8

RESISTANCE IN HUMAN PATHOGENS

8. Resistance in human pathogens

Highlights: The **incidence of positive blood cultures** with pathogenic species increased overall from 474 per 100,000 inhabitants in 2015 to 612 per 100,000 inhabitants in 2024 (an increase of 29 %). The number of individual registered invasive cases per year for the decade increased for *E. coli* from 4,597 cases to 5,957 cases, for *S. aureus* from 1,876 to 2,442 cases, for *K. pneumoniae* from 939 to 1,457 cases and for *P. aeruginosa* from 441 to 488 cases. Decreasing numbers were observed for *S. pneumoniae* from 747 to 600 annual cases, for *E. faecium* from 693 to 584 cases and for *E. faecalis* from 610 to 594 cases.

Resistance levels for invasive ***E. coli*** showed decreasing or stagnating trends for most antimicrobials, including for combined resistance to ciprofloxacin, cephalosporin and gentamicin (2.3% in 2015 to 1.0% in 2024) and combined resistance to ampicillin and gentamicin (6.3% in 2015 to 4.0% in 2024). Resistance to piperacillin-tazobactam increased in three of the five healthcare regions, leading to an overall increase from 4.9% in 2015 to 6.5% in 2024. Resistance to carbapenems remained below 1%.

In invasive ***K. pneumoniae*** **the resistance level** for piperacillin/tazobactam has been increasing steadily since 2021 and has now reached 10.9% (7.5% in 2021). However, combined resistance to 3rd generation cephalosporins, ciprofloxacin and gentamicin remains low at 1.4 %. Additionally, resistance to carbapenem remained below 1%. For *K. pneumoniae* from hospital urine, resistance to piperacillin/tazobactam is now also at 10.9% mirroring the increasing resistance levels in invasive infections.

Carbapenemase-producing organisms/Enterobacterales (CPO/CPE). CPE were increasingly spreading in Danish hospitals, with cases increasing by 14% from 2023 to 2024, reaching 497 individual cases. CPE, historically linked to travel, are now increasingly found domestically. CPE outbreaks increased in hospitals despite extensive screening and cleaning efforts. 166 new CPO patients were associated with outbreaks in Denmark in 2024. Although bloodstream infections remained rare, the rise in hospital-acquired CPE indicates the emergence of domestic reservoirs. For non-outbreak related cases, 110 patients reported travelling outside Nordic countries, however, the number of cases with no travel information reported was high (256 cases). Additionally, 41 cases were patients from Ukraine.

Staphylococcus aureus. The number of *S. aureus* bacteraemia cases was 2,461 in 2024 and at the same level as in 2023. Of these, 47 cases (1.9%) were caused by methicillinresistant *S. aureus* (MRSA) with seven being livestock-associated-MRSA (LA-MRSA). Resistance to penicillin appears stable and was 68% in 2024. There were 3,372 cases of MRSA from both screening (41% of cases) and infections (59%), which was an 8% decrease compared to 2023. Thirty-eight MRSA outbreaks were registered at hospitals, nursing homes and other institutions for a total of 191 cases with 86 being infections.

Neiserria gonorrhoeae. Over the decade the number of received isolates and of reported cases increased significantly. In 2024, the reference laboratory at SSI received 1,852 isolates from 1,803 individual cases. Ciprofloxacin resistance was at 61%. Azithromycin-resistance was found in 3.5% of tested isolates in 2023 compared to 6.0% of tested isolates in 2022.

8.1 Introduction

The Danish national surveillance programme of antimicrobial resistance in human clinical bacteria collects data on routine diagnostics from all of Denmark. It is an active digital catchment system collecting results from all clinical and screening samples from patients. Data coverage is high and microbiology data from all hospitals and the majority of general practitioners feed into the system. Primarily included are data from invasive infections and urines, and in selected cases data from other specimen or sample sites.

In addition, the programme includes phenotypic resistance and typing results from the reference laboratories at SSI. Isolates are submitted to SSI either as part of the programme on mandatory notifiable diseases or based on voluntary submission of bacterial species carrying resistance mechanisms of concern. Table 8.1 gives an overview of inclusion criteria for data from the digital surveillance system and the reference laboratories.

Table 8.1 Inclusion criteria for bacterial species and types in the national antimicrobial resistance surveillance in humans, Denmark, 2024 DANMAP 2024

Routine diagnostics from all 10 DCM in Denmark. All data are extracted from EpiMiBa	
Species	**Inclusion criteria**
Escherichia coli *Klebsiella pneumoniae*	First isolate per patient per year from blood or cerebrospinal fluid, from urine in hospitalised patients and from urine from primary health care
Pseudomonas aeruginosa *Acinetobacter* species *Enterococcus faecalis* *Enterococcus faecium*	First isolate per patient per year from blood or cerebrospinal fluid
Voluntary submissions of isolates to the reference laboratories at SSI	
Species or type	**Inclusion criteria**
Staphylococcus aureus Beta-haemolytic streptococci	One isolate per patient per episode from blood or cerebrospinal fluid
Neisseria gonorrhoeae	One isolate per patient per episode from any sample site
3rd generation cephalosporin-resistant *Escherichia coli*	First isolate per patient within 12 months from blood
Vancomycin-resistant enterococci	First isolate per patient within 12 months from any sample site (excluding screening samples)
Enterococci with specific phenotype of concern (e.g. linezolid, daptomycin and tigecycline R)	First isolate per patient within 12 months from any sample site (clinical and screening samples)
All bacterial species with other exceptional phenotypes (e.g. acquired colistin resistance)	One isolate per patient per episode from any sample site
Mandatory submissions of isolates to the reference laboratories at SSI	
Species or type	**Inclusion criteria**
Carbapenemase-producing organisms	First isolate per patient within 12 months from any sample site (clinical and screening samples)
Methicillin-resistant *Staphylococcus aureus*	First isolate from all new cases of MRSA postive patients from any sample site (clinical and screening samples)
Streptococcus pneumoniae	One isolate per patient per episode from blood or cerebrospinal fluid
Haemophilus influenzae serotype b, Hib	All invasive isolates

Irrespective of number of isolates analysed per patient, only one isolate per given bacterial species per patient is included

8.1.1 Surveillance based on data from the Danish Microbiology Database (MiBa)

An important part of the national surveillance programme consists of systematically extracted data from a register (EpiMiBa) linking to the Danish Microbiology Database (MiBa). MiBa was established in 2010 with the aim of building a cross-national database that included and made available all microbiology analyses performed by the individual DCM. MiBa simultaneously delivers real time patient data to the DCM for clinical use and data to SSI for national surveillance. Until the establishment of MiBa, surveillance was based on voluntary manual reporting from the individual DCM, in the beginning including data from just two DCM in 1995, but quickly expanding to cover more than fifty percent of the DCM. Since 2015, all DCM have contributed to the program resulting in a 100% coverage of hospitalised patients and – since the DCM perform microbiology analyses for GPs and private specialists as well – also a very high coverage of results from the primary sector.

A description of MiBa and the usage and validation of data from the associated database EpiMiBa can be found on the following homepage [https://mibaen.ssi.dk/] and in DANMAP 2018, Textbox 8.1.

The MiBa-based surveillance includes all invasive isolates of *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Enterococcus faecium, Pseudomonas aeruginosa* and *Acinetobacter* species and all urine isolates of *E. coli* and *K. pneumoniae*. For inclusion, the following case definition applies: The first sample of each given bacterial species per individual patient per year, by date of sample collection; an approach identical to the surveillance performed by the European Antimicrobial Resistance Surveillance Network (EARS-Net). All duplicates, patient-related or sample-related within the year of observation, are excluded.

Materials and methods are further described in paragraph 10.10 in Chapter 10.

8.1.2 Surveillance based on data from the reference laboratories

Antimicrobial resistance is also monitored in isolates submitted to the reference laboratories at SSI.

Submission of isolates began in 1957 with the voluntary referral of *S. aureus* from bloodstream infections. Still today, many isolates are sent as part of voluntary programmes; however, the majority of isolates are referred as part of surveillance programmes for notifiable diseases.

The mandatory programme includes methicillin-resistant *S. aureus* (MRSA) and carbapenemase-producing organisms (CPO) from clinical and screening samples, *S. pneumoniae* and *Haemophilus influenzae* serotype b (Hib) from invasive infections and *Nesseria gonorrhoeae* from all clinical samples. The latter three irrespective of findings of antimicrobial resistance, but resistance mechanisms are investigated both locally and at SSI (Table 8.1).

The voluntary programme includes day-to-day referral of vancomycin-resistant enterococci and monthly or periodically reporting of ESBL-positive invasive *E. coli*, invasive beta-haemolytic streptococci and invasive *S. aureus*.

In addition, the reference laboratory for antimicrobial resistance at SSI receives highly resistant strains or strains carrying atypical antimicrobial resistance mechanisms of specific concern irrespective of bacterial species.

Since 2015/2016, characterisation of antimicrobial resistance mechanisms in bacteria has been performed primarily by whole genome sequencing (WGS).

8.1.3 Number of invasive cases

The total numbers of invasive cases of the monitored bacterial species included in the surveillance programmes for both DANMAP and EARS-Net from 2015 to 2024 are presented in Figure 8.1. Invasive cases caused by *Acinetobacter* species are not shown in the figure due to the small numbers of isolates (ranging from 55 to 97 cases/year between 2015 and 2024).

Between 2015 and 2024, the number of registered individual invasive cases increased by 22% from 9,975 to 12,214 cases in Denmark: *E. coli* 4,597 to 5,957 cases (30% increase), *S. aureus* 1,876 to 2,442 cases (30%) and *K. pneumoniae* 939 to 1,457 cases (55%).

Figure 8.1 Number of invasive cases for bacterial species under surveillance, Denmark, 2015-2024 DANMAP 2024

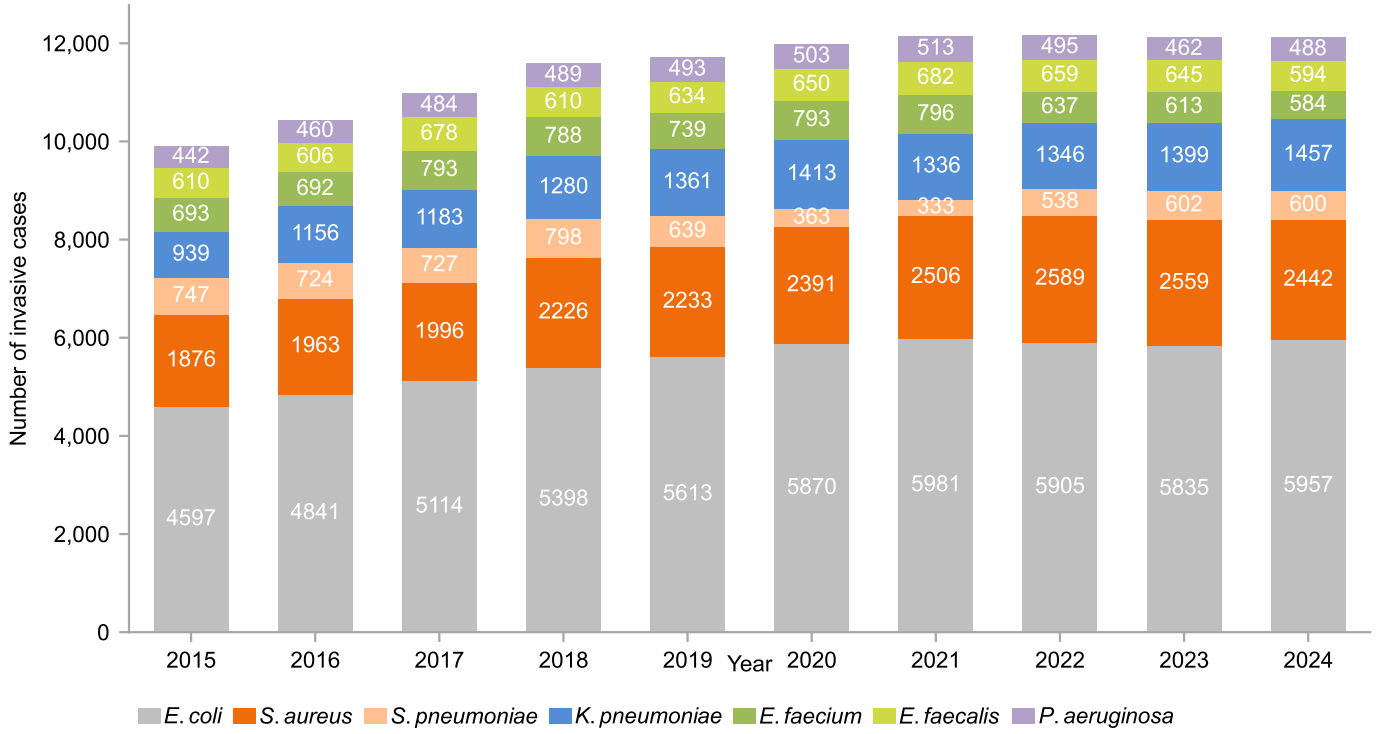
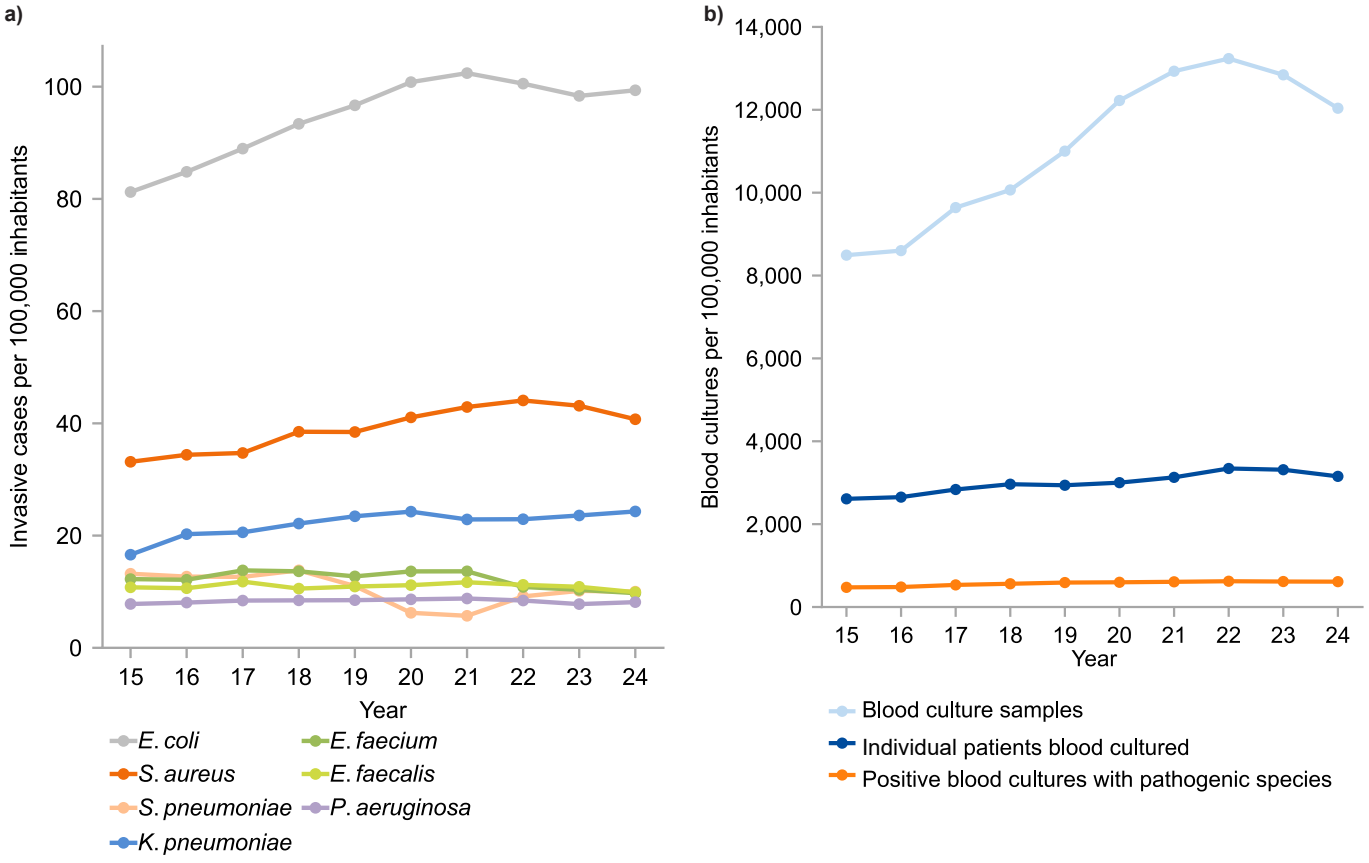


Figure 8.2a shows the incidence of invasive cases of the seven monitored species per 100,000 inhabitants in Denmark per year from 2015 to 2024. During this period, the Danish population increased by 5.9% (from 5,659,715 inhabitants in 2015 to 5,995,628 inhabitants in 2024).

For comparison, Figure 8.2b shows the total number of blood cultures taken per 100,000 inhabitants per year and the number of individual patients with minimum one blood culture taken per 100,000 inhabitants per year, for the same period. The total number of blood samples taken per 100,000 inhabitants increased by 42% and the number of individual patients with at least one blood culture taken by 21% (from 2,611 patients per 100,000 inhabitants in 2015 to 3,153 patients per 100,000 inhabitants in 2024). The incidence of positive blood cultures with pathogenic species increased from 474 per 100,000 inhabitants in 2015 to 612 per 100,000 inhabitants in 2024.

The following sections present results of resistance monitoring in Denmark for the individual bacterial species and/or resistance types under surveillance.

Figure 8.2 a) Invasive cases and b) blood cultures taken per 100,000 inhabitants, Denmark, 2014-2023 DANMAP 2024



8.2 Results from MiBa data surveillance

8.2.1 *Escherichia coli*

Escherichia coli is by far the most frequent cause of community and hospital acquired bacteraemia and urinary tract infections (UTI) in Denmark. The pathogen is part of the normal intestinal flora in both animals and humans, where it comes into close proximity to many other bacterial species. Transferable resistance mechanisms are frequently seen in these gut bacteria as well as resistance conferred by mutations. Since *E. coli* is the most frequent cause of UTI and bacteraemia, it is also responsible for a large proportion of the antimicrobials used to treat these conditions.

The percentages of resistance in invasive *E. coli* isolates for each key antimicrobial are presented in Table 8.2, as are urine samples from hospitals and primary health care (see details in later paragraphs).

Invasive cases from hospital patients

In 2024, a total of 5,957 individual patients with invasive *E. coli* isolates were identified in EpiMiBa. Antimicrobial susceptibility test results for key antimicrobials were also extracted for these isolates (See Chapter 10 'Material and methods').

Figure 8.3 and Table 8.3 show the total annual number of invasive isolates and proportion of resistant isolates by region between 2015 and 2024. Most resistance levels decreased or stagnated over the last decade, apart from resistance to piperacillin-tazobactam, which increased in three of the five healthcare regions, leading to an overall increase from 4.9% in 2015 to 6.5% in 2024.

Resistance to carbapenems remained below 1%. The percentages of multidrug resistant invasive isolates are presented in Table 8.4. Combined resistance to ciprofloxacin, cephalosporins and gentamicin decreased from 2.3% in 2015 to 1.0% in 2024 and combined resistance to ampicillin and gentamicin decreased from 6.3% to 4.0%.

Urinary cases from hospitals

In 2024, *E. coli* was isolated from urine samples of 40,624 individual hospital patients. As for invasive *E. coli* increasing resistance to piperacillin-tazobactam was observed (5,6% in 2024). In Table 8.2 summarized antimicrobial susceptibility results for *E. coli* isolates (invasive and urine specimen) are shown. In Figure 8.4 and Table 8.5, resistance for *E. coli* urine isolates from hospitalised patients are shown for 2015-2024.

Urinary cases from primary health care

In 2024, *E. coli* were isolated from urine samples from 93,436 individual patients in primary health care, a notable decrease compared to 2023. This is due to changes in workflow at one of the DCMs in the Capital Region causing data from that DCM to be excluded from the analysis. Susceptibility results for all tested antimicrobials are shown in Table 8.2. In Figure 8.5 and Table 8.6, resistance for *E. coli* urine isolates from primary health care are shown for the past decade.

Conclusion

The number of invasive cases of *E. coli* appears to have reached a plateau. Resistance levels are generally stable for all specimen types, however, the slow rise in piperacillin-tazobactam resistance in *E. coli* from invasive infections and hospital urines are cause for concern.

Table 8.2 *Escherichia coli*. Resistance (%) in isolates from humans, Denmark, 2024 DANMAP 2024

Substance	Invasive isolates, hospitals %	Urine isolates, hospitals %	Urine isolates, primary health care %
Ampicillin	42	40	34
Mecillinam	6.1	6.7	3.9
Piperacillin/tazobactam	6.5	5.6	3.6 (1)
Amoxicillin/clavulanic acid	31 (6)	10.3	6.5
Sulfonamide		30 (5)	23.7
Trimethoprim		22	19.4
Nitrofuratoin		0.8	0.5
Gentamicin	4.4	4.9	3.2 (1)
Ciprofloxacin	10.9	10.2	7.7
Cefuroxime	9.9	8.1	6.7 (3)
3rd generation cephalosporins	6.5	6.9	5.6
Carbapenem	0.1	0.0	0.0 (1)
Max. number of isolates tested for resistance to the presented antibiotics	5,950	40,624	93,436

Note: Included are results from all DCMs where >75% of the isolates in each antibiotic/sample group were susceptibility tested
Numbers in parantheses indicate the number of DCMs included if less than six

Figure 8.3 Antimicrobial resistance in invasive *Escherichia coli* isolates from humans by region, Denmark, 2015-2024 DANMAP 2024

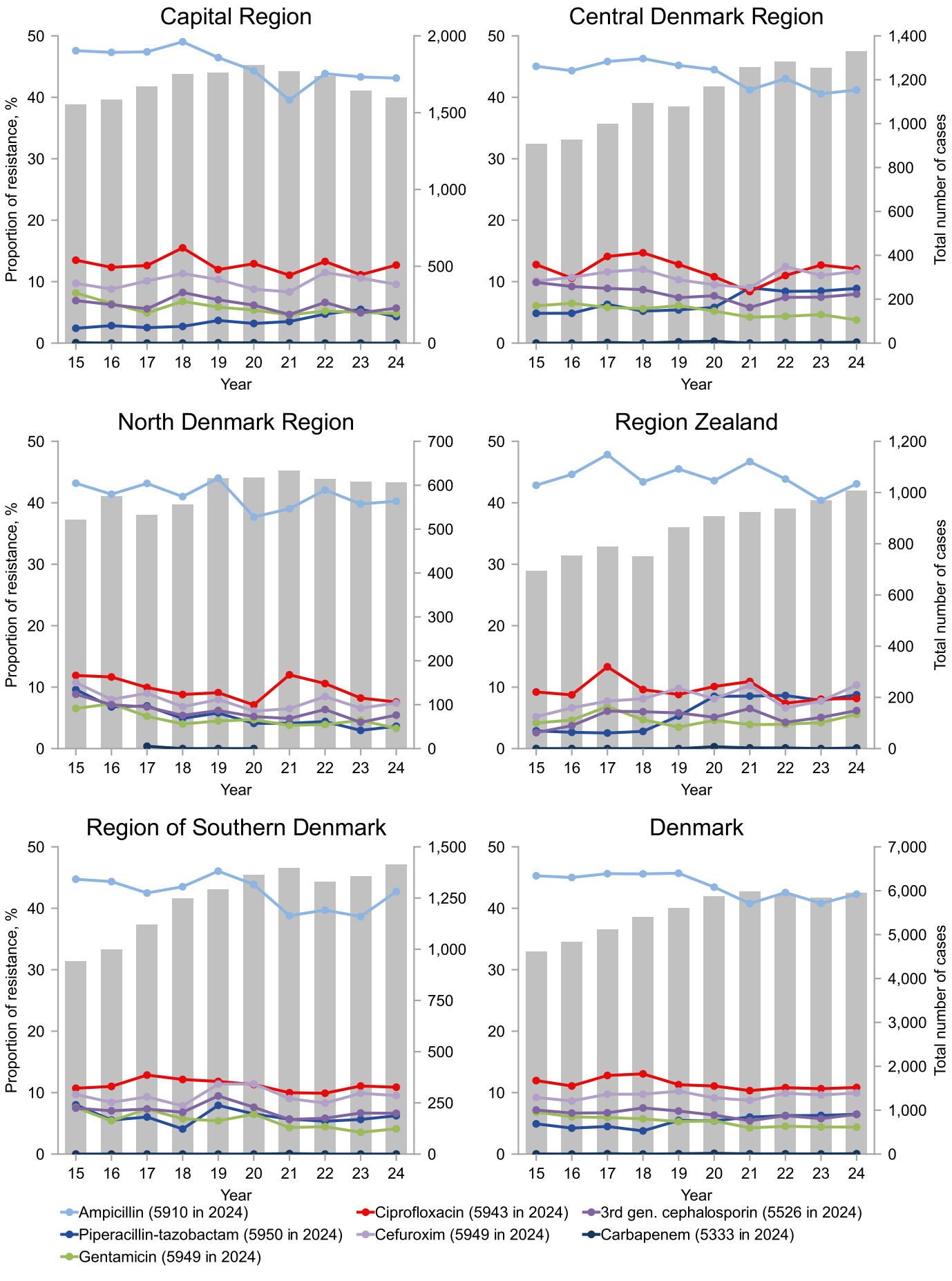


Table 8.3 Invasive *Escherichia coli*. Table of resistance percentages, 2015-2024 DANMAP 2024

Substance	Percent resistant invasive *E. coli* isolates									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Ampicillin	45.3	45.0	45.6	45.5	45.7	43.4	40.7	42.6	40.8	42.3
Piperacillin-tazobactam	4.9	4.2	4.5	3.8	5.5	5.4	6.0	6.3	6.3	6.5
Gentamicin	6.8	6.1	6.0	5.7	5.3	5.4	4.3	4.5	4.4	4.4
Ciprofloxacin	12.0	11.1	12.8	13.0	11.3	11.1	10.3	10.8	10.6	10.8
Cefuroxime	9.2	8.6	9.7	9.8	10.2	9.2	8.7	9.9	9.6	9.9
3rd gen.cephalosporins	7.2	6.7	6.7	7.3	6.9	6.2	5.4	6.2	5.8	6.5
Carbapenem	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.1
Total number of isolates	4,618	4,841	5,114	5,398	5,613	5,870	5,981	5,905	5,835	5,957

Table 8.4 Invasive *Escherichia coli*. Combined resistance to 1) ampicillin and gentamicin and 2) 3rd generation cephalosporins, ciprofloxacin, and gentamicin (multiresistance) in invasive isolates from humans, Denmark, 2015-2024 DANMAP 2024

Combination		2015 % (N)	2016 % (N)	2017 % (N)	2018 % (N)	2019 % (N)	2020 % (N)	2021 % (N)	2022 % (N)	2023 % (N)	2024 % (N)
AMP/GEN	Resistance	6.3 (254)	5.8 (278)	5.8 (289)	5.5 (284)	5.2 (275)	5.1 (287)	4.0 (229)	4.1 (233)	4.1 (231)	4.0 (235)
	Percentage (no.) of isolates tested	87 (4,009)	99 (4,816)	98 (5,015)	96 (5,170)	95 (5,308)	95 (5,583)	96 (5,745)	96 (5,679)	96 (5,602)	99 (5,903)
3GC/CIP/ GEN	Resistance	2.3 (93)	1.8 (87)	1.8 (88)	2.0 (100)	1.8 (93)	1.5 (82)	1.1 (60)	1.3 (70)	1.2 (63)	1.0 (54)
	Percentage (no.) of isolates tested	88 (4,071)	98 (4,763)	95 (4,883)	93 (4,997)	94 (5,259)	93 (5,470)	93 (5,564)	93 (5,474)	93 (5,417)	93 (5,515)
	Total number of invasive isolates	4,614	4,841	5,114	5,398	5,613	5,870	5,981	5905	5,835	5,957

Table 8.5 *Escherichia coli* from hospital urines. Table of resistance percentages, Denmark, 2015-2024 DANMAP 2024

Substance	Resistance in *E. coli* urine isolates from hospitals									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Ampicillin	42.1	41	41.9	42.1	43.7	40.6	39.2	40.0	39.4	39,6
Mecillinam	7.7	7.4	7.5	7.4	8.1	7.3	6.9	6.8	6.5	6,7
Piperacillin-tazobactam	3.9	3.3	3.7	3.5	4.4	4.3	4.5	5.4	5.4	5,6
Sulfonamide	32	34.9	31.1	31*	31.4*	29.4*	28.5*	28.2*	30.9*	30.0*
Gentamicin	5.1	5.3	4.9	4.7	4.6	4.6	4.2	4.3	4.5	4,9
Ciprofloxacin	11	10.9	10.4	11	10.6	9.6	8.7	9.3	9.9	10,2
Cefuroxime	7	6.8	7.1	7.2	7.8	7.2	6.7	7.5	7.7	8,1
3rd gen. cephalosporins	5.9	5.9	6.2	6.4	6.9	6.3	5.8	6.2	6.5	6,9
Carbapenem	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
Total number of isolates	46,723	46,865	46,884	47,914	47,235	48,962	49,986	48,559	44,389	40,624

* Indicates less than 6 DCMs reporting routine susceptibility testing

Table 8.6 *Escherichia coli* from urines from primary health care. Table of resistance percentages, Denmark, 2015-2024 DANMAP 2024

Substance	Resistance in *E. coli* urine isolates from primary health care									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Ampicillin	38.5	38.3	37.9	37.4	38.1	36.5	34.3	34.6	34.2	34.3
Mecillinam	5.4	5.6	5.5	5.1	5.3	4.9	4.6	4.3	4.0	3.9
Sulfonamide	30.9	29.5	29.1	28.3	27.9	26.7	25.2	25.0	25.5	23.7
Ciprofloxacin	8.6	10.1	8.4	8.1	8.0	7.5	6.9	6.9	7.5	7.7
3rd gen. cephalosporins	4.3	4.3	4.5	4.9	5.2	5.0	4.4	4.8	5.3	5.6
Total number of isolates	61,083	67,798	73,497	80,851	86,508	88,462	99,077	104,376	106,236	93,436

Figure 8.4 Antimicrobial resistance in *Escherichia coli* isolates from urine in humans (hospitals) by region, Denmark, 2015-2024

DANMAP 2024

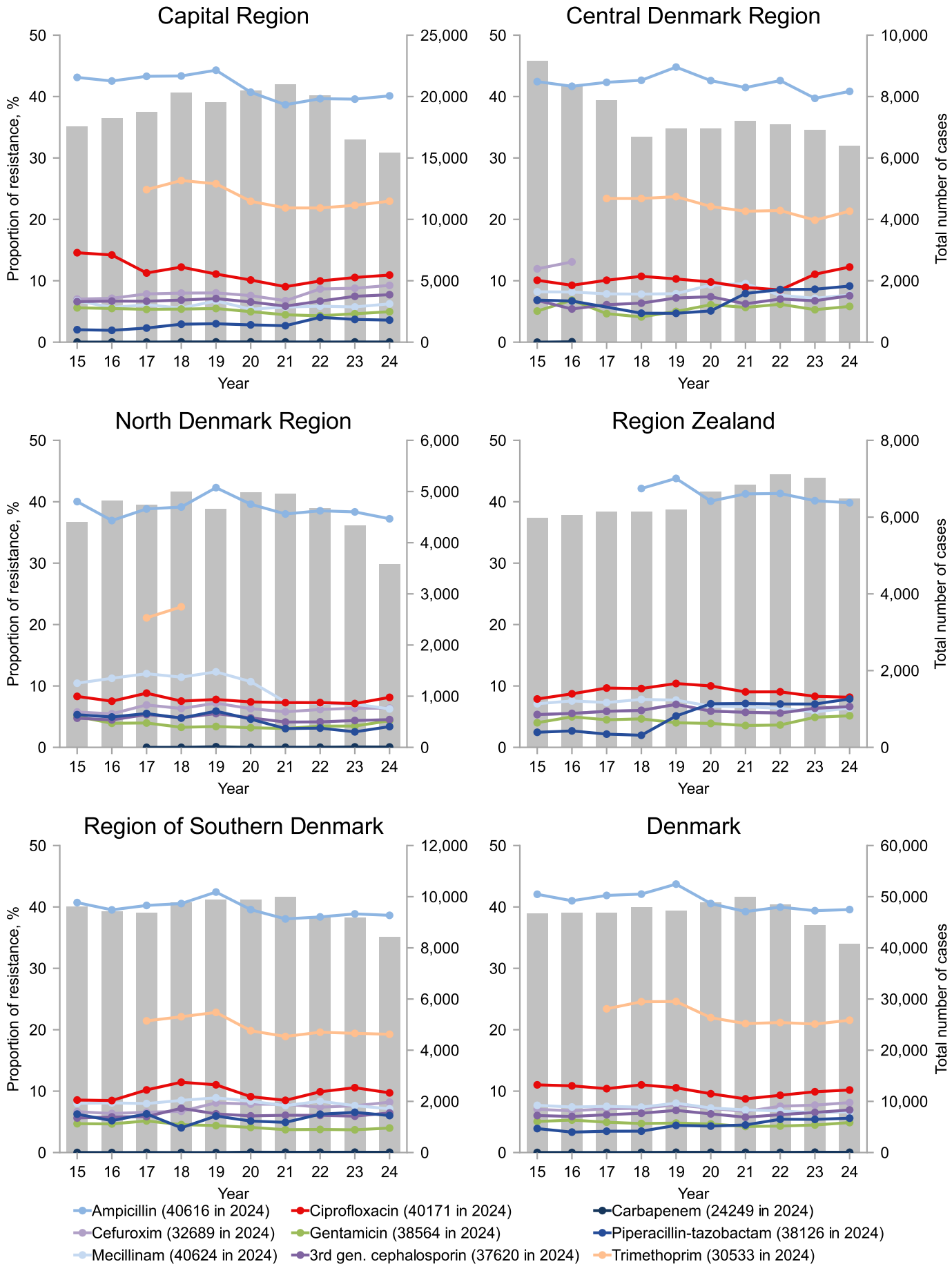
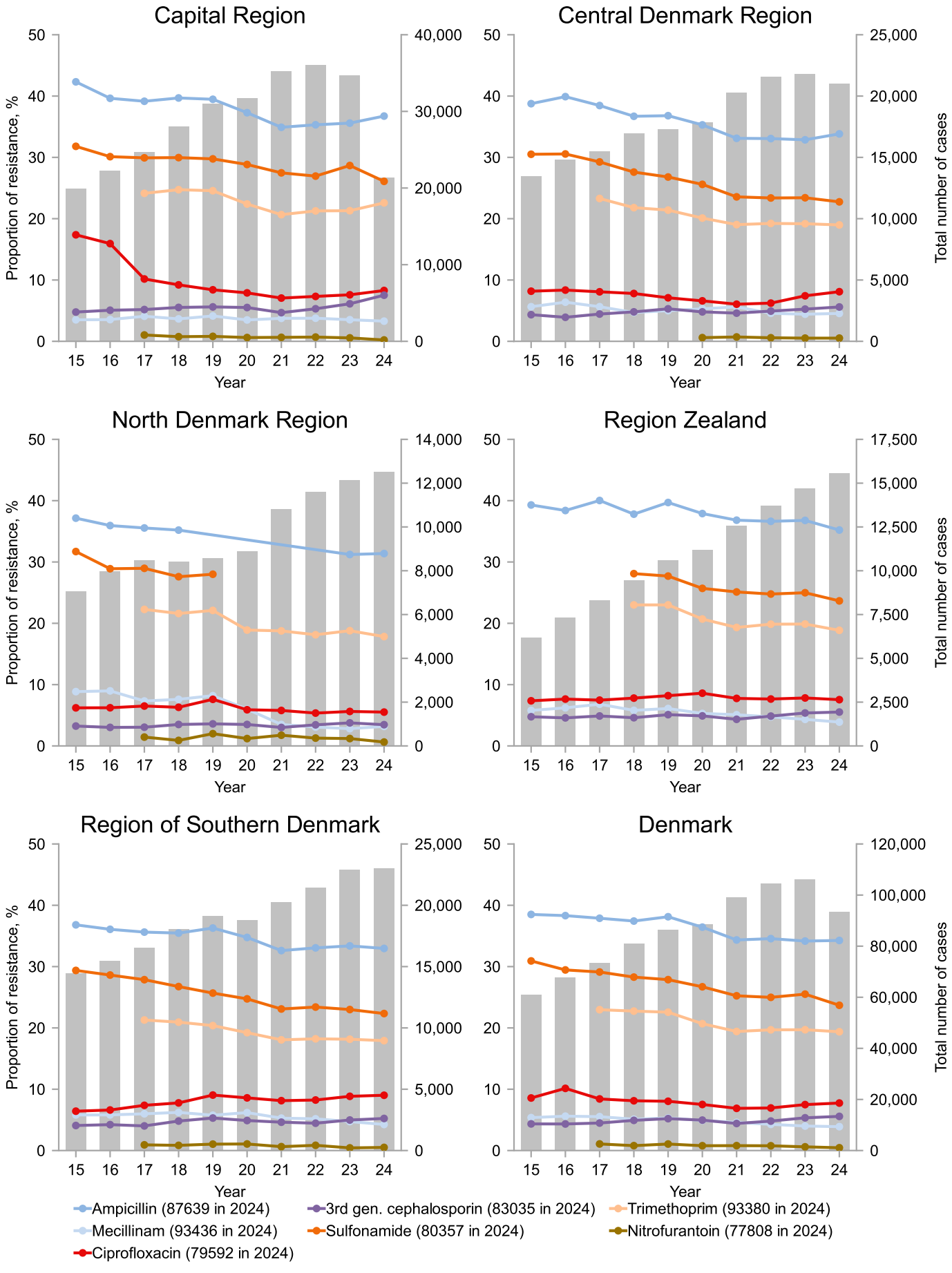


Figure 8.5 Antimicrobial resistance in *Escherichia coli* isolates from urine in humans (primary health care) by region, Denmark, 2015-2024

DANMAP 2024



8.2.2 *Klebsiella pneumonia*

Klebsiella pneumoniae is part of the human intestinal tract. The bacteria cause urinary tract infections, intra-abdominal infections, bacteraemia and ventilator-associated pneumonia (VAP). *K. pneumoniae* may cause nosocomial outbreaks. *K. pneumoniae* frequently displays plasmid-mediated resistance mechanisms, which are transferrable to other bacterial species.

The percentage of resistance in *K. pneumoniae* isolates for key antimicrobials in isolates from invasive infections, urines from hospitals and urines from general praxis, respectively, is presented in Table 8.7.

Invasive cases from hospitals

In 2024, a total of 1,457 individual patients were registered in MiBa with invasive *K. pneumoniae* isolates. From 2015 to 2021, particularly for cephalosporins decreasing trends in resistance were observed. From 2022 to 2024, resistance levels reverted and showed increases for most of the monitored antibiotics. Of particular interest is the almost continuous increase in resistance levels to piperacillin-tazobactam, which increased from 5.9% in 2015 to 10.9% in 2024 in total, an increase that was observed for all regions. The resistance level to carbapenems remained low (<1%), as did combined resistance to ciprofloxacin, cephalosporins and gentamicin (1.4% in 2024).

Figure 8.6 shows total annual numbers and numbers and percentages of resistance in invasive isolates by region and in total, for 2015 to 2024. The proportions of isolates resistant to key antimicrobials for the decade are presented in Table 8.8. The percentages of multidrug resistant invasive isolates are presented in Table 8.9.

Table 8.7 *Klebsiella pneumoniae*. Resistance (%) in isolates from humans, Denmark, 2024 DANMAP 2024

Substance	Invasive isolates, hospitals %	Urine isolates, hospitals %	Urine isolates, primary health care %
Mecillinam	7.1	10.0	7.9
Piperacillin/tazobactam	10.9	10.9	6.3 (2)
Amoxicillin/clavulanic acid	15.3 (5)	7.8	4.9 (5)
Sulfonamide		22.8 (4)	14.2
Trimethoprim		15.1	12.5
Nitrofuratoin		35	30
Gentamicin	2.7	3.4	1.4 (1)
Ciprofloxacin	8.3	8.6	5.4 (5)
Cefuroxime	10.0	9.5	6.1 (3)
3rd generation cephalosporins	5.7	6.2	4.5
Carbapenem	0.2	0.4	0.0 (1)
Max. number of isolates tested for resistance to the presented antibiotics	1,457	7,362	12,336

Note: Included are results from all DCMs where >75% of the isolates in each antibiotic/sample group were susceptibility tested
Numbers in parantheses indicate the number of DCMs included if less than six

Figure 8.6 Invasive *Klebsiella pneumoniae* isolates from humans: proportion of resistant isolates and annual number of isolates from individual cases, Denmark, 2015-2024

DANMAP 2024

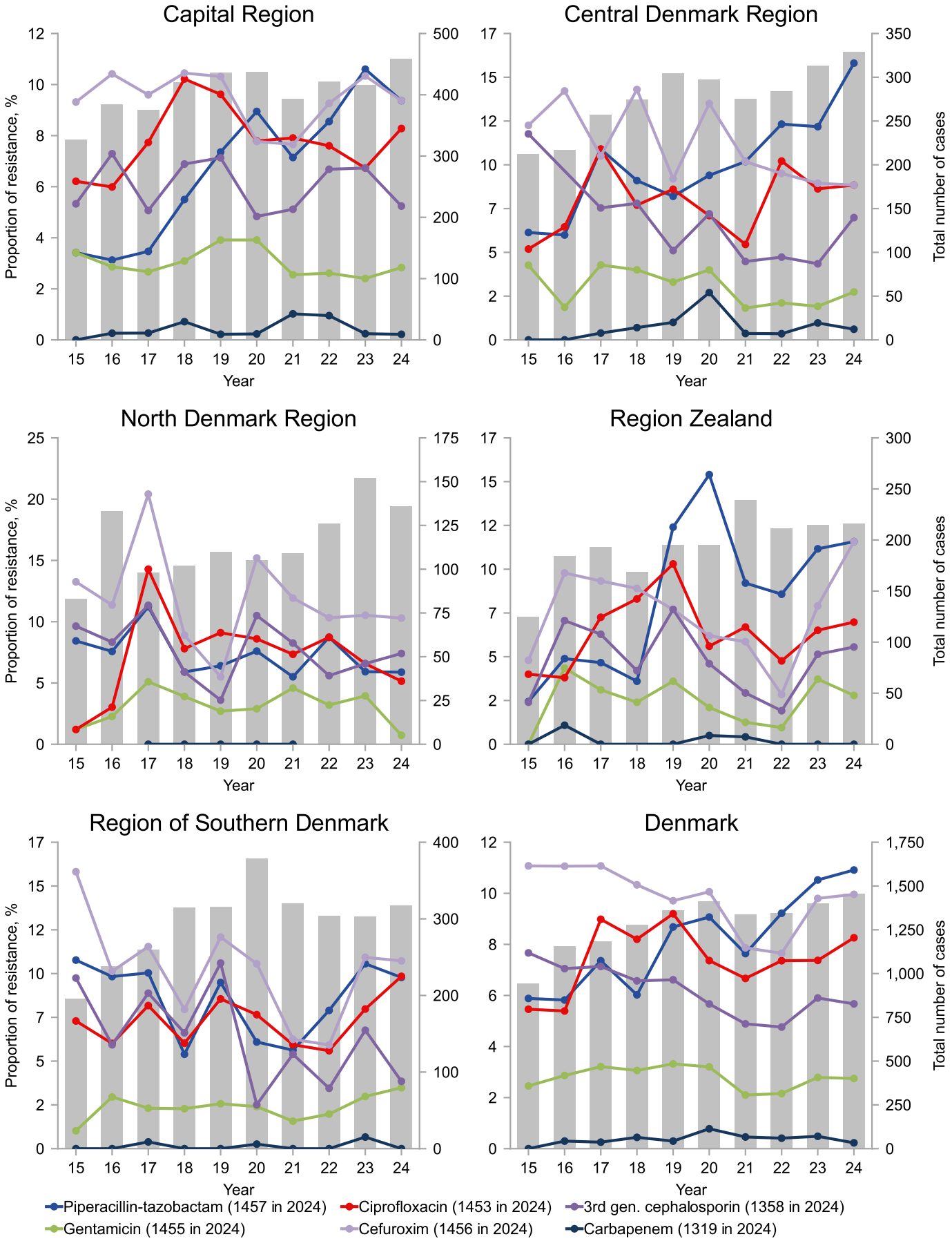


Table 8.8 Invasive *Klebsiella pneumoniae*. Table of resistance percentages, 2015-2024 DANMAP 2024

Substance	Percent resistant invasive *K. pneumoniae* isolates									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Piperacillin/tazobactam	5.9	5.8	7.4	6.1	8.7	9.1	7.5	9.2	10.5	10.9
Gentamicin	2.5	2.9	3.2	3.1	3.3	3.2	2.1	2.2	2.8	2.7
Ciprofloxacin	5.5	5.4	9.0	8.1	9.2	7.4	6.7	7.4	7.4	8.3
Cefuroxime	11.1	11.1	11.1	10.3	9.7	10.1	7.9	7.7	9.8	10.0
3rd gen. cephalosporins	7.7	7.3	7.1	6.1	6.6	5.3	4.9	4.8	5.9	5.7
Carbapenem	0.0	0.3	0.3	0.5	0.3	0.8	0.5	0.4	0.5	0.2
Total number of isolates	939	1,156	1,183	1,280	1,361	1,413	1,336	1,346	1,399	1,457

Table 8.9 Invasive *Klebsiella pneumoniae*. Combined resistance to 3rd generation cephalosporins, ciprofloxacin, and gentamicin (multidrug-resistance) in invasive isolates from humans, Denmark, 2015-2024 DANMAP 2024

	2015 % (N)	2016 % (N)	2017 % (N)	2018 % (N)	2019 % (N)	2020 % (N)	2021 % (N)	2022 % (N)	2023 % (N)	2024 % (N)
Resistance	1.1 (9)	1.6 (18)	2.4 (27)	1.7 (20)	2.4 (30)	1.5 (19)	1.0 (13)	1.0 (13)	1.9 (24)	1.4 (19)
Percentage (no.) of isolates tested for combined resistance (multiresistance)	89 (840)	98 (1,131)	95 (1,122)	93 (1,188)	94 (1,275)	93 (1,308)	93 (1,248)	94 (1,259)	92 (1,287)	93 (1,356)
Total number of invasive isolates	943	1,156	1,183	1,280	1,361	1,413	1,336	1,346	1,399	1,457

Table 8.10 *Klebsiella pneumoniae* from hospital urines. Table of resistance percentages, Denmark, 2015-2024 DANMAP 2024

Substance	Resistance in *K. pneumoniae* urine isolates from hospitals									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Mecillinam	10	8.9	15.7	16.9	13.2	11.7	10.6	9.4	10.0	10.0
Piperacillin/tazobactam	6.3	5.6	6.7	8.7	8.5	8.0	8.7	9.9	10.5	10.9
Gentamicin	3.7	3.2	3.6	3.2	3.0	2.9	2.4	2.3	2.3	3.4
Ciprofloxacin	6.2	6.1	7.6	8.9	7.4	7.2	7.2	7.2	7.5	8.6
Cefuroxime	9.5	9.1	9.4	9.5	8.6	8.5	8.4	8.1	9.4	9.5
3rd gen. cephalosporins	6.8	6.8	7.1	6.8	6.0	5.5	5.4	4.7	5.7	6.2
Total number of isolates	7,175	7,467	8,106	8,047	7,926	7,814	7,701	7,911	7,492	7,362

Table 8.11 *Klebsiella pneumoniae* from urines from primary health care. Table of resistance percentages, Denmark, 2015-2024 DANMAP 2024

Substance	Resistance in *K. pneumoniae* urine isolates from primary health care									
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Mecillinam	9.4	9.0	16.6	15.9	11.5	9.4	8.6	7.9	7.2	7.9
Sulfonamide	18.7	19.3	25.5	24.6	18.9	15.5	13.8	11.9	13.4	14.2
Ciprofloxacin	5.2	5.6	5.4	6.4	5.5	5.2	4.9	5.1	5.2	5.4
3rd gen. cephalosporins	4.8	5.4	4.9	5.3	4.5	4.4	3.7	3.4	4.6	4.5
Total number of isolates	6,372	7,615	8,948	9,227	9,696	9,387	10,196	11,039	11,502	12,336

Figure 8.7 *Klebsiella pneumoniae* isolates from urines in humans (hospitals): proportion of resistant isolates and annual number of isolates from individual cases, Denmark, 2015-2024

DANMAP 2024

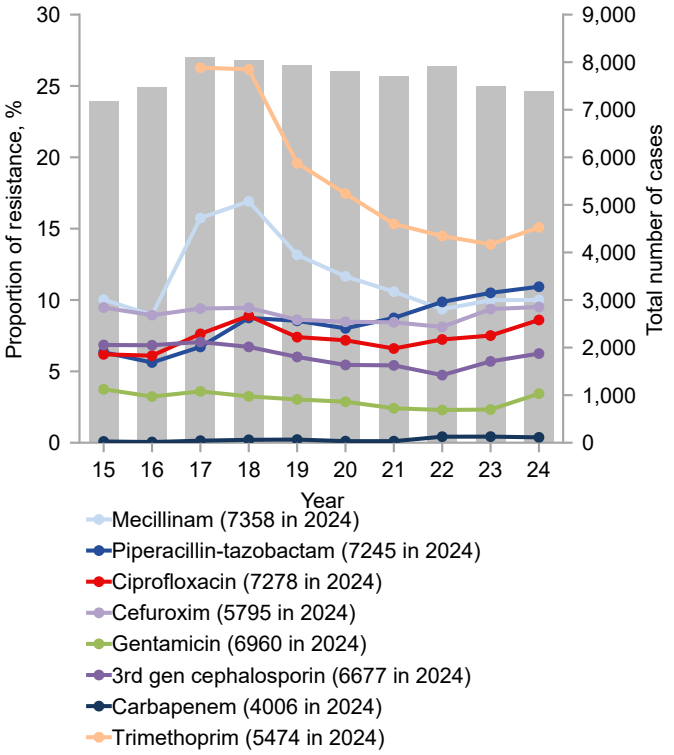
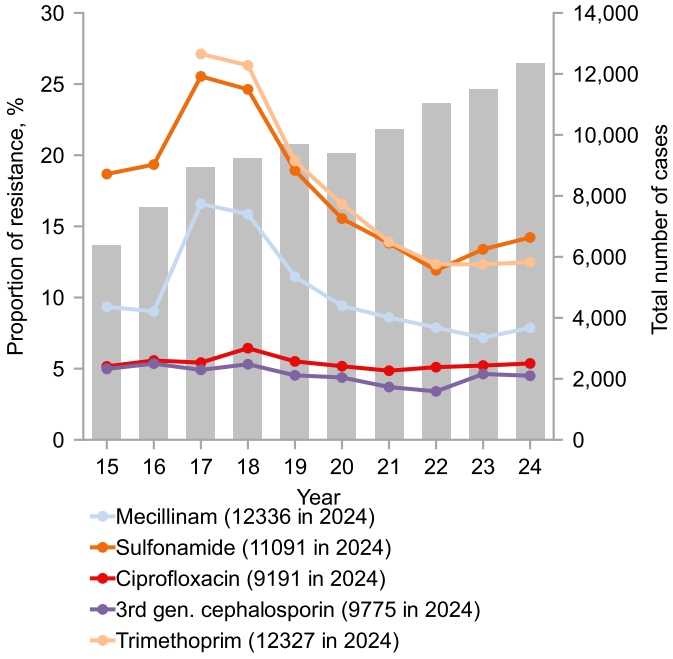


Figure 8.8 *Klebsiella pneumoniae* isolates from urines in humans (primary health care): proportion of resistant isolates and annual number of isolates from individual cases, Denmark, 2015-2024

DANMAP 2024



Urinary cases from hospitals

In 2024, *K. pneumoniae* from urine samples were isolated from 7,362 individual hospital patients in Denmark.

Summarized antibiotic-specific susceptibility results for *K. pneumoniae* isolates (invasive and urine specimen) for 2024 are shown in Table 8.7. In Figure 8.7 and Table 8.10, resistance for *K. pneumoniae* urine isolates from hospitals is shown for 2015-2024.

Urinary cases from primary health care

In 2024, *K. pneumoniae* was isolated from urine samples of 12,336 individual patients in primary health care. As for the results from invasive isolates and isolates from hospital urine samples susceptibility results for all tested antimicrobials are shown in Table 8.7. In Figure 8.8 and Table 8.11, resistance for *K. pneumoniae* urine isolates from primary health care is shown for the past decade.

Conclusion

The number of invasive cases of *K. pneumoniae* have increased by 55% since 2015. As for *E. coli*, a concerning trend is seen with regards to piperacillin-tazobactam for which resistance levels have now surpassed 10% for both invasive infections and hospital urines.

8.2.3 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is an opportunistic pathogen that can colonise the lung, urinary tract, burn wounds, superficial wounds and cause invasive infections. The pathogen is capable of biofilm formation and has the ability to colonise medical devices (e.g. indwelling catheters and implants) which in many cases causes complicated infections requiring prolonged and combination treatment with two broad spectrum antimicrobials. *P. aeruginosa* infections are more prevalent in certain at-risk groups such as immunocompromised, diabetes and cystic fibrosis patients. *P. aeruginosa* exhibits intrinsic resistance to various antimicrobial agents through chromosomal gene mutations and has the ability to acquire β-lactamases (extended-spectrum β-lactamases (ESBLs) and carbapenemases (especially class B carbapenemases or metallo-β-lactamases [MBLs]) by horizontal transmission.

Invasive cases from hospital patients

In 2024, a total of 488 individual patients with invasive *P. aeruginosa* isolates were registered in Denmark. Figure 8.9 shows the total annual number of invasive isolates and proportion of resistant isolates between 2015 and 2024.

Conclusion

The occurrence of invasive *P. aeruginosa* in Denmark is stable regarding the number of cases reported and resistance levels are low.

8.2.4 *Acinetobacter* species

The genus *Acinetobacter* includes several species and is found widespread in nature (soil and water) as well as in animals and humans. In humans, *Acinetobacter* species (spp.) can colonise the skin and wounds but may also cause hospital-acquired infections such as central line-associated bloodstream infections, nosocomial pneumonia, UTIs and wound infections, most often in severely ill patients. Many of the different subspecies are phenotypically alike, and thus identification at species level can be difficult. Species belonging to the *A. baumannii* group are considered as the most clinically important. *Acinetobacter* spp. is intrinsically resistant to a broad range of antimicrobials mediated by a low membrane permeability and constitutive expression of various efflux systems.

Invasive cases from hospitals

In 2024, a total of 92 individual patients with invasive *Acinetobacter* species were reported. Data are presented in Table 8.12 and in Figure 8.10.

Conclusion

The number of invasive *Acinetobacter* spp. appears to have stabilized at a new level compared to the marked increase from 2020 to 2021; however, the proportion of invasive isolates resistant to key antimicrobials remained low in Denmark.

Figure 8.9 Invasive *Pseudomonas aeruginosa* isolates from humans: proportion of resistant isolates and annual number of isolates from individual cases, Denmark, 2015-2024 DANMAP 2024

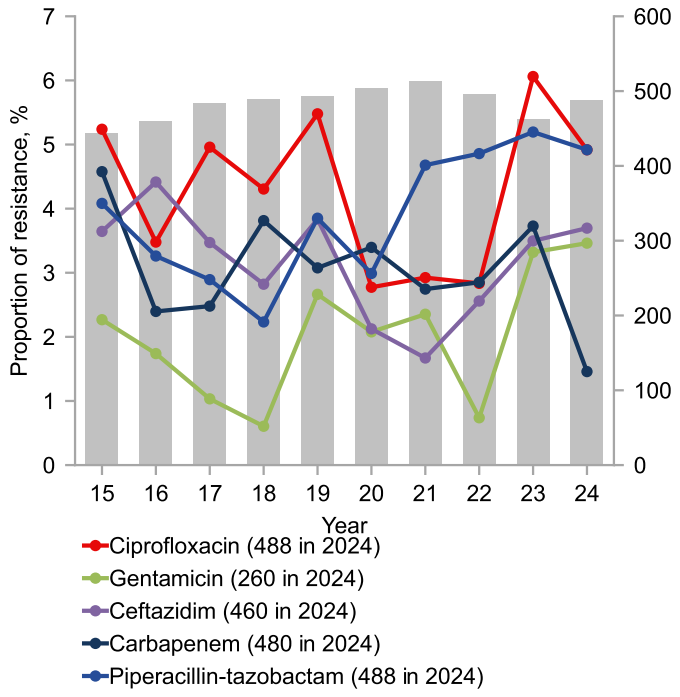


Figure 8.10 Invasive *Acinetobacter* spp. isolates from humans: a) annual number of isolates from individual cases and b) proportion of resistant isolates, Denmark, 2015-2024 DANMAP 2024

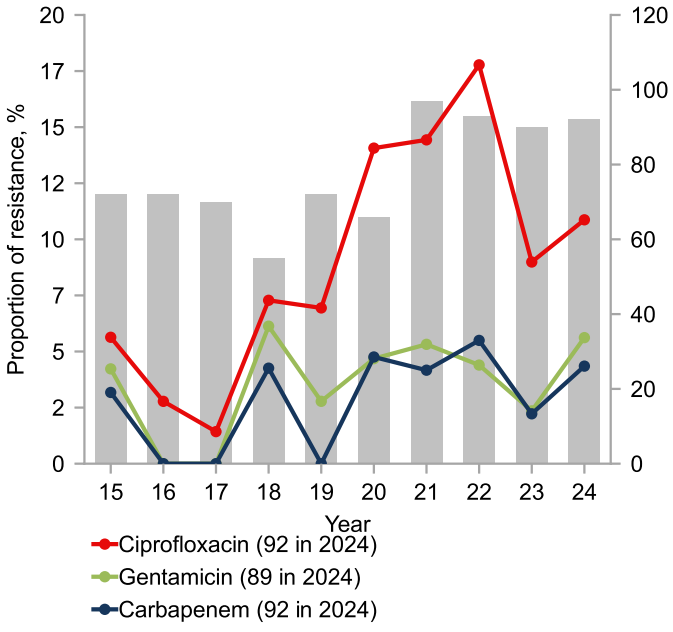


Table 8.12 *Acinetobacter* spp. tested and resistant invasive isolates, Denmark, 2015-2024 DANMAP 2024

	2015		2016		2017		2018		2019		2020		2021		2022		2023		2024	
	res.	n	res.	n	res.	n	res.	n	res.	n	res.	n	res.	n	res.	n	res.	n	res.	n
Ciprofloxacin	4	71	2	72	1	70	4	55	5	72	9	64	14	97	16	92	8	89	10	92
Gentamicin	3	71	0	70	0	70	3	49	2	72	3	64	5	94	4	92	2	85	5	89
Carbapenem	3	68	0	69	0	67	2	47	0	72	3	63	4	96	5	93	2	90	4	92
Total number of invasive isolates	71		72		70		55		72		66		97		93		90		92	

Note: res. = number of resistant isolates. n = number of tested isolates

8.2.5 Enterococci

Enterococci are part of the normal intestinal microbiota in humans and animals. More than 54 species belonging to the genus *Enterococcus* have been described. The majority of human infections are caused by *E. faecalis* and *E. faecium* and in rare cases by *E. casseliflavus, E. gallinarum* and *E. raffinosus*. Most common clinical infections include urinary tract infections, intra-abdominal infections, bacteraemia and infective endocarditis. Enterococci are intrinsically resistant to many groups of antimicrobials which gives them a selective advantage in e.g. hospitalised patients under antibiotic treatment, leading to colonization or infection. The source of hospital infection is often associated with invasive medical devices and abdominal catastrophes.

Invasive cases from hospitals

In 2024, *E. faecalis* isolated from 594 individual patients and *E. faecium* isolated from 584 individual patients were reported in MiBa. Table 8.13 shows resistance percentages towards the most important antibiotics for both species for 2024 and Figure 8.11 shows the annual numbers of invasive isolates and resistance to vancomycin.

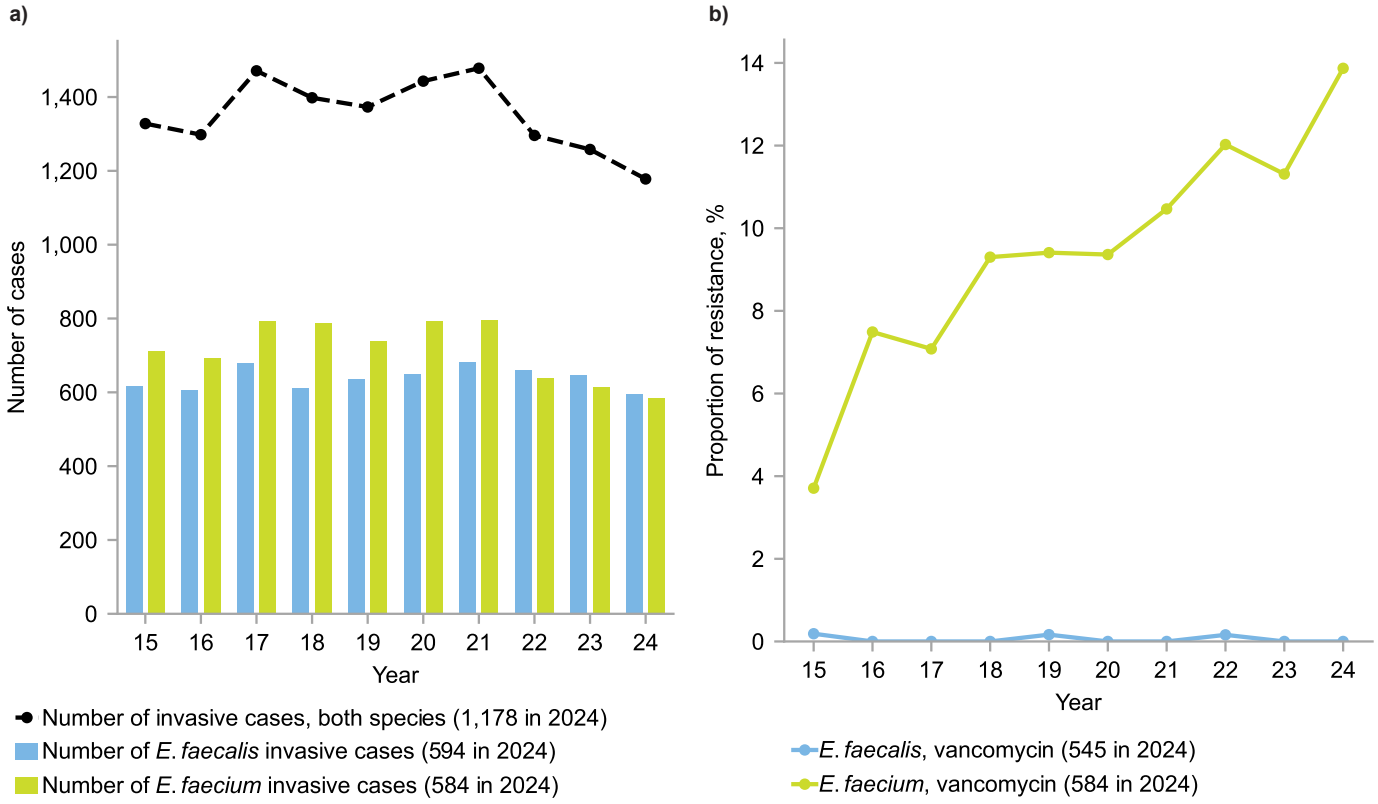
Table 8.13 Enterococci. Resistance (%) in invasive isolates from humans, 2024 DANMAP 2024

	E. faecalis	*E. faecium*	Number of included isolates (number of DCM)	
	%	%	*E. faecalis*	*E. faecium*
Ampicillin	0.0	91	591 (10)	566 (9)
Vancomycin	0.0	13.9	545 (9)	584 (10)
Linezolid	1.5	0.2	465 (7)	460 (7)
Teicoplanin	1.0	1.8	209 (2)	171 (2)
Tigecycline	0.0	3.7	95 (1)	81 (1)

All proportions of resistance are presented for each antibiotic as a mean of the resistance rates reported by the DCMs. Included are all DCMs that reports routine testing (>75% of the isolates). The number in parentheses tells the number of included DCMs

Figure 8.11 Invasive *Enterococci faecalis/faecium* isolates from humans:
a) annual number of isolates from individual cases and b) proportion of vancomycin resistant isolates, Denmark, 2015-2024

DANMAP 2024



Conclusion

The number of invasive cases for both *E. faecium* and *E. faecalis* has been decreasing since 2021, for *E. faecalis* following peaks during 2017 to 2021. Resistance to vancomycin has only rarely been observed in *E. faecalis* and no invasive cases with vancomycin resistance were detected in 2024, however for *E. faecium* it has been increasing for the last decade and has surpassed 10% for the past four years.

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8.3 Results from the reference laboratories

8.3.1 Characterization of ESBL- and pAmpC-producing *Escherichia coli* from bloodstream infections

Background

Resistance to third-generation cephalosporins in *Escherichia coli* often occurs through production of extended-spectrum beta-lactamases (ESBLs), carbapenemases, plasmid-mediated AmpC (pAmpC) or through mutations within the promoter/attenuator region of chromosomal AmpC (cAmpC) leading to overexpression/hyperproduction.

Since 2014, the Danish Departments of Clinical Microbiology (DCMs) have, on a voluntary basis, submitted third-generation cephalosporin-resistant *E. coli* (3GC-R *Ec*) from bloodstream infections for further characterization at the National Reference Laboratory for Antimicrobial Resistance at Statens Serum Institut (SSI) by adhering to the EUCAST criteria for reduced susceptibility towards cefpodoxime, ceftriaxone, cefotaxime or ceftazidime.

At SSI, the 3GC-R *Ec*'s collected in Denmark through 2024, were phenotypically tested for ESBL-production. ESBL- and/ or pAmpC-positive isolates from January, March, May, July, September, and November were subjected to whole-genome sequencing and characterized according to Multilocus Sequence Types (MLST) and the encoding ESBL-, pAmpC- and carbapenemase genes.

Results

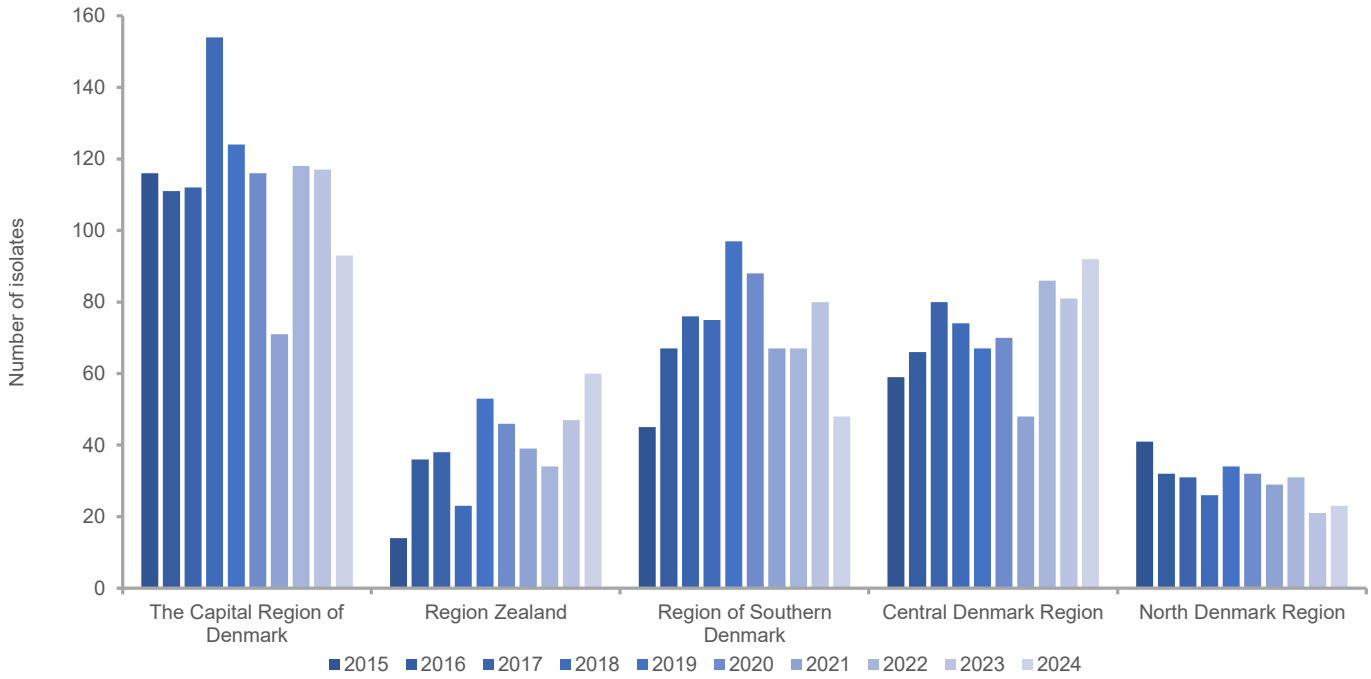
In 2024, a total of 316 *E. coli* blood isolates from individual patients, were identified with phenotypic test, as ESBL- and/ or AmpC- and/or carbapenemase positive isolates. Compared to 2023 (comprising 346 isolates), this represents a slight decrease in numbers of isolates forwarded to SSI. Demographic data was available for all 316 *E. coli* isolates; the median age at diagnosis was 70 years, ranging from ten years to 99 years. In 2024, the proportion of 3GC-R *Ec* from male patients remained at 47% (148/316), thus repeating the observation made in 2023 where 3GC-R *Ec* from female patients outnumbered those from male patients for the first time since the origin of the surveillance in 2014.

The regional distribution of the 316 isolates with ESBL-, AmpC- or carbapenemase phenotype was compared to data from previous years (Figure 8.12 and Table 8.14). Forwarded isolates from the Region of Southern Denmark decreased significantly from 80 isolates in 2023 to 48 isolates in 2024 (40%). The numbers of isolates from the remaining four regions did not change as markedly.

Whole genome sequencing data were obtained from 168 *E. coli* isolates (as only isolates from every second month and carbapenemase producing *E. coli* were sequenced). Genes encoding ESBL, pAmpC and/or carbapenemase were detected in 149 isolates, and 19 isolates were AmpC hyperproducers caused by cAmpC mutations. The AmpC hyperproducers were not included in the further analysis.

In 2024, 16 different genes associated with ESBL-, and pAmpC enzymes were detected among the 149 sequenced isolates encoding ESBL and/or pAmpC genes, (Table 8.15). As in previous years, CTX-M-15 was the most prevalent enzyme, albeit significantly decreasing in occurrence from 58% in 2023 to 40% in 2024. Similarly, the proportion of CTX-M-14 observed, decreased significantly from 9% in 2023 to 2% in 2024. This is

Figure 8.12. ESBL/pAmpC producing *E. coli* from bloodstream infections by region, 2015-2024, Denmark DANMAP 2024



the lowest observed proportion of these two enzymes since the origin of the surveillance in 2014. In addition, eight carbapenemase producing isolates (five OXA-244 producers, two OXA-48 producers and one NDM-5 producer) was observed among the 149 whole genome sequenced blood infection isolates.

In 2024, the 149 analyzed whole genome sequenced *E. coli* isolates belonged to 29 different known STs; a less diverse distribution of STs compared to the 46 observed in 2023. ST131 was still the most common ST in 2024 (47%), followed by ST69 (13%). No significant changes in the distribution of STs were observed compared to the distribution in 2023 (Table 8.16).

Table 8.14 Distribution of ESBL, pAmpC and Carbapenemase producing *E. coli* from bloodstream infections Denmark, 2015-2024

DANMAP 2024

Region	DANMAP 2015 Numbers	DANMAP 2016 Numbers	DANMAP 2017 Numbers	DANMAP 2018 Numbers	DANMAP 2019 Numbers	DANMAP 2020 Numbers	DANMAP 2021 Numbers	DANMAP 2022 Numbers	DANMAP 2023 Numbers	DANMAP 2024 Numbers
The Capital Region of Denmark	116	111	112	154	124	116	71	118	117	93
Region Zealand	14	36	38	23	53	46	39	34	47	60
Region of Southern Denmark	45	67	76	75	97	88	67	67	80	48
Central Denmark Region	59	66	80	74	67	70	48	86	81	92
North Denmark Region	41	32	31	26	34	32	29	31	21	23
Total Numbers	275	312	337	352	375	352	254	336	346	316

Table 8.15 Most common ESBL enzymes and carbapenemases detected in *E. coli* from bloodstream infections, Denmark, 2016-2024

DANMAP 2024

Enzyme	DANMAP 2016 Number	%	DANMAP 2017 Number	%	DANMAP 2018 Number	%	DANMAP 2019 Number*	%	DANMAP 2020 Number*	%	DANMAP 2021 Number*	%	DANMAP 2022 Number*	%	DANMAP 2023 Number*	%	DANMAP 2024 Number*	%
CTX-M-1	8	3	17	5	25	7	8	4	7	4	6	4	1	<1	3	2	0	0
CTX-M-14	40	13	48	14	31	9	33	17	15	8	12	9	17	9	17	9	3	2
CTX-M-14b	9	3	3	1	10	3	3	2	4	2	0	0	3	2	2	1	10	7
CTX-M-15	157	50	164	49	200	57	82	43	100	52	63	46	94	52	103	57	60	40
CTX-M-27	44	14	52	15	53	15	37	19	36	19	29	21	34	19	32	18	40	27
CTX-M-3	7	2	8	2	5	1	4	2	1	1	3	2	1	<1	0	0	3	2
CTX-M-55	6	2	13	4	4	1	8	4	4	2	5	4	3	2	1	<1	4	3
CMY-2	10	3	7	2	6	2	5	3	5	3	2	1	2	1	3	2	1	1
DHA-1	5	2	6	2	10	3	4	2	7	4	3	2	11	6	9	5	14	9
SHV-12	5	2	3	1	4	1	2	1	5	3	3	2	3	2	3	2	3	2
Other CMY variants	3	1	3	1	3	1	5	3	0	0	1	1	1	<1	1	<1	5	3
Other ESBL enzymes	17	5	10	3	10	3	3	2	8	4	6	4	7	4	2	1	3	2
Carbapenemase enzymes	1	<1	1	<1	5	1	0	0	7	4	4	3	5	3	1	<1	8	5

In some isolates more than one enzyme was detected
* Numbers based on sequenced data from odd months

Table 8.16 Distribution of MLSTs in *E. coli* from bloodstream infections, Denmark, 2016-2024

DANMAP 2024

MLST	DANMAP 2016 Number	%	DANMAP 2017 Number	%	DANMAP 2018 Number	%	DANMAP 2019 Number*	%	DANMAP 2020 Number*	%	DANMAP 2021 Number*	%	DANMAP 2022 Number*	%	DANMAP 2023 Number*	%	DANMAP 2024 Number*	%
ST131	177	57	175	52	189	54	93	47	89	46	64	49	89	50	68	38	66	47
ST69	16	5	20	6	27	8	14	7	20	10	7	5	9	5	27	15	19	13
ST38	21	7	23	7	22	6	13	7	8	4	1	1	11	6	7	4	13	9
ST1193	10	3	7	2	8	2	6	3	9	5	9	7	5	3	7	4	6	4
ST95	5	2	4	1	4	1	3	2	4	2	3	2	2	1	5	3	6	4
ST73	4	1	2	1	6	2	4	2	8	4	1	1	5	3	5	3	4	3
Other STs[1]	65	21	100	30	89	25	59	30	50	26	39	30	51	29	47	26	25	18

[1] Found in less than 3% in 2024
* Numbers based on sequenced data from odd months

Among the 68 *E. coli* isolates belonging to ST131, CTX-M-15 (50%) was the most common enzyme, followed by CTX-M-27 (46%). Further, among the 19 *E. coli* isolates belonging to ST69, CTX-M-15 (43%) was also the most common enzyme, followed by DHA-1 (33%), CTX-M-27 and CMY-4 (both 11%).

Conclusion

In 2024, the number of ESBL- and/or AmpC positive isolates decreased slightly compared to 2023. The significant shift in the gender distribution noted from 2022 to 2023 was also observed in 2024. CTX-M-15 remained the most prevalent ESBL enzyme in Danish *E. coli* (3GC-R *Ec*) in 2024 (40%), albeit proportionally decreasing compared to 2023. The relative occurrence of isolates belonging to the two most common STs, ST131 and ST69, remained stable compared to 2023.

In 2024, eight carbapenemase producer were observed among the 149 sequenced ESBL- and/or pAmpC blood infection isolates. The relative distribution of sequence types for the whole genome sequenced isolates was stable compared to the previous year; the worldwide disseminated ST131 clone was still strongly represented in 2024 (47%).

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8.3.2 Carbapenemase-producing organisms (CPO)

Background

Carbapenems comprise one of the only classes of antimicrobial agents that can be used for treatment of infections caused by multidrug-resistant Gram-negative bacteria like *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Treatment options for infections with carbapenem-resistant bacteria are often none or suboptimal. Resistance can be expressed by the presence of various carbapenemases of which the five most frequently occurring are *K. pneumoniae* carbapenemase (KPC), Oxacillinase (OXA), Verona integrin encoded metallo-β-lactamase (VIM), New Delhi metallo-β-lactamase (NDM) and Imipenemase (IMP).

Carbapenemase-producing organisms (CPO) comprise two main groups: 1) Intestinal bacteria: Carbapenemase-producing Enterobacterales (CPE), e.g., *E. coli* and *K. pneumoniae*, and 2) environmental bacteria: *P. aeruginosa* and *A. baumannii*. The term CPE is used to designate intestinal bacteria. Thus, CPE are a subset of CPO.

CPO have been notifiable in Denmark since the guideline from 5th September 2018 [https://www.retsinformation.dk/eli/lta/2018/1091]. Before this date, Danish departments of clinical microbiology (DCMs) have submitted carbapenem-resistant isolates for verification and genotyping at the National Reference Laboratory for Antimicrobial Resistance at Statens Serum Institut on a voluntary basis. This section describes findings for carbapenemase-producing Enterobacterales (CPE), *Pseudomonas* spp. and *Acinetobacter* spp.

During 2024, 677 CPOs were identified from 527 patients compared with 589 CPO isolates from 458 patients in 2023 (Figure 8.13, Table 8.17). More than one isolate from the same patient was included if the isolates belonged to different bacterial species and/or if the isolates harbored different carbapenemases.

Collection of travel information is part of the CPO surveillance in Denmark. Thus, information of travelling abroad in the period of 6 months prior to testing positive for CPO is requested and reported to SSI, together with the clinical sample information.

Carbapenemase-producing Enterobacterales

In 2024, 616 CPE isolates were reported from 497 patients compared with 552 CPE from 436 patients in 2023 (Figure 8.13). In 2024, 41 of the 616 CPE isolates produced both NDM and OXA-48 group enzymes, 425 produced OXA-48-like enzymes alone and 121 were only NDM-producing. Furthermore, 21 KPC-, two VIM-, one IMI-, one IMP-, one KPC-/NDM-/OXA-48-group as well as one KPC/OXA-48 group, one KPC/VIM and one KPC/NDM-producing CPE isolate(s) were identified (Figure 8.14).

Figure 8.13 Number of CPO/CPE isolates and cases in Denmark from 2015-2024 DANMAP 2024

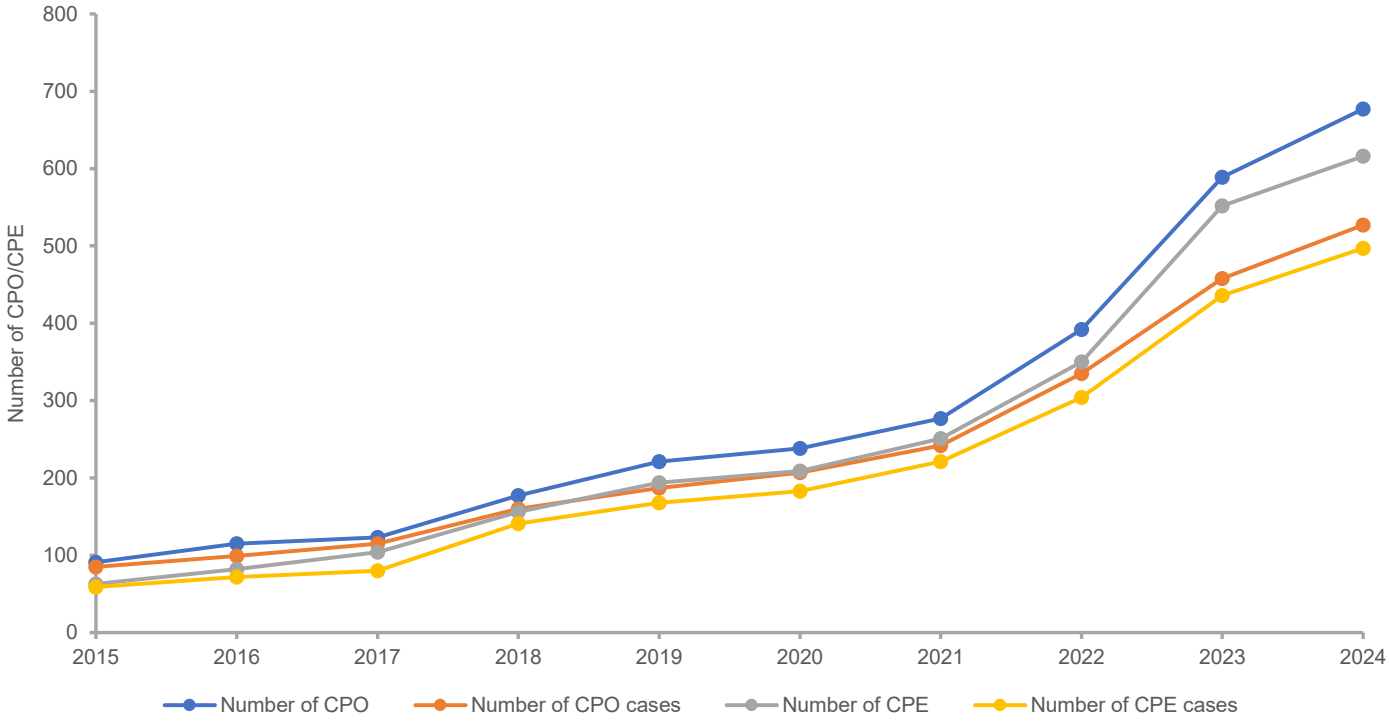


Figure 8.14 Numbers of carbapenemase-producing Enterobacterales (CPE), Denmark, 2008-2024 DANMAP 2024

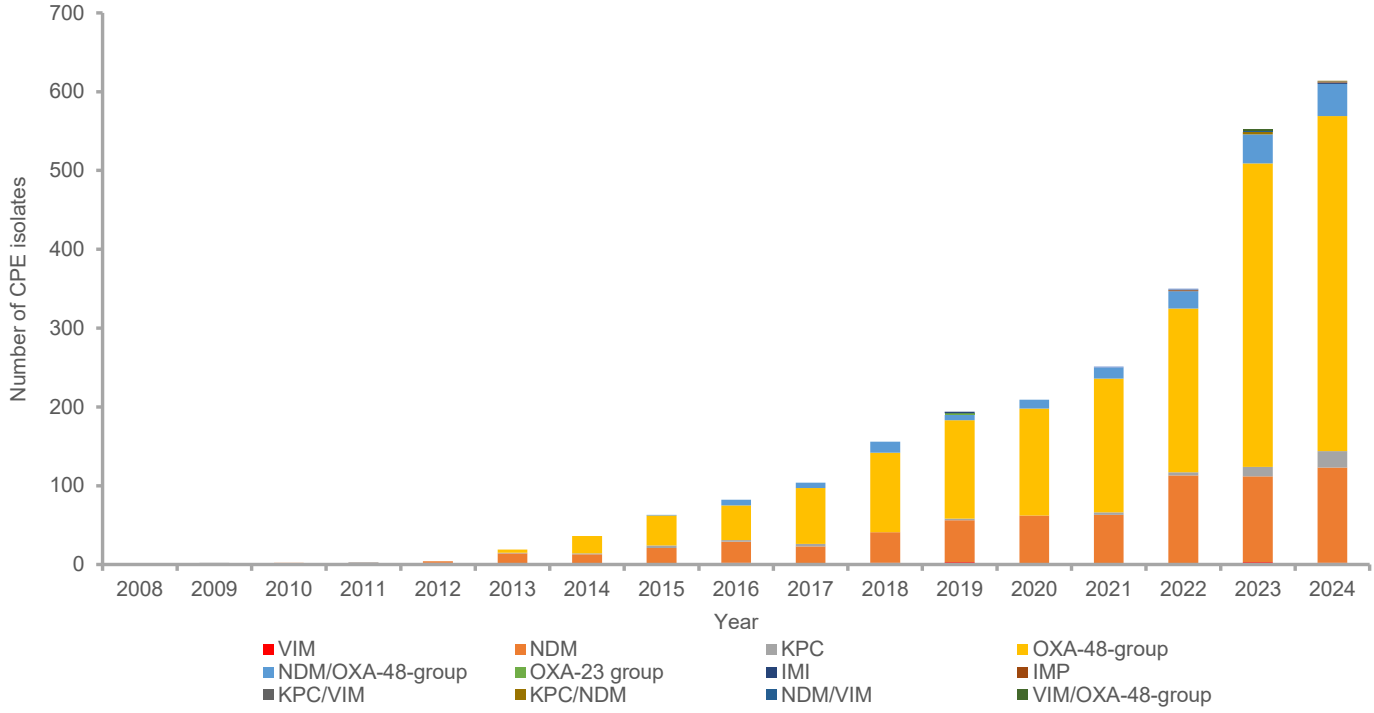


Table 8.17 Number of CPO/CPE isolates and cases in Denmark from 2015-2024 DANMAP 2024

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Number of CPO isolates	91	115	123	177	221	238	277	392	589	677
Number of CPO cases	85	99	115	160	187	207	242	335	458	527
Number of CPE isolates	63	82	104	156	194	209	251	350	552	616
Number of CPE cases	59	72	80	141	168	183	221	304	436	497

Carbapenemase-producing *Acinetobacter* spp.
In 2024, 40 carbapenemase-producing *Acinetobacter* spp. isolates were reported from 39 patients, compared with 21 isolates from 21 patients in 2023. Of these 39 patients, 9 patients were part of two outbreaks (Table 8.17) and 24 patients had been travelling abroad or had relation to Ukraine prior to identification of the carbapenemase-producing *Acinetobacter* spp. No information was reported for six of the patients.

A single patient had both an OXA-23 producing *Acinetobacter baumannii* and an OXA-24 producing *A. baumannii*. In 2024, 37 carbapenemase-producing *Acinetobacter baumannii* with the following enzymes were identified: OXA-23 (23), OXA-24 (1), OXA-23/OXA-58 (1), OXA-72 (2), OXA-72/NDM (1), OXA-23/OXA-72 (1) and NDM group/OXA-23 (8). Furthermore, two NDM-1 producing *Acinetobacter johnsonii* and, one OXA-72 *Acinetobacter bereziniae* were identified. (Figure 8.15).

Carbapenemase-producing *Pseudomonas* spp.
In 2024, 20 carbapenemase-producing *Pseudomonas* spp. isolates from 20 patients were reported compared to 16 isolates in 2023. Of these 20 patients, nine patients had been travelling abroad, seven patients had relation to Ukraine and no information was given for four patients prior to identification of the carbapenemase-producing *Pseudomonas* spp. In 2024, 19 carbapenemase-producing *Pseudomonas aeruginosa* with the following enzymes were identified: NDM-1 (10), VIM (3), IMP (5) and NDM/IMP (1). Furthermore, an NDM-producing *Pseudomonas putida* was detected.

In general, the number of carbapenemase-producing *Pseudomonas* spp. seems to be relatively stable over the years until the onset of Covid-19, which led to a large decrease in the number of isolates. This might be explained by less travel abroad. An increased in Carbapenemase-producing *Pseudomonas* spp. has been seen after the onset of the war in Ukraine (Figure 8.16).

Figure 8.15 Carbapenemase-producing *Acinetobacter* spp. and enzymes identified, Denmark, 2008-2024 DANMAP 2024

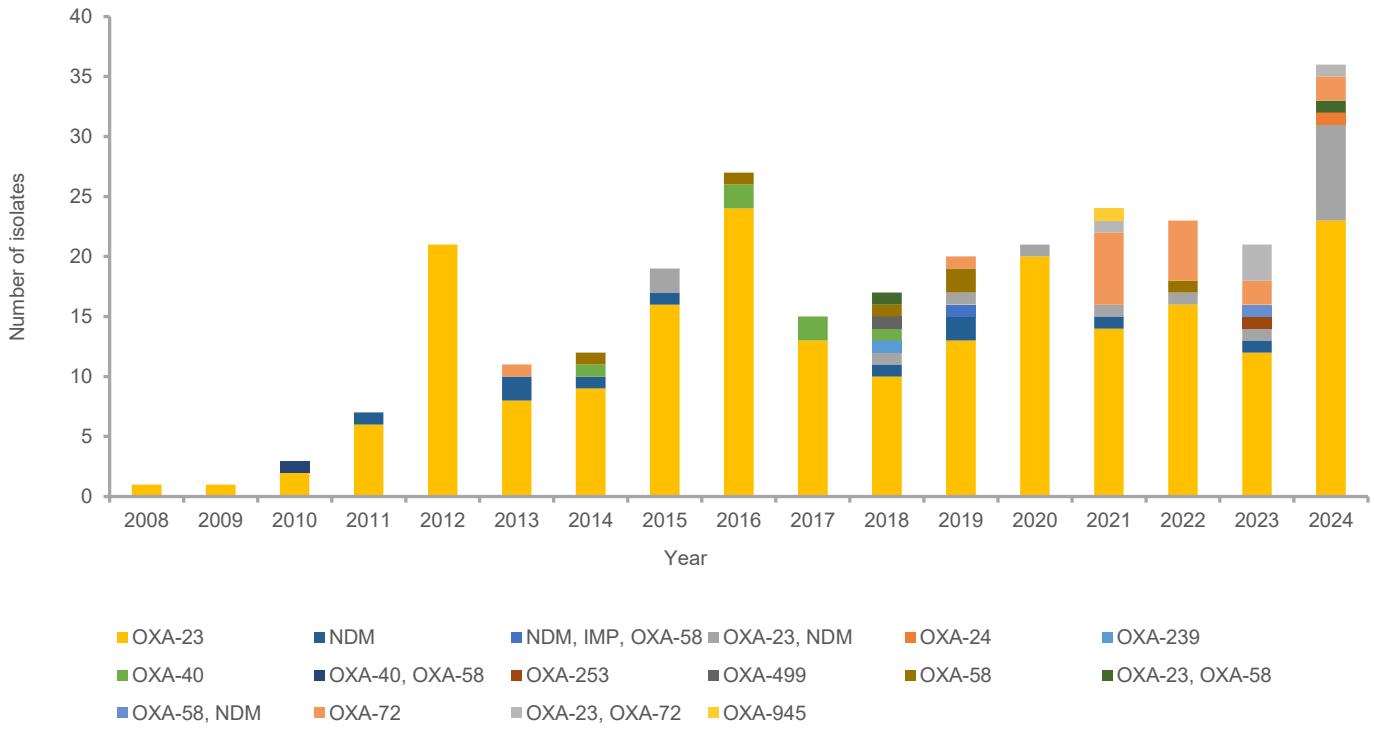
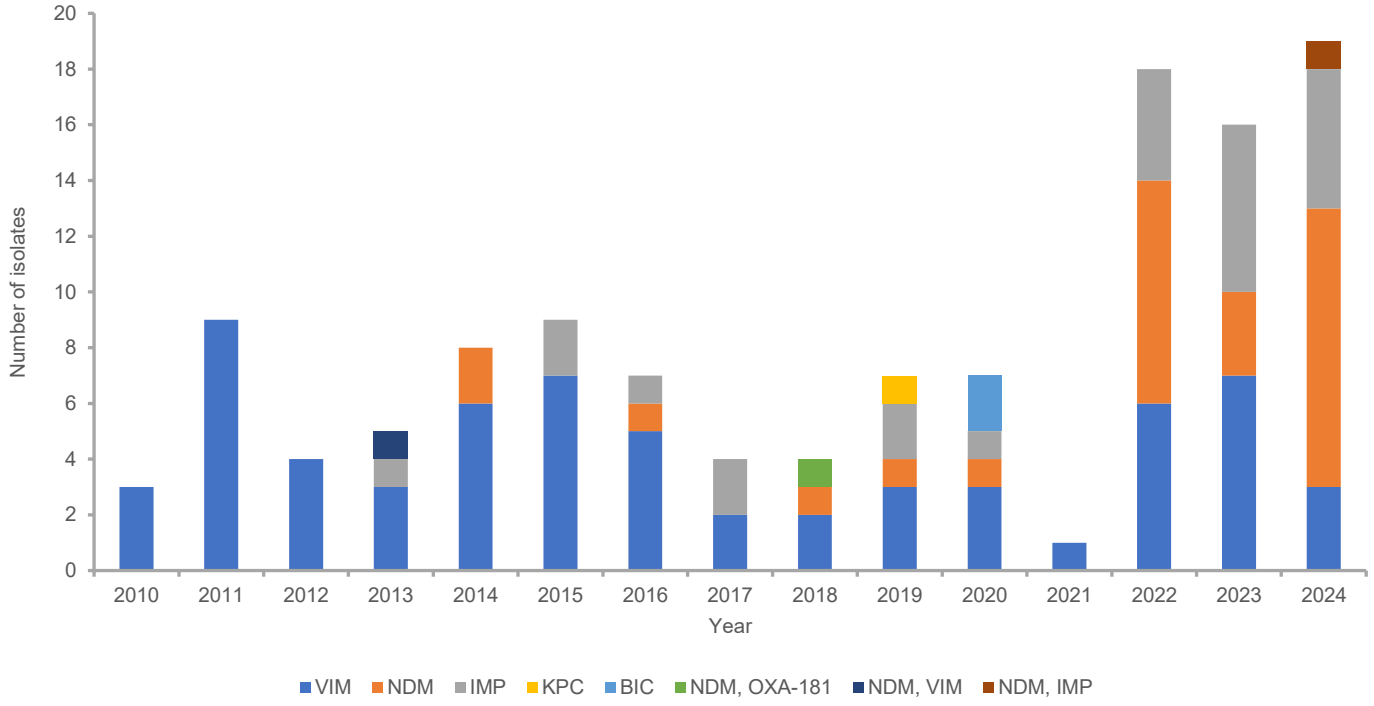


Figure 8.16 Carbapenemase-producing *Pseudomonas* spp. and enzymes identified, Denmark, 2010-2024 DANMAP 2024



CPO - Place of origin 2019-2024

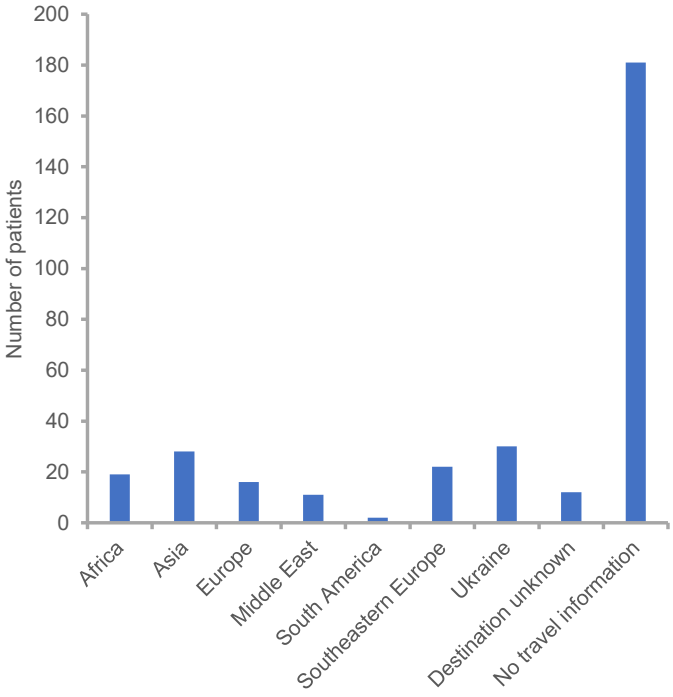
The Clinical Departments or a clinical physician can report travel in the period of six months before a colonization with CPO is detected, and the CPO-patient will be classified as a travel-associated CPO-patient. In order to qualify the information regarding the origin of a colonization with CPO in a Danish patient, the reported CPO-data from 2019 to 2024 has been evaluated and categorized into four categories: 1) Denmark, 2) Danish outbreak, 3) travel outside the Nordic countries, and 4) unknown (Figure 8.17).

The Clinical Departments or a clinical physician can also report a CPO-patient to be colonized in Denmark implicating that the patient has not been travelling prior to colonization. A CPO-patient can be affected by a Danish nosocomial outbreak and will be classified as an outbreak-patient. For some patients, no information is reported and the classification for place of origin will be unknown. The presumed index patient (the first patient identified) in an outbreak will be registered according to possible travel information.

In 2024, the reported travel data show that 110 of 527 CPO-positive patients reported travelling outside the Nordic countries. These cases were not part of nosocomial outbreaks. The number of cases where no travel information was provided is high (49%). In total, there was no travel information for 256 cases, suggesting that the actual travel rate is higher. Denmark was reported as the origin of the CPO-infection or colonization in 64 of the cases.

The most frequent reported travel destinations in 2024 were Asia (28), Southeastern Europe (22), Europe (16) and Middle East (11). The most single reported travel destinations were Turkey (20), Egypt (13), India (7), Thailand (6) and Pakistan (5).

Figure 8.17 Place of origin of CPO, 2019-2024 DANMAP 2024



Due to the still ongoing war in Ukraine, a number of patients from Ukraine are still receiving care in the Danish health care system. According to the Danish Health Authority, Denmark received a total of 41 patients from Ukraine as part of medical evacuations in 2024. These patients are screened for CPO according to the guideline. In 2024, a total of 57 CPO isolates were collected from 30 patients from Ukraine. More than one isolate was included from individual patients, if the isolates belonged to different bacterial species and/or had different carbapenemases. Among the 57 CPO, 46 were CPE isolates, seven were *Pseudomonas* ssp. and four were *Acinetobacter* ssp. The findings show that the patients originating from Ukraine were colonized and/or infected by several CPO per patient [Skjold Stolberg et al. 2023, Genotypic characterization of carbapenemase-producing organisms obtained in Denmark from patients associated with the war in Ukraine - ScienceDirect, https://www.sciencedirect.com/science/article/pii/S2213716523000917].

Outbreaks with CPO during 2024

In Denmark, outbreaks caused by CPO in healthcare settings are registered at SSI in the national database (KURS). The database also includes CPO-outbreaks identified in community settings, e.g. nursing homes and travel related outbreaks. At SSI, CPO isolates are routinely characterized by whole genome sequencing (WGS). Cluster analysis is conducted on all isolates using cgMLST to detect possible clustering between the CPO isolates. A genomic cluster is defined as at least two isolates (from different patients) belonging to the same cgMLST cluster (or having less than 15 alleles difference between the isolates). Due to the risk of long-term colonization of the patients, cluster analysis is carried out regardless of the time of isolation. When epidemiological investigations can establish a link between at least two patients in a genomic cluster (e.g. the patients had been at the same hospital ward at the same time), the patients are classified as belonging to a "verified outbreak". When no epidemiological link can be established, the patients related to the genomic cluster are classified as part of a possible outbreak (Materials and methods, section 9.12).

In 2024, a total of 33 CPO-outbreaks were registered compared to 26 CPO-outbreaks in 2023 (Table 8.17). In 15 of the outbreaks, an epidemiological link could be established between the majority of the patients, thereby indicating that the outbreaks were connected to healthcare settings. In health care settings the verified outbreaks were found to be caused by patients sharing the same ward or staying at the same hospital at the same time. In all, 19 of the 31 outbreaks have been ongoing for more than two years and two outbreaks for more than ten years, meaning that new patients have been identified as belonging to the same cgMLST cluster as found in the previous years.

In total, 166 new patients were associated with CPO-outbreaks in Denmark in 2024. Of these, seven patients were part of more than one outbreak. This is an increase compared to 2023 where 138 new patients were affected. Of the 33 outbreaks registered in 2024, nine new small clusters were identified involving 2 - 3 patients each. It is suspected that a part of the detected outbreaks may be attributable to the potential transfer of plasmids between different species, suggesting some smaller outbreaks actually belong to the same outbreak. The role of plasmid transfer in CPO-outbreaks will be further investigated.

Outbreaks with CPO of special interest

The ST18 NDM-1-producing *Citrobacter freundii* outbreak (ID41), which started in 2012 in the North Denmark Region, continued in 2024 [Hammerum et al. 2016, J. Antimicrob. Agents, 71:3117-3124]. Since 2012, the outbreak has spread to all five Danish regions. The main reason for the spread is the movement of infected patients between the regions. By the end of 2024, a total of 113 cases were involved in this outbreak. The number of new detected cases has been decreasing over the last two years. In 2024, a total of five new cases were identified, representing a decrease from the 15 cases registered in 2023 and the 20 cases in 2022. None of the cases had a history of travel.

Since 2015, another large outbreak (ID21) has been ongoing, primarily in two regions, Region Zealand and the Capital Region. The outbreak is associated with the spread of ST410 NDM-5/OXA-181 *E. coli*. [Roer et al. 2018, mSphere;3(4).]. Fifteen new cases were detected as part of this outbreak. By the end of 2024, a total of 111 cases had been identified as part of this outbreak. With the exception of the initial cases reported in 2015, who had been traveling to Egypt [Overballe-Petersen et al. 2018, Genome Announc.6(5): e01542-17], none of the other cases had a history of travel.

Since 2021, twelve isolates have been detected positive for ST131 OXA-244 *E. coli* in the Danish surveillance of CPO (ID1091). The cases were distributed across the country and no epidemiological link to the Danish health care system has been identified. In March 2024, the national contact point for EURGen-Nets at Staten Serum Institut (SSI) contacted the European Centre for Disease Prevention and Control (ECDC) regarding the increasing detection of OXA-244-producing *E. coli* ST131 in Denmark. ECDC initiated a European investigation involving 17 countries. The investigation showed a considerable heterogeneity in the geographical distribution and speed of spread of specific carbapenemase genes. This heterogeneity was particularly evident in the recent rapid emergence of ST131 isolates carrying chromosomally localised bla OXA-244 associated with large multi-country clusters [Kohlenberg, et al., Euro Surveill. 2024;29(47)]).

As part of the national surveillance of CPO-outbreak in Danish hospital, a cluster of *K. pneumoniae* ST39 CT7737 KPC-2 NDM-1 with eight cases was identified. This specific genotype has not previous been identified in Denmark. The cases were reported from different parts of the country involving all five Danish regions. Investigation revealed that the cases originated from Ukraine and presumably had been colonized with the CPO genotype in Ukraine (data not shown in Table 8.17).

In Denmark, CPO-outbreaks due to *Acinetobacter baumannii* are rare. In 2024, eight cases of ST2063 OXA-23 *A. baumannii* were detected in the national surveillance as part of an outbreak. The initial four outbreak cases with the same *A. baumannii* were reported in 2022 – 2023. The cases are spread all over the country. The investigation identified that the outbreak was primarily attributable to the medical evacuations from Ukraine. In total, twelve cases have been involved in this outbreak (ID1141).

Table 8.18 Outbreaks of carbapenemase-producing organisms (CPO) during 2024, Denmark, n=33 DANMAP 2024

Outbreak ID	Year	Patients total	Patients 2024	Carbapene-mase	Type of outbreak	Species (clonal spread)	Regions	Status
41	2012-2024	113	5	NDM-1	Clonal/plasmid	ST18 *C. freundii*	1 / 2 / 3 / 4 / 5	Verified
48	2013-2024	44	6	OXA-436	Clonal/plasmid	ST90 *E. hormaechei*/ST22 *C. freundii*	1 / 4 / 5	Verified
21	2015-2014	111	15	NDM-5/OXA-181	Clonal	ST410 *E. coli*	1 / 2 / 5	Verified
42	2015-2024	18	2	OXA-48	Clonal	ST65 *C. freundii*	1 / 3 / 5	Verified
1066	2017-2024	62	38	OXA-48	Clonal	ST91 *C. freundii*	1 / 5	Verified
1070	2017-2024	15	6	OXA-48	Clonal	*C. farmeri*	5	Possible
1145	2017-2024	11	7	OXA-48	Clonal/plasmid	ST65 *C. freundii*	3	Possible
1052	2018-2024	8	3	NDM-1	Clonal	ST18 *C. freundii*	2 / 4	Possible
43	2019-2024	33	11	OXA-48	Clonal/plasmid	ST323 *C. freundii*	1 / 5	Possible
1061	2020-2024	18	4	OXA-181	Clonal	ST22 *C. freundii*	2	Possible
1062	2020-2024	40	1	NDM-5	Clonal/plasmid	ST79 *E. hormaechei*	National	Verified
1091	2021-2024	12	5	OXA-244	Clonal	ST131 *E. coli*	1 / 2 / 3 / 4 / 5	Verified
1107	2022-2024	10	5	OXA-181	Clonal	ST636 *C. freundii*	5	Possible
1108	2022-2024	5	1	OXA-181	Clonal	ST410 *E. coli*	2	Possible
1113	2022-2024	11	5	OXA-48	Clonal	ST22 *C. freundii*	5	Verified
1115	2022-2024	9	5	NDM-1	Clonal	ST2 *K. oxytoca*	3	Verified
1141	2022-2024	12	8	OXA-23	Clonal	ST2063 *A. baumannii*	1 / 2 / 3 / 4	Verified
1148	2022-2024	4	2	OXA-48	Clonal	ST214 *C. freundii*	5	Possible
1154	2022-2024	5	4	KPC-3	Clonal/plasmid	ST22 *C. freundii*	4	Possible
1135	2023-2024	4	1	OXA-181	Clonal	ST36 *K. oxytoca*	5	Possible
1139	2023-2024	7	3	OXA-181	Clonal	ST65 *C. freundii*	5	Possible
1146	2023-2024	12	8	OXA-244	Clonal	ST13730 *E. coli*	1 / 2 / 3 / 5	Possible
1172	2023-2024	2	1	OXA-48	Clonal	ST116 *C. freundii*	2	Verified
1150	2024	2	2	OXA-48	Clonal	ST135 *K. aerogenes*	5	Possible
1162	2024	2	2	OXA-48	Clonal	*A. subterranea*	1	Verified
1170	2024	2	2	KPC-3	Clonal	ST307 *K. pneumoniae*	5	Possible
1176	2024	2	2	OXA-48	Clonal	ST4081 *K. pneumoniae*	5	Verified
1179	2024	2	2	OXA-232	Clonal	ST18 *C. freundii*	2	Verified
1180	2024	2	2	OXA-48	Clonal	ST114 *C. freundii*	5	Possible
1181	2024	2	2	OXA-48	Clonal	ST111 *C. freundii*	5	Possible
1183	2024	2	2	OXA-181	Clonal	ST98 *C. freundii*	5	Possible
1184	2024	2	2	OXA-48	Clonal	ST405 *E. coli*	5	Verified
1186	2024	2	2	OXA-244	Clonal	ST46 *E. coli*	3	Possible

1 Regions will be listed as: 1) Capital Region, 2) Central Denmark Region, 3) North Denmark Region, 4) Southern Denmark Region and 5) Zealand Region

Conclusion

The occurrence of carbapenemase-producing bacteria in Denmark continued to increase throughout 2024. The patients received from Ukraine are contributing to this increase, but the main contributing factor is a general increase in positive findings of CPO in humans and the increase in CPO nosocomial outbreaks. Furthermore, intensified screening also contributed to the increase in CPO cases in 2024.

The number of new nosocomial detected outbreaks in 2024 has increased since 2023, mainly due to the detection of small new outbreak clusters. Some of these outbreaks may be attributable to the potential transfer of plasmids between different species. The role of plasmid transfer in CPO-outbreaks will be further investigated. Intensified screening regime for CPO also identified more outbreaks than previous years. The screening strategy recommended in the CPO guideline is an important tool, together with the infection control measures (IPC) to control and stop outbreak due to antimicrobial resistance.

Travel outside the Nordic countries is a contributing factor to the number of CPO isolates detected in Denmark. The most frequently reported travel destinations in 2024 were Asia and Southeastern Europe. The number of cases where no travel information is provided is high, suggesting that the actual travel rate is higher than reported.

The spread of CPO among patients in Denmark is of concern, since Enterobacterales can be carried in the intestine for a long time (years) without any symptoms of infection, which makes outbreak control difficult and have consequences for medical treatment.

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8.3.3 Vancomycin-resistant/vancomycin-variable enterococci

Background

Enterococci are intrinsically resistant to a number of first-line antimicrobial agents, including cephalosporins, which increases the risk of enterococci being selected for in hospital environments and emerging in patients that receive cephalosporins for other conditions. Most hospital-acquired *Enterococcus faecium* are resistant to ampicillin, further limiting the treatment options. Vancomycin is an important drug for the treatment of severe *E. faecium* infections, however an increase in the occurrence of vancomycin resistant enterococci (VRE) has been observed within the last decade, both internationally and in Denmark. Newer antibiotics such as linezolid and daptomycin can be used for treatment of VRE, but both antimicrobial agents may lead to adverse events. In recent years, in various countries isolates of phenotypically vancomycin-susceptible *E. faecium* have been described to harbor a *vanA*-gene complex. These isolates are referred to as vancomycin-variable enterococci (VVE). In 2016, a new VVE clone belonging to ST1421-CT1134, displaying variable vancomycin susceptibility due to a deletion in the *vanX* gene, was detected [TA Hansen et al., J. Antimicrob. Agents, 2018, 73: 2936–2940]. The VVE clone has spread to all five Danish regions [Hammerum et al. Euro Surveill. 2024;29(23)]. Conclusively, VVE may be of clinical relevance and timely detection as well as continuous monitoring are critical to avoid treatment failure and further transmission.

Surveillance of VRE/VVE

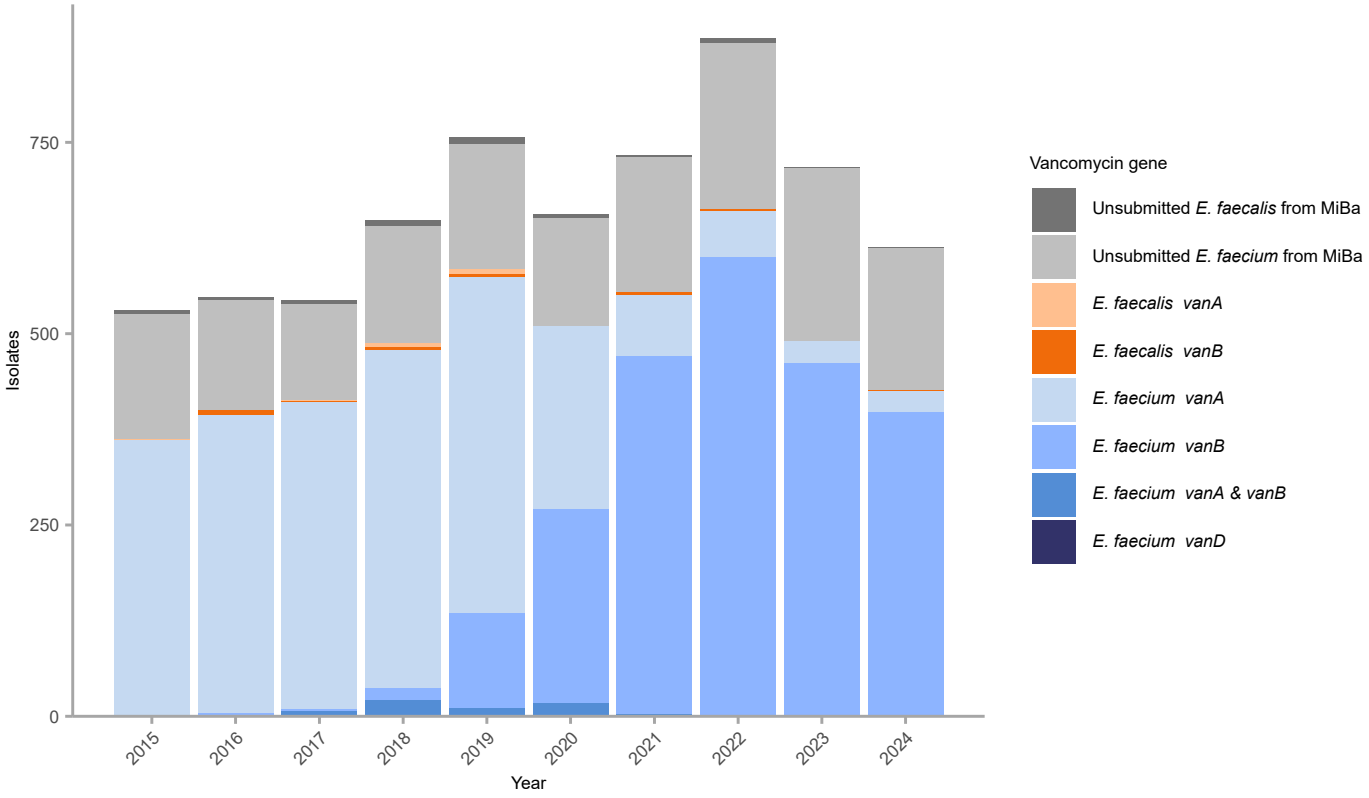
Since 2005, Danish departments of clinical microbiology (DCMs) have voluntarily submitted clinical VRE (one VRE/VVE isolate per patient, isolated within 12 months) for species identification, genotyping and surveillance purposes to the Reference Laboratory for Antimicrobial Resistance at Statens Serum Institut (SSI).

Since 2015, the received clinical VRE/VVE isolates have been analysed using whole-genome sequencing (WGS). The WGS data are used for *in silico* genotyping of isolate characteristics such as species identification, multilocus sequence typing (MLST), core genome sequence typing (cgMLST) and detection of van-genes and core locus MLST (cgMLST) combined for clonal detection (see Section 9.13.3).

To determine any underreporting in the submissions of VRE isolates, the number of VRE/VVE isolates submitted to SSI since 2015 were compared to data from clinical VRE in MiBa (the Danish Microbiology Database). This comparison showed that the number of submitted VRE/VVE isolates to SSI was not complete (Figure 8.18). The isolates only recorded in MiBa were distributed evenly throughout the study period and it did not seem to be a systematic loss. In 2024, 426 VRE/VVE isolates were submitted to SSI, and were genotyped by WGS. Furthermore, 187 VRE/VVE isolates were identified in MiBa, which had not been submitted to SSI and hence have not been genotyped. This was a decrease compared to 2023, were 494 VRE/VVE isolates were sent to SSI, while 228 VRE/VVE isolates were identified in MiBa yet not submitted to SSI (Figure 8.18).

Figure 8.18 Overview and distribution of vancomycin resistance genes in *E. faecium* and *E. faecalis*, Denmark, 2015-2024

DANMAP 2024



Of the 426 clinical VRE/VVE isolates sequenced in 2024, 28 were *vanA E. faecium*, 397 *vanB E. faecium*, and 1 *vanB E. faecalis* (Figure 8.18). Until 2020, *vanA E. faecium* were most common, but during the last years this has changed. In 2024, 93% of the *E. faecium* isolates had the *vanB* gene.

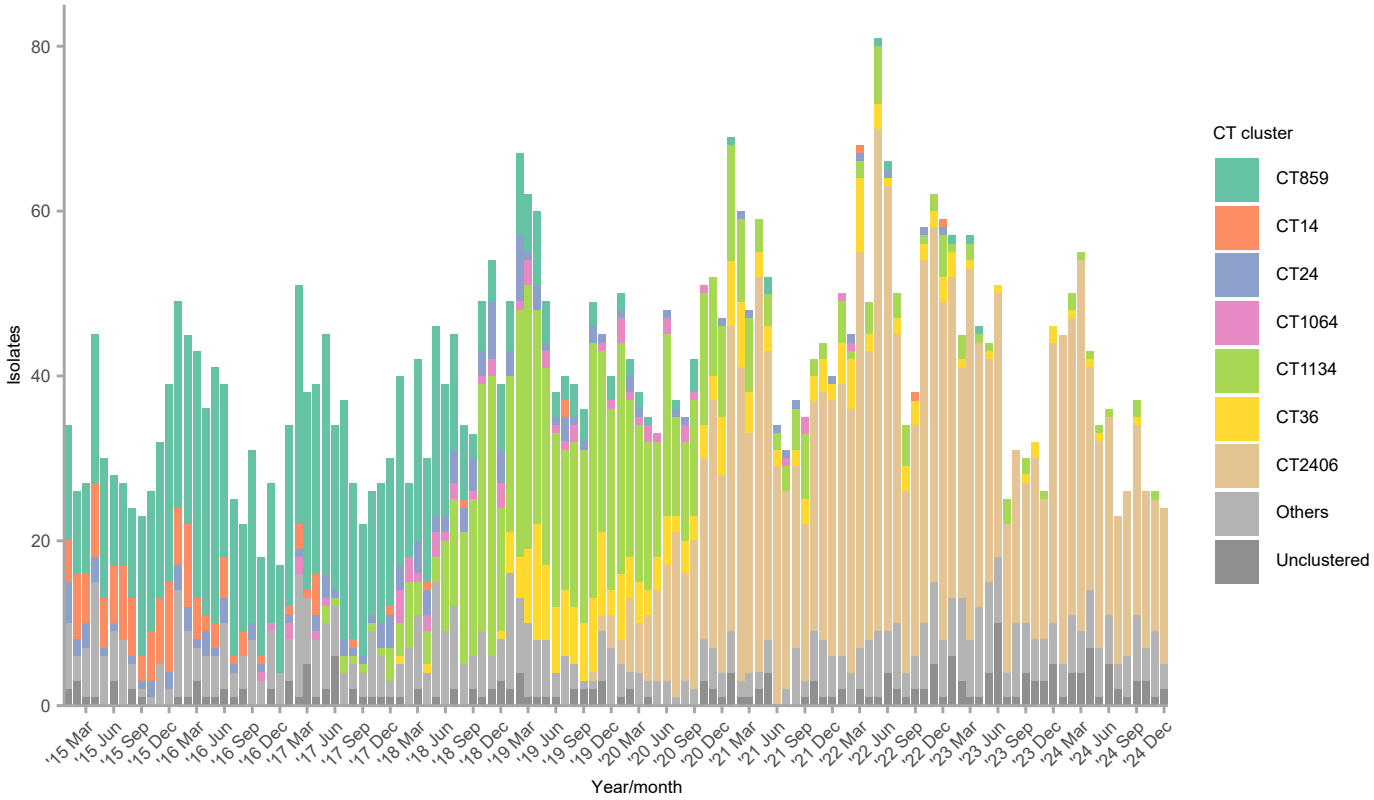
WGS-based cgMLST analysis was performed on the 425 *E. faecium* isolates using SeqSphere+ (Ridom). The 425 *E. faecium* isolates belonged to unique 113 CT clusters. When investigating the composition of sequence types (ST) and clonal types (CT) for *E. faecium*, we observed a clustering tendency between isolates, where ST's and CT's were diverging while the allelic differences were minimal within each cluster. Minimum Spanning Tree (MST) clusters were set up using the MST algorithm of SeqSphere+, setting the maximal allelic distances to 20. The top seven complex type clusters was devised, based on clustering of the isolates. Each complex type cluster were named according to the ST and CT of the earliest observed isolate within each cluster. One clonal group (covering several different CTs but presumably originating from the same clone) was predominant: The ST80-CT2406 *vanB E. faecium* group containing 312 isolates (73%) (Table 8.19).

Table 8.19 Description of the most common types of *vanA* and/or *vanB Enterococcus faecium* according to MLST and Complex type cluster, Denmark, 2016-2024

DANMAP 2024

Complex type Cluster	2016		2017		2018		2019		2020		2021		2022		2023		2024	
	n = 393		n = 410		n = 478		n = 574		n = 510		n = 551		n = 660		n = 490		n = 425	
ST203-CT859	250	63.6%	261	63.7%	153	32.0%	57	9.9%	12	2.4%	3	0.5%	2	0.3%	3	0.6%	0	0%
ST80-CT14	37	9.4%	12	2.9%	2	0.4%	2	0.3%	0	0%	0	0%	3	0.5%	0	0%	0	0%
ST117-CT24	18	4.6%	20	4.9%	39	8.2%	25	4.4%	8	1.6%	6	1.1%	5	0.8%	0	0%	0	0%
ST80-CT1064	2	0.5%	6	1.5%	23	4.8%	12	2.1%	14	2.7%	3	0.5%	2	0.3%	0	0%	0	0%
ST1421-CT1134	0	0%	13	3.2%	161	33.7%	285	49.7%	197	38.6%	63	11.4%	35	5.3%	14	2.9%	9	2.1%
ST117-CT36	0	0%	0	0%	3	0.6%	94	16.4%	54	10.6%	43	7.8%	41	6.2%	12	2.4%	4	0.9%
ST80-CT2406	0	0%	0	0%	0	0%	7	1.2%	178	34.9%	370	67.2%	476	72.1%	332	67.8%	312	73.4%
Other clusters	72	18.3%	74	18.0%	83	17.4%	73	12.7%	37	7.3%	45	8.2%	73	11.1%	87	17.8%	66	15.5%
Unclustered	14	3.6%	24	5.9%	14	2.9%	19	3.3%	10	2.0%	18	3.3%	23	3.5%	42	8.6%	34	8.0%

Figure 8.19 Timeline of the complex type clusters prevalence in all sequenced VRE isolates. Complex type clusters are named according to sequence type and complex type of the earliest observed member, Denmark, 2015-2024 DANMAP 2024



From 2015 to 2024, seven *E. faecium* clusters dominated: ST80-CT14 vanA, ST117-CT24 *vanA*, ST203 -CT859 *vanA*, ST1421-CT1134 *vanA*, ST80-CT1064 *vanA*/*vanB*, ST117-CT36 *vanB* and ST80-CT2406 *vanB* [Hammerum et al. Euro Surveill. 2024;29(23)]. Figure 8.19 shows the monthly count of these seven clusters alongside the remaining clusters during the period 2015 to 2024.

During 2015, We detected ST80-CT14 *vanA E. faecium* in all Danish Regions. On a national level, the numbers of ST80-CT14 *vanA E. faecium* decreased signifcantly from 2016 to 2019, disappearing completly from 2020. In 2022, a few isolates ST80-CT14 *vanA E. faecium* were detected. ST117-CT24 *vanA E. faecium* was first detected in the Capital Region in January 2015. Between 2015 and 2022 it was detected in all five regions. ST203-CT859 *vanA E. faecium* was first detected in Denmark in December 2014. It was one of the dominating clones from 2015 through July 2018 and was detected in all five regions. In 2022, only a few isolates belonging to ST203-CT859 *vanA E. faecium* were detected. ST80-CT1064 *vanA-vanB E. faecium* was first detected in Central Denmark Region in October 2016. It spread to the North Jutland Region during April 2018. During 2019, a single case of ST80-CT1064 *vanA-vanB E. faecium* was detected. This clone disappeared during January 2022. *E. faecium* isolates belonging to ST1421-CT1134 *vanA E. faecium* (VVE cluster) were first detected in clinical samples in 2016. In 2018, 34% of the *E. faecium* isolates belonged to ST1421-CT1134, and they were mostly detected in The Capital Region. During 2019, ST1421-CT1134 *vanA E. faecium* was the most prevalent type (44%) but decreased during 2021 and 2022. ST117-CT36 *vanB E. faecium* was detected in January 2019 in Capital Region of Denmark. During 2019, ST117-CT36 *vanB E. faecium* was detected in all five Danish Regions. In October 2019, the first clinical ST80-CT2406 *vanB E. faecium* sample was detected in a patient hospitalised in the Capital Region. It spread further to other patients in the Capital Region in 2019. During 2020, this cluster was detected in all Danish regions except the Northern Region of Denmark but during 2021, it was also detected there [Hammerum et al. Euro Surveill. 2020;25(32)]. Since 2022, the ST80-CT2406 has been and continues to be, the main dominant complex type cluster in all Danish regions [Hammerum et al. Euro Surveill. 2024;29(23)].

Infection prevention and control guidelines for VRE

Acting in compliance with the national guidelines for infection prevention and control (published by National Centre for Infection Control at SSI) is key in preventing the spread of multidrug-resistant microorganisms (MDRO), with correct hand hygiene and correct use of personal protective equipment (PPE) among the most important control measures [https://hygiejne.ssi.dk/NIRgenerelle]. The supplemental national guideline for infection prevention and control (IPC) includes specific guidance on VRE/VVE and should be followed when examining and treating patients, residents and citizens with these (and other) multidrug-resistant microorganisms [https://hygiejne.ssi.dk/

NIRsupplerende]. According to the national supplemental (IPC) guideline, screening of a patient is recommended on admission to hospital if the patient: 1) is transmitted from a hospital outside the Nordic countries, 2) has been hospitalised outside the Nordic countries within the last 6 months, 3) has been hospitalised in wards in Denmark or another Nordic country with outbreaks of VRE within the last 6 months or 4) previously has been diagnosed with a VRE-infection or carrier state. Isolation is recommended in the national supplemental IPC-guideline in case of verification of VRE in the patient. Precautions include the use of PPE such as a disposable gown and gloves and proper cleaning of the environment [https://hygiejne.ssi.dk/NIRdesinfektion]. Moreover, the guidelines emphasise the importance of prescribing antibiotics with caution.

Conclusion

The number of VRE/VVE cases have decreased from 2022 to 2024. While the decrease is a desired development, the level of VRE infections is still high. Therefore, more prevention strategies are required to prevent spread of VRE in the Danish health care system.

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8.3.4 *Staphylococcus aureus*

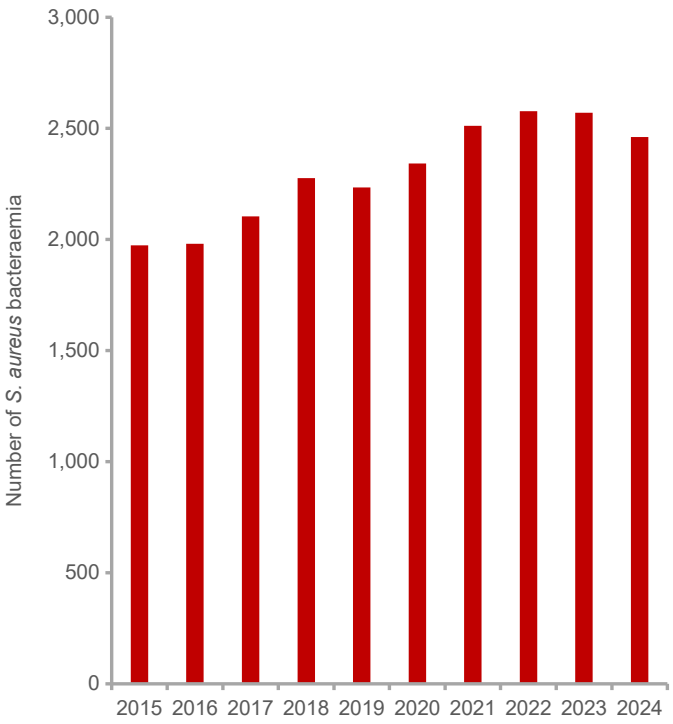
Staphylococcus aureus is part of the normal flora of the skin and mucosa. Approximately 50% of humans will be colonized with *S. aureus* in their nose or throat at any given time, some of these carrying the strain only intermittently, others for longer periods of time. *S. aureus* causes infections ranging from superficial skin infections e.g. impetigo and boils to deeper and invasive life-threatening infections such as bacteraemia, septic arthritis, osteomyelitis, endocarditis. The infections can be healthcare-associated such as postoperative wound infections and infections related to intravenous catheters and prosthetic devices or the bacteria can spread endogenously.

In Denmark, a voluntary surveillance program of all *S. aureus* bacteraemia cases was established in 1957. By comparison with the numbers of bacteraemia cases registered in the Danish Microbiology Database (MiBa) since 2010, the number of reported cases and bacterial isolates submitted to SSI demonstrates almost complete reporting and submission (94-97%). Laboratory and clinical notification of all cases of methicillin-resistant *S. aureus* (MRSA) has existed since November 2006.

Surveillance of *S. aureus* bacteraemia

The number of *S. aureus* bacteraemia cases were 2,461 in 2024 corresponding to 41 cases per 100,000 inhabitants. This is slightly less compared to 2023 (n=2,571), but the long-term trend is still an increasing number of cases (Figure 8.20). Within 30 days from the bacteraemia onset, 572 (23%) patients died (all-cause mortality). Forty-seven (1.9%) of the bacteraemia cases were caused by methicillin-resistant *S. aureus* (MRSA). During the last decade this proportion of MRSA bacteraemia cases has been between 1.5% and 2.2% and remains below most other European countries participating in the European Antimicrobial Resistance Surveillance Network (EARS-Net). Livestock-associated MRSA (LA-MRSA) CC398 caused seven of the 47 MRSA bacteraemia cases. The 30-day all-cause mortality for the MRSA bacteraemia cases was 13%.

Figure 8.20 Number of new *Staphylococcus aureus* bacteraemia cases in Denmark 2015-2024 DANMAP 2024



The antimicrobial susceptibility remained at the same level as in previous years for most agents (Table 8.20). The highest frequency of resistance to antimicrobials other than penicillin was observed for fusidic acid (13%), erythromycin (9%) and clindamycin (9%).

Typing revealed a high diversity with 709 different *spa* types distributed in 30 different clonal complexes (CCs). The ten most prevalent *spa* types, representing 31% of the total number, are presented in Table 8.21. The distribution of the most prevalent *spa* types has been very stable over the last decade with only minor changes in the relative order. The PVL toxin was present in 32 (1.3%) cases of which four were MRSA. The 38 isolates with the PVL gene were distributed among 22 different *spa* types.

Table 8.20 Resistance (%) in isolates from *Staphylococcus aureus* bacteraemia cases 2015-2024, Denmark DANMAP 2024

	2015	2016	2017	2018	2019	2020*	2021	2022	2023	2024
Antimicrobial agent	%	%	%	%	%	%	%	%	%	%
Methicillin	1.5	2.1	2.2	1.6	2.1	1.6	1.6	1.9	1.5	1.9
Penicillin	71	71	72	72	72	72	69	68	68	69
Erythromycin	7	7	6	5	9	7	7	9	9	9
Clindamycin	7	6	5	4	8	7	7	8	8	9
Tetracycline	4	3	3	3	2	3	2	3	2	3
Fusidic acid	16	12	14	17	14	14	13	13	12	13
Rifampicin	<1	<1	<1	<1	<1	<1	<1	<1	<1	1
Moxifloxacin#	6	4	4	4	5	6	4	4	4	3
Gentamicin	3	<1	1.1	1.0	<1	<1	<1	1.1	1.2	1
Linezolid	0	0	0	0	0	0	0	0	0	0
Mupirocin	<1	0	<1	0	<1	<1	<1	<1	<1	<1
Trimethoprim-sulfamethoxazole	<1	<1	<1	0	<1	<1	<1	<1	<1	<1

Notes: * From 2020 and onwards, resistance data was extracted from the Danish Microbiology database, MiBa. # Prior to 2021 testing for fluoroquinolone resistance was reported for norfloxacin

Table 8.21 The ten most prevalent *spa* types demonstrated in SAB cases 2024 DANMAP 2024

spa type	CC group	No. of cases
t127	CC1	135
t084	CC15	114
t091	CC7	107
t002	CC5	83
t1451	CC398	71
t008	CC8	53
t571	CC398	50
t230	CC45	50
t012	CC30	49
t021	CC30	47

Surveillance of methicillin-resistant *S. aureus*

In 2024, a total of 3,372 MRSA new cases were detected (57 per 100,000 inhabitants), an 8% decrease compared to 2023 (3,649; Figure 8.21a). A case was defined as the first time an individual tested positive for a specific MRSA strain regardless of clinical context (infection or colonisation). A case was defined as infection or colonisation based on the information in the notification form. Infections constituted 59% of the cases. The proportion of infections in the years 2015 to 2024 has varied between 38% to 59% (Figure 8.21b).

Figure 8.21a Number of new MRSA cases in Denmark 1994-2024 DANMAP 2024

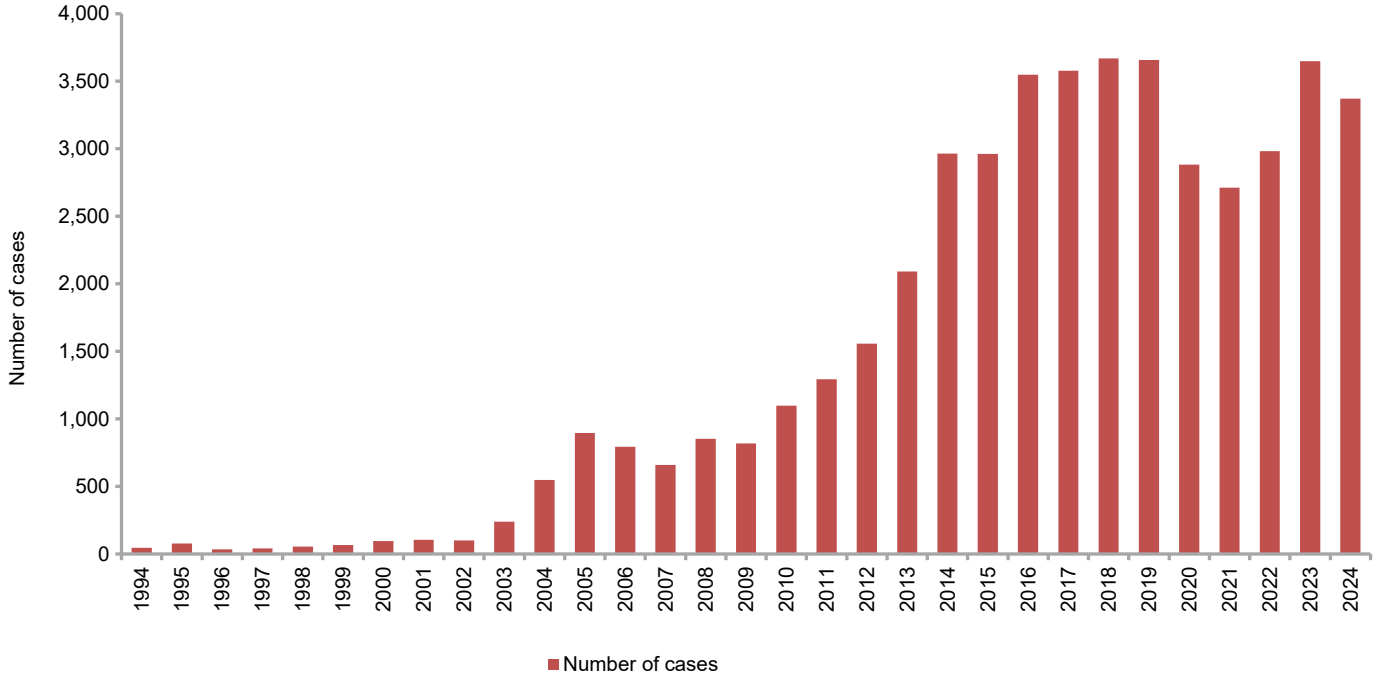
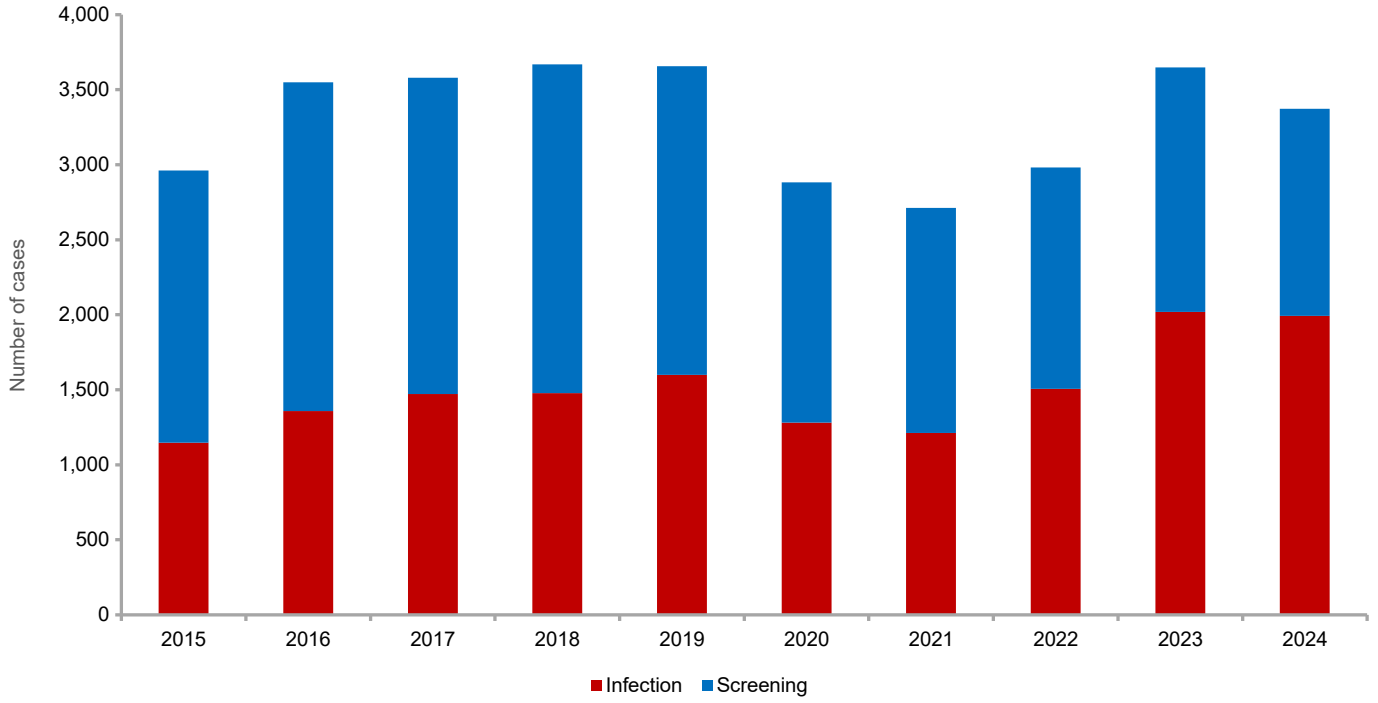


Figure 8.21b Number of new MRSA cases 2015-2024, Denmark, divided in infection and screening samples DANMAP 2024



CC398 cases constituted 22% (n=744) of new MRSA cases, of which 701 belonged to LA-MRSA CC398 and the remaining 43 to a human adapted variant harbouring the PVL encoding genes. A higher proportion of LA-MRSA CC398 isolates (65%) were identified in healthy carriers compared to other MRSA types (34%), likely reflecting the active screening of patients with livestock contact upon admission to healthcare facilities.

MRSA isolates carrying *mecC* were detected in 66 cases (2%). Fifty-one of the cases (77%) had infections at the time of diagnosis. None of the patients reported contact to hedgehogs, which recently has been shown to be a major environmental reservoir for *mecC* MRSA. Two patients had occupational exposure to pigs and one to horses, and two patients had other exposure to horses, while the remaining 61 patients did not report any contact to livestock or other animals.

spa typing revealed 404 different strain types. Among the infections, 349 *spa* types were identified. The 10 dominating non-LA-CC398 *spa* types isolated in 2024 are listed in Table 8.22. They constituted 48% of the total number of non-LA-CC398 MRSA isolates. Table 8.22 does not list *spa* types in CC398, which for many years has been the dominating CC. *spa* types t304 and t223 have been among the five most prevalent *spa* types since 2016, when their increase was linked to the refugee crisis following the civil war in Syria. For the second year in a row *spa* type t127 was the second most numerous. This type has been involved in several outbreaks in neonatal units in recent years but is also a common type among community associated cases.

The PVL encoding gene was detected in 33% of the infections and in 12% of the asymptomatic carriers and most often in relation to isolates with *spa* types t008 (n = 66), t355 (n = 61), t005 (n = 46), t021 (n = 43) and t034 (n = 31).

Thirty-eight MRSA outbreaks were registered at hospitals, nursing homes and other institutions (Table 8.23). These outbreaks comprised a total of 191 cases of which 86 had an infection. Four of the outbreaks occurred in neonatal departments, comprising a total of 72 cases. Additionally, eight outbreaks were registered in other hospital department, comprising 24 patients and twelve outbreaks were observed in nursing homes (counting a total of 27 patients). The number of outbreaks in nursing homes has increased in the last 5 years. The average number of outbreaks in 2015-2019 was 4 and in 2020-2024 11.

The total number of cases and the number of cases presenting with infection according to epidemiological classification are shown in Table 8.24. Most of the cases (85%) were acquired in Denmark.

Table 8.22 The ten most prevalent spa types demonstrated in non-LA-CC398-MRSA in Denmark 2024 DANMAP 2024

spa type	CC group	No. of cases	No. causing infections (%)
t304	CC6	288	167 (58)
t127	CC1	210	101 (48)
t223	CC22	138	69 (50)
t008	CC8	135	98 (73)
t002	CC5	129	77 (60)
t4549	CC8	100	93 (93)
t688	CC5	89	61 (69)
t355	ST152/377	63	47 (75)
t005	CC22	63	51 (81)
t021	CC30	55	42 (76)

Table 8.23 Outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) during 2024 in Denmark DANMAP 2024

Start of outbreak (year)	Patients in total	Patients in 2024	*spa* type	CC	Place of outbreak	Region
2016	35*	7	t2846	CC97	Nursing home	Capital Region of Denmark
2017	23	3	t3802	CC6	Hospital	Central Denmark Region
2019	136*	39	t127	CC1	Hospital (neonatal)	Capital Region of Denmark
2019	8	2	t5485	CC22	Nursing home	North Denmark Region
2019	16	1	t002	CC5	Nursing home	Capital Region of Denmark
2021	22	1	t034	CC398 pvl+	Educational facility	Central Denmark Region
2021	9	1	t136	CC30	Community acquisition	Region of Southern Denmark[
2022	14	5	t553	CC45	Home care	Region Zealand
2022	7	1	t304	CC6	Hospital	Capital Region of Denmark
2022	7*	1	t511	CC45	Nursing home	Capital Region of Denmark
2023	61*	26	t272	CC121	Child care institution	Region of Southern Denmark[
2023	7	4	t701	CC8	Hospital	Capital Region of Denmark
2023	10	2	t 11822 / t9867	CC80	Hospital (neonatal)	North Denmark Region
2023	24	23	t037	CC30	Hospital (neonatal)	Region of Southern Denmark[
2024	7	7	t1802	CC22	Hospital	Capital Region of Denmark
2024	8	8	t1476	CC8	Hospital (neonatal)	Central Denmark Region
2024	6*	4	t359	CC97	Educational facility	Region Zealand
Multiple (21 smaller outbreaks)	68*	49	Multiple	Multiple	Various	Denmark

* Including patients until May 2025

Table 8.24 Epidemiological classification of new MRSA cases, Denmark 2024 DANMAP 2024

Epidemiologic classification	Exposure	No. of cases (% of total)	No. (%) of cases with infections (% of cases in same epi. class)
Imported (IMP)		**515 (15)**	373 (72)
Hospital-acquired (HA)		**83 (2)**	16 (19)
Health-care associated, community onset (HACO)		**304 (9)**	
	with known exposure	21	16 (76)
	without known	283	262 (93)
Health care worker		**36 (1)**	15 (42)
Community-acquired (CA)		**1,734 (51)**	
	with known exposure	684	102 (15)
	without known	1049	968 (92)
LA-MRSA CC398		**701 (21)**	
	with known exposure	563	127 (23)
	without known	138	114 (83)
Total		**3,372**	**1,993**

Note: Numbers shown in bold are totals

Figure 8.22 Number of MRSA infections according to epidemiological classification, 2015-2024, Denmark DANMAP 2024

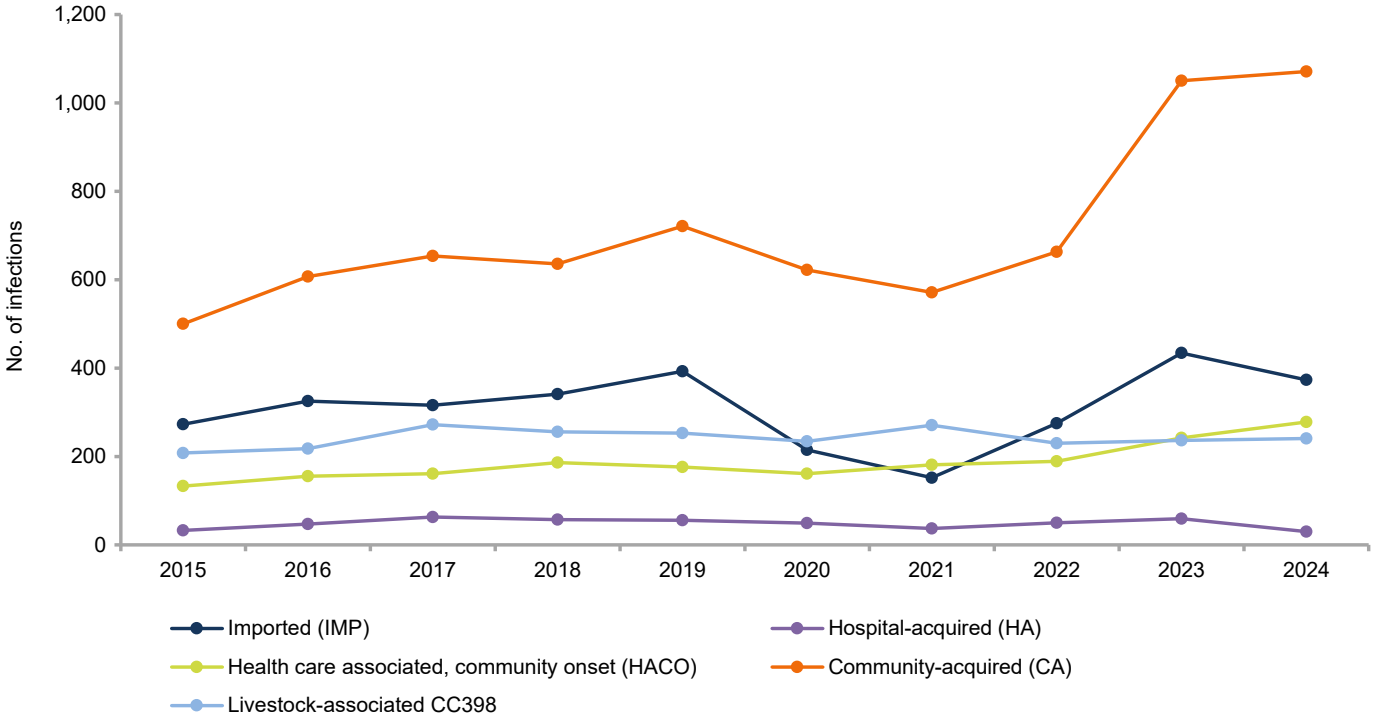


Table 8.25 Resistance (%) in non Livestock-associated CC398 MRSA isolates, 2015-2024, Denmark DANMAP 2024

	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Erythromycin	37	34	34	33	33	30	29	34	32	33
Clindamycin	29	25	27	28	23	22	19	21	21	22
Tetracycline	24	26	24	26	22	22	21	23	21	24
Fusidic acid	19	18	16	18	23	22	21	22	26	27
Rifampicin	<1	1	1	1	<1	<1	<1	<1	1	<1
Moxifloxacin#	21	19	20	21	21	17	19	23	24	26
Linezolid	0	<1	0	<1	0	<1	<1	<1	<1	<1
Mupirocin	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Trimethoprim-sulfamethoxazole	4	2	3	3	4	2	<1	1	1	2
Number of tested isolates	1,242	1,184	1,193	1,233	1,025	1,920*	1,520*	2,043*	2,696*	2,605*

* Not all isolates were tested for all listed antimicrobials
# Prior to 2021 testing for fluoroquinolone resistance was reported for norfloxacin

The trend of MRSA infections for 2015-2024 based on their epidemiological classification is shown in Figure 8.22. The number of infections in imported cases and hospital-acquired cases decreased in 2024 when compared to 2023. Importantly, number of infections among hospital-acquired MRSA remained low in 2024 (30 cases).

Resistance among MRSA isolates

Resistance data for non-LA-CC398 isolates are presented in Table 8.25. Resistance prevalences were similar to previous years, with the highest resistance to erythromycin (33%), fusidic acid (27%), moxifloxacin (26%), tetracycline (24%) and clindamycin (22%), and low resistance (<1%-2%) to trimethoprim-sulfamethoxazole, linezolid, mupirocin and rifampicin.

Conclusion

The number of *S. aureus* bacteraemia cases was 2,461 in 2024, a slight decrease compared to 2023. Of these, 47 cases (1.9%) were caused by methicillin-resistant *S. aureus* (MRSA) with seven being livestock-associated-MRSA (LA-MRSA).

There were 3,372 cases of MRSA from both screening (41% of cases) and infections (59%), which was an 8% decrease compared to 2023. Thirty-eight MRSA outbreaks were registered at hospitals, nursing homes and other institutions for a total of 191 cases with 86 being infections.

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8.3.5 *Streptococcus pneumoniae*

Background

Streptococcus pneumoniae (*S. pneumoniae*) (pneumococcus) causes various infectious diseases that are classified as either non-invasive or invasive. Among these, invasive pneumococcal diseases (IPD) are the most severe, while non-invasive pneumococcal infections are less severe, but much more commonly observed. Pneumonia, which can be categorized as non-invasive or invasive, is estimated to be the most frequent pneumococcal disease worldwide, affecting both children and adults. This is followed by the severe cases of the invasive diseases bacteraemia and meningitis.

Pneumococcus often causes acute otitis media (AOM) in children, with more than half of Danish children estimated to experience this conditionduring their childhood. AOM is frequently treated with antibiotics, although their effectiveness is uncertain. In addition to these well-known pneumococcal diseases, pneumococci are also associated with other common non-invasive infections such as sinusitis and bronchitis, as well as invasive diseases like endocarditis, peritonitis, and septic arthritis.

Laboratory surveillance

The laboratory surveillance of IPD in Denmark is conducted through mandatory submission of isolates from invasive cases to Statens Serum Institut (SSI). At SSI, the isolates are serotyped and tested for antimicrobial susceptibility. Cases without a submitted isolate are identified through The Danish Microbiology Database (MiBa).

Results

In 2024, 634 cases of IPD were registered (Table 8.26). Pneumococci were mainly found in either blood (567) or cerebrospinal fluid (44). For 23 cases, pneumococci were found in other normally sterile sites. Before 2023, only cases with pneumococci found in blood or cerebrospinal fluid were included in the DANMAP report. For the years 2023 and 2024 all IPD cases are included in the report. Among the 634 IPD cases identified in MiBa for 2024, 594 isolates were received at the reference laboratory. Regarding the 40 remaining cases where isolates were not submitted, data were retrieved from MiBa. Serotypes for these cases are unknown. Failure of submitting an isolate for serotyping was mainly due to non-viable isolates (n = 25) or diagnosis achieved by PCR (n = 15). Data for serotype and penicillin susceptibility were thus available for 594 cases.

The predominant serotype in 2024 was serotype 3 (15.3%) (Table 8.26). All 91 serotype 3 isolates were susceptible to penicillin. The second and third most frequently isolated serotypes were serotype 22F (75; 12.6%) and serotype 8 (50; 8.4%), and these isolates were all susceptible to penicillin.

Figure 8.23 The incidence of invasive pneumococcal infection (IPD) and the percentage of penicillin non-susceptible IPD isolates in Denmark, 2000-2024

DANMAP 2024

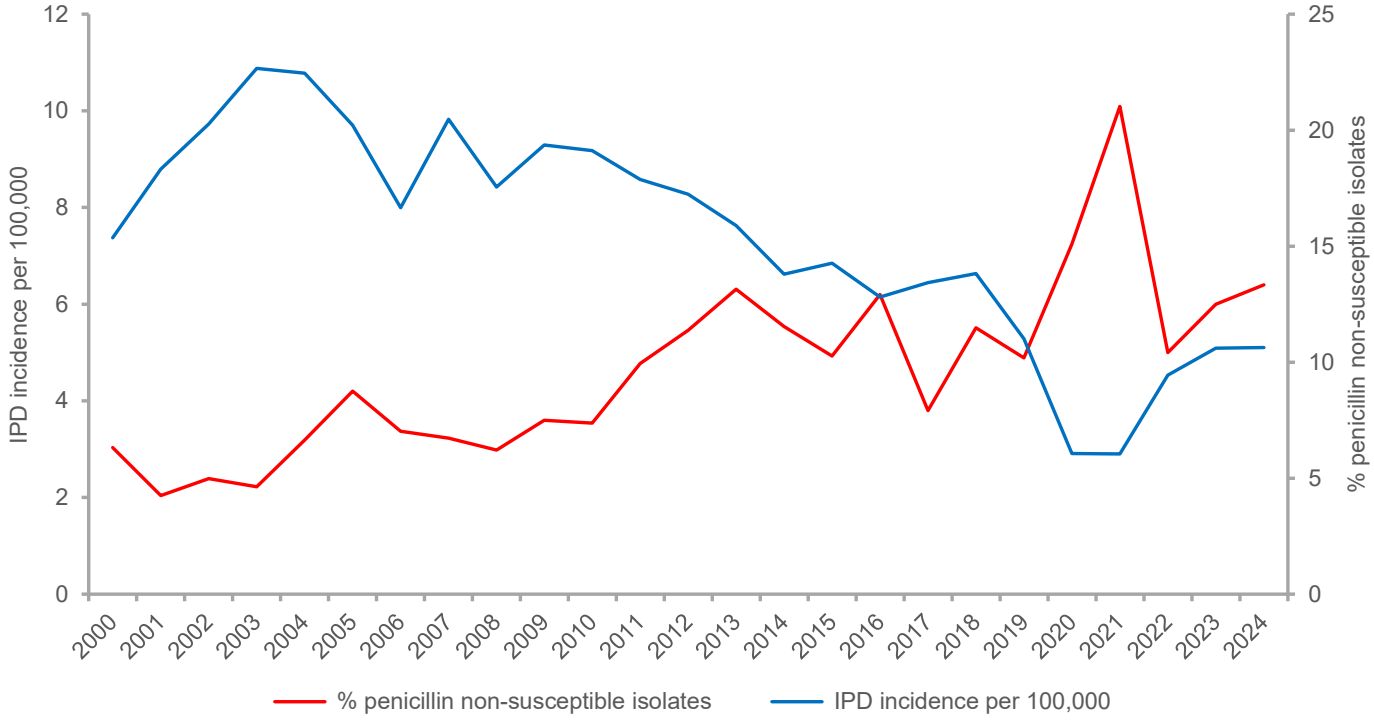

Table 8.26 Number of cases of invasive pneumococcal disease in Denmark 2024; serotype distribution and penicillin susceptibility

DANMAP 2024

Serotype	Included in pneumococcus vaccines					Total number	Penicillin susceptible, numbers			% Pen-S
	PCV13	PCV15	PCV20	PCV21	PPV23		Pen-S	Pen-non-S	Unknown	
3	+	+	+	+	+	91	91	0		100%
22F		+	+	+	+	75	75	0		100%
8			+	+	+	50	50	0		100%
9N				+		49	48	1		98%
33F		+	+	+	+	29	29	0		100%
24F				+		24	24	0		100%
19A	+	+	+	+	+	23	20	3		87%
15A				+		22	15	7		68%
10A			+	+	+	17	17	0		100%
23A		+	+	+	+	15	13	2		87%
11A			+	+	+	14	14	0		100%
19F	+	+	+		+	12	10	2		83%
31				+		12	12	0		100%
15C				+		10	9	1		90%
35B				+		10	6	4		60%
23B				+		8	1	7		13%
12F			+	+	+	7	5	2		71%
15B			+		+	7	7	0		100%
16F				+		7	7	0		100%
17F				+		6	3	3		50%
4	+	+	+		+	4	4	0		100%
7F	+	+	+	+	+	3	3	0		100%
20				+		2	2	0		100%
6A	+	+	+	+		1	1	0		100%
23F	+	+	+		+	1	0	1		0%
6B	+	+	+		+	1	1	0		100%
38						28	28	0		100%
7C						19	19	0		100%
6C						15	13	2		87%
35F						9	9	0		100%
10B						3	3	0		100%
17A						3	3	0		100%
35A						3	2	1		67%
24A						2	2	0		100%
28F						2	2	0		100%
35D						2	1	1		50%
7B						2	1	1		50%
13						1	1	0		100%
27						1	1	0		100%
29						1	1	0		100%
34						1	1	0		100%
9A						1	1	0		100%
9L						1	1	0		100%
Unknown						40	25	0	15 (*)	
Total						634	581	38	15 (*)	

Pen-S = penicillin susceptible; Pen-non-S = penicillin non-susceptible; % Pen-S = percentage of isolates susceptible to penicillin; (*) = no penicillin susceptibility resultats available if pneumococci were diagnosed by PCR only

Conclusion
The incidence of IPD per 100,000 population was unchanged in 2024 compared to 2023. The level of penicillin non-susceptible IPD isolates in 2024 (6.4%) was slightly higher than that in 2023. Both the great fluctuation in the prevalence of penicillin non-susceptible IPD isolates and the general IPD incidence in the years 2020 and 2021 is assumed to be an effect of the COVID-19 restrictions on the general prevalence of infectious diseases associated with respiratory droplet transmission. Such fluctuations have been seen in other countries as well [Shaw et al., Lancet Digit Health. 2023 Sep;5(9)]

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8.3.6 Beta-haemolyic streptococci

Beta-haemolytic streptococci (BHS) are classified into serological groups according to antigenic properties of the polysaccharide capsule. In human infections, groups A, B, C and G are the most frequent species. Approximately 10% of humans are asymptomatic throat carriers of BHS of any group.

Streptococcus pyogenes (group A streptococci; GAS) cause pharyngitis, tonsillitis, otitis media, wound infections, and superficial skin infections, but also more severe infections, e.g., bacteraemia, necrotizing soft tissue infections, and rarely meningitis. In Denmark, the rate of asymptomatic throat carriage of GAS is approximately 2%.

Streptococcus agalactiae (group B streptococci; GBS) may be present in the vaginal flora of 20-25% of women in the childbearing age. If these bacteria are transferred to the child during labour, meningitis and septicaemia may develop in the newborn. Such infections also occur in elderly or immunocompromised patients.

Streptococcus dysgalactiae subsp. *equisimilis*, which comprise group C streptococci (GCS) and group G streptococci (GGS) predominantly cause soft-tissue infections and sometimes bacteraemia.

This report presents data on antimicrobial resistance in non-duplicate invasive isolates (i.e. from blood, cerebrospinal fluid or other normally sterile anatomical sites) submitted from the departments of clinical microbiology (DCMs) in 2024 to the Neisseria and Streptococcus Reference laboratory (NSR). This report includes only non-duplicate isolates, i.e. isolates obtained with an interval of more than 30 days. Isolates are received from all DCMs in Denmark. It is voluntary to submit isolates of BHS.

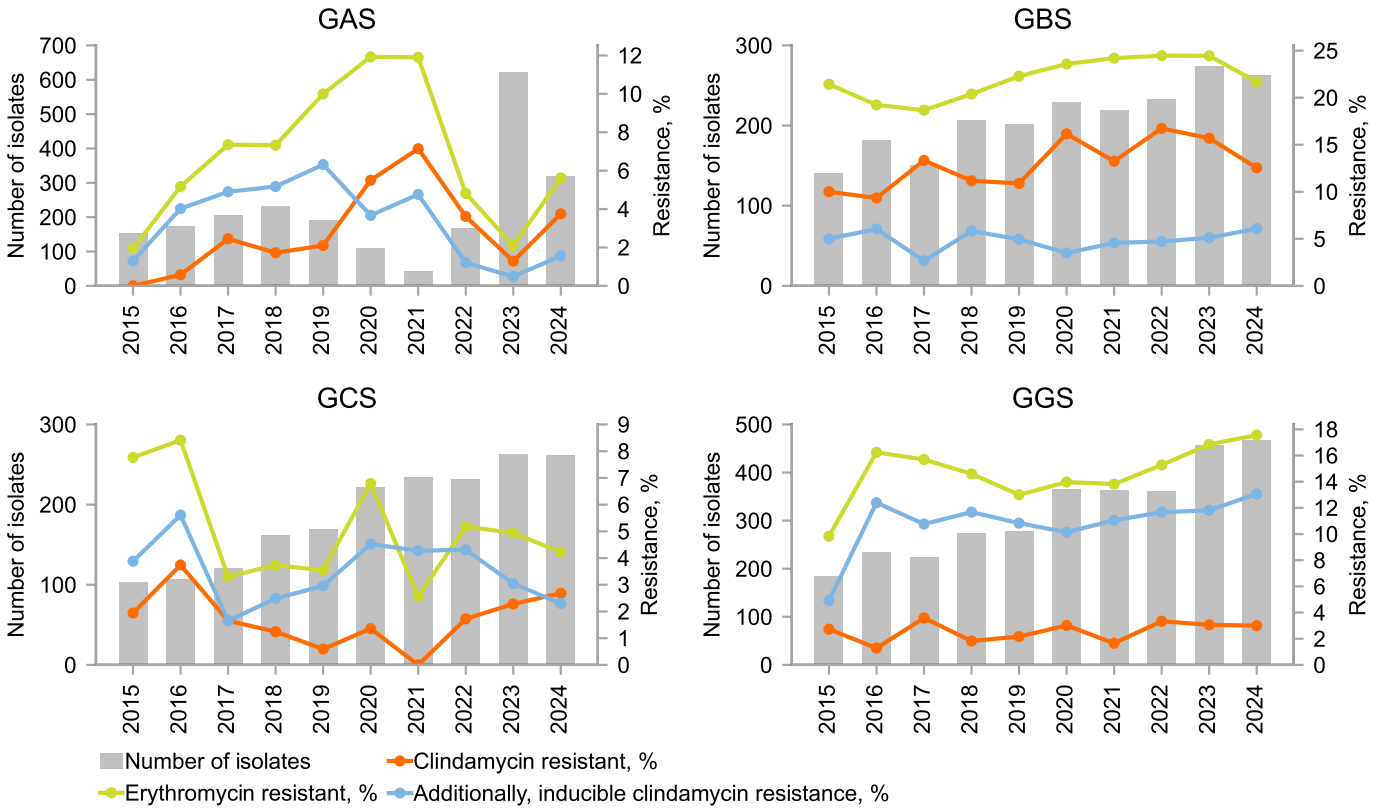
Infections with BHS are usually treated with penicillins or macrolides. All submitted isolates of BHS were therefore tested for susceptibility to penicillin, erythromycin and clindamycin as well as inducible clindamycin resistance. Susceptibility testing was performed with disk diffusion methods. If resistance was observed, MIC was determined with Etest. All results were interpreted according to MIC breakpoints issued by EUCAST (http://www.eucast.org/) (version 14.0).

In 2024, a total of 1,343 isolates from invasive cases were received. The number of isolates from individual invasive cases was 1,311, a decrease of 19% compared to 2023 (1,615).

The number of GAS isolates changed by a factor 0.52 compared to 2023, while the number in 2023 had increased by a factor 3.7 compared to 2022. For GBS these ratios were 0.96 and 1.2, respectively. For GCS they were 0.99 and 1.1, respectively, and for GGS they were 1.0 and 1.3.

Figure 8.24 shows the resistance findings for the years 2015 through 2024. All isolates were fully susceptible to penicillin. Comparing GAS in 2024 to 2023, the rates of erythromycin resistance, clindamycin resistance, and inducible clindamycin resistance had all increased, but not to higher levels than they were in 2022. For GBS, GCS and GGS these rates all remained nearly unchanged. The percentage of fully susceptible isolates compared to 2023 was decreased for GAS (94% versus 98%), increased for GBS (78% versus 74%), and remained virtually unchanged for the two other serogroups.

Figure 8.24 Invasive beta-haemolytic streptococci, Denmark, 2015-2024: Antimicrobial resistance testing results DANMAP 2024



Comments and conclusions

The substantial increase from 2021 to 2022 and further in 2023 for GAS was part of the national as well as international surge of invasive and non-invasive GAS infections, including a high proportion of cases with a serious course (Johannesen, et al., Euro Surveill. 2023 Jun;28(26):2300291). This increase was probably a consequence of discontinued COVID-19 related restrictions on upper respiratory tract colonization and airborne transmission of this species. In 2024, this effect waned in the second half of 2023, and the number of submitted GAS isolates in 2024 was only 0.52 of the number in 2023.

The increase cannot be explained by changes in the prevalence of antimicrobial resistance. All isolates were fully susceptible to penicillin.

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8.3.7 *Neiserria gonorrhoeae*

Neisseria gonorrhoeae is the causative agent of the sexually transmitted infection gonorrhoea, which is usually located in the urethra in males and cervix in females. *N. gonorrhoeae* (gonococci) may also sometimes be demonstrated in specimens from the pharynx or rectum in either gender. In females, the finding of gonococci in ano-rectal specimens is usually due to contamination with vaginal secretion, while in men who have sex with men (MSM) it is due to unprotected anal sex leading to infection. In both genders, the condition is generally asymptomatic. Pharyngeal gonorrhoea is virtually always asymptomatic.

Complications of gonorrhoea include e.g. salpingitis, epididymitis, orchitis, and prostatitis. Furthermore, conjunctivitis may occur in new-borns after transmission from an infected mother during labour and rarely in adults following direct or indirect inoculation.

Laboratory surveillance

Since 1962, the departments of clinical microbiology in Denmark have voluntarily submitted isolates of gonococci to the Neisseria and Streptococcus Reference (NSR) laboratory at Statens Serum Institut for national surveillance of antimicrobial resistance.

Both resistant and intermediary susceptible isolates were categorized as resistant in this report. However, isolates with intermediary susceptibility are non-existing according to EUCAST breakpoints for ceftriaxone and azithromycin and they are exceedingly rare regarding ciprofloxacin.

As part of NSR's participation in ECDC's surveillance (Euro-GASP) of sexually transmitted infections since 2009, approximately 100-200 gonococcus isolates are collected consecutively each year in September-October and investigated for susceptibility to an expanded panel of antimicrobial agents. This panel includes cefixime and in selected years also tetracycline, spectinomycin, and sometimes gentamicin.

Results and discussion

The annual number of received isolates increased considerably from 2011 through 2017 (Figure 8.25). This was most likely due to the widespread use of combined nucleic acid amplifications tests (NAATs) for *Chlamydia trachomatis* and *N. gonorrhoeae* which have identified unexpected cases of gonorrhoea (sometimes followed by culture), and also to an increasing incidence of gonorrhoea, especially among young heterosexual persons, among whom an increasing proportion until 2016 were women. The proportion of female cases has decreased slightly since 2017, but it is still substantially higher than in the beginning of the observation period (2003-2016). A decrease in the annual number of isolates from individual cases was seen in 2018 followed by an increase in 2019-2021 and in particular from 2021 to 2023 (Pedersen et al., Euro Surveill 2024 Feb;29(7)). It should be recalled, however, that many cases diagnosed by NAATs are not followed-up by culture.

Repetitive detections of gonococci in a patient are considered to represent individual cases of gonorrhoea if separated by more than 21 days. The same distinction is applied when enumerating individual episodes of testing. In 2024, there were 365,263 episodes of testing for gonococci, for the most part consisting of dual testing for gonococci and *Chlamydia trachomatis*. Among these episodes of testing, 5,108 were positive for gonococci, including 1,852 individual episodes of positive cultures. The NSR laboratory received isolates from 1,803 individual cases of gonorrhoea (1,218 males, 585 females). Only one isolate from each individual case is counted in this report.

If more than one isolate is received from an individual episode of gonorrhoea, the following hierarchy of the isolates are used, in accordance with the ECDC guidelines for Euro-GASP:

Males: 1. Pharyngeal 2. Rectal 3. Urethral 4. Other
Females: 1. Pharyngeal 2. Cervical 3. Other anogenital (high vaginal swab/rectal/urethral) 4. Other

Among the isolates included in this report, 1,353 were from urogenital sites, 152 from anorectal areas, 119 from pharynx, one from blood, one from conjunctiva, and 177 from uninformed or other anatomical sites, such as joint fluid, Bartholin's abscess, etc. The high number of uninformed sites is mainly caused by sparse details given in electronic information accompanying the isolates

The ciprofloxacin resistance rate was 61% in 2024 (63% in 2023 and 40% in 2022), (Figure 8.25). Only 2.5% of the isolates were classified as ciprofloxacin intermediate (MIC 0.047-0.064 mg/L).

The percentage of strains producing penicillinase was 16% (14% in 2023 and in 2022). Previously, it has fluctuated between 22% in 2005 and 7% in 2016. Azithromycin resistance (MIC above the present ECOFF 1 mg/L) was found in 3.5% of the tested isolates (6.0% in 2023 and 2.9% in 2022).

Figure 8.25 Number of submitted gonococcus isolates from individual cases of gonorrhoea in males and females, and the percentage of isolates with ciprofloxacin resistance, azithromycin resistance, and penicillinase production, Denmark, 2003-2024 DANMAP 2024

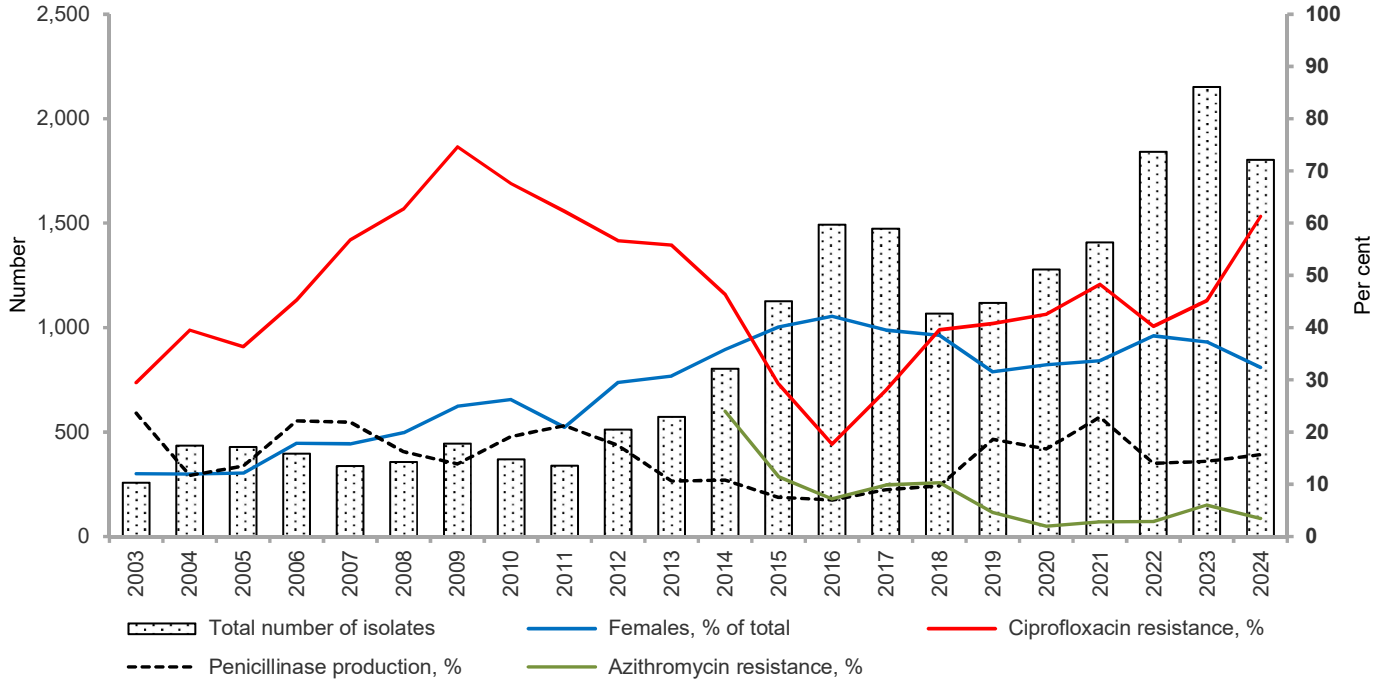


Figure 8.26 Distribution of ceftriaxone MIC (mg/L) values in gonococci, Denmark, 2003–2024 DANMAP 2024

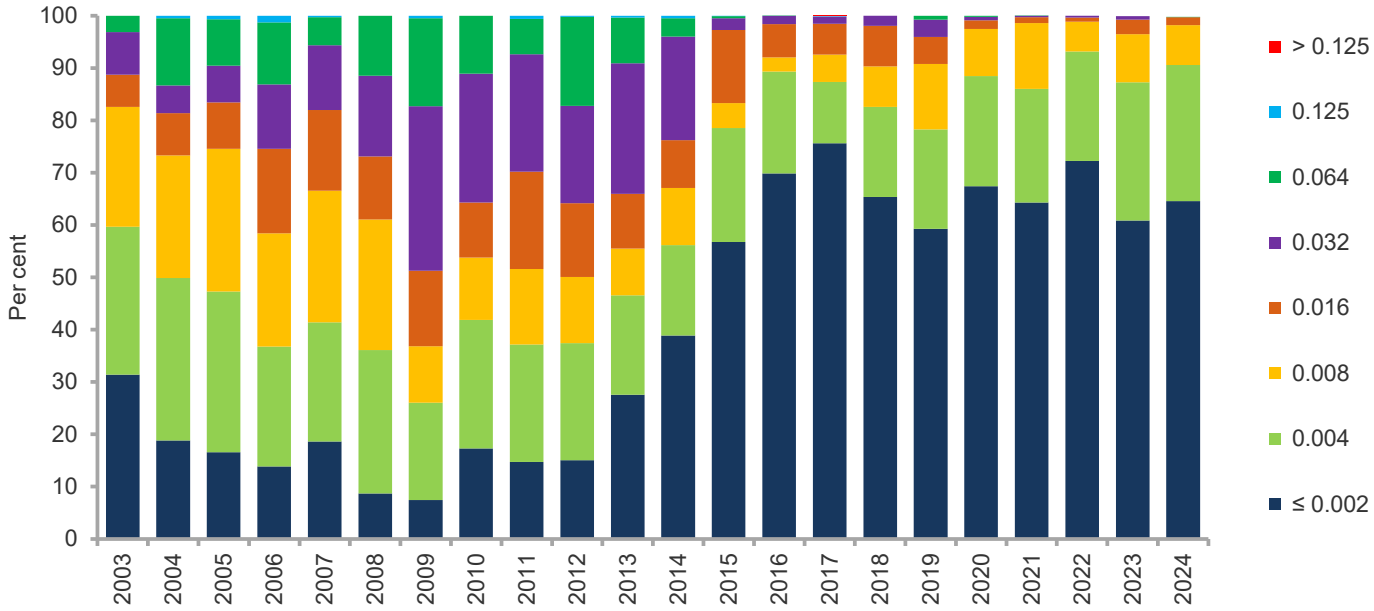


Figure 8.27 Distribution of cefixime MIC (mg/L) values in gonococci, Denmark, 2003–2024 DANMAP 2024

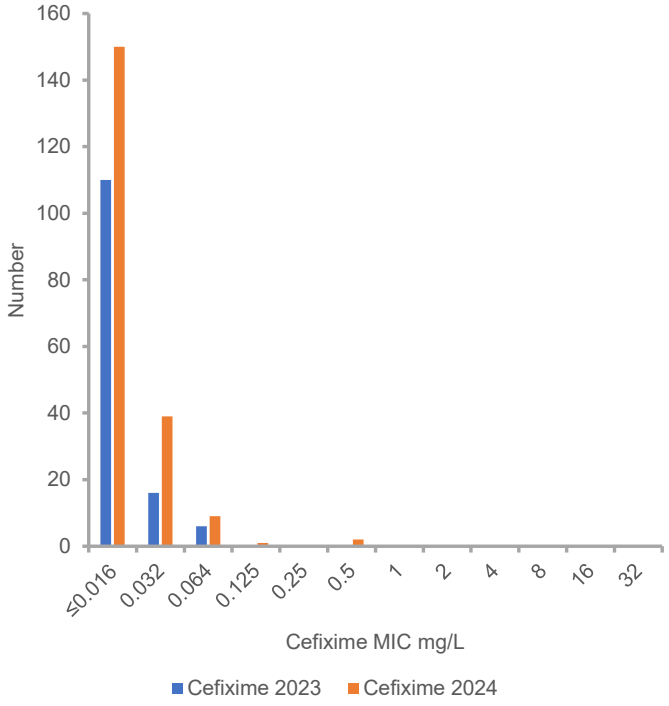
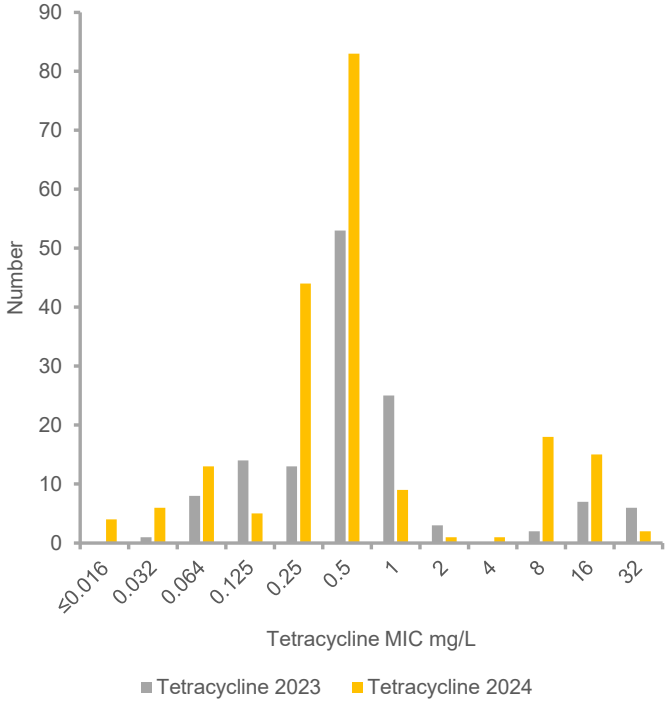


Figure 8.28 Distribution of tetracycline MIC (mg/L) values in gonococci, Denmark, 2003–2024 DANMAP 2024



Ceftriaxone resistant gonococci (MIC >0.125 mg/L) as well as ceftriaxone treatment failure in patients with gonorrhoea have occurred in several countries during recent years. As shown in Figure 8.26, the ceftriaxone MIC distribution changed from 2003 through 2009 with the highly susceptible isolates becoming gradually less frequent. However, since then, this change has completely reversed. In 2017, there was a single case among the submitted isolates with ceftriaxone MIC of 0.25 mg/L (i.e. resistant) and azithromycin MIC of 0.25 mg/L.

Secondary cases were not reported and no strains with ceftriaxone resistance have been encountered among the submitted isolates since 2017.

The Danish National Board of Health issued guidelines in 2015 for the diagnosis and treatment of sexually transmitted infections. A combination of ceftriaxone (500 mg i.m.) and azithromycin (2 g p.o.) was recommended for the empiric treatment of gonorrhoea. This therapeutic regimen has gradually been abandoned during 2019 and onwards by most clinicians.

Ciprofloxacin (500 mg p.o. as a single dose) may still be used for treatment if the strain is fully susceptible and if appropriate investigation has excluded pharyngeal gonorrhoea.

Participation in Euro-GASP

In a subset of 201 isolates tested as part of the Danish participation in Euro-GASP, resistance against cefixime (MIC >0.125 mg/L) was 0% in 2023 as in 2022, and 1% in 2024, Figure 8.27. Cefixime is an oral cephalosporin that has never been used in Denmark. Resistance against tetracycline (MIC >0.5 mg/L) was 33% in 2023 and 23% in 2024, Figure 8.28. Susceptibility testing against spectinomycin and gentamicin are only performed in selected years and was not carried out in 2024.

Resistance findings by gender and anatomical origin of the isolates

In males, the ciprofloxacin resistance rate was higher in anorectal isolates than in urogenital and pharyngeal isolates, while no major difference was observed among isolates from females (Table 8.27).

In males as well as in females, the azithromycin resistance rate was higher in pharyngeal isolates than in anorectal and urogenital isolates (Table 8.28).

In males, penicillinase production was demonstrated at a similar rate (approximately 16%), irrespective of the site of infection. In females, it was highest in pharyngeal isolates. (Table 8.29).

Table 8.27 Ciprofloxacin resistance rates by gender and anatomical origin of the isolates, 2024 DANMAP 2024

	Males		Females		Total	
	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant
Urogenital	546 / 878	62	249 / 475	52	795 / 1,353	59
Anorectal	104 / 143	73	5 / 9	56	109 / 152	72
Pharynx	45 / 73	52	27 / 46	59	72 / 119	61
Blood	1 / 1	100	0 / 0	-	1 / 1	100
Eye	1 / 1	100	0 / 0	-	1 / 1	100
Other or unknown	89 / 122	73	40 / 55	73	129 / 177	73
Total	786 / 1,218	65	321 / 585	55	1,107 / 1,803	61

Table 8.28 Azithromycin resistance rates by gender and anatomical origin of the isolates, 2024 DANMAP 2024

	Males		Females		Total	
	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant
Urogenital	31 / 878	3,5	17 / 475	3,6	48 / 1,353	3,5
Anorectal	1 / 143	0,7	0 / 9	0	1 / 152	6,6
Pharynx	3 / 73	4,1	3 / 46	6,5	6 / 119	5
Blood	0 / 1	0	0 / 0	-	0 / 1	0
Eye	0 / 1	0	0 / 0	-	0 / 1	0
Other or unknown	7 / 122	5,7	2 / 55	3,6	9 / 177	5,1
Total	42 / 1,218	3,4	22 / 585	6,6	64 / 1,803	3,5

Table 8.29 Penicillinase production by gender and anatomical origin of the isolate, 2024 DANMAP 2024

	Males		Females		Total	
	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant	No. resistant / total no.	% resistant
Urogenital	149 / 878	17	63 / 475	13	212 / 1,353	16
Anorectal	24 / 143	17	1 / 9	11	25 / 152	27
Pharynx	11 / 73	15	9 / 46	20	20 / 119	16
Blood	1 / 1	100	0 / 0	-	1 / 1	100
Eye	0 / 1	0	0 / 0	-	0 / 1	0
Unknown	17 / 122	14	8 / 55	-	25 / 177	14
Total	202 / 1,218	17	81 / 585	15	283 / 1,803	16

Conclusions

The ciprofloxacin resistance rate was at the same high level (61%) as in in 2023 (63%) and thus substantially higher than in 2022 (40%). However, the ceftriaxone MIC distribution was unchanged and showed no signs of a drift towards resistance. Although resistance problems among gonococci are still not present in Denmark, the frequent emergence globally of gonococcal resistance to antibiotics underlines the importance of maintaining the centralised national surveillance of antimicrobial resistance in gonococci.

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8.3.8 *Haemophilus influenzae*

Background

Haemophilus influenzae is part of the normal upper respiratory tract flora, with colonization varying by age. *H. influenzae* frequently causes upper and lower respiratory infections, while invasive infections are relatively rare and primarily occur in young children and elderly individuals, particularly those with underlying conditions like chronic obstructive pulmonary disease or cancer. Bacteraemia/sepsis is the predominant form (80-90%), while meningitis is observed in approximately 10% of cases. *H. influenzae* is categorized into six capsular serotypes (a, b, c, d, e, and f), also known as Hia, Hib, Hic, Hid, Hie, and Hif, and there are noncapsular (non-typeable, NTHi) strains as well. The introduction of the polysaccharide type b vaccine in 1993 significantly reduced the incidence of systemic infection caused by *H. influenzae* type b (Hib), as the vaccine specifically protects against Hib. Antimicrobial resistance in *H. influenzae* is an increasing problem globally, especially within beta-lactam antibiotics. The molecular antibiotic resistance in *H. influenzae* is complex, where both beta-lactamase production and alterations in penicillin binding proteins (PBPs), contribute to resistance to beta-lactam antibiotics.

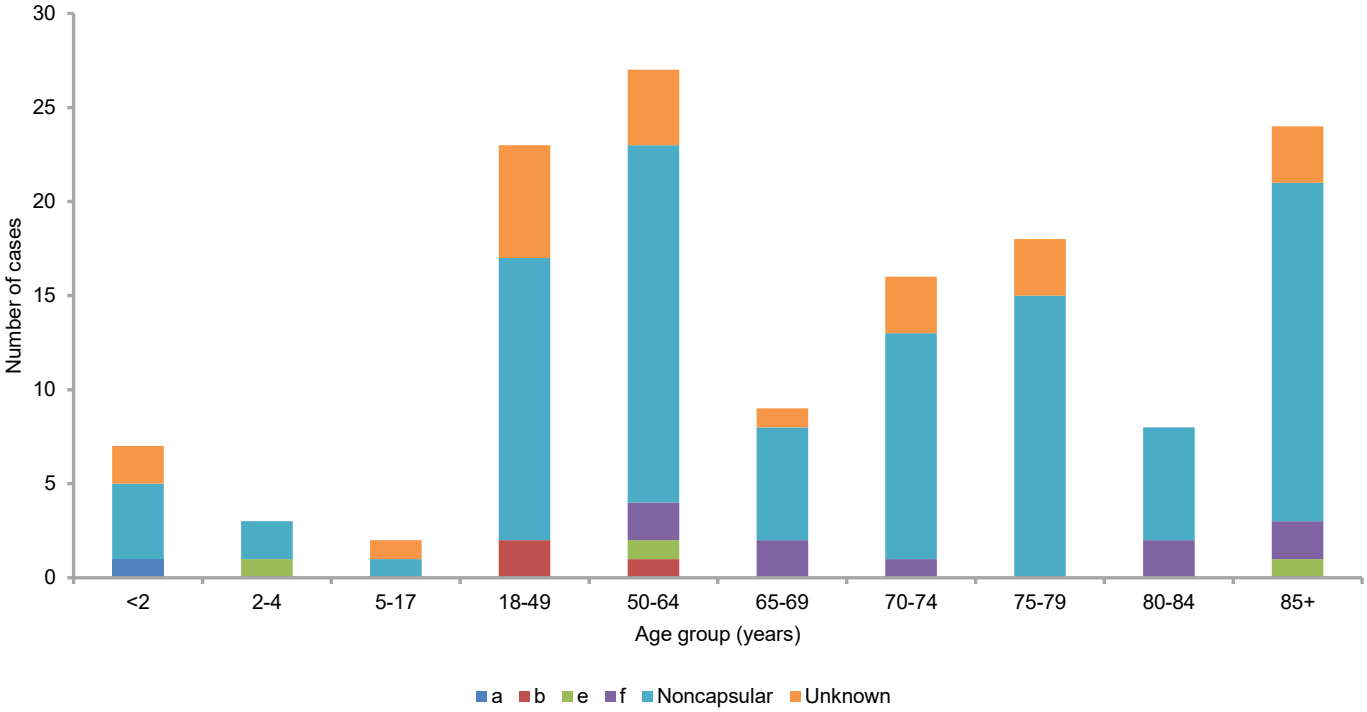
Surveillance of *Haemophilus influenzae*

The surveillance of *H. influenzae* causing invasive disease in Denmark involves submitting clinical isolates to Statens Serum Institut (SSI). Cases without a submitted isolate are identified through MiBa. At SSI, the isolates are only subjected to whole-genome sequencing to extract the serotype, sequence type, and beta-lactam resistance genes (beta-lactamase genes and mutations in the *ftsI* gene encoding penicillin-binding protein 3). Phenotypic beta-lactam susceptibility is retrieved through MiBa, if available.

Results

In 2024, a total of 137 cases of invasive *H. influenzae* were registered. The majority of cases were in blood (117), cerebrospinal fluid (10), or both (4). In three cases, *H. influenzae* was found in pleural fluid and in one case of each of the following: Blood and pleural fluid, joint fluid, and peritoneal-dialysis fluid. 114 isolates were submitted to SSI as part of the Danish surveillance program. The patient age and serotype distribution of the submitted isolates can be seen in Figure 8.29.

Figure 8.29 Distribution of invasive *H. influenzae* cases by age group and serotype (a, b, e, and f), Denmark, 2024 DANMAP 2024



Noncapsular *H. influenzae* is still the most commonly tested type (98/114; 86%), with Hif being the most common serotype (7.9%), followed by Hib (2.6%), Hie (2.6%), and Hia (0.9%).

Data on both molecular and phenotypic antimicrobial susceptibility were available for 89 *H. influenzae* isolates. Of these, 29% were penicillin/ampicillin-resistant (Table 8.30). Fourteen isolates were tested positive for TEM beta-lactamase genes (all were TEM-1). BLNAR-defining mutations in the *ftsI* gene were found in 12 isolates (11 had the N526K mutation and one had the R517H mutation). The most common *ftsI* type were IIa and IIb (four each), and one each of IIc, IId, III+ and III-like+.

Table 8.30 Phenotypic resistance against penicillin/ampicillin in *Haemophilus influenzae* DANMAP 2024

Sensitivity	Number (%)
Resistant	63 (71)
Susceptible	26 (29)
Total	89

A comparison between phenotypic beta-lactam susceptibility and beta-lactam resistance mechanisms (BLNAS = beta-lactamase-negative ampicillin-susceptible; BLPAR = beta-lactamase positive ampicillin-resistant; BLNAR = beta-lactamase negative ampicillin-resistant; BLPACR = beta-lactamase-positive amoxicillin-clavulanic acid-resistant) can be found in Table 8.31. A 98% concordance was observed between phenotypic susceptibility testing and molecular resistance gene detection: one isolate with no beta-lactam resistance markers was tested penicillin/ampicillin resistant, and one isolate with a BLNAR resistance mechanism was tested penicillin/ampicillin susceptible.

Table 8.31 Phenotypic resistance against penicillin/ampicillin vs. beta-lactam resistance mechanism in *Haemophilus influenzae* DANMAP 2024

Beta-lactam resistance mechanism	Pen/ampi resistant	Pen/ampi susceptible	Total (%)
BLNAS	1	62	63 (71)
BLPAR	13	0	13 (15)
BLNAR	11	1	12 (13)
BLPACR	1	0	1 (1)
Total	26	63	89

BLNAS = beta-lactamase-negative ampicillin-susceptible; BLPAR = beta-lactamase positive ampicillin-resistant; BLNAR = beta-lactamase negative ampicillin-resistant; BLPACR = beta-lactamase-positive amoxicillin-clavulanic acid-resistant

No *H. influenzae* isolates had other resistance genes.

Conclusions

The number of invasive *H. influenzae* cases in 2024 were 137, somewhat higher than the 123 cases in 2023 and 118 cases in 2022. The majority of isolates are still of the noncapsular type (86%) while Hif was the most common serotype (7.9%). Resistance towards penicillin and ampicillin was 26% with 13% BLNAR and 15% BLPAR, and one isolate with a BLPACR resistance mechanism.

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8.3.9 Meningococci

Neisseria meningitidis (meningococci) are capable of causing invasive meningococcal disease (IMD), usually meningitis or septicaemia or both, which may be life threatening and may cause permanent neurological sequelae. Asymptomatic throat carriage is frequent and only rarely leads to invasive disease. Non-invasive meningococcal diseases include, e.g. conjunctivitis and urethritis. IMD is usually treated with intravenous penicillin or ceftriaxone. Single-dose ciprofloxacin or rarely rifampicin may be used for prophylaxis to close contacts to patients with IMD.

Meningococci are classified into serological groups (A, B, C, W, X, Y, Z, and 29E) according to antigenic properties of the polysaccharide capsule. In Denmark, serogroups B and C are the most frequent ones in most years, although serogroup W was quite frequent in 2016 through 2019 and serogroup Y has been increasingly prevalent during 2022-2024. Vaccination against meningococci has never been part of the Danish childhood immunization programme but is used for prophylaxis to close contacts to patients with IMD. Specific vaccines exist for group B and combined vaccines for groups A, C, W, and Y.

This report presents data on antimicrobial resistance in non-duplicate invasive isolates (i.e. usually from blood, cerebrospinal fluid) submitted from the departments of clinical microbiology (DCMs) during 2012-2024 to the Neisseria and Streptococcus Reference laboratory (NSR). Isolates are received from all DCMs in Denmark. As of November 1, 2023, it became mandatory to submit isolates of meningococci, but the coverage rate until then was estimated to be 100% when compared to the mandatory clinical notification system. The two surveillance systems continuously supplement each other.

Figure 8.30 Number and serogroup of meningococcal isolates received during 2012-2024 DANMAP 2024

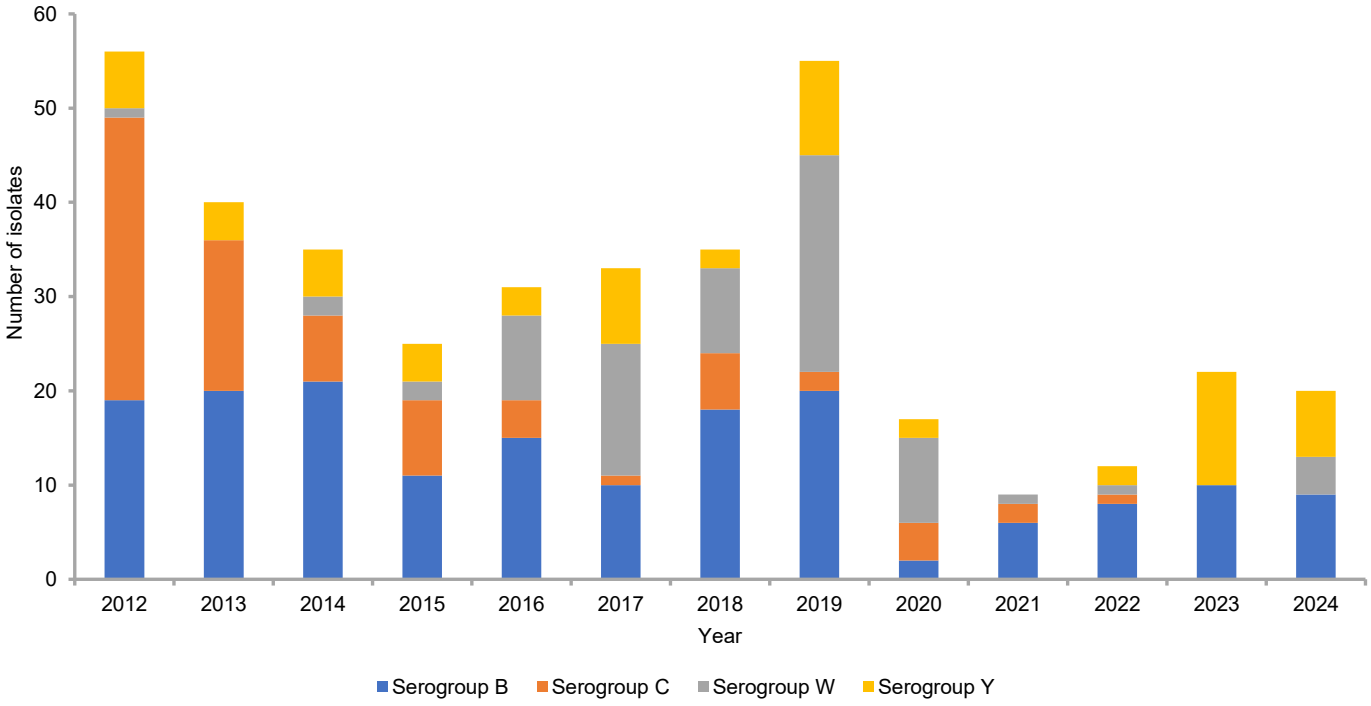


Figure 8.31 Distribution of ceftriaxone MIC values (mg/L) by serogroup of meningococcal isolates, 2012-2024 DANMAP 2024

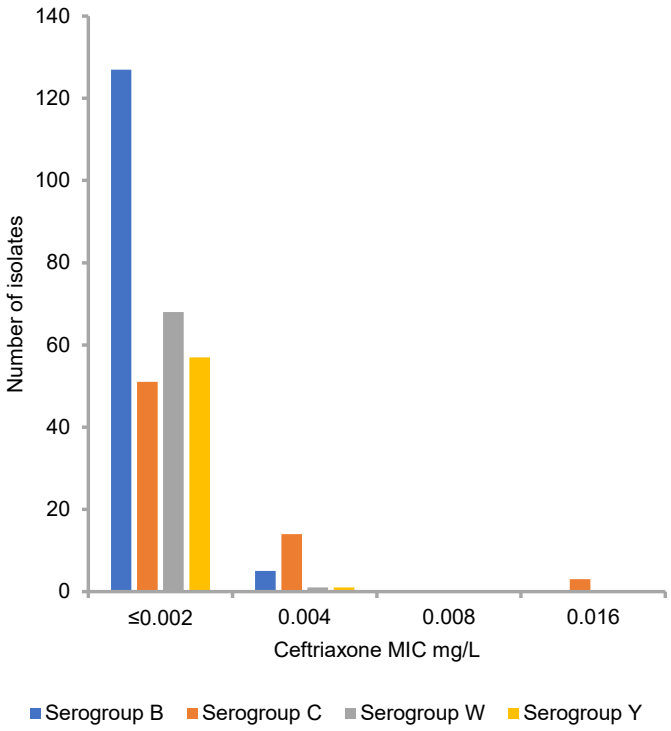
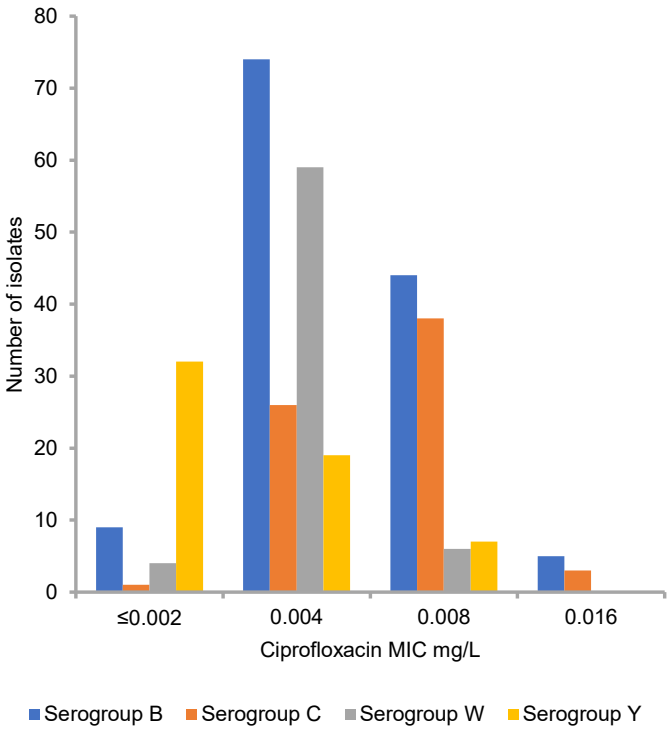


Figure 8.32 Distribution of ciprofloxacin MIC values (mg/L) by serogroup of meningococcal isolates, 2012-2024 DANMAP 2024



During the years 2012 through 2019, 18 to 52 isolates were received annually. In 2020, where restrictions to counteract the spread of COVID-19 were implemented, the number was 14, decreasing to 8 and 11, respectively, in 2021 and 2022. Figure 8.30 shows the number of isolates of groups B, C, W, and Y received during 2012-2024. Because of low numbers the following have been omitted: One isolate of group 29E (2017), three isolates of group X (2016, 2019 and 2023), and two isolates which were non-groupable (2019 and 2023). The susceptibility pattern of these six isolates did not show any specific deviations from the remaining findings and are therefore not further included in the present report.

All isolates were susceptible to ceftriaxone (MIC ≤0.125 mg/L), Figure 8.31.

All isolates were susceptible to ciprofloxacin (MIC ≤0.016 mg/L), Figure 8.32. Isolates of serogroup W (none in 2023 and 4 in 2024) and serogroup Y (11 in 2023 and 7 in 2024) tended to have slightly lower levels of ciprofloxacin MIC values than isolates of serogroup B and C.

Regarding rifampicin, only one (0.3%) of the isolates received during the study period was resistant (MIC ≤0.25 mg/L), Figure 8.34.

In total, 95% of the isolates during the study period were susceptible to penicillin (MIC ≤0.25 mg/L), Figure 8.33.

Figure 8.33 Distribution of penicillin MIC values (mg/L) by serogroup, 2012-2024 DANMAP 2024

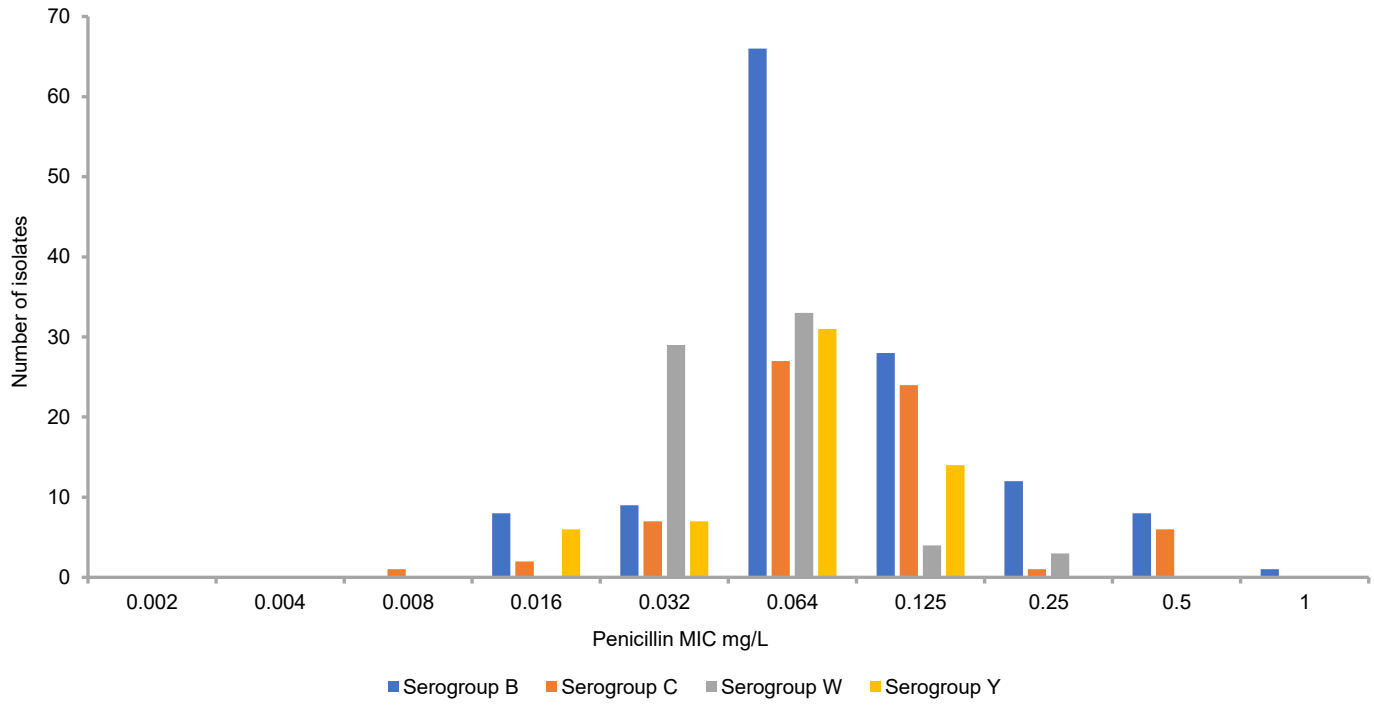


Figure 8.34 Distribution of rifampicin MIC values (mg/L) by serogroup, 2012-2024 DANMAP 2024

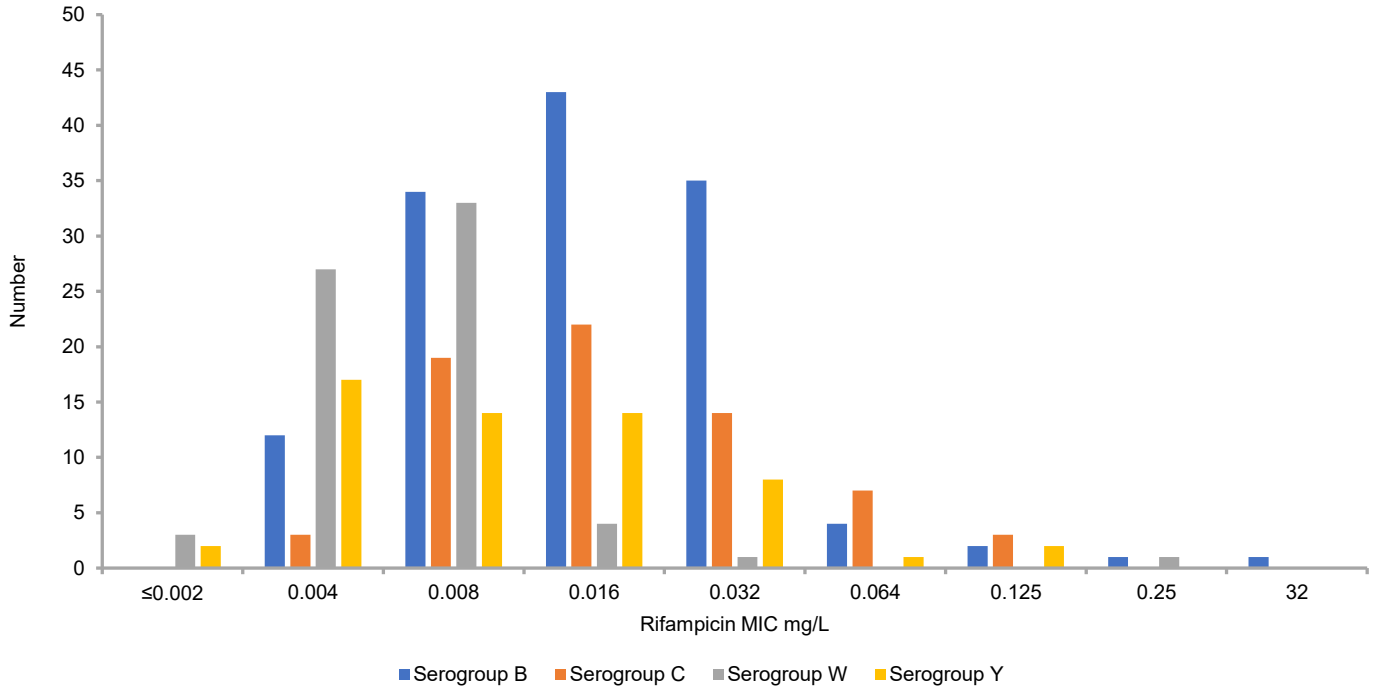


Table 8.31 Number of penicillin-resistant meningococcal isolates (MIC≥ 0.5 mg/L), serogroups B and C, 2013-2024 DANMAP 2024

	2013	2014	2016	2017	2018	2020	2022	2023	2024
Serogroup B	1	2	1	2			1	1	1
Serogroup C		1			2	3			

Only one isolate had an MIC value at 1 mg/L (serogroup B in 2024)

Nine isolates of serogroup B including one from each of the years 2022, 2023, and 2024, and six isolates of serogroup C were penicillin-resistant (MIC ≥0,5 mg/L), Table 8.33. Only one isolate had an MIC value at 1 mg/L (serogroup B in 2024).

Comments and conclusions

The substantial decrease of received meningococcal isolates during and following 2020 is most likely due to the social restrictions implemented in April 2020 because of COVID-19. Likewise, the modest increase during 2023 and also in 2024 probably represent the influence of the lifting of the restrictions which have enabled more respiratory transmission than during the preceding 2-3 years.

The antibiotic susceptibility patterns of meningococci do not reveal any imposing threats of resistance.

During the first six months of 2025 a total of 21 cases of IMD have been diagnosed in Denmark (not described in this report).

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