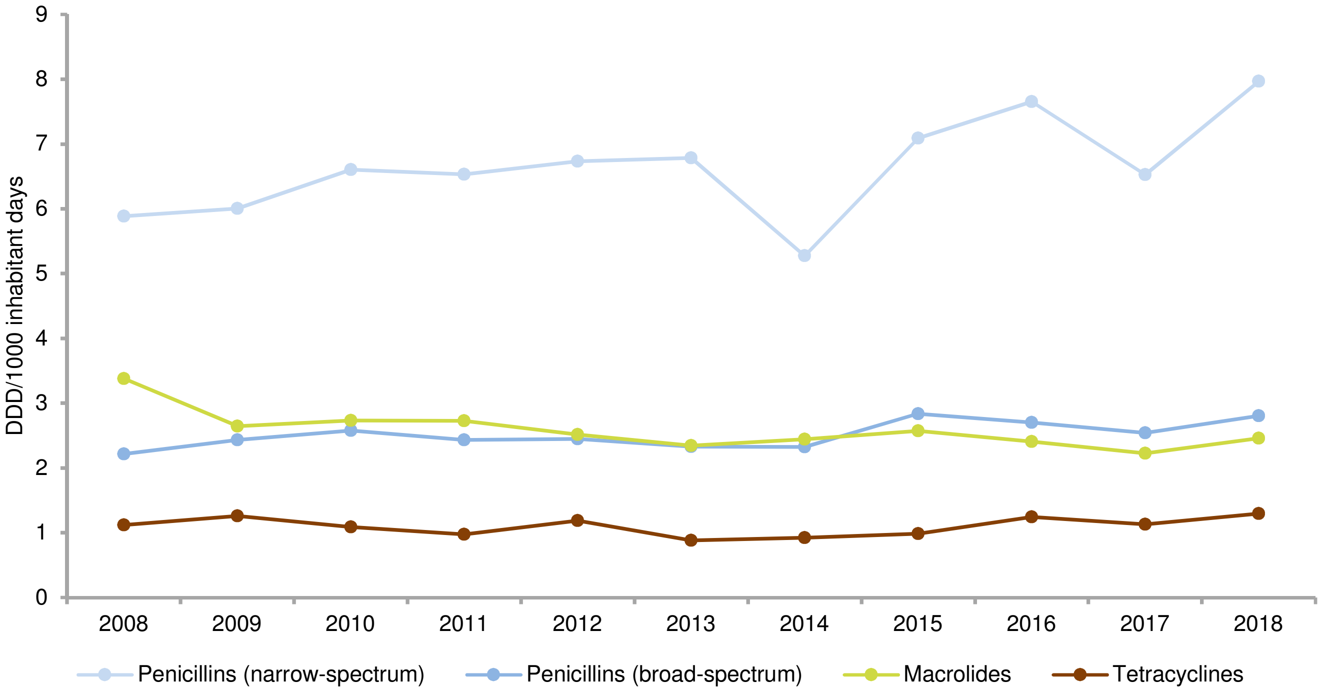
Textbox 5.1

Incidence of multiresistant bacteria and consumption of antimicrobial agents in Greenland

Background. Greenland has a population of 55,877 inhabitants (January 2018) and Nuuk is the capital with around 18,000 inhabitants. Greenland is an autonomous administrative country of Denmark; it has its own Ministry of Health and the country is divided into five health regions. Although sparsely populated, due to its big geographic dispersion, 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 at least once a year. Patients with specific or serious diseases that cannot be treated at Dronning Ingrids Hospital (DIH) are transferred to Denmark or Iceland for further treatment e.g. haemodialysis, cancer treatment, brain surgery etc.

Resistant bacteria. From 2000 to 2018, 50 patients were diagnosed with methicillin resistant *Staphylococcus aureus* (MRSA), 104 patients with extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, three patients with vancomycin resistant enterococci (VRE), and 165 patients with *Clostridium difficile* infection among whom 54 had the 027 type.

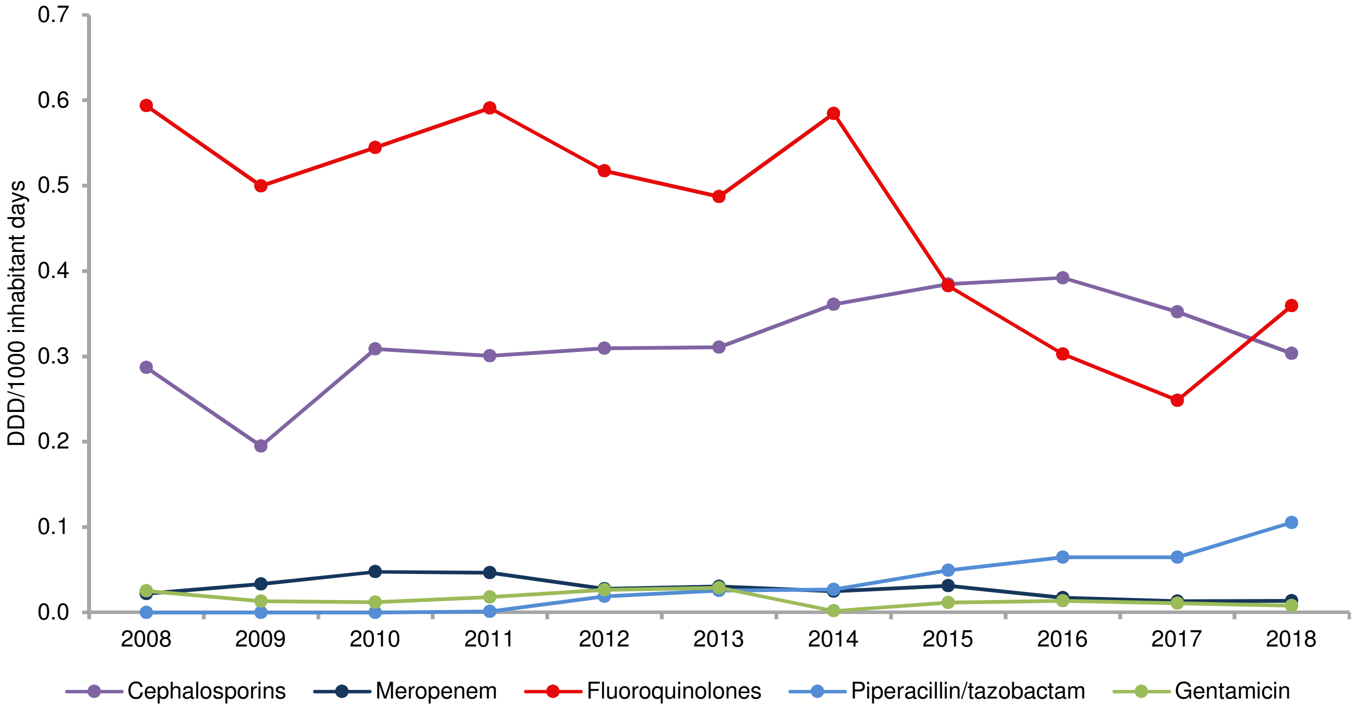
Figure 1a Consumption of selected antimicrobial agents in humans in Greenland (DID) 2008–2018: consumption of narrow- and broad-spectrum penicillins, macrolides and tetracyclines DANMAP 2018



Note: Narrow-spectrum penicillins include benzylpenicillin, phenoxymethylpenicillin, and dicloxacillin. Broad-spectrum penicillins include ampicillin, pivampicillin, amoxicillin and amoxicillin with enzyme inhibitor.

continued ... Textbox 5.1

Figure 1b Consumption of selected antimicrobial agents in humans in Greenland (DID) 2008–2018: consumption of cephalosporins, meropenem, fluoroquinolones, piperacillin/tazobactam and gentamicin DANMAP 2018



MRSA. Since 2015, a nearly four fold increase in incidence of MRSA has been observed. The largest increase was seen during 2017, and the main reason for this was an outbreak involving 12 persons in Tasiilaq at the East coast of Greenland (described in details in DANMAP 2017). In 2018, only four persons were reported with MRSA: three adults with infections (wound: 2; UTI: 1), and one premature child being MRSA-carrier in nose and throat. The child was colonised with MRSA while hospitalised in Denmark due to an MRSA-outbreak at the neonatal ward. The mother of the child was MRSA-negative at time of the detection, but in later samples (February 2019) she was also tested positive from the nose. There was no further transmission at DIH or among family members in Greenland.

VRE. In spite of ongoing VRE-outbreaks in Denmark, only three patients have been diagnosed with VRE in Greenland. Two patients were colonised with VRE in the rectum and one patient had pleurisy – in all three cases VRE occurred after hospitalisation in Denmark. No transmission was observed 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 *Enterobacteriaceae*, treatment with broad-spectrum antimicrobial agents in Greenland probably selected for these bacteria. From 2012 to 2013, there were outbreaks with *C. difficile* type 027 in several hospitals and transmission within the country occurred. But due to a great effort in infection prevention and control from the hospital staff, these outbreaks were quickly stopped. Of the 18 new patients with *C. difficile* infection diagnosed in 2018, five were infected with the 027 type.

Consumption of antimicrobial agents: All antimicrobial agents in Greenland are purchased and distributed from the National Pharmacy. Figure 1a and b shows the total purchase of selected antimicrobial agents in DDD per 1,000 inhabitants per day (DID) from 2008 to 2018. From 2008 to 2018 a larger increase in the consumption of narrow-spectrum (35.3%) and broad-spectrum penicillins (26.7%) was observed but only a minor increase of 4.1 and 3.7%, respectively, from 2016 to 2018. Increases in broad-spectrum antimicrobial agents such as macrolides (2%), tetracyclines (4.4%), and piperacillin-tazobactam (64.1%) were also observed from 2016 to 2018. Simultaneously, large decreases in consumption of gentamicin (42.9%), cephalosporins (22.7%), and meropenem (17.6%) were registered for the same period. From 2008 to 2018 an overall decrease of 39.6% was observed in consumption of fluoroquinolones with the largest decrease (57.4%) from 2014 to 2017. Unfortunately, from 2017 to 2018 a large increase of 44.2% was observed. The reason for this increase is not fully understood but will be on the agenda the next year.

Conclusion: The consumption data for antimicrobial agents are based on purchases and fluctuations are therefore seen from year to year. It is noteworthy that the increased focus on prescription of antibiotics due to teaching the doctors in the recent years has resulted in remarkable decreases in purchases of cephalosporins and meropenem, and in continued increase in purchase of piperacillin-tazobactam. It is – however – worrying that the purchase of fluoroquinolones has increased once again after the large decrease seen from 2014 to 2017.

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 remains very important in Greenland also in the future.

Anne Kjerulf, Jette Holt, Anne Birgitte Jensen, Peter Poulsen, Inge Mortensen
For further information: Anne Kjerulf (alf@ssi.dk)

Textbox 5.2

Antibiotics in dentistry

According to the “National Action plan on the reduction of antibiotics in humans” issued in July 2017, dentists were responsible for approximately 7% of the total consumption of antibiotics in primary health care in 2016. Further, the number of prescriptions pr. 1000 inhabitants increased from 1999-2015 (1) and did not level off around 2011 as for general practitioners and other medical specialists. Based upon a 24% increase in the number of persons administered antibiotics by a dentist from 2005-2014, in 2015 the Danish Health Authority initiated drawing up a “National clinical guideline on use of antibiotics in dentistry” in order to identify focus areas for guidance of dentists in their use of antibiotics (2). The guideline with a key message of limiting the indications for use of antibiotics in both treatment and prophylaxis was issued in 2016, where the first decline in dental prescriptions was observed. Since then the decline in usage has been considerable, corresponding to a 31% decrease in 2018 from the peak of 39.4 prescriptions per 1000 inhabitants in 2015, (Figure 1).

Figure 1 Total annual number of dental prescriptions per 1000 inhabitants, Denmark DANMAP 2018

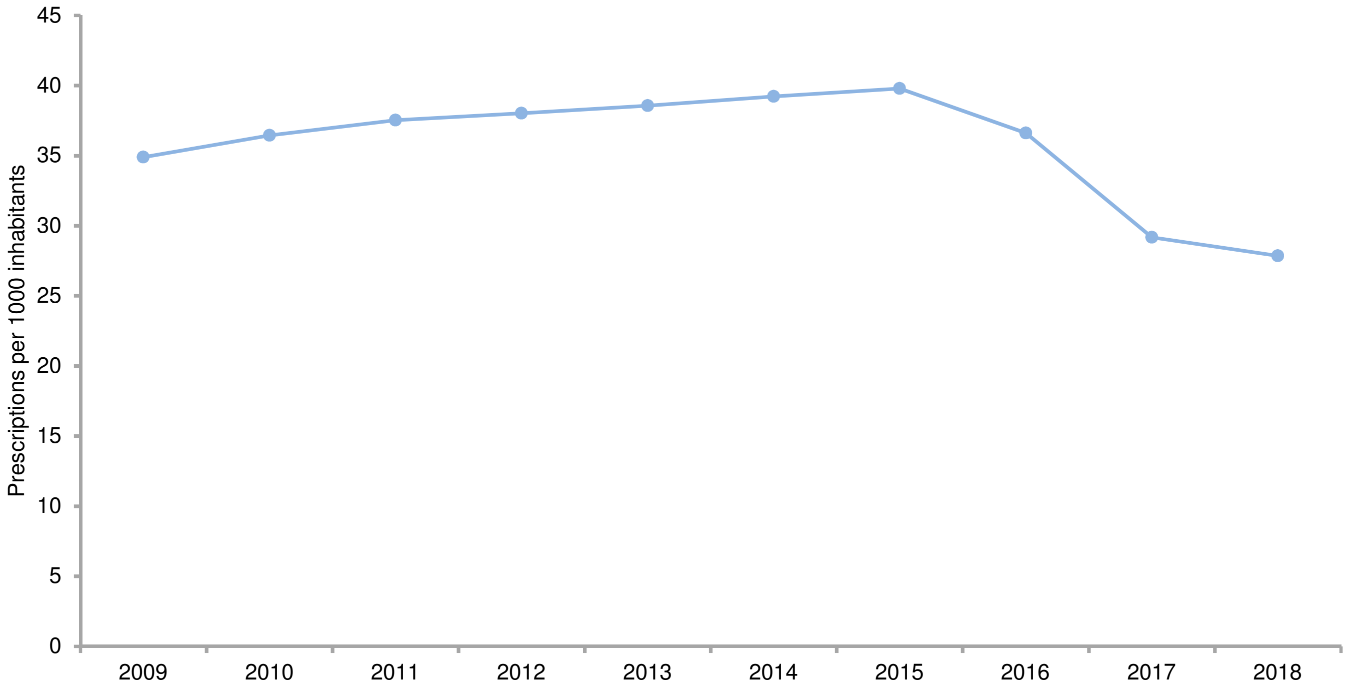
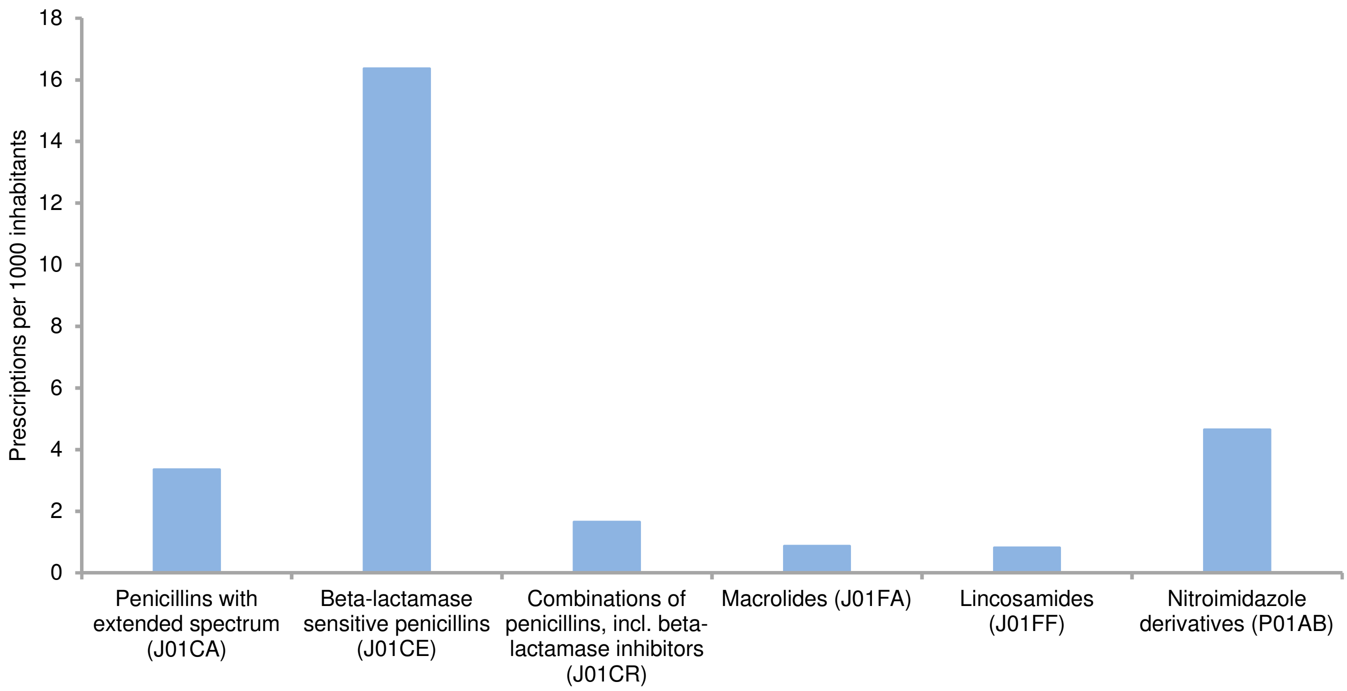


Figure 2 shows how the antibiotics prescribed by dentists are distributed among groups of antibiotics. Phenoxymethyl penicillin accounts for almost 60% of total prescriptions, which is far above the goal of 36% to be achieved in primary health care in 2020 (1). Metronidazole accounts for 17% followed by amoxicillin alone (11%) and in combination with beta-lactamase inhibitors (6%). Metronidazole in combination with phenoxymethyl penicillin is recommended for treatment of acute odontogenic infections (2), while amoxicillin is the drug of choice for prophylaxis.

The first goal of the “National Action plan on the reduction of antibiotics in humans”, i.e. a 25% reduction in the total number of prescriptions from 2016-2020 was achieved by dentists in 2018. However, given the rather high level of dental prescriptions in 2016, a continued reduction in total dental prescriptions may still be achievable. In addition, further reductions in use of broad spectrum antibiotics, especially amoxicillin with beta-lactamase inhibitors and possibly clindamycin may be attained. Adopting

Figure 2 Number of prescriptions per 1000 inhabitants of the antibotics most frequently used by dentists in 2018, Denmark

DANMAP 2018



more detailed information on dental prescriptions regarding diagnosis and specific indications for use would allow access to gather more specific information on the patterns of antibiotic usage among dentists. This would create the base for informed decision making on where to take action in future efforts and guidelines in order to further strengthen the awareness of antibiotic prescribing habits among dentists.

Karoline Skjold Selle Pedersen, Karen Geismar and Tove Larsen
For further information: Tove Larsen, tla@sund.ku.dk

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Tove Larsen, lektor, ph.d.
Odontologisk Institut
Det Sundhedsvidenskabelige Fakultet
Københavns Universitet
tla@sund.ku.dk

Textbox 5.3

Infection Prevention and Control can Combat Antibiotic Resistance

Over- and misuse of antibiotics in the treatment of humans and animals alike has been well described as the main driver of antimicrobial resistance (AMR). Moreover, once resistant bacteria have been introduced into a given population it is crucial to detect their existence, since spreading them within the population will further worsen the situation. Thus, naturally there are two main ways of tackling AMR:

- To reduce and control consumption of antimicrobial agents in both human beings and animals
- To prevent the spread of antibiotic resistant microorganisms – especially among human beings.

Both ways have to go hand in hand in order to prevent the further development and escalation of AMR.

This textbox will focus on the infection prevention and control (IPC) aspects. Crucial for success is the establishment of an infection control program, which should contain the following four main elements:

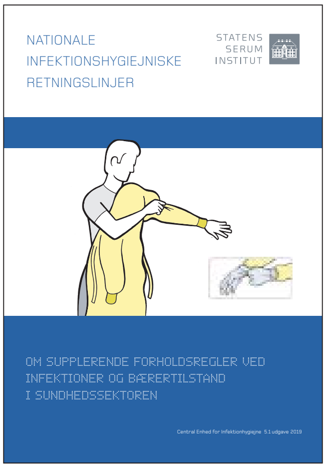
- An organisation focusing on reducing healthcare-associated infections, and infections caused by antibiotic resistant bacteria
- Education of healthcare staff
- Guidelines for infection prevention and control
- Surveillance of healthcare-associated infections (HAI) and AMR

Of further importance is the establishment of these on both local and national level. In Denmark, all the above four elements have existed for many years.

On the central level, the National Center for Infection Control (NCIC) was established in 1977 at Statens Serum Institut (SSI). The purpose of the center is to provide national guidelines for infection prevention and control; to guide the Ministry of Health, the Danish Health Authority and other authorities in the management of IPC and AMR; to disseminate knowledge of IPC, e.g. by developing e-learning programs in hand hygiene; to evaluate disinfection products for use in the Danish healthcare system; to guide healthcare staff by email or phone consultations; and finally to support education of nurses and doctors within IPC. A new Nordic education at Gothenburg University will be starting in September 2019 and NCIC is assisting the university.

At the local level, there are infection control teams in all five regions with infection prevention nurses (May 2018: 108 nurses) and a few part time infection prevention doctors (clinical microbiologists). The local infection control teams develop local guidelines based on the national guidelines, perform audits in hand hygiene and universal precautions, and educate nurses and other healthcare professionals to become link staff. Most clinical departments at Danish hospitals have a link nurse or other link professionals dedicated to infection prevention and control.

National guidelines for infection prevention and control are developed by the NCIC in collaboration with infection prevention nurses and doctors from all five regions, clinical experts and other experts, depending on the subject. They are whenever possible evidence-based and mainly based on already existing national and foreign guidelines. The two essential national guidelines are on universal precautions and on isolation precautions. The latter has a more detailed description on AMR. All the guidelines are in Danish, free of charge and easy to download from the SSI website.

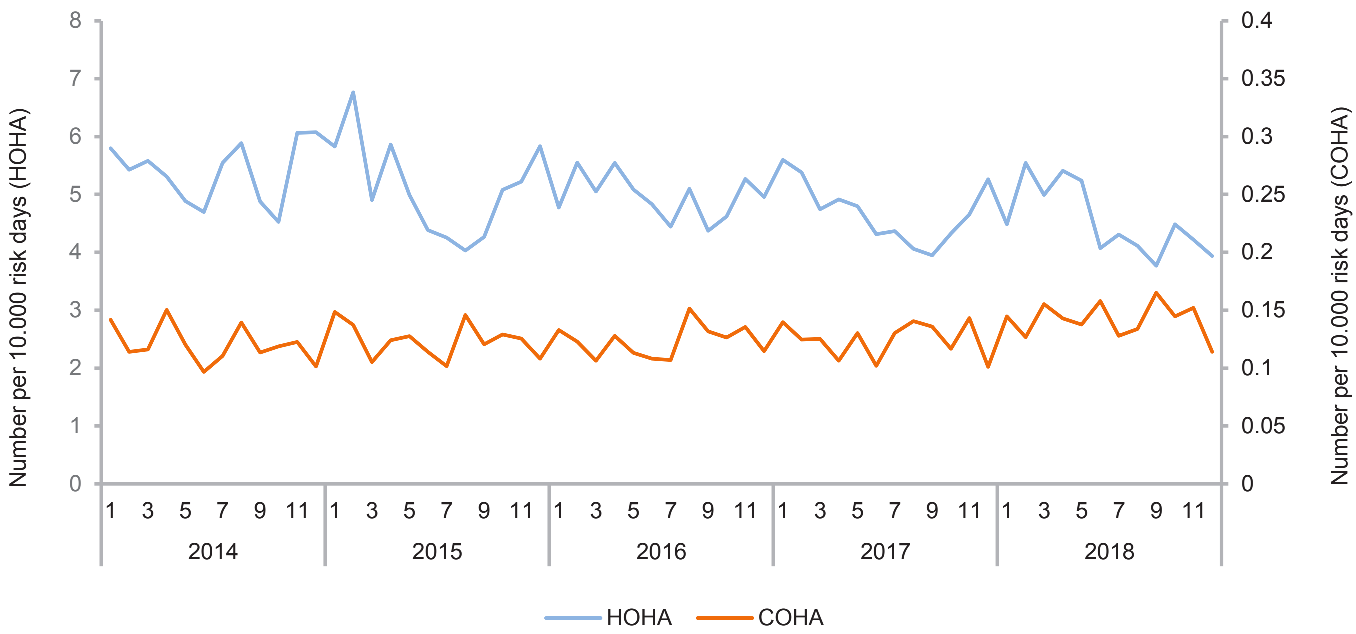


In addition, two detailed national guidelines exist on AMR from the Danish Health Authority – one on the prevention and tackling of methicillin resistant *Staphylococcus aureus* (MRSA) and one on carbapenemase-producing organisms (CPO). The purpose of both guidelines is to minimize the spread of these often highly resistant bacteria to the ill and weak patients at hospitals and in long term care facilities, simultaneously keeping the occurrence of these bacteria on a continued low level. The guidelines contain recommendations for active screening of patients on admission to hospital, based on assesment of certain risk situations, e.g. admission to a hospital abroad during the last six months. Both guidelines are free of charge and easy to download from the Danish Health Authority website www.sst.dk, see the MRSA guideline (available in English) and the CPO guideline (available in Danish),, respectively.

Appendices to the guidelines with detailed instructions on AMR infection prevention and control are published on the SSI site at www.ssi.dk, see the appendices for MRSA and CPO, respectively (at the moment only available in Danish).

Denmark has a long tradition concerning surveillance of HAI. Point prevalence surveys on HAI were performed twice a year for many years but were discontinued in 2014, with the simultaneous development and establishment of a new automated electronic surveillance system for HAI called HAIBA (for a detailed description see DANMAP 2014 and on the SSI website). Case definitions and surveillance have been established for the following HAIs: Bacteraemia, urinary tract infection, *Clostridium difficile* infection (CDI) and deep infection after planned total hip and knee replacement surgery. An example regarding the surveillance system is shown in Figure 1 for CDI: Surveillance of CDI during the last five years from 2014-2018 has shown a significant decrease in incidence of hospital onset hospital-acquired (HOHA) infections. The opposite is seen regarding the incidence of community onset hospital-acquired (COHA) infections with a significant increase.

Figure 1. Surveillance of *Clostridium difficile* infection (CDI) from 2014 to 2018 DANMAP 2018



Active national surveillance of human AMR has been done on a voluntary basis for many years by SSI and the DANMAP group. Notification is mandatory only for MRSA and CPO, since October 2006 and September 2018, respectively.

Anne Kjerulf, Elsebeth Tvenstrup Jensen, Sophie Gubbels and Brian Kristensen
For further information: Anne Kjerulf, alf@ssi.dk

Textbox 5.4, part 1

Candidaemia in Denmark: Epidemiology, antifungal consumption and resistance

Candidaemia is a serious and potentially life threatening condition which occurs mainly in hospitalised patients suffering from severe conditions. Risk factors for acquiring a candidaemia are among others stay at the intensive care unit (ICU), the presence of central vascular catheter, prior and particularly repeated or complicated abdominal surgery and exposure to broadspectrum antibiotics (1). The 30-day mortality is approximately 40%, being highest for patients in the ICU (2). *Candida albicans* is the most frequently found organism (1). However, over the past fifteen years an increase in *Candida glabrata* has been observed which is worrisome as this species is intrinsically less susceptible to fluconazole (3). Echinocandins are the drug of choice in the primary treatment of candidaemia with de-escalation to azoles once susceptibility is confirmed and the patient is stabile (4). However echinocandin resistance is emerging especially in *C. glabrata* (3)(5).

A Danish nationwide surveillance has existed since 2004 involving all the Danish clinical microbiology departments. The departments culture and identify the *Candida* species from blood cultures and refer the isolate(s) to Statens Serum Institut (SSI)) for confirmation of identification and susceptibility testing. In addition, *FKS* sequencing is done at SSI for isolates with reduced echinocandin susceptibilities.

The episode rate of candidaemia peaked in 2011 with an incidence rate of 10.1/100.000 inhabitants, but has otherwise remained stablie (Figure 1) (6). As mentioned above the proportion of *C. albicans* has decreased and *C. glabrata* increased (Figure 1) (6). Due to this proportional change in species distribution the fluconazole susceptibility rate has also decreased from 69% in the period 2004-2007 to 60% in the period 2016-2018 (unpublished data). Echinocandin resistance was not observed during 2004-2007 (6). However, the latest published surveillance study by Astvad et al. in 2018 found an echinocandin resistance rate of 1.7% for the period 2012-2015 (6) and similarly, we found 1.4% echinocandin resistance rate for 2016-2018 (not yet published data).

Figure 1 Species distribution 2004-18 and episoderate DANMAP 2018

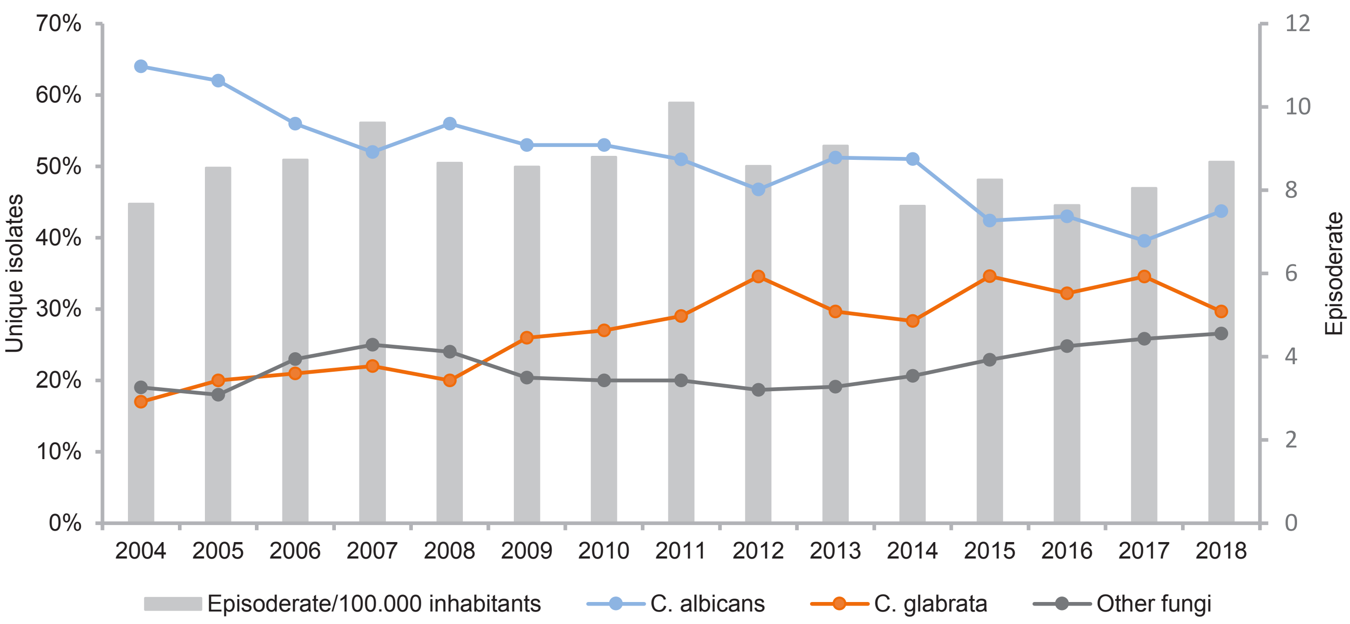


Figure 1. Episode rate and species distribution from the Danish nationwide candidemia surveillance 2004-18. A unique isolate is defined as: if found >21 days apart, confirmation of another species or different susceptibility pattern. Episode rate is defined as: one unique isolate or one polyfungal infection or one admission at one centre per 100.000 inhabitants. Other fungi are: Other Candida species, Magnusiomyces, Saccharomyces, Cryptococcus, Rhodotorula and other moulds.

In parallel with the increasing fluconazole and emerging echinocandin resistance rates the antifungal use in Denmark has changed. In 2016 and 2017 Denmark continued to have a higher consumption of fluconazole, itraconazole and posaconazole than the other Nordic countries. However, the use of amphotericin B and echinocandins were almost comparable across the Nordic countries (Figure 2). The consumption of the azoles in 2016 per 1000 inhabitants was: 225 DDDs for Denmark and 94, 114 and 152 DDD for Norway, Sweden and Finland, respectively. In 2017, consumption of azoles per 1000 inhabitants continued to be higher for Denmark than the other Nordic countries (212 DDD for Denmark and 89 and 144 DDD for Norway and Finland, respectively) despite a decrease in fluconazole consumption from 2016 to 2017 in Denmark for both hospital and primary health care sector (Figure 2). The decrease was greater for the primary health care sector. Caspofungin continued to be the main echinocandin used in 2016 and accounted for 62% of the echinocandin use. However, in 2017 anidulafungin accounted for 61% of the echinocandin use. These two compounds are regarded clinically equal and the choice between them is mainly driven by price.

In conclusion, although the episode rate has been stabile over the past 15 years the species distribution has changed considerably. *C. glabrata* continues to rise while the rate of *C. albicans* continues to decrease at a much greater extent than in our neighbouring Nordic countries. This epidemiological change is worrisome since it explains the decrease in the fluconazole susceptibility rate and furthermore might be a result of the high antifungal use. Acquired resistance is still low, however, echinocandin resistance is of concern and will be closely monitored in the future since echinocandin is first line therapy in candidaemia and one of the few options for *C. glabrata* candidaemia.

Acknowledgements to the ten Danish Clinical Microbiology Departments at Danish hospitals for their interest and participation in the Danish *Candida* surveillance program including the submission of invasive *Candida* isolates of all types to the reference lab at SSI.

We would also like to thank the staff of the laboratory at the Mycology Unit at Statens Serum Institut.

Malene Risum, Raluca Datcu and Maiken Cavling Arendrup
For further information: Maiken Cavling Arendrup, maca@ssi.dk

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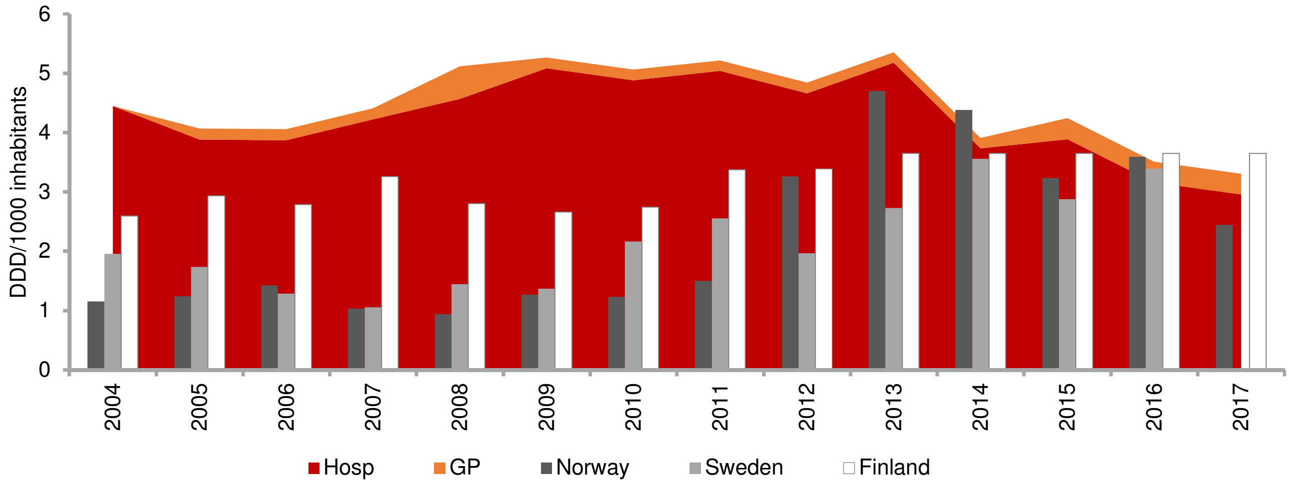
continued ... Textbox 5.4, part 1

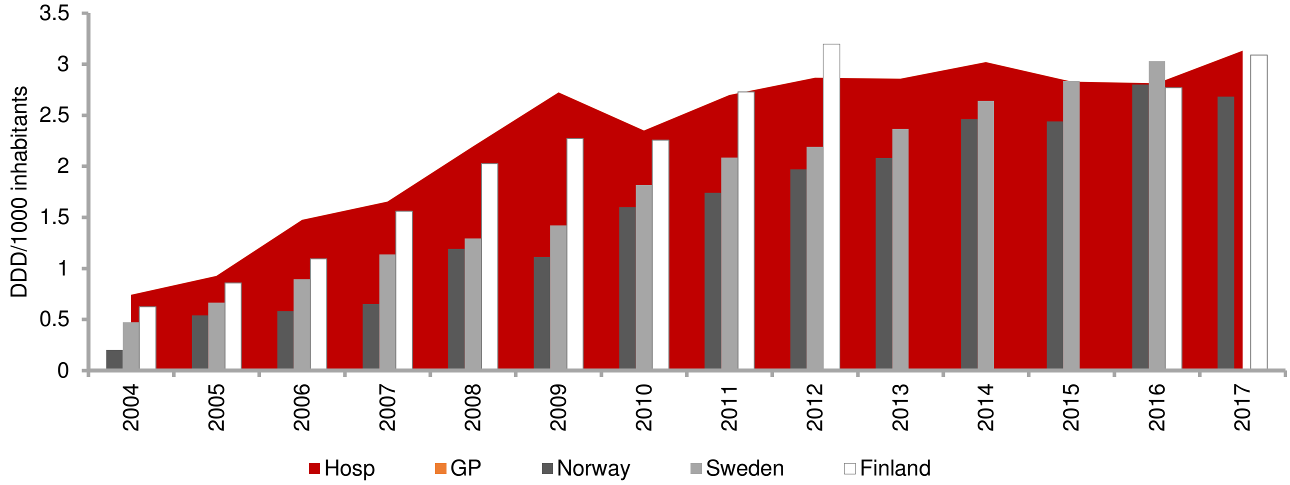
Figure 2 Annual consumption of amphotericin B (A), echinocandins (B) and fluconazole (C) in DDDs/1,000 inhabitants in 2004 to 2017

DANMAP 2018

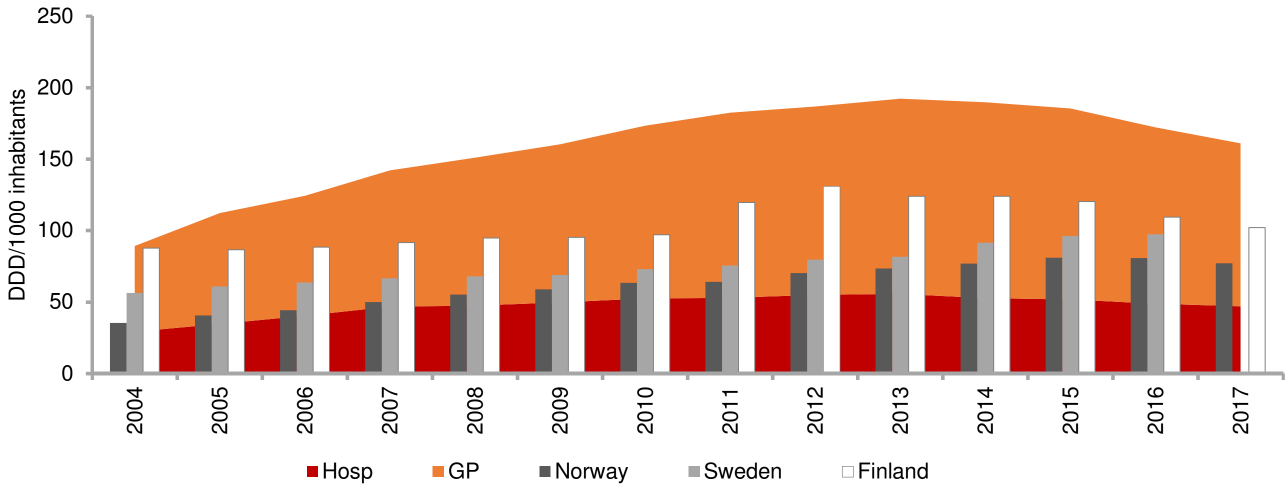
a) Amphotericin B 0.035 g/DDD



b) Echinocandins 0.5-1 g/DDD



c) Fluconazole 0.2 g/DDD



Annual consumption of amphotericin B (A), echinocandins (B) and fluconazole (C) in DDDs/1,000 inhabitants in 2004 to 2017. DDD: Defined daily dosage per 1000 inhabitants
Data on antifungal consumption was not available for Sweden in 2017

Textbox 5.4, part 2

Azole resistance in *Aspergillus* spp. Preliminary six months data from the newly established surveillance in Denmark

Azoles are the cornerstone in the treatment of aspergillosis due to superior efficacy and due to being the only antifungal drug class with oral formulations. Azole resistance (azole-R) in *Aspergillus* has been increasingly reported worldwide. The use of azole fungicides in the environment has been proposed to contribute to the emergence of azole-R *Aspergillus fumigatus*, and isolates harbouring the resistance mechanisms TR_{34}/L98H or TR_{46}/Y121F/T289A have been dominant among azole-R *A. fumigatus* from azole naïve patients as well as the environment (1). These two resistance genotypes have been sporadically found in clinical (2,3) as well as environmental samples in Denmark, although only TR_{34}/L98H from environmental samples has been previously published (4).The size of the problem remains unknown. It is noteworthy, however, that azole-R *A. fumigatus* isolate (TR_{34}/L98H) has previously been detected from soil outside Rigshospitalet in Copenhagen, and recently (June, 2019) a TR_{46}/Y121F/T289A isolate was discovered in a courtyard sample near intensive care unit at Aarhus University Hospital (AUH). This illustrates the ubiquitous presence of azole-R *A. fumigatus* underlining the severity of the problem. Therefore, a nationwide surveillance programme of azole-resistant *A. fumigatus* and underlying resistance mechanisms was established in 2018. Here we report data from the first six month's study period.

Unique *Aspergillus* isolates were included from all ten Danish clinical microbiological departments during the period October 2018 to March 2019. Isolates from same patients were defined as unique if 1) found >30 days apart, 2) confirmation of another species or 3) different susceptibility pattern. Inclusion criteria were: a) *Aspergillus* isolates regarded clinically significant, or b) any *Aspergillus* isolate detected on a Monday throughout the study period regardless of clinical significance to reflect the susceptibility pattern in general of circulating *A. fumigatus*. Included isolates originated from patients from both primary health sector and the hospital sector. Referral practices varied. Most laboratories referred all detected moulds or all *Aspergillus* isolates which then underwent species identification and susceptibility testing at the reference laboratory at Statens Serum Institut (SSI). One laboratory (AUH) performed species identification and susceptibility testing for most isolates locally, and the results were sent to SSI. Resistant isolates were sent to SSI for confirmation and molecular characterisation.

Table 1. Species distribution and susceptibility for *Aspergillus* complexes and *A. fumigatus* DANMAP 2018

		Itraconazole		Posaconazole		Voriconazole		Isavuconazole	
Species	No.	Range	MIC50	Range	MIC50	Range	MIC50	Range	MIC50
A. flavus	21	≤0.03-1	0.125	0.125-0.25	0.125	0.5-1	1	0.5-4	1
A. fumigatus	411	0.06->16	0.25	0.03->4	0.06	0.25-8	0.5	0.5-16	1
A. nidulans	3	0.125	0.125	0.06-0.125	0.125	0.125-0.25	0.25	0.125-0.25	0.125
A. niger	61	0.25->16	1	0.125-0.5	0.5	0.5-2	1	1-8	2
A. terreus	18	0.06->16	1	0.03-0.5	0.5	0.25-4	1	0.25-16	2
Other *Aspergillus*	8	0.06->16	0.5	0.03->4	0.25	0.25-16	0.5	0.25-8	0.5

At SSI the referred *A. fumigatus* isolates underwent screening for azole-R following the EUCAST E.Def 10.1 method and using VIPcheck azole agar plates (Mediaproducts BV, Grönningen, NL). Screening positive *A. fumigatus* isolates and all non-*fumigatus Aspergillus* isolates underwent EUCAST E.Def 9.3.1 susceptibility testing. Isolates with azole MIC(s) above the EUCAST BP(s) underwent *cyp51A* gene sequencing.

A total of 695 *Aspergillus* isolates were included of which 503 were *A. fumigatus*. Susceptibility testing was performed for 411 *A. fumigatus* isolates from 319 patients at time of writing (Table 1). For *A. fumigatus*, 92.7% isolates were azole susceptible, 1.7% intermediate and 5.6% azole-R. From 19 out of 319 patients azole-R *A. fumigatus* isolates was recovered (6%). Among these, 18 out of the 19 patients (95%) harboured an isolate with a *cyp51A* mutation (Table 2). Fourteen out of 19 (73.7%) resistant isolates harboured a TR_{34}/L98H mutation derived from the environment. Furthermore, two patients harboured three azole resistant *Aspergillus terreus* isolates, each with a *cyp51A* mutation (Table 2).

continued ... Textbox 5.4, part 2

Table 2 Cyp51A profiles of resistant *A. fumigatus* and *A. terreus* isolates DANMAP 2018

A. fumigatus		
No. of patients	**Cyp51A profile**	**Azole resistance**
13	TR_{34}/L98H	Pan-azole resistant
1	TR_{34}^{3}/L98H*	Pan-azole resistant
2	G54R	Itraconazole and posaconazole resistant
1	G432S	Pan-azole resistant
1	M220K	Itraconazole and posaconazole resistant
A. terreus		
No. of patients	**Cyp51A profile**	**Azole resistance**
1**	M217I	Pan-azole resistant
1**	Y491H	Intermediate resistant
1	G51A	Itraconazole and posaconazole resistant

* Patient harboured both TR_{34}/L98H and TR_{34}^{3}/L98H isolates, the latter potentially evolved in vivo
** Same patient with two different mutant isolates

We report a nationwide azole-R rate of 6% in *A. fumigatus* at the patient level from the first six months of the nationwide surveillance. The underlying resistance mechanisms was target gene mutations in all but one case and notably, the vast majority were of environmental origin linked to the use of azole fungicides. The fact that such isolates have increasingly been found in Denmark since 2009 is concerning and suggests that a one-health approach involving human and environmental azole management is necessary to limit further rise in azole-R *A. fumigatus*.

Acknowledgements to the ten Danish Departments of Clinical Microbiology, who have been close collaborators and contribute with isolates to the surveillance program.

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Malene Risum[1], Rasmus Krøger Hare[1], Nissrine Abou-Chakra[1], Jan Berg Gertsen[2], Lise Kristensen[2] and Maiken Cavling Arendrup[1]
[1]Mycology Unit, Statens Serum Institut
[2]Department of Clinical Microbiology Aarhus University Hospital

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