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NORM
NORM-VET

Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM)

Veterinærinstituttet
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INTRODUCTION

Antimicrobial resistance is an emerging problem worldwide. It reduces the effectiveness of antimicrobial treatment of infectious diseases in humans and animals thereby leading to increased morbidity and mortality, as well as higher costs. It is well established that there is a strong association between the usage of antimicrobial agents and the occurrence of resistance. The selective pressure exerted following use of antimicrobial agents is a key issue in the epidemiology of resistance. In this report the term antimicrobial resistance is used synonymously with antibiotic resistance, although the term actually includes resistance in other microbes as well. Antimicrobial resistance can be disseminated through the spread of resistant pathogenic organisms themselves or by horizontal transfer of resistance genes from one type of organisms to another. Such transfer is not limited to closely related organisms; it can also take place between organisms of different evolutionary origins and/or ecological niches. Thus, antimicrobial drug usage and resistance in one ecological compartment can have consequences for the occurrence of resistance in another compartment. When addressing antimicrobial resistance – the occurrences, causes, consequences and preventive measures – a holistic approach is needed, encompassing both data on usage and resistance in human and veterinary medicine, as well as organisms in the food production chain.

In response to the growing concern about antimicrobial resistance, the Norwegian Ministry of Health and Social Affairs issued the first national action plan against antimicrobial resistance in March 2000. The importance of monitoring the human and animal health sectors as well as food production, was emphasised. The action plan recognised the need for ongoing surveillance as a fundamental component of the strategy. The NORM and NORM-VET programmes were consequently established in order to provide and present data on the occurrence and distribution of antimicrobial resistance over time. The national action plan formally expired by the end of 2004. However, the need for continued surveillance of both resistance and antimicrobial usage was emphasised at subsequent consultations and an integrated national strategy for prevention of infections in the health service and antibiotic resistance (2008-2012) was issued in the summer of 2008. A new national strategy (2015-2020) was launched by the Norwegian government in 2015 including an explicit target of 30% reduction in antibiotic consumption in human medicine by 2020 compared to 2012. For food-producing terrestrial animals and companion animals the target was 10% and 30% reduction in the usage, respectively, by 2020, with 2013 as reference year. Additional specific targets in the food production chain were that livestock associated MRSA should not be established in the Norwegian pig population, and that ESBL in the poultry production should be reduced to a minimum. Also, the action plan stated that the government will carry out mapping of reservoirs of antimicrobial resistant bacteria in humans, in food and in relevant animal populations and in sentinel environments. Due to the coronavirus pandemic, the expiry of this strategy has been postponed until an updated version is available, but the government has initiated the process to develop a new framework for the coming years.

The NORM surveillance programme for antimicrobial resistance in human pathogens was established in 1999 and is coordinated by the Department of Microbiology and Infection Control at the University Hospital of North Norway in Tromsø. The NORM-VET monitoring programme for antimicrobial resistance in animals, food and feed was established in 2000 and is coordinated by the Norwegian Veterinary Institute commissioned by the Norwegian Food Safety Authority. The NORM/NORM-VET reports also present data on the usage of antimicrobial agents in humans and animals in Norway. The NORM and NORM-VET programmes are valuable tools for setting policies, assessing risks and evaluating interventions.

This report, which is the twenty-fourth annual joint report from NORM and NORM-VET, presents data on resistance and usage for 2023. The editors would like to thank all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Ås / Oslo, September 2024

SAMMENDRAG

Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM) og Norsk overvåkingsprogram for antibiotikaresistens i mikrober fra fôr, dyr og næringsmidler (NORM-VET) utgir en felles årlig rapport. Årets rapport presenterer data om forekomst av antibiotikaresistens og forbruk av antibiotika til mennesker og dyr i 2023. Data fra relevante prosjekter som ikke er med i de kontinuerlige overvåkingsprogrammene, presenteres også. NORM og NORM-VET ble etablert som deler av Regjeringens tiltaksplan mot antibiotikaresistens offentliggjort i 2000. NORM koordineres av Avdeling for mikrobiologi og smittevern, Universitetssykehuset Nord-Norge i Tromsø. NORM-VET koordineres av Veterinærinstituttet.

Forbruk av antibiotika til dyr

I 2023 utgjorde salget av antibakterielle veterinærpreparater til landdyr totalt 4 479 kg som er 143 kg lavere enn i 2022 og det laveste salget rapportert (data tilgjengelig fra 1993).

Salget av antibakterielle veterinærpreparater til matproduserende landdyr, inkludert hest, var på 4 107 kg. Data rapportert til Veterinært legemiddelregister (VetReg) viser at til storfe, gris, sau, geit og fjørfe ble det i all hovedsak brukt penicilliner og av disse var det nesten utelukkende beta-laktamaseømfintlige penicilliner (benzylpenicillinprokain) som ble benyttet. Fra 2013 til 2023 var det en nedgang i salget av antibakterielle veterinærpreparater som i hovedsak benyttes til de viktigste matproduserende artene (storfe, gris, sau, geit og fjørfe) på 31 % målt i kg aktivt stoff. Når salget relateres til dyrepopulasjonen, var nedgangen i forbruket 27 %. Til hest ble det i hovedsak brukt trimetoprim-sulfa som oralpasta.

Salget av antibakterielle veterinærpreparater til flokkbehandling er fortsatt lavt; i 2023 representerte salg av slike preparater 3,7 % av totalsalget til matproduserende landdyr, inkludert hest.

Forbruket av veterinære antibakterielle midler til oppdrettsfisk (forbruk til rensefisk inkludert) var fortsatt svært lavt i 2023 og utgjorde 548 kg. Dette representerer en nedgang på over 99 % sammenlignet med 1987 da forbruket var på sitt høyeste. I 2023 ble det foretatt behandling med antibiotika i 3,3 % av sjølokalitetene for laks og regnbueørret.

Til kjæledyr (hund og katt) ble det i 2023 solgt 372 kg antibakterielle veterinærpreparater. Dette er en nedgang på 30 % sammenlignet med 2013. Data rapportert til VetReg for hund og katt for perioden 2015-2023 viser en reduksjon på totalt 31 % (i kg) i forskrivningen av antibakterielle humanpreparater til hund og katt, noe som indikerer at redusert salg av antibakterielle veterinærpreparater ikke har blitt erstattet av forskrivning av antibakterielle humanpreparater.

Det Europeiske legemiddelbyrået (EMA) har anbefalt å begrense bruken av enkelte antibakterielle midler til dyr, dvs. 3.-4. generasjon cefalosporiner, kinoloner (fluorokinoloner og andre kinoloner) og polymyksiner, på grunn av den potensielle risikoen for folkehelsa. Av disse antibakterielle midlene selges det kun kinoloner til matproduserende landdyr og oppdrettsfisk. Salget av kinoloner utgjorde en svært liten andel (0,9 %) av totalsalget av veterinære antibakterielle midler til dyr, inkludert fisk, i 2023. Hovedparten brukes til oppdrettsfisk.

Narasin ble faset ut som fôrtilsetningsmiddel til slaktekylling sommeren 2016. Bruken av antibiotika til behandling har vært svært lav i etterkant av utfasingen og i 2023 ble kun to slaktekyllingflokker behandlet med antibiotika.

Forbruk av antibiotika hos mennesker

I 2023 var det totale salget av antibakterielle midler til systemisk bruk hos mennesker (J01 unntatt metenamin) 13,1 DDD (definerte døgndoser)/1 000 innbyggere/døgn. Siden 2012 har det vært en markant nedgang i total antibiotikabruk, i alt en reduksjon på 23 %. Under COVID-19-pandemien ble det observert en signifikant reduksjon i bruken av systemiske antibiotika, men forbruket er nå tilbake til noenlunde samme nivå som før pandemien.

Rundt 84 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. Penicilliner (J01C) er oftest forskrevet i primærhelsetjenesten og representerte i 2023; 41 % av alle DDD og 58 % av reseptene i ATC-gruppe J01, ekskl. metenamin, etterfulgt av tetracykliner (J01A); 19 % av alle DDD og 9 % av alle resepter. De seks hyppigst foreskrevne antibiotika i 2023 var fenoksymetylpenicillin, pivmecillinam, metenamin, dicloksacillin, amoksicillin og doksycyklin. Disse seks utgjorde 72 % av alle resepter og 77 % av alle antibiotika DDD brukt i primærhelsetjenesten. I Norge er luftveisinfeksjoner vanligste indikasjon for smalspektret penicillin, og i 2023 ble fenoksymetylpenicillin forskrevet på 27 % av alle antibiotikaresepter og utgjorde 22 % av alle DDD. Metenamin utgjorde 27 % av alle DDD og 9 % av antibiotikareseptene i primærhelsetjenesten. Det har vært en økning i bruk i primærhelsetjenesten etter pandemien, men over det siste tiåret har det vært en generell jevn nedgang i antibiotikabruk i primærhelsetjenesten. Dette kan skyldes økt oppmerksomhet om antimikrobiell resistens, både blant helsepersonell og i befolkningen generelt. Etter innføringen av regjeringens handlingsplan mot antimikrobiell resistens (AMR) i 2016 har en stor andel allmennleger gjennomført kvalitetsforbedrende kurs om riktig antibiotikaforskrivning. Selv om mye er oppnådd, er det sannsynligvis fremdeles forbedringsområder, f.eks. unngå antibiotikaforskrivning til virale infeksjoner, riktig valg av antibiotika, individualisering av doser eller varighet av kur. Det er essensielt å ha oppdaterte retningslinjer for bruk og kontinuerlige antibiotikastyringsprogrammer i primærhelsetjenesten for å kunne oppnå ytterligere smalspektret terapiprofil og en ytterligere reduksjon i antibiotikaforbruket.

Antibiotikasalg (i DDD) til sykehus utgjorde 7 % av totalt salg av antibakterielle midler til mennesker i 2023. Salget er redusert med 3 % i DDD/1 000 innbygger/dag sammenliknet med 2019, men har økt med 10 % siden 2021. I norske sykehus ble det gjennomsnittlig brukt 82 DDD/100 liggedøgn i 2023. Dette er en økning siden 2019, og en økning på 20 % siden 2012. I samme periode økte DDD/innleggelse med 5 %. Terapimønsteret for antibakterielle midler på sykehus endrer seg ikke mye fra ett år til et annet,

men det er en klar trend mot mer bruk av antibiotika anbefalt i retningslinjene. Bruken av bredspektret antibiotika er redusert siden 2012. De utgjorde 20 % av bruken målt i DDD/100 liggedøgn i 2023 og 26 % i 2012. Denne gunstige utviklingen kan forklares med opprettelse av antibiotikastyringsprogram i sykehus, kontinuerlig god oppfølging av antibiotikateamene (A-team) og oppdaterte retningslinjer. I sykehus ble penicilliner (J01C) mest brukt (nesten halvparten av bruken målt i DDD). Cefalosporiner er den nest største antibiotikagruppen med 18 % av alle DDD. Det er store variasjoner mellom sykehus, både målt i volum (i DDD/100 liggedøgn) av antibiotika som brukes og i terapiprofil. Variasjonene kan ikke forklares med forskjeller i aktivitet eller pasientsammensetning alene.

Resistens hos kliniske isolater fra dyr

I 2023 ble det undersøkt *Escherichia coli* og *Staphylococcus pseudintermedius* fra ulike infeksjoner hos hund, samt *Pasteurella multocida* og *Pasteurella canis* fra infeksjoner hos forskjellige dyrearter.

Omtrent halvparten (53,8 %) av 65 *E. coli* var fullt følsomme for de antibakterielle klassene de ble testet for, mens 15,4 % var multiresistente (resistens mot tre eller flere antibakterielle klasser). To av *E. coli* isolatene ble identifisert som ekstendert-spektrum cefalosporinresistente (ESC-resistente). Kjente mutasjoner i det kromosomale *ampC* genet ble påvist som bakenforliggende årsak hos ett av isolatene, og det siste isolatet ble genotypet som $bla_{\text{CMY-2}}$.

Av 195 *S. pseudintermedius* var 42,6 % fullt følsomme for de antibakterielle klassene når resistens mot benzylpenicillin, gentamicin og sulfonamider ble ekskludert fra beregningene. Multiresistens ble påvist i 21,5 % av isolatene. Resistens mot benzylpenicillin ble utledet fra påvisning av betalaktamaseproduksjon, og påvist hos 72,3 % av isolatene. Fjorten (7,2 %) av isolatene var meticillinresistente.

Majoriteten av både *P. multocida* (89,5 % av 143) og *P. canis* (85,5 % av 62) var fullt følsomme for de antibakterielle midlene de ble testet for. Multiresistens ble påvist hos bare 0,7 % av *P. multocida*, og ingen av *P. canis*.

Resistens hos indikatorbakterier fra dyr og mat

Resultatene fra 2023 bekrefter at situasjonen i Norge er god med tanke på antibiotikaresistens hos bakterier fra dyr og mat. Forekomsten av multiresistens og spesielle resistensformer av særlig interesse, slik som ESC-resistente *E. coli*, er fremdeles lav. Forekomsten av multiresistente *Enterococcus faecium* hos gris har imidlertid økt de siste årene. Karbapenemaseproduserende *Enterobacterales* (CPE) ble påvist for første gang fra produksjonsdyr i 2023. Prøven var en tilfeldig utplukket blindtarmsprøve fra storfe tatt ut på slakteri.

NORM-VET følger de krav til overvåking av antibiotikaresistens i indikatorbakterier og i zoonotiske bakterier som er satt i EU-regelverket (2020/1729/EU). I tillegg undersøkes det prøver av dyr og matvarer ut ifra nasjonale hensyn. *E. coli* og *Enterococcus* spp. benyttes som indikatorbakterier, dvs. sensitivitetstesting av *E. coli og Enterococcus* spp. benyttes som indikator for forekomst av antibiotikaresistens. I tillegg er *Staphylococcus* spp. inkludert som en indikator for forekomst av antibiotikaresistens hos kjæledyr. Selektive metoder benyttes til overvåking av ESC-resistente *E. coli*, CPE, vankomycinresistente *Enterococcus* spp. (VRE), linezolidresistente *Enterococcus* spp. (LRE), meticillinresistente *S. aureus* (MRSA) og meticillinresistente *Staphylococcus pseudintermedius* (MRSP). MRSA i svinepopulasjonen er overvåket via et eget omfattende program, som har som mål å identifisere MRSA-positive besetninger. Resultatene fra dette programmet oppsummeres også i denne rapporten.

I 2023 ble det undersøkt blindtarmsprøver fra storfe og fra slaktegris, ett dyr per besetning. Fra disse ble det isolert og sensitivitetstestet *E. coli, Enterococcus faecalis* og *E. faecium*. Prøvene ble også undersøkt for forekomst av ESC-resistente *E. coli* og CPE. Fra hund ble det undersøkt svabre fra avføring for isolering og sensitivitetsundersøkelse av *E. coli*, samt for forekomst av ESC-resistente *E. coli* og CPE. I tillegg ble svabre fra munn-/neseslimhinne/perineum undersøkt for isolering og sensitivitetsundersøkelse av *S. pseudintermedius*, samt for forekomst av MRSA og MRSP. Matprøver inkludert i 2023 var prøver fra storfe- og svinekjøtt som ble undersøkt for forekomst av ESC-resistente *E. coli* og CPE.

Majoriteten av de 271 *E. coli* isolatene fra storfe var fullt følsomme for de antibakterielle midlene de ble testet for (93,7 %), og kun 0,8 % av isolatene var multiresistente. Forekomsten av fullt følsomme *E. coli* isolater har vært relativt stabil de siste årene (2015-2023). Kun to *E. faecalis* og 16 *E. faecium* ble påvist fra storfe. Av disse var en av de to *E. faecalis* og syv av *E. faecium* isolatene fullt følsomme, og ingen var multiresistente. Resultatene er i samsvar med resultatene fra 2019 og 2021.

Også i prøvene fra slaktegris var flesteparten (84,6 %) av *E. coli* isolatene (n=331) fullt følsomme for de antibakterielle midlene de ble testet for. Totalt var 1,2 % av isolatene multiresistente. Forekomsten av fullt følsomme isolater har vært relativt stabil mellom 80 % og 90 % siden 2015. Forekomsten av antibiotikaresistens er høyere hos enterokokker. Kun 3,4 % av 61 *E. faecalis* isolater og 38,4 % av 86 *E. faecium* isolater var fullt følsomme for de antibakterielle midlene de ble testet for. Multiresistens ble påvist hos 19,8 % av *E. faecium* isolatene. Sammenliknet med resultater fra 2019, har det vært en økning i resistens mot flere antibakterielle klasser, men særlig mot ampicillin. Dette har ført til en økning i forekomst av multiresistente *E. faecium* isolater fra 0,9 % i 2019 til hhv. 21,3 % i 2021 og 19,8 % i 2023.

Forekomsten av ESC-resistente *E. coli* var hhv. 5,4 % hos storfe (15 av 277 prøver) og 19,8 % hos gris (66 av 333 prøver), samt fra fire av 283 kjøttprøver fra svin. Ingen av de 286 kjøttprøvene fra storfe var positive. Kjente mutasjoner i det kromosomale *ampC* genet ble identifisert som bakenforliggende årsak hos tolv av isolatene fra storfe og hos 56 av isolatene fra svin, samt hos de fire isolatene fra kjøtt. De resterende isolatene ble genotypet som hhv. $bla_{\text{CMY-2}}$ (tre fra svin), $bla_{\text{CTX-M-55}}$ (to fra storfe og ett fra svin), $bla_{\text{CTX-M-15}}$ (fem fra svin), $bla_{\text{OXA-1}}$ (ett fra svin), og det siste isolatet viste seg å være resistent mot karbapenemer og ble genotypet som $bla_{\text{NDM-5}}$. CPE ble også påvist i samme prøve ved bruk av selektive metoder (0,4 % av totalt 277 undersøkte prøver fra storfe). Dette var første gang CPE ble påvist fra produksjonsdyr i Norge.

I prøvene fra hund var majoriteten (72,9 %) av 232 *E. coli* isolater fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for. Multiresistens ble påvist hos 4,3 % av

isolatene. Det har vært en økning i resistens mot sulfametoxazol fra 5,8 % i 2019 til 18,5 % i 2023. Kun ett av isolatene var resistent mot ESC og ble genotypet som *bla*$_{\text{CTX-M-15}}$. Forekomsten av ESC-resistente *E. coli* var 5,6 % av de undersøkte 251 hundeprøvene. Kromosomale mutasjoner i *ampC* genet ble påvist som årsak hos syv av isolatene, ett ble genotypet som *bla*$_{\text{DHA-1}}$, tre som *bla*$_{\text{CTX-M-15}}$ og de siste tre som hhv. *bla*$_{\text{CTX-M-1}}$, *bla*$_{\text{CTX-M-3}}$, og *bla*$_{\text{SHV-12}}$. Det ble ikke påvist noen CPE fra hundeprøvene. Det ble isolert 163 *S. pseudintermedius* isolater fra svaberprøvene fra munn-/neseslimhinne/perineum. Av disse var 40,5 % fullt følsomme når resistens mot benzylpenicillin, gentamicin og sulfonamider ble ekskludert fra beregningene. Multiresistens ble påvist hos 16,0 % av isolatene. Resistens mot benzylpenicillin, utledet fra påvisning av betalaktamaseproduksjon, ble påvist hos 76,7 % av isolatene. Ingen av de 163 isolatene var meticillinresistente, men med den selektive isoleringsmetoden ble MRSP med *mecA* genet påvist fra én av prøvene.

Resistens hos zoonotiske bakterier og andre enteropatogene bakterier

Zoonosebakterier isolert fra dyr og fra mat

Den norske husdyrpopulasjonen er regnet som tilnærmet fri for *Salmonella*. Totalt ble det i 2023 sensitivitetstestet 24 *Salmonella* spp. isolater fra dyr (åtte fra villsvin, tre fra kylling, tre fra gris, tre fra storfe, to fra hest, to fra hund, og én hver fra hhv. katt, due og pinnsvin). Disse isolatene kom fra det nasjonale *Salmonella* overvåkingsprogrammet, fra overvåkingsprogrammet for villsvin, og fra andre undersøkelser ved Veterinærinstituttet. Ett isolat var resistent mot tetrasykliner og ampicillin (*Salmonella* Typhimurium, monofasisk (4,[5],12 : i : -). I tillegg til isolatene fra dyr, ble det undersøkt åtte *Salmonella* spp. isolater fra kjøtt eller andre matvarer som ikke var av norsk opprinnelse, og som var innsendt til Nasjonalt referanselaboratorium for *Salmonella*. Alle åtte var fullt følsomme for de antibiotika som var inkludert i testpanelet.

Campylobacter spp. fra storfe og slaktegris ble også undersøkt. Majoriteten (79,8 %) av de 124 testede *C. jejuni* isolatene fra storfe var fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for. Kun 2,4 % av isolatene var multiresistente. Full følsomhet var også resultatet for majoriteten (79,0 %) av de 281 testede *C. coli* isolatene fra gris, og multiresistens ble påvist hos kun ett av isolatene (0,4 %).

Kliniske isolater av tarmpatogene bakterier fra mennesker

Referanselaboratorium for enteropatogene bakterier (NRL) utfører årlig antimikrobiell følsomhetstesting for *Salmonella, Campylobacter, Yersinia* og *Shigella* isolater. Fra og med 2020 har NRL screenet alle *Enterobacterales* isolater for antimikrobielle resistensdeterminanter etter helgenomsekvensering for å påvise genotypisk resistens. I 2020 og 2021 ble reiserestriksjoner håndhevet som ett av smitteverntiltakene under COVID-19 pandemien, noe som reduserte antallet reiseassosierte infeksjoner vesentlig. Trender for antibiotikaresistens må tolkes deretter.

For *Salmonella* Typhimurium og den monofasiske varianten av *S*. Typhimurium var det totale resistensnivået høyere for stammer fra reiseassosierte infeksjoner sammenliknet med innenlandservervede stammer. Multiresistens (MDR) var en karakteristisk egenskap for et betydelig antall monofasiske *Salmonella* Typhimurium (84,2 %). Ni isolater var ESBL-produserende (ekstendert spektrum betalaktamase) og genotypet til *bla*$_{\text{CTX-M}}$ (n=8) og *bla*$_{\text{DHA}}$ (n=1).

For *Campylobacter jejuni* var det generelle resistensnivået for ciprofloksacin og tetracyklin høyere for stammer fra reiseassosierte infeksjoner sammenliknet med innenlandservervede stammer. Forekomsten av antibiotikaresistens i *Yersinia enterocolitica* er fortsatt lav. En økende trend med resistens mot ciprofloksacin og utvidet spektrum cefalosporiner ble observert både hos *Shigella sonnei* og *Shigella flexneri*. Tjueni og seks ESBL-produserende stammer ble identifisert blant henholdsvis *S. sonnei* og *S. flexneri* isolater, og karakterisert med *bla*$_{\text{CTX-M}}$ gener. En høy andel av *Shigella* stammer ble karakterisert som MDR (> 80 %). Mutasjoner i *pmrB*-genet assosiert med colistinresistens ble identifisert i alle *S. flexneri* isolater.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2023. *Staphylococcus aureus* og *Staphylococcus lugdunensis* isolater fra blodkultur og sårprøver var generelt følsomme for alle relevante antibiotika. Det ble påvist 31 tilfeller av meticillinresistente *S. aureus* (MRSA) blant 1 695 blodkulturisolater (1,8 %). Resultatet samsvarer med tall fra laboratorienes datasystemer som rapporterte 39 MRSA isolater blant 2 196 *S. aureus* (1,8 %) fra blodkultur og spinalvæske i 2023. Dette er en svak økning fra 0,8 % i 2021 og 1,0 % i 2022. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 1 109 tilfeller av MRSA infeksjon i 2023. De fleste tilfellene var pasienter med overfladiske sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (12 av 898; 1,3 %) slik de også har gjort i tidligere år (1,5 % i 2021; 1,6 % i 2022). MSIS registrerte videre 1 435 tilfeller av MRSA kolonisering i 2023. I alt ble det meldt funn av MRSA hos 2 544 personer i 2023 sammenliknet med 2 008 i 2022 (antall korrigert fra tidligere rapport). Dette utgjør en insidensrate på 46 per 100 000 personår i 2021 sammenliknet med 32 i 2021 og 38 i 2022. Insidensen av MRSA er nå på samme nivå som før COVID-19 pandemien (2 424 personer registrert i 2016). Det månedlige antall MRSA infeksjoner har ikke endret seg signifikant gjennom de siste åtte årene, og insidensen av invasive infeksjoner har holdt seg stabil på et lavt nivå. En betydelig andel av tilfellene (26 %) ble smittet i utlandet, men for mange (43 %) var smittested ukjent. Det påvises svært få tilfeller av landbruksassosiert MRSA i Norge.

Blodkulturisolater av *E. coli* viste stort sett uendret forekomst av resistens mot bredspektrede antibiotika i 2023. Andelen av gentamicinresistente isolater var 5,4 % i 2023 sammenliknet med 5,6 % i 2021 og 5,1 % i 2022, mens forekomsten av resistens mot ciprofloxacin var uendret på 10,0 %. *Klebsiella* spp. har omtrent samme forekomst av resistens mot gentamicin (4,3 %) og ciprofloxacin (8,1 %) som *E. coli*. Produksjon av ESBL er et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 129 av 2 240 (5,8 %) *E. coli* og 57 av 1 028 (5,5 %) *Klebsiella* spp. fra blodkultur ble rapportert som ESBL-positive i 2023. Forekomsten er nå stabil både for *E. coli* (5,8 % i 2021; 6,0 % i 2022) og *Klebsiella* spp. (5,5 % både i 2021 og 2022). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (5,8 %) enn fra urinprøver (3,9 %). Karbapenemaseproduserende

Enterobacterales (CPE), *Pseudomonas aeruginosa* og *Acinetobacter* spp. har vært meldepliktige til MSIS siden 2012. Antall pasienter med CPE økte skarpt fra 60 tilfeller i 2021 til 152 i 2022, og økningen fortsatte i 2023 med 237 rapporterte tilfeller. Antall pasienter med karbapenemase-produserende *P. aeruginosa* (n=27) og *Acinetobacter* spp. (n=31) økte også, fra henholdsvis n=18 og n=30 i 2022. Multiresistente Gram-negative bakterier kan ofte knyttes til import fra land med høy forekomst av slike mikrober. Også i 2023 utgjorde isolater fra ukrainske pasienter ved norske sykehus en betydelig andel av totalen. *P. aeruginosa* og *Acinetobacter* spp. blodkulturisolater fra den generelle befolkningen var stort sett følsomme for alle relevante antibiotika.

Antallet systemiske isolater av *Haemophilus influenzae* og *Neisseria meningitidis* var stabilt fra 2022 til 2023, men er fortsatt på et historisk lavt nivå etter pandemien. Det var en økt andel av systemiske *H. influenzae* isolater med produksjon av beta-laktamase (15,7 % i 2023 mot 10,8 % i 2022), men dette kan skyldes tilfeldig variasjon. Forekomsten av kromosomal beta-laktamresistens (10,7 %) var uendret. Det var en betydelig økning av antallet *Neisseria gonorrhoeae* isolater fra 220 i 2021 til 830 i 2022 og nå 1 500 i 2023. Antallet tilfeller meldt til MSIS fortsatte å øke fra 1 857 i 2022 til 2 985 i 2023. Det ble påvist utbredt resistens mot penicillin G (15,7 %), og bare 4,2 % var følsomme for standard dosering av penicillin G svarende til villtype-populasjonen. Hele 51,3 % var resistente mot ciprofloxacin. To isolater (0,1 %) var resistente mot ceftriaxon og det perorale cefalosporinet cefixim. Alle isolater var fullt følsomme for spectinomycin.

Det ble påvist to enterokokkisolater fra blodkultur med klinisk signifikant vankomycinresistens (VRE) i 2023 (en *vanA* og en *vanB E. faecium*). Forekomsten av resistens mot ampicillin i *E. faecium* var som tidligere rundt 70-80 %, mens høygradig gentamicinresistens stort sett var uendret hos både *E. faecalis* (6,9 % i 2022; 6,4 % i 2023) og *E. faecium* (44,3 % i 2022; 50,7 % i 2023). Nesten alle *E. faecium* isolater med høygradig gentamicinresistens var også resistente mot ampicillin. Det ble funnet fire *E. faecium* isolater med genetisk verifisert linezolidresistens (LRE). Både VRE og LRE er meldepliktige til MSIS, og det ble bekreftet funn av 89 VRE (34 i 2021; 74 i 2022) og 66 LRE (16 i 2021; 38 i 2022) på referanselaboratoriet ved Nasjonal kompetansetjeneste for påvisning av antibiotika-resistens (K-res) på UNN i 2023. Fire av disse isolatene var resistente mot både vankomycin og linezolid. Forekomsten av VRE varierer med utbrudd fra år til år, men har tilsynelatende returnert til nivået før pandemien. Antallet påvisninger av LRE er økende, men dette kan delvis skyldes økt fokus på slike mikrober i laboratoriene.

Overvåkingen av resistens hos *Streptococcus pneumoniae* (pneumokokker) viste at bare 0,3 % av isolatene fra blodkultur og spinalvæske, og ingen av luftveisisolatene, var resistente mot penicillin G. Imidlertid var henholdsvis 7,9 % av de systemiske isolatene (9,7 % i 2022) og 15,0 % av luftveisisolatene (8,3 % i 2020) bare følsomme for økt eksponering av dette middelet. Fire isolater fra blodkultur (0,7 %) og to fra luftveier (1,1 %) hadde nedsatt følsomhet for ett eller flere 3.-generasjon cefalosporiner. Forekomsten av makrolidresistens blant pneumokokker fra blodkultur var 6,5 % i 2023 sammenliknet med 4,6 % i 2022. Blant luftveisisolatene var hele 10,0 % erytromycinresistente (9,8 % i 2020). Alle isolater av *S. pyogenes* (beta-hemolytiske streptokokker gruppe A) fra blodkultur var følsomme for penicillin G, og forekomsten av erytromycinresistens (6,5 %) var uendret fra 2022. Systemiske isolater av *Streptococcus agalactiae* (beta-hemolytiske streptokokker gruppe B) var også følsomme for penicillin G, men hadde høy forekomst av resistens mot erytromycin (21,2 % i 2022; 22,7 % i 2023) og tetracyklin (74,6 % i 2022; 72,0 % i 2023).

I alt 152 pasienter med tuberkulose ble meldt til MSIS i 2023. Femten isolater (11,8 %) ble definert som multi-resistente (MDR) mot både rifampicin og isoniazid sammenliknet med 7,2 % i 2022. Pasientene hadde ervervet sine infeksjoner i Europa utenom Norge (n=12), Asia (n=2) og Afrika (n=1).

Det ble utført resistensbestemmelse av 250 *Candida* blod-kulturisolater fra 226 ulike pasienter. De vanligste artene var *C. albicans* (n=134), *C. glabrata* (n=39), *C. para-psilosis* complex (n=25), *C. tropicalis* (n=14) og *C. dubliniensis* (n=11). Alle *C. albicans* var følsomme for de undersøkte midlene med unntak av to echinocandin-resistente isolater og ett isolat med nedsatt følsomhet for fluconazol. Det ble kun påvist enkelte non-*albicans* isolater med ervervet resistens, men som forventet var det høy forekomst av resistens mot azoler hos *C. glabrata* (12,8 %). Nøyaktig speciesbestemmelse er nødvendig for å forutsi iboende resistens og velge effektiv behandling. Resultatene samsvarer med tidligere studier fra Norge.

Konklusjon

I Norge er forekomsten av antibiotikaresistens fortsatt lav i bakterier fra mennesker og dyr. Dette skyldes lavt forbruk av antibiotika, et fordelaktig forbruksmønster, og effektive tiltak mot spredning av resistente bakterier. Resultatene som presenteres i rapporten, viser at strategiene mot antibiotikaresistens har vært vellykkede både i husdyr-holdet og i helsevesenet. Det er imidlertid nødvendig med kontinuerlig innsats for å bevare den gunstige situasjonen slik at antibiotika også i fremtiden vil være effektive for de som trenger det. NORM/NORM-VET-rapporten er viktig for å dokumentere utviklingen av antibiotikaforbruk og resistens hos mennesker og dyr, og for å evaluere effekten av tiltak.

SUMMARY

This joint report from the surveillance programme for antimicrobial resistance in human pathogens (NORM) and the monitoring programme for antimicrobial resistance in bacteria from feed, food and animals (NORM-VET) presents data on the occurrence of antimicrobial resistance and the usage of antimicrobial agents in humans and animals for the year 2023. The NORM and NORM-VET programmes were established as part of the Norwegian Government's Action Plan against Antimicrobial Resistance issued in 2000. NORM is coordinated by the Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø. NORM-VET is coordinated by the Norwegian Veterinary Institute.

Usage of antimicrobial agents in animals

The total sales of antibacterial veterinary medicinal products (VMPs) for terrestrial animals in Norway were 4,479 kg antibacterial ingredients in 2023, which is 143 kg lower than in 2022 and the lowest annual level reported (data available since 1993).

Sales of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,107 kg in 2023. Penicillins continued to be the most-selling antibacterial class for the major species – i.e. cattle, pigs, goats, sheep and poultry - and were mostly accounted for by beta-lactamase sensitive penicillins. From 2013-2023, the estimated sales of antibacterial VMPs for cattle, pigs, sheep, goats and poultry declined by 31% when measured in kg and 27 % when measured in mg/PCU (population correction unit). For horses, the usage was mainly accounted for by trimethoprim-sulfa (oral paste).

The sales (kg) of antibacterial VMPs applicable for group treatment of terrestrial food-producing animals in Norway continued to be very low. In 2023, such products accounted for only 3.7% of the total sales.

In 2023, the sales (kg) of antibacterial VMPs for farmed fish (cleaner fish included) were 548 kg. This is a reduction of more than 99% compared to 1987, when the sales were at its highest. For Atlantic salmon and rainbow trout, fish in 3.3% of the on-grower locations were subjected to antibacterial treatment in 2023.

The sales (kg) of antibacterial VMPs marketed for companion animals were 372 kg in 2023. From 2013-2023 the sales of such VMPs for use in companion animals have been reduced by 30%. Prescriptions for dogs and cats of human antibacterial medicinal products reported to the Veterinary Prescription Register declined by 31% (in kg) from 2015 to 2023. This indicates that the decline in the sales of antibacterial VMPs for these species has not been substituted by prescribing of human products.

The European Medicines Agency (EMA) has suggested to restrict the use of some antibacterial classes in animals due to the potential risk to public health – i.e. 3rd and 4th generation cephalosporins, quinolones (fluoroquinolones and other quinolones) and polymyxins. In Norway, only quinolones are sold for use in food-producing terrestrial animals and farmed fish. The proportion sold of quinolones of the total sales of antibacterial VMPs was very low (0.9%) and was mainly accounted for by sales for use in farmed fish.

In February 2015, the Norwegian poultry industry launched a project aiming at phasing out use of narasin as coccidiostat feed additive in broilers, a goal that was reached in June 2016. The usage of therapeutic antibiotics for broilers continues to be very low; in 2023 two broiler flocks were subjected to such treatment.

Usage of antimicrobial agents in humans

In 2023, the total sales of antibacterial agents for systemic use in humans (J01 excl. methenamine) was 13.1 DDD (defined daily doses)/1,000 inhabitants/day. Since 2012 there has been a marked decline in total antibiotic use with a reduction of 23%. During the COVID-19 pandemic a significant reduction in the use of systemic antibiotics was observed, but consumption is now back to approximately the same level as before the pandemic.

Around 84% of the total human sales of antibacterials are used in primary care, i.e. outside hospitals and nursing homes. For ambulatory care, the most important antibiotic group in 2023 was penicillins, J01C; 41% of DDDs and 58% of prescriptions in ATC group J01, excl. methenamine, followed by tetracyclines, J01A (19% of DDDs and 9% of prescriptions). The six antibiotic substances most often prescribed for outpatients in 2023 were phenoxymethylpenicillin, pivmecillinam, methenamine, dicloxacillin, amoxicillin and doxycycline. These six antibiotics represented 72% of all prescriptions and 77% of all DDDs of the antibacterial group J01. In Norway, the main indication for narrow-spectrum penicillins in primary care is respiratory tract infections, of which phenoxymethylpenicillin is first choice. In 2023, phenoxymethylpenicillin was prescribed in 27% of the prescriptions representing 22% of DDDs. The urinary antiseptic methenamine represented 9% of J01 prescriptions and 27% of DDDs. In primary care, the use of antibiotics has increased since the COVID-19 pandemic, however, overall there has been a steady decrease in the last decade. This may be due to an increased attention towards antimicrobial resistance, both among the public and health personnel. A large proportion of general practitioners have completed quality improvement courses after the introduction of the Government's Action Plan against Antimicrobial Resistance (AMR) in 2016. Although a lot has been achieved there are probably still areas for improvement, e.g. in avoiding antibiotics for viral infections, choosing narrow-spectrum antibiotics where indicated, shorter duration of courses and individualisation of doses. One should expect that through effective antibiotic stewardship in primary care together with trustworthy and updated Guidelines it will be possible to keep the narrow-spectrum profile and achieve a further lowering of consumption rate.

In 2023, the antibacterial sales (in DDDs) to hospitals represented 7% of total sales of antibacterials for human use in the country. There has been a decrease of 3% in DDD/1,000 inhabitants/day since 2019 (i.e. before the pandemic) but an increase by 10% compared to 2021. In 2023, a mean use of 82 DDD/100 bed days was observed, an increase since 2019 and an increase by 20% since 2012.

In the same period DDD/admission increased by 5%. Therapy pattern of antibacterials in hospitals does not change much from one year to another but there is a clear trend towards more use of antibiotics recommended in Guidelines. The use of broad-spectrum antibiotics is reduced since 2012. They accounted for 20% in hospitals in 2023 compared to 26% in 2012 (measured in DDD/100 bed days). This favorable development can be explained by the creation of stable antibiotic stewardship programmes in hospitals and updated guidelines. Penicillins (J01C) accounts for around half of the use, measured in DDDs, in hospitals. The second largest group is the cephalosporins; 18% of all DDDs. There are large variations between the hospitals in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile. The variations cannot be accounted for by differences in activity or patient case mix alone.

Resistance in animal clinical isolates

The isolates included in 2023 were *Escherichia coli* and *Staphylococcus pseudintermedius* from clinical infections in dogs, and *Pasteurella multocida* and *Pasteurella canis* from clinical infections in various animal species.

About half (53.8%) of 65 *E. coli* isolates were fully susceptible to the antimicrobial classes in the test panel, while 15.4% were multi-drug resistant (MDR), i.e. resistance to three or more antimicrobial classes. Two of the isolates were identified as extended-spectrum cephalosporin (ESC)-resistant *E. coli*, one with mutations in the chromosomally located *ampC* gene and one genotyped as *bla*$_{\text{CMY-2}}$.

A total of 42.6% of 195 *S. pseudintermedius* isolates were fully susceptible to the antimicrobial classes when resistance to benzylpenicillin, gentamicin and sulfonamides were excluded from the calculations. MDR was detected in 21.5% of the isolates. Resistance to benzylpenicillin, deduced from detection of beta-lactamase production, was detected in 72.3% of the isolates. Fourteen (7.2%) of the isolates were methicillin resistant.

The majority of both *P. multocida* (89.5% of 143 isolates) and *P. canis* (85.5% of 62 isolates) were fully susceptible to the antimicrobial agents in the test panel. MDR was detected in only 0.7% of the *P. multocida*, and in none of the *P. canis*.

Resistance in indicator bacteria from animals and food

The 2023 data confirm that the situation regarding antimicrobial resistance in bacteria from animals and food in Norway is good. The occurrence of MDR, and specific emerging resistant bacteria/mechanisms, such as resistance to ESC, is low. Though, occurrence of MDR *E. faecium* in pigs has increased the last years. Carbapenemase-producing *Enterobacterales* (CPE) was for the first time detected from production animals (i.e. in caecal sample from cattle taken at slaughter) in 2023.

NORM-VET is following the requirements set in the Commission Implementing Decision 2020/1729/EU on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria. In addition, antimicrobial susceptibility testing of bacteria from sources other than those covered by this legal requirement are included. *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria, i.e. susceptibility testing of these bacteria is used as an indicator for the occurrence of antimicrobial resistance in the bacterial population. In addition, *Staphylococcus* spp. is included as an indicator for the occurrence of antimicrobial resistance in pets. Selective methods are used for detection of ESC-resistant *E. coli*, CPE, vancomycin resistant *Enterococcus* spp. (VRE), linezolid resistant *Enterococcus* spp. (LRE), methicillin resistant *S. aureus* (MRSA) and methicillin resistant *S. pseudintermedius* (MRSP). MRSA in the Norwegian pig population is investigated thoroughly through a separate specially designed surveillance programme aimed at identifying positive herds. The results from this separate MRSA programme are summarised in the NORM/NORM-VET report as well.

In 2023, animal samples included caecal samples from cattle and fattening pigs for susceptibility testing of *E. coli* and *Enterococcus* spp., and detection of emerging resistant bacteria/resistance mechanisms such as ESC-resistant *E. coli* and CPE. Faecal swab samples from dogs were also included for susceptibility testing of *E. coli*, and for detection of *E. coli* resistant to ESC and CPE. Oral/nasal/perineum swabs were included for isolation and susceptibility testing of *S. pseudintermedius* and selective isolation of MRSA and MRSP. Food samples consisted of beef and pork, and were used for detection of *E. coli* resistant to ESC and CPE.

In samples from cattle, a majority (93.7%) of the *E. coli* (n=271) was fully susceptible to the antimicrobial classes in the test panel, and only 0.8% were MDR. The proportion of fully susceptible *E. coli* isolates has been relatively stable over the last years (2015-2023). Full susceptibility to all antimicrobial classes included in the test panel was also present in one of the two *E. faecalis* isolates and seven of the 16 *E. faecium* isolates from cattle. None of the isolates were MDR. This is in concordance with the results from 2019 and 2021.

Also, from fattening pigs, a majority (84.6%) of the detected *E. coli* isolates (n=331) were fully susceptible to the antimicrobial agents in the test panel. Altogether, 1.2% of the isolates were MDR. The proportion of isolates being fully susceptible has been relatively stable between 80-90% over the years 2015 to 2023. The occurrence of resistance is higher in enterococci. Only 3.4% of the 61 *E. faecalis* and 38.4% of the 86 *E. faecium* isolates from fattening pigs were fully susceptible to the antimicrobial agents in the test panel. MDR was detected in 19.8% of the *E. faecium*. Compared to the results from 2019, there has been an increase in resistance to several antimicrobial classes, especially to ampicillin. This increase in ampicillin resistance has affected the occurrence of MDR *E. faecium* isolates, with an increase in MDR from 0.9% in 2019 to 21.3% and 19.8% in 2021 and 2023, respectively.

ESC-resistant *E. coli* were detected from 15 of the cattle (5.4%) and 66 of the fattening pig (19.8%) samples, and from four of the 283 pork samples (1.4%), and none of the 286 beef samples. Known mutations in the chromosomally located *ampC* gene were identified in twelve of the isolates from cattle, 56 of the isolates from fattening pigs and in the four isolates from pork. The remaining isolates were genotyped as *bla*$_{\text{CMY-2}}$ (i.e. three pig isolates), *bla*$_{\text{CTX-M-55}}$ (i.e. two cattle and one pig isolate), *bla*$_{\text{CTX-M-15}}$ (i.e. five pig isolates), *bla*$_{\text{OXA-1}}$ (i.e. one pig isolate), and the last isolate

displayed a CARBA phenotype and was genotyped as *bla*$_{NDM-5}$. This carbapenemase-producing *E. coli* was also detected by selective methods (0.4% of 277 cattle samples), and was the first finding of CPE in Norwegian production animals.

In faecal samples from dogs, the majority (72.9%) of the detected *E. coli* isolates (n=232) were fully susceptible to the antimicrobial agents in the test panel. MDR was detected in 4.3% of the isolates. There has been an increase in resistance to sulfamethoxazole from 5.8% in 2019 to 18.5% in 2023. Only one of the *E. coli* isolates displayed resistance to ESC and was genotyped as *bla*$_{CTX-M-15}$. A total of 14 (5.6%) out of 251 dogs were positive for ESC-resistant *E. coli* in the selective screening. Known mutations in the chromosomally located *ampC* gene were identified in seven of these, one was genotyped as *bla*$_{DHA-1}$, three as *bla*$_{CTX-M-15}$, and the last three as *bla*$_{CTX-M-1}$, *bla*$_{CTX-M-3}$, and *bla*$_{SHV-12}$, respectively. No CPE were detected from the dog samples.

A total of 40.5% of the 163 *S. pseudintermedius* isolates from 251 oral/nasal/perineum samples from dogs were fully susceptible to the antimicrobial classes when resistance to benzylpenicillin, gentamicin and sulfonamides was excluded from the calculations. MDR was detected in 16.0% of the isolates. Resistance to benzylpenicillin, deduced from detection of beta-lactamase production, was detected in 76.7% of the isolates. None of the isolates were methicillin resistant. By selective isolation methods, MRSP was detected from one sample and genotyped as *mecA*.

Resistance in zoonotic bacteria and non-zoonotic enteropathogenic bacteria

Animal and meat isolates

The Norwegian population of production animals is considered virtually free from *Salmonella* spp. In 2023, a total of 24 *Salmonella* spp. isolates from animals isolated through the Salmonella surveillance programme, the surveillance of wild boar, and from clinical submissions or necropsies were susceptibility tested (i.e. from eight wild boars, two dogs, three chicken, three pigs, three cattle, two horses, one cat, one pigeon and one hedgehog). One isolate was resistant to tetracyclines and ampicillin (*Salmonella* Typhimurium, monophasic (4,[5], 12 : i : -)). Additionally, eight *Salmonella* spp. isolates from non-domestic meat or other non-domestic food products obtained from submissions to the National Reference Laboratory for Salmonella were susceptibility tested. These isolates were all fully susceptible.

Campylobacter spp. from cattle and fattening pigs were also included. In total, 79.8% of the 124 tested *C. jejuni* isolates from cattle were susceptible to all antimicrobial agents included in the test panel. MDR was detected in 2.4% of the isolates. Among the 281 *C. coli* isolates from pigs, 79.0% were susceptible to all antimicrobial agents included in the test panel. MDR was detected in one (0.4%) isolate.

Human clinical enteropathogenic isolates

The National Reference Laboratory for Enteropathogenic bacteria (NRL) annually performs antimicrobial susceptibility testing for *Salmonella*, *Campylobacter*, *Yersinia* and *Shigella* isolates. 2020 onwards the NRL has screened all *Enterobacterales* isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance. In 2020 and 2021, during the COVID-19 pandemic, the government enforced infection control measures including travel restrictions that critically reduced travel associated infections. Trends in antibiotic resistance are interpreted accordingly.

For *Salmonella* Typhimurium and its monophasic variant, overall resistance levels were higher in strains with travel associated infections compared to domestically acquired infections. Multi-drug resistance (MDR) was a characteristic trait for a considerable number of monophasic *Salmonella* Typhimurium (84.2%). Nine isolates were characterised as ESBL producers and genotyped with *bla*$_{CTX-M}$ (n=8) and *bla*$_{DHA}$ (n=1) genes.

For *Campylobacter jejuni*, overall resistance levels for ciprofloxacin and tetracycline were higher in travel associated infections compared to domestically acquired cases. Antimicrobial resistance in *Yersinia enterocolitica* remains low. An increasing trend of resistance towards ciprofloxacin and extended-spectrum cephalosporins was observed in *Shigella sonnei* and *Shigella flexneri.* Twenty-nine and six ESBL producing strains were identified from *S. sonnei* and *S. flexneri* isolates, respectively, and characterised with *bla*$_{CTX-M}$ genes. A high proportion of *Shigella* strains were MDR (> 80%). Mutations in the *pmrB* gene associated with colistin resistance was identified in all *S. flexneri* isolates.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2023. *Staphylococcus aureus* and *Staphylococcus lugdunensis* from blood cultures and wound specimens were generally susceptible to all relevant antibiotics. Only 31 methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,695 strains included in NORM in 2023 (1.8%). The total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 2,196 including 39 MRSA strains (1.8%). This is a minor increase from 0.8% in 2021 and 1.0% in 2022. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 1,109 cases of MRSA infections in 2023. The majority of MRSA cases were reported as superficial wound infections and/or abscesses. The proportion of MRSA among non-invasive *S. aureus* isolates is still very low at 1.3% (12/898) and comparable to previous years (1.5% in 2021; 1.6% in 2022). Furthermore, MSIS registered 1,435 MRSA colonisations in 2023. A total of 2,544 persons were thus reported with MRSA in 2023 compared to 2,008 in 2022 (number adjusted from previous report). This corresponds to an incidence rate of 38 per 100,000 person-years compared to 32 in 2021 and 38 in 2022. The incidence of MRSA is now at the same level as before the COVID-19 pandemic (2,424 persons registered in 2016). The monthly number of MRSA infections has not changed significantly over the last eight years, and the incidence of invasive disease has remained stable at a low level. A large proportion of MRSA cases are still infected abroad (26%), but for many (43%) the location of acquisition was unknown. Very few cases of livestock-associated MRSA are detected in Norway.

The rates of resistance to broad-spectrum antimicrobials in *E. coli* blood culture isolates remained essentially unchanged in 2023. The prevalence of gentamicin resistance

was 5.4% in 2023 compared to 5.6% in 2021 and 5.1% in 2022, while the prevalence of ciprofloxacin resistance remained unchanged at 10.0%. *Klebsiella* spp. isolates demonstrate approximately the same rates of resistance to gentamicin (4.3%) and ciprofloxacin (8.1%) as *E. coli*. Extended-spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 129/2,240 (5.8%) *E. coli* and 57/1,028 (5.5%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2023. The prevalence is now stable for both *E. coli* (5.8% in 2021; 6.0% in 2022) and *Klebsiella* spp. (5.5% in both 2021 and 2022). The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (5.8%) than from the urinary tract (3.9%). Carbapenemase-producing *Enterobacterales* (CPE), *P. aeruginosa* and *Acinetobacter* spp. have been notifiable to MSIS since 2012. The number of CPE patients increased sharply from 60 in 2021 to 152 in 2022, and the tendency continued in 2023 with 237 reported cases. The number of notifications with carbapenemase-producing *P. aeruginosa* (n=27) and *Acinetobacter* spp. (n=31) also increased from n=18 and n=30 in 2022, respectively. Many multi-drug resistant Gram-negative isolates were imported from countries with high prevalences of these organisms. As in 2022, isolates from hospital patients transferred from Ukraine represented a significant proportion of the total number in 2023. *P. aeruginosa* and *Acinetobacter* spp. blood culture isolates from the general population were mostly susceptible to all relevant antimicrobials.

The numbers of *Haemophilus influenzae* and *Neisseria meningitidis* isolates from blood cultures and cerebrospinal fluids were stable from 2022 to 2023, but still at historically low levels in the aftermath of the COVID-19 pandemic. The proportion of systemic *H. influenzae* isolates demonstrating beta-lactamase production increased from 10.8% in 2022 to 15.7 % in 2023, but this may be due to random variation. The frequency of chromosomally encoded beta-lactam resistance (10.7%) did not change. The number of *Neisseria gonorrhoeae* isolates increased sharply from 220 in 2021 to 830 in 2022 and now 1,500 in 2023, and the number of clinical cases reported to MSIS continued to increase from 1,857 in 2022 to 2,985 in 2023. Many isolates displayed resistance to penicillin G (15.7%), and only 4.2% were susceptible to standard penicillin G dosage corresponding to the wild type population. Ciprofloxacin resistance was detected in 51.3% of isolates. Two isolates (0.1%) were resistant to ceftriaxone and the oral cephalosporin cefixime. All isolates were susceptible to spectinomycin.

Two enterococcal blood culture isolates with clinically relevant vancomycin resistance (VRE) were detected in 2023 (one *vanA* and one *vanB E. faecium*). The prevalence of ampicillin resistance in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) was essentially unchanged in both *E. faecalis* (6.9% in 2022; 6.4% in 2023) and *E. faecium* (44.3% in 2022; 50.6% in 2023). Almost all HLGR *E. faecium* isolates were also resistant to ampicillin. There were four genetically confirmed linezolid resistant isolates (LRE) in the NORM surveillance programme in 2023 (all *E. faecium*). Both VRE and LRE should be reported to the national notification system (MSIS), and 89 VRE (34 in 2021; 74 in 2022) and 66 LRE (16 in 2021; 38 in 2022) were verified at the National Reference Laboratory at K-res/UNN in 2023. Four of these isolates were resistant to both vancomycin and linezolid. The prevalence of VRE varies over time due to outbreaks, but has apparently returned to the pre-pandemic level. There has been an increasing number of patients reported with LRE, but this may in part be due to increased diagnostic vigilance.

Surveillance of resistance in *Streptococcus pneumoniae* (pneumococci) revealed that only 0.3% of isolates from blood cultures and cerebrospinal fluids, and none from respiratory tract specimens, were resistant to penicillin G. However, 7.9% (9.7% in 2022) and 15.0% (8.3% in 2020) would require increased exposure to be susceptible to this agent, respectively. Four blood culture isolates (0.7%) and two isolates from the respiratory tract (1.1%) displayed reduced susceptibility to one or more 3rd generation cephalosporins. The prevalence of macrolide resistance in systemic isolates was 6.5% in 2023 compared to 4.6% in 2022. Among respiratory tract isolates, 10.0% were erythromycin resistant (9.8% in 2020). All *S. pyogenes* (beta-haemolytic group A streptococci) blood culture isolates were susceptible to penicillin G, and the rate of erthromycin resistance (6.5%) was unchanged from 2022. Systemic *Streptococcus agalactiae* isolates (beta-haemolytic group B streptococci) isolates were also susceptible to penicillin G, but often resistant to erythromycin (21.2% in 2022; 22.7% in 2023) and tetracycline (74.6% in 2022; 72.0% in 2023).

A total of 152 patients with tuberculosis were reported to MSIS in 2023. Fifteen isolates (11.8%) were defined as multi-drug resistant (MDR) to both rifampicin and isoniazid compared to 7.2% in 2022. The patients had acquired their infections in Europe outside Norway (n=12), Asia (n=2) and Africa (n=1).

Susceptibility testing was performed on 250 *Candida* spp. blood culture isolates from 226 unique patients. The most common species were *C. albicans* (n=134), *C. glabrata* (n=39), *C. parapsilosis* complex (n=25), *C. tropicalis* (n=14) and *C. dubliniensis* (n=11). All *C. albicans* were susceptible to the substances examined with the exception of two echinocandin resistant isolates and one isolate with reduced susceptibility to fluconazole. Only single non-*albicans* isolates with acquired resistance were detected, but as expected there was a high prevalence of resistance to azoles among *C. glabrata* (12.8%). Precise species identification is essential to predict inherent resistance and select appropriate antifungal therapy. The results are in accordance with previous data from Norway.

Conclusion

Antimicrobial resistance is still a limited problem among humans and food-producing animals in Norway. This reflects the low usage of antibacterial agents in human and veterinary medicine, a favourable usage pattern, as well as effective infection control measures. The data presented in this report show that strategies for containment of antimicrobial resistance have been successful both in the food-producing animal sector and in the healthcare sector. Continuous efforts and awareness rising are needed to preserve the favourable situation and ensure that antimicrobials are effective when needed. The NORM/ NORM-VET report is vital in order to document the trends in antibiotic usage and occurrence of resistance in humans and animals, and to evaluate the effectiveness of interventions.

POPULATION STATISTICS

Population statistics for human and animal populations are presented in order to facilitate comparison of Norwegian data with corresponding figures from other countries. The data are collected by Norwegian authorities as shown in the various tables below.

TABLE 1. Human population in Norway as of 21.02.2024. Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	276,076	141,450	134,626
5 to 14 years	635,052	326,531	308,521
15 to 24 years	668,032	343,655	324,377
25 to 44 years	1,511,886	772,367	739,519
45 to 64 years	1,422,989	724,159	698,830
65 years and older	1,036,168	487,556	548,612
All age groups	5,550,203	2,795,718	2,754,485

TABLE 2. Livestock population in Norway in 2023. Data provided by the Register of Production Subsidies as of 31.03.2023.

	Number* of	
Animal category	Herds	Animals
Cattle	12 300	886 000
Dairy cows only**	6 500	203 000
Suckling cow only**	6 000	109 000
Combined production (cow)**	1 100	
Goats	1 600	76 300
Dairy goats**	260	34 600
Sheep	13 200	915 000
Breeding sheep > 1 year**	13 200	915 000
Swine	1 600	710,800
Breeding animal > 6 months**	800	38,300
Fattening pigs for slaughter**	1 200	360,000
Laying hen flocks > 50 birds	590[1]	4,100,000
Broilers	556[1]	76,500,000[2]
Turkey, ducks, geese for slaughter (flock > 250 birds)	61[1]	1,380,7002

*Numbers > 100 rounded to the nearest ten, numbers > 1,000 rounded to the nearest hundred. **Included in above total. [1]Included in the official surveillance programme of *Salmonella*, [2]Figures from the Norwegian Agriculture Agency (based on delivery for slaughter).

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2023. Data provided by the Norwegian Directorate of Fisheries updated by 12.06.2023.

Year	Atlantic salmon (tonnes)	Rainbow trout (tonnes)	Cod (tonnes)	Arctic char (tonnes[2])	Halibut (tonnes[2])	Blue mussels (tonnes)	Scallops[1] (tonnes)	Oysters (tonnes)
1992	141,000	-	-	-	-	-	-	-
1993	170,000	-	-	-	-	-	-	-
1994	204,686	14,571	569	262	63	542	-	-
1995	261,522	14,704	284	273	134	388	-	-
1996	297,557	22,966	191	221	138	184	-	-
1997	332,581	33,295	304	350	113	502	-	-
1998	361,879	48,431	203	200	291	309	-	-
1999	425,154	48,692	147	498	451	662	67	41
2000	440,061	48,778	169	129	548	851	38	8
2001	435,119	71,764	864	318	377	920	22	3
2002	462,495	83,560	1,258	319	424	2,557	5	2
2003	509,544	68,931	2,185	272	426	1,829	1	2
2004	563,915	63,401	3,165	365	648	3,747	46	3
2005	586,512	58,875	7,409	352	1,197	4,885	3	2
2006	629,888	62,702	11,087	897	1,185	3,714	4	1
2007	744,222	77,381	11,104	394	2,308	3,165	6	4
2008	737,694	85,176	18,052	468	1,587	2,035	4	3
2009	862,908	73,990	20,924	421	1,568	1,649	7.7	3.8
2010	939,575	54,451	21,240	492	1,610	1,930	10.3	2.1
2011	1,064,868	58,472	15,273	276	2,767	1,743	13	2
2012	1,241,482	70,364	10,033	309	1,741	1,967	21	2
2013	1,168,324	71,449	3,770	281	1,385	2,328	23	5
2014	1,258,356	68,910	1,213	285	1,257	1,983	13	4
2015	1,303,346	72,921	5	257	1,243	2,731	21	10
2016	1,233,619	87,446	0	330	1,461	2,231	12	11
2017	1,236,353	66,902	117	339	1,623	2,383	29	17
2018	1,282,003	68,216	495	285	1,843	1,649	28	18
2019	1,364,042	83,290	896	515	1,524	2,134	12	10
2020	1,388,434	96,132	662	502	1,870	2,033	11	20
2021	1,562,415	94,660	1,622	501	2,716	2,163	13	15
2022	1,564,948	85,223	5,116	638	2.291	2,612	18	16
2023[3]	1,517,516	86,338	*	*	*	2,112[4]		

[1]From the wild population. [2]After 2001 in numbers of 1,000 individuals. [3]Preliminary numbers. [4]Includes Scallops and Oysters. *After 2022, specific statistic per species not available.

Import of live animals

Import of live animals (excluding fish and companion animals) to Norway in 2023 was one camelide and 20, 786 day old chicks of chicken, guinea fowl, turkey and duck, according to the yearly report from KOORIMP and KIF; https://www.animalia.no/no/Dyr/koorimp---import/arsmeldinger-koorimp-og-kif/

USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

Kari Olli Helgesen and Kari Grave

Sales data for the years 1993-2023 for antibacterial veterinary medicinal products (VMP) for terrestrial animal species obtained at wholesaler's level, have been stratified into sales of antibacterial VMPs approved for terrestrial food-producing animals including horses, and those approved solely for companion animals, respectively (see Appendix 1). The data are based on sales to Norwegian pharmacies from medicine wholesalers of VMPs. This includes all pharmaceutical formulations approved for food-producing terrestrial animals, including horses, and for companion animals as well as VMPs used on special permit (products approved in another European Economic Area (EEA) country). In addition, data obtained from the Veterinary Prescription Register (VetReg) have been used for some data analyses, including for supplementary information (see Appendix 1). Calculation of kg active substance per VMP presentation follows the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) protocol (see Appendix 1).

Usage of antibacterial agents

Overall, the sales in Norway of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals, including horses, and companion animals in 2023 were 4,479 kg. A decline of the annual sales (kg) of such VMPs of 51% in the period 1993-2023 is observed (Figure 1).

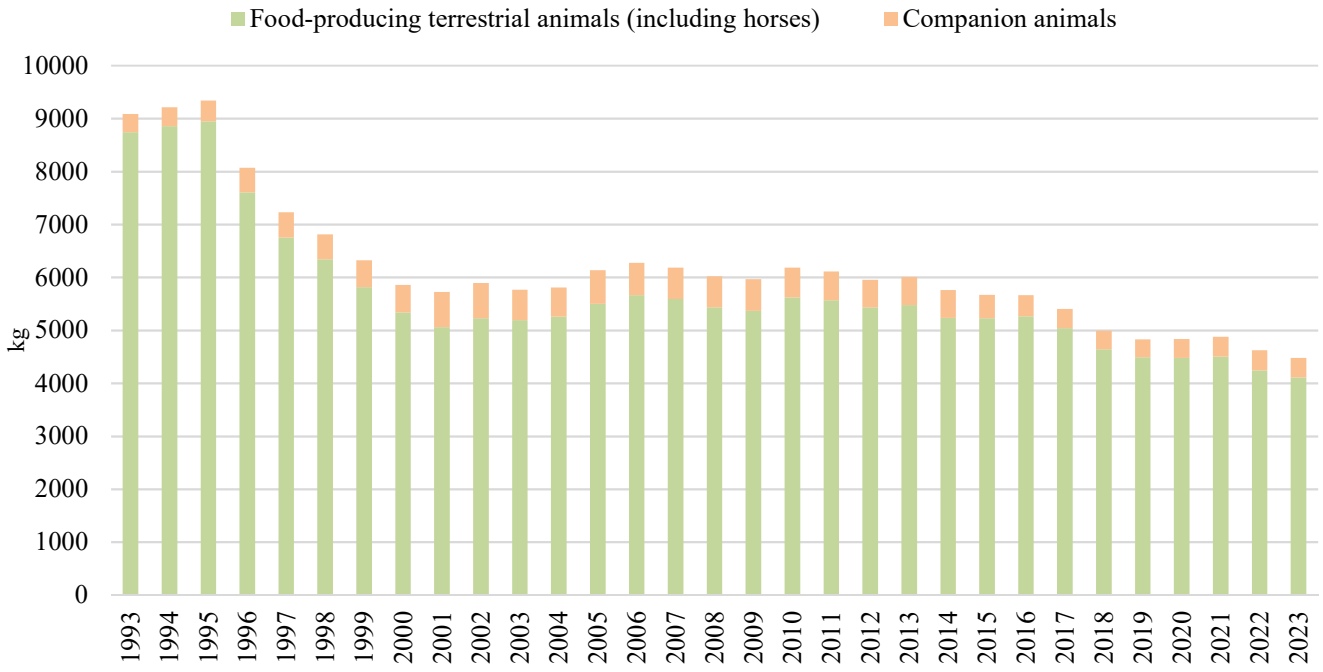

FIGURE 1. Total sales, in kg active substance, for food-producing terrestrial animals (including horses) and companion animals, of antibacterial veterinary medicinal products for therapeutic use in Norway in 1993-2023.

Food-producing terrestrial animals, including horses

In 2023 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,107 kg. Compared to 1993, a decrease in the sales of such VMPs of 53% is observed (Figure 2). In total, 63% of the sales (kg) of antibacterial VMPs for this animal category in 2023 contained penicillins only, of which 95% were beta-lactamase sensitive penicillins. Of the total sales for use in terrestrial food-producing animals in 2023, 28% were sold as orale paste containing trimethoprim+sulfa marketed for horses.

The proportion of sales of VMPs containing only penicillins for terrestrial food-producing animals increased from 18% to 63% during the period 1993-2023. This is mainly due to reduced sales of injectable and intra-mammary combination VMPs of penicillins and an aminoglycoside (dihydrostreptomycin) that have been gradually replaced by VMPs containing penicillins as the sole antibacterial agents.

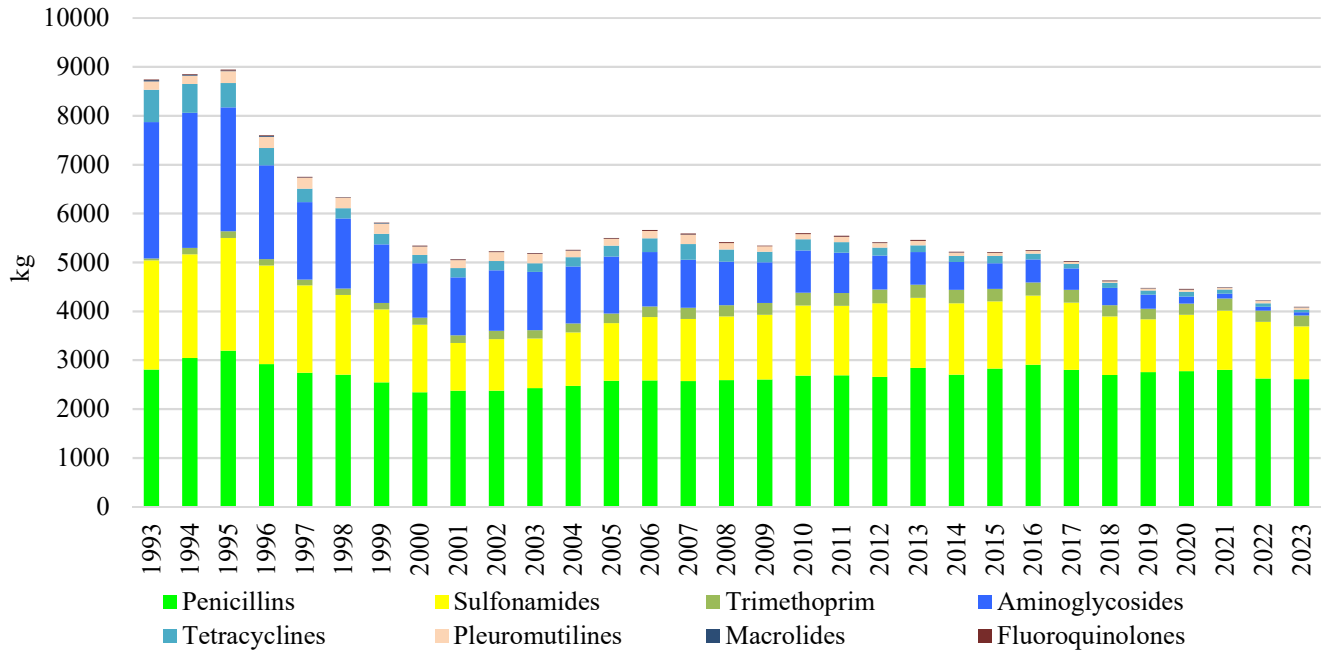

FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals (including horses) in Norway 1993-2023. In addition, minor sales of baquiloprim 1994-2000 (range 0.2-1.8 kg), 3rd generation cephalosporines 2012-2023 (range 0.001-0.07 kg), and amphenicols 2008-2023 (range 16-27 kg).

Of the antibacterials for which restriction of use in animals is recommend at EU/EEA level due to potential public health risks – i.e. 3rd and 4th generation cephalosporins, polymyxins and quinolones (fluroquinolones and other quinolones) (1, 2), only fluoroquinolones are marketed in Norway for food-producing terrestrial animals. From 1993 to 2023, the proportion of sales of fluoroquinolones for food-producing terrestrial animals has been very low and stable varying between 0.1% and 0.3% of the total sales (see also Figures 4, 5 and 6). During 1993-2023 no VMPs containing 3rd and higher generation cephalosporins have been approved for food-producing animals in Norway via national procedures. Several 3rd generation cephalosporin VMPs have been approved via community procedures, but they are not marketed in Norway. Applications for special permits to use such VMPs marketed in other EEA countries for food-producing animals are normally not approved, and approval would only be given for specific animals if sensitivity testing precludes all other options. This is also the case for polymyxins (Knud Torjesen, Norwegian Medicines Agency, personal communication). Glycopeptides and carbapenems are not allowed for food-producing animals in EU/EEA countries.

In Norway, sales of antibacterial VMPs for treatment of food-producing terrestrial animals are dominated by pharmaceutical forms for treatment of individual animals (Figure 3) and primarily by injectables. This reflects that the livestock is characterised by small herds, but it can also partly be explained by type of infections and therapeutic traditions. In 2023, only 3.7% of the sales of antibiotic VMPs for food-producing terrestrial animals were for VMPs applicable for group treatment (oral treatment).

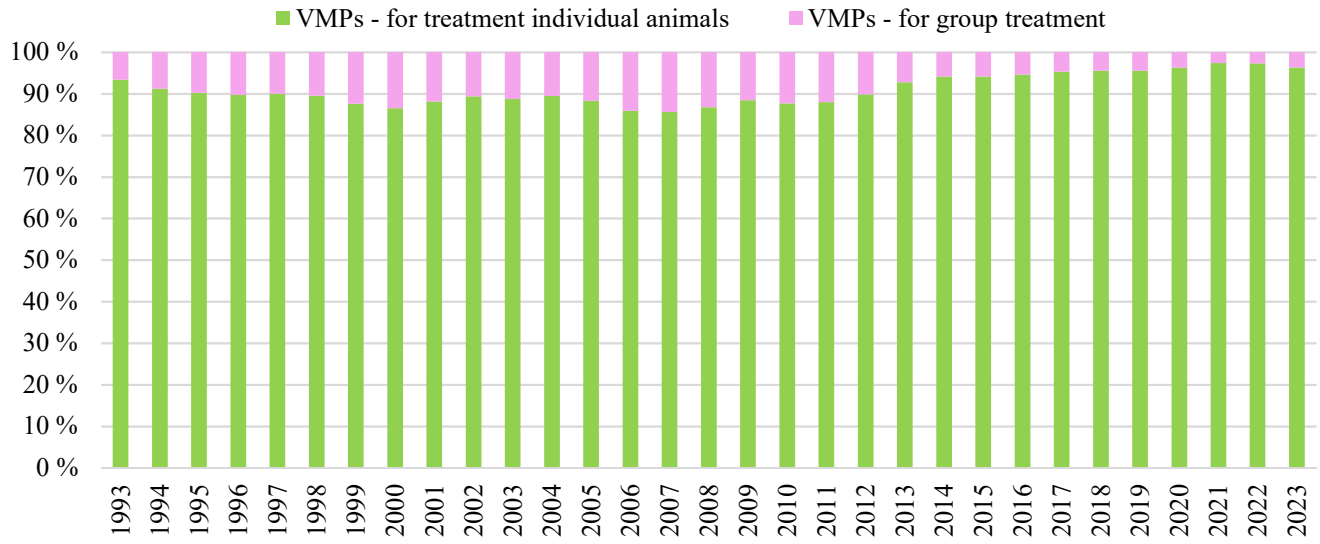

FIGURE 3. Proportion of sales in Norway (in kg active substance), of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals, including horses (bolus, injectables, intramammary preparations, intrauterine preparations, oral paste and some tablet VMP presentations – see Appendix 1) and applicable for group treatment through feed or drinking water (oral solution and oral powder. No premixes were sold for terrestrial food-producing animals).

Usage patterns - major terrestrial food-producing animals (VetReg data)

The usage patterns presented represent the data reported to VetReg (see Appendix 1) for 2023. The data were extracted from the VetReg database 15 March 2024. Of the reported amounts (kg) of antibacterial VMPs for cattle, pigs, sheep and goats, 0.5% was for goats and therefore data for this animal species are not presented. Of the amounts antibacterial VMPs and human medicinal products reported to VetReg for which EMA advice restriction of the use due to potential public health risks, the proportions accounted for by cattle, pigs and sheep were 0.2%, 0.1% and 0.03%, respectively, and only fluoroquinolones were used (Figure 4, 5 and 6).

Cattle

Of the prescriptions (VetReg data) of antibacterial veterinary and human medicinal products for cattle in 2023, 90.8% were for penicillins (kg active substance); 87.9% were for beta-lactamase sensitive penicillins (Figure 4).

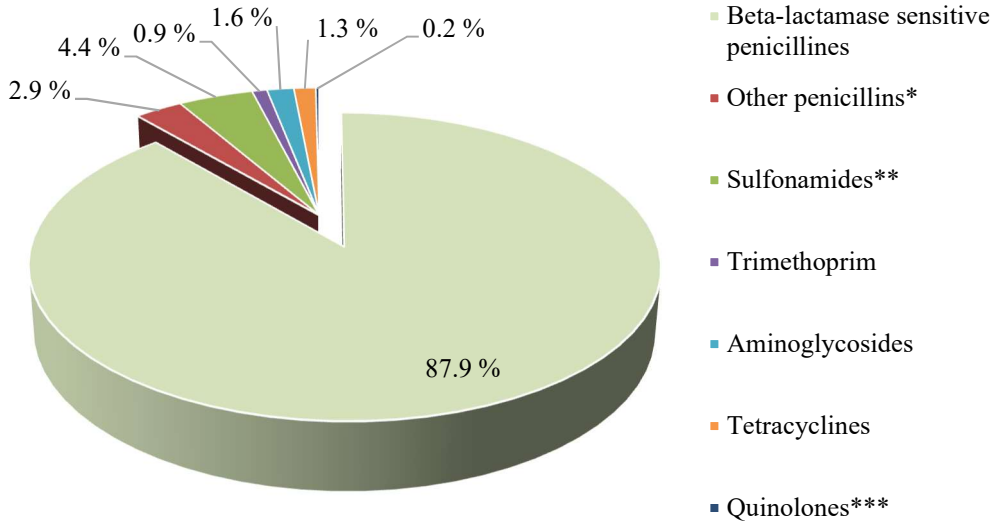

FIGURE 4. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for cattle in Norway in 2023. Data were obtained from the Veterinary Prescription Register (products for topical treatment not included in data in the figure). *Penicillins with extended-spectrum and beta-lactamase resistant penicillins. **In combination with trimethoprim only. ***Fluoroquinolones only. In addition, 0.8% of the prescribed amounts were for amphenicols, 1st generation cephalosporins, lincosamides and macrolides.

Pigs

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of pigs in 2023 (Figure 5), 90.0% of the total amount reported to VetReg was penicillins; 85.3% was for beta-lactamase sensitive penicillins only and this proportion has increased from 65% in 2016.

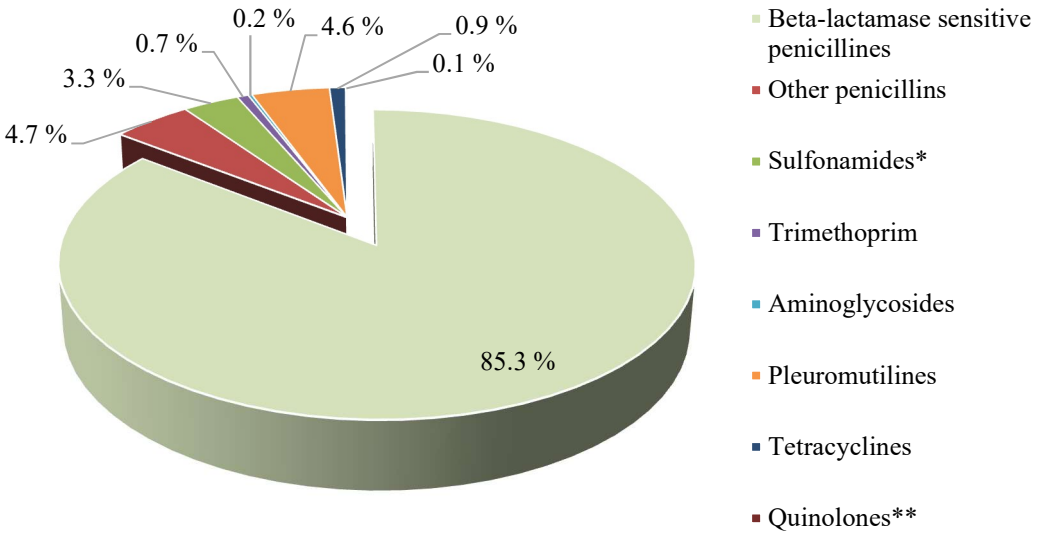

FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for pigs in Norway in 2023 (preparations for topical treatment not included in the figure). Data are obtained from the Veterinary Prescription Register. *In combination with trimethoprim only. **Fluoroquinolones only. In addition, 0.2% of the prescribed amounts were for macrolides.

Sheep

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of sheep (Figure 6), 85.8% of the toal amount reported to VetReg was penicillins; 84.3% was for beta-lactamase sensitive penicillins only and this proportion has increased gradually from 69.8% in 2016.

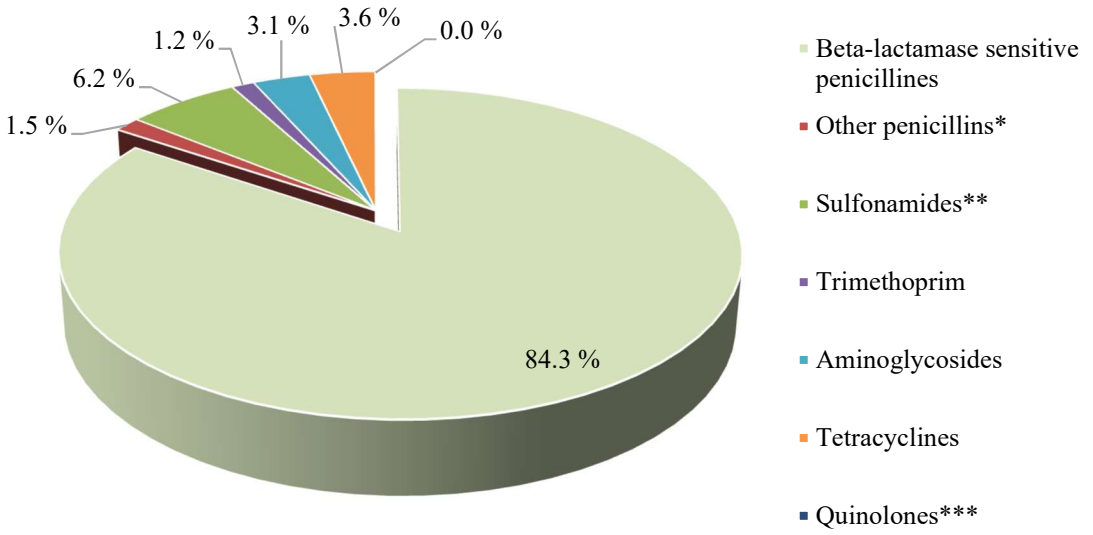

FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for sheep in Norway in 2023. Data are obtained from the Veterinary Prescription Register (preparations for topical treatment not included in the figure). *In combination with trimethoprim only. **Fluoroquinolones only. In addition, 0.02% of kg active substance prescribed was for amphenicols, lincosamides and macrolides.

Farmed fish

In 2023, the total amounts of antibacterials prescribed for use in aquaculture in Norway was 548 kg (Table 4); of this 0.4 kg were prescribed for use in cleaner fish. Of the antibacterials for which restriction of use in animals is recommend at EU/EEA level, adviced due to potential public health risk (1, 2), only "other quinolones" are used for farmed fish. From 2015 to 2023, the proportion of sales of quinolones has fluctuated; in 2023 this proportion was 5.8% (32 kg) (Table 4).

TABLE 4. Use, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2015-2023. Data represent prescription data obtained from the Veterinary Prescription Register (see Appendix 1). Note that data include antibacterials for use in cleaner fish[1,2].

Active substance	2015	2016	2017	2018	2019	2020	2021	2022	2023
Tetracyclines									
Oxytetracycline	0	0	0	20	0	0.16	0	0	0
Amphenicols									
Florfenicol	183	134	264	857	152	113	531	397	516
Quinolones									
Flumequine	0	0	0	0	0	0	0	0	0
Oxolinic acid	84	66	343	54	66	107	57	28	32
Enrofloxacin	0.02	0.050	0.01		0.01	0.12	0.44	0.10	0.05
Total	**267**	**199**	**607**	**930**	**218**	**220**	**588**	**425**	**548**

[1]The total amounts (kg) given may be deviating due to rounding of each single value. [2] Differences in the figures for the years 2015-2022 compared to the 2022 NORM-VET report are due to updated calculation of the amounts prescribed for one florfenicol and one oxytetracycline medicinal product (range 1-8 kg lower).

From 2013 to 2021 the major proportion of prescriptions was for fish in the pre-ongrowing phase. However, in 2022 and 2023 this trend discontinued; the proportion of prescriptions for fish in the ongrower phase was 63% and 74%, respectively (Figure 7). The number of prescriptions of antibacterial VMPs for Atlantic salmon ongrowers were, however, low during the period 2015-2023 (range 5-29 prescriptions), considering that Atlantic salmon production in this period varied between 1.3 and 1.7 million tonnes per year. This is a strong indication that the vaccines used in Atlantic salmon are efficient and that the coverage of vaccination of fingerlings is very high.

A considerable increase in the number of treatments for marine species in the "ongrowing" category in both 2022 and 2023 is observed (Figure 7); from 13 in 2021 to 32 and 55 in 2022 and 2023, respectively. Of the 55 prescriptions for this production stage in 2023, 46 were for the treatment of halibut. The total consumption, in kilograms, of antibacterial agents for marine species was only 55 kg of the total consumption of 548 kg.

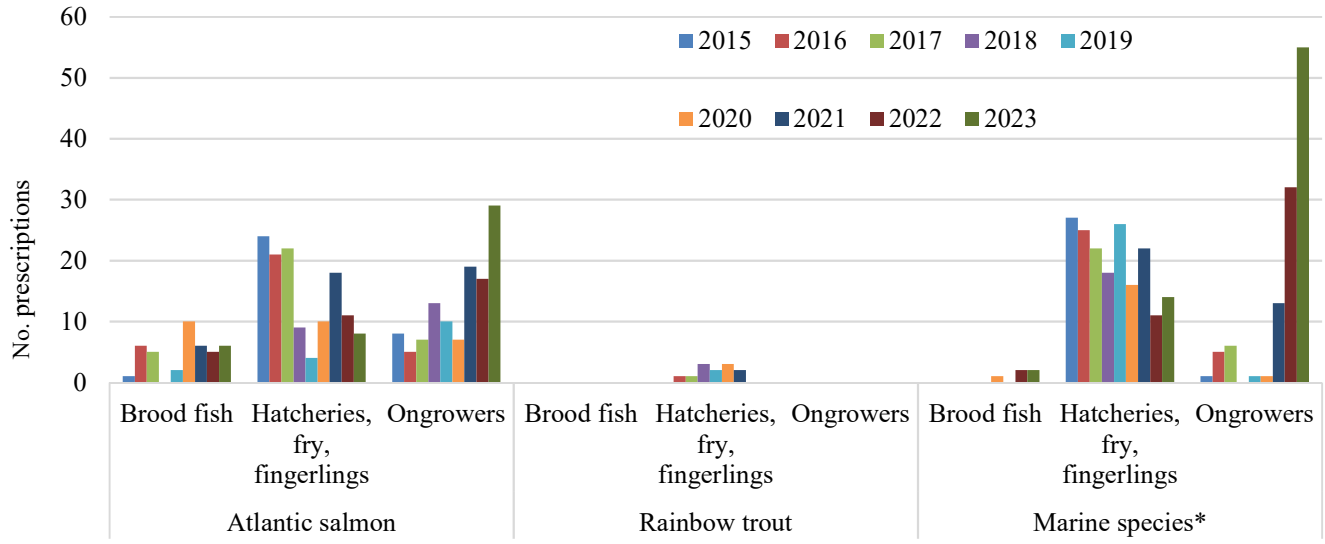

FIGURE 7. Number of prescriptions of antibiotics by fish species, split into production stages/types, in Norway in 2015-2023. Data were obtained from the Veterinary Prescription Register. *Arctic char, cod, halibut, pollack and/or wolffish. Note that cleaner fish are not included.

The annual sales of antibacterial VMPs for use in aquaculture peaked in 1987 when it amounted to 48 tonnes (Figure 8) – i.e. 876 mg/PCU. The corresponding figure in 2023 was 0.34 mg/PCU. Thus, the sales in mg/population correction unit (PCU) have declined by 99.9% (Table 4).

The significant decrease in the usage of antibacterial agents in Norwegian aquaculture from 1987 is mainly attributed to the introduction of effective vaccines against bacterial diseases in Atlantic salmon and rainbow trout, but also prevention of bacterial diseases and their spread.

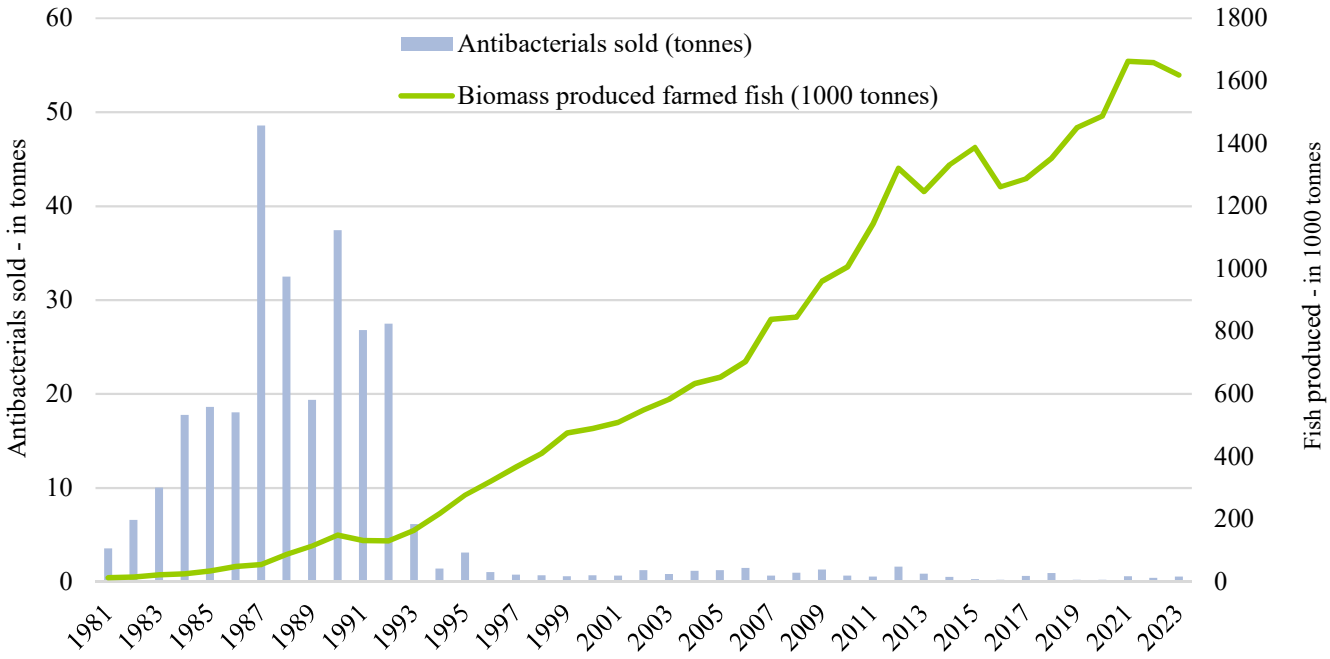

FIGURE 8. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish (including cleaner fish) in Norway in 1981-2023 versus tonnes produced (slaughtered) farmed fish. For the years 1981-2012 the data represent sales data provided by the Norwegian Institute of Public Health; for 2013-2023 data represent prescription data obtained from the Veterinary Prescription Register. Data on slaughtered biomass farmed fish (Atlantic salmon, rainbow trout, other salmonid and marine species) were obtained from the Norwegian Directorate of Fisheries (Akvakultur-statistikk på www.fiskeridir.no).

In a report from 2018 (3) it was shown that only a low percentage of Atlantic salmon and rainbow trout in the ongrower phase were subjected to treatment with antibiotics (range 0.6-1.4%). This was also the case for the years 2018-2023; these figures were 1.6%, 1.2%, 0.8%, 2.2%, 1.9% and 3.3%, respectively.

Companion animals (dogs and cats)

The sales in 2023 of antibacterial VMPs approved solely for companion animals (includes VMPs formulated as tablets, oral solution, injectable and oral paste) were 372 kg; in 2022 this figure was 382 kg. As shown in Figure 9, a steady increase in the sales from 1993 to 2001 was observed. This can in part be explained by an increase in the availability of antibacterial VMPs marketed for dogs and cats during that period. When the availability of VMPs for dogs and cats was lower, it is likely that antibacterial human medicinal products (HMPs) were prescribed for dogs and cats. In 1993, only eight antibacterial VMP presentations (name, pharmaceutical form, strength and pack size) were approved in Norway for dogs and cats only, while in 2023 the corresponding number was 35.

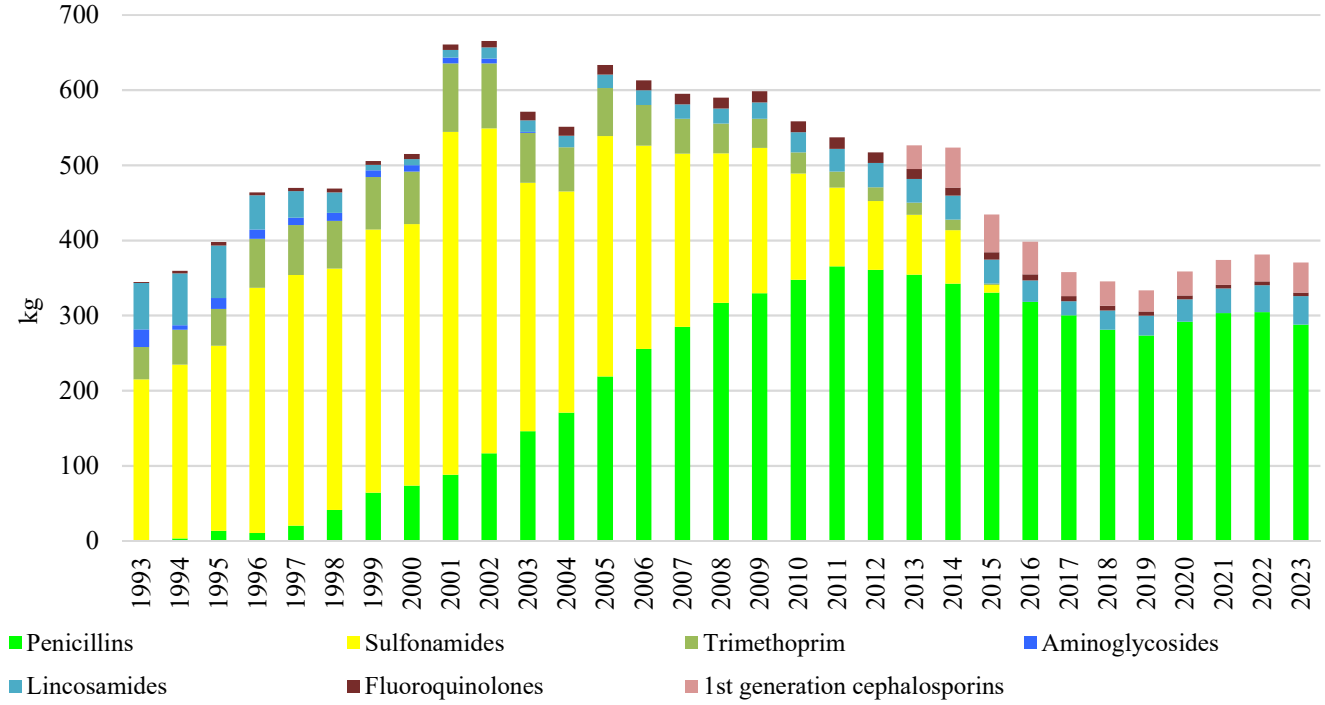

FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables, oral paste, oral solution and tablets; note the exceptions for tablets: see Appendix 1) in Norway for the period 1993-2023. Minor annual sales of a 3rd generation cephalosporin injectable VMP (range 0.3-1.1 kg) during 2008-2023 and of macrolide VMPs (0.4-5 kg) during 1996-2003 were observed.

The sales patterns of antibacterial VMPs marketed solely for companion animals (dogs and cats) have changed significantly during the period 1993-2023 (Figure 9). The first penicillin VMP as tablets – i.e. amoxicillin (an aminopenicillin) was marketed for dogs and cats in 1994. Since then the proportion belonging to the penicillins (only aminopenicillin VMPs marketed) sold of total sales of antibacterial VMPs approved for such animals has increased from 1% to 81% (Figure 9). Among penicillin VMPs, amoxicillin combined with clavulanic acid accounted for 81% of the sales in 2023 (Figure 10).

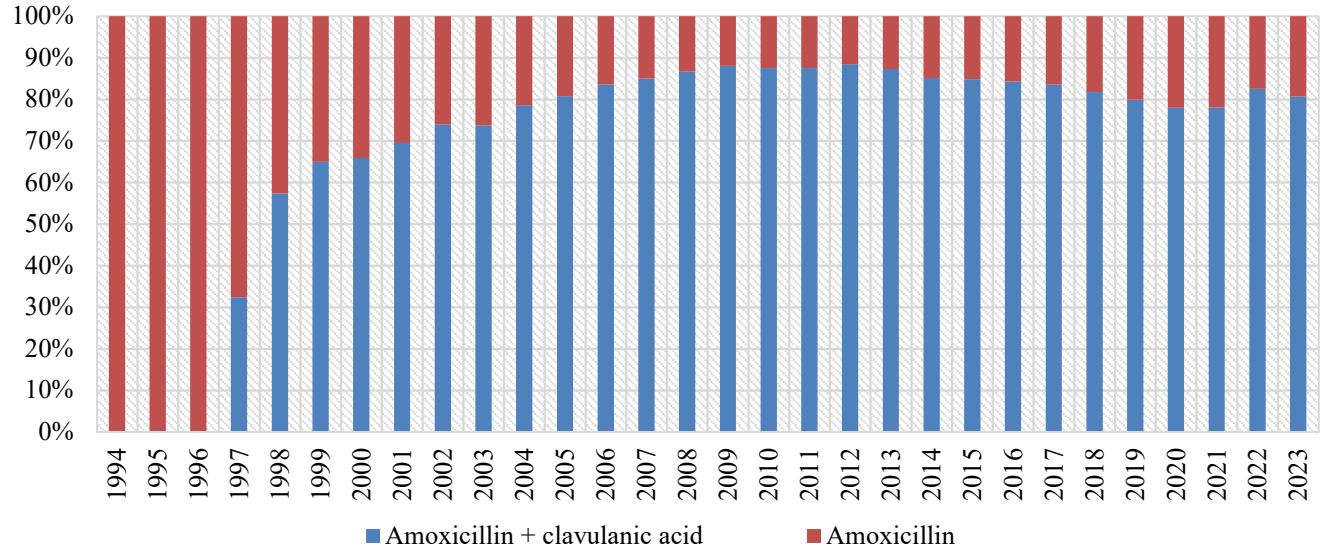

FIGURE 10. Proportions of sales (in kg active substance), of VMPs with amoxicillin combined with clavulanic acid versus amoxicillin for dogs and cats in Norway during 1994-2023.

From 1993 to 2023 the proportion of sales of fluoroquinolones has been very low, accounting for 0.5% of the total sales for this animal category in 1993 increasing marginally to 2.8% in 2011 and since then this proportion has decreased slighly to 1.3% in 2023 (Figure 9; Figure 11).

The proportion of the total sales for dogs and cats of 3rd generation cephalosporins has been low since such VMPs were marketed in Norway in 2008; this figure was 0.2% in 2008 and 0.1% in 2023 (Figure 11).

Antibacterials for which use in animals is adviced to be restricted

In 2019, the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency (EMA) published a categorisation (1, 2) of antibiotics for use in animals for prudent and responsible use at EU/EEA level. For certain classes – i.e. quinolones (fluoroquinolones and other quinolones), 3rd- and 4th generation cephalosporins and polymyxins - it is advised that the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. Figure 11 shows the amounts sold, in kg of the antibacterials, belonging to the categories for which AMEG advices to restrict the use of compared to the total sales of antibacterial VMPs, stratified by animal categories. In total, 0.9% of the total sales of antibacterial VMPs in 2023 belonged to the AMEG category that EMA has adviced to restrict the use of, and this was primarily accounted for by use in farmed fish. Of note is that apart from two VMPs for local ear treatment, other pharmaceutical forms of VMPs containing polymyxins are not marketed in Norway.

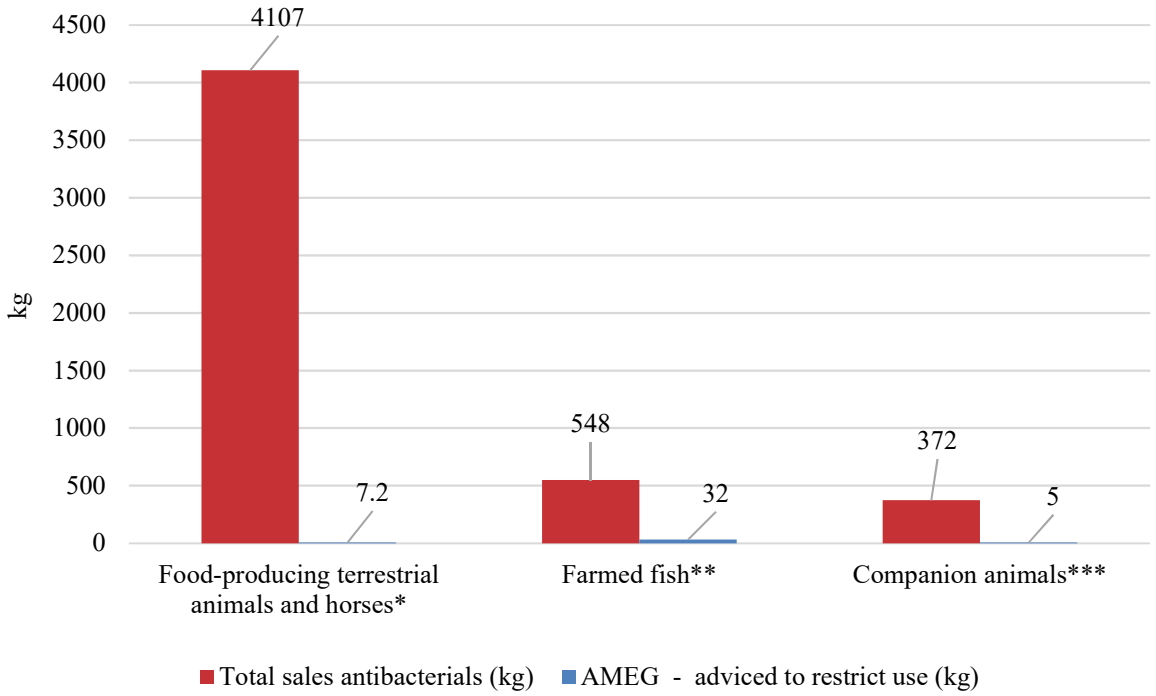

FIGURE 11. Total sales and sales of antibacterial veterinary medicinal products (VMPs) in 2023, for which the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency advises to restrict the use, stratified by animal category (1, 2). Of note – VMPs for topical treatment are not included. *Fluoroquinolones. **Other quinolones. ***3rd generation cephalosporins and fluoroquinolones.

References

1. EMA/CVMP/CHMP/682198/2017. Categorisation of antibiotics in the European Union. Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals. EMA, 2019 (https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf).
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3. Kari Grave and Kari Olli Helgesen. Antibacterials for farmed fish – prescribing, usage and diagnoses 2013-2017 (In Norwegian: Antibakterielle midler til oppdrettsfisk – rekvirering, forbruk og diagnose 2013-2017). Rapport 5: Veterinærinstituttet, 2018.

National Strategy against Antibiotic Resistance
Targets for reduction of antibiotic usage in animals and farmed fish – Changes according to targets

Previous targets for food-producing terrestrial animals

In 1996, the Norwegian livestock industry set a target for reduction of the usage of antibacterial VMPs, in weight of active substance, by 25% within five years with 1995 as the reference year. This target was reached already after two-three years (Figure 12). After five years the observed reduction was 40% and up to 2012 the usage for this animal category remained approximately on the same level – i.e. on average the sales for the period 1999-2012 was 39% lower than in 1995 (Figure 2, Figure 12).

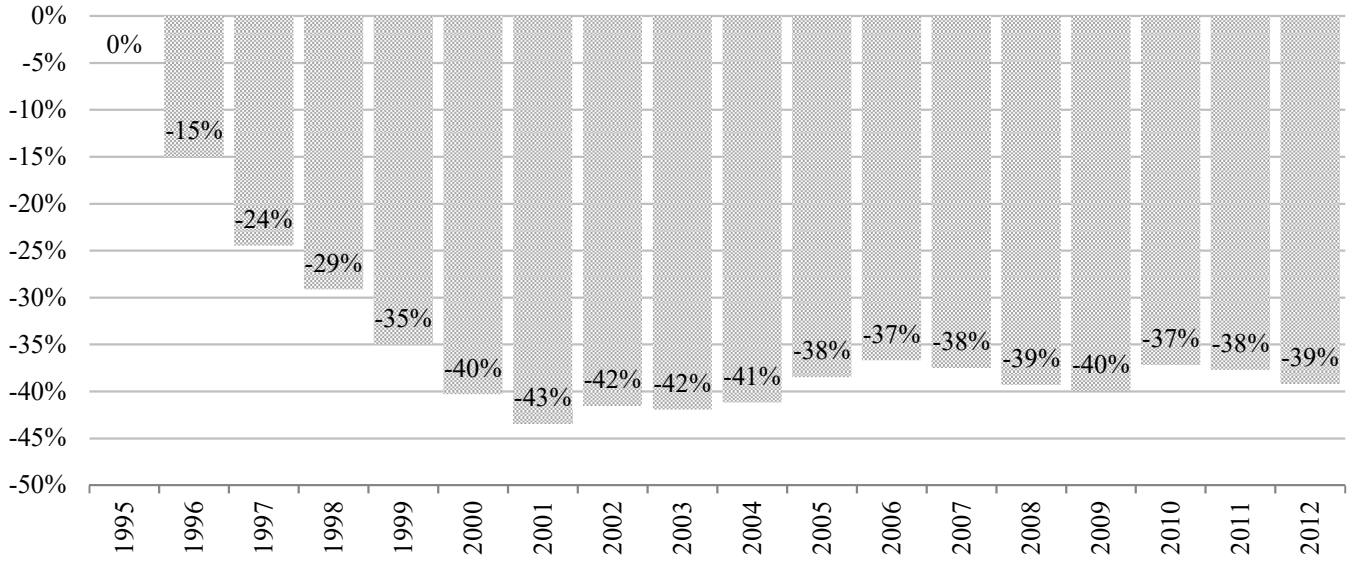

FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMP) approved for use in food-producing terrestrial animals, including horses, with 1995 as the reference year.

Targets 2015 – 2020

In 2015, a National Strategy against Antibiotic Resistance (2015-2020) was agreed upon. Among others, this strategy has set four targets for reduction of usage of antibacterials in terrestrial animals and farmed fish:

1. To reduce the usage of antibacterials in food-producing terrestrial animals by 10% by 2020, with 2013 as reference year.
2. In 2020, usage of antibacterials in farmed fish should be at the same level or lower than the average for the period 2004-2014.
3. To reduce the usage of antibacterials in companion animals by 30% by 2020, with 2013 as reference year.
4. Phasing out use of narasin and other coccidiostat feed additives with antibacterial properties in the broiler production without
    a. compromising animal health or animal welfare
    b. increasing the therapeutic use of antibacterials

A new national strategy against antibiotic resistance has not yet been adopted. Therefore, this report presents the development in reference to targets given in the National Strategy against Antibiotic Resistance (2015-2020).

Approach – assessment of changes

To evaluate progress in terms of reaching the goals set down in the national strategy, sales data for 2013-2023 have been further refined in order to obtain estimate on the sales that are more accurate in terms of identifying changes across time by sector. Data on prescribing per animal species obtained from the Veterinary Prescription Register (VetReg) have been used as supportive information for this refinement (see Appendix 1).

Food-producing terrestrial animals

In order to achieve Target 1 of the national strategy, Animalia, whose role is to provide Norwegian farmers with knowledge and expertise, initiated and coordinated the development and implementation of a joint action plan against antibiotic resistance (1). The suggested key measures to reduce the use of antibacterials in the livestock industry are prevention of diseases, biosecurity, as well as optimising the use of antibiotics. This action plan covers cattle, pigs, sheep, goats and poultry.

The indicators used to express the use are kg (active substance) and mg (active substance)/PCU (population correction unit) (see Appendix 1).

The result of this analysis shows that the reduction in the usage of antibacterial VMPs for cattle, pigs, sheep, goats and poultry from 2013 to 2023 was 31% and 27%, when measured in kg and in mg/PCU, respectively (Figure 13). The sales patterns (data from wholesalers) have been stable across the period 2013 to 2023, both in terms of the proportion by antibacterial classes and by phamaceutical forms. The figures are therefore assumed not to be biased by changes towards products/antibacterial substances with higher or lower dosing per treatment.

Injectable antibacterial VMPs are typically approved for several species. VetReg data show that the proportion of prescribing of such products for horses were relatively stable (and very low) across 2015-2023. Therefore, in this analysis all sales of injectable antibacterial VMP have been included in sales for food-producing terrestrial animals (horses excluded in Figure 13). Antibacterial human medicinal products (HMPs) are allowed to be used for animals according to the so-called cascade (Regulation (EU) 2019/6, Article 112-114) – i.e. if there is no VMP authorised for the condition, a HMP is allowed to be used. For food-producing species it requires that a maximum residue level (MRL) has been established for the antibacterial substance in question or that it is shown that MRL is not nessecary. HMPs used for animals are not included in Figure 13.

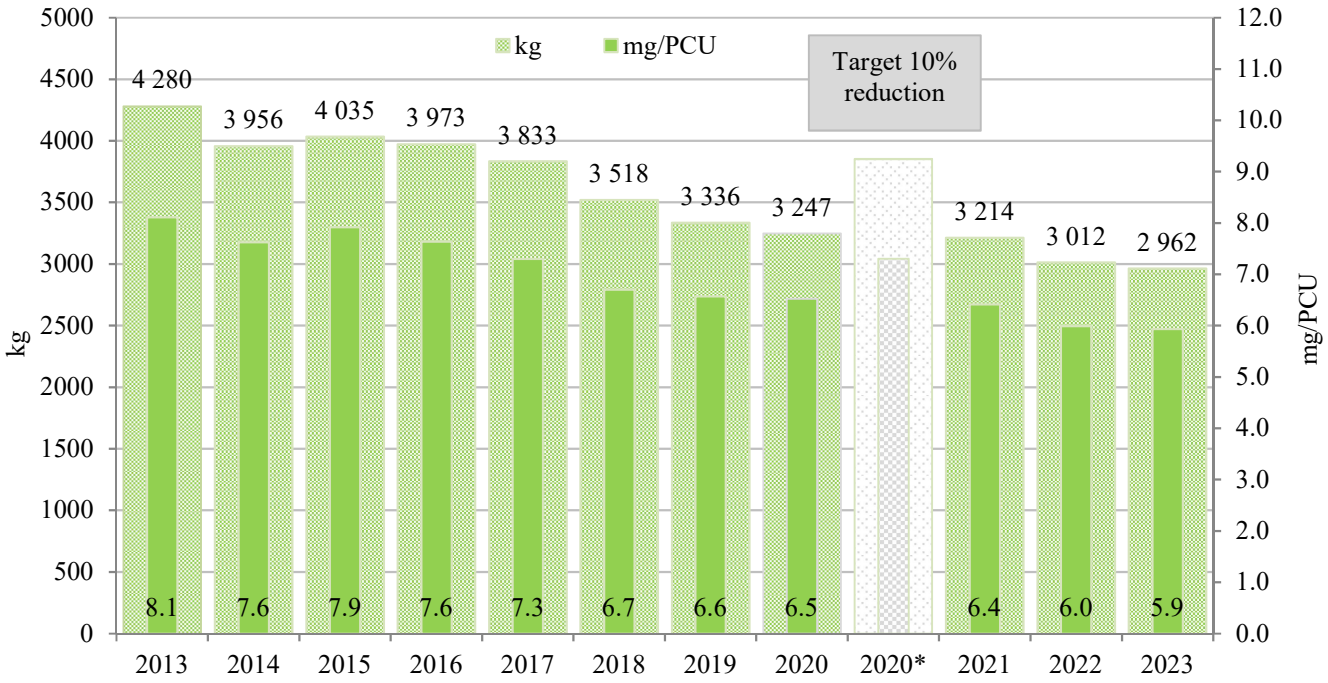

FIGURE 13. Estimated sales, in kg active substance and in mg/PCU (PCU=1 kg and represents the population correction unit for cattle, pigs, sheep, goats and poultry), of antibacterial veterinary medicinal products for cattle, pigs, sheep, goats and poultry in Norway in 2013 to 2023 and the target (2020*, grey bar) according to the National Strategy. Sales data at package level were obtained from the Norwegian Institute of Public Health. Note the starting points and the differences in the scales of the Y-axes.

Farmed fish

For farmed fish the goal was that the use of antibacterials should be at the same level or lower in 2020 than the average for the period 2004-2014 – i.e. the usage should not be above 1,003 kg or 1.14 mg/PCU (maximum levels).

Figure 14 shows that sales of antibacterial VMPs for farmed fish have been below the maxium level set for the years 2015-2023.

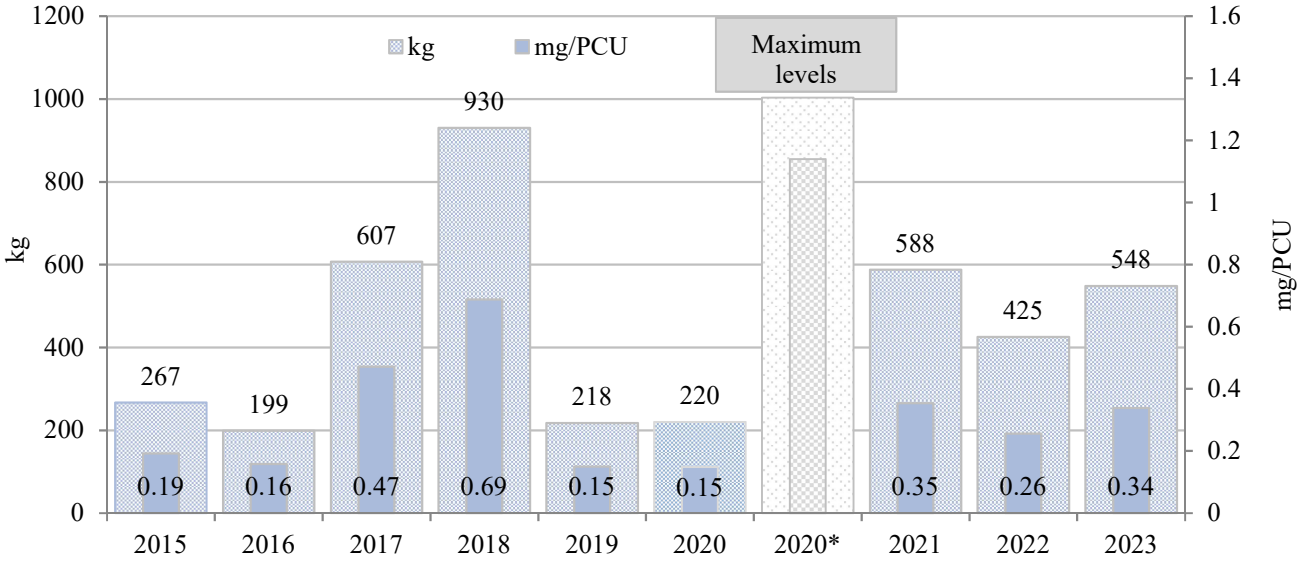

FIGURE 14. Prescription, in kg active substance and in mg/PCU (PCU=1 kg biomass farmed fish slaughtered), of antibacterial VMPs for farmed fish, in Norway in the period 2015 to 2023 and the maximum levels (2020*, grey bar) according to the National Strategy. Maximum levels are based on the average for the period 2004-2014. Prescription data were obtained from the Veterinary Prescription Register and include prescription for cleaner fish. Note the differences in the scales of the Y-axes. Minor differences in the figures compared to the 2022 NORM/NORM-VET report are due to updated calculation of the amounts prescribed for one florfenicol and one oxytetracycline product (range 1-8 kg lower).

Companion animals (dogs and cats)

Sales of antibacterial VMPs for companion animals include tablets, oral solution, injectable and oral paste approved for dogs and cats only (see Appendix 1 for exception for tablets). From 2013 to 2023 a reduction in the sales of such antibacterial VMPs for companion animals of 30% is observed (Figure 15). If use of human antibacterial products (HMPs) for dogs and cats, reported to VetReg, is included in the data, the decline is also 30%. As shown in Figure 15, the sales of antibacterial VMPs for companion animals declined gradually from 2013 to 2019; in 2020 a minor increase was observed and since then such sales have been relatively stable.

Of note is that the prescribing (kg) of human antibacterial products (HMPs) for dogs and cats, reported to VetReg, declined by 31% from 2015 to 2023. This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substituted by prescribing antibacterial HMPs.

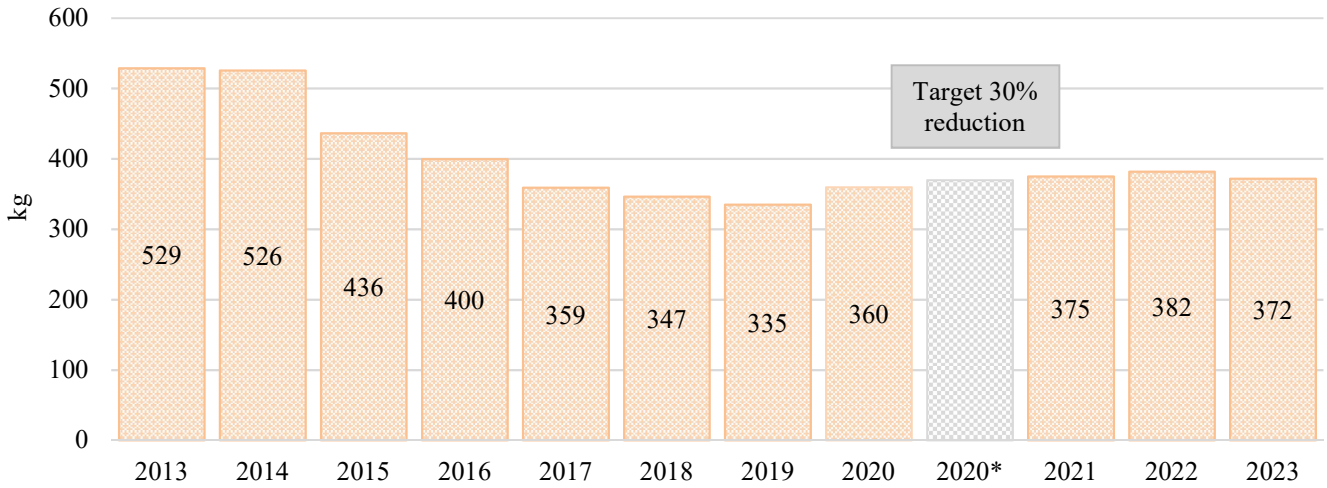

FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (injectables, oral paste, oral solution and tablets; exceptions for tablets - see Appendix 1) in the period 2013-2023 and the target (2020*, grey bar) according to the National Strategy.

Phasing out narasin in the broiler production

Narasin was gradually phased out as coccidiostat feed additive by the Norwegian broiler industry during the periode February 2015 to June 2016 (see NORM/NORM-VET 2019, Table 5). One of the targets stated in the National Strategy against Antibiotic Resistance are phasing out use of narasin as coccidiostat feed additive in the Norwegian broiler industry, without increasing the usage of antibacterials for therapeutic use or compromising animal health or animal welfare. One of the main concerns related to outphasing of narasin was that it could lead to increased occurrence of necrotic enteritis (*Clostridium perfringens*) in broilers.

Data on number of treatments with antibiotics in the broiler production were obtained from Animalia (Thorbjørn Refsnes, personal communication) as the quality of VetReg data on antibiotic use for poultry in particular was unsatisfactory. Table 5 shows that the annual number of broiler flocks treated with antibiotics has been very low during the years 2013 to 2023. Concurrent with, and in the years subsequent to, the discontinuation of the use of the coccidiostat feed additive narasin in broilers, the Norwegian broiler industry has explored various measures in order to prevent increased occurrence of necrotic enteritis (NE). In cases where NE has been diagnosed or suspected, in particular a probiotic based on a *Bacillus subtilis* strain administered through drinking water has shown promising potential in preventing NE (see text box page 29 in NORM/ NORM-VET 2021).

TABLE 5. Number of broiler flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs)[1] in Norway in the period 2013-2023. Data were obtained from HelseFjørfe, Animalia.

Broiler production	2013	2014	2015[3]	2016[4]	2017	2018	2019	2020	2021	2022	2023
	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated	No. of flocks treated
Breeders P[5] (Rearing)	1	2	1	0	0	0	0	0	0	0	0
Breeders P[5] (Layers)	1	0	1	2	0	1	1[2]	1[2]	0	0	0
Broiler	8	2	1	3	7	4	2	2	0	3	2
No. flocks treated	**10**	**4**	**3**	**5**	**7**	**5**	**3**	**3**	**0**	**3**	**2**

[1]Mostly phenoxymethylpenicillin VMPs, minor use of amoxicillin VMPs up to 2017. [2]Treated with oxytetracycline. [3]Phasing out narasin as coccidiostat feed additive started February 2015. [4] Out-phasing of narasin as feed additive finished June 2016 (since then narasin has been used to some extent therapeutically against necrotic eneteritis annually). [5] Parents.

References

1. Animalia, 2017. The Norwegian livestock industry's joint action plan on antimicrobial resistance. https://www.animalia.no/contentassets/05c57591f69d4e1da9bb5c44668bd0c1/eng_husdyrnaringas-hplan-amr-endelig-enkeltsider_220617.pdf).

Total usage in humans, animals and fish, measured in weight of active substance

In a one-health perspective it is interesting to assess antibiotic use according to the use in different sectors. We have used the Norwegian drug wholesales statistics database to collect data on humans and animals and added wholesales data for fish farming as reported to the Norwegian Institute of Public health. We have used ATC codes and ATCvet codes to allocate drugs to the sectors, Table 6.

TABLE 6. Antibacterial agents occur in several ATC groups. Antibacterials are approved and given an ATC/ATCvet code accordingly. In the figure we have defined use in the different sectors according to which ATC code it has been assigned. Data from the Norwegian drug wholesales statistics database.

Human sector – ATC codes included	Alimentary tract (A01, A07), Dermatological (D06, D07, D09, D10, R01AX), Gynecological (G01), Antibacterials for systemic use (J01, P01AB), Eye/ear-drops (S01, S02, S03)
Animal sector – ATCvet codes included	Alimentary tract (QA07), Dermatological (QD06, QD07), Intrauterine (QG51), Antibacterials for systemic use (QJ01), Intramammarie (QJ51), Eye/ear-drops (QS01, QS02, QS03)
Farmed fish – ATCvet codes included	Antibacterials for systemic use (QJ01)

In 2023, the overall sales in Norway of antibacterials for use in humans, terrestrial animals and farmed fish measured in weight of active substance were 58.4 tonnes (Figure 16). Of the total sales of antibacterials in Norway, sales for human use (excl. methenamine) accounted for 90.6 % of use, for terrestrial animals 8.1 % and for fish only for 1.2 %. An overall decrease in the level of use (when excluding methenamine) was observed since 2012, however, in 2022 and 2023 there was an increase in human use and total weight of antibiotics is now at the same level as in 2015. The penicillins are the most commonly used antibacterial group and represent 69% of total weight of antibacterials (excl. methenamine) in all sectors in 2023 whereas in 2012, the percentage was 61%.

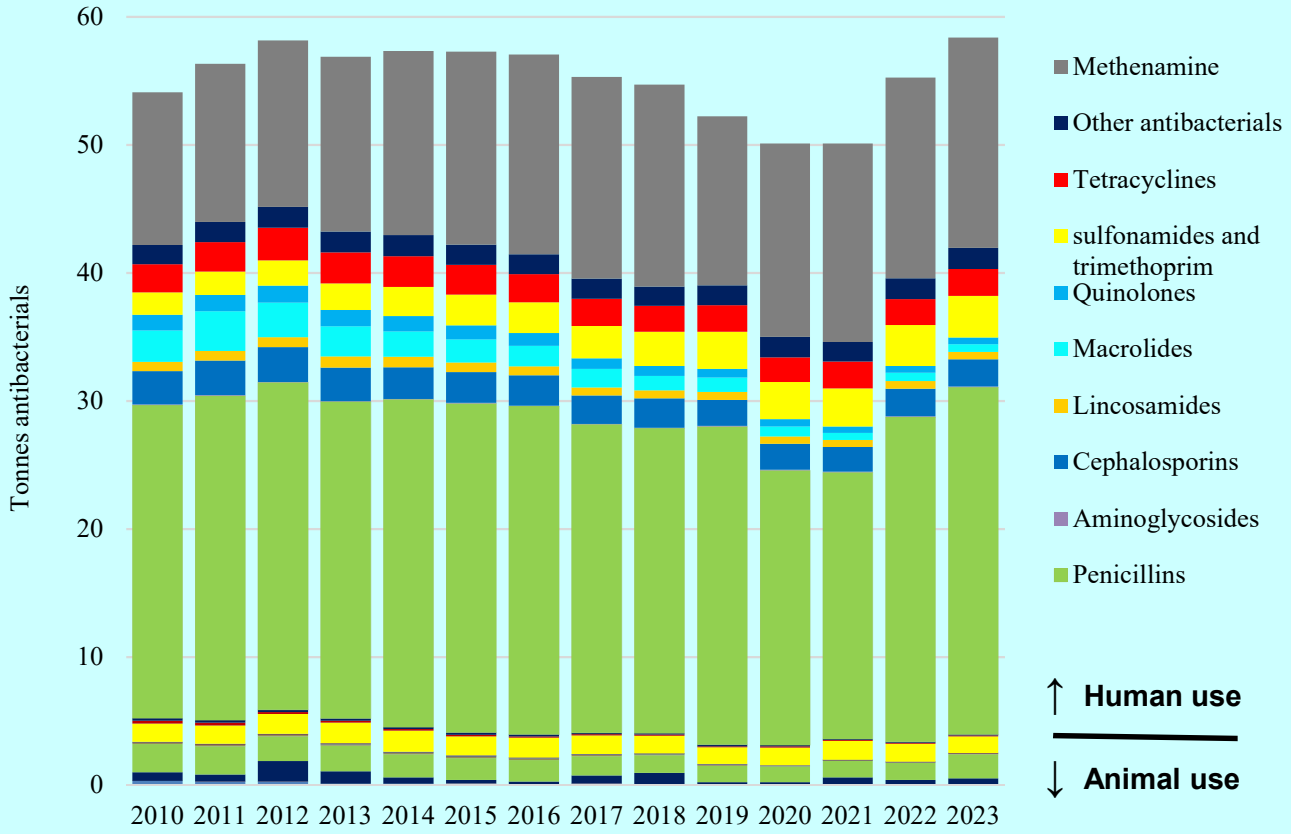

FIGURE 16. Sales, in tonnes of active substance, of antibacterials for humans, animals and farmed fish, for the years 2010-2023. The use in farmed fish is too low to be show separately in the figure. Data collected from the Norwegian Institute of Public Health.

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USAGE IN HUMANS

Hege Salvesen Blix, Marion Neteland, Per Espen Akselsen, Sigurd Høye and Live Storehagen Dansie

Overall antibiotic sales

In 2023, the total sales of antibacterials for systemic use in humans (J01, excluding methenamine) increased by 3% compared to 2022; from 12.7 to 13.1 DDD/1,000 inhabitants/day (Table 7). There has been a stable decrease in the use of antibacterials since 2012, with a large drop (13% decrease from 2019-2020) during the COVID-19 pandemic. The use is now back to the same level as prepandemic years. Compared to the use in 2012 when a *Mycoplasma pneumoniae* epidemic caused a very high prescription rate of macrolides and tetracyclines, the overall consumption in 2023 (J01, excluding methenamine) has decreased by 23%. During the COVID-19 pandemic there was a significant reduction in the use of systemic antibiotics, mainly due to reduced use of antibiotics indicated for respiratory tract infections (RTI-AB), but overall consumption is now "back to normal" (Figure 17). International and national shortage situations in the latest years have caused fluctuations in sales from wholesalers. The main fluctuations in 2022 and 2023 are caused by shortage of penicillins and erythromycin. During shortage periods generics have been made available for the market and the shortage situations in 2022/2023 do not seem to have impacted antibiotic consumption patterns to a large extent.

During the last decade a lot has been achieved by lowering the volume of use and increasing the use of Guidelines recommended antibiotics, but there are probably still areas for improvement, e.g. in adherence to Guidelines by using narrow-spectrum and targeted antibiotics, individualisation of doses or duration of course length, so one should expect that it is possible to achieve a further lowering of consumption rate and a better narrow-spectrum profile.

Antibiotics are prescription-only drugs in Norway. Overall antibiotic consumption includes all sales of antibiotics to humans in Norway i.e. in primary care, in hospitals and in long-term care institutions. Around 85% of the human use of antibacterials is used by patients outside health institutions. In 2023, hospitals covered 7.3% of total DDDs of antibiotics and long-term care institutions around 6-7%.

In the latest years, decreased sales are observed for many of the main antibiotic subgroups (Figure 18). During the COVID-19 pandemic, the closing down of society and the higher threshold for consulting general practitioners, combined with increased infection control led to lower incidence of infections handled by health care. Especially respiratory tract infections were sparsely reported during the COVID-19 pandemic. This is now "back to normal". In Norway, narrow-spectrum penicillins are first line treatment when antibiotics are warranted for respiratory tract infections. Over years the proportion of narrow-spectrum penicillins (J01CE) of total sales (J01, excluding methenamine) has been quite stable (around 27%), but it was lower in 2020 and 2021 (24%). In 2022 and 2023, the proportion was 28% and 29%, respectively. The increasing trend could be due to increased adherence to Guidelines.

TABLE 7. Human usage of antibacterial agents in Norway 2012, 2014, 2016, 2018, 2020, 2022 and 2023 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and % change 2022-2023. Data from Norwegian drug wholesales statistics database. Methodology of data collection on human usage of antimicrobial agents is shown in Appendix 2.

		Year							Change (%)
ATC	Groups of substances	2012	2014	2016	2018	2020	2022	2023	2022-2023
J01A	Tetracyclines	3.87	3.46	3.16	2.86	2.65	2.82	2.91	+3
J01B	Amphenicols	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
J01CA	Penicillins with extended spectrum	2.79	2.90	2.62	2.46	2.22	2.35	2.41	+3
J01CE	Beta-lactamase sensitive penicillins	4.31	3.88	3.73	3.43	2.77	3.50	3.77	+8
J01CF	Beta-lactamase resistant penicillins	0.90	0.91	0.90	0.90	0.95	1.04	1.07	+3
J01CR	Combination of penicillins, incl. beta-lactamase inhibitors	0.04	0.07	0.10	0.08	0.11	0.15	0.16	+2
J01D	Cephalosporins, monobactams, carbapenems	0.53	0.46	0.42	0.39	0.37	0.37	0.36	-4
J01E	Sulfonamides and trimethoprim	0.87	0.88	0.85	0.88	0.90	0.92	0.92	-1
J01F	Macrolides, lincosamides and streptogramins	2.26	1.68	1.33	1.05	0.80	0.75	0.71	-5
J01G	Aminoglycosides	0.08	0.08	0.08	0.09	0.10	0.10	0.09	-11
J01M	Quinolones	0.74	0.67	0.53	0.42	0.30	0.29	0.28	-1
J01X*	Other antibacterials	0.47	0.43	0.38	0.32	0.34	0.37	0.38	+4
J01	**Total excluding methenamine**	**16.9**	**15.4**	**14.1**	**12.9**	**11.5**	**12.7**	**13.1**	**+3**
J01XX05	Methenamine	3.57	3.86	4.09	4.08	3.85	3.96	4.10	+4
J01	**Total all antimicrobial agents**	**20.4**	**19.3**	**18.2**	**15.3**	**15.2**	**16.6**	**17.2**	**+3**

*J01X incl. glycopeptides, colistin, fusidic acid, metronidazol (i.v.), nitrofurantoin, fosfomycin, linezolid, daptomycin and tedizolid. Methenamine is excluded.

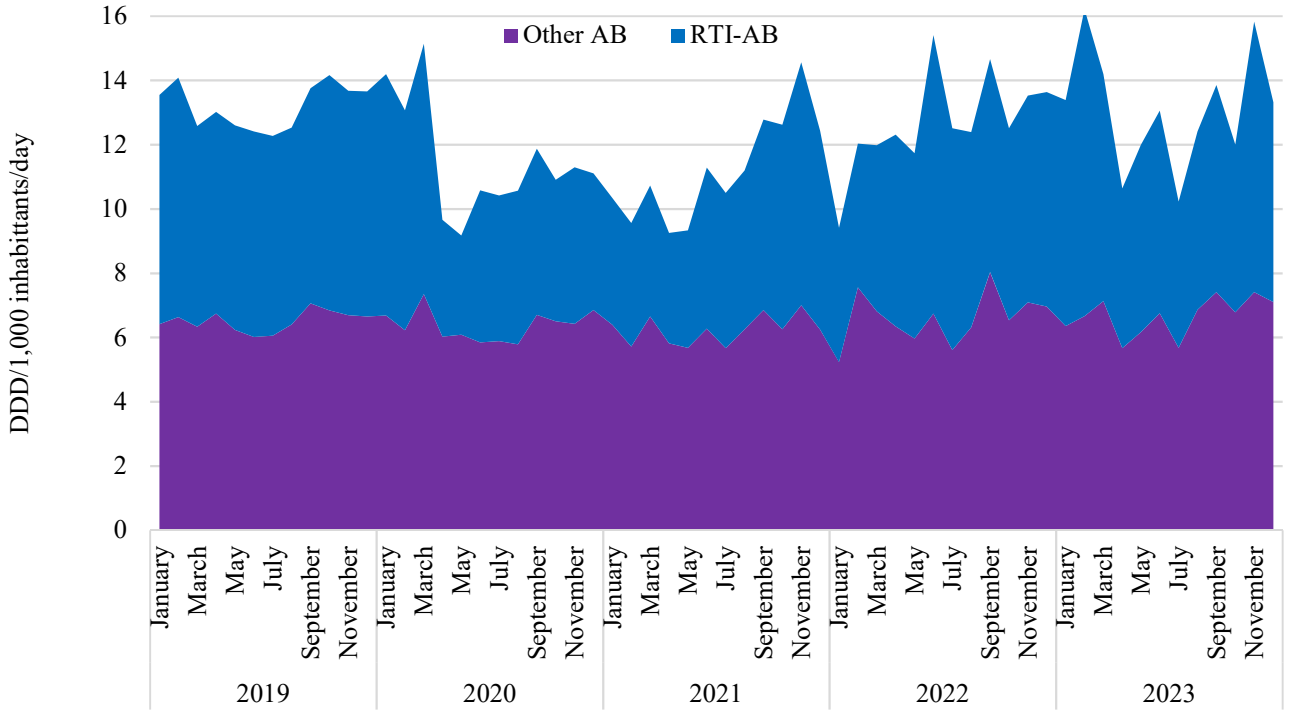


FIGURE 17. Monthly sales of antibiotics in 2019-2023 as measured in DDD/1,000 inhabitants/day. Sales of antibiotics for respiratory tract infections (RTI-AB) is defined as amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline. Other antibiotics (AB) is defined as all other antibiotics in ATC group J01, excluding methenamine. Data from the Norwegian drug wholesales statistics database.

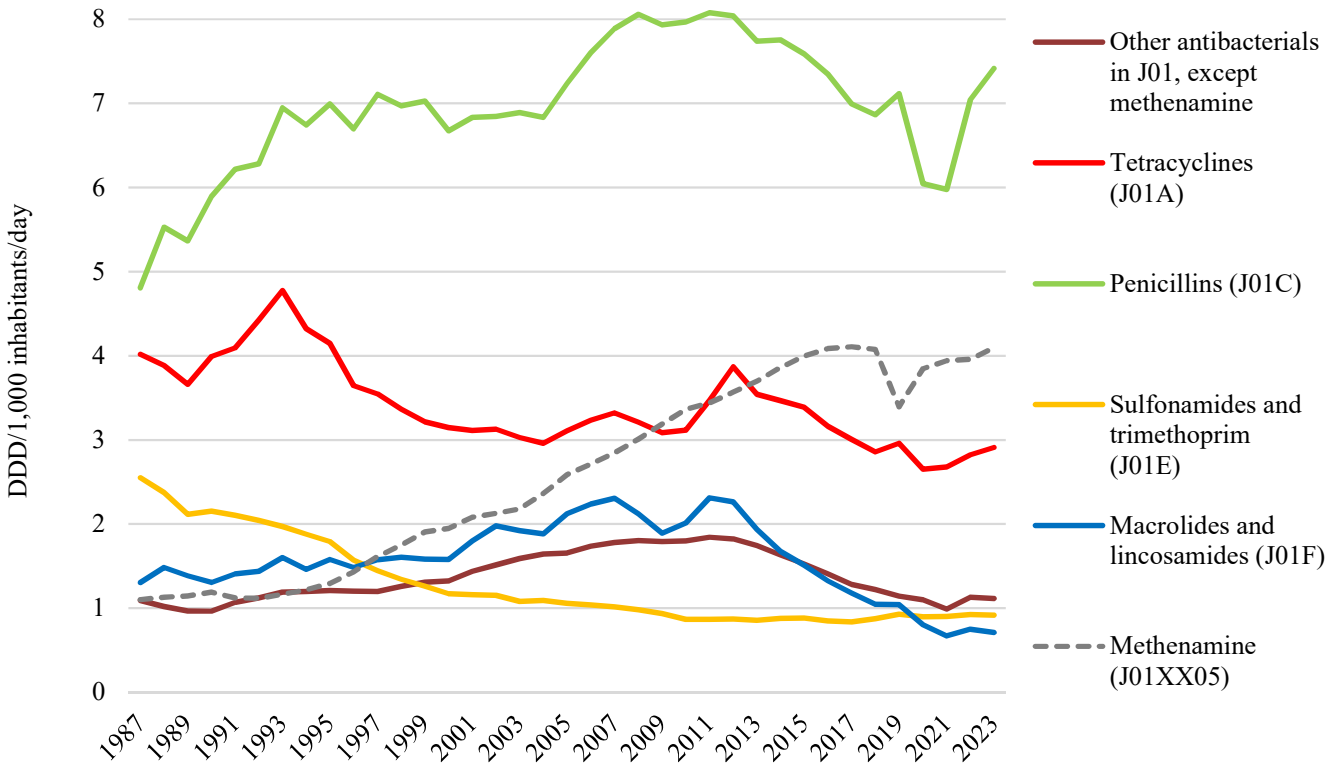


FIGURE 18. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine and other antibacterials in Norway 1987-2023. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05). Data from the Norwegian drug wholesales statistics database.

The beta-lactamase sensitive penicillin group (J01CE), the tetracyclines (J01A) and penicillins with extended spectrum (J01CA) were the three most used antibacterial groups in Norway in 2023. The urinary prophylactic agent methenamine creates the largest amounts of DDDs of all antibiotics used in Norway, mainly because it is used continuously and every day. In spring 2019 we experienced a major shortage, and in 2023 the use was back to the 2016 level (Figure 18, Table 7). Methenamine accounted for 24% of total antibacterial use in 2023. Of the tetracyclines (J01A), doxycycline is the most frequently used, followed by lymecycline, a drug indicated for acne (Table 8).

In 2023, the penicillins (ATC group J01C) accounted for 43% of the total antibacterial use in Norway (Figure 19). Over the years there has been a shift towards use of more broad-spectrum penicillins. In 2023, beta-lactamase sensitive penicillins accounted for half of the penicillin group (51% share) measured in DDDs compared to around 70% some decades ago. Penicillins with extended spectrum (J01CA) represent 33% of the J01C group. This is mainly due to increasing use of amoxicillin and pivmecillinam. An increased use of penicillins with beta-lactamase inhibitors (J01CR) has been observed in the latest years (Table 7). In May 2017, oral co-amoxiclav was approved in Norway, and since then a significant increase has been observed. It is recommended in some very few situations in the Norwegian primary care guidelines. Pivmecillinam is the main antibiotic used for urinary tract infections, although pivmecillinam, trimethoprim and nitrofurantoin are all equal recommendations for acute cystitis.

After many years of decreasing use of trimethoprim, the subgroup of sulfonamides and trimethoprim as a whole is now increasing because the combination co-trimoxazole is increasing (Figure 18-19, Table 8).

Since 2012 the use of macrolides has dropped markedly, (Tables 7-8, Figures 18-19). The use of the group J01F macrolides, lincosamides and streptogramins has followed a wavy pattern over the years. The shifts in use could be explained to some degree by the recurrent epidemics of *M. pneumoniae* in Norway, occurring with four- to six-year intervals. Furthermore, until 2014, azithromycin and doxycycline were both recommended for genital chlamydia infections in the primary care treatment guidelines. Since then, doxycycline has been the only first line treatment. Reduction in the use of macrolides has been a focus in the primary care part of the National Action Plan. The use of macrolides is now at the same level as in the 1970s.

In the latest years, the sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased, mainly due to decreased use of 1st and 2nd generation cephalosporins (Tables 7-8, Figure 19). Since 2019 there has been a slight reduction in the sales of cefotaxime, which may have at least two causes. Reduction in the use of cefotaxime and other 3rd generation cephalosporins were specifically targeted in the National Action Plan. Another factor is that since 2019 the European breakpoint committee EUCAST has recommended 1g x 3 as the standard dose for cefotaxime, whereas the most common dose in Norway has been 2g x 3. The new dosage has gradually been incorporated in guidelines and other recommendations in Norway.

The quinolones represent only a small fraction (2%) of total antibacterial sales (Table 7-8, Figure 19) and the use has steadily decreased since 2012. Focus has been put on the resistance driving effect of the quinolones, and in combination with "dear doctor" letters on severe adverse effects of fluoroquinolones, this has driven the decrease. Ciprofloxacin is the main substance accounting for 94% of the quinolone group in 2023.

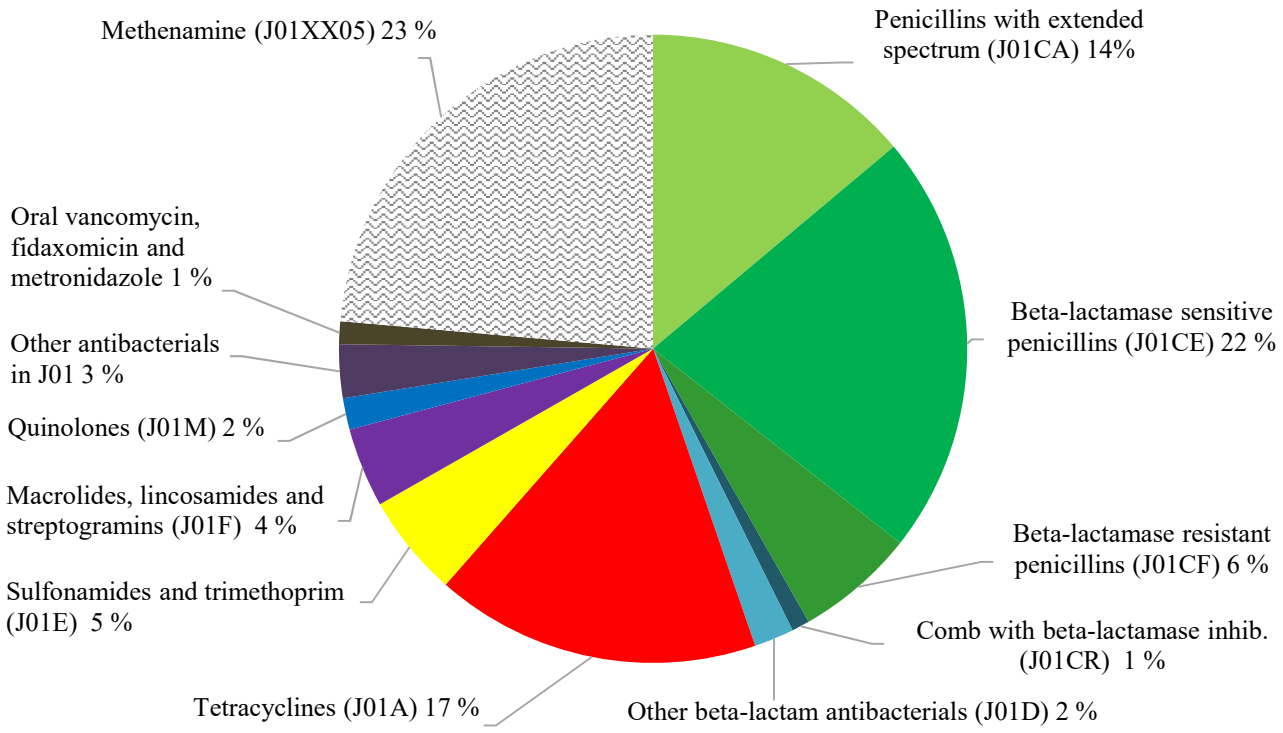


FIGURE 19. Relative amounts of antibacterial agents for systemic use in 2023 in Defined Daily Doses (DDD) (total sales in the country). Data from the Norwegian drug wholesales statistics database.

TABLE 8. Total human usage of single antibacterial agents for systemic use in Norway. Sales for overall use are given in DDD/1,000 inhabitants/day. Data from the Norwegian drug wholesales statistics database. ATC-version 2024 is used. The methodology for collection of data on human usage of antibacterial agents is presented in Appendix 2.

ATC group	ATC code	Substance	2012	2014	2016	2018	2020	2022	2023
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	1.99	1.82	1.60	1.38	1.51	1.55
	J01A A04	Lymecycline	0.90	0.96	0.94	0.93	1.08	1.12	1.17
	J01A A06*	Oxytetracycline		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01A A07	Tetracycline	0.62	0.50	0.40	0.32	0.19	0.20	0.20
	J01A A08*	Minocycline	0.006	0.003	0.002	0.001	0.001	0.001	0.001
	J01A A12	Tigecycline	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01B - Amphenicols	J01B A01*	Chloramphenicol	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.03	0.04	0.04	0.05	0.05	0.05	0.05
	J01C A04	Amoxicillin	0.97	0.97	0.88	0.84	0.65	0.74	0.79
	J01C A08	Pivmecillinam	1.78	1.87	1.69	1.57	1.52	1.56	1.57
	J01C A11	Mecillinam	0.008	0.008	0.005	0.002	0.003		
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.24	0.24	0.23	0.24	0.23	0.18	0.18
	J01C E02	Phenoxymethyl-penicillin	4.07	3.64	3.50	3.18	2.53	3.32	3.59
	J01C E08*	Benzathine benzylpenicillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CF - Beta-lactamase resistant penicillins	J01C F01	Dicloxacillin	0.76	0.72	0.74	0.74	0.78	0.84	0.87
	J01C F02	Cloxacillin	0.14	0.19	0.17	0.16	0.16	0.19	0.20
	J01C F05*	Flucloxacillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CR - Combination of penicillins, incl. beta-lactamase inhibitors	J01C R01*	Ampicillin and enzyme inhibitor							<0.001
	J01C R02	Amoxicillin and enzyme inhibitor	0.00	0.01	0.01	0.03	0.05	0.09	0.09
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.07	0.09	0.05	0.06	0.07	0.07
J01DB – 1st generation cephalosporins	J01D B01	Cefalexin	0.18	0.14	0.10	0.09	0.07	0.06	0.06
	J01D B03	Cefalotin	0.08	0.09	0.09	0.07	0.02	0.02	0.02
	J01D B04	Cefazolin				0.03	0.08	0.09	0.09
J01DC – 2nd generation cephalosporins	J01D C02	Cefuroxime	0.08	0.06	0.04	0.03	0.03	0.02	0.01
J01DD – 3rd generation cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	0.11	0.13	0.12
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.008	0.006	0.004	0.003
	J01D D04	Ceftriaxone	0.03	0.02	0.02	0.02	0.03	0.02	0.02
	J01D D08*	Cefixime			<0.001	<0.001	<0.001	<0.001	<0.001
	J01D D52	Ceftazidime and avibactam				<0.001	<0.001	<0.001	<0.001
J01DF - Monobactams	J01D F01	Aztreonam	<0.001	0.001	0.001	<0.001	<0.001	0.001	0.003
J01DH - Carbapenems	J01D H02	Meropenem	0.03	0.03	0.03	0.02	0.03	0.03	0.02
	J01D H03	Ertapenem	0.002	0.002	0.002	0.002	0.002	0.002	0.002
	J01D H51	Imipenem and enzyme inhibitor	0.002	0.002	0.002	0.002	0.002	0.001	0.001
	J01D H52*	Meropenem and vaborbactam						<0.001	
	J01D H56	Imipenem, cilastatin and relebactam						<0.001	<0.001

ATC group	ATC code	Substance	2012	2014	2016	2018	2020	2022	2023
J01DI – Other cephalosporins and penems	J01D I02	Ceftaroline fosamil		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01D I04	Cefiderocol						<0.001	<0.001
	J01DI54	Ceftolozane and enzyme inhibitor			<0.001	<0.001	0.001	<0.001	<0.001
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.46	0.38	0.34	0.33	0.29	0.27
	J01E B02*	Sulfamethizole					<0.001	<0.001	
	J01E C02*	Sulfadiazine			0.001	<0.001	<0.001	<0.001	<0.001
	J01E E01	Sulfamethoxazole and trimethoprim	0.36	0.40	0.44	0.53	0.57	0.63	0.65
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.75	0.60	0.44	0.29	0.21	0.18
	J01F A02	Spiramycin	0.01	0.005	0.003	0.002	0.002	0.001	<0.001
	J01F A06*	Roxithromycin		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01F A09	Clarithromycin	0.39	0.23	0.14	0.11	0.09	0.09	0.08
	J01F A10	Azithromycin	0.48	0.35	0.30	0.24	0.19	0.21	0.22
	J01FS15	Telithromycin	<0.001	<0.001	<0.001				
	J01F G01*	Pristinamycin							<0.001
	J01F F01	Clindamycin	0.33	0.34	0.28	0.25	0.23	0.23	0.23
J01G - Aminoglycosides	J01GA01*	Streptomycin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01G B01	Tobramycin	0.03	0.02	0.02	0.01	0.01	0.01	0.01
	J01G B03	Gentamicin	0.05	0.05	0.06	0.08	0.09	0.09	0.08
	J01G B06	Amikacin	0.001	0.001	0.001	0.001	0.001	<0.001	<0.001
J01M - Quinolones	J01M A01	Ofloxacin	0.02	0.01	0.01	0.01	0.01	0.004	<0.001
	J01M A02	Ciprofloxacin	0.71	0.64	0.51	0.39	0.28	0.27	0.27
	J01MA12	Levofloxacin	0.002	0.002	0.003	0.004	0.005	0.006	0.006
	J01MA14*	Moxifloxacin	0.004	0.007	0.009	0.011	0.009	0.01	0.01
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.02	0.02	0.02	0.02	0.02	0.02
	J01X A02*	Teicoplanin	0.001	<0.001	<0.001	<0.001		<0.001	<0.001
	J01X A04	Dalbavancin							<0.001
	J01X B01	Colistin	0.004	0.005	0.006	0.006	0.008	0.01	0.01
	J01X C01	Fusidic acid	0.005	0.004	0.003	0.003	<0.001	<0.001	<0.001
	J01X D01	Metronidazole	0.07	0.05	0.03	0.04	0.04	0.04	0.04
	J01X E01	Nitrofurantoin	0.37	0.35	0.31	0.25	0.26	0.29	0.31
	J01XX01	Fosfomycin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01X X05	Methenamine	3.57	3.86	4.09	4.08	3.85	3.96	4.10
	J01XX08	Linezolid	0.01	0.007	0.010	0.009	0.009	0.009	0.009
	J01XX09	Daptomycin	0.001	<0.001	0.001	0.001	0.001	0.001	0.001
	J01X X11	Tedizolid			<0.001	<0.001	0.001	0.002	0.003
Antibiotics in other ATC groups	A07A A09	Vancomycin	0.002	0.002	0.002	0.002	0.003	0.004	0.005
	A07A A12	Fidaxomicin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
	P01A B01	Metronidazole	0.23	0.24	0.23	0.21	0.21	0.20	0.20

*Drugs not licensed in the Norwegian market in 2023.

Antibiotic use in primary care

Around 84% of the total human sales of antibacterials are sold as prescriptions from pharmacies - that is prescribed to persons in primary care, mainly those living at home. The basis for this data is captured from the Norwegian Prescribed Drug Registry (NorPD) that includes all prescriptions of antibacterials dispensed to persons living in Norway (included those antibiotics prescribed from hospitals to discharged patients and out-patients), see Appendix 2.

The decrease in total use of antibacterials during the period after the outbreak of the COVID-19 pandemic was mainly due to decreased use in primary care. In 2023, the use of antibacterials (J01, excluding methenamine) in primary care was 10.5 DDD/1,000 inhabitants/day, i.e. at the same level as in 2019. For primary care, the most important antibiotic group in 2023 was the penicillins, J01C (41% of DDDs and 58% of prescriptions in ATC group J01). Tetracyclines (J01A) was the second most used group (19% of DDDs and 9% of prescriptions) followed by sulfonamides and trimethoprim (J01E, 5% of DDDs and 10% of prescriptions). The six antibiotic substances most often prescribed for outpatients in 2023 were phenoxymethylpenicillin, pivmecillinam, methenamine, dicloxacillin, amoxicillin and doxycycline. These six antibiotics represented 72% of all prescriptions and 77% of all DDDs of the antibacterial group J01. Phenoxymethylpenicillin was prescribed in 27% of the prescriptions representing 22% of DDDs while methenamine represented 27% of the DDDs and 9% of the J01 prescriptions.

The use in primary care is now approximately at the same level as the year before the COVID-19 pandemic (2019). Whether the decrease observed between 2012 and 2019 will continue is currently difficult to predict, however, there is an increased attention towards antimicrobial resistance, both among the public and health care personnel. A large proportion of general practitioners have completed quality improvement courses after the introduction of the Government's Action plan against AMR in 2016.

The usage of antibacterials varies among the Norwegian regions, Table 9. The ranking is similar in all regions, except for azithromycin being more prevalent in Health Region West. Nitrofurantoin has climbed on the list since 2022 and increased at the expense of trimethoprim. In addition to pivmecillinam, these two substances are recommended as first line treatment for urinary tract infections.

None of the regions have reached the prescription target set in National Strategy against Antibiotic Resistance of 250 Rx/1,000 inhabitants/year when excluding methenamine (Figure 19). The North has the lowest Rx/1,000 inhabitants/year and the lowest DDD/1,000 inhabityants/day, Figure 20. The South-East Region has the highest proportion of phenoxymethylpenicillin (23% of all DDDs) and the North Region has the lowest (17%). The North Region has the highest proportion (15%) of all DDDs of urinary tract antibiotics (pivmecillinam, trimethoprim and nitrofurantoin) and South-East has the lowest (12%).

Females use more antibiotics than males. In 2023, 23.6% of the females purchased at least one antibiotic prescription (methenamine excluded) compared to 15.9% of the males. This is approximately at the same level as 2019. The prevalence of antibiotic use has decreased over the years, more so in young children than in the elderly. Young children, young women and the elderly are high users of antibiotics (Figure 21). Between 2012 and 2019, there was a reduced prevalence of use in all age groups with the largest reduction in small children (0-9 years) and the lowest reduction for young adults (20-29 years) and elderly above 70 years. Moreover, the use in men is reduced more than in women. There was a dramatic reduction during the pandemic in 2020, which was mainly due to lower prescribing of antibiotics for respiratory tract infections (Figure 22). The prevalence varies somewhat from one year to another according to the burden of infection, and for children the use of antibiotics increased in 2023 compared to earlier years. In autumn 2023 there was increased reporting of *Bordetella pertussis* and *Mycoplasma pneumoniae*, which could partly explain the increased use of antibiotics in 2023 compared to 2022.

Among those who are prescribed antibacterials, the elderly population are prescribed more. For those above 75 years, 2.2 prescriptions/user for females and 2.1 prescriptions/user for males are dispensed every year compared to around 1.5 prescriptions/user for younger persons (men and women together) (Figure 23). This has been a stable trend over years. The mean number of antibacterial prescriptions delivered from pharmacies is reduced since 2012 for men and women and in all age groups, however, since 2019 hardly any reduction is observed, Figure 24. The target of 250 prescriptions/1,000 inhabitants/year is for the general population. The differences according to age and gender group indicate that interventions should not only be targeted towards the general population, but that focus should be put on treatment patterns in different age- and gender groups.

Over the years there are differences in the therapy patterns according to recommendations in Guidelines. In Norway, narrow-spectrum antibiotics are first line antibiotics. Figure 25 shows variation in use of antibiotics recommended as first line versus not first line treatment, and the figure is indicating a higher prescribing of the recommended antibiotics in recent years. This could be caused by increased attention towards AMR as well as increased adherence to Guidelines by health care workers in the period. Precriptions (Rx) per 1,000 inhabitants per year (J01, excluding methenamine) is reduced by 26% since 2012, and in 2023 the number was 336 Rx/1,000 inhabitants/year for the general population.

Dentists

The proportion of the population being prescribed antibacterials (J01 and P01AB metronidazole) by dentists was 2.4% of the population in 2023, a slight increase since 2019 when the proportion was 2.1%.

TABLE 9. Human usage of the 15 single antibacterial agents for systemic use most often prescribed by doctors in ambulatory care in the four health regions in Norway in 2023. Sales are given in DDD/1,000 inhabitants/day. Data from the Norwegian Prescribed Drug Registry.

	Health region				Norway
	Mid	North	South-East	West	
Methenamine	4.40	4.11	3.64	3.63	3.78
Phenoxymethylpenicillin	2.92	2.22	3.24	3.07	3.09
Pivmecillinam	1.50	1.37	1.29	1.32	1.34
Doxycycline	1.30	1.15	1.31	1.28	1.30
Lymecycline	1.08	1.00	1.14	1.32	1.16
Dicloxacillin	0.72	0.77	0.78	0.71	0.76
Amoxicillin	0.62	0.54	0.65	0.59	0.63
Sulfamethoxazole and trimethoprim	0.52	0.56	0.49	0.51	0.51
Nitrofurantoin	0.32	0.35	0.25	0.30	0.29
Trimethoprim	0.29	0.29	0.21	0.20	0.23
Tetracycline	0.18	0.17	0.21	0.17	0.19
Ciprofloxacin	0.18	0.18	0.20	0.17	0.19
Azithromycin	0.15	0.15	0.19	0.22	0.19
Clindamycin	0.16	0.16	0.19	0.16	0.18
Erythromycin	0.15	0.11	0.19	0.15	0.17

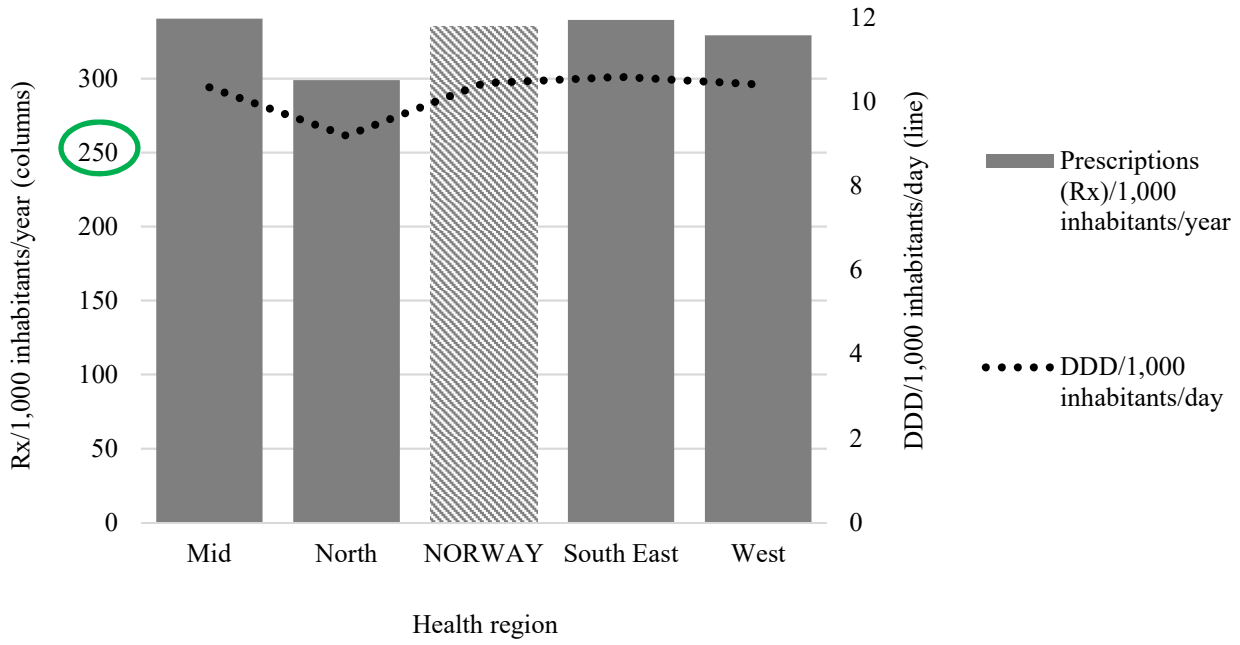


FIGURE 20. Consumption of antibacterial agents for systemic use (ATC group J01, excluding methenamine) in outpatients in the different health regions of Norway in 2023. Measured as number of prescriptions (Rx)/1,000 inhabitants and in DDD/1,000 inhabitants/day. Data from NorPD (excluding health institutions). Prescription target set in National Strategy against Antibiotic Resistance is 250 Rx/1,000 inhabitants/year (green ring).

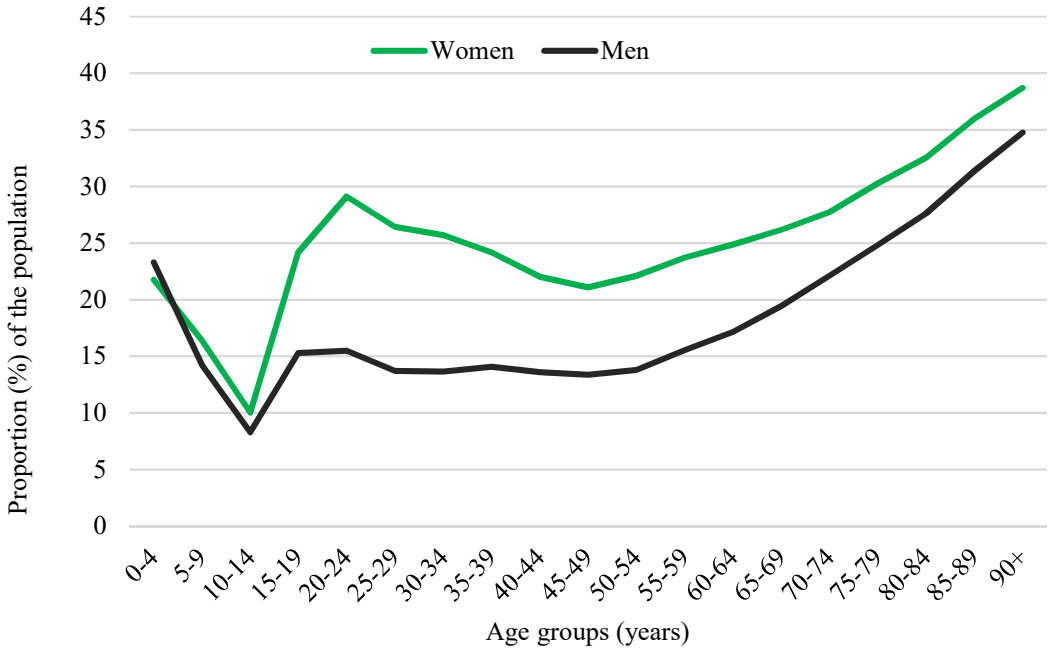


FIGURE 21. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care by gender and age in Norway 2023. Antibacterials included are antibacterials for systemic use (ATC group J01), vancomycin (A07AA09), fidaxomicin (A07AA12) and metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions. Data from NorPD.

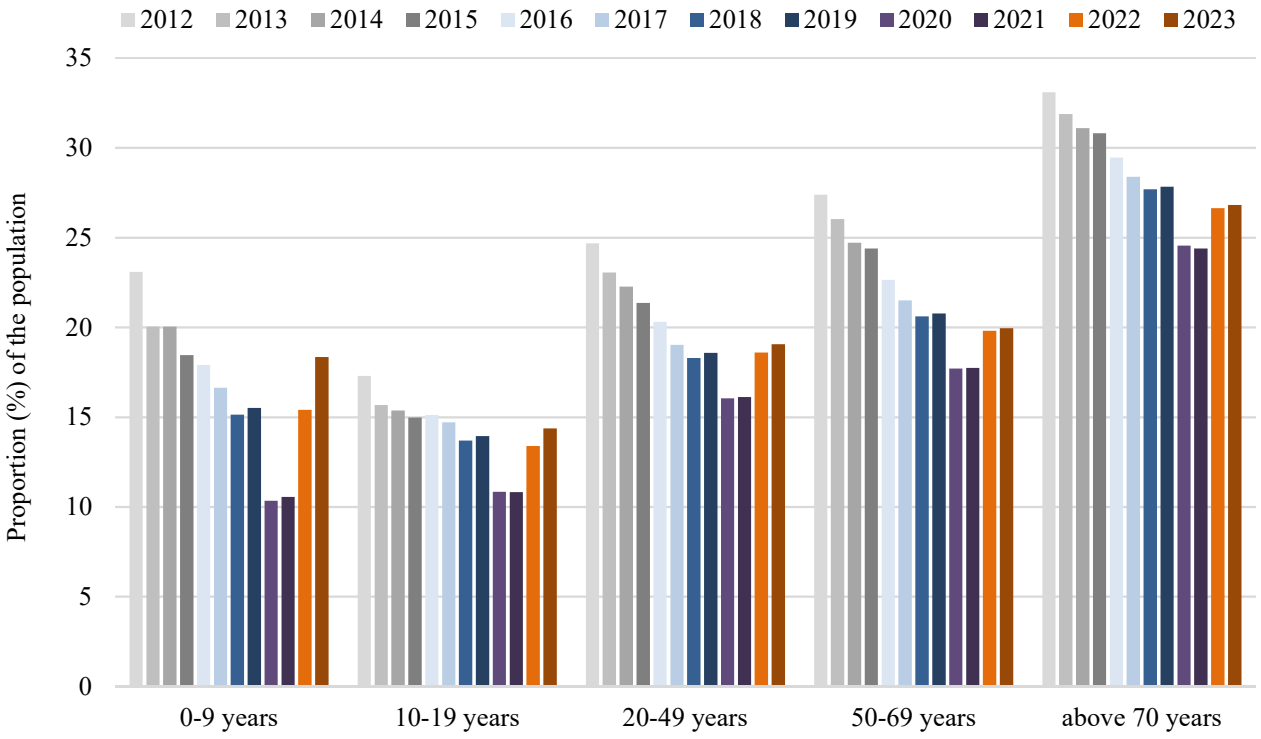


FIGURE 22. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care in Norway 2012-2023. Antibiotics included are antibacterials for systemic use (ATC group J01, excluding methenamine). Data from NorPD.

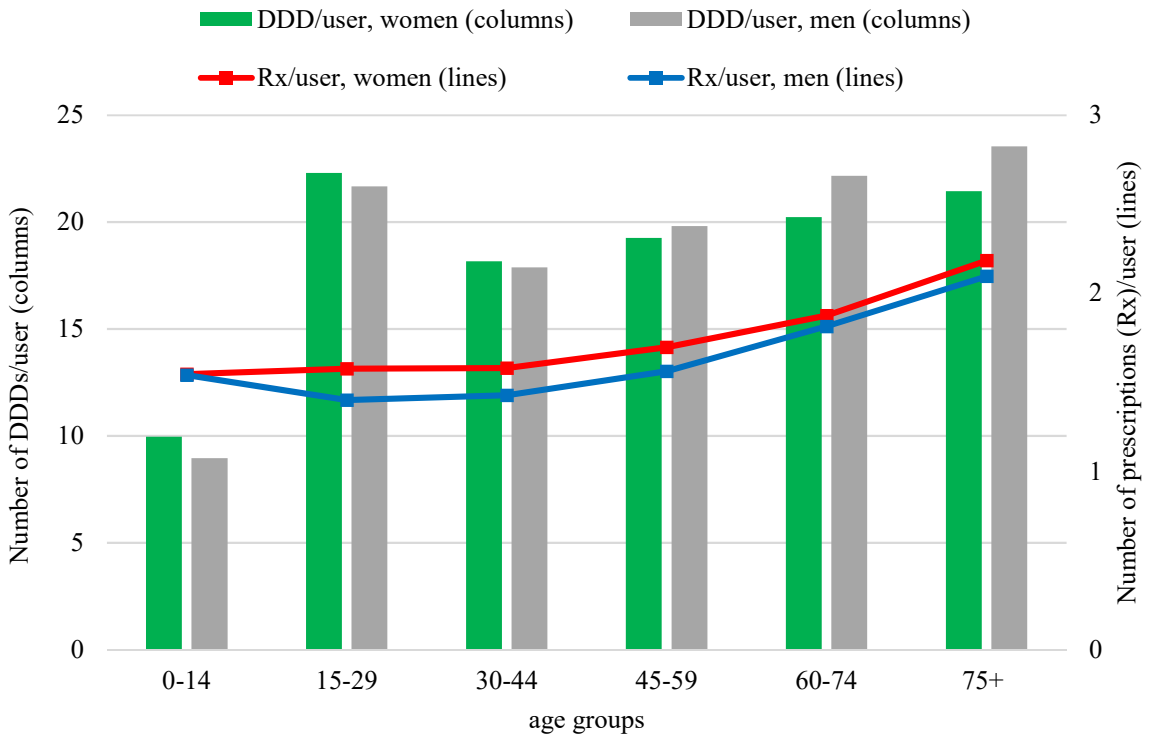


FIGURE 23. Mean number of prescriptions (Rx) per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway 2023. Antibacterials included are antibacterials for systemic use (ATC group J01, excluding methenamine). Data from NorPD.

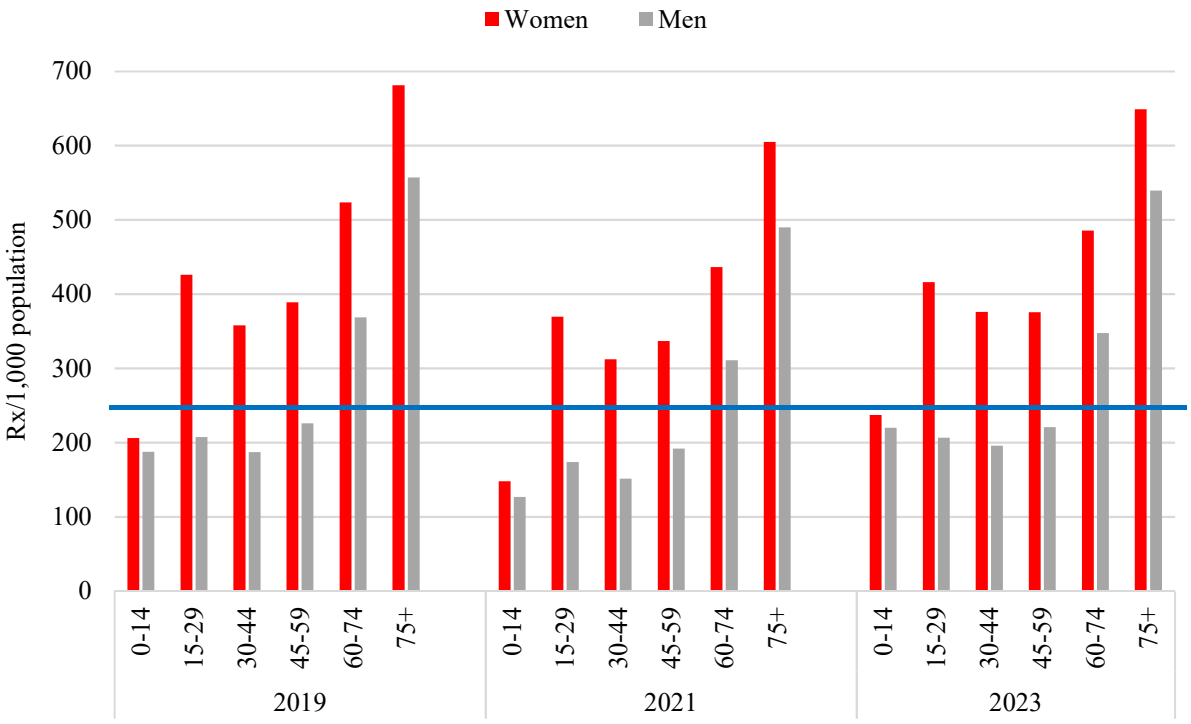


FIGURE 24. Mean number of prescriptions (Rx)/1,000 population of antibacterials (J01, excluding methenamine) in ambulatory care by gender and age groups; 2019, 2021 and 2023. The blue line indicates the target of 250 prescription/1,000 population/year. Data from NorPD.

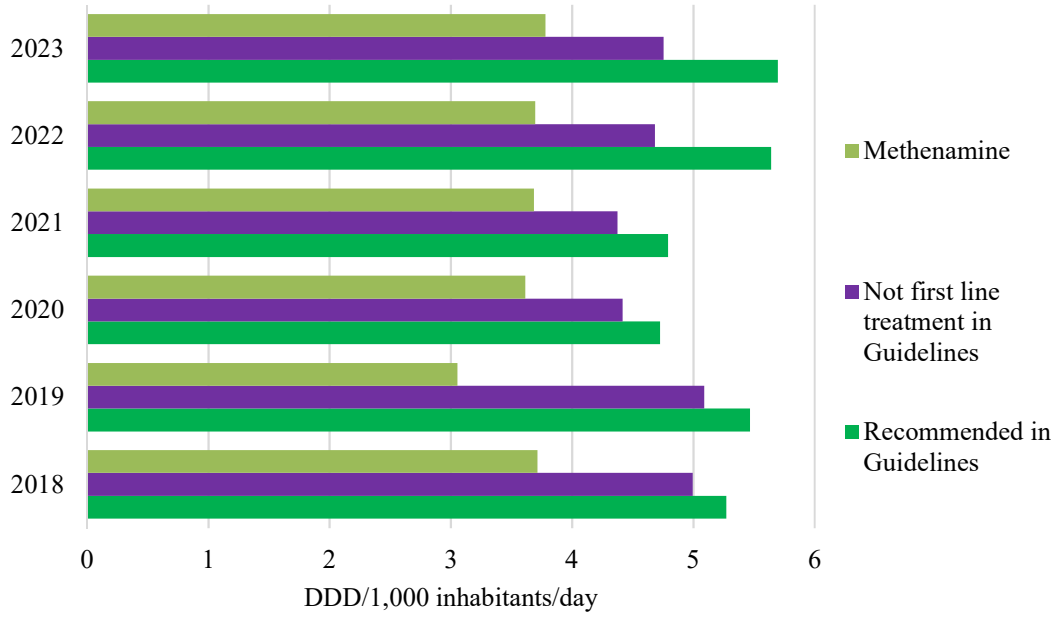


FIGURE 25. Consumption of antibacterial agents for systemic use (ATC group J01) in outpatients in Norway 2023. Aggregated in three groups; a) recommended as first line treatment in the Guidelines for primary care (phenoxymethylpenicillin for respiratory tract infections, pivmecillinam, trimethoprim and nitrofurantoin for urinary tract infections and dicloxacillin for skin infections), b) not first line treatment includes all other antibiotics in J01, and c) methenamine. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

Antibiotic consumption in hospital care

In 2023, antibacterial sales (in DDDs) to hospitals represented around 7% of total sales of antibacterials for human use in the country. There was a decrease of 3% in DDD/1,000 inhibitants/day compared to 2019 and an increase of 10% since 2021 (Figure 26). The decrease in 2020 and 2021 is related to the COVID-19 pandemic under which the hospitals restructured their departments and postponed elective surgery as preparation for the expected high numbers of inpatients with severe COVID-19 disease. This resulted in fewer admissions and fewer bed days as most hospitals turned out to actually have surplus capacity.

In the three years before the COVID-19, total sales of antibiotics to hospitals have been stable with regard to volume of DDD/1,000 inhabitants/day but a change in pattern of use has occurred with increased use of narrow-spectrum antibiotics. The narrow-spectrum penicillins are highly utilised, and for this group the theoretical value of DDDs is lower than the therapeutic doses most commonly prescribed in Norway. Furthermore, combination regimens with a narrow-spectrum penicillin plus an aminoglycoside will account for more DDDs than monotherapy with a cephalosporin or carbapenem. This implies that the total count of DDDs will show higher values for volume when combination therapy is used compared to broad-spectrum single agents.

The therapy pattern of antibacterials in hospitals does not change much from one year to another, however, a decrease in use of selected broad-spectrum antibiotics has been observed since 2012. Broad-spectrum antibiotics (defined as J01_CR/DC/DD/DI/DF/DH/MA) accounted for 20% of total DDDs for hospitals in 2023 compared to 26% in 2012. The share of beta-lactamase sensitive penicillins (J01CE) in 2023 was 16% of the total (Figure 26).

Penicillins (J01C) represent 49% of the use measured in DDDs in hospitals (J01CE 16%, J01CA 10%, J01CF 17% and J01CR 6%). The second largest group is the cephalosporins with 18% of all DDDs, the dominant subgroup being 3rd generation cephalosporins (J01DD). In 2023, twelve substances accounted for 75% of all DDDs used in hospitals (DU75). These are cloxacillin, benzyl-penicillin, cefotaxime, cefazolin, gentamicin, doxycycline, piperacillin/tazobactam, co-trimoxazole, pivmecillinam, ampicillin, phenoxymethylpenicillin and metronidazole. Three single substances accounted for 34% of all antibacterial DDDs in hospitals; cloxacillin (14%), benzylpenicillin (12%), and cefotaxime (8%). The fourth most used substance - cefazolin (6% of all antibacterial DDDs) - is mainly used for surgical prophylaxis.

The share of antibiotics used for prophylaxis has been shown to be quite stable over the years. The national point-prevalence surveys (PPS) includes information on indication for prescribing. Four antibiotics are relevant to look at when evaluating the use of antibiotics for prophylaxis in hospitals. According to the PPS almost all prescribings (above 95%) for the two 1st generation cephalosporins cefazolin and cefalotin are for prophylaxis while approximately 40% of parenteral metronidazole use and 40% of co-trimoxazole use are for prophylaxis. Furthermore, the levels of use have been approximately the same in all PPS since 2015. In figure 27 this information has been applied to the sales data. The proportion for prophylaxis was around 9% of DDDs in 2012 compared to 12% in 2023.

The classification of antibacterials into aware-, watch- or reserve-antibiotics (the WHO AWaRe classification) is utilised as a tool for antibiotic stewardship policies for optimising antibiotic use and curb antimicrobial resistance.

WHO includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics. In Norwegian hospitals, the access group has increased from 70% in 2012 to 76% in 2023. However, the use of Reserve antibiotics has also doubled from 2012-2023 from 0.4% of total use to 0.8%. Linezolid is the most commonly used Reserve antibiotic and holds 65% of all Reserve DDDs, followed by aztreonam (17%, Figure 28).

Figure 29 shows annual trends in national antibiotic use in hospitals by hospital activity data presented as DDD/100 bed days and in DDD/admission instead of population statistics – DDD/1,000 inhabitants/day. The length of stay (LOS) in Norwegian hospitals in the latest years is relatively stable according to national statistics, but number of admissions and bed days are both going down. Data for antibiotic use in hospital care are usually presented as DDD/Number of bed days or DDD/Number of admissions to correct for activity, because that makes comparisons between hospitals possible. The reduced number of bed days in Norway the latest years (apart from the effects of the COVID-19 pandemic) does probably not reflect reduced hospital activity in the country as a whole, but a shift from in-patient treatment to day-care and out-patient treatment. Figure 30 visualises the impact of the reduction in bed days on antibiotic consumption statistics.

Seven selected groups that mainly are used in hospitals are shown in Figure 31. The use of piperacillin/tazobactam has been increasing for many years but was markedly reduced in 2017 and 2018 due to a nationwide shortage. In 2019, there was no shortage, and in 2020 and 2021 an increase was observed. In 2023, there was decreased use of penicillins with beta-lactamase inhibitors, 2nd and 3rd generation cephalosporins and carbapenems compared to 2022. Moreover, an increase in the use of aminoglycosides was observed in 2023. Compared to 2016, the use of aminoglycosides increased by 50% as measured in DDDs. The use of glycopeptides has increased by 27% in the same period. The use of carbapenems peaked in 2014 after many years of increasing use and seems to have reached a stable level probably due to implementation of antibiotic stewardship programmes in Norwegian hospitals from 2016. In general, mainly parenteral formulations of 2nd, 3rd and higher generation cephalosporins as well as carbapenems are licensed in Norway and these are most often used in hospitals. Figure 32 shows the distribution between "Preferred antibiotics" (which largely reflects standard treatment regimens in national guidelines) and resistance driving antibiotics for the different Norwegian hospitals. Proportions of preferred antibiotics vary among hospitals, between 79% and 56%.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between the hospitals. Figure 33 shows use of the five selected groups of broad-spectrum antibiotics targeted in the National Action Plan in all Norwegian hospitals/health trusts. The variations cannot be accounted for by differences in activity or case mix alone but are probably related to different prescribing practices.

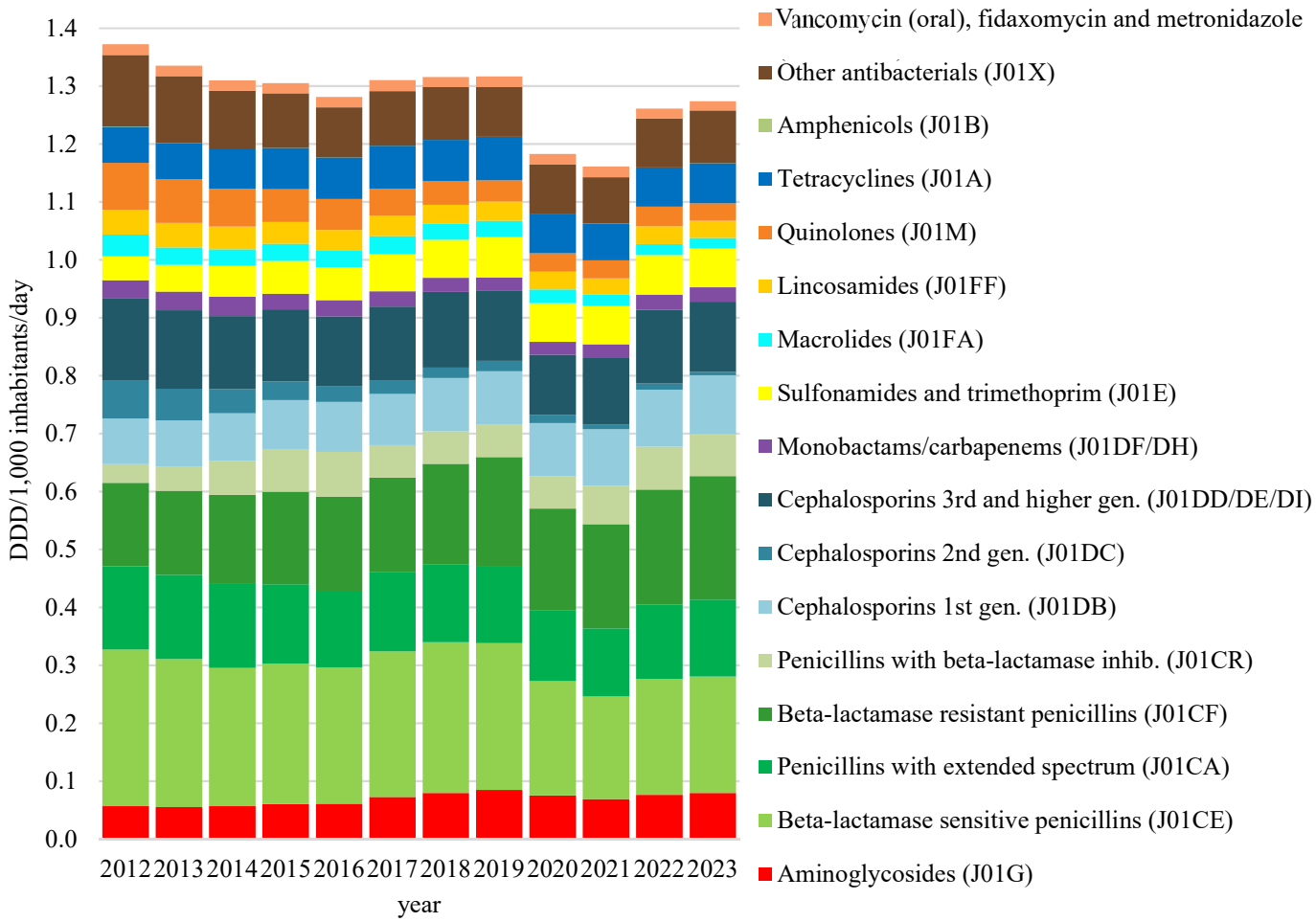


FIGURE 26. Proportions of antibacterial agents for systemic use (J01), vancomycin (A07AA09), fidaxomicin and oral metronidazole (P01AB01) in Norwegian hospitals 2012-2023, measured in DDD/1,000 inhabitants/day. Data source; hospital pharmacies drug statistics database.

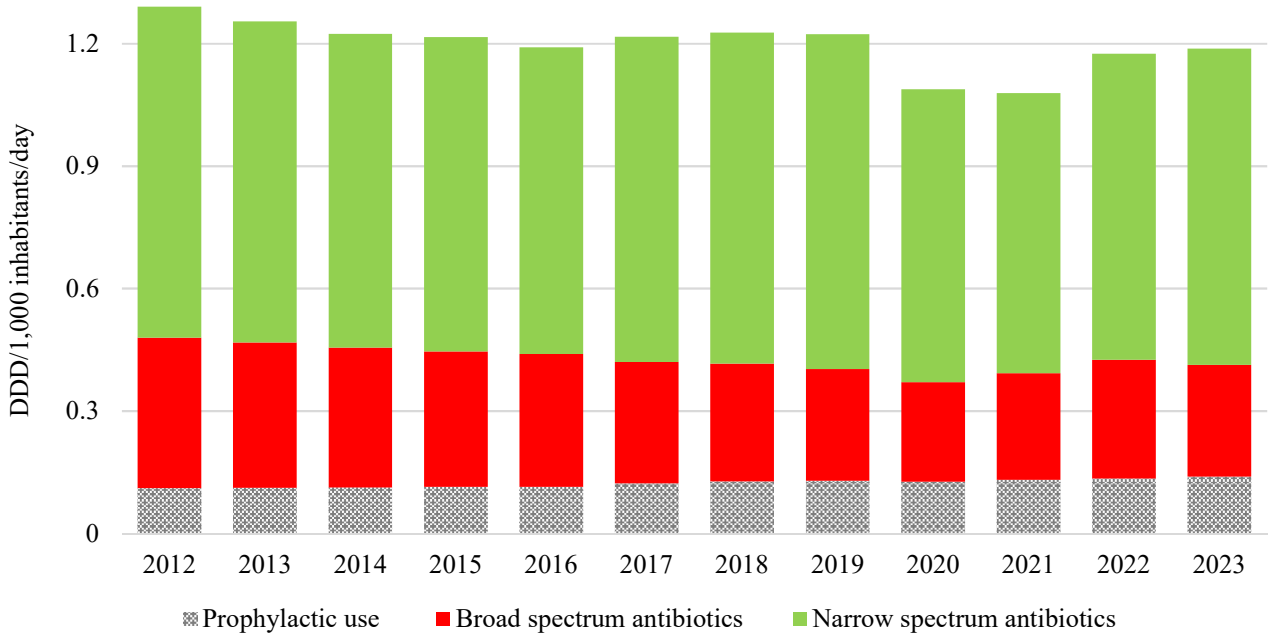


FIGURE 27. Proportions of prophylactic antibacterial agents for systemic use, broad-spectrum and narrow-spectrum antibiotics in Norwegian somatic hospitals 2012-2023, measured in DDD/1,000 inhabitants/day. The volume of antibiotics for prophylactic use is estimated. Information on prescribing indications from the national point-prevalence surveys were used to recalculate the sales data. Included in prophylactic use are all DDDs of the 1st generation cefalosporins cefazolin and cefalotin and 40% of the DDDs from metronidazole i.v. and co-trimoxazole, respectively. Broad-spectrum antibiotics are defined as J01CR, J01DC/DD/DI/DH, J01M, J01XA. Narrow-spectrum antibiotics are defined as all other antibiotics in J01. Data source; hospital pharmacies drug statistics database.

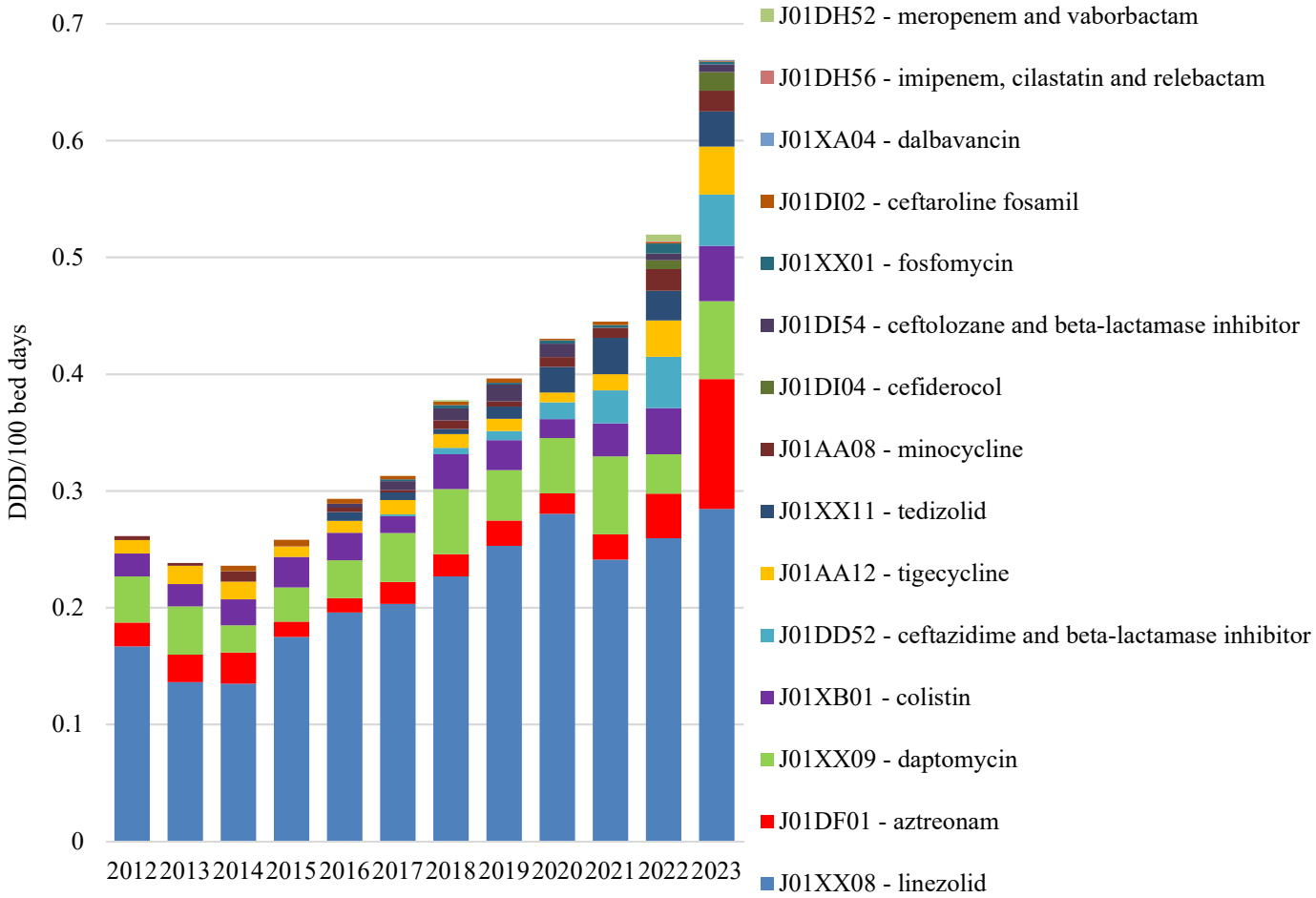


FIGURE 28. Reserve antibiotics (as defined according to the AWaRe 2021 classification) used in Norwegian hospitals (somatic) 2012-2023, measured in DDD/100 bed days. Data source; hospital pharmacies drug statistics database.

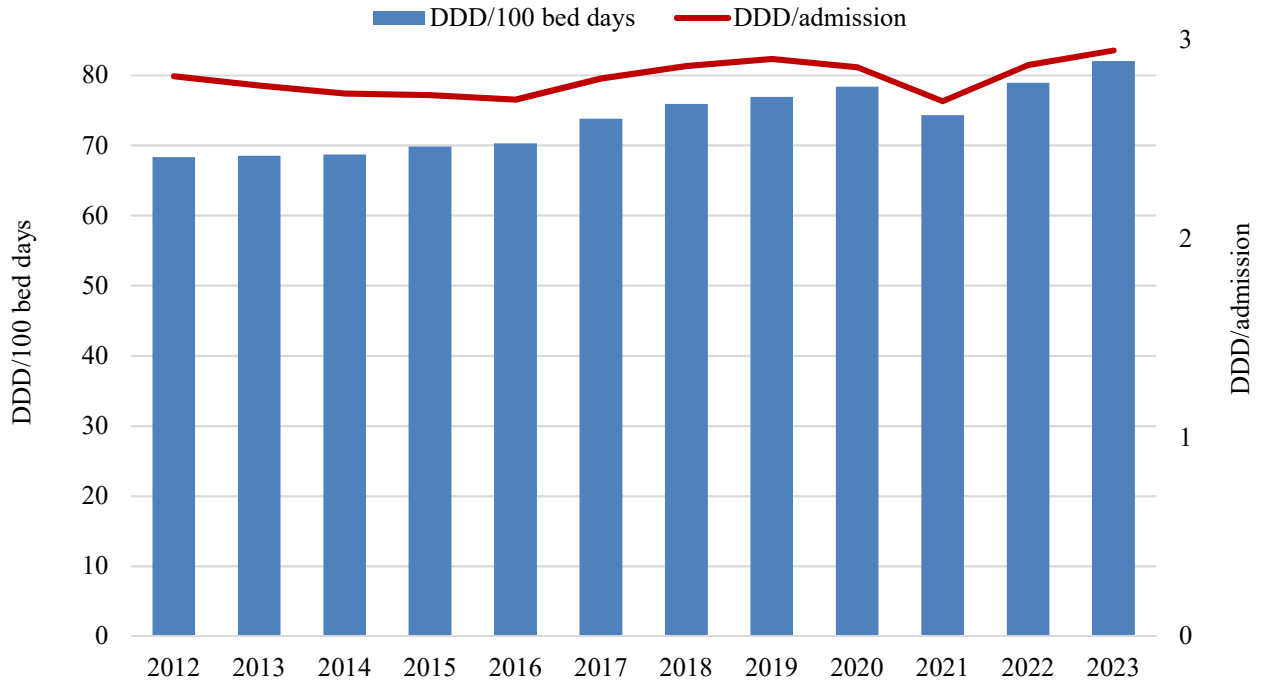


FIGURE 29. Total use of antibiotics in Norwegian hospitals (somatic) 2012-2023, measured in DDD/100 bed days and in DDD/admission. Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal). Data source; hospital pharmacies drug statistics database.

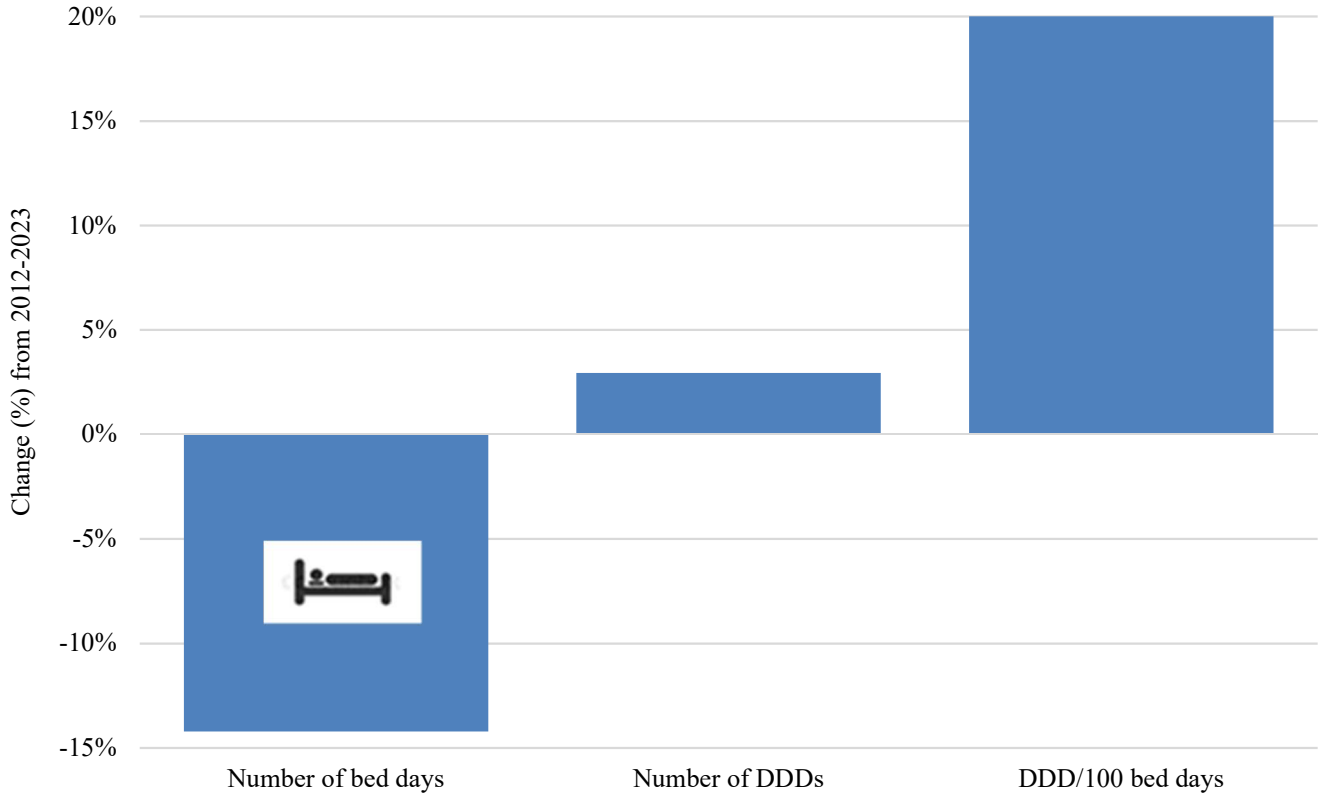


FIGURE 30. Proportional change will vary according to the measures used. Antibiotic usage in hospitals is often presented in DDD/100 bed days, but total number of DDDs may also be used as a measure. The number of bed days has been reduced by 14% since 2012. The figure visualises the impact of the reduction in bed days on antibiotic consumption statistics of antibacterial agents for systemic use (J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal)) in Norwegian hospitals 2012-2023, measured as % change either as change of total DDDs (3% increase) or change of DDD/100 bed days (20% increase).

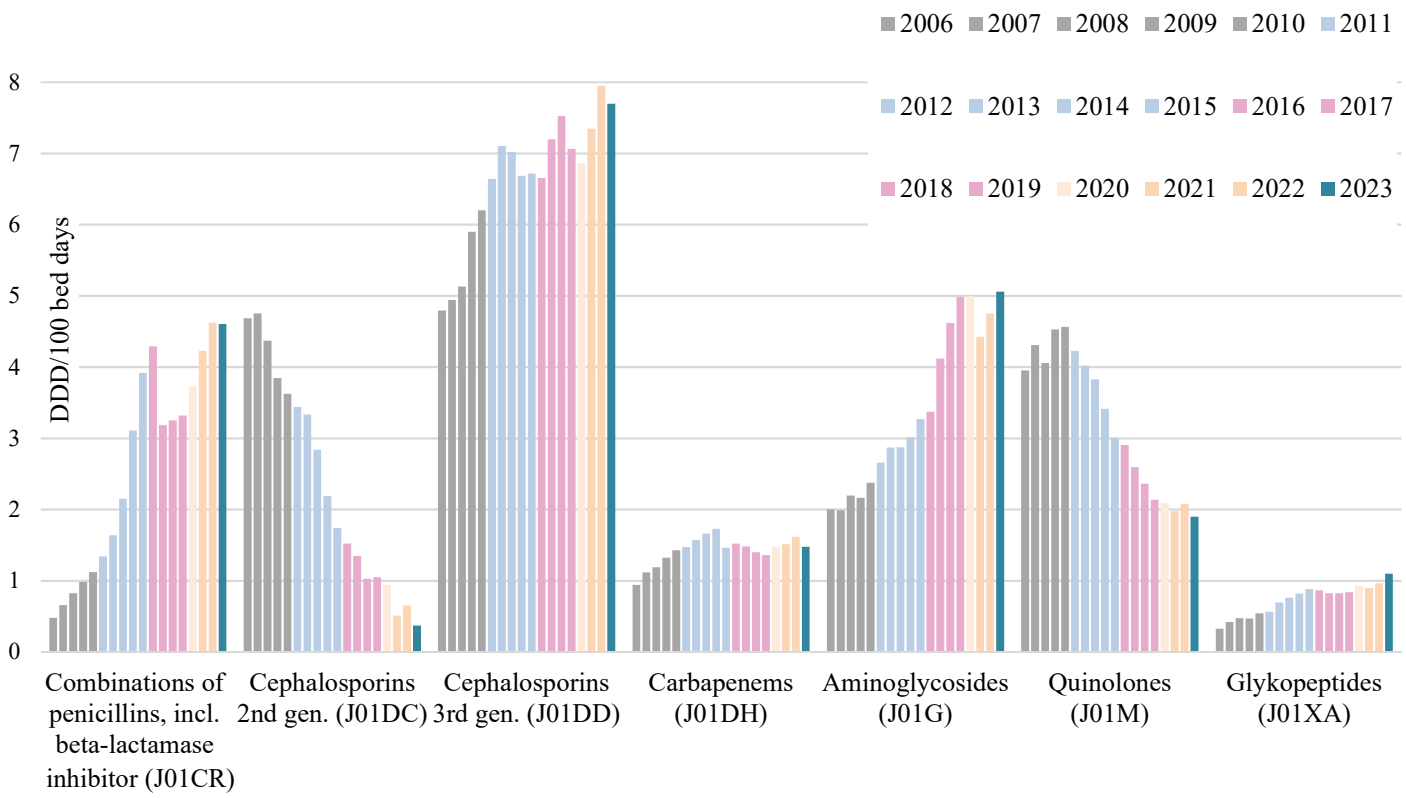


FIGURE 31. Consumption of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2023, measured in DDD/100 bed days. Data source; hospital pharmacies drug statistics database.

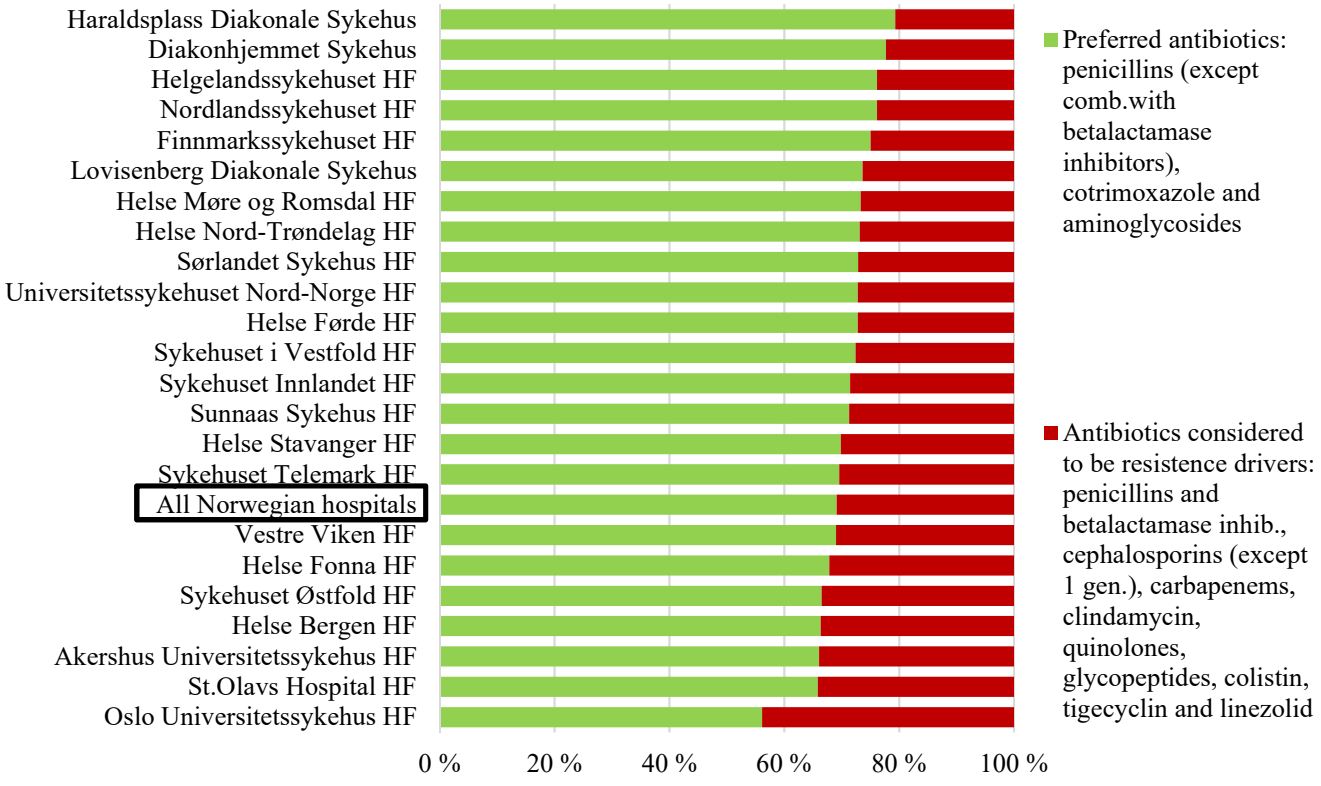


FIGURE 32. Proportions (% of DDDs) of preferred antibiotics (green part of the column) and antibiotics that are considered to be drivers of antibiotic resistance (red part i.e. belonging to ATC groups J01CR, J01DC, J01DD, J01DE, J01DI, J01DH, J01M, J01XA, J01XB, J01AA12 and J01XX08) in Norway, presented per hospital/health trust in 2023. 1st generation cephalosporins and tetracyclines are not included as they in hospitals mainly are used for surgical prophylaxis. Metronidazole is also excluded from the figure because it does not readily fit either of the descriptions "preferred" or "resistance driver", and there are no alternative drugs mainly targeting anaerobic bacteria. Data source; hospital pharmacies drug statistics database.

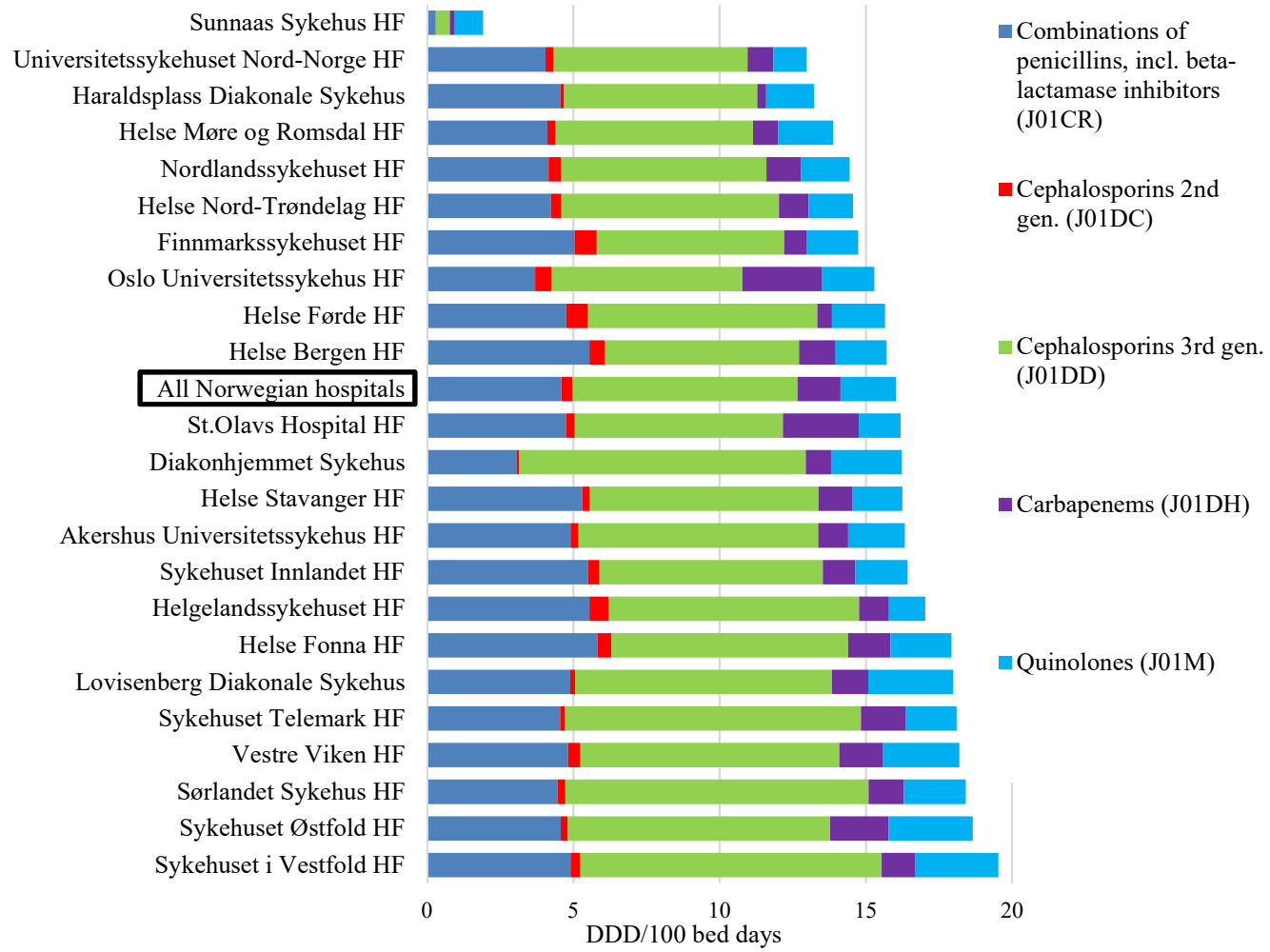


FIGURE 33. Consumption of selected antibacterial agents for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2023, measured in DDD/100 bed days. All hospitals, except one (Sunnaas Sykehus) are acute care hospitals. Data source; hospital pharmacies drug statistics database.

Are shortages partially behind increased sales of pediatric broad-spectrum antibiotics?

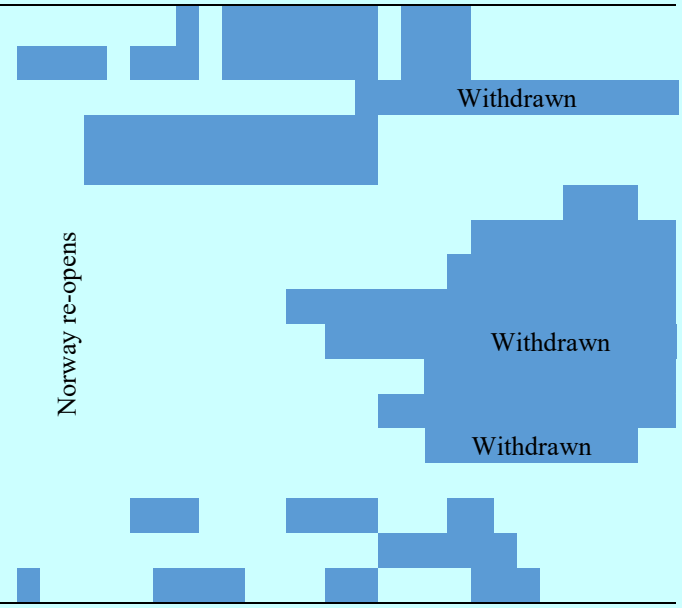
For several priority pediatric antibiotics, Norway is dependent upon sole suppliers. When infections increased post COVID-19, suppliers struggled to meet demand. Between 2018 to 2023, Norway had two companies with marketing authorisation for phenoxymethylpenicillin (PcV), including two pediatric formulations, a tablet (165 mg) and an oral suspension (50 mg/ml). In February 2021, one company withdrew its syrup after months of shortage, leaving a sole syrup supplier.[1] In March 2021, the tablet was withdrawn.[1] Thus, during the pandemic, when demand was low due to infection prevention and control measures, Norway became reliant upon a sole supplier of pediatric PcV, a first line antibiotic for many pediatric infections.

Figure 34 illustrates shortages reported to the Norwegian Medical Products Agency (DMP) for selected pediatric antibiotics during 2022 and 2023.[1] A shortage is not a stock-out but the inability to fill an order. Hence, despite reporting a shortage, oftentimes wholesalers and pharmacies will still have sufficient stocks. Almost immediately after re-opening in March 2022 shortages of pediatric amoxicillin were notified from one of Norway's two suppliers due to increased international sales and insufficient supply. As schools started again in September 2022, shortage notifications for priority antibiotics increased, including PcV. To address the uncertain supply, Norway's Antibiotic Center for Primary Care (ASP) published advice to primary care physicians regarding which antibiotics to prescribe when PcV oral suspension was unavailable, giving seven alternatives ranging from narrow to broadest spectrum.[2] January 2023 saw the greatest number of prioritised antibiotics notifying shortages. Anecdotal reports of pediatric antibiotic stockouts were reported in newspapers.[3]

Despite the shortages, Norway maintained access to effective antibiotics during winter 2022/23. A primary care medicine stockpile, including syrup formulations of PcV and erythromycin, was operational with up to six months of stock. Wholesalers continued to sell PcV, amoxicillin, and other priority antibiotics. Yet when assessing the wholesaler sales of the ASP prioritised antibiotic syrups in addition to clarithromycin and azithromycin, two broad-spectrum antibiotics saw a doubling in sales, amoxicillin/clavulanic acid and azithromycin (Figure 35).

When demand outstrips supply, it will be almost impossible for manufacturers to expedite production. Penicillins are produced via fermentation, a process that cannot be hastened, requiring over one month to produce the active pharmaceutical ingredient (API) and finished antibiotic. Fermenting sugar into API is energy intensive. Norway (and the world) reopened at the same time that Russia invaded Ukraine, which dramatically increased energy prices, and therefore the cost of antibiotic production. Shortages were not unique to Norway; amoxicillin shortages were ubiquitous in the global press during winter 2022/23.

ASP Rank	Antibiotic	Substance
1	Weifapenin 50 mg/ml (100ml)	PcV
1	Weifapenin 50 mg/ml (200ml)	PcV
2	Imaxi 100 mg/ml (60 ml)	AMX
2	Amoxicillin Sandoz 100 mg/ml (60 ml)	AMX
2	Amoxicillin Sandoz 100 mg/ml (100 ml)	AMX
3	Keflex 50 mg/ml (100 ml)	CEF
3	Ery-Max 100 mg/ml (50 ml)	ERY
3	Ery-Max 100 mg/ml (100 ml)	ERY
3	Abboticin 40 mg/ml (100 ml)	ERY
3	Abboticin 40 mg/ml (200 ml)	ERY
3	Abboticin 100 mg/ml (50 ml)	ERY
3	Abboticin 100 mg/ml (100 ml)	ERY
3	Abboticin 100 mg/ml (200 ml)	ERY
4	Bactrim 40/8 mg/ml (100 ml)	SXT
5	Augmentin 80/11.4 mg/ml (70 ml)	AMC
6	Dalacin 15 mg/ml (80 ml)	CLI
--	Azitromax 40 mg/ml (15 ml)	AZI



PcV=Phenomymethylpenicillin, AMX=Amoxicillin, CEF=Cefalexin, ERY=Erythromycin, SXT=Trimethoprim/Sulfamethoxazole, CLI=Clindamycin, AZI=Azithromycin.

FIGURE 34. Reported shortages to the Norwegian Medical Products Agency (DMP), for syrup formulations of the prioritised Antibiotic Centre for Primary Care (ASP) antibiotics in addition to azithromycin. A product is indicated as a shortage (blue) if it was reported to DMP for more than six days during the month as of June 24, 2024.

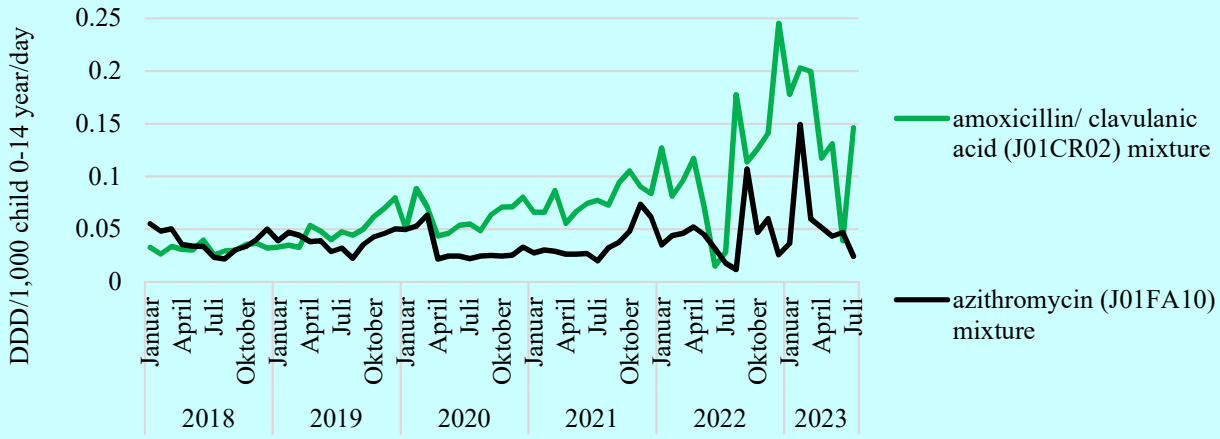


FIGURE 35. Sales, measured in DDD/1,000 child 0-14 years, of oral suspension (mixtures) formulations of J01CR02 amoxicillin and clavulanic acid and J01FA10 azithromycin pr month in Norway, January 2018 to July 2023. Of all antibiotic mixtures, 93-96% are prescribed to children 0-14 years, hence this population is used to present the data. Drug data from the Norwegian drug wholesales statistics database and population data from Statistics Norway, SSB.

Without data regarding the actual prescriptions and indications, it is not possible to conclude why broad-spectrum pediatric formulation sales increased during winter 2022/23. Yet the large number of narrow(er)-spectrum antibiotics in shortage indicates that physicians likely prescribed the antibiotics that they knew to be available at pharmacies. Although the increase appears sharp, the actual number of units was still modest. Several interventions have been adopted to avert shortages in Norway, including the formation of national medicine stockpiles in 2020. DMP increased unit prices for many older antibiotics in 2023 and secured an additional marketing authorisation holder for PcV syrup as of March 2024. Lastly, Norway is active within the second EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI-2), which is working on mitigating some of the underlying causes of shortages, particularly older, narrow-spectrum antibiotics like PcV.

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Effect of methenamine shortage on antibiotic prescribing for urinary tract infections in Norway - an interrupted time series analysis

Background
Urinary tract infections (UTIs) are common infections among women, with increasing disease burden with age. To slow down the progression of AMR, it is important to explore non-antibiotic preventive treatment strategies. Despite a lack of conclusive evidence of effect, methenamine is widely prescribed as preventive treatment for recurrent UTIs in Norway[1]. A national discontinuation of methenamine treatment due to a 4-month drug shortage in 2019 presented an opportunity to evaluate its preventive effect on UTIs among regular users[2].

Objective
To estimate the impact of the methenamine drug shortage on prescription frequency of UTI antibiotics.

Methods
Data from Norwegian Prescribed Drug Registry was analysed using an interrupted time series design (ITSA). ITSA is a quasi-experimental study design well suited to investigate the effects of defined population-level interventions where randomised controlled trials (RCTs) are not feasible. In this study, the time-limited national drug shortage of methenamine was utilised to retrospectively evaluate the effect of the shortage on UTI antibiotic use. The time series consisted of 56 time periods of 14 days. The model included two naturally occurring interruptions: (i) the methenamine drug shortage, and (ii) reintroduction of the drug. The study population were 18,345 women ≥50 years receiving ≥2 prescriptions of methenamine in the study period before the shortage. The main outcome measure was number of prescriptions of UTI antibiotics (defined as first-choice drugs for acute cystitis in the Norwegian guidelines: pivmecillinam, nitrofurantoin and trimethoprim) per 1,000 methenamine users.

Results
We found a significant increase of 2.41 prescriptions per 1,000 methenamine users per 14-day period during the drug shortage (95% CI 1.39, 3.43, p<0.001), followed by a significant reduction of -2.64 prescriptions after reintroduction (95% CI -3.66, -1.63, p<0.001).

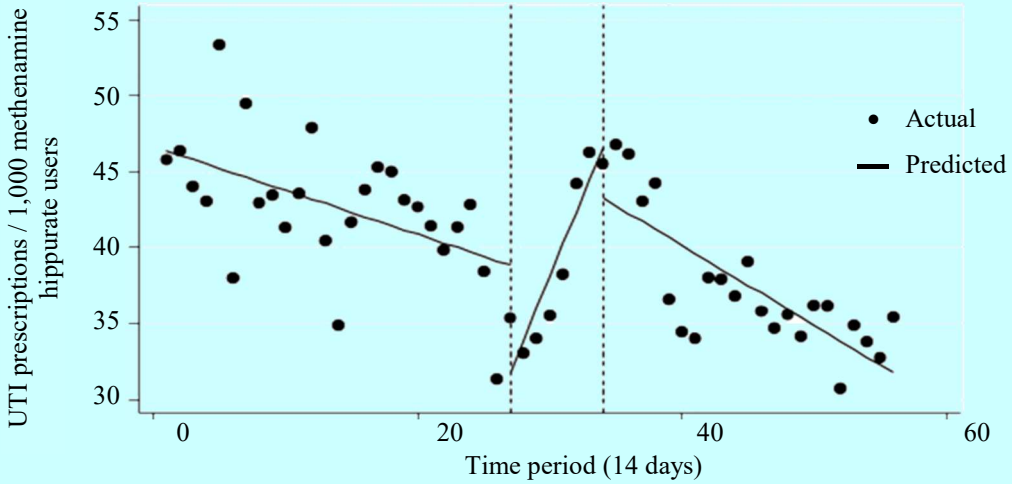

FIGURE 36. ITSA with two 'interventions' in time periods 27 (15.01.19-28.01.19) and 34 (23.04.19-06.05.19) for prescriptions of UTI antibiotics among women ≥50 years that had received ≥2 prescriptions of methenamine in the study period before the drug shortage. The first vertical line indicates the start of the drug shortage, the second vertical line indicates the end of the shortage[2].

Conclusions
During the methenamine drug shortage, we found a significant increase in prescribing trend for UTI antibiotics followed by a significant decrease in prescribing trend after reintroduction. This change in trend seems to reflect a preventive effect of the drug on recurrent UTIs. More information on the study can be found in the published research paper[2].

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National Action Plan against Antibiotic Resistance in Healthcare – National Targets for Antibiotic Use and change according to target

In 2015, a National Strategy against Antibiotic Resistance was agreed upon, aiming to reduce the total volume of antibiotics by 30%, as compared to 2012, by the end of 2020. Due to the COVID-19 pandemic the strategy period has been extended until a new strategy is in place. The National Strategy against Antibiotic Resistance was followed by a National Action Plan, issued January 2016, with suggested measures to reach the targets. The overall goal for total human consumption was a reduction of DDDs by 30%. In addition, two sector specific goals in ambulatory care were introduced; reduction of average number of prescriptions (target; 250 prescriptions per 1,000 inhabitants per year) and reduction of antibiotics for respiratory tract infections by 20% (in DDD/1,000 inhabitants/day). Figure 37 shows total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to National targets. DDD/1,000 inhabitants/day for J01 is reduced by 16% since 2012. When excluding methenamine the reduction in use is 23% (Table 7).

For hospitals, the main target was 30% reduction in combined use of five selected groups of antibiotics. To reach this goal, the National Action Plan also made antibiotic stewardship programs mandatory in Norwegian hospitals. Figure 38 shows the annual variation of total hospital use of these groups in the years 2006-2023 according to the national target.

For all hospitals in Norway together there was 8% reduction in use of the five selected groups of broad-spectrum antibiotics from 2012 to 2023 when adjusted for activity (bed days). The number of bed days is going down every year and there is a large increase in outpatient consultations. Using only bed days as an indicator of clinical activity confounds the drug use data, and it it likely that the use of other activity indicators would produce different results. Unadjusted sales data measured in DDDs show a reduction of 21% for the same period (see also Figure 30).

Norway has two national advisory units for antibiotic use and antibiotic stewardship interventions, one for primary care (established in 2006); the Antibiotic Centre for Primary Care (ASP), and one for hospitals/specialist services (established in 2011); the National Centre for Antibiotic Use in Hospitals (NSAS). These advisory units were strengthened and appointed key roles in the National Action plan. The Norwegian Directorate of Health has, in collaboration with the advisory units, issued National Antibiotic Treatment Guidelines for antibiotic use for ambulatory care, nursing homes, dentists and hospitals.

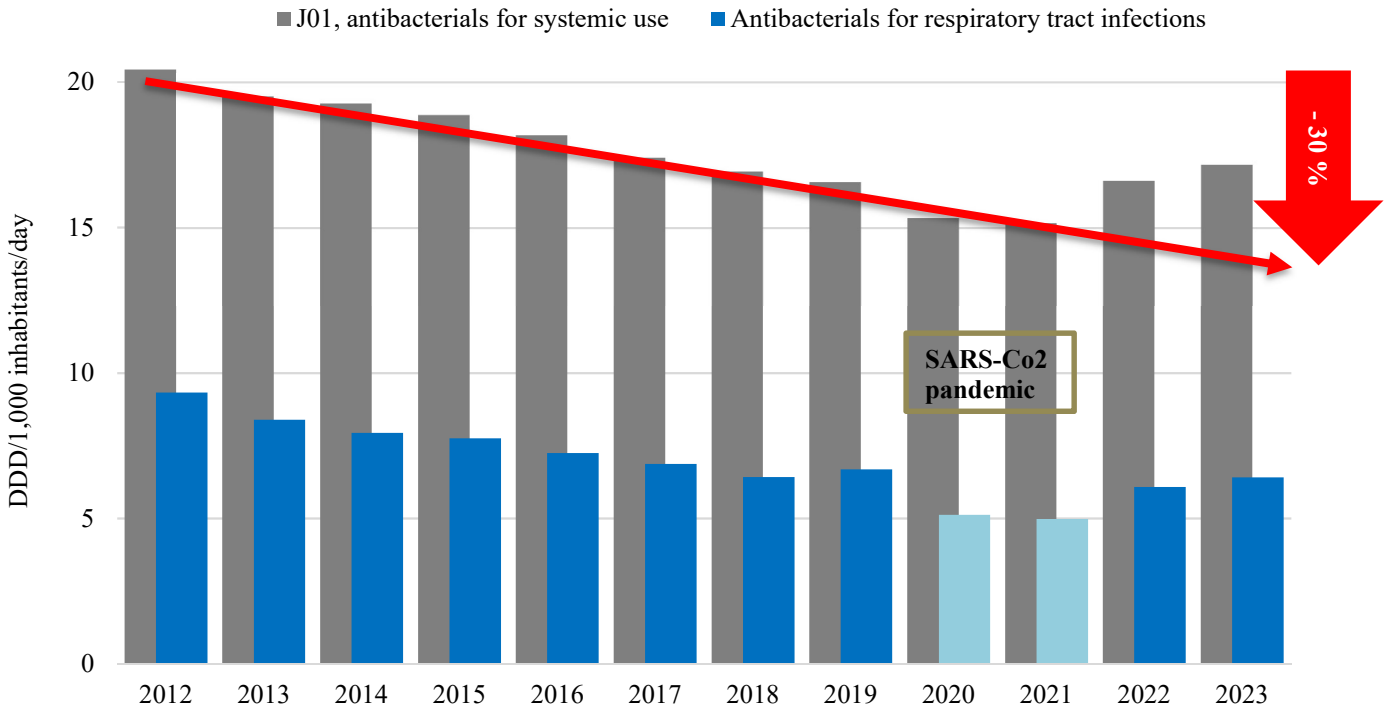

FIGURE 37. Total human sales of antibacterial agents for systemic use (ATC group J01) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway 2012-2023 measured in DDD/1,000 inhabitants/day. According to the National Action Plan (NAP), the target was 30% reduction of total use since 2012, measured in DDDs (end of red line). Bars show measured use 2012-2023 (grey; J01, blue; antibiotics for respiratory tract infections). Data from the Norwegian drug wholesales statistics database.

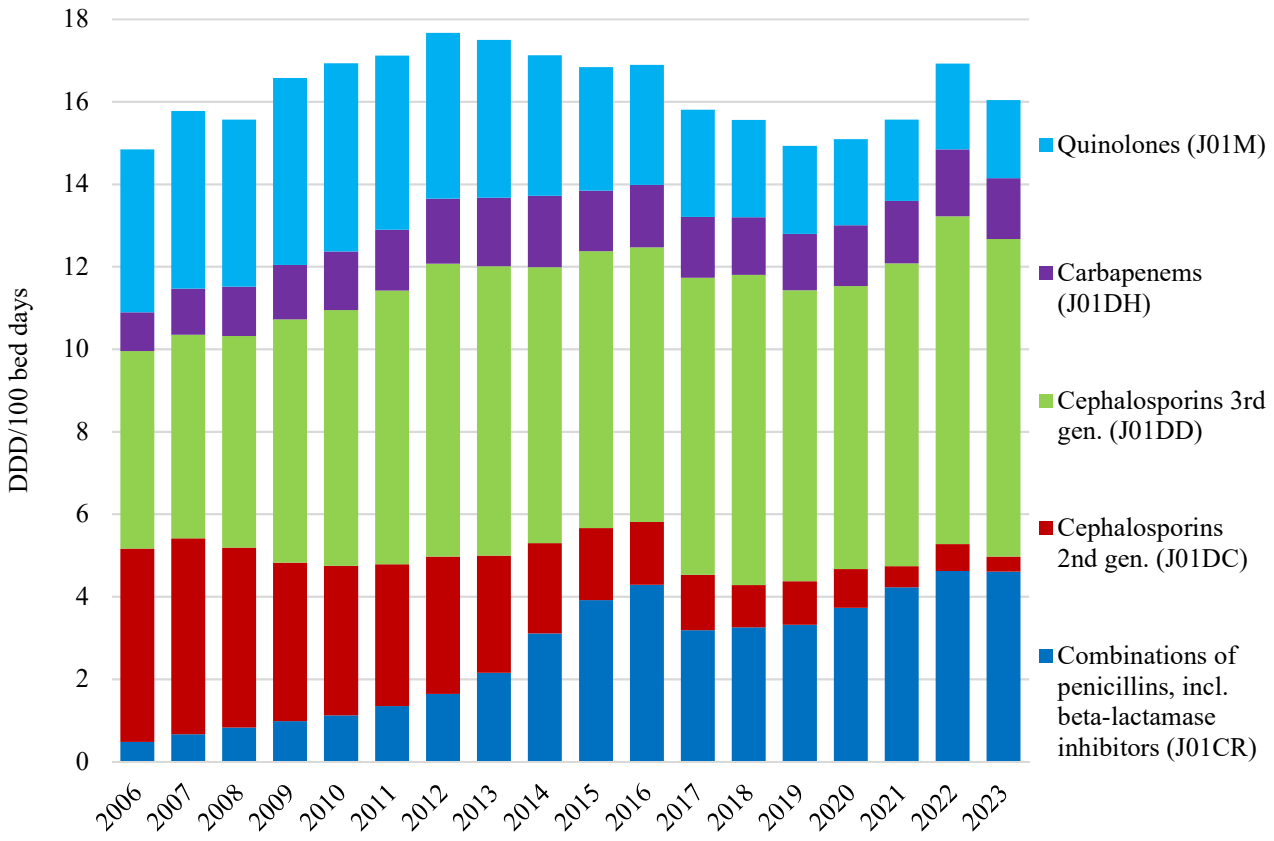

FIGURE 38. Consumption of selected antibacterial agents for systemic use (ATC-groups J01CR, J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2023, measured in DDD/100 beddays. Data source; hospital pharmacies drug statistics database.

New Automated Antibiotic Report for Prescribers

Both international research, as well as experience from Norwegian general practice, show that reviewing and providing feedback on one's own antibiotic prescribing contributes to lower and more appropriate use of antibiotics (1). As part of the Action Plan against Antibiotic Resistance from 2016, the Antibiotic Centre for Primary Care was tasked with developing and implementing a quality improvement course for general practitioners, where personal antibiotic reports were a key element. The course, called RAK (Riktigere Antibiotikabruk i Kommunene), was offered to all Norwegian list-holding GPs, county by county, from 2016 to 2021. Up to half of all GPs enrolled, and antibiotic use was significantly improved among participating GPs. In the RAK course, the personal reports were produced in a rather manual way, with orders sent from the Antibiotic Centre to Norwegian Prescribed Drug Registry (NorPD) at the Norwegian Institute of Public Health (NIPH), and the reports were then printed and sent by mail to participating doctors.

Based on the effect of the RAK course and the feedback from participants, there was a need to continue the audit and feedback scheme. However, the manual report generation from the first round of RAK was not feasible if such a solution was to be offered continuously to all GPs in Norway. Hence, NIPH and ASP applied for and received funding from the Research Council, under the call Innovation Project in the Public Sector, to develop an online login solution that could automatically provide each prescriber with their own antibiotic report whenever they wished. Simultaneously, studies were conducted on what was necessary for GPs to be willing to make use of such a solution (2,3).

In May 2024, the solution was launched. The report retrieves drug data from NorPD and activity data from Norwegian Registry for Primary Health Care (NRPHC). The activity data make it possible to calculate a prescription rate, i.e. at how many infection consultations the doctor prescribes antibiotics. The report consists of a total of 21 tables and figures, showing numbers for the latest self-defined period compared with a previous, self-defined period. In this way, prescribers can examine whether their prescribing has changed over time. The report is divided into an introductory section, an overview of total antibiotic prescribing, and then chapters addressing respiratory antibiotics, urinary tract antibiotics, and acne treatment. For many of the tables and figures, the individual GP can compare their own prescribing with the mean prescribing of GPs in the county and in Norway.

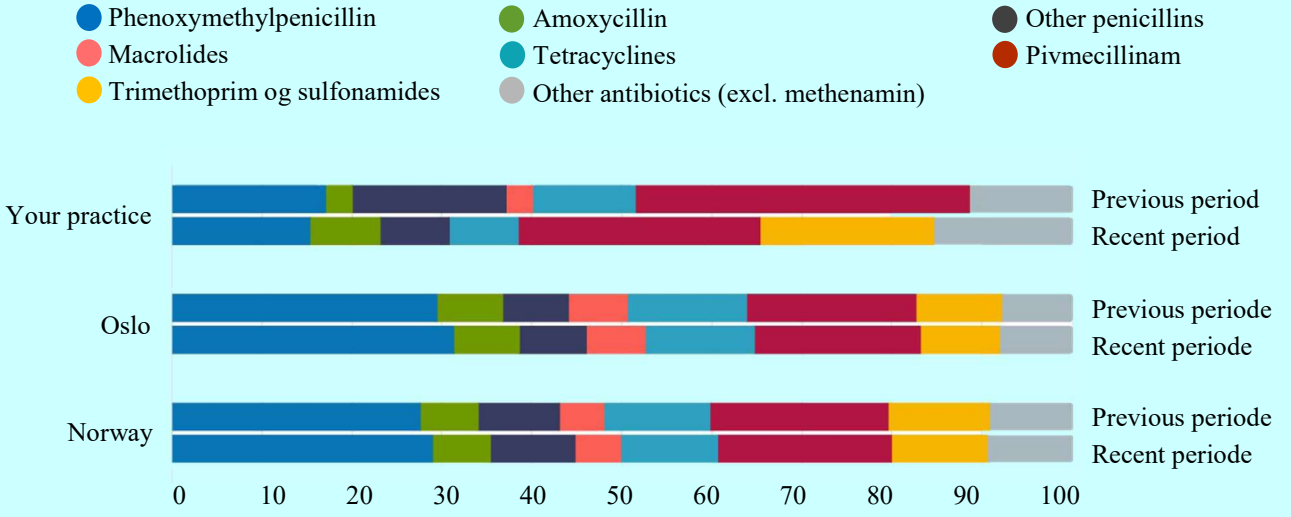

FIGURE 39. Example from an individual report: Proportion of prescriptions within each antibiotic group in the previous and in the last 12-month period compared to the average GP prescription in Oslo and Norway.

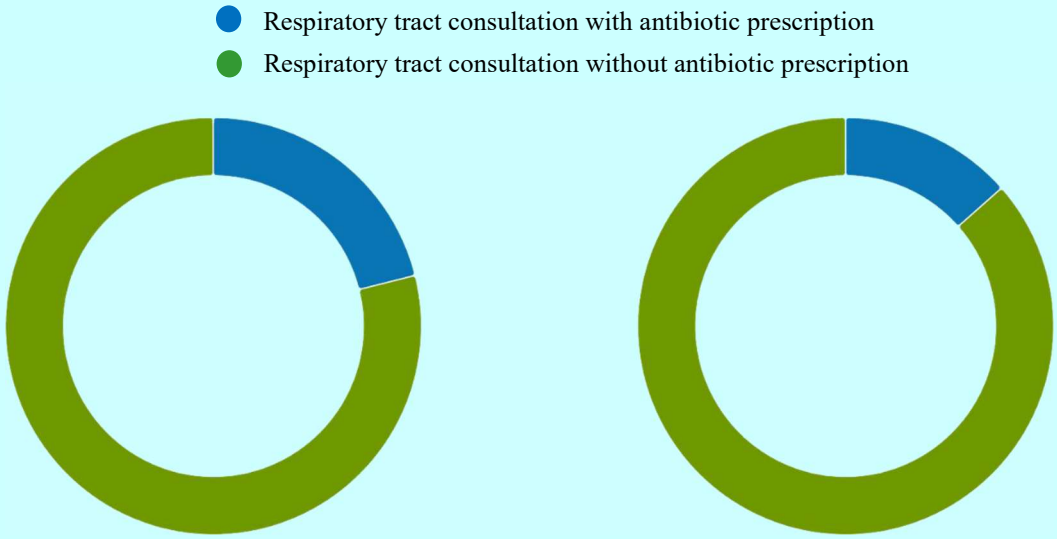

FIGURE 40. Antibiotic prescription rates for respiratory tract infections in the previous and in the last 12-month period.

Studies have shown that access to an antibiotic report alone does not necessarily lead to improvement (4). It is therefore crucial that the report is used within a framework of quality improvement, as in the first round of RAK. ASP is therefore in the process of developing courses and quality improvement schemes specifically tailored to the new antibiotic report. The courses are designed so that they easily can be used in the general practitioners' continuing medical education groups.

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Access to antibiotics in Norway

The transferral of Ukrainian war patients with wounds colonised or infected with multi-drug resistant (MDR) bacteria in May 2022 and onwards, showed the Norwegian medical community the wicked face of antimicrobial resistance (AMR) and the importance of having effective antibiotics available (Norge har for dårlig antibiotikaberedskap, 2022). After a few hectic weeks, several newer broad-spectrum "last resort" antibiotics were procured as a result of a joint effort by several key actors.

Shortages and limited access to antibiotics is a global problem. The causes are complex, and despite several initiatives to ensure availability and access in Norway, this progressively will challenge the treatment of patients suffering from infectious diseases in the years to come. The antimicrobial resistance situation in Norway is favourable and most infections are treated with narrow-spectrum antibiotics, unlike in most other countries.

Examples of clinically relevant limited supply of antibiotics in Norway

Piperacillin/tazobactam – global disruption of supply 2016-2017. A fire in the manufacturing unit of the active pharmaceutical ingredient (API) in China led to shortages of piperacillin-tazobactam, which disrupted the global supply for many months (Larsson, 2017). However, several alternatives with overlapping antibacterial activity were available, such as meropenem, or combination regimens with ampicillin, gentamicin and metronidazole.

Medevac patients from Ukraine – antibiotics to treat MDR-infections. Many of these patients developed complicated infections, for which effective antibiotics had to be procured. There were several issues to address: a) There were no national or local guidelines available, only European and US guidelines; b) There was a need for a prioritised list of antibiotic agents effective against MDR infections, which was developed by the National Advisory Unit for Antibiotic Use in Hospitals in collaboration with several infectious disease specialists. Most of the listed antibiotics were not available in Norway; c) Technical issues, such as antimicrobial susceptibility testing, had to be clarified; d) Funding for purchase of antibiotics had to be secured, as newer antibiotics might cost 100-fold more than conventional first line antibiotics. The medical directors of the four regional health authorities approved the purchase.

Phenoxymethylpenicillin – unstable supply, especially pediatric formulations, ongoing. Phenoxymethylpenicillin is the most used antibiotic in Norway. There has been an unstable supply of phenoxymethylpenicillin tablets with different strengths in 2023-2024. However, generics have so far been available. During the winter 2022/2023, there was a surge in infections with invasive strains of group A streptococci (GAS), especially scarlatina, in children (Streptokokk gruppe A-infeksjon – håndbok for helsepersonell, 2024). This coincided with a shortage of mixture formulations of phenoxymethylpenicillin, which led to increased use of mixture formulations of other antibiotics. Tablet strengths of phenoxymethylpenicillin (165mg, 330mg) suitable for children were previously marketed in Norway, but these are no longer available.

Consequences of poor access to antibiotics

In Norway, the low-stock alert of piperacillin/tazobactam provided an opportunity for antibiotic stewardship focussing on indications for antibiotic treatment, and the recommendation of an ecologically favourable combination treatment of ampicillin, gentamicin and metronidazole for abdominal infections. The case of Medevac patients from Ukraine highlighted the importance of access to antibiotics with activity against carbapenem resistant antibiotics as lifesaving remedies. The unavailability of narrow-spectrum penicillins (phenoxymethylpenicillin and benzylpenicillin) does not pose an immediate threat to patient safety, if alternative antibiotics are available. However, a prolonged shortage may induce a permanent shift in the doctors' prescribing practices towards more broad-spectrum alternatives, especially for respiratory tract infections, and thus facilitate spread of AMR.

Access and supply, how can Norway prepare?

The supply of narrow-spectrum antibiotics to Norway, in particular oral solutions, is vulnerable, due to few suppliers, small markets/volume and low profits. This problem has been raised in several reports:

- In 2017, the Norwegian Institute of Public Health, FHI, (Folkehelseinstituttet) published the report «Sikre riktig bruk, bevaring og tilgjengelighet av særskilt viktige antibiotika i den norske helsetjenesten - Erfaringer med forsøk på å utvikle en norsk pilot og en fremtidig modell». The report was commissioned by the steering committee for The National Action Plan against Antibiotic Resistance in the Norwegian health care services.
- In 2019, the Norwegian Directorate of Health published a report on National drug preparedness. As a sub-project, a survey of access to important antibiotics was carried out.
- In 2022, the Norwegian Directorate of Health published "Mulighetsstudie for antibiotikaproduksjon", listing 5 recommended measures.

Many actors are involved in drug preparedness. Of notice, "Mangelsenteret" is owned by the Regional health authorities and is only responsible for serving specialist healthcare (hospitals). There is no equivalent center for primary healthcare.

TABLE 10. Key actors in drug preparedness in Norway

Government bodies and key actors	Most important responsibilities and functions
Norwegian Directorate of Health (HDir)	National drug preparedness authority, responsible for coordination during a crisis of supply.
Directorate for Medical Products (DMP)	Monitoring supply and resolving day-to-day shortages in the event of a low-stock alert. Granting licenses for the sale of foreign packages. The Marketing Authorisation holder is obliged to inform DMP in all cases of supply failures in the Norwegian market.
National center for drug shortages and drug preparedness in the specialist healthcare (Mangelsenteret)	Prevents, detects, and solves drug shortages in specialist healthcare and gives advice to local-and regional drug and therapeutics committees. Gives advice concerning drug preparedness on local, regional and national level.
The Norwegian Hospital Procurement Trust (Sykehusinnkjøp)	Conducts tenders for medicines, including antibiotics, on behalf of Norwegian hospitals.
The Norwegian statutory emergency storage of selected medicines	Includes storage of five oral antibiotic formulations, and three parenteral formulations.
The Norwegian Pharmaceutical Stockpile, B180, (Nasjonalt legemiddelberedskapslager)	Counteracting situations with shortages of critically important medicines in the event of low supply. Includes 20 parenteral antibiotic formulations.

International initiatives with Norwegian participation

The Nordic Pharmaceutical Forum. The forum focuses on critical areas such as narrow-spectrum antibiotics and other scarce products. The aim is to foster a more sustainable and reliable supply chain by leveraging collective volume and addressing pricing concerns. Parenteral formulations for eight antibiotic substances (ampicillin, cefuroxime, ciprofloxacin, gentamicin, meropenem, metronidazole, piperacillin/tazobactam and vancomycin) were included in Joint Nordic Tender (Denmark, Iceland and Norway) for 2025.

The European Union's Health Emergency Preparedness and Response (HERA). HERA's responsibility is to ensure that the EU and Member States are ready to act in the face of cross-border health threats. The Critical Medicines Alliance (CMA) in HERA aims to strengthen the supply of critical medicines in the EU, ultimately enhancing efforts to prevent and address shortages effectively. The Nordic Pharmaceutical Forum is a member of the Critical Medicines Alliance.

The second EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI-2) started in 2024 and runs for four years. Norway (Norwegian Institute of Public Health) and Sweden (Public Health Agency of Sweden) lead the work package to strengthen access to antibiotics, as well as veterinary vaccines. The aim is to improve access to antibiotics that are both important and have vulnerable supply chains, such as narrow-spectrum penicillins and pediatric formulations.

Conclusions

Supply of antibiotics in Norway is vulnerable and shortages are likely to increase over the next years. Long term strategies, national preparedness and international collaborations are necessary to limit their consequences.

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Antimycotics for systemic use

Since 2012 the total use of antimycotics for systemic use (ATC group J02A), measured in DDD/1,000 inhabitants/days, has been quite stable. The azoles are the most used - fluconazole most frequently - both in primary care and in hospitals. Hospital use represented 12% of total J02A in 2023, measured in DDDs. In ambulatory care, almost all use (99% of DDDs) was oral in 2023, while in hospitals this proportion was 54%. In 2020, a jump in the use of fluconazole in primary care was observed and has since persisted (Figure 41). A common indication for fluconazole is vaginal candidiasis. From 2015, fluconazole became available as OTC, but the share of 150 mg capsules in small packs (one capsule in a pack) of total DDDs of fluconazole has decreased; in 2015 and 2016 13% and in 2023 11%. For antimycotics for systemic use the overall DDD/individual user outside hospitals has increased over the years. This may indicate that more individuals are treated for other fungal infections or treatment is of longer duration. The increased use of fluconazole outside hospitals warrants further investigation.

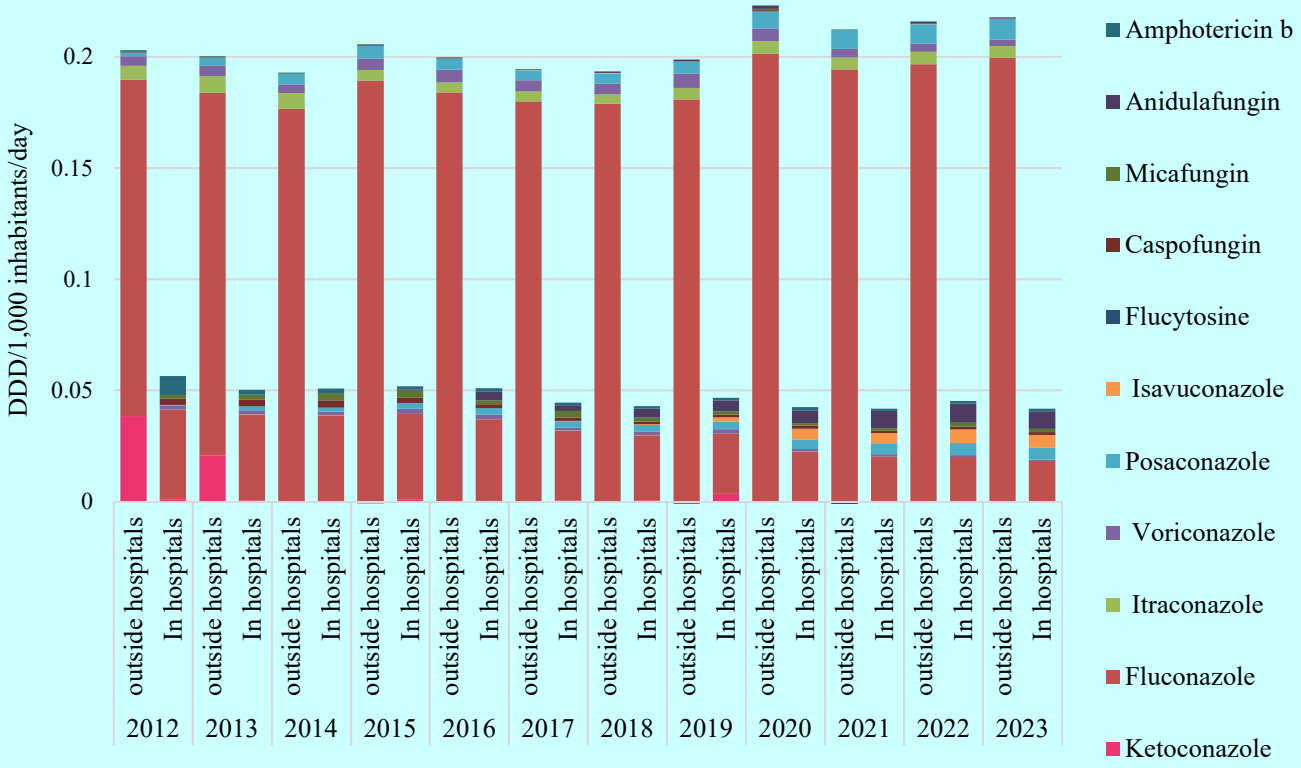

FIGURE 41. Usage of antimycotics for systemic use (ATC group J02A) in Norway outside hospitals and in hospitals 2012-2023, measured in DDD/1,000 inhabitants/year.

Within hospitals the pattern of use has changed (Figure 42). The use of fluconazole is decreasing, while both the echinocandins (micafungin, anidulafungin and caspofungin), isavuconazole and posaconazole are increasingly used. The chapter on invasive fungal infections in the National Treatment Guidelines for Hospitals was updated in autumn 2020 and the echinocandins became first line treatment for invasive candidiasis (earlier fluconazole). The three echinocandins are regarded as equal, but national drug tenders through the Norwegian Hospital Procurement Trust influence the choice and currently anidulafungin is the standard. Isavuconazole became available in 2017 and has now replaced voriconazole as first choice for treating invasive *Aspergillus* infections, but the reduced use of voriconazole does not explain the increase in the use of isavuconazole alone.

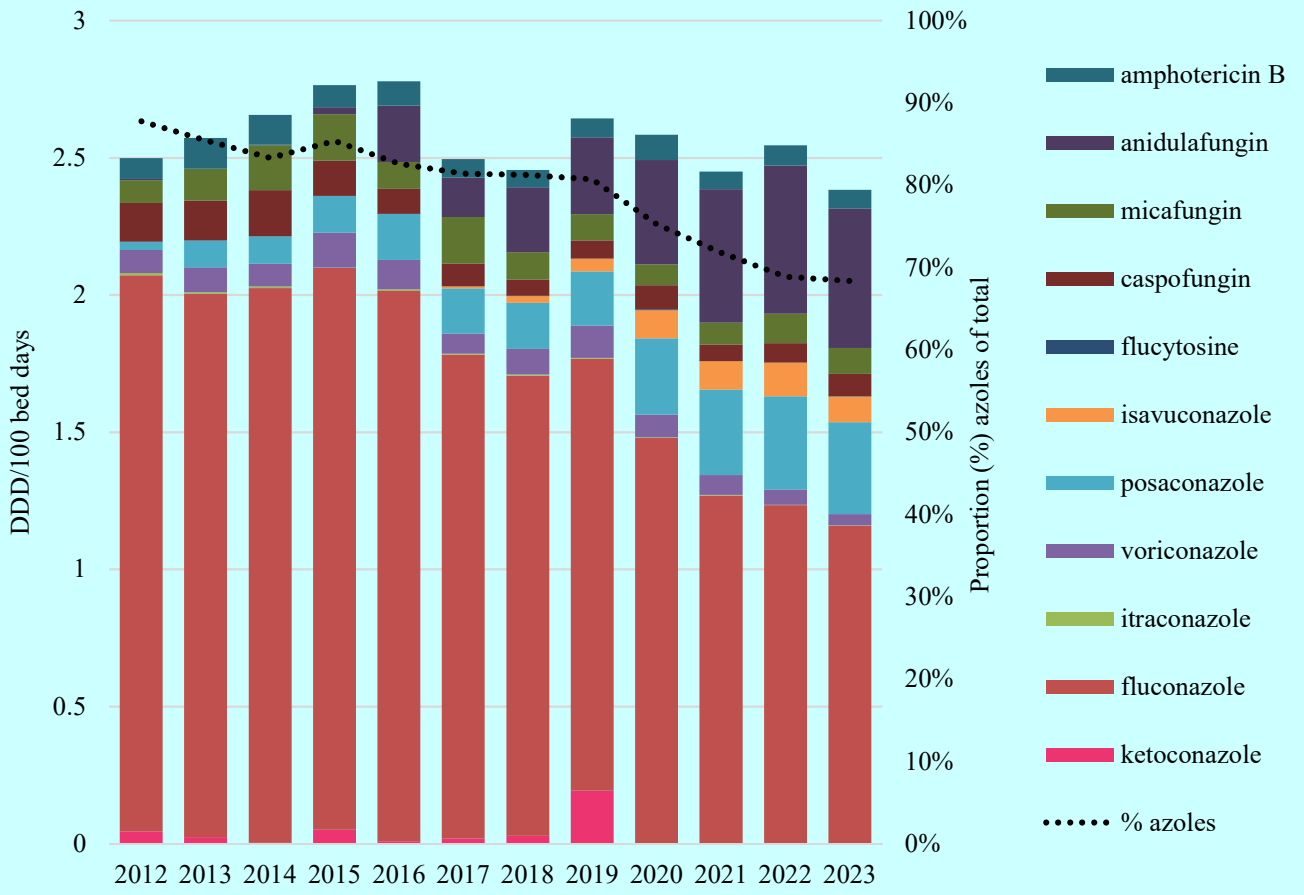

FIGURE 42. Usage of antimycotics for systemic use (J02) in hospitals in Norway 2012-2023, measured in DDD/100 bed days (columns) and percentage of azole of total use (dotted line).

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OCCURRENCE OF ANTIMICROBIAL RESISTANCE

ANIMAL CLINICAL ISOLATES

Madelaine Norström, Jannice Schau Slettemeås, Marianne Sunde and Anne Margrete Urdahl

The clinical isolates included in NORM-VET 2023 were *Escherichia coli* and *Staphylococcus pseudintermedius* from infections in dogs, and *Pasteurella multocida* and *Pasteurella canis* from infections in various animals. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from dogs

A total of 65 isolates of *Escherichia coli* from clinical submissions in dogs were collected between 2021 and 2023. The results are presented in Table 11, Figures 43-44, and in the text.

TABLE 11. Antimicrobial resistance in *Escherichia coli* from clinical infections in dogs (n=65) from 2021-2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	15.4	[6.5 – 24.7]								70.8	12.3	1.5		1.5	13.8			
Tigecycline	0.0	[0.0 – 5.5]					96.9	3.1										
Chloramphenicol	6.1	[1.7 – 15.0]										76.9	16.9	1.5	1.5	3.1		
Ampicillin	32.3	[21.2 – 45.1]								10.8	36.9	20.0			32.3			
Cefotaxime	3.1	[0.4 – 10.7]					96.9	1.5		1.5								
Ceftazidime	1.5	[0.0 – 8.3]					87.7	10.8				1.5						
Meropenem	0.0	[0.0 – 5.5]		100														
Trimethoprim	13.8	[6.5 – 24.7]					43.1	40.0	3.1					13.8				
Sulfamethoxazole	26.1	[16.0 – 38.5]										6.2	29.2	29.2	9.2	4.6		21.5
Azithromycin	1.5	[0.0 – 8.3]								15.4	46.2	35.4	1.5		1.5			
Gentamicin	0.0	[0.0 – 5.5]]						64.6	35.4									
Amikacin	0.0	[0.0 – 5.5]									93.8	6.2						
Ciprofloxacin	10.8	[4.4 – 21.0]	63.1	26.2			1.5	4.6	1.5			1.5	1.5					
Nalidixic acid	10.8	[4.4 – 21.0]									87.7	1.5			1.5	9.2		
Colistin	0.0	[0.0 – 5.5]							98.5	1.5								

*Bold vertical lines denote epidemiological cut-off values (ECOFFs) for resistance. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. Clinical breakpoints are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFF, ECOFF are shown. Clinical breakpoints defined by CLSI used for tetracycline, and for chloramphenicol EUCAST 2020 clinical breakpoints are shown. Clinical breakpoints not given for sulfamethoxazole, azithromycin and nalidixic acid.

RESULTS AND COMMENTS

In total, 53.8% of the isolates were susceptible to all antimicrobial classes included in the susceptibility testing. The following proportions of isolates were resistant to one or more antimicrobial classes: 20.0% were resistant to one, 10.8% to two and 15.4% to three or more antimicrobial classes. Resistance towards ampicillin, sulfamethoxazole, tetracycline, trimethoprim, and quinolones was most common as shown in Table 11 and Figure 43.

Two isolates displayed reduced susceptibility to the extended-spectrum cephalosporins cefotaxime and/or ceftazidime (3.1%; 95% CI: 0.4-10.7). These isolates displayed an AmpC beta-lactamase phenotype where one was genotyped *bla*$_{\text{CMY-2}}$ and one had the point mutation at n.-42C>T in the chromosomally located *ampC* gene causing upregulation of this gene. None of the *E. coli* isolates displayed resistance to the carbapenem meropenem.

Epidemiological cut-off values were used for the classification of resistance in these clinical *E. coli* isolates, facilitating comparison with surveillance results for indicator *E. coli*. There is a higher proportion of overall antimicrobial resistance in these clinical *E. coli* isolates compared to antimicrobial resistance in indicator *E. coli* from dogs as presented in Figures 62-64, page 76.

Clinical breakpoints are shown in dotted blue lines in Table 11. However, these clinical breakpoints are defined in order to indicate if treatment of a specific pathogen is likely to succeed or not, and factors like dosage, formulations, site of infection and host species will affect the clinical result.

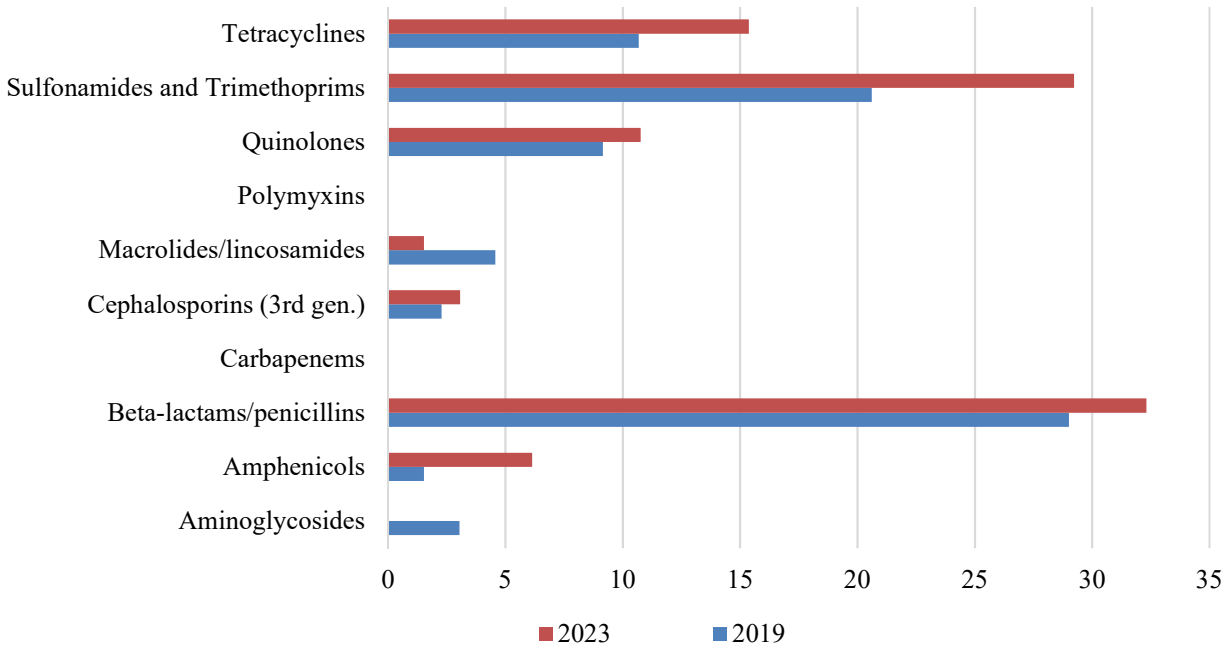

FIGURE 43. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from clinical infections in dogs, i.e. 131 isolates sampled between 2016 and 2018 (NORM-VET 2019) and 65 isolates from 2021-2023. The epidemiogical cut-off values used in NORM-VET 2023 were applied.

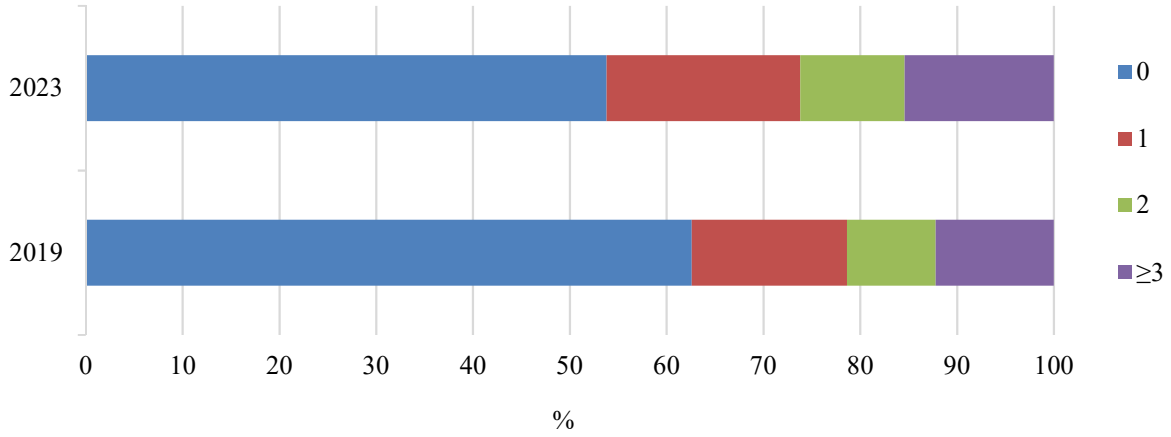

FIGURE 44. Antimicrobial resistance profiles for *Escherichia coli* from clinical infections in dogs, i.e. 131 isolates sampled between 2016 and 2018 (NORM-VET 2019) and 65 isolates from 2021-2023. Percentage of isolates susceptible to all (0), resistant to one (1), two (2), or three (3) or more antimicrobial classes are illustrated. The epidemiogical cut-off values used in NORM-VET 2023 were applied.

Compared to the data from 2019, the last time *E. coli* isolates from clinical submission from dogs were included (NORM-VET 2019), there has been a decrease in occurrence of fully susceptible isolates and an increase in occurrence of resistant isolates (Figure 44). This change in occurrence is mainly due to an increase in resistance to sulfonamides, trimethoprim, and tetracyclines as shown in Figure 43. In 2019, 20.6% of the isolates were resistant to sulfonamides, while this had increased to 29.2% in 2023. Resistance to tetracyclines increased from 10.7% in 2019 to 15.4% in 2023. None of these changes are, however, statistically significant, and further monitoring is needed to explore whether these are truly increasing trends.

E. coli is also included in the separate text box summarising the results from AniCura Diagnostic Laboratory (page 59). Comparing results is difficult due to differences in methodology. However, in both laboratories, resistance to beta-lactams/penicillins was commonly detected.

Staphylococcus pseudintermedius from dogs

A total of 195 of *Staphylococcus pseudintermedius* isolates from clinical infections in dogs were included. The isolates were collected through the years 2019 and 2023.

The results are presented in Table 12, Figures 45-46, and in the text.

TABLE 12. Antimicrobial resistance in *Staphylococcus pseudintermedius* from clinical infections in dogs (n=195) in 2019-2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.01			0.12												
			6	0.03	0.06	5	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	26.1	[20.1 – 32.9]						73.9				1.0		25.1				
Chloramphenicol	12.8	[8.5 – 18.3]									78.5	8.7		0.5	12.3			
Benzylpenicillin	ND	ND			31.3	2.1	13.3	7.2	6.2	40.0								
Cefoxitin	1.0	[0.1 – 3.7]						93.3	2.1	3.1	0.5	0.5		0.5				
Trimethoprim	20.0	[14. 6 – 26.3]							23.6	56.4	10.8	0.5	0.5	8.2				
Sulfamethoxazole	ND	ND													43.6	6.7	29.2	20.5
Erythromycin	20.0	[14. 6 – 26.3]					79.0	1.0	0.5				19.5					
Clindamycin	20.0	[14.6 – 26.3]				79.5	0.5	0.5			1.5	17.9						
Quinupristin-dalfopristin	1.5	[0.3 – 4.4]						95.9	2.6	1.5								
Streptomycin	20.0	[14. 6 – 26.3]									79.5	0.5		1.5	18.5			
Gentamicin	NA							91.3	0.5	1.5	4.1	1.0	1.5					
Kanamycin	21.0	[15.5 – 27.2]									79.0			3.6	17.4			
Ciprofloxacin	4.6	[2.1 – 8.6]					91.3	1.5	1.5	1.0			4.6					
Vancomycin	0.5	[0.0 – 2.8							98.5	1.0	0.5							
Fusidic acid	24.5	[18.7 – 31.3]					74.4	1.0	1.5	1.5		21.5						
Tiamulin	1.5	[0.3 – 4.4]						97.4		1.0		1.5						
Linezolid	0.0	[0.0 – 1.9]							100									
Mupirocin	0.0	[0.0 – 1.9]						100										
Rifampicin	0.5	[0.0 – 2.8]	97.4	2.1	0.5													

*Bold vertical lines denote epidemiological cut-off values (ECOFFs) for resistance. ND = not defined. NA = not applicable, CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. Clinical breakpoints are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFFs, only ECOFFs are shown. Clinical breakpoints are not defined by EUCAST for sulfamethoxazole, streptomycin, kanamycin and tiamulin, therefore ECOFFs only are included for these substances. For chloramphenicol, EUCAST 2020 clinical breakpoint is applied. Benzylpenicillin resistance was deduced from beta-lactamase production analysis.

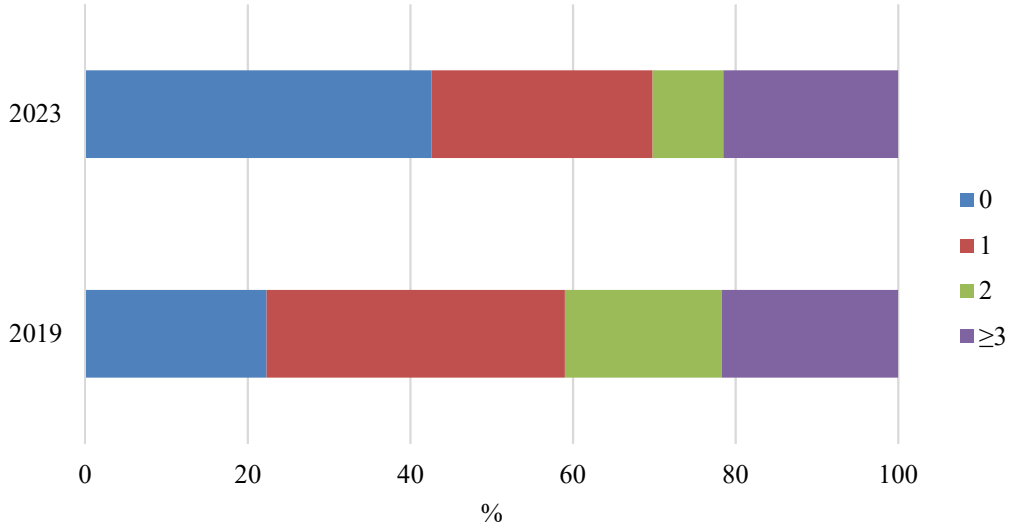

FIGURE 45. Antimicrobial resistance profile for *Staphylococcus pseudintermedius* from infections in dogs, i.e. 166 isolates sampled between 2017 and 2018 (NORM-VET 2019) and 195 isolates from 2019-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. The occurrence of resistance to penicillins, sulfamehoxazole and gentamicin were not included in the calculations. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

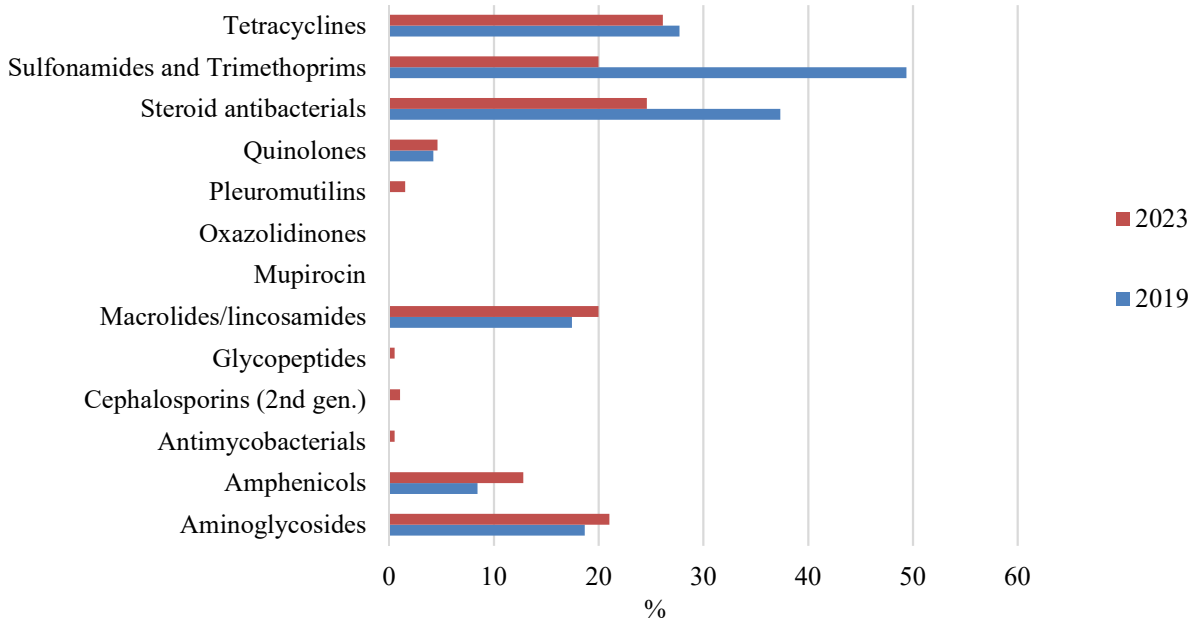

FIGURE 46. Prevalence of resistance to various antimicrobial classes in *Staphylococcus pseudintermedius* from infections in dogs, i.e. 166 isolates sampled between 2017 and 2018 (NORM-VET 2019) and 195 isolates from 2019-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. The occurrence of resistance to penicillins, sulfamehoxazole and gentamicin were not included in the calculations.

RESULTS AND COMMENTS

In total, 42.6% of the isolates were fully susceptible to all antimicrobial classes included in the calculations, 27.2% resistant to one, 8.7% resistant to two, and 21.5% resistant to three or more classes. Resistance to benzylpenicillin, gentamicin and sulfonamides were not included in these calculations. Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to fusidic acid, kanamycin, trimethoprim, erythromycin, clindamycin and streptomycin.

Resistance to benzylpenicillin was deduced from detection of beta-lactamase production using the clover leaf test. A total of 72.3% (95% CI: 65.5-78.5) of the isolates were defined as resistant. The majority, though not all, of the isolates with a positive beta-lactamase test had penicillin MIC values >0.125 mg/L, which is the ECOFF given by EUCAST. The majority of beta-lactamase negative isolates had penicillin MIC-values ≤0.125 mg/L.

S. pseudintermedius from infections in dogs were also included in the NORM-VET 2019 report. Compared to 2019 there has been an increase in occurrence of totally susceptible isolates (Figure 45). This is mainly due to significant decreases in resistance to trimethoprim from 49.4% in 2019 (NORM-VET 2019) to 20.0% in 2023 ($p<0.001$), and to steroid antibacterials (i.e fusidic acid) from 37.4% in 2019 to 24.6% in 2023 ($p=0.01$) as shown in Figure 46.

Oxacillin, the preferred indicator for identifying MRSP, is not included in the sensitivity test panel. The *S. pseudintermedius* isolates were therefore additionally subjected to oxacillin susceptibility testing using disk diffusion. Fourteen of the 195 isolates (7.2%; 95% CI: 4.0-1.8) were resistant to oxacillin and all were MRSP carrying the *mecA* gene.

The Sensititre® test panel used for susceptibility testing is designed for monitoring of staphylococcal isolates associated with both human and animal hosts. Some of the substances included may therefore not be of relevance for clinical use in companion animals. However, the substances are relevant in a One Health perspective and to allow for evaluation of resistance development in the future.

ECOFFs for *S. aureus* were used for the classification of resistance in these clinical isolates, facilitating comparison to the surveillance results for carriers, see page 79. Clinical breakpoints are shown in dotted blue lines in Table 12. However, these clinical breakpoints are defined in order to indicate if treatment of a specific pathogen is likely to succeed or not, and factors like dosage and formulations will affect the clinical result.

Overall, there is more multi-drug resistance among these clinical isolates compared to the *S. pseudintermedius* carrier isolates from healthy dogs as shown in Figure 65, page 79.

S. pseudintermedius is also included in the separate text box summarising the results from AniCura Diagnostic Laboratory (page 59). Comparing results is difficult due to differences in methodology. However, the results for the substances that were included in both panels (i.e. for tetracycline, benzylpenicillin, erythromycin, clindamycin and gentamicin) were rather similar indicating that the results were in concordance.

Pasteurella multocida from various animal species

A total of 143 *Pasteurella multocida* isolates from clinical infections (primarily respiratory infections) in various animal species were included (i.e. mainly cats, cattle, dogs and pigs). The isolates were collected through the years 2017 and 2023. The results are presented in Table 13, Figure 47, and in the text.

TABLE 13. Antimicrobial resistance in *Pasteurella multocida* from clinical infections (mainly respiratory infections) in various animal species (n=143) in 2017-2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*											
			0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Doxycycline	0.7	[0.0 – 3.9]			0.7	20.3	61.5	16.1	0.7	0.7				
Tetracycline	0.7	[0.0 – 3.9]				0.7	4.2	68.5	23.8	2.1	0.7			
Chloramphenicol	4.2	[1.6 – 8.9]							95.8	4.2				
Florfenicol	2.8	[0.8 – 7.0]							97.2	2.1	0.7			
Ampicillin	0.0	[0.0 – 2.5]				28.7	68.5	2.8						
Benzylpenicillin	0.0	[0.0 – 2.5]				90.2	9.1	0.7						
Amoxicillin-clavulanic acid	0.0	[0.0 – 2.5]				7.7	86.0	6.3						
Cefalexin	0.7	[0.0 – 3.9]								92.3	6.3	0.7	0.7	
Cefovecin	ND	ND				95.1	3.5	1.4						
Trimethoprim-sulfamethoxazole	3.5	[1.1 – 8.0]				96.5	3.5							
Erythromycin	NA	NA								53.9	44.1	2.1		
Clindamycin	ND	ND										100		
Gentamicin	0.0	[0.0 – 2.5]						4.2	7.0	73.4	15.4			
Enrofloxacin	1.4	[0.2 – 5.0]	63.6	33.6	1.4		0.7		0.7					
Pradofloxacin	ND		87.4	10.5	0.7	0.7	0.7							

*Bold vertical lines denote epidemiological cut-off values (ECOFFs) for resistance. ND = not defined. NA = not applicable. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. Clinical breakpoints are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFFs, only ECOFFs are shown. Clinical breakpoints are not defined for chloramphenicol, cefalexin, gentamicin, erythromycin and clindamycin, therefore ECOFFs only are included for these substances. Clinical breakpoints are defined by CLSI for tetracycline, florfenicol, cefovecin, enrofloxacin and pradofloxacin.

RESULTS AND COMMENTS

In total, 89.5% of the *P. multocida* isolates were susceptible to all antimicrobial agents included in the susceptibility testing. The following proportions of isolates were resistant to one or more antimicrobial classes: 9.8% were resistant to one (mainly amphenicols), and 0.7% to three antimicrobial classes (amphenicol, trimethoprim-sulfamethoxazole and enrofloxacin), respectively (Figure 47). *P. multocida* has not been included in NORM-VET previously.

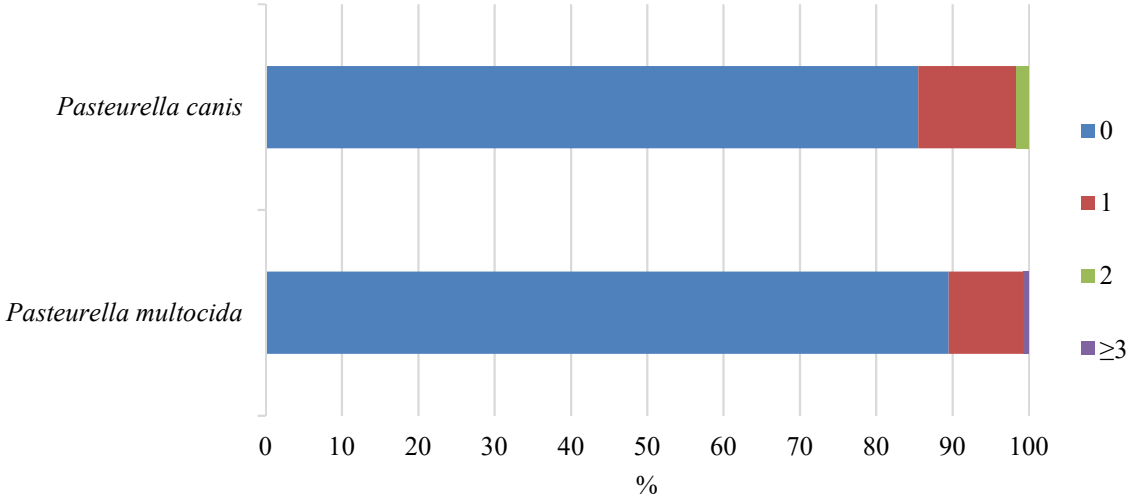

FIGURE 47. Antimicrobial resistance profile for *Pasteurella multocida* (n=143) and *Pasteurella canis* (n=62) from clinical infections in various animal species in 2017-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

Pasteurella canis from various animal species

A total of 62 of *Pasteurella canis* isolates from clinical infections in animals were included. The isolates were mainly from ear and skin infections in dogs in 2017-2023, though some isolates were from cattle and cats as well. The results are presented in Table 14, Figure 47, and in the text.

TABLE 14. Antimicrobial resistance in *Pasteurella canis* from clinical infections in animals (n=62) in 2017-2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*											
			0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32
Doxycycline	0.0	[0.0 – 5.8]			6.5	51.6	38.7	3.2						
Tetracycline	0.0	[0.0 – 5.8]				3.2	50.0	35.5	9.7	1.6				
Chloramphenicol	8.1	[2.7 – 17.8]							91.9	8.1				
Florfenicol	4.8	[1.0 – 13.5]							95.2	4.8				
Ampicillin	0.0	[0.0 – 5.8]			46.8	50.0	3.2							
Benzylpenicillin	0.0	[0.0 – 5.8]				96.8	1.6	1.6						
Amoxicillin-clavulanic acid	0.0	[0.0 – 5.8]				90.3	9.7							
Cefalexin	0.0	[0.0 – 5.8]								100				
Cefovecin	ND	ND				98.4		1.6						
Trimethoprim-sulfamethoxazole	3.2	[0.4 – 11.2]				96.8	3.2							
Erythromycin	0.0	[0.0 – 5.8]								95.2	4.8			
Clindamycin	ND	ND									9.7	90.3		
Gentamicin	0.0	[0.0 – 5.8]				6.5	3.2	62.9	14.5	11.3	1.6			
Enrofloxacin	3.2	[0.4 – 11.2]	91.9	4.8			1.6	1.6						
Pradofloxacin	ND	ND	96.8				3.2							

*Bold vertical lines denote epidemiological cut-off values (ECOFFs) for resistance. ND = not defined. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. Clinical breakpoints are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFFs, only ECOFFs are shown. Clinical breakpoints are not defined for chloramphenicol, cefalexin, gentamicin, erythromycin and clindamycin, therefore ECOFFs only are included for these substances. Clinical breakpoints are defined by CLSI for tetracycline, florfenicol, cefovecin, enrofloxacin and pradofloxacin.

RESULTS AND COMMENTS

In total, 85.5% of the *P. canis* isolates were susceptible to all antimicrobial agents included in the susceptibility testing. The following proportions of isolates were resistant to one or more antimicrobial classes: 12.9% were resistant to one (amphenicols), and 1.6% to two (amphenicols and quinolones) antimicrobial classes, respectively (Figure 47). *P. canis* has not been included in NORM-VET previously.

Antimicrobial susceptibility testing of clinical isolates from dogs and cats at AniCura Diagnostic Laboratory in 2023

Introduction

Better surveillance of antimicrobial resistance (AMR) in clinical bacterial isolates from dogs and cats is one of the focused target areas in the AMR Action Plan from the Ministry of Agriculture and Food. Clinical bacterial isolates from dogs have occasionally been included in the national AMR surveillance, i.e. in NORM-VET. To expand the surveillance further, the Norwegian Veterinary Institute (NVI) initiated a collaboration with the AniCura Diagnostic Laboratory (ADL) to assess the possibility to use their data on susceptibility testing of clinical isolates from dogs and cats. This is the second year ADL provides data for the national AMR surveillance in clinical bacterial isolates from dogs and cats.

ADL retrieves and analyses samples from veterinary clinics all around Norway. The laboratory carries out bacteriological examinations, including susceptibility testing of bacteria, and thereby constitutes an important additional source of data for national AMR surveillance purposes.

Material and methods

Data from ADL were anonymised before being sent to NVI. The only metadata shared in addition to bacterial species and susceptibility data, was information on animal species, source of infection, sampling date and requesting veterinary clinic. The two latter for the purpose of assessing overall national representativeness.

The data consisted of susceptibility testing results for a total of 90 *Escherichia coli*, 24 *Staphylococcus aureus* and 160 *Staphylococcus pseudintermedius* isolates. The *E. coli* were retrieved from urinary tract infections from a total of 69 dogs and 21 cats. The *S. aureus* were from skin and ear infections, abscesses etc. from 18 dogs and six cats, while the *S. pseudintermedius* were from skin and ear infections, abscesses and surgical wounds in dogs. Only one isolate per infection per animal was included.

All isolates were identified using VITEK® MS (bioMérieux). Susceptibility testing was done using a microdilution system on VITEK® 2 Compact, as recommended by the manufacturer. VITEK® AST-GN97 Gram-negative Susceptibility Card and VITEK® AST-GP80 Gram-positive Susceptibility Card were used for *E. coli* and the staphylococci, respectively.

Data management and analyses were performed using R version 4.2.2 Copyright (C) 2023 (The R Foundation for Statistical Computing Platform). We applied clinical breakpoint (CBP) values for defining an isolate as resistant or susceptible as the tested ranges for many cases were not compliable with the epidemiological cut-off (ECOFF) values. MIC values equal to, or lower than the lowest concentration tested are given as the lowest concentration tested, and resistant isolates can therefore not be defined by using ECOFFs in cases were ECOFFs are below the tested range. This was the case for trimethoprim-sulfamethoxazole in *E. coli* (Table 15), amoxicillin-clavulanic acid, cefalotin, trimethoprim-sulfamethoxazole and neomycin in *S. aureus* (Table 16) and doxycycline, amoxicillin-clavulanic acid, gentamicin and neomycin in *S. pseudintermedius* (Table 17). The CBP applied were mainly defined by EUCAST, but if these were not defined the CLSI CBPs were applied. In the tables we have included both the ECOFFs and the CBPs as far as these have been defined; either by EUCAST or CLSI.

Results and comments

Escherichia coli from urinary tract infections in dogs and cats

In total, results of susceptibility testing of *E. coli* from 69 dogs and 21 cats were included. Table 15 and Figure 48 show the results from the susceptibility testing.

In total, 63.8% of the *E. coli* isolates from dogs were susceptible to all antimicrobial agents included. Resistance to beta-lactams/penicillins (i.e. ampicillin) were the most frequently identified resistance determinants, followed by resistance to amphenicols (i.e. chloramphenicol) (Figure 48). Altogether, 23.2% of the isolates were resistant to one antimicrobial class, 10.1% to two and 2.9% to three or more antimicrobial classes, respectively (Figure 49).

Among the 21 *E. coli* isolates from cats, 15 isolates were susceptible to all antimicrobial agents included, two isolates were resistant to one antimicrobial class, two to two antimicrobial classes and two to three antimicrobial classes. The number of isolates from cats was few and any comparisons between the two animal species, as well as between years, have to be made with caution.

One isolate from a dog showed reduced susceptibility to the extended-spectrum cephalosporin cefovecin (1.4%; 95% CI: 0.04-7.8), and was additionally resistant to beta-lactams/penicillins and 1st generation cephalosporins. The isolate was susceptible to the carbapenem imipenem (data not shown).

TABLE 15. Antimicrobial resistance in *Escherichia coli* from urinary infections in dogs (n=69) and cats (n=21) in 2023.

Substance	Animal	Resistance (n)	Distribution (n) of MIC values (mg/L)*													
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Doxycycline	Dog	1				6	57	4		1	1					
	Cat	2				4	14	1			2					
Tetracycline	Dog	2					61	3	3		2					
	Cat	2					17	1	1		2					
Chloramphenicol	Dog	14						14	21	20	14					
	Cat	3						6	8	4	2		1			
Ampicillin	Dog	16						26	14	13	3	13				
	Cat	4						11	4	2		4				
Amoxicillin-clavulanic acid	Dog	2						44	17	6		2				
	Cat	1						16	2	2	1					
Cefalexin	Dog	0							11	53	5					
	Cat	0							6	14	1					
Cefpodoxime	Dog	0			45	15	6	3								
	Cat	0			17	3	1									
Cefovecin	Dog	1				57	8	3		1						
	Cat**	0				18	2									
Trimethoprim-sulfamethoxazole	Dog	3					66				3					
	Cat**	1					19				1					
Gentamicin	Dog	0					68	1								
	Cat	0					21									
Neomycin	Dog**	0						62								
	Cat**	1						18					1			
Amikacin	Dog	0						67	2							
	Cat	0						21								
Enrofloxacin	Dog	0		68			1									
	Cat	1		20					1							
Marbofloxacin	Dog	0				69										
	Cat	1				20			1							
Nitrofurantoin	Dog	0									66		3			
	Cat	0									20	1				

*Bold vertical lines denote epidemiological cut-off (ECOFF) values for resistance. White fields show range tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. Clinical breakpoints (CBP) are marked in blue dotted lines. CBPs for doxycycline, tetracycline, ampicillin, amoxicillin-clavulanic acid, amikacin and nitrofurantoin are the same as the ECOFFs and only ECOFFs are shown in the table. ECOFFs not defined for cefovecin and marbofloxacin. **Missing MIC results for some isolates.

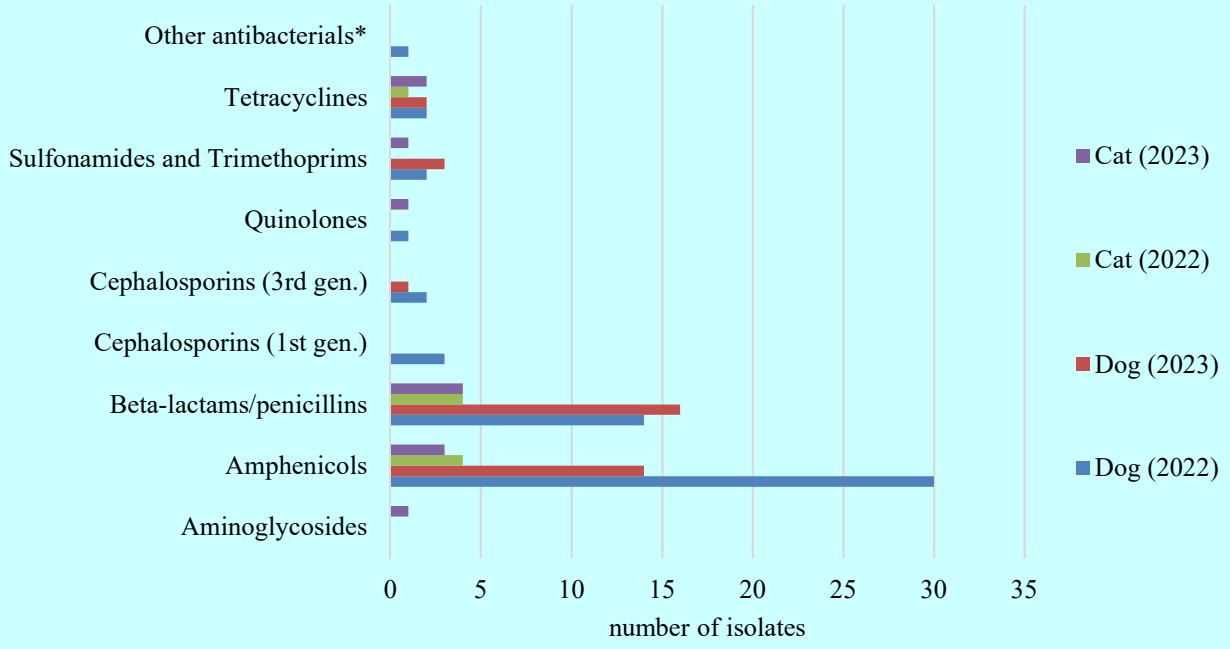

FIGURE 48. Antimicrobial resistance (number of isolates) in *Escherichia coli* from urinary tract infections in dogs (n=84, n=69) and cats (n=20, n=21) in 2022 and 2023, respectively. *i.e. nitrofurantoin.

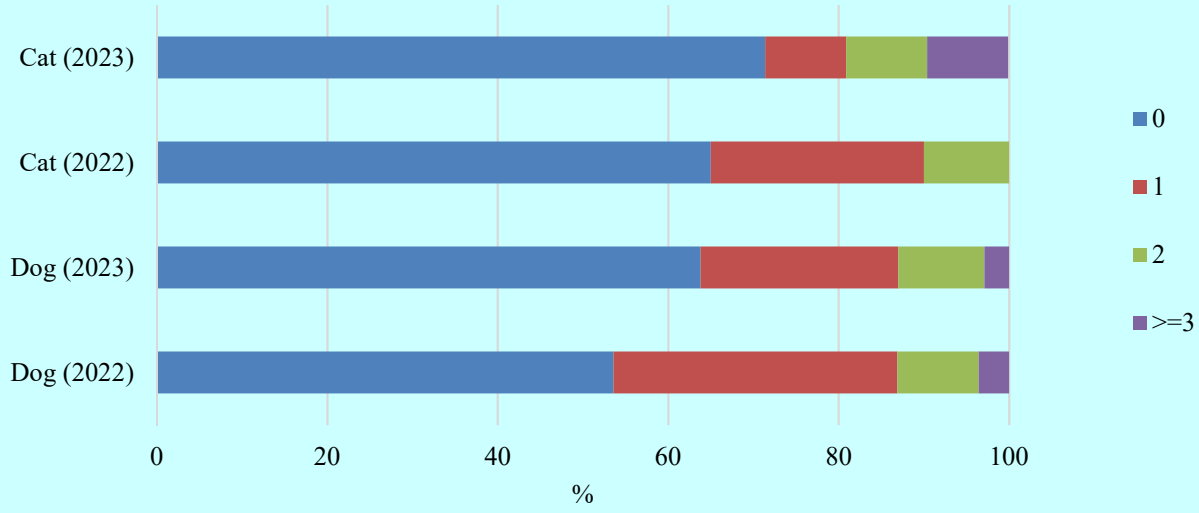

FIGURE 49. Antimicrobial resistance profile for *Escherichia coli* from urinary tract infections in dogs (n=84, n=69) and cats (n=20, n=21) in 2022 and 2023, respectively. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

The results from 2023 are in concordance with the results from 2022, although less isolates were resistant to chloramphenicol in 2023 (20.3%) compared to 2022 (35.7%) (non-significant decrease). *E. coli* isolates from infections in dogs were also included in the data retrieved from the NVI (see page 53). Comparing results are difficult due to differences in methodology. However, in both laboratories, resistance to beta-lactams/penicillin benzylpenicillin was commonly detected.

Staphylococcus aureus from skin and ear infections in dogs and cats

In total, results of susceptibility testing of *S. aureus* from 18 dogs and six cats were included. Table 16 and Figure 50 show the results from the susceptibility testing.

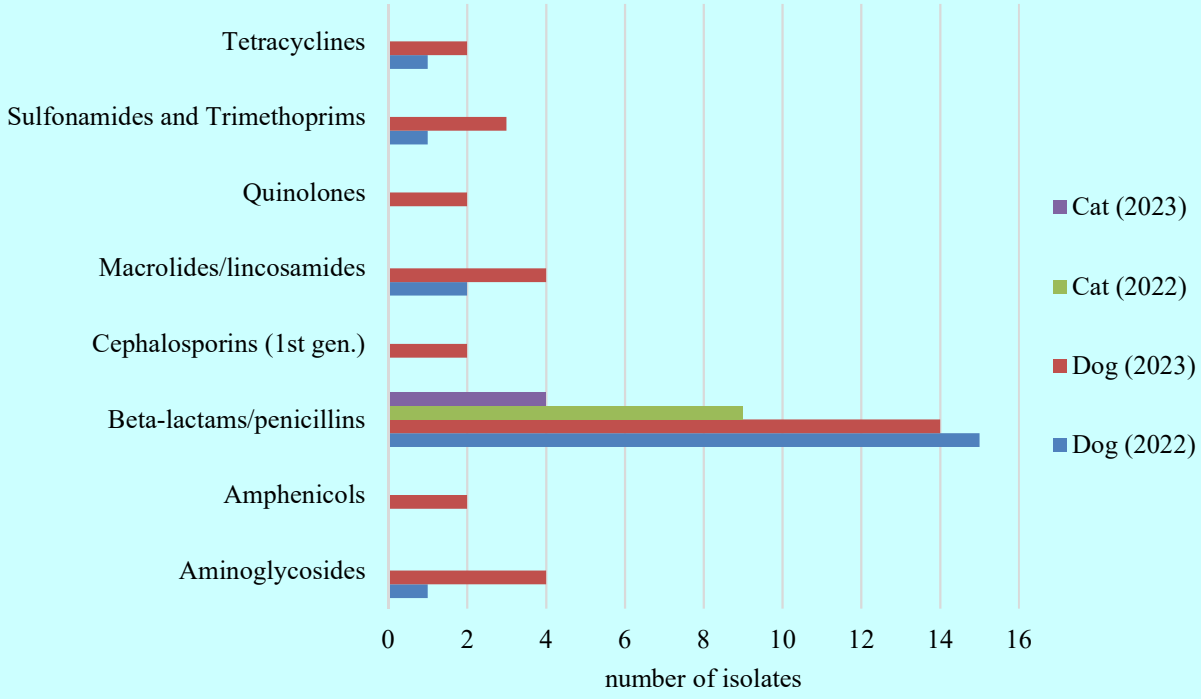

FIGURE 50. Antimicrobial resistance in *Staphylococcus aureus* from skin and ear infections in dogs (n=25, n=18) and cats (n=14, n=6) in 2022 and 2023, respectively.

TABLE 16. Antimicrobial resistance in *Staphylococcus aureus* from skin and ear infections in dogs (n=18) and cats (n=6) in 2023.

			Distribution (n) of MIC values (mg/L)*													
Substance	Animal	Resistance (n)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Doxycycline	Dog	1					17		1							
	Cat	0					6									
Tetracycline	Dog	2						16				2				
	Cat	0						6								
Chloramphenicol	Dog	2								12	4			2		
	Cat	0								6						
Benzylpenicillin	Dog	14	3	1		1	13									
	Cat	4	1		1		4									
Oxacillin	Dog	3				8	4		3	3						
	Cat	0				3	2		1							
Amoxicillin-clavulanic acid	Dog	2							15	1			2			
	Cat	0							6							
Cefalotin	Dog	2							16			2				
	Cat	0							6							
Cefovecin	Dog	3					1	11	3		3					
	Cat	0						3	3							
Trimethoprim-sulfamethoxazole	Dog	3					15					1				2**
	Cat	0					6									
Erythromycin	Dog	3				15					3					
	Cat	0				6										
Clindamycin	Dog	2			1	15				2						
	Cat	0				6										
Gentamicin	Dog	2					16				2					
	Cat	0					6									
Neomycin	Dog	2							16				2			
	Cat	0							6							
Enrofloxacin	Dog	2					15	1		2						
	Cat	0					6									
Marbofloxacin	Dog	2					14	2		2						
	Cat	0					6									
Nitrofurantoin	Dog	0										13	5			
	Cat	0										5	1			

*Bold vertical lines denote epidemiological cut-off (ECOFF) values for resistance. White fields show range tested for each antimicrobial substance. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. Clinical breakpoints (CBP) are marked in blue dotted lines. CBPs for tetracycline, benzylpenicillin oxacillin, erythromycin, clindamycin and gentmicin are the same as the ECOFFs and only ECOFFs are shown in the table for these substances. **Two isolates with MIC values at 160 mg/L.

In total, eight and four of the 18 and six isolates from dogs and cats, respectively, were resistant to one antimicrobial class (mainly beta-lactam/penicillins). Two and four of the 18 isolates from dogs were resistant to two and three or more antimicrobial classes, respectively. Three methicillin resistant *S. aureus* (MRSA) were identified among the dog isolates, and presence of the *mecA* gene was confirmed by real-time PCR.

Comparison to the results from 2022 has to be done with caution due to the low number of tested isolates. However, both in 2022 and in 2023 resistance to the beta-lactams/penicillins was the most common detected resistance determinant (Figure 50).

Staphylococcus pseudintermedius from skin and ear infections in dogs

In total, results of susceptibility testing for *S. pseudintermedius* from 160 dogs were included, 66 from skin (including abscesses and postoperative wound infections) and 94 from ear infections. Table 17 and Figures 51-52 show the results of the susceptibility testing.

TABLE 17. Antimicrobial resistance in *Staphylococcus pseudintermedius* from skin (including abscesses and postoperative wound infections) (n=66) and ear (n=94) infections in dogs in 2023.

Substance	Sample	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*												
				0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Doxycycline	Ear	21.3	[14.3 – 32.1]					78.7	1.1	10.6	4.3	4.3	1.1			
	Skin	16.7	[8.6 – 27.9]					83.3		12.1	4.5					
Tetracycline	Ear	22.4	[15.3 – 33.3]						77.7	1.1			21.3			
	Skin	18.2	[9.8 – 29.6]						81.8				18.2			
Chloramphenicol	Ear	2.1	[0.3 – 7.5]								61.7	36.2			2.1	
	Skin	15.2	[7.5 – 26.1]								59.1	25.8		1.5	13.6	
Benzylpenicillin	Ear	73.4	[63.3 – 82.0]	26.6			6.4	67.0								
	Skin	80.3	[68.7 – 89.1]	19.7			1.5	78.8								
Oxacillin	Ear	2.1	[0.3 – 7.5]				97.9			2.1						
	Skin	1.5	[0.0 – 8.2]				98.5				1.5					
Amoxicillin-clavulanic acid	Ear	0.0	[0.0 – 3.8]							100						
	Skin	0.0	[0.0 – 5.4]							100						
Cefalotin	Ear	0.0	[0.0 – 3.8]							98.9			1.1			
	Skin	0.0	[0.0 – 5.4]							100						
Cefovecin	Ear	1.1	[0.0 – 5.8]					97.9			1.1	1.1				
	Skin	0.0	[0.0 – 5.4]					97.0	1.5	1.5						
Trimethoprim-sulfamethoxazole	Ear	1.1	[0.0 – 5.8]					97.9	1.1				1.1			
	Skin	12.1	[5.4 – 22.5]					87.9					12.1			
Erythromycin	Ear	5.3	[1.7 – 12.0]				86.2	6.4	2.1	2.1		3.2				
	Skin	16.7	[8.6 – 27.9]				78.8	4.5				16.7				
Clindamycin	Ear	7.4	[3.0 – 14.7]			11.7	80.9	2.1			5.3					
	Skin	12.1	[5.4 – 22.5]			9.1	78.8	3.0			9.1					
Gentamicin	Ear	0.0	[0.0 – 3.8]					100								
	Skin	3.0	[0.3 – 10.5]					97.0			1.5		1.5			
Neomycin	Ear	0.0	[0.0 – 3.8]							96.8			3.2			
	Skin	9.1	[3.4 – 18.7]							84.8			6.1	9.1		
Enrofloxacin	Ear	1.1	[0.0 – 5.8]					97.9	1.1		1.1					
	Skin	3.0	[0.4 – 10.5]					97.0			3.0					
Marbofloxacin	Ear	1.1	[0.0 – 5.8]					97.9	1.1		1.1					
	Skin	3.0	[0.4 – 10.5]					97.0			3.0					
Nitrofurantoin	Ear	0.0	[0.0 – 3.8]										98.9	1.1		
	Skin	0.0	[0.0 – 5.4]										98.5	1.5		

*Bold vertical lines denote epidemiological cut-off (ECOFF) values for resistance. CI = confidence interval. White fields show range tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. Clinical breakpoints (CBP) are marked in blue dotted lines. CBPs for tetracycline and clindamycin are the same as the ECOFFs and only ECOFFs are shown in the table for these substances. For chloramphenicol, no current CBP exist.

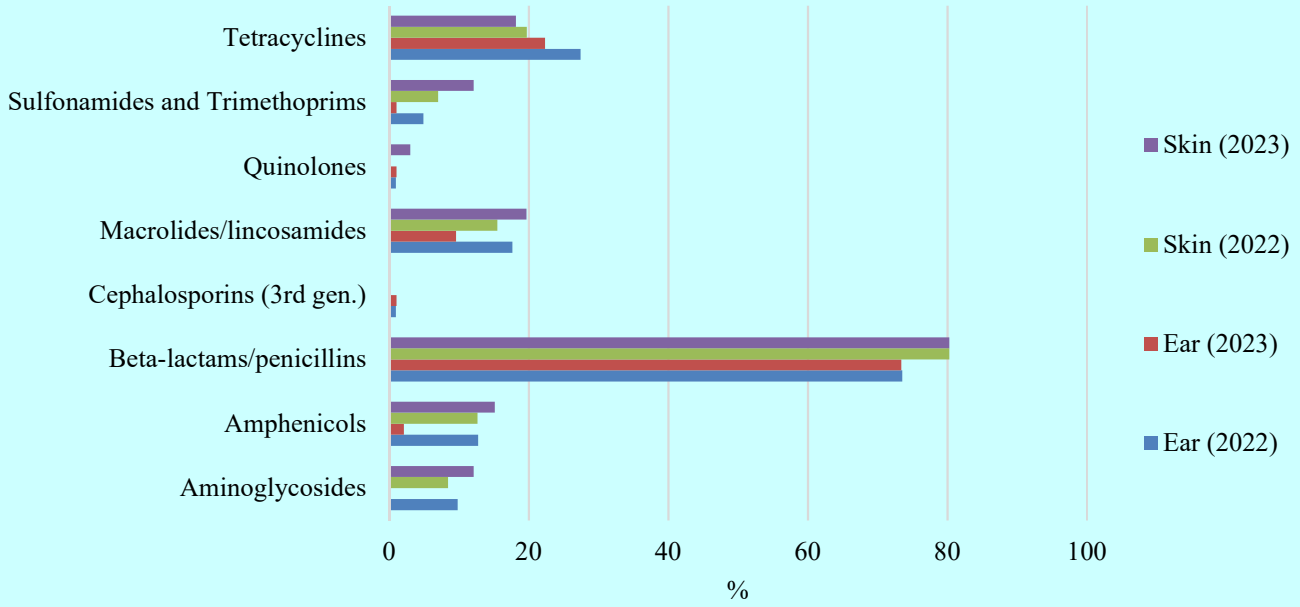

FIGURE 51. Antimicrobial resistance (%) in *Staphylococcus pseudintermedius* from skin (n=71, n=66) and ear (n=102, n=94) infections in dogs in 2022 and 2023, respectively.

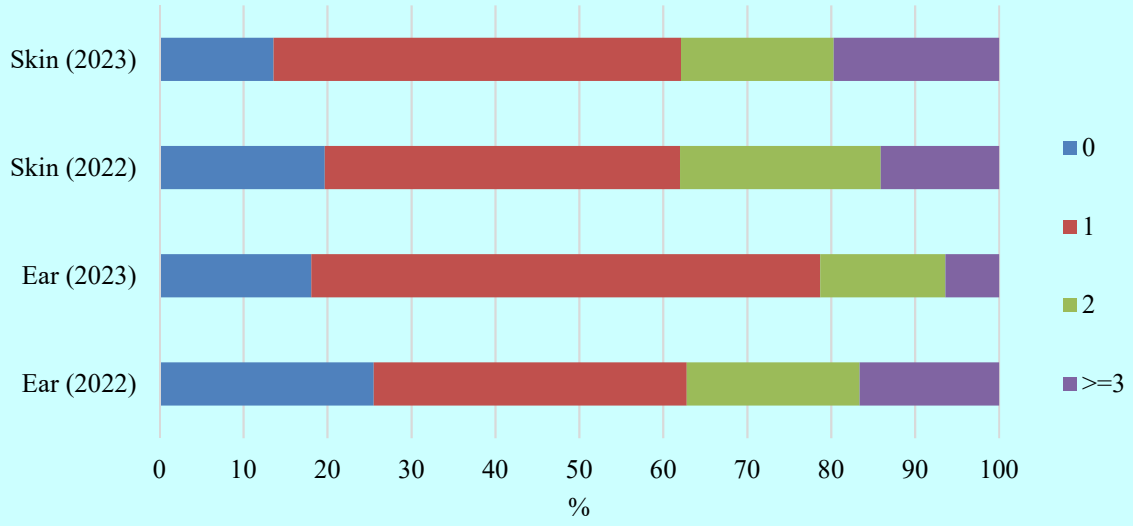

FIGURE 52. Antimicrobial resistance profile for *Staphylococcus pseudintermedius* from skin (n=71, n=66) and ear (n=102, n=94) infections in dogs in 2022 and 2023, respectively. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2) or three or more (≥3) antimicrobial classes are illustrated.

Among the *S. pseudintermedius*, 18.0% of the isolates from ear infections and 14.0% of the isolates from skin infections were susceptible to all antimicrobial agents included. Resistance to beta-lactams/penicillins were the most frequently identified resistance determinants, followed by resistance to tetracyclines. Altogether, 61.0% and 49.0% of the isolates from skin and ear, respectively, were resistant to one antimicrobial class, 15.0% and 18.0% to two, and 6.4% and 20.0% to three or more antimicrobial classes (Figure 52). Three isolates were resistant to oxacillin, one from skin and two from ear samples, and the presence of the *mecA* gene was confirmed by real-time PCR.

The results from 2023 are in concordance with the results from 2022 as shown in Figure 52. Although, Figure 52 shows an overall increase in occurrence of resistant isolates. However, this is not significant and further monitoring is needed to follow this in the years to come. *S. pseudintermedius* isolates from infections in dogs were also included in the data retrieved from the NVI (see page 55). Comparing results are difficult and need to be done with caution due to differences in methodology. However, the results for the substances that were included in both panels (i.e. for tetracycline, benzylpenicillin, erythromycin, clindamycin and gentamicin) were rather similar indicating that the results were in concordance.

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Antimicrobial resistance testing in routine mastitis diagnostics in Norway 2023

Background

The Norwegian dairy co-operative TINE SA operates the TINE Mastitis Laboratory in Molde. The laboratory currently performs all bacteriological analyses for mastitis control in Norway. Approximately 60,000 quarter milk samples from dairy cows, and 5,000 udder half samples from goats are analysed at the laboratory per year. The laboratory performs antimicrobial susceptibility testing of selected isolates, an important contribution to the antimicrobial resistance (AMR) surveillance in milk producing animals. Results from the mastitis diagnostics are reported to the Norwegian Dairy Herd Recording System (NDHRS) (1, 2). Statistics from the mastitis diagnostics of dairy cows are published yearly in the TINE udder health report (3).

The most common bacterial findings in milk samples from dairy cows in 2023 is presented in Figure 53. *Staphylococcus aureus* is the leading cause of mastitis of both dairy cows and goats in Norway (3, 4). Since benzylpenicillin procaine is the first choice for treatment of mastitis in both Norwegian dairy cows and goats (5), testing for beta-lactamase production of *S. aureus* is the primary focus of the AMR testing in the mastitis diagnostics.

Methods

Results from AMR testing of isolates from dairy cows and goats from 2023 were retrieved from the NDHRS. *S. aureus* (all reasons for sampling) are routinely tested for beta-lactamase production by the clover leaf assay (6). Penicillin resistant *S. aureus* and *Enterobacterales* from clinical mastitis are tested by disk diffusion for amoxicillin-clavulanic acid, ampicillin, cefoxitin (*S. aureus*) and trimethoprim-sulfamethoxazole (*Enterobacterales*). Other bacterial species from clinical mastitis may also be tested. Streptococci are considered sensitive to penicillin (7) and are therefore not routinely tested.

A total of 6,604 isolates were tested in 2023, whereof 336 came from goat milk, and 6,268 from cow milk. The tested isolates were *S. aureus* (n=5,419, 82%), *Enterobacterales* (n=626, 9%), non-aureus staphylococci (n=442, 7%) and other bacteria (n=117, 2%). The isolates from cow milk were from 4,424 cows in 1,920 farms. The isolates from goat milk came from 234 goats in 54 farms. The results from testing of *S. aureus* and *E. coli* are presented here.

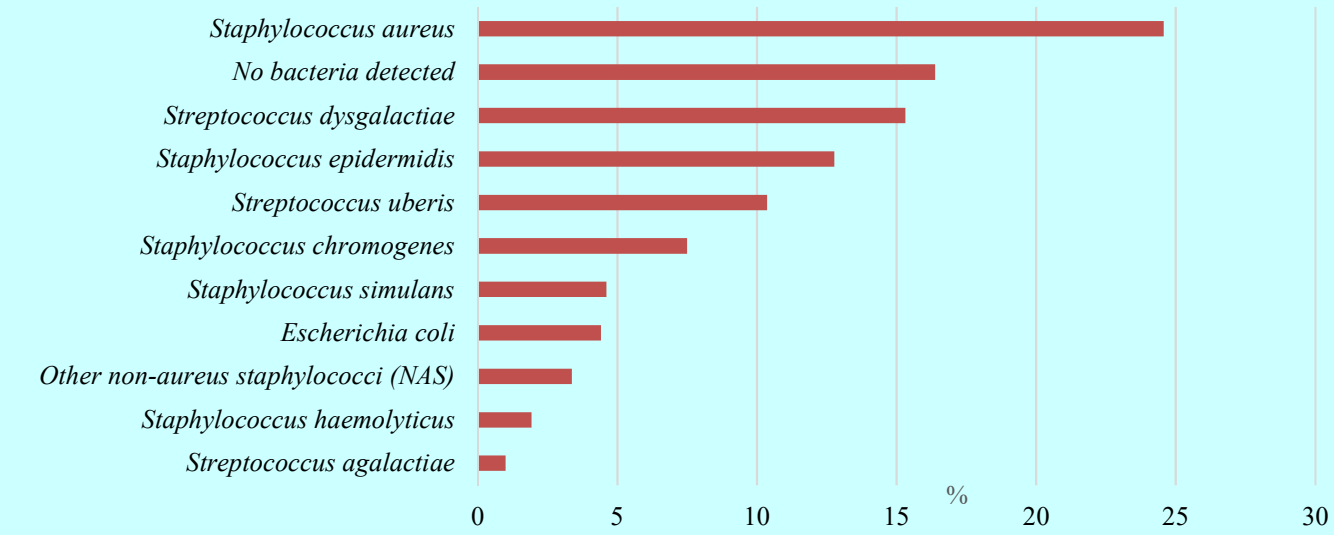

FIGURE 53. The most common findings (%) in milk samples from cows analysed at the TINE Mastitis laboratory in 2023.

Results and discussion

Among the tested *S. aureus* from cows, 107/4,717 (2.3%) isolates were resistant by the clover leaf assay, meaning that 97.7% of *S. aureus* from bovine mastitis in Norway were sensitive to penicillin. The proportion of penicillin resistant *S. aureus* in milk samples from Norwegian dairy cows has been low the last 20 years, ranging from 1.5-3.5% (2). From goat milk, 246 *S. aureus* were tested by the clover leaf assay, whereof 21 (8.5%) showed beta-lactamase production. Hence, the level of resistance in *S. aureus* in dairy goats is higher than in dairy cows. However, the samples came from a lower number of farms, and preliminary results from the research project GoatMilkSCC (8) show a strong clustering of resistant *S. aureus* in some dairy goat farms. Results from disk diffusion using amoxicillin-clavulanic acid were available for 103 *S. aureus* from cows, all of which were sensitive. From goats, all 25 *S. aureus* tested by disk diffusion were sensitive to amoxicillin-clavulanic acid. Other results from disk diffusion of *S. aureus* were not available. MRSA was not detected in the routine mastitis diagnostics in 2023.

Table 18 shows the results of the susceptibility testing for amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole of *E. coli* in 2023. All isolates came from cows. A majority of the isolates were susceptible to trimethoprim-sulfamethoxazole. In the routine mastitis diagnostics, *E. coli* susceptible to amoxicillin-clavulanic acid is reported as "susceptible with increased exposure to amoxicillin-clavulanic acid (I)" because of low expected response to treatment. According to the therapy guidelines (5), *E. coli* clinical mastitis does not benefit from antimicrobial treatment and could be treated with supportive therapy only.

TABLE 18. Susceptibility testing of *Escherichia coli* from mastitis in Norwegian dairy cows in 2023. Number of isolates (%) is given for each category susceptible (S), susceptible with increased exposure (I) and resistant (R).

	Amoxicillin-clavulanic acid (n=596)		Trimethoprim-sulfamethoxazole (n=549)		
Species	I	R	S	I	R
E. coli	529 (88.8%)	67 (11.2%)	527 (96.0%)	2 (0.4%)	20 (3.6%)

In conclusion, *S. aureus* remains the most common cause of mastitis in Norwegian dairy goats and cows. The level of penicillin resistant *S. aureus* from mastitis samples is very low in dairy cows (2.3%) and slightly higher (8.5%) in dairy goats. *E. coli* is an important cause of severe clinical mastitis in Norway but does not benefit from antimicrobials and could, if identified at the time of clinical examination, be treated only with supportive therapy.

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INTRODUCTION TO CHAPTER ON INDICATOR BACTERIA

The prevalence of acquired antimicrobial resistance among certain bacteria of the normal enteric microbiota can be used as an indicator of the selective pressure from use of antimicrobial agents. These bacteria may form a reservoir of transferrable resistance genes from which antimicrobial resistance can be spread to other bacteria, including those responsible for infections in animals or humans. Thus, monitoring of resistance among indicator bacteria of the normal enteric microbiota from healthy animals, as well as from feed and food, is important to get an overview of the prevalence of antimicrobial resistance, detect trends and evaluate effects of interventions.

Bacterial resistance to critically important antimicrobials, such as extended-spectrum cephalosporins (ESC) and carbapenems, has received special attention over the last years. These are defined by the WHO as critically important for antimicrobial treatment of human infections. Monitoring the resistance to these substances in the bacterial population is therefore of special interest. A reservoir of such resistant bacteria in food production animals and the food chain is of concern as they may have an impact on resistance development in human bacterial populations.

NORM-VET has since 2014 taken into account the requirements for harmonised monitoring and reporting of AMR in zoonotic and commensal bacteria set in Commission Implementing Decisions 2013/652/EU, later replaced by 2020/1729/EU. In addition, NORM-VET includes antimicrobial susceptibility testing of bacteria from sources other than those covered by this legal act and use of selective methods targeting specific antimicrobial resistant bacteria. The use of selective methods is especially relevant for low prevalence sources, as it enables early detection of important resistance mechanisms; thereby enabling these to be monitored and characterised.

Escherichia coli and *Enterococcus* spp. are used as indicator bacteria for surveillance of antimicrobial resistance in animals. In addition, selective methods are used for detection of *E. coli* resistant to ESC, carbapenemase-producing *Enterobacterales* (CPE), linezolid resistant *Enterococcus* spp. (LRE), methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus pseudintermedius* (MRSP).

INDICATOR BACTERIA FROM ANIMALS

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In 2023, samples from animals included caecal samples from cattle and fattening pigs, as well as faecal swabs from dogs, for isolation of indicator bacteria and some emerging resistant bacteria. In addition, oral/nasal/perineum swabs from dogs were included for detection of *Staphylococcus pseudintermedius* and MRSA/MRSP. The results from the surveillance programme for MRSA in pigs are described as well (separate presentation).

Some of the cut-off values defining resistance applied in NORM-VET have been changed over the years. To facilitate comparisons in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2023. For cattle and fattening pigs, only data retrieved following the requirements set in decision 2013/652/EU and 2020/1729/EU are shown. For previous data, please see the respective annual reports. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from cattle and pigs

Caecal samples from a total of 277 cattle and 333 fattening pig were examined. *E. coli* isolates were obtained from 271 (97.8%) of the cattle and 331 (99.4%) pig samples. One isolate per positive sample was susceptibility tested. The results are presented in Table 19 and Figures 54-56, and in the text.

TABLE 19. Antimicrobial resistance in *Escherichia coli* isolates from caecal samples of cattle (n=271) and fattening pigs (n=331) in 2023.

Substance	Animal	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
				0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Cattle	1.1	[0.2 – 3.2]								72.7	25.5	0.7			1.1			
	Pig	5.7	[3.5 – 8.8]								73.4	20.0	0.9		0.3	5.4			
Tigecycline	Cattle	0.0	[0.0 – 1.4]					99.6	0.4										
	Pig	0.0	[0.0 – 1.1]					99.7	0.3										
Chloramphenicol	Cattle	0.7	[0.1 – 2.6]										91.5	7.8		0.4	0.4		
	Pig	0.3	[0.0 - 1.7]										95.5	4.2	0.3				
Ampicillin	Cattle	1.1	[0.2 – 3.2]							0.4	17.3	73.4	7.8		0.4	0.7			
	Pig	3.3	[1.7 – 5.9]							2.4	31.4	59.8	3.0			3.3			
Cefotaxime	Cattle	0.7	[0.1– 2.6]					99.3		0.7									
	Pig	0.3	[0.0 – 1.7]					99.7			0.3								
Ceftazidime	Cattle	0.7	[0.1– 2.6]					97.1	2.2		0.7								
	Pig	0.3	[0.0 – 1.7]					97.9	1.8			0.3							
Meropenem	Cattle	0.0	[0.0 – 1.4]		100														
	Pig	0.0	[0.0 – 1.1]		100														
Trimethoprim	Cattle	0.0	[0.0 – 1.4]					64.9	34.7	0.4									
	Pig	3.3	[1.7 – 5.9]					66.2	30.2	0.3					3.3				
Sulfamethoxazole	Cattle	5.2	[2.9 – 8.5]										22.9	39.1	24.7	8.1	1.1		4.1
	Pig	9.1	[6.2 – 12.7]										29.6	30.5	23.0	7.9	0.6	0.6	7.9
Azithromycin	Cattle	0.0	[0.0 – 1.4]								4.8	53.1	41.7	0.4					
	Pig	0.0	[0.0 – 1.1]								14.2	60.1	25.7						
Gentamicin	Cattle	0.0	[0.0 – 1.4]						70.9	28.0	1.1								
	Pig	0.6	[0.0 – 2.2]						68.9	28.1	2.4	0.6							
Amikacin	Cattle	0.0	[0.0 – 1.4]									98.9	1.1						
	Pig	0.3	[0.0 – 1.7]									96.7	3.0		0.3				
Ciprofloxacin	Cattle	0.0	[0.0 – 1.4]	84.1	15.9														
	Pig	1.2	[0.3 – 3.1]	86.1	12.4	0.3	0.9						0.3						
Nalidixic acid	Cattle	0.4	[0.0 – 2.0]									98.9	0.7	0.4					
	Pig	1.2	[0.3 – 3.1]									97.9	0.9	0.3			0.9		
Colistin	Cattle	0.4	[0.0 – 2.0]							99.6			0.4						
	Pig	0.0	[0.0 – 1.1]							99.7	0.3								

*Bold vertical lines denote epidemiological cut-off values for resistance. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

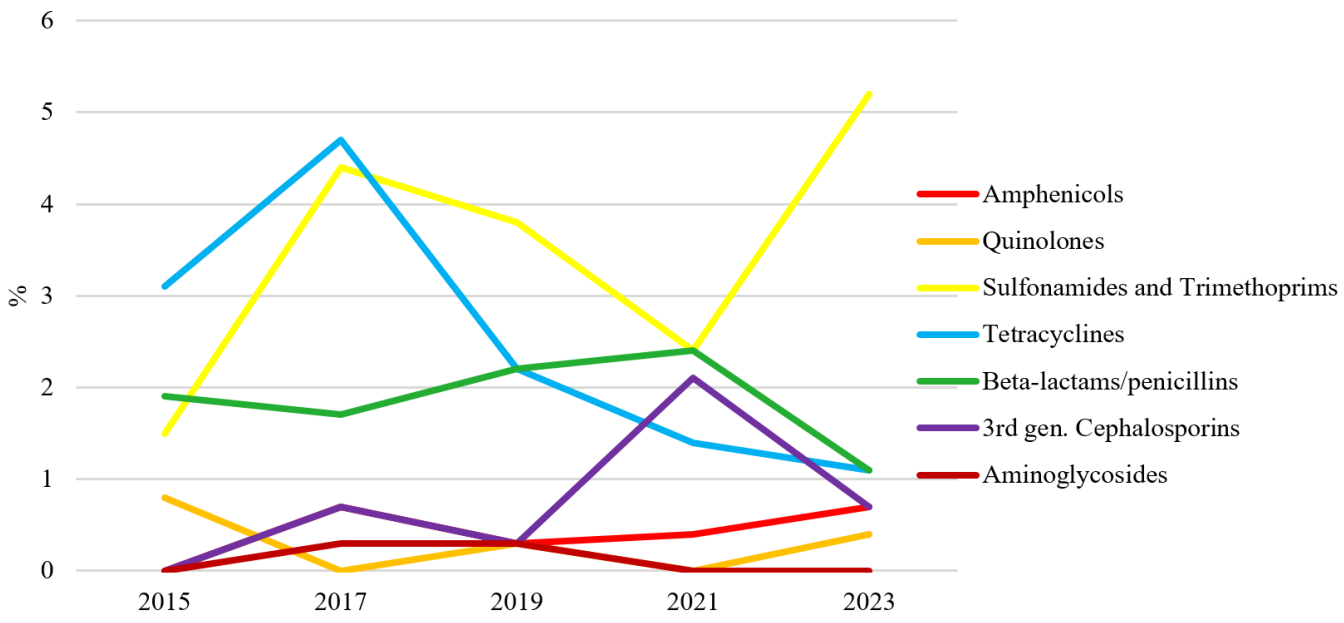

FIGURE 54. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from caecal samples from cattle collected in 2015-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied.

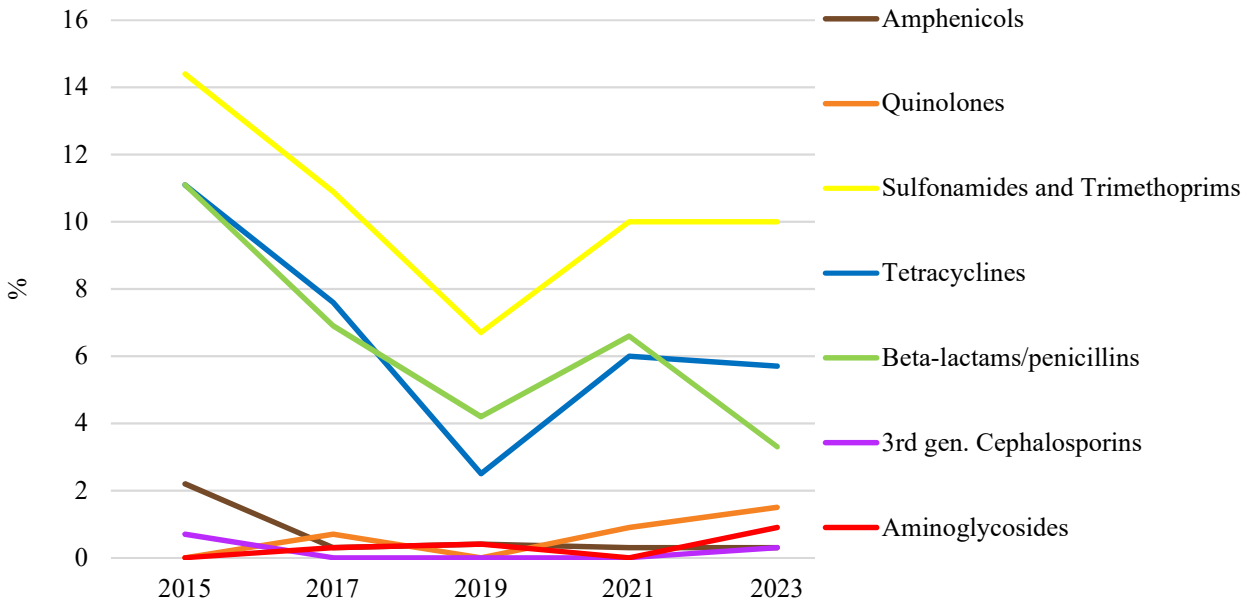

FIGURE 55. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from caecal samples from fattening pigs collected in 2015-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied.

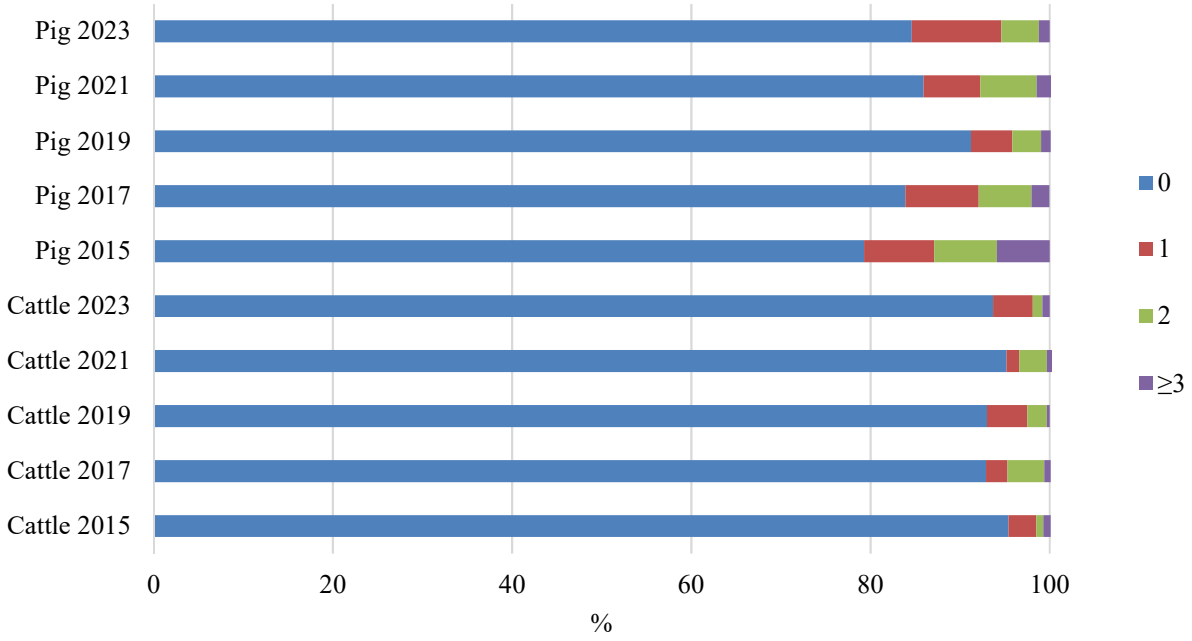

FIGURE 56. Antimicrobial resistance profile for *Escherichia coli* from caecal samples from fattening pigs and cattle collected in 2015-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

CATTLE

A total of 93.7% of the *E. coli* isolates from cattle caecal samples were susceptible to all antimicrobial agents included in the test panel, indicating a low occurrence of resistance among *E. coli* from cattle caecal samples according to the EFSA classification described in Appendix 6. The low detected occurrence is in concordance with the results from previous years, i.e. 2015-2021 as shown in Figure 56. Altogether, 4.4% of the isolates were resistant to one antimicrobial class, 1.1% to two and 0.8% to three or more antimicrobial classes. Resistance to sulfamethoxazole was the most frequently identified resistance phenotype (Figure 54).

Two of the isolates displayed resistance to the extended-spectrum cephalosporins cefotaxime and ceftazidime (0.7%; 95% CI: 0.09-2.6). These isolates displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. In addition, selective methods were applied on the same sample material to investigate both the occurrence of *E. coli* resistant to ESC CPE in cattle (see pages 71-73). None of the 271 *E. coli* isolates displayed resistance to meropenem, the preferred carbapenem used for detecting carbapenem resistance.

In a European perspective, the occurrence of resistance among *E. coli* from cattle in Norway is among the lowest of the countries reporting to EFSA (EFSA and ECDC Summary Report 2021-2022). This situation corresponds to the limited use of antibiotics in the Norwegian cattle production.

PIG

A total of 84.6% of the *E. coli* isolates from pig caecal samples were susceptible to all antimicrobial agents tested, indicating a moderate occurrence of resistance among *E. coli* from caecal samples of fattening pigs according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole, followed by resistance to tetracycline, were the most frequently identified resistance phenotypes (Figure 55). Altogether, 10.0% of the isolates were resistant to one antimicrobial class, 4.2% to two, and 1.2 % to three or more antimicrobial classes.

As shown in Figure 56, the number of isolates being fully susceptible has been relatively stable between 80-90% over the years 2015-2023. Comparisons to data from years before 2015 have to take into consideration changes made in the panel of antimicrobial agents tested for. Resistance to streptomycin, which is no longer part of the panel, has historically been most frequently identified in isolates from pig with 17.2% resistant isolates in 2011 (NORM/NORM-VET 2011). See text box page 70 for further investigation on streptomycin resistance. After the changes made to the test panel, resistance to sulfamethoxazole has been most frequently identified. Resistance to sulfamethoxazole was previously the second most frequently identified resistance determinant.

Four isolates displayed resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid). One of the isolates displayed resistance to the ESCs cefotaxime and ceftazidime (0.3%; 95% CI: 0.01-1.7). This isolate displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. None of isolates displayed resistance to meropenem, the preferred carbapenem used for detecting carbapenem resistance. In addition, selective methods were applied on the same sample material to investigate the occurrence of both *E. coli* resistant to ESC and CPE in fattening pigs (see pages 71-73).

In a European perspective, the occurrence of resistance among *E. coli* from fattening pigs in Norway is among the lowest (EFSA and ECDC Summary Report 2021-2022). The occurrence varies markedly between countries reporting to EFSA, ranging from very few susceptible isolates and up to nearly 80% fully susceptible, with the levels of full susceptibility decreasing in a north to south gradient. This favourable Norwegian situation corresponds to the limited use of antibiotics in the Norwegian pig production.

Reduction of resistance to streptomycin among *Escherichia coli* from pigs

Background

Resistance to streptomycin used to be the most frequently identified resistance among *Eschericha coli* from Norwegian pigs with 17.2% resistant isolates in 2011. However, with the implementation of the EFSA harmonised panels from 2014, streptomycin is no longer included in the test panel. Therefore there has been a lack of knowledge whether resistance to streptomycin still is dominant among *E. coli* from pigs. To investigate this matter, the 331 *E. coli* isolates from pigs in 2023 were additionally susceptibility tested for streptomycin.

Material and Methods

Isolates were tested for antimicrobial susceptibility using an agar diffusion method where minimum inhibitory concentration (MIC) values were obtained using streptomycin gradient strips (ETEST) from bioMérieux. In short, a 0.5 McFarland solution of bacteria suspended in saline was inoculated on a Mueller Hinton agar plate (Oxoid, ThermoFisher). An ETEST containing streptomycin with range from 0.064-1,024 mg/L was placed on the agar plate. After incubation at 35±1°C for 16-24 hours, the MIC values were determined.

Data from previous NORM-VET years, i.e. from 2004 to 2011 when streptomycin was included in the antimicrobial susceptibility test panel, were retrieved from the NORM-VET database. Prevalence of streptomycin resistance was recalculated using the ECOFF values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 09.03.2023), i.e. with a streptomycin ECOFF at 16 mg/L. All data management and statistical analyses were performed using R version 4.2.3 Copyright (C) 2023 (The R Foundation for Statistical Computing Platform). The 95% confidence intervals were calculated using the exact binomial test and the Chi-square test was applied to compare the prevalence of streptomycin resistance from 2011 and 2023. A difference yielding a p-value <0.05 was considered as statistically significant.

FIGURE 57. Occurrence of streptomycin resistance in *Escherichia coli* isolates from pigs monitored in NORM-VET since 2004. The ECOFF values used in NORM-VET 2023 were applied. The stippled line shows the trend of reduction of streptomycin resistance.

Results and comments

Overall, 7.9% (95% CI; 5.2-11.3] of the *E. coli* isolates were resistant to streptomycin. This is a significant reduction compared to 2011 (p=0.002). Although there has been a clear reduction in streptomycin resistance among *E. coli* from pigs, the resistance profile of *E. coli* as shown in Figure 56 would to some degree be affected with streptomycin included in the EFSA harmonised test panel. As the prevalence of aminoglycoside resistance in Figure 55 would be higher, the occurrence of fully susceptible isolates would decrease, and the occurrence of resistant isolates, including the multi-drug resistant isolates, would increase. The reduction in resistance to streptomycin corresponds to a reduction in the use of aminoglycosides for therapeutic use in food-producing animals as shown in Figure 2 in the chapter on usage in animals.

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Extended-spectrum cephalosporin resistant *Escherichia coli* from cattle and pigs

A total of 277 cattle and 333 pig samples were examined for the presence of *E. coli* resistant to ESC by selective methods. One isolate per positive sample was susceptibility tested. Results are presented in Tables 20-21, Figures 58-59, and in the text.

TABLE 20. Antimicrobial resistance in *Escherichia coli* isolates resistant to extended-spectrum cephalosporins from caecal samples of cattle (n=15) in 2023.

Substance	n (resistance)	Distribution (n) of MIC values (mg/L)*															
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	5								8	2			1	4			
Tigecycline	0					15											
Chloramphenicol	3										12			2	1		
Ampicillin	15													15			
Cefotaxime	15							2	9	1	3						
Ceftazidime	15									7	6	2					
Meropenem	1		14							1							
Trimethoprim	3					9	3						3				
Sulfamethoxazole	7										1	1	5	1			7
Azithromycin	0									8	7						
Gentamicin	1						8	5	1			1					
Amikacin	0									15							
Ciprofloxacin	0	10	2			2	1										
Nalidixic acid	2									13		1	1				
Colistin	0							15									

*Bold vertical lines denote epidemiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

TABLE 21. Antimicrobial resistance in *Escherichia coli* isolates resistant to extended-spectrum cephalosporins from caecal samples of fattening pigs (n=66) in 2023.

Substance	Animal	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
				0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Pig	18.2	[18.2 – 29.6]								69.7	12.1				18.2			
Tigecycline	Pig	0.0	[0.0 – 5.3]						97.0	3.0									
Chloramphenicol	Pig	1.5	[0.0 – 8.2]										90.9	7.6			1.5		
Ampicillin	Pig	100	[94.6 – 100]													100			
Cefotaxime	Pig	100	[94.6 – 100]							3.0	80.3	6.1	10.6						
Ceftazidime	Pig	98.5	[91.8 – 100]							1.5	1.5	74.2	16.7	6.1					
Meropenem	Pig	0.0	[0.0 – 5.3]			100													
Trimethoprim	Pig	25.8	[15.8 – 38.0]					63.6	9.1	1.5			1.5		24.2				
Sulfamethoxazole	Pig	24.2	[14.5 – 36.4]										15.2	25.8	30.3	4.6			24.2
Azithromycin	Pig	3.0	[0.4 – 10.5]									48.5	47.0	1.5			3.0		
Gentamicin	Pig	1.5	[0.0 – 8.2]						80.3	15.2	3.0	1.5							
Amikacin	Pig	0.0	[0.0 – 5.3]									97.0	3.0						
Ciprofloxacin	Pig	13.6	[6.4 – 24.3]	53.0	30.3	3.0		7.6	1.5					4.6					
Nalidixic acid	Pig	13.6	[6.4 – 24.3]									84.9	1.5	3.0			10.6		
Colistin	Pig	0.0	[0.0 – 5.3]							100									

*Bold vertical lines denote epidemiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

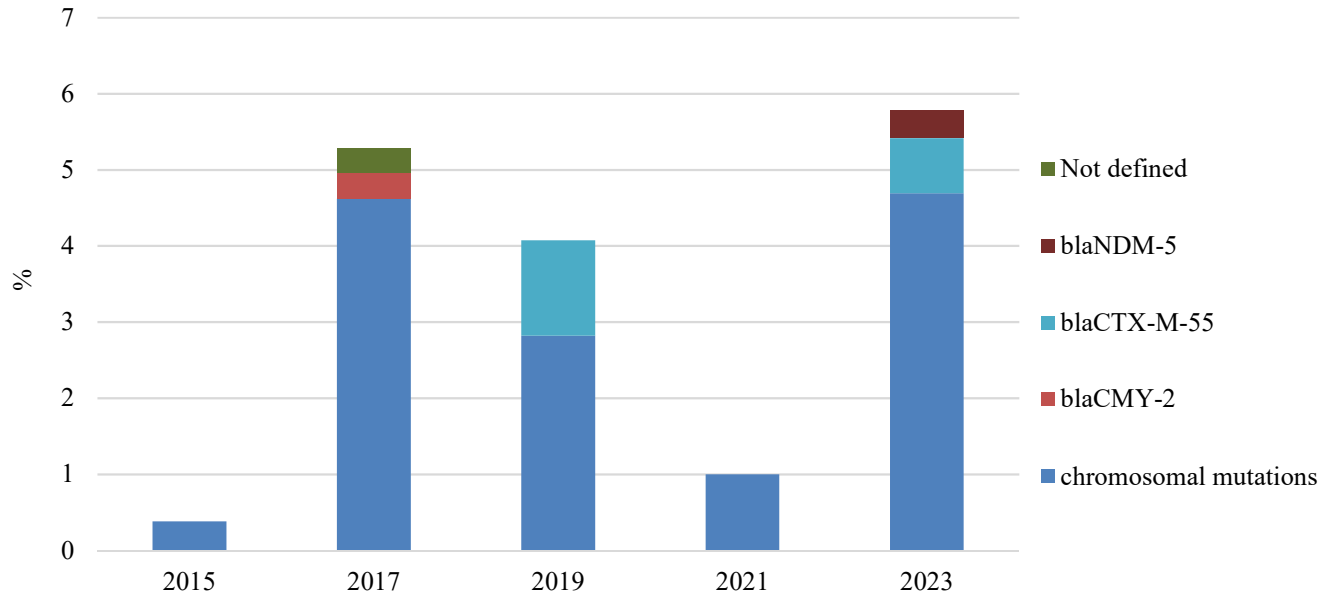

FIGURE 58. Occurrence (%) of different ESC-resistant *Escherichia coli* from cattle 2015-2023.

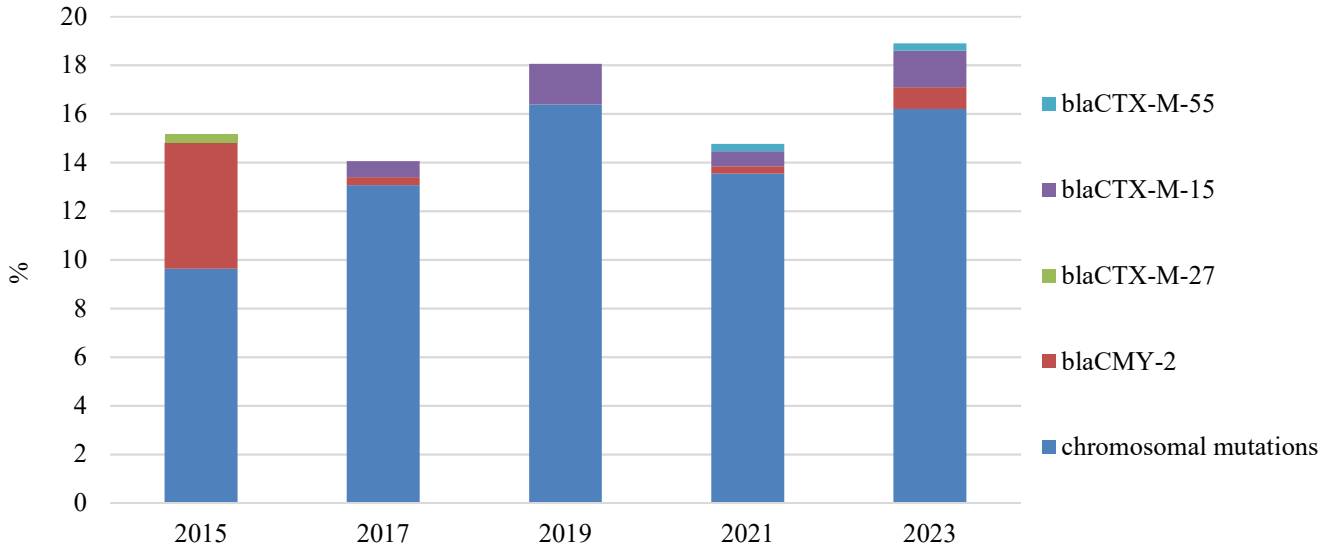

FIGURE 59. Occurrence (%) of different ESC-resistant *Escherichia coli* from fattening pigs 2015-2023.

RESULTS AND COMMENTS

ESC-resistant *E. coli* were detected from 15 of the cattle (5.4%; 95% CI: 3.1-8.8) and 66 of the pig (19.8%; 95% CI: 15.7-24.5) samples. In addition to being resistant to beta-lactams, i.e. ampicillin and the ESCs cefotaxime and ceftazidime, resistance to sulfamethoxazole, tetracycline, trimethoprim and quinolones were most commonly detected among both cattle and pig isolates. One cattle isolate showed reduced susceptibility to meropenem, the preferred carbapenem used for detecting carbapenem resistance.

Twelve of the cattle isolates displayed an AmpC beta-lactamase phenotype. For these isolates the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. Two isolates displayed an ESBL phenotype and were genotyped *bla*$_{\text{CTX-M-55}}$. In addition both isolates carried the *qnrB19* gene encoding quinolone resistance. The last isolate displayed a CARBA phenotype and were genotyped *bla*$_{\text{NDM-5}}$. This isolate carried in addition several other antimicrobial resistance genes (see more info in text box page 73).

Of the 66 pig isolates, 59 displayed an AmpC beta-lactamase phenotype where three were genotyped *bla*$_{\text{CMY-2}}$. In the last 56 isolates, the AmpC phenotype was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. Seven isolates displayed an ESBL phenotype. Five were genotyped as *bla*$_{\text{CTX-M-15}}$, where one isolate in addition carried the *qnrS1* gene encoding quinolone resistance and another the *mph(A)* gene encoding macrolide resistance (azithromycin). One isolate was genotyped as *bla*$_{\text{CTX-M-55}}$, and this isolate also carried the *qnrS1* gene. In the last isolate, the *bla*$_{\text{OXA-1}}$ gene was detected. This gene was known to cause resistance to ampicillin only, but in

recent years isolates carrying this gene have also expressed resistance to ESC. Nevertheless, OXA-1 enzymes are weak hydrolysers of cefotaxime and ceftazidime that may cause the expression of an ESBL phenotype.

Compared to previous results, the overall occurrence of all genotypes of ESC-resistant *E. coli* in cattle is similar to the results from 2017 and 2019, while the occurrence was slightly lower in 2015 and 2021 (NORM/NORM-VET 2015, NORM/NORM-VET 2017, NORM/NORM-VET 2019 and NORM/NORM-VET 2021). This is mainly due to variation in the resistance detemined by chromosomal mutations. In pigs, the overall occurrence of all genotypes is in concordance with previous years. The occurrence of *E. coli* resistant to ESC is in both cattle and pigs mainly due to isolates with mutations in the chromosomally located *ampC* gene. Additionally, there were some ESC-resistant *E. coli* isolated from pig in 2015 due to occurrence of $bla_{\text{CMY-2}}$. A few *E. coli* displaying an ESBL phenotype due to plasmid encoded genes have been detected as well through the years (Figures 58-59). The source of introduction of plasmid encoded resistance in *E. coli* to cattle and pigs in Norway, as well as their ability to disseminate further, are currently unknown. There is negligible numbers of import of live cattle and pigs to Norway, which is a preventive measure against importing *E. coli* resistant to ESC from areas/ countries with higher prevalence.

In a European perspective, the occurrence of *E. coli* resistant to ESC in cattle and in fattening pigs in Norway is among the lowest, though the occurrences vary markedly between countries reporting to EFSA (EFSA and ECDC Summary Report 2021-2022). A continued awareness of animal bacterial reservoirs resistant to ESC is of importance to be able to implement control measures if needed.

Carbapenemase-producing *Enterobacterales* from cattle and pigs

Selective method for detection of CPE was performed on a total of 277 samples from cattle and 328 samples from pigs. CPE was detected in one caecal sample from cattle (0.4%; 95% CI: 0.0-2.0). See text box below for further description. None of the samples from pigs were positive for CPE (95% CI: 0.0-1.1).

Carbapenems are not approved for use in food-producing animals in the EU and EEA countries. Nevertheless, resistance to these critically important antimicrobial agents has sporadically been reported from animals in some of the EU/EEA countries, and further monitoring is recommended to follow the situation in the years to come.

First finding of *Escherichia coli* resistant to carbapenems in production animals

Introduction

In autumn 2023, carbapenemase-producing *Escherichia coli* was detected from cattle. The isolate originated from a sample of caecal material taken at slaughter under the auspices of the harmonised monitoring programme for antimicrobial resistance and following the Commission Implementing Decision 1729/2020/EU. This is the first finding of a carbapenem resistant *Enterobacterales* from production animals in Norway. The occurrence of carbapenem resistant bacteria isolated from human infections in Norway is low, though increasing.

Follow-up sampling at the farm, i.e. both faecal samples from the animals and environmental samples (boot swabs), were performed twice (October 2023 and January 2024) and initiated by the Norwegian Food Safety Authority to gather more knowledge on the in-herd occurrence.

Material and methods

For the follow-up sampling, a selective approach was used where samples were enriched in buffered peptone water containing 0.125 mg/L meropenem (MEM) before plating on selective agar plates. In short, 1±0.1 g of faecal material was mixed with 9 mL of BPW-ISO containing 0.125 mg/L MEM (BPW-ISO MEM) and boot swabs were enriched in 300-500 mL of BPW-ISO MEM before all samples were incubated at 37±1°C for 18-22 hours. One loop-full (10 µL) was streaked on both CHROMID® CARBA (bioMérieux) and MacConkey containing 1 mg/L cefotaxime and 0.125 mg/L MEM. Species identification of pure culture was done using Matrix-Assisted Laser Desorption/Ionization - Time of Flight (MALDI-TOF, Bruker Daltonics). Isolates were further tested for antimicrobial susceptibility and genotyped by whole genome seqencing as described in Appendix 3.

Results and comments

In the initial sampling at slaughter, the carbapenem resistant *E. coli* was isolated from selective isolation using both MacConkey agar supplemented with 1 mg/L cefotaxime and CHROMID CARBA (bioMérieux).

In the first follow-up sampling, carbapenem resistant *E. coli* was detected in two of the 30 samples (26 individual faecal samples and four environmental samples), both in one individual animal and in the barn environment. In the second follow-up sampling, none of the 34 samples (31 individual faecal samples and three environmental samples) were positive.

Whole genome sequencing confirmed that the isolates harboured the $bla_{\text{NDM-5}}$ gene in addition to several other resistance genes including *qnrS1*. The isolates will be long-read sequenced using Oxford Nanopore Technology to further investigate whether the $bla_{\text{NDM-5}}$ gene is plasmid encoded.

Jannice Schau Slettemeås and Anne Margrete Urdahl, Norwegian Veterinary Institute, Norway

Enterococcus spp. from cattle and pigs

Caecal samples from a total of 277 cattle and 333 fattening pigs were examined. *E. faecalis* was obtained from two (0.7%) and *E. faecium* from 16 (5.8%) of the cattle caecal samples. From pigs, *E. faecalis* was obtained from 61 (18.0%) and *E. faecium* from 86 (25.8%) of the samples. One isolate of *E. faecalis* and/or *E. faecium* per positive sample was susceptibility tested. The results are presented in the text, in Tables 22-23 and Figures 60-61.

TABLE 22. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from fattening pigs (n=61) in 2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
			0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	65.6	[53.3 – 77.3]						34.4				4.9	26.2	18.0	16.4			
Tigecycline	0.0	[0.0 – 5.9]	1.6	31.2	49.2	18.0												
Chloramphenicol	0.0	[0.0 – 5.9]								3.3	96.7							
Ampicillin	0.0	[0.0 – 5.9]						27.9	72.1									
Erythromycin	0.0	[0.0 – 5.9]						68.9	29.5	1.6								
Quinupristin–dalfopristin	0.0	[0.0 – 5.9]							1.6	1.6	29.5	65.6	1.6					
Gentamicin	0.0	[0.0 – 5.9]									45.9	52.5	1.6					
Ciprofloxacin	0.0	[0.0 – 5.9]					11.5	83.6	4.9									
Vancomycin	0.0	[0.0 – 5.9]						55.7	42.6	1.6								
Teicoplanin	0.0	[0.0 – 5.9]					100											
Linezolid	0.0	[0.0 – 5.9]							98.4	1.6								
Daptomycin	0.0	[0.0 – 5.9]					9.8	55.7	31.2	3.3								

*Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC-value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

TABLE 23. Antimicrobial resistance in *Enterococcus faecium* (n=86) from caecal samples from fattening pigs in 2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
			0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	32.6	[22.8 – 43.5]						67.4				1.2	1.2	29.1	1.2			
Tigecycline	0.0	[0.0 – 4.2]	23.3	53.5	23.3													
Chloramphenicol	0.0	[0.0 – 4.2]									91.9	8.1						
Ampicillin	23.2	[14.8 – 33.6]					7.0	14.0	26.7	29.1	23.2							
Erythromycin	0.0	[0.0 – 4.2]						36.1	53.5	10.5								
Quinupristin–dalfopristin	53.5	[42.4 – 64.3]					12.8	25.6	8.1	52.3	1.2							
Gentamicin	0.0	[0.0 – 4.2]									91.9	8.1						
Ciprofloxacin	0.0	[0.0 – 4.2]				3.5	53.5	14.0	16.3	9.3	3.5							
Vancomycin	0.0	[0.0 – 4.2]						94.2	5.8									
Teicoplanin	0.0	[0.0 – 4.2]					96.5	3.5										
Linezolid	0.0	[0.0 – 4.2]						3.5	95.4	1.2								
Daptomycin	0.0	[0.0 – 4.2]				1.2	4.7	19.8	50.0	24.4								

*Bold vertical lines denote microbiological cut-off values for resistance. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC-value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

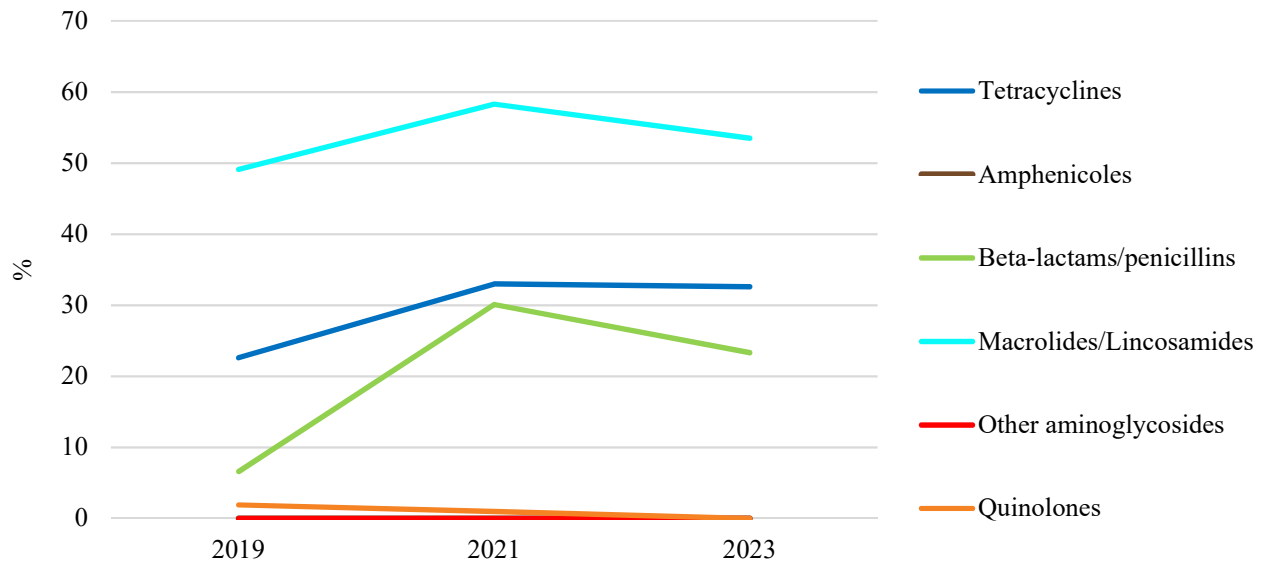

FIGURE 60. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* from caecal samples from fattening pigs collected in 2019-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied.

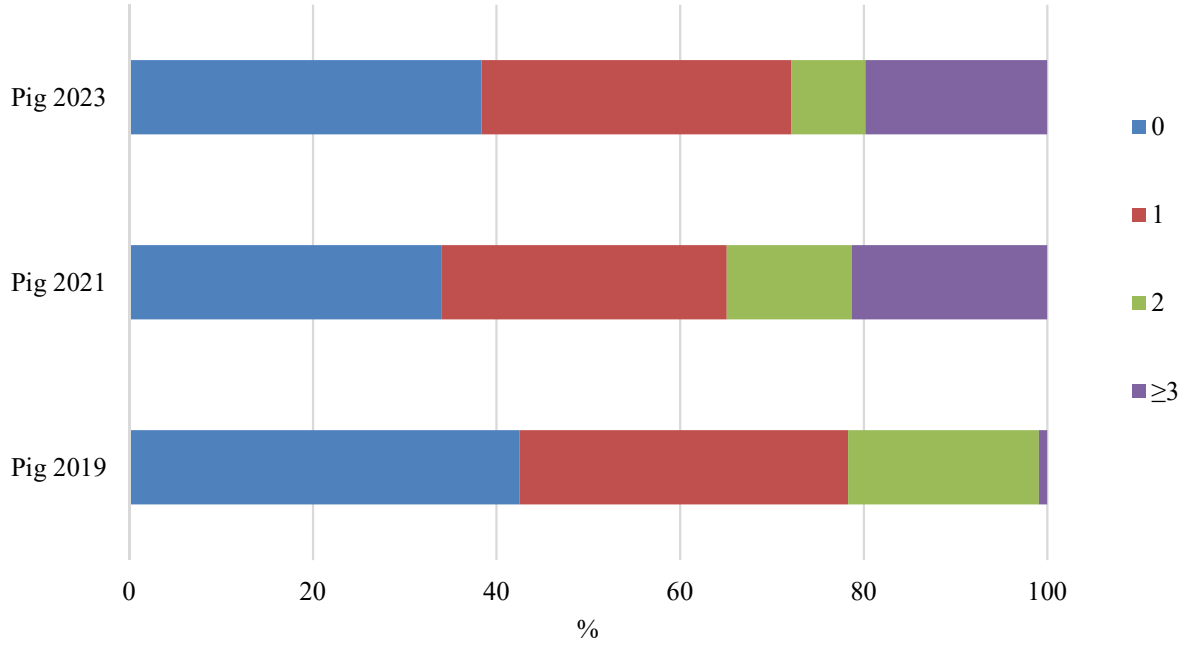

FIGURE 61. Antimicrobial resistance profile for *Enterococcus faecium* from caecal samples from fattening pigs collected in 2019-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

CATTLE

The 2023 data showed that one of the two *E. faecalis* isolates and seven of the 16 *E. faecium* isolates from cattle caecal samples were susceptible to all antimicrobial agents included in the test panel. The second *E. faecalis* isolate was resistant to erythromycin and gentamicin. The remaining nine *E. faecium* isolates were resistant to the streptogramin quinupristin-dalfopristin. This is in concordance with the results from 2019 and 2021, though some isolates were then also resistant to tetracycline.

PIG

The 2023 data showed that 34.4% of the 61 *E. faecalis* and 38.4% of the 86 *E. faecium* isolates from pig caecal samples were susceptible to all antimicrobial agents included in the test panel. The remaining *E. faecalis* isolates (65.6%) were resistant to one antimicrobial class (tetracyclines), indicating a very high occurrence of resistance in *E. faecalis* according to EFSA classification described in Appendix 6.

Among the *E. faecium* isolates, 33.7% were resistant to one antimicrobial class, 8.1% were resistant to two antimicrobial classes (tetracyclines and macrolides/lincosamides) and 19.8% were resistant to three antimicrobial classes. Resistance to the streptogramin quinupristin-dalfopristin was the most frequently identified resistance determinant, followed by resistance to tetracycline. In total, 61.6% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a very high occurrence of resistance according to the EFSA classification described in Appendix 6.

Compared to the results from 2019, there has been an increase in resistance to several antimicrobial classes, especially to the beta-lactam ampicillin as shown in Figure 60, i.e. from 6.6% in 2019 to 23.2% in 2023 (p=0.008). This increase in ampicillin resistance has affected the occurrence of MDR isolates, with an increase in MDR from 0.9% in 2019 to 21.3% and 19.8% in 2021 and 2023, respectively. It has also resulted in a slight decrease in totally susceptible *E. faecium* isolates in 2021 and 2023, from 42.5% in 2019 to 34.0% and 38.4% in 2021 and 2023, respectively.

Linezolid resistant *Enterococcus* spp.

Selective method for detection of LRE was performed on a total of 235 samples from cattle and 278 samples from pigs.

No LRE were detected in cattle (95% CI: 0.0-1.6), nor in pigs (95% CI: 0.0-1.3).

SPORTS AND FAMILY ANIMALS

Escherichia coli from dogs

Faecal swab samples from a total of 251 dogs were examined, and *E. coli* isolates were obtained from 233 (92.8%) of these. One isolate per positive sample was susceptibility tested. The results are presented in the text, Table 24 and Figures 62-63.

TABLE 24. Antimicrobial resistance in *Escherichia coli* isolates (n=233) from faecal samples from dogs in 2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	3.0	[1.2 – 6.1]								81.1	15.5	0.4			3.0			
Tigecycline	0.0	[0.0 –1.6]					97.4	2.6										
Chloramphenicol	0.4	[0.0 – 2.4]										90.1	9.4	0.4				
Ampicillin	14.2	[10.0 – 19.3]								15.9	59.7	10.3	0.9		13.3			
Cefotaxime	0.4	[0.0 – 2.4					99.6					0.4						
Ceftazidime	0.4	[0.0 – 2.4]					96.6	3.0			0.4							
Meropenem	0.0	[0.0 – 1.6]		99.6	0.4													
Trimethoprim	5.6	[3.0 – 9.4]					32.6	57.5	3.9	0.4				5.6				
Sulfamethoxazole	18.5	[13.7 – 22.0]										10.7	19.7	32.2	18.9	5.2	0.9	12.4
Azithromycin	0.0	[0.0 – 1.6]								14.2	52.8	31.8	1.3					
Gentamicin	1.7	[0.5 – 4.3]						75.1	20.6	2.6	1.3			0.4				
Amikacin	0.9	[0.1 – 3.1]									94.4	4.7	0.4	0.4				
Ciprofloxacin	5.2	[2.7 – 8.8]	62.7	30.9	1.3		2.2	3.0										
Nalidixic acid	4.7	[2.4 – 8.3]									92.7	2.6	1.3		0.4	3.0		
Colistin	0.0	[0.0 – 1.6]							99.6	0.4								

*Bold vertical lines denote epidemiological cut-off values for resistance. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

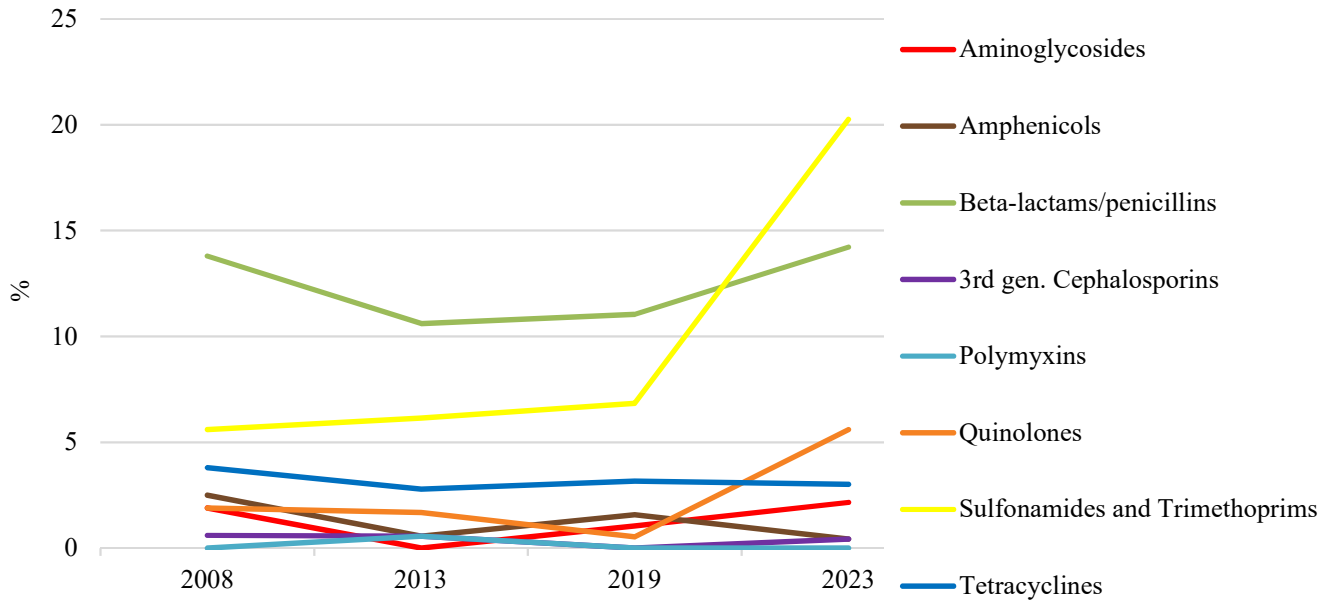

FIGURE 62. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from faecal samples from dogs, collected in 2008-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. Note irregular time intervals on the x-axis. Resistance to streptomycin that previous to 2019 was part of the test panel is not included.

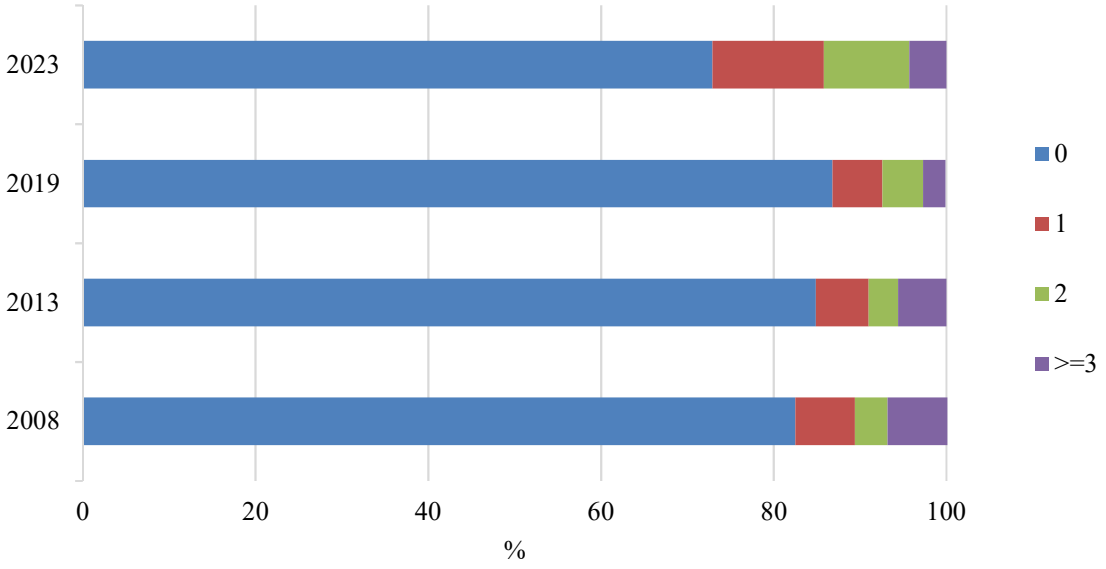

FIGURE 63. Antimicrobial resistance profile for *Escherichia coli* from dogs in 2008-2023. The epidemiological cut-off values used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated. Resistance to streptomycin that previous to 2019 was part of the test panel is not included.

RESULTS AND COMMENTS

A total of 72.9% of the isolates were susceptible to all antimicrobial agents included. Altogether, 12.9% of the isolates were resistant to one antimicrobial class, 9.9% to two, and 4.3% to three or more antimicrobial classes. Resistance to sulfamethoxazole was the most frequently identified resistance determinant, followed by resistance to ampicillin.

In total, twelve isolates showed decreased susceptibility to the quinolones ciprofloxacin and/or nalidixic acid, while one of the isolates displayed resistance to the extended-spectrum cephalosporins (ESC) cefotaxime and ceftazidime and expressed an ESBL phenotype. This isolate was genotyped $bla_{\text{CTX-M-15}}$ and carried in addition *qnrS1* encoding quinolone resistance. None of the isolates displayed resistance to meropenem, the preferred carbapenem used for detecting carbapenem resistance. Selective methods were also used on the same sample material to investigate both the occurrence of *E. coli* resistant to ESC and carbapenemase-producing *Enterobacterales* (see next page) in these samples.

Samples from dogs have previously been included in NORM-VET in 2004, 2008, 2013 and 2019. Since 2019, there has been changes in the antimicrobial resistance profile as shown in Figure 63. Occurrence of isolates fully susceptible has decreased, and the occurrence of isolates resistant to one, two or three classes has increased. This is mainly due to an increase in resistance to sulfamethoxazole from 5.8% in 2019 to 18.5% in 2023 (p=0.0009), though there is also a slight increase in resistance to quinolones and beta-lactams/penicillins adding to this picture (Figure 62). The cause of this increase in resistance to sulfamethoxazole is unknown. There is no sale of sulfonamides of veterinary medicine products as shown in Figure 9, page 22 in the chapter on usage in animals. Resistance to beta-lactams/penicillins, however, being the second most commonly detected resistance corresponds well to the usage data showing that penicillins are the most commonly used antimicrobial substance for companion animals (Figure 9, page 22).

There is a lower proportion of overall antimicrobial resistance in these indicator *E. coli* isolates compared to the results for *E. coli* from infections in dogs as presented in Figure 44, page 54.

Extended-spectrum cephalosporin resistant *Escherichia coli* from dogs

A total of 251 faecal swab samples from dogs were investigated by selective methods for detection of *E. coli* resistant to ESC. *E. coli* resistant to ESC were found in 14 (5.6%; 95% CI: 3.1-9.2) of the samples. Eight of the isolates displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation in seven of these. The last isolate was genotyped as $bla_{\text{DHA-1}}$ and carried several other antimicrobial resistance genes including *mph(A)* and *qnrB4* encoding resistance to macrolides and quinolones, respectively. Six isolates displayed an ESBL phenotype where three were genotyped as $bla_{\text{CTX-M-15}}$ and also carrying the *qnrS1* gene enconding resistance to quinolones. The last three were genotyped as $bla_{\text{CTX-M-1}}$, $bla_{\text{CTX-M-3}}$, and $bla_{\text{SHV-12}}$, respectively.

Compared to previous results (Figure 64), the overall occurrence of all genotypes of ESC-resistant *E. coli* in dogs has increased from 1.3% in 2019 (NORM/NORM-VET 2019) to 5.6% in 2023. This increase is, however, not significant and further monitoring is needed to follow this in the years to come.

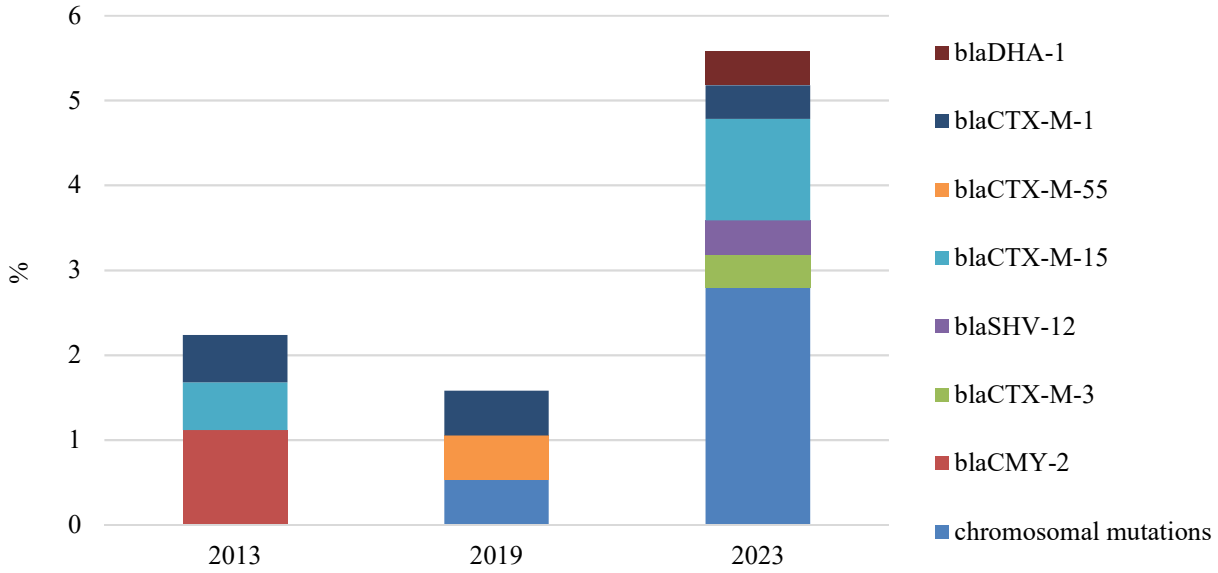

FIGURE 64. Occurrence (%) of different ESC-resistant *Escherichia coli* from dogs 2013-2023.

Carbapenem resistant *Enterobacterales* from dogs

A total of 251 samples from dogs were investigated for the presence of CPE by selective methods. No CPE isolates were detected (95% CI: 0.0-1.5). This is in concordance with the results from 2019.

Staphylococcus pseudintermedius from dogs

A total of 251 samples from dogs were investigated for detection of *Staphylococcus pseudintermedius*. *S. pseudintermedius* was detected from 163 of these (64.9%). One isolate per positive sample was susceptibility tested. The results are presented in Table 25 and Figure 65, and in the text.

TABLE 25. Antimicrobial resistance in *Staphylococcus pseudintermedius* isolates (n=163) from samples from dogs in 2023.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.016	0.032	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	24.5	[18.2 – 31.9]						75.5		0.6			1.2	22.7				
Chloramphenicol	7.4	[3.9 – 12.5]									81.6	11.0		2.5	4.9			
Benzylpenicillin	ND	ND			33.1	6.8	11.7	6.8	9.2	32.5								
Cefoxitin	2.4	[0.7 – 6.1]						96.3		0.6	0.6			2.4				
Trimethoprim	21.4	[15.4 – 25.6]							14.7	63.8	14.7	1.8		4.9				
Sulfamethoxazole	ND	ND													36.8	7.4	23.3	32.5
Erythromycin	11.0	[6.7 – 16.9]					81.0	8.0	0.6	0.6			9.8					
Clindamycin	12.3	[7.7 – 18.3]				84.6	3.1					12.3						
Quinupristin-dalfopristin	2.5	[0.7 – 6.2]						97.6				2.5						
Streptomycin	15.3	[10.2 – 21.8]									83.4	1.2			15.3			
Gentamicin	NA	NA						95.1		0.6	3.7	0.6						
Kanamycin	15.3	[10.2 – 21.8]									84.7			3.7	11.7			
Ciprofloxacin	0.0	[0.0 – 2.2]					93.3	3.7	3.1									
Vancomycin	0.0	[0.0 – 2.2]							98.8	1.2								
Fusidic acid	35.6	[28.2 – 43.4]					63.8	0.6		0.6	1.2	33.7						
Tiamulin	2.4	[0.7 – 6.1]						97.6				2.4						
Linezolid	0.0	[0.0 – 2.2]							98.8	1.2								
Mupirocin	2.4	[0.7 – 6.1]						97.6									2.4	
Rifampicin	3.1	[1.0 – 7.0]	93.9	3.1		0.6			2.5									

*Bold vertical lines denote microbiological cut-off values for resistance. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC-value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. ECOFFs for *Staphylococcus aureus* used for all but tetracycline, benzylpenicillin, sulfamethoxazole, erythromycin, clindamycin and gentamicin. For benzylpenicillin, resistance was deduced from beta-lactamase production analysis.

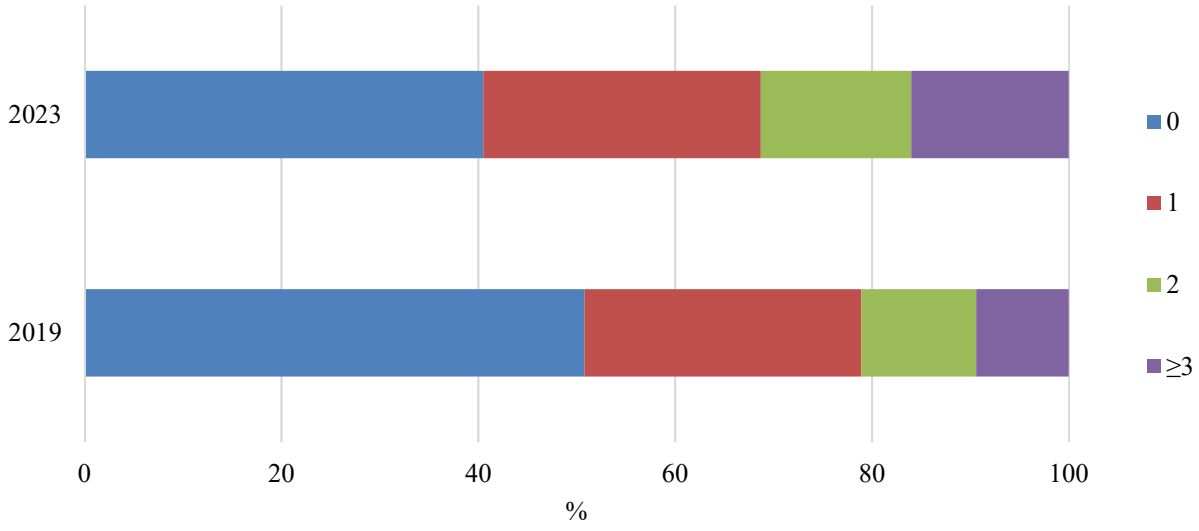

FIGURE 65. Antimicrobial resistance profile for *Staphylococcus pseudintermedius* from dogs in 2019 and 2023. The epidemiological cutoffs used in NORM-VET 2023 were applied. The occurrence of resistance to penicillins, sulfamethoxazole and gentamicin were not included in the calculations. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 40.5% of the *S. pseudintermedius* isolates were fully susceptible to all the antimicrobial agents included in the calculations, 28.2% of the isolates were resistant to one antimicrobial class, 15.3% to two, and 16.0% to three or more antimicrobial classes. Resistance to benzylpenicillin, gentamicin and sulfonamides were not included in these calculations. Resistance to fusidic acid was the most frequently identified resistance determinant, followed by resistance to tetracycline.

Resistance to benzylpenicillin was deduced from detection of beta-lactamase production in the clover leaf test. A total of 76.7% (95% CI: 69.4-82.9) of the isolates were defined as resistant. The majority of isolates with a positive beta-lactamase test, though not all, had penicillin MIC values >0.125 mg/L, which is the ECOFF given by EUCAST. Also, the majority of beta-lactamase negative isolates had penicillin MIC values ≤0.125 mg/L.

Oxacillin, the preferred indicator for identifying MRSP, is not included in the sensitivity test panel. The *S. pseudintermedius* isolates were therefore additionally subjected to oxacillin susceptibility testing using disk diffusion. None of the isolates were resistant to oxacillin. In addition, selective isolation methods were applied on the same sample material to investigate the occurrence of methicillin resistant staphylococci in dogs (see below).

Isolation and susceptibility testing of *S. pseudintermedius* from healthy dog samples have previously been performed in 2019 (NORM-VET 2019). As shown in Figure 65, there has been a decrease in occurrence of fully susceptible isolates from 50.8% in 2019 to 40.5% in 2023, and an increase in occurrence of resistant isolates. The increase is mainly due to occurrence of MDR isolates that has increased from 9.4% in 2019 to 16.0% in 2023. These changes are however not significant and further monitoring is needed to follow this in the years to come to assess whether it is a truly increasing trend.

The 2019 isolates were not tested for beta-lactamase production and benzylpenicillin resistance was then defined by *S. aureus* ECOFF, i.e. at MIC values >0.125 mg/L. Since the beta-lactamase test results from 2023 do not consistently follow this cut-off, comparison of results is difficult. However, it looks like there has been a shift to higher MIC values in 2023 compared to 2019. This may indicate that there has been an increase in resistance to benzylpenicillin in *S. pseudintermedius* from healthy dogs the last years. Though this needs to be followed up to evaluate whether this is a true trend.

Overall, there is less multi-drug resistance among these *S. pseudintermedius* from healthy dogs compared to the clinical isolates as shown in Figure 45, page 55.

Methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus pseudintermedius* (MRSP) from dogs

A total of 251 samples from dogs were investigated for the presence of MRSA and MRSP. There were no MRSA detected (95% CI: 0.0-1.5%), though one MRSP isolate was detected (0.4%; 95% CI: 0.0-2.2%), positive for *mecA*.

The results are in concordance with the results from NORM-VET 2019 where none of the dog samples were positive for MRSA and MRSP. Both MRSA and MRSP have, though, been detected among clinical isolates from dogs in Norway since 2008, indicating that these are present in the Norwegian dog population. Some MRSP isolates were also among the clinical *S. pseudintermedius* included in 2019 (NORM-VET 2019) and in 2023 (see pages 62-64).

Emerging reservoirs in dogs of MRSA, and especially MRSP, constitute a challenge to infection and prevention control management programmes. Moreover, as dogs live in close contact with humans, zoonotic transmission between dogs and humans may occur.

Methicillin resistant *Staphylococcus aureus* (MRSA) in pig in Norway in 2023

There are several varieties of methicillin resistant *Staphylococcus aureus* (MRSA), some of which are associated with animals (especially pigs), and are collectively referred to as LA-MRSA (livestock associated MRSA). Within a few years, LA-MRSAs have become widespread in pig populations around the world, thereby representing a risk for dissemination to the human population. LA-MRSA in European pig production has mainly been attributed to clonal complex (CC) 398. As the only country in the world, Norway implemented a control strategy from 2013 including measures to eradicate MRSA in pigs as described in Grøntvedt *et al.* 2016 (1). The rationale behind this strategy was to prevent the pig population from becoming a domestic reservoir of MRSA with the potential of zoonotic transmission, as MRSA is not a significant cause of disease in pig.

As part of this strategy, an extensive yearly surveillance programme was implemented from 2014. The aim of the programme is to identify MRSA positive pig herds. Each year the nucleus and multiplier herds, as well as central units of sow pool herds and the 20 biggest sow herds are sampled twice, while the remaining sow herds are sampled once. Every third year finisher pig herds are sampled instead of the sow herds. In 2023, 541 herds were included, of which 70 were genetic nucleus or multiplier herds, 11 herds were central units of the sow pool herds, 14 were of the largest farrow to grower or farrow to finish herds, and the remaining 446 were herds with more than 10 sows. The surveillance programme did not detect any pig herds with MRSA. Further details can be found in the report "The surveillance programme for methicillin resistant *Staphylococcus aureus* in pig in Norway 2023" (2).

Throughout the years there have been a few additional MRSA findings from herds not included in the surveillance, as well as herds detected through contact tracing. Table 26 shows the number of herds identified by the MRSA surveillance programme and the total number of detected MRSA positive herds from 2013-2023, as well as results from MRSA typing. Various MRSA types have been detected. Not all of these have been regarded as LA-MRSA. In Norway, LA-MRSA is defined as an MRSA that has been previously shown or is currently showing ability to establish and spread between animals or animal herds. An example of this was seen in 2015 when an MRSA CC1 t177 was detected from several pig herds. This is further described in Elstrøm *et al.* 2019 (3).

TABLE 26. Pig herds positive for methicillin resistant *Staphylococcus aureus* 2013-2023.

Year	No. MRSA positive herds detected by the MRSA surveillance programme (Total No. of positive herds)	Herds investigated in the MRSA surveillance programme	MRSA typing*
2013	(22**)		CC398 t034 (some also with t12359) (22)
2014	1 (5)	986	CC398 t034 (2), CC398 t011 (3)
2015	4 (34)	821	CC398 t034 (25), CC1 t177 (9)
2016	1 (8)	872	CC398 t034 (8)
2017	2 (6)	826	CC7 t091 (2), CC8 t024 (2), CC130 t843 (1), CC425 t6292 (1)
2018	0	716	
2019	1 (9)	722	CC398 t034 (3), CC398 t011 (5), CC130 t843 (1)
2020	0	641	
2021	0	763	
2022	0	591	
2023	0	541	
Total	9 (84**)		CC398 t034 (60), CC398 t011 (8), CC1 t177 (9), CC7 t091 (2), CC8 t024 (2), CC130 t843 (2), CC425 t6292 (1)

**mecC*-gene detected for CC130 t843 and CC425 t6292, *mecA*-gene detected for the others. **Number of positive herds detected during 2013 before the MRSA surveillance programme was implemented.

References

1. Grøntvedt. C.A., Elstrøm. P., Stegger. M., Skov. R.L., Skytt Andersen. P., Larssen. K.W., Urdahl. A.M., Angen. Ø., Larsen. J., Åmdal. S., Løtvedt. S.M., Sunde. M., Bjørnholt. J.V. Methicillin-Resistant *Staphylococcus aureus* CC398 in Humans and Pigs in Norway: A "One Health" Perspective on Introduction and Transmission. Clin Infect Dis. 2016 Dec 1;63(11):1431-1438.
2. Urdahl AM, Norström M, Welde H, Bergsjø B, Grøntvedt CA. The surveillance programme for methicillin resistant *Staphylococcus aureus* in pigs in Norway 2023. *Surveillance programmes for terrestrial and aquatic animals in Norway. Annual report 2023*. Norwegian Veterinary Institute 2024.
3. Elstrøm P, Grøntvedt CA, Gabrielsen C, Stegger M, Angen Ø, Åmdal S, Enger H, Urdahl AM, Jore S, Steinbakk M, Sunde M. Livestock-associated MRSA CC1 in Norway; introduction to pig farms, zoonotic transmission and eradication. Frontiers in Microbiology 2019, 8;10:139.

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INDICATOR BACTERIA FROM FOOD

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In 2023, food samples included beef and pork. One isolate per positive sample was susceptibility tested. Some of the cut-off values defining resistance applied in NORM-VET have changed over the years. To facilitate comparisons in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2023. Sampling, laboratory methods and data processing are described in Appendix 3.

MEAT

Extended-spectrum cephalosporin resistant *Escherichia coli* from beef and pork

In total, 286 beef and 283 pork samples were examined for the presence of *E. coli* resistant to, i.e. cefotaxime and/or ceftazidime. Results are presented in the text and in Figure 66.

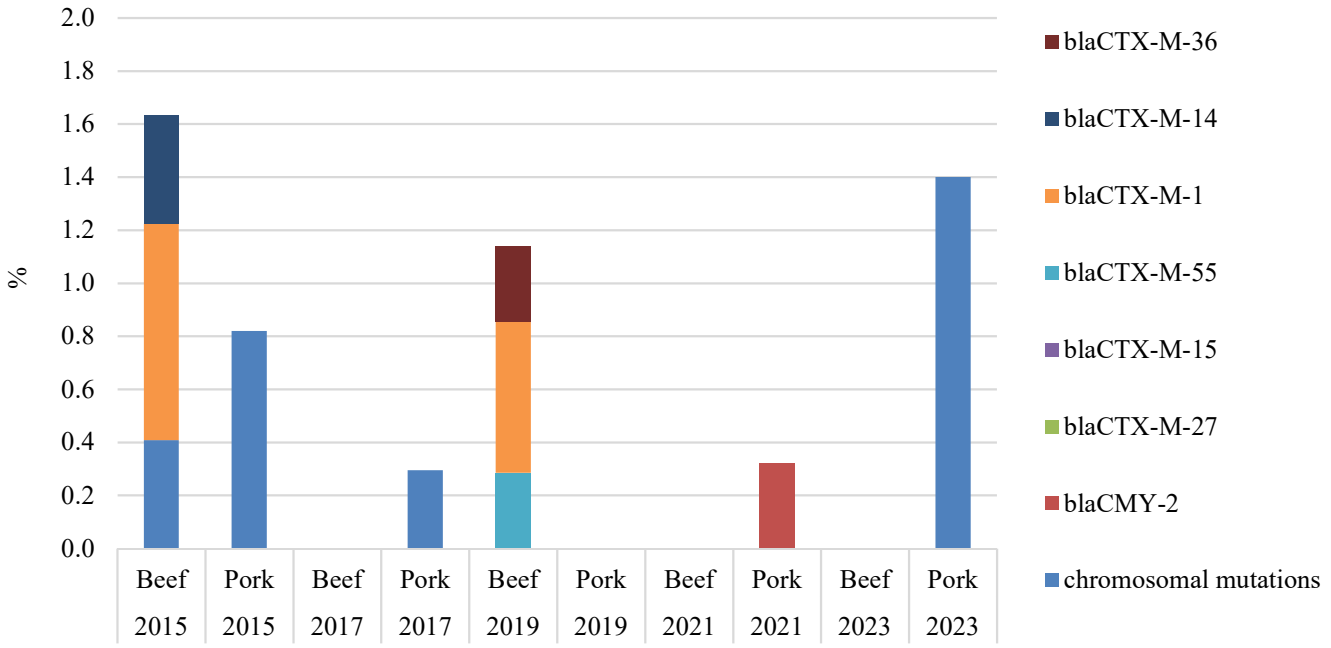

FIGURE 66. Occurrence of ESC-resistant *Escherichia coli* isolates from beef and pork from 2015-2023

RESULTS AND COMMENTS

ESC-resistant *E. coli* were detected in four of the 283 pork samples (1.4%; 95% CI: 0.4-3.6). All isolates displayed an AmpC phenotype and the resistance was due to the n.-42C>T point mutation in the chromosomally located *ampC* gene. ESC-resistant *E. coli* were not detected in any of the 286 beef samples (0%; 95% CI: 0.0-1.3). The occurrence is in concordance with previous results, though with some variations in detected resistance genes as shown in Figure 66.

In a European perspective, the occurrence of *E. coli* resistant to ESC in Norwegian beef and pork continues to be among the lowest reported to EFSA (EFSA and ECDC Summary Report 2021-2022).

Transmission of bacteria, including *E. coli* resistant to ESC, between food-producing animals and meat thereof to humans may occur. However, several studies indicate that there is only a small proportion of bacteria resistant to ESC in humans that may have animals and meat thereof as a source of infection (Day et al. 2019, Dorado-Garcia et al. 2018). Such studies reflect the situation at the time of the study, and prevalence changes in animals may lead to an increase in this proportion in humans. A continued awareness of animal/food bacterial reservoirs resistant to ESC is important in order to be able to implement control measures if needed.

Carbapenemase-producing *Enterobacterales* from beef and pork

A total of 286 beef and 283 pork samples were examined for the presence of CPE. No CPE were detected in beef samples (95% CI; 0.0-1.3), nor in pork (95%; CI: 0.0-1.3). This is in concordance with the results from previous years. Carbapenems are not approved for use in food-producing animals in the EU and EEA countries. Nevertheless, resistance to these antimicrobial agents has sporadically been reported from animals in some of the EU/EEA countries. Carbapenems are defined by the WHO as critically important for treatment of human infections, and a possible development of a significant reservoir of carbapenem resistant bacteria in animals and food is therefore of concern. Further monitoring is recommended to follow the situation in the years to come.

ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

Umaer Naseer, Madelaine Norström, Jannice Schau Slettemeås and Anne Margrete Urdahl

Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. The presence of acquired antimicrobial resistance in these bacteria represents a further concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum.

Included from animals and food are *Salmonella* spp., *Campylobacter coli* and *Campylobacter jejuni* isolates. One isolate of each serovar per incident was included for susceptibility testing.

From human cases, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates. Sampling, laboratory methods and data processing are described in Appendix 4.

SALMONELLA SPP.

Salmonella from animals and meat

The situation regarding occurrence of *Salmonella* spp. in food-producing animals in Norway is very favourable as such animal populations are considered virtually free from *Salmonella* spp.. To document and maintain this favourable situation, Norway has extensive surveillance programmes covering live animals and meat of pigs and cattle, and live poultry, poultry meat and eggs.

The *Salmonella* isolates examined in NORM-VET 2023 included those that were detected in the Salmonella surveillance programmes, as well as isolates obtained from submissions to the National Reference Laboratory for Salmonella and from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). The data are presented in Tables 27-28 and in the text.

TABLE 27. Antimicrobial resistance in *Salmonella* spp. (n=24) from animals (eight wild boars, two dogs, three chicken, three pigs, three cattle, two horses, one cat, one pigeon, and one hedgehog); *S.* Typhimurium (n=6) and other *Salmonella* spp. (n=18) in 2023.

Substance	n (resistance)	Distribution (n) of MIC values (mg/L)*															
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	1								23					1			
Tigecycline	ND					22	2										
Chloramphenicol	0										24						
Ampicillin	1							12	11					1			
Cefotaxime	0					24											
Ceftazidime	0					14	10										
Meropenem	ND		21	3													
Trimethoprim	0					22	2										
Sulfamethoxazole	ND										3	7	11	2			1
Azithromycin	0								3	16	5						
Gentamicin	0						23	1									
Amikacin	0									24							
Ciprofloxacin	0	14	10														
Nalidixic acid	0									24							
Colistin	ND							22	2								

*Bold vertical lines denote microbiological cut-off values, i.e. for *Salmonella enterica*. ND = not defined. White fields show range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

TABLE 28. Antimicrobial resistance in *Salmonella* spp. (n=8) from different food products in 2023.

Substance	n (resistance)	Distribution (n) of MIC values (mg/L)*															
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	0								8								
Tigecycline	ND					8											
Chloramphenicol	0										8						
Ampicillin	0							5	3								
Cefotaxime	0					8											
Ceftazidime	0					2	6										
Meropenem	ND		7	1													
Trimethoprim	0					8											
Sulfamethoxazole	ND										1	3	3	1			
Azithromycin	0										6	2					
Gentamicin	0						7	1									
Amikacin	0									8							
Ciprofloxacin	0	2	6														
Nalidixic acid	0									8							
Colistin	ND								8								

*Bold vertical lines denote microbiological cut-off values, i.e. for *Salmonella enterica*. ND = not defined. White fields show range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

RESULTS AND COMMENTS

In total, 24 *Salmonella* spp. isolates from animals isolated through the Salmonella surveillance programmes, from clinical submissions or necropsies were susceptibility tested. The animal isolates included were eight wild boars, two dogs, three chicken, three pigs, three cattle, two horses, one cat, one pigeon and one hedgehog. In total, there were six *S.* Typhimurium isolates, of which one was monophasic (4,[5],12 : i : -), six *S. enterica* subsp. *diarizonae*, two *S.* Hessarek, two *S.* Abony, and one each of *S.* Infantis, *S.* Kisarawe, *S.* Mbandaka, *S.* Offa, *S.* Saintpaul, and *S.* Anatum. Two isolates were from non-specified serovars.

One isolate was resistant to tetracyclines and ampicillin (*S.* Typhimurium, monophasic (4,[5],12 : i : -)).

Additionally, eight *Salmonella* spp. isolates from non-domestic meat or other food products obtained from submissions to the National Reference Laboratory for Salmonella were susceptibility tested. The serovars of these isolates were *S.* Derby, *S.* Napoli, *S.* Youroba, *S.* Anatum, two isolates were *S.* Amsterdam, *S.* Senftenberg and a non-specified serovar. These isolates were all fully susceptible to the antimicrobial agents included in the panel.

Salmonella from human clinical specimens

In 2023, 757 human cases of nontyphoidal salmonellosis and 14 cases of typhoid fever were notified to the Norwegian Surveillance System for Communicable Disease (MSIS). Most of the cases were travel associated (55%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 681 *Salmonella* isolates from the primary diagnostic laboratories for further characterisation. Fifty-three isolates were linked to nine clusters/outbreaks, and 640 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 419 isolates, including all *Salmonella* Typhi and *Salmonella* Paratyphi A and B isolates, 95% of *Salmonella* Typhimurium isolates, 92% of monophasic *Salmonella* Typhimurium isolates, and 85% of domestically acquired isolates of *Salmonella* Enteritidis and 82% of the domestically acquired isolates of other serovars (Table 29). Isolates were susceptibility tested against six antibiotic classes: penicillin (ampicillin), extended-spectrum cephalosporins (cefotaxime and ceftazidime), carbapenems (meropenem), fluoroquinolones (ciprofloxacin/pefloxacin), phenicol (chloramphenicol) and tetracyclines (tetracycline).

TABLE 29. Number of *Salmonella* isolates tested for phenotypic antimicrobial susceptibility (AST) and screened for predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2023, by serovar and place of acquisition.

Salmonella serovars	No. of isolates tested in 2023		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. Typhimurium	72	73	32	33	28	28	12	12
S. Typhimurium monophasic	35	36	15	16	18	18	2	2
S. Enteritidis	105	228	41	44	51	164	13	20
S. Typhi	14	14	1	1	13	13	0	0
S. Paratyphi A and B	21	31	3	3	15	25	3	3
Other *Salmonella*	172	258	97	103	47	125	28	30
Total	**419**	**640**	**189**	**200**	**172**	**373**	**58**	**67**

A total of 50 isolates were recovered form blood cultures representing 12% of all tested *Salmonella* isolates, including 12 *S.* Typhi (85.7%), 2 *S.* Paratyphi A (66.7%), 14 *S.* Enteritidis (13.3%), 1 *S.* Paratyphi B (5.6%), 3 *S.* Typhimurium (4.2%), and 18 *Salmonella* isolates of other serovars (10.5%). The results from the antimicrobial susceptibility testing and genomic resistance screening for *Salmonella* are presented in Tables 30-44, Figures 67-78, and in the text.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHIMURIUM

TABLE 30. Percentage distributions of antimicrobial susceptibility categories in domestically acquired *Salmonella* Typhimurium (n=32) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	93.8	-	6.2
Cefotaxime	≤ 1	> 2	96.9	0.0	3.1
Ceftazidime	≤ 1	> 4	96.9	3.1	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	96.9	-	3.1
Tetracycline[2]	≥ 17 mm	< 17 mm	87.5	-	12.5
Chloramphenicol[3]	≤ 16	> 16	93.8	-	6.2

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. [1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0). [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

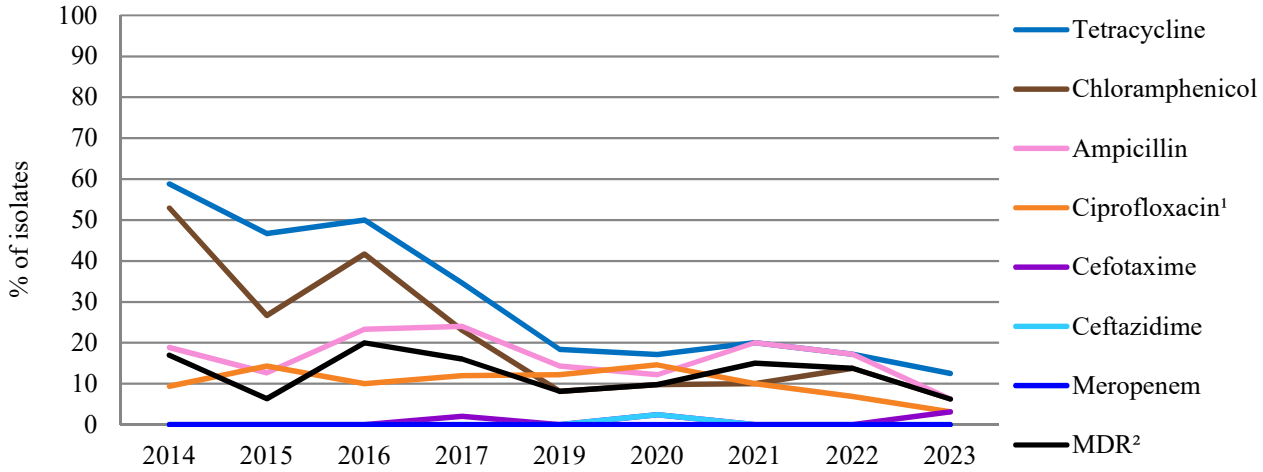

FIGURE 67. Trend 2014-2023. Percentage of domestically acquired *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 31. Percentage distributions of predicted genotypic resistance in domestically acquired *Salmonella* Typhimurium (n=33) compared to phenotypic wild type/non-wild type distribution (n=32) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	97.0	3.0
Streptomycin	-	-	87.9	12.1
Ampicillin	93.8	6.2	90.9	9.1
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	96.9	3.1	97.0	3.0
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	93.8	6.2	90.9	9.1
Ciprofloxacin	96.9	3.1	93.9	6.1
Sulfonamide	-	-	93.9	6.1
Tetracycline	87.5	12.5	84.8	15.2
Trimethoprim	-	-	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

TABLE 32. Percentage distributions of antimicrobial susceptibility categories in travel associated *Salmonella* Typhimurium (n=28) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	89.3	-	10.7
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	89.3	-	10.7
Tetracycline[2]	≥ 17 mm	< 17 mm	53.6	-	46.4
Chloramphenicol[3]	≤ 16	> 16	82.1	-	17.9

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0). [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

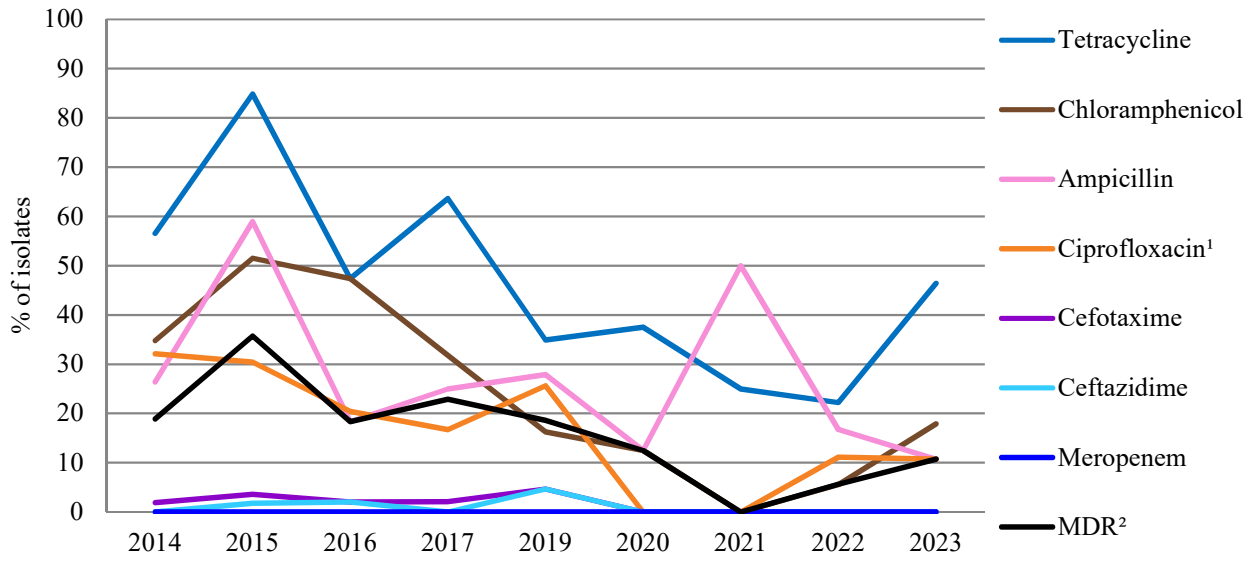

FIGURE 68. Trend 2014-2023. Percentage of travel associated *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 33. Percentage distributions of predicted genotypic resistance in travel associated *Salmonella* Typhimurium (n=28) compared to phenotypic wild type/non-wild type distribution (n=28) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	57.1	42.9
Ampicillin	85.7	14.3	89.3	10.7
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	100.0	0.0	100.0	0.0
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	82.1	17.9	89.3	10.7
Ciprofloxacin	89.3	10.7	89.3	10.7
Sulfonamide	-	-	64.3	35.7
Tetracycline	53.6	46.4	53.6	46.4
Trimethoprim	-	-	92.9	7.1

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

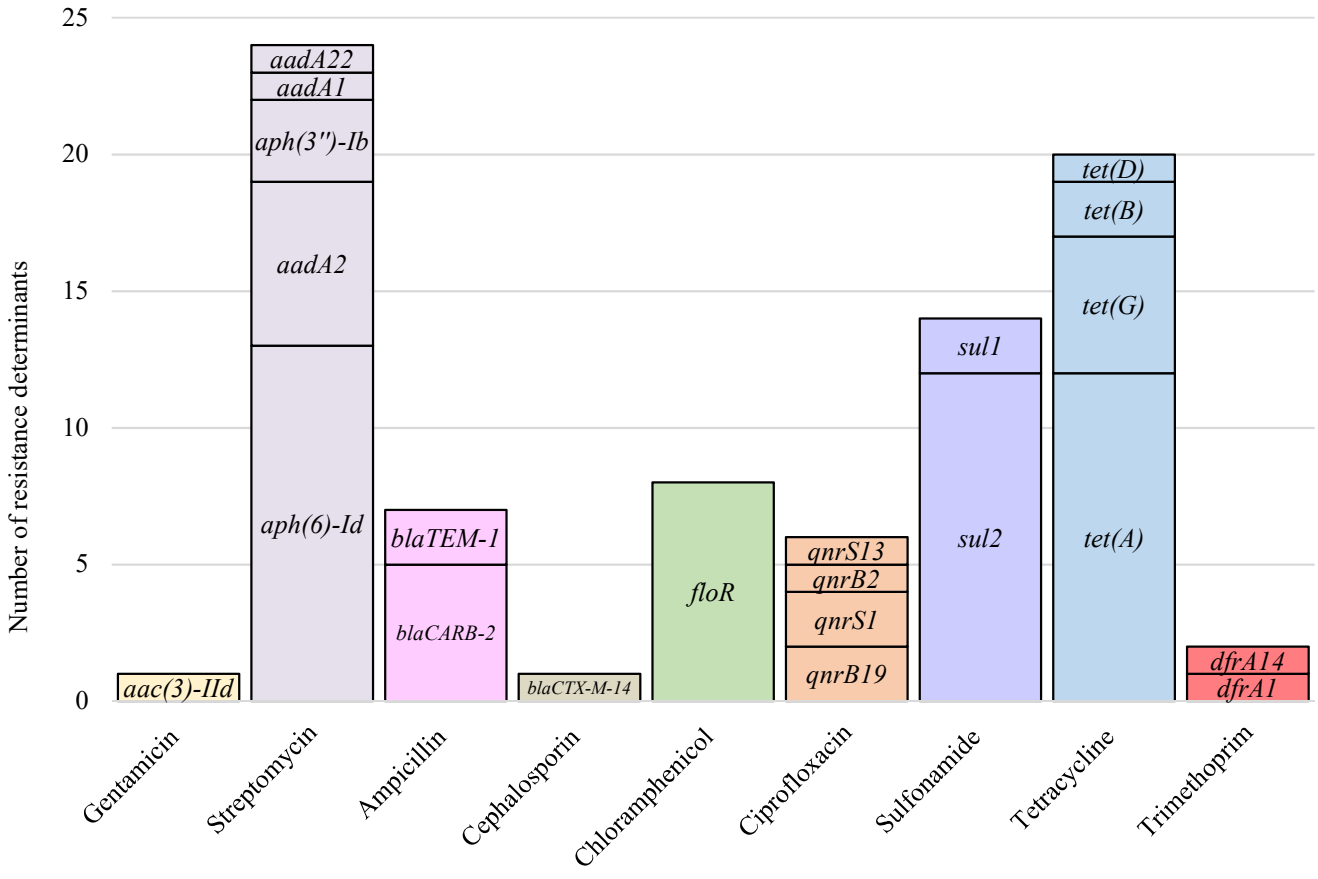

FIGURE 69. Identified resistance determinants in *Salmonella* Typhimurium (n=73) to selected antimicrobial agents in Norway 2023.

ANTIMICROBIAL RESISTANCE IN MONOPHASIC SALMONELLA TYPHIMURIUM

TABLE 34. Percentage distributions of antimicrobial susceptibility categories in domestically acquired monophasic *Salmonella* Typhimurium (n=15) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	6.7	-	93.3
Cefotaxime	≤ 1	> 2	93.3	0.0	6.7
Ceftazidime	≤ 1	> 4	93.3	6.7	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	93.3	-	6.7
Tetracycline[2]	≥ 17 mm	< 17 mm	13.3	-	86.7
Chloramphenicol[3]	≤ 16	> 16	80.0	-	20.0

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0).[2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

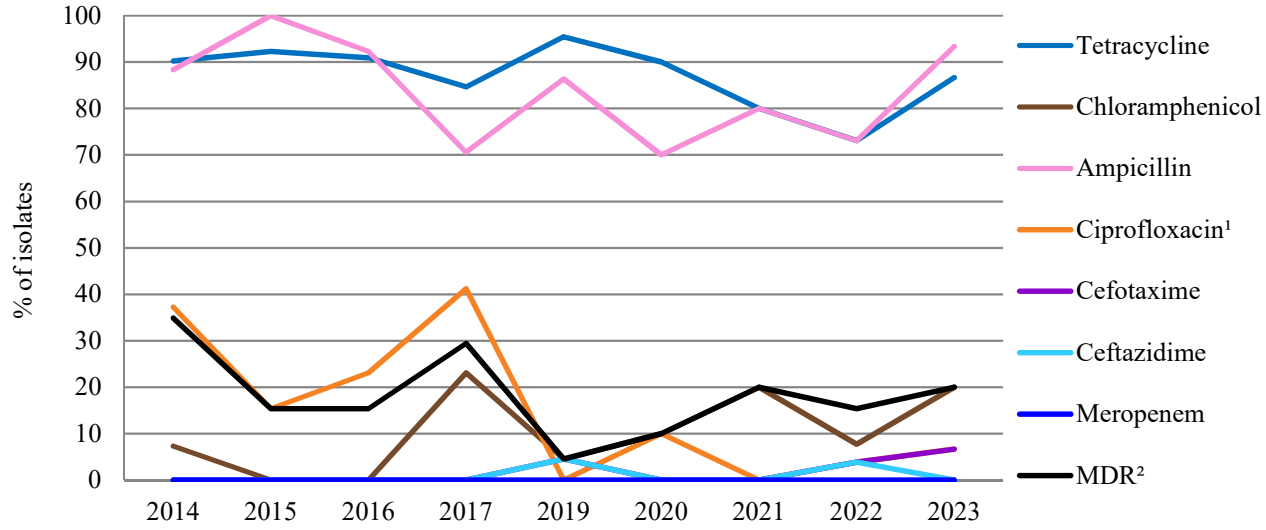

FIGURE 70. Trend 2014-2023. Percentage of domestically acquired monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 35. Percentage distributions of predicted genotypic resistance in domestically acquired monophasic *Salmonella* Typhimurium (n=16) compared to phenotypic wild type/non-wild type distribution (n=15) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	93.8	6.2
Streptomycin	-	-	18.8	81.2
Ampicillin	6.7	93.3	12.5	87.5
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	93.3	6.7	93.7	6.3
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	80.0	20.0	81.2	18.8
Ciprofloxacin	93.3	6.7	87.5	12.5
Sulfonamide	-	-	18.8	81.2
Tetracycline	13.3	86.7	18.8	81.2
Trimethoprim	-	-	87.5	12.5

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

TABLE 36. Percentage distributions of antimicrobial susceptibility categories in travel associated monophasic *Salmonella* Typhimurium (n=18) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	5.6	-	94.4
Cefotaxime	≤ 1	> 2	94.4	0.0	5.6
Ceftazidime	≤ 1	> 4	94.4	5.6	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	83.3	-	16.7
Tetracycline[2]	≥ 17 mm	< 17 mm	22.2	-	77.8
Chloramphenicol[3]	≤ 16	> 16	83.3	-	16.7

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0). [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

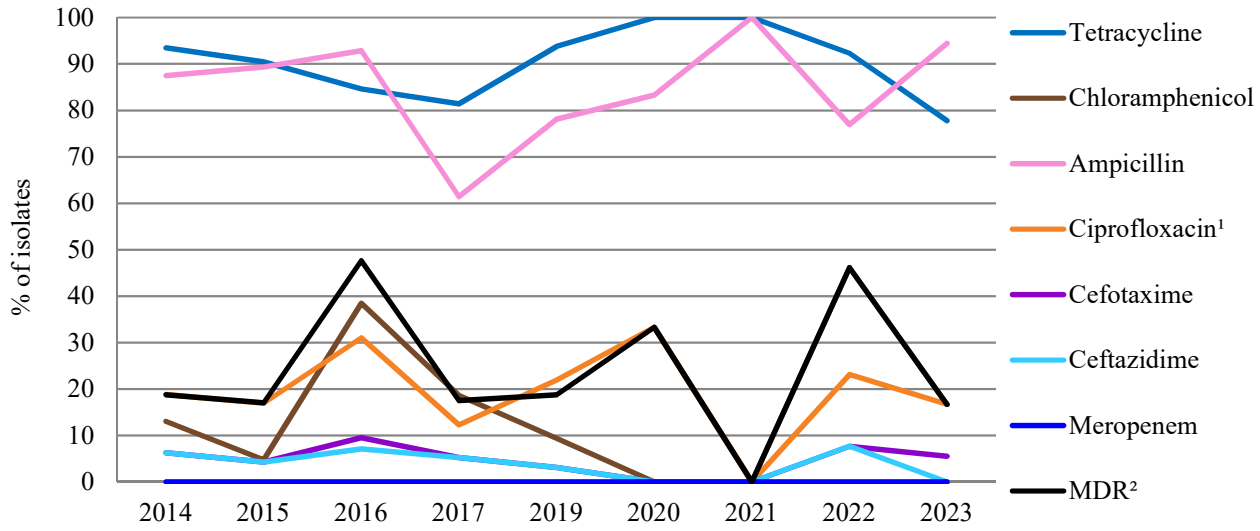

FIGURE 71. Trend 2014-2023. Percentage of travel associated monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 37. Percentage distributions of predicted genotypic resistance in travel associated monophasic *Salmonella* Typhimurium (n=18) compared to phenotypic wild type/non-wild type distribution (n=18) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	88.9	11.1
Streptomycin	-	-	11.1	88.9
Ampicillin	5.6	94.4	5.6	94.4
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	94.4	5.6	94.4	5.6
Ceftazidime[3]	100.0	0.0		
Colistin[3]	-	-	100.0	0.0
Chloramphenicol	83.3	16.7	88.9	11.1
Ciprofloxacin	83.3	16.7	77.8	22.2
Sulfonamide	-	-	11.1	88.9
Tetracycline	22.2	77.8	27.8	72.2
Trimethoprim	-	-	88.9	11.1

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

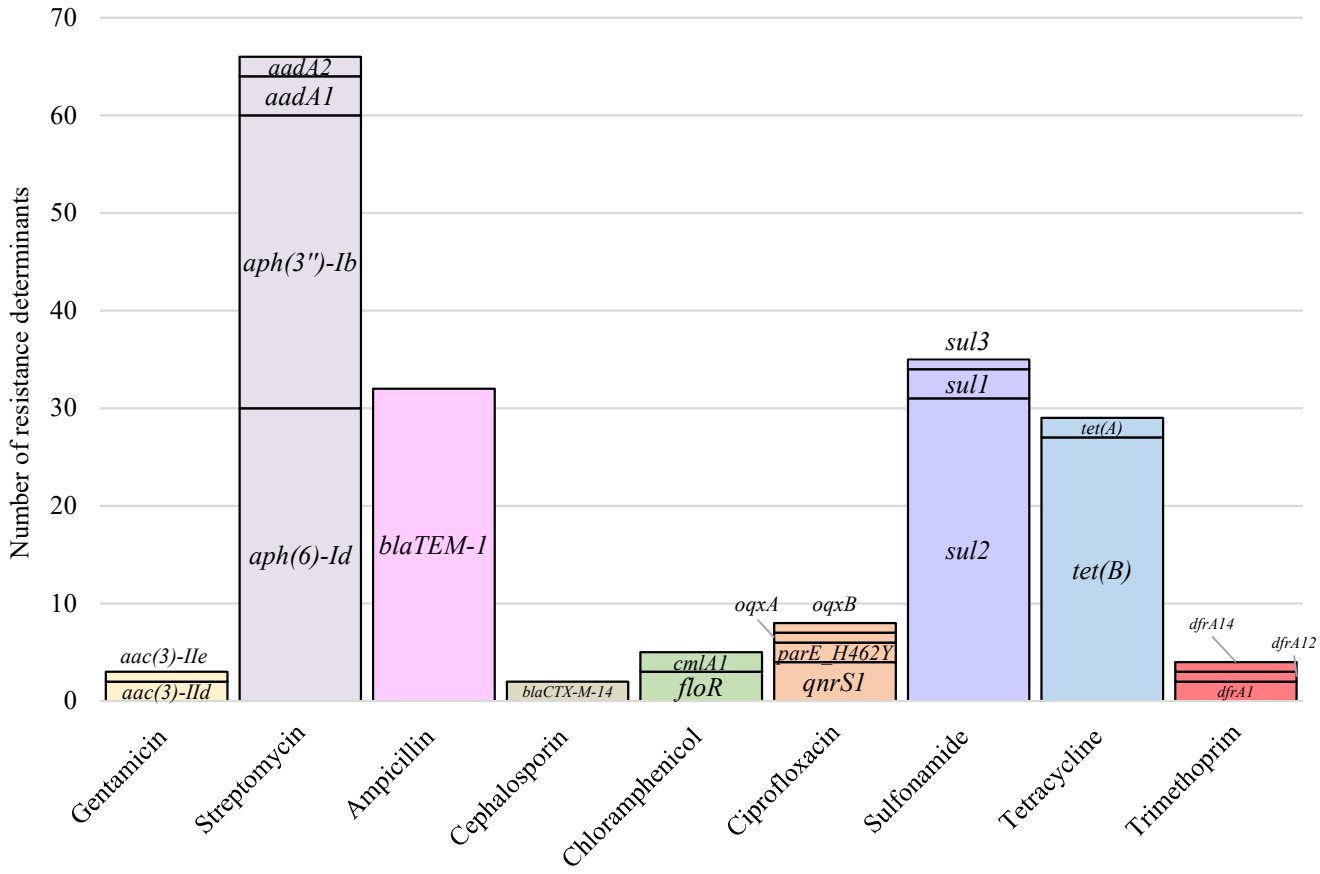

FIGURE 72. Identified resistance determinants in monophasic *Salmonella* Typhimurium (n=35) to selected antimicrobial agents in Norway 2023.

ANTIMICROBIAL RESISTANCE IN SALMONELLA ENTERITIDIS

TABLE 38. Percentage distributions of antimicrobial susceptibility categories in *Salmonella* Enteritidis (n=105) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	89.5	-	10.5
Cefotaxime	≤ 1	> 2	99.0	0.0	1.0
Ceftazidime	≤ 1	> 4	99.0	1.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	68.6	-	31.4
Tetracycline[2]	≥ 17 mm	< 17 mm	93.3	-	6.7
Chloramphenicol[3]	≤ 16	> 16	99.0	-	1.0

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0). [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

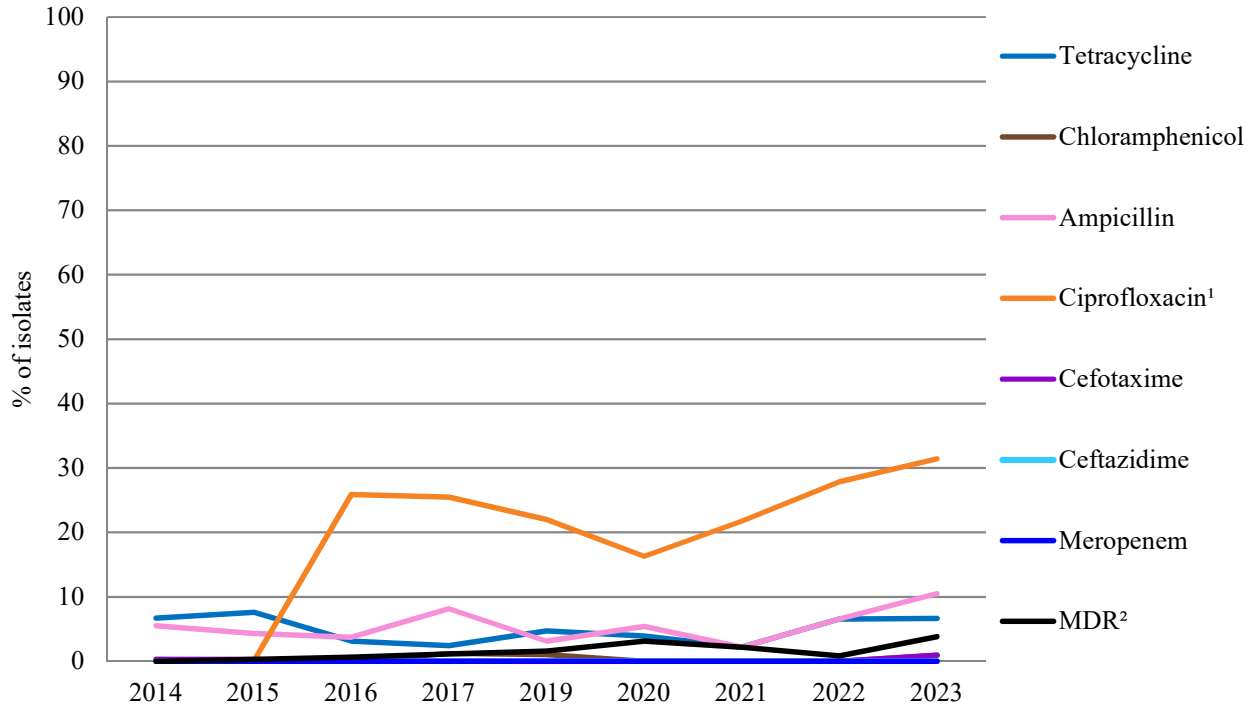

FIGURE 73. Trend 2014-2023. Percentage of *Salmonella* Enteritidis resistant to selected antimicrobial agents from all human clinical specimens tested in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 39. Percentage distributions of predicted genotypic resistance in *Salmonella* Enteritidis (n=228) compared to phenotypic wild type/non-wild type distribution (n=105) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	99.6	0.4
Ampicillin	89.5	10.5	93.4	6.6
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	99.0	1.0	100.0	0.0
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	99.0	1.0	99.6	0.4
Ciprofloxacin	68.6	31.4	68.0	32.0
Sulfonamide	-	-	99.6	0.4
Tetracycline	93.3	6.7	96.5	3.5
Trimethoprim	-	-	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

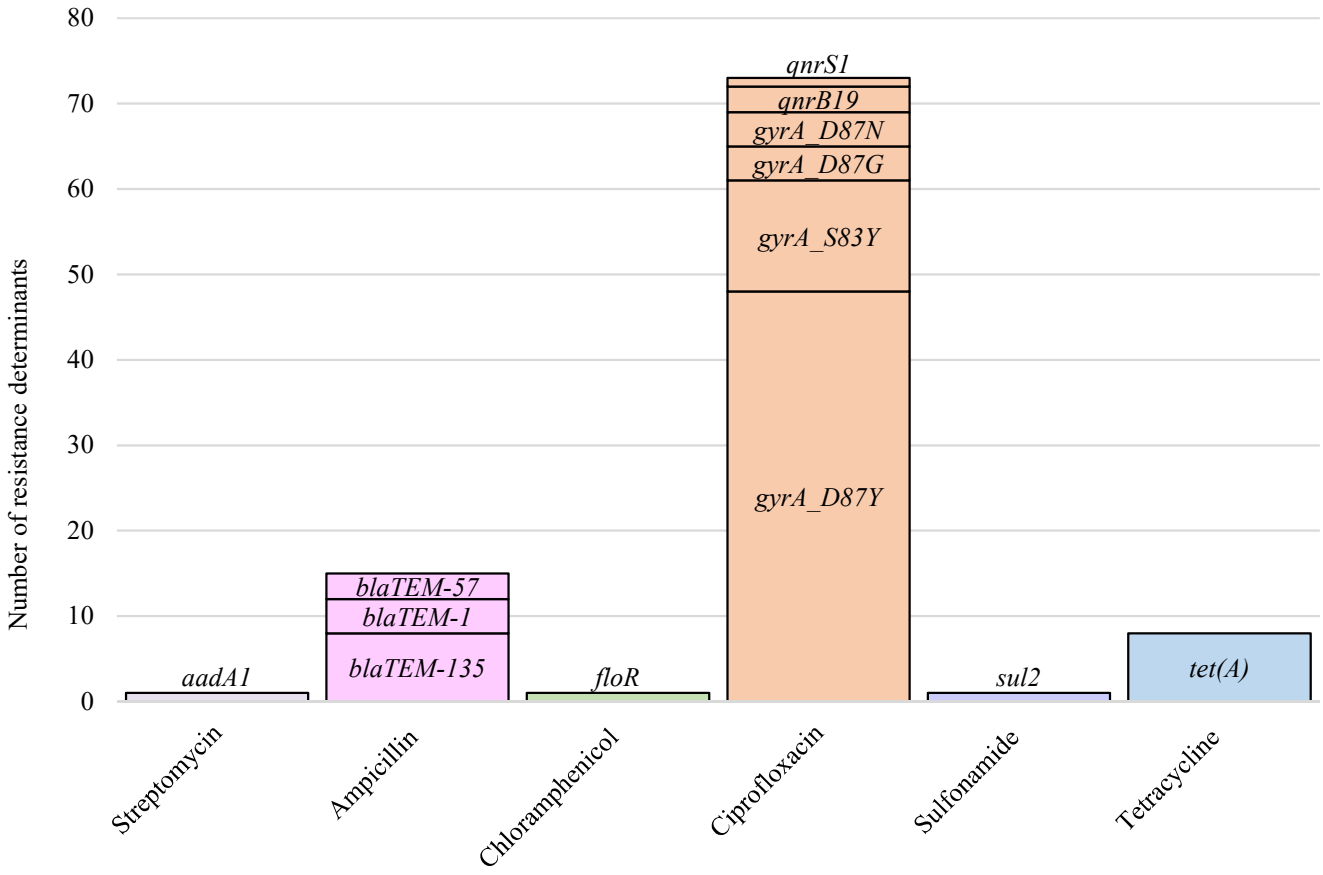

FIGURE 74. Identified resistance determinants in *Salmonella* Enteritidis (n=228) to selected antimicrobial agents in Norway 2023.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHI

TABLE 40. Percentage distributions of antimicrobial susceptibility categories in *Salmonella* Typhi (n=14) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	64.3	-	35.7
Cefotaxime	≤ 1	> 2	85.7	0.0	14.3
Ceftazidime	≤ 1	> 4	85.7	0.0	14.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	14.3	-	85.7
Tetracycline[2]	≥ 17 mm	< 17 mm	100.0	-	0.0
Chloramphenicol[3]	≤ 16	> 16	71.4	-	28.6

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0). [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

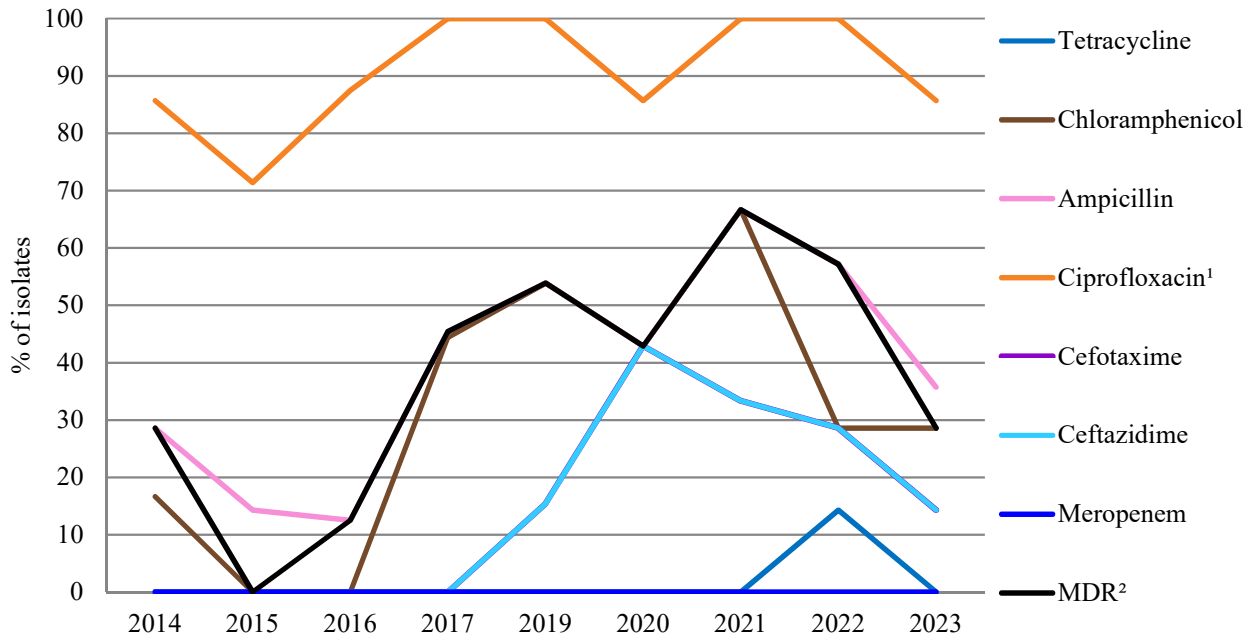

FIGURE 75. Trend 2014-2023. Percentage of *Salmonella* Typhi resistant to selected antimicrobial agents from all human clinical specimens tested in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 41. Percentage distributions of predicted genotypic resistance in *Salmonella* Typhi (n=14) compared to phenotypic wild type/non-wild type distribution (n=14) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	78.6	21.4
Ampicillin	64.3	35.7	64.3	35.7
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	85.7	14.3	85.7	14.3
Ceftazidime[3]	85.7	14.3		
Colistin	-	-	100.0	0.0
Chloramphenicol	71.4	28.6	71.4	28.6
Ciprofloxacin	21.4	78.6	14.3	85.7
Sulfonamide	-	-	71.4	28.6
Tetracycline	100.0	0.0	100.0	0.0
Trimethoprim	-	-	71.4	28.6

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

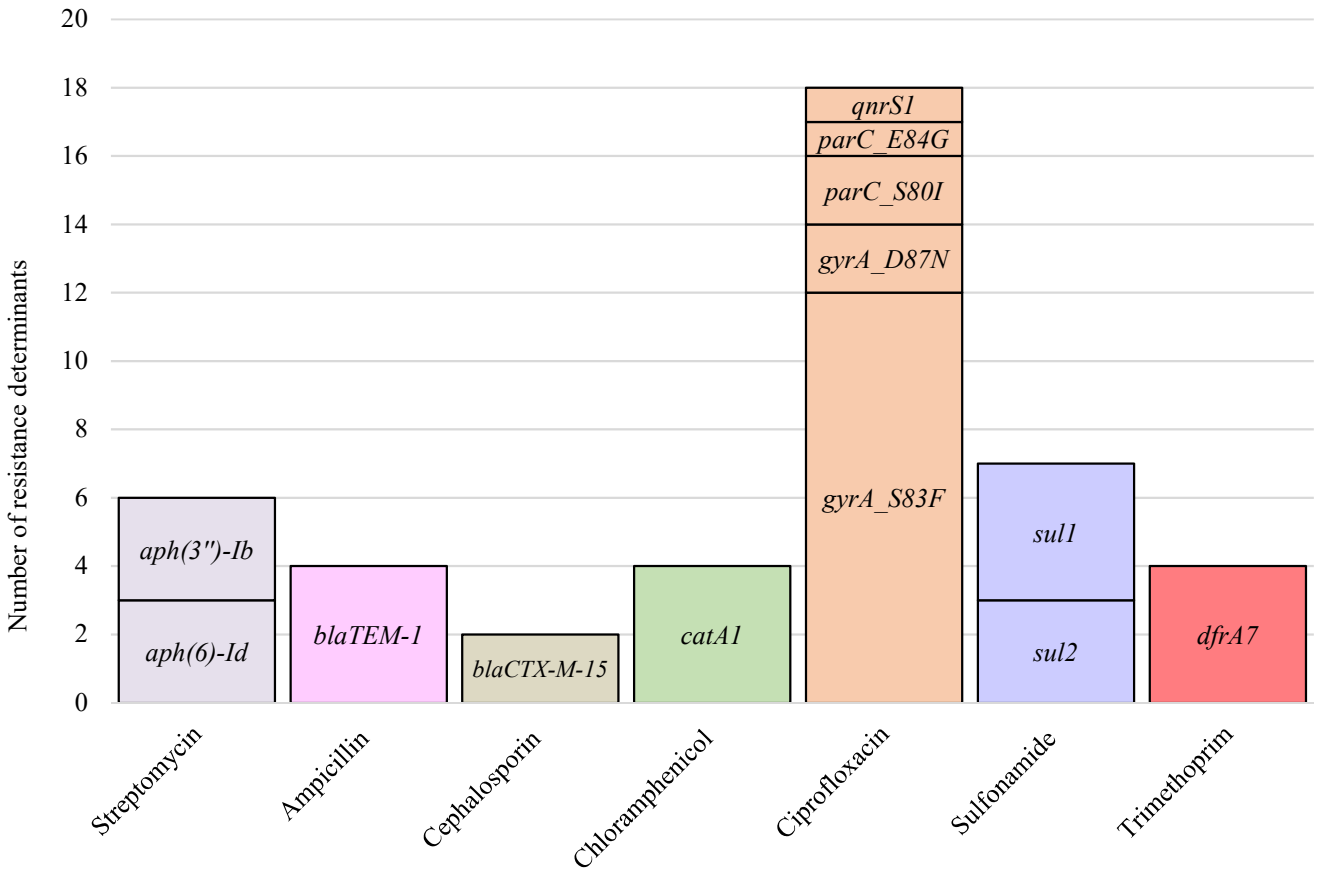

FIGURE 76. Identified resistance determinants in *Salmonella* Typhi (n=14) to selected antimicrobial agents in Norway 2023.

ANTIMICROBIAL RESISTANCE IN OTHER SALMONELLA SEROTYPES

TABLE 42. Percentage distributions of predicted genotypic resistance in other *Salmonella* serotypes (n=258) to phenotypic wild type/non-wild type distribution (n=172) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	98.4	1.6
Streptomycin	-	-	93.8	6.2
Ampicillin	90.7	9.3	91.1	8.9
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	99.4	0.6	98.8	1.2
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	97.7	2.3	97.3	2.7
Ciprofloxacin	90.1	9.9	89.9	10.1
Sulfonamide	-	-	93.4	6.6
Tetracycline	88.4	11.6	87.2	12.8
Trimethoprim	-	-	98.1	1.9

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

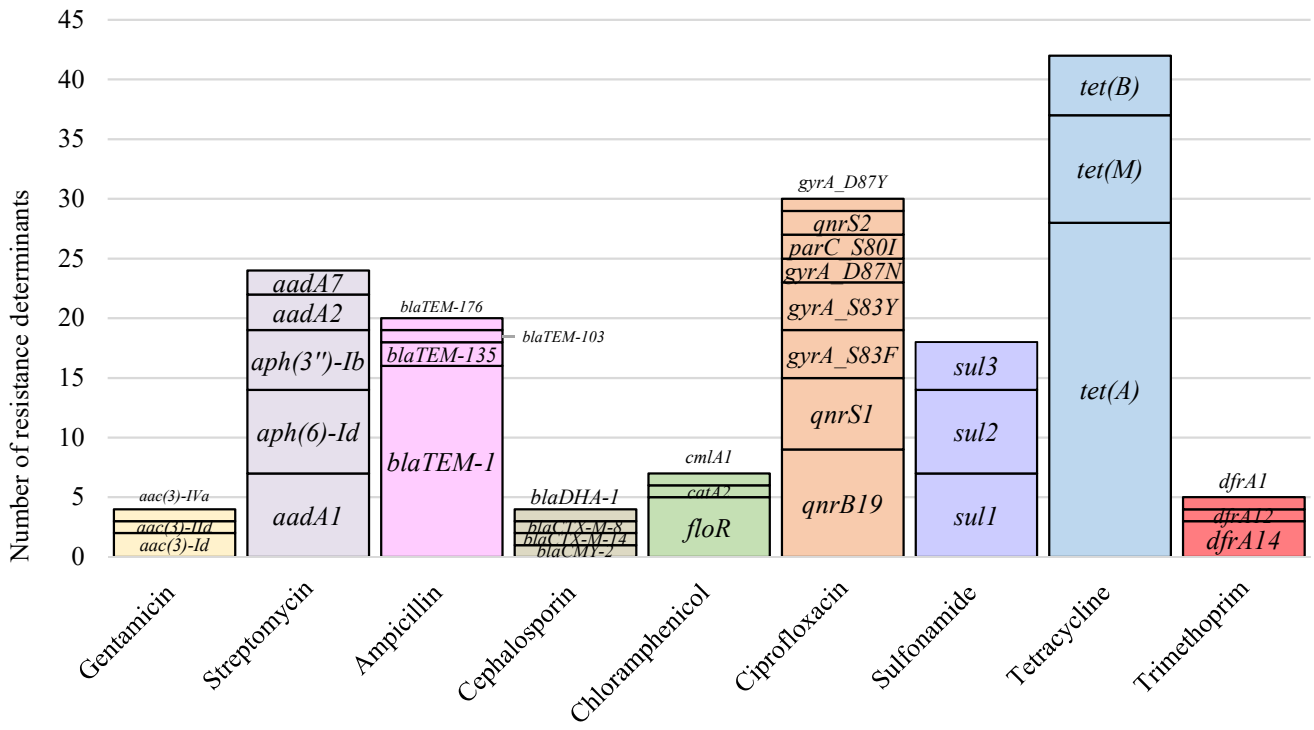

FIGURE 77. Identified resistance determinants in other *Salmonella* serotypes (n=258) to selected antimicrobial agents in Norway 2023.

MULTI-DRUG RESISTANCE IN SALMONELLA

TABLE 43. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates identified in Norway 2023, stratified according to serotype and resistance to different antibiotic categories.

Salmonella serotypes	MDR[1]	Antibiotic categories[2]							
		STR	AMP	ESP	CHL	CIP	SUL	TET	TMP
monophasic *Salmonella* Typhimurium	32	31	32	2	5	6	31	25	4
Salmonella Typhimurium	19	18	8	1	8	4	12	19	2
Salmonella Typhi	4	3	4	1	4	4	4	0	4
Salmonella Enteritidis	4	0	4	0	1	3	1	3	0
Other *Salmonella*	21	16	13	3	6	14	17	20	5
Total no. of MDR isolates	**80**	**68**	**61**	**7**	**24**	**31**	**65**	**67**	**15**

[1]Multi-drug resistance (MDR) defined as predicted genotypic resistance to 3 ≥ antibiotic categories. [2]Antibiotic category: STR: Streptomycin, AMP: Ampicillin, ESP: Extended-Spectrum Cephalosporin, CHL: Chloramphenicol, CIP: Ciprofloxacin, SUL: Sulfonamide, TET: Tetracycline, TMP: Trimethoprim.

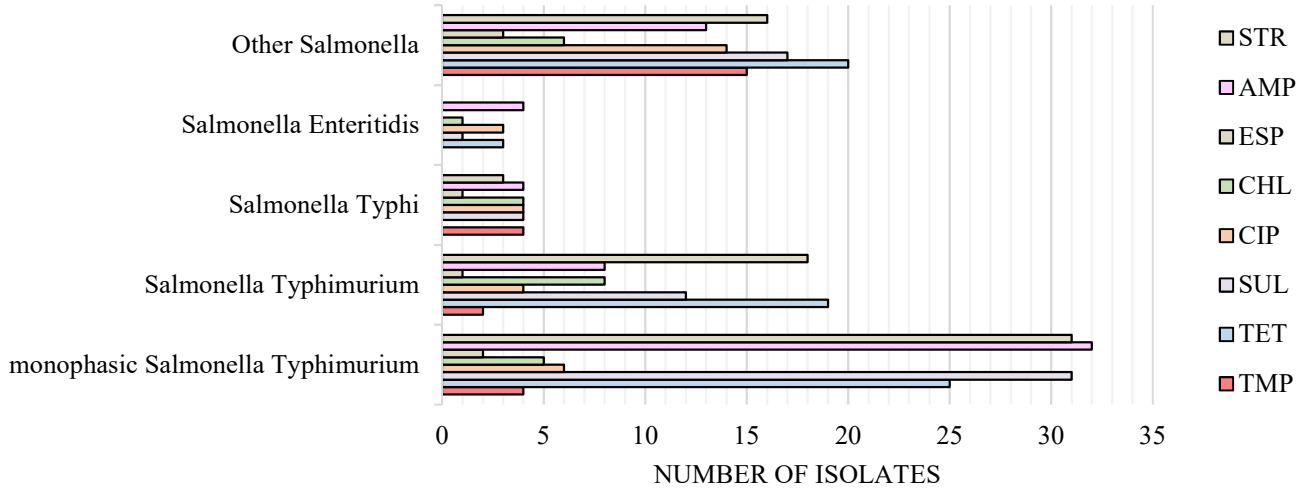

FIGURE 78. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates (n=80) identified in Norway 2023, stratified according to serotype and resistance to different antibiotic categories; STR: Streptomycin, AMP: Ampicillin, ESP: Extended-Spectrum Cephalosporin, CHL: Chloramphenicol, CIP: Ciprofloxacin, SUL: Sulfonamide, TET: Tetracycline, TMP: Trimethoprim.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN SALMONELLA

TABLE 44. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Salmonella* isolates identified in Norway 2023.

Antibiotic categories	Tested	Phenotype WT[1]		Phenotype NWT[1]		Sensitivity (%)	Spesificity (%)
		Genotype R	Genotype S	Genotype R	Genotype S		
Penicillins	419	2	342	68	7	97.1	98.0
ESC[2]	419	1	411	6	1	85.7	99.8
Carbapenems	419	0	419	0	0	-	100.0
Fluoroquinolones	419	5	339	72	3	93.5	99.1
Tetracycline	419	3	340	73	3	96.1	99.1
Phenicols	419	1	393	20	5	95.2	98.7

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Salmonella enterica* (v.14.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins (ESC).

RESULTS AND COMMENTS

The NRL annually performs antimicrobial susceptibility testing on a selection of the received *Salmonella* isolates. Selection criteria are set to ensure inclusion of the most important *Salmonella* serovars and important antibiotics for the monitoring of emergence and dissemination of antimicrobial resistance in Norway. Additionally, 2020 onwards the NRL has screened all *Salmonella* isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance. In 2020 and 2021, during the COVID-19 pandemic, infection control measures including travel restrictions substantially reduced travel associated *Salmonella* infections. Analysis of trends in antimicrobial resistance for this period must be interpreted accordingly.

In 2023 the NRL identified a total of 9 outbreak clusters: *S.* Agona (n=13), *S.* Enteritidis (n=9), *S.* Enteritidis (n=6), *S.* Napoli (n=6), *S.* Ball (n=5), *S.* Typhi (n=4), *S.* Typhimurium (n=3), monophasic *S.* Typhimurium (n=3), and *S.* Enteritidis (n=3). The *S.* Agona cluster was part of the national outbreak involving 89 cases in 2022 and 2023 where the suspected vehicle was imported cucumber. Clusters of *S.* Typhi, and two *S.* Enteritidis were associated with travel, the remaining clusters were of domestically acquired cases. Antimicrobial resistance results from only a single isolate from each of these clusters except for *S.* Typhi are included in this report.

The overall resistance in *S.* Typhimurium was higher in strains associated with travel compared to strains from domestically acquired infections. We observed a stable trend in resistance to most tested antibiotics in strains from domestically acquired infections. We observed an increase in tetracycline resistance for strains from infections associated with travel. A single ESBL producer was identified. Variants of the plasmid-mediated quinolone resistance gene *qnr* were identified as probable mediator for the observed ciprofloxacin resistance. An MDR genotype was assigned to 25.0% of the isolates, largely attributed to resistance to streptomycin, sulfonamide, and tetracycline.

The overall resistance level in the monophasic variant of *S.* Typhimurium was higher than for *S.* Typhimurium. We observed a stable trend in resistance over the last five years for all the tested antibiotics. High levels of resistance were seen for ampicillin and tetracycline in strains from both domestically acquired and travel associated infections. A single ESBL producing isolate was identified encoding $bla_{\text{CTX-M-14}}$. An MDR genotype was identified for 84.2% of the isolates, largely attributed to resistance against streptomycin, ampicillin, sulfonamide, and tetracycline.

Antibiotic resistance in *S.* Enteritidis is generally low. An apparent emergence of ciprofloxacin resistance in 2016 was linked to a change in the antibiotic used for testing fluoroquinolone resistance (from ciprofloxacin to pefloxacin). When screening for genotypic resistance determinants, the presence of various mutations in the quinolone resistance-determining regions (QRDRs) of *gyrA*, as well as the presence of *qnr*, was confirmed. No ESBL producing isolates were identified. An MDR genotype was identified for 1.6% of the isolates, attributed to resistance against ampicillin, ciprofloxacin, and tetracycline.

The overall level of antibiotic resistance in *S.* Typhi is high. Two ESBL producing isolates were identified, both encoding $bla_{\text{CTX-M-15}}$. An MDR genotype was identified for 28.6% of the isolates, largely attributed to resistance against streptomycin, ampicillin, chloramphenicol, ciprofloxacin, sulfonamide, and trimethoprim.

Among other *Salmonella* serotypes (n=258), the most common serotypes identified were *S.* Stanley (n=32), *S.* Paratyphi B variant Java (n=23), *S.* Newport (n=18), *S.* Agona (n=17), *S.* Chester (n=17), *S.* Infantis (n=12), *S.* Napoli (n=11), *S.* Saintpaul (n=11) and *S.* Montevideo (n=10). Overall predicted genotypic resistance was low (<10%) across all screened antibiotics, except for quinolones (10.1%) and tetracycline (12.8%). Three ESBL producing isolates were identified, encoding $bla_{\text{CTX-M-8}}$, $bla_{\text{CTX-M-14}}$, and $bla_{\text{DHA-1}}$. In addition, the isolate encoding $bla_{\text{CTX-M-8}}$ also encoded $bla_{\text{CMY-2}}$. Presence of various mutations in the QRDRs of *gyrA* and variants of *qnr* were predicted as conferring resistance to quinolones. An MDR genotype was identified in 7.5% of the *Salmonella* isolates of other serotypes. The MDR genotype was largely attributed to resistance towards streptomycin, ampicillin, ciprofloxacin, sulfonamide, tetracycline, and trimethoprim.

In total, nine isolates were predicted as genotypically resistant to extended-spectrum cephalosporins: *S.* Typhi (n=2), monophasic *S.* Typhimurium (n=2), *S.* Typhimurium (n=1), *S.* Minnesota (n=1), *S.* Cannstatt (n=1), *S.* Paratyphi B variant Java (n=1), and *S.* Stanley (n=1). Resistance was mediated by different variants of $bla_{\text{CTX-M}}$ (n=8), $bla_{\text{CMY-2}}$ (n=1) and $bla_{\text{DHA-1}}$ (n=1) genes. The overall correlation between phenotypic resistance and predicted genotypic resistance was high, both sensitivity and specificity were generally above 95% for all tested and screened antibiotics.

CAMPYLOBACTER SPP.

Campylobacter spp. from cattle and pig

Caecal samples from 277 cattle and 333 fattening pigs were examined. *Campylobacter jejuni* was detected from 128 (98.5%) cattle and 14 (4.7%) pig samples. *Campylobacter coli* isolates were obtained from 296 (99.3%) of the pig samples and none of the samples from cattle. Of these, 124 *C. jejuni* isolates from cattle and 281 *C. coli* isolates from fattening pigs were susceptibility tested. The results are presented in Tables 45-46, Figures 79-81, and in the text.

TABLE 45. Antimicrobial resistance in *Campylobacter jejuni* isolates from caecal samples of cattle (n=124) in 2023.

Substance	Resistance (%)	[95% CI]	Distribution (%) of MIC values (mg/L)*													
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	4.0	[1.3 – 9.2]				96.0		1.6				0.8	0.8	0.8			
Chloramphenicol	0.0	[0.0 – 2.9]						96.0	2.4	1.6							
Ertapenem	7.3	[3.4 – 13.3]		92.7		4.0	1.6	0.8	0.8								
Erythromycin	0.8	[0.0 – 4.4]					97.6	1.6									0.8
Gentamicin	0.0	[0.0 – 2.9]				8.9	69.4	21.8									
Ciprofloxacin	15.3	[9.5 – 22.9]		75.8		8.9				0.8	2.4	12.1					

*Bold vertical lines denote microbiological cut-off values. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

TABLE 46. Antimicrobial resistance in *Campylobacter coli* isolates from caecal samples of fattening pigs (n=281) in 2023.

Substance	Resistance (%)	[95% CI]	Distribution (%) of MIC values (mg/L)*													
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	1.4	[0.4 – 3.6]				96.4	1.4	0.7	0.7		0.7						
Chloramphenicol	0.0	[0.0 – 1.3]						85.1	14.6	0.4							
Ertapenem	ND	ND		84.7	12.8	1.1		1.1		0.4							
Erythromycin	0.7	[0.1 – 2.6]					98.2							0.4	0.4		
Gentamicin	0.4	[0.0 – 2.0]			1.8	29.2	66.6	2.1				0.4					
Ciprofloxacin	20.6	[16.0 – 25.9]		78.7	0.7			1.1	7.5	11.4	0.4	0.4					

*Bold vertical lines denote microbiological cut-off values. ND = not defined. CI = confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

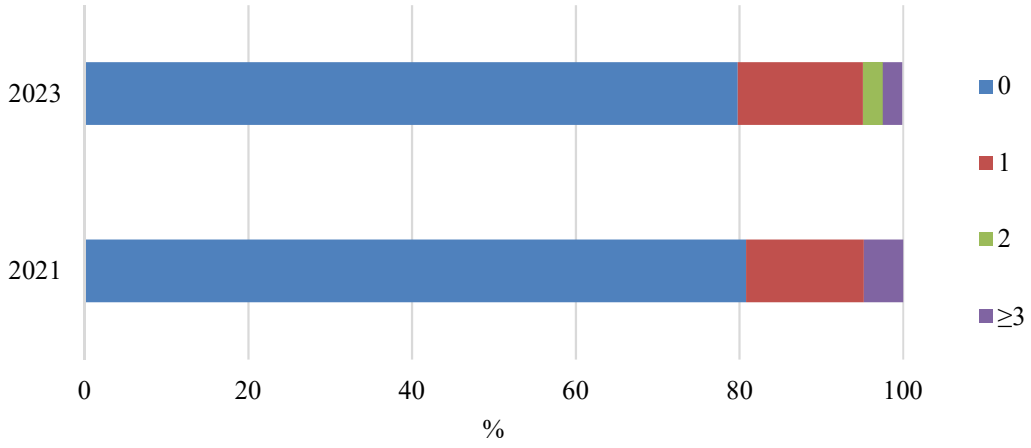

FIGURE 79. Antimicrobial resistance profile for *Campylobacter jejuni* from caecal samples from cattle collected in 2021-2023. The epidemiological cutoffs used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

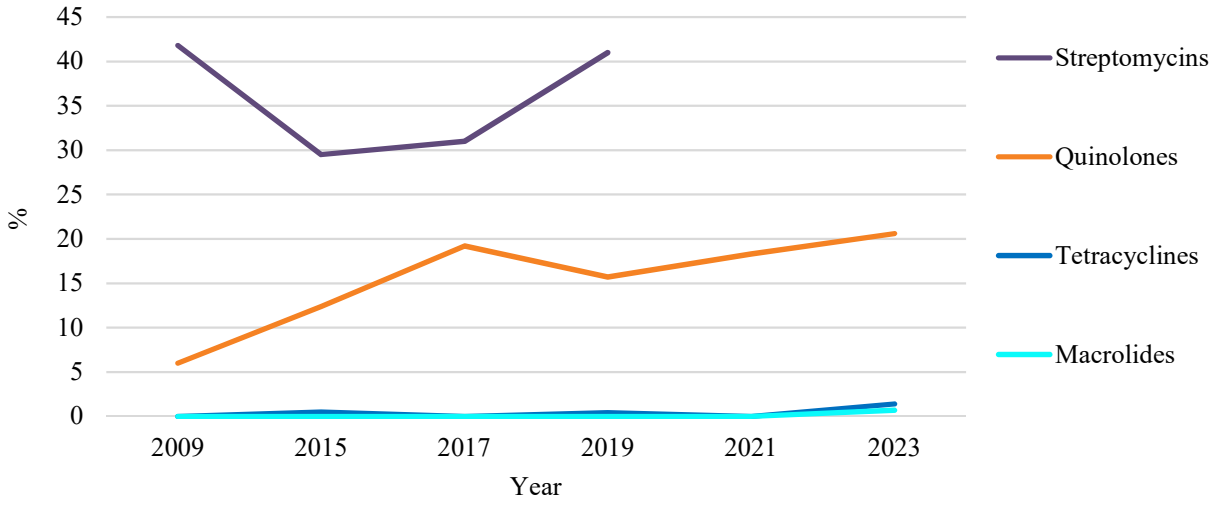

FIGURE 80. Prevalence of resistance to various antimicrobial classes in *Campylobacter coli* from pig faecal or caecal samples isolated between 2009-2023. The epidemiological cutoffs used in NORM-VET 2023 were applied.

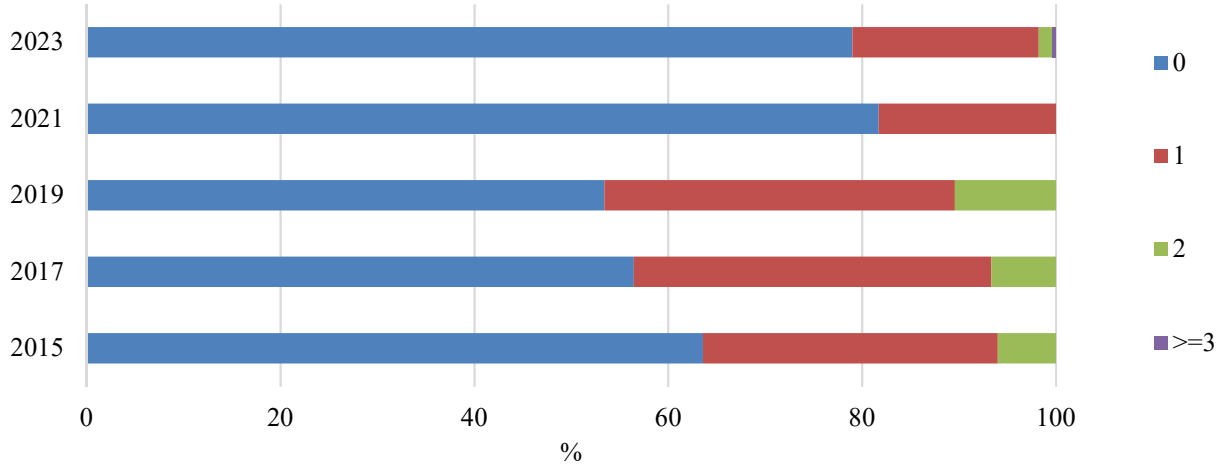

FIGURE 81. Antimicrobial resistance profile for *Campylobacter coli* from caecal samples from fattening pigs collected in 2015-2023. The epidemiological cutoffs used in NORM-VET 2023 were applied. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated. Please observe that resistance to streptomycin is included for the years 2015-2019, but not for 2021-2023. See text for further discussion of results.

RESULTS AND COMMENTS

CATTLE

A total of 79.8% (95% CI: 71.7-86.5) of the *C. jejuni* isolates from cattle were fully susceptible to all antimicrobial agents included in the test panel.

Altogether, 15.3% (95% CI: 9.8-22.9) were resistant to one antimicrobial class and 2.4% (95% CI: 0.5-6.9) to two or to three or more of the antimicrobial classes, respectively. According to the EFSA classification described in Appendix 6, this corresponds to a high occurrence of resistance among *C. jejuni* from cattle.

C. jejuni from cattle has previously been investigated in 2010 and 2021. However, comparison to 2010 is difficult due to differences in methodology as well as the fact that very few isolates were investigated in 2010. The results from 2023 are in concordance with the results from 2021.

The occurrence of resistance among *C. jejuni* varies between the countries reporting to EFSA with Norway being among the countries with the lowest occurrence. In the EFSA and ECDC Summary Report from 2021 and 2022, resistance to tetracyclines and ciprofloxacin were the most commonly detected resistance determinantes among *C. jejuni* from cattle, i.e. 68.8% and 54.7%, respectively (EFSA and ECDC Summary Report 2021-2022). This was based on data from ten countries. Only 0.8% of these showed combined resistance to ciprofloxacin and erythromycin. The occurrence of *Campylobacter* spp. isolates displaying combined resistance to ciprofloxacin and erythromycin is of great importance to public health, since both compounds are recognised as critically important antimicrobials for the treatment of *Campylobacter*

infections in humans (WHO, 2019). One of the cattle isolates from 2023 showed reduced susceptibility to erythromycin. Whole genome sequencing did not detect known genes responsible for this. The isolate did not show combined resistance towards ciprofloxacin.

PIG

A total of 79.0% (95% CI: 73.8-83.6) of the *C. coli* isolates from fattening pigs were susceptible to all antimicrobial agents included in the test panel. Altogether, 19.2% (95% CI: 14.8-24.3) were resistant to one of the antimicrobial classes tested, 1.4% (95% CI: 0.4-3.6) to two and 0.4% (95% CI: 0.1-2.0) to three or more antimicrobial classes. According to the EFSA classification described in Appendix 6, this corresponds to a high occurrence of resistance among *C. coli* from fattening pigs.

C. coli has previously been investigated in 2009, 2015, 2017, 2019 and 2021. There have, however, been changes to the antimicrobial test panel for *Campylobacter* spp., and therefore comparison to the years before 2021 has to be done with caution. Streptomycin is no longer part of the test panel, and streptomycin resistance has previously been common in *C. coli* isolates from pigs as shown in Figure 80. In 2019, 41% (95% CI: 34.8-47.4) of the isolates were streptomycin resistant. Streptomycin is rarely used in Norwegian pig production, and streptomycin resistance in *C. coli* is therefore difficult to explain.

The quinolone ciprofloxacin has been included in the test panel all these years, and as shown in Figure 80 there has been an increasing trend in resistance to quinolones over the years, with 4.5% (95% CI: 1.2-13.4) in 2009 to 20.6% (95% CI: 16.0-25.9) in 2023 being resistant to ciprofloxacin.

In the EFSA and ECDC Summary Report from 2021 and 2022, resistance to tetracyclines and ciprofloxacin were the most commonly detected resistance determinants among *C. coli* from pigs, i.e. 69.3% and 51.7%, respectively (EFSA and ECDC Summary Report 2021-2022). This was based on data from 27 countries. The occurrence of resistance among *C. coli* varies between the reporting countries. The results from Norway are still among the lowest reported. This situation is most likely due to the rather limited use of antibiotics in the Norwegian pig production. Among the European isolates, 1.7% showed combined resistance to ciprofloxacin and erythomycin. The occurrence of *Campylobacter* spp. isolates displaying combined resistance to ciprofloxacin and erythromycin is of great importance to public health, since both compounds are recognised as critically important antimicrobials for the treatment of *Campylobacter* infections in humans (WHO, 2019). Two of the pig isolates from 2023 showed reduced susceptibility to erythromycin. Whole genome sequencing did not detect any resistance determinants causing erythromycin resistance. One of these isolates showed combined resistance to ciprofloxacin and whole genome sequencing detected the mutation p.T86I in the *gyrA* gene in one of these.

Campylobacter spp. from human clinical cases

In 2023, a total of 3,034 human campylobacteriosis cases were notified to MSIS. Most cases with known place of acquisition were infected abroad (50.1%). Surveillance data suggested that the vast majority of cases were sporadic. The first ten *Campylobacter* isolates each month from two and first five from two sentinel regional laboratories were submitted to the NRL for Enteropathogenic Bacteria at the NIPH. In addition, isolates recovered from blood cultures, and isolates that were part of an outbreak investigation were submitted to the NRL for surveillance purposes. A total of 366 isolates were received at NRL, and antimicrobial susceptibility testing was performed on 363 unique *Campylobacter jejuni* and *Campylobacter coli* isolates (Table 47) against four different antibiotic groups: macrolides (erythromycin), aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin), and tetracycline. The results from the antimicrobial susceptibility testing are presented in Tables 48-50, Figures 82-84, and in the text.

TABLE 47. Number of antimicrobial susceptibility tested *Campylobacter* spp. isolates recoved from human clinical specimens in Norway 2023, by species and place of acquisition.

Campylobacter spp.	No. of isolates tested in 2023	Place of acquistion		
		Norway	Abroad	Unknown
Campylobacter jejuni	351	169	129	53
Campylobacter coli	12	1	8	3
Total	**363**	**170**	**137**	**56**

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER JEJUNI

TABLE 48. Percentage distributions of antimicrobial susceptibility categories in domestically acquired *Campylobacter jejuni* (n=169) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	90.5	-	9.5
Erythromycin	≤ 4	> 4	100.0	-	0.0
Gentamicin[1]	≤ 2	> 2	99.4	-	0.6
Ciprofloxacin[2]	≤ 0.001	> 0.5	0.0	78.7	21.3

[1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0)

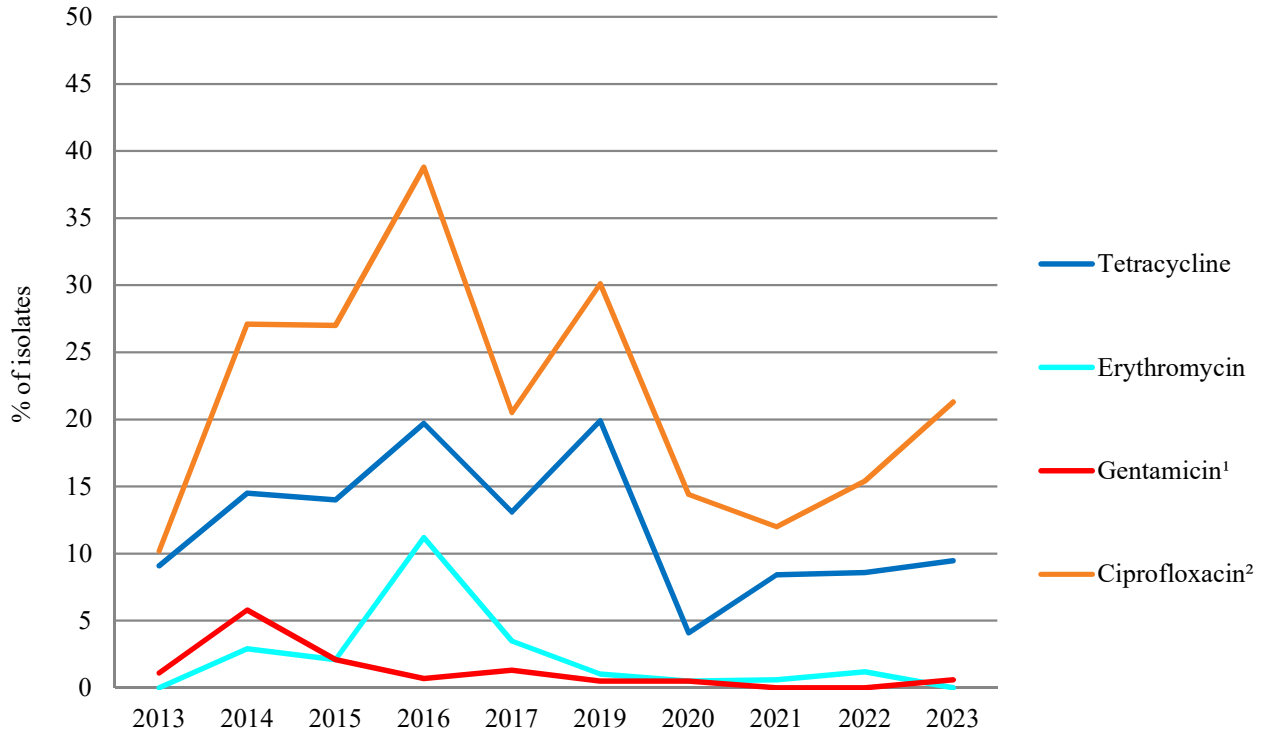

FIGURE 82. Trend 2013-2023. Percentage of domestically acquired *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0).

TABLE 49. Percentage distributions of antimicrobial susceptibility categories in travel associated *Campylobacter jejuni* (n=129) from human clinical specimens in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	32.6	-	67.4
Erythromycin	≤ 4	> 4	99.2	-	0.8
Gentamicin[1]	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin[2]	≤ 0.001	> 0.5	0.0	18.6	81.4

[1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0)

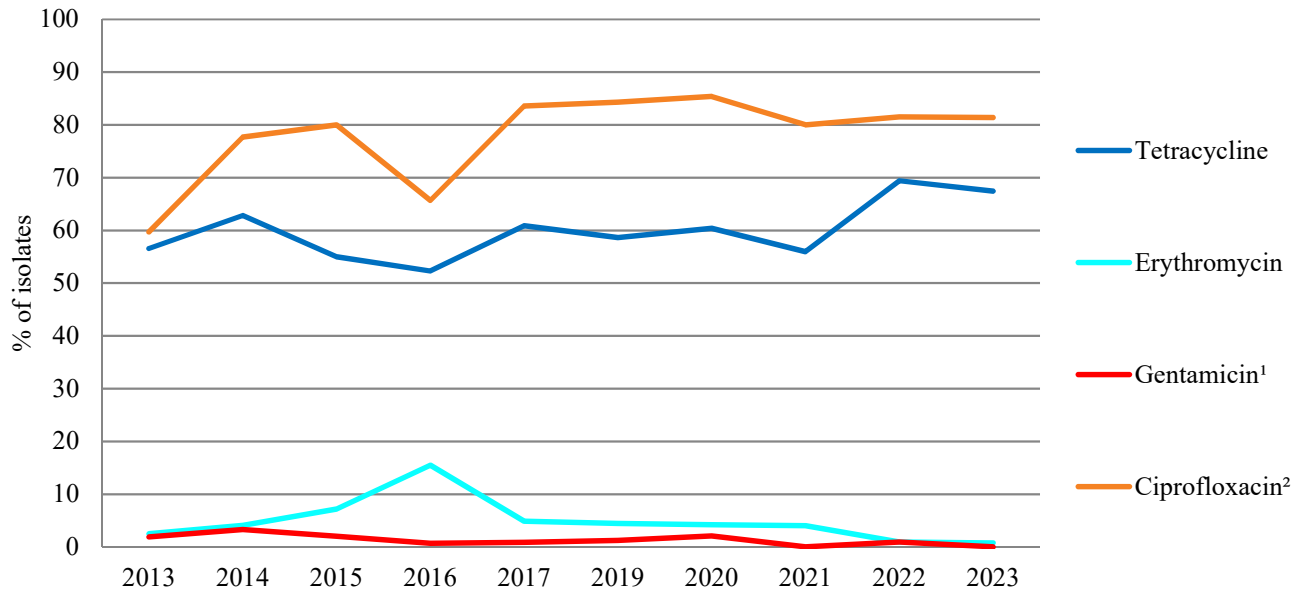

FIGURE 83. Trend 2013-2023. Percentage of travel associated *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0).

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER COLI

TABLE 50. Percentage distributions of antimicrobial susceptibility categories in *Campylobacter coli* (n=12) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	41.7	-	58.3
Erythromycin	≤ 8	> 8	100.0	-	0.0
Gentamicin[1]	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin[2]	≤ 0.001	> 0.5	0.0	0.0	100.0

[1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0).

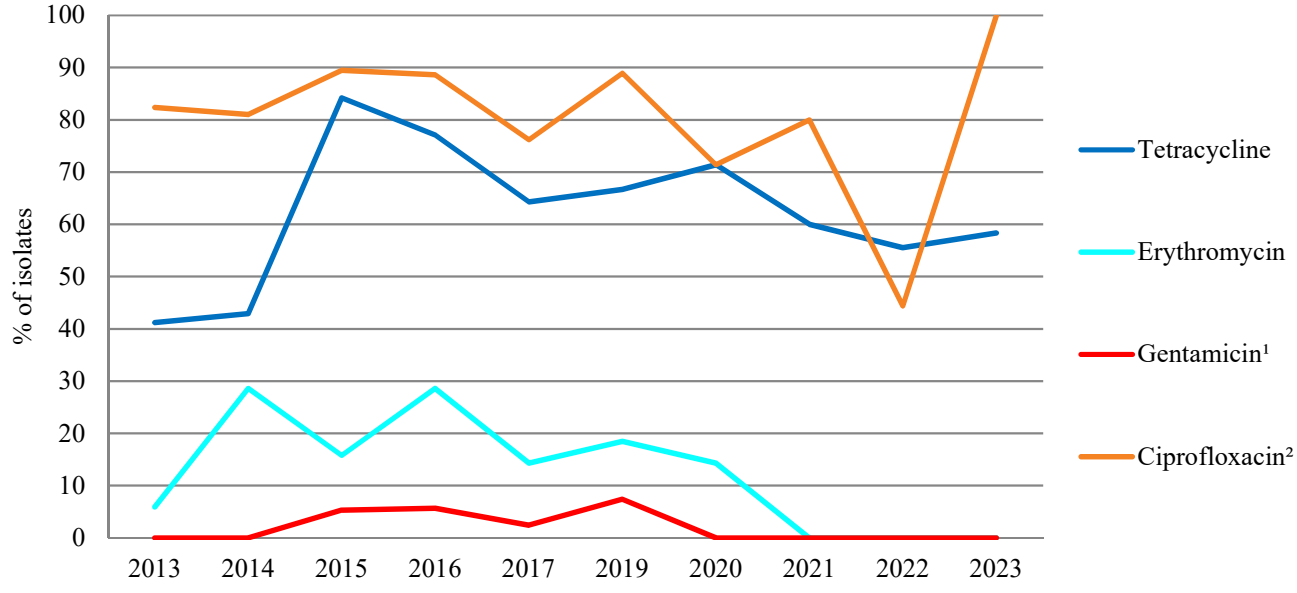

FIGURE 84. Trend 2013-2023. Percentage of *Campylobacter coli* resistant to selected antimicrobial agents from all human clinical specimens tested in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.14.0).

RESULTS AND COMMENTS

The NRL annually performs antimicrobial susceptibility testing on all *C. jeuni* and *C. coli* isolates received at NRL as part of the sentinel surveillance system. As of 31 October 2020, the EUCAST Scientific Committee adjusted the breakpoints for fluroquinolone sensitive isolates of both *C. jejuni* and *C. coli* from ≤0.5 mg/L to ≤0.001mg/L, introducing a new I-definition between the sensitive and resistant isolates. Data in this report have retrospectively been adjusted from 2020 onwards to reassign resistant isolates within this new definition as intermediate.

For *C. jejuni*, we observed a stable trend in resistance to all tested antibiotics. Resistance levels against tetracycline and ciprofloxacin were higher in strains from travel associated infections compared to domestically acquired infections.

For *C. coli,* we observed a stable level of resistance to all tested antibiotics. All strains were resistant to ciprofloxacin irrespective of place of acquisition.

We identified an MDR phenotype in one travel associated *C. jejuni* isolate, displaying resistance to ciprofloxacin, tetracycline, and erythromycin.

YERSINIA ENTEROCOLITICA

Yersinia enterocolitica from human clinical specimens

In 2023, 86 human yersiniosis cases were notified to MSIS. Most cases were domestically acquired (62%). The National Reference Laboratory (NRL) for Entero-pathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 89 isolates of pathogenic *Yersinia* from the primary diagnostic laboratories. Eight isolates were linked to 1 cluster, and 82 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 77 isolates (Table 51) against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chlor-amphenicol. The results are presented in Tables 52-54 and Figures 85-86, and in the related text.

TABLE 51. Number of *Yersinia enterocolitica* isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2023, by serotype and place of acquisition.

Yersinia enterocolitica	No. of isolates tested in 2023		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
Y. enterocolitica O:3	59	64	39	41	15	15	5	8
Y. enterocolitica O:9	11	11	4	4	1	1	6	6
Y. entericolitica (other serotypes)	7	7	3	3	1	1	3	3
Total	**77**	**82**	**46**	**48**	**17**	**17**	**14**	**17**

ANTIMICROBIAL RESISTANCE IN YERSINIA ENTEROCOLITICA SEROTYPE O:3 AND O:9

TABLE 52. Percentage distributions of antimicrobial susceptibility categories in *Yersinia enterocolitica* O:3 and O:9 (n=70) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	0.0	-	100.0
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Tetracycline[1]	≥ 17 mm	< 17 mm	97.1	-	2.9
Chloramphenicol[2]	≤ 8	> 8	81.4	-	18.6

[1]Breakpoints according to national zone distributions. [2]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

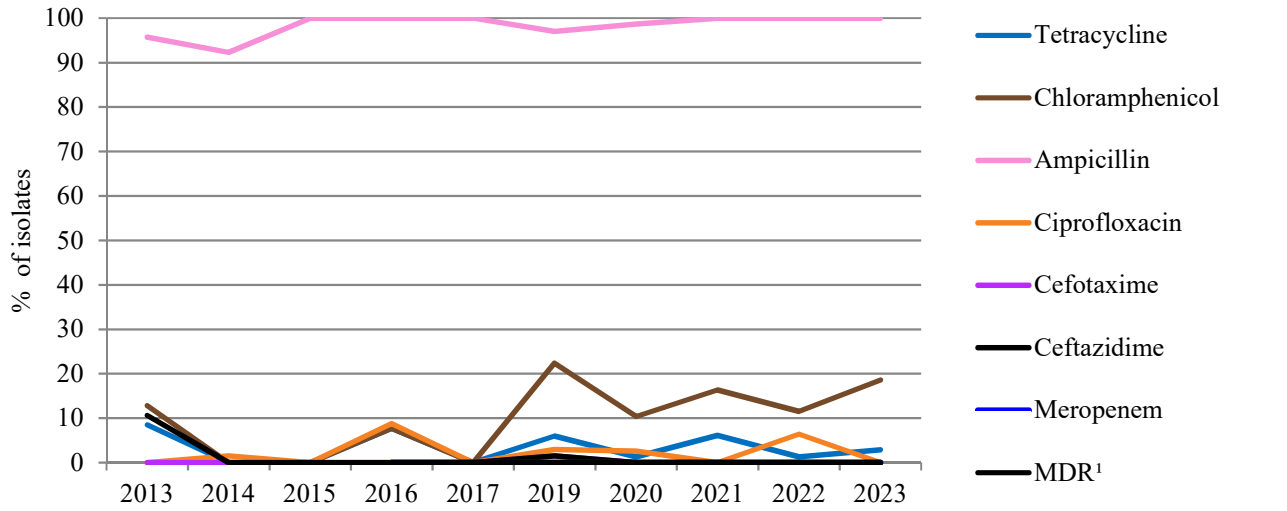

FIGURE 85. Trend 2013-2023. Percentage of *Yersinia enterocolitica* O:3 and O:9 resistant to selected antimicrobial agents from all human clinical specimens tested in Norway.

TABLE 53. Percentage distributions of genotypic resistance in *Yersinia enterocolitica* O:3 and O:9 (n=75) compared to phenotypic wild type/non-wild type distribution (n=75) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	80.0	20.0
Ampicillin	100.0	0.0	0.0	100.0
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	100.0	0.0	100.0	0.0
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	81.4	18.6	81.3	18.7
Ciprofloxacin	100.0	0.0	100.0	0.0
Sulfonamide	-	-	81.3	18.7
Tetracycline	97.1	2.9	98.7	1.3
Trimethoprim	-	-	98.7	1.3

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Yersinia enterocolitica* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

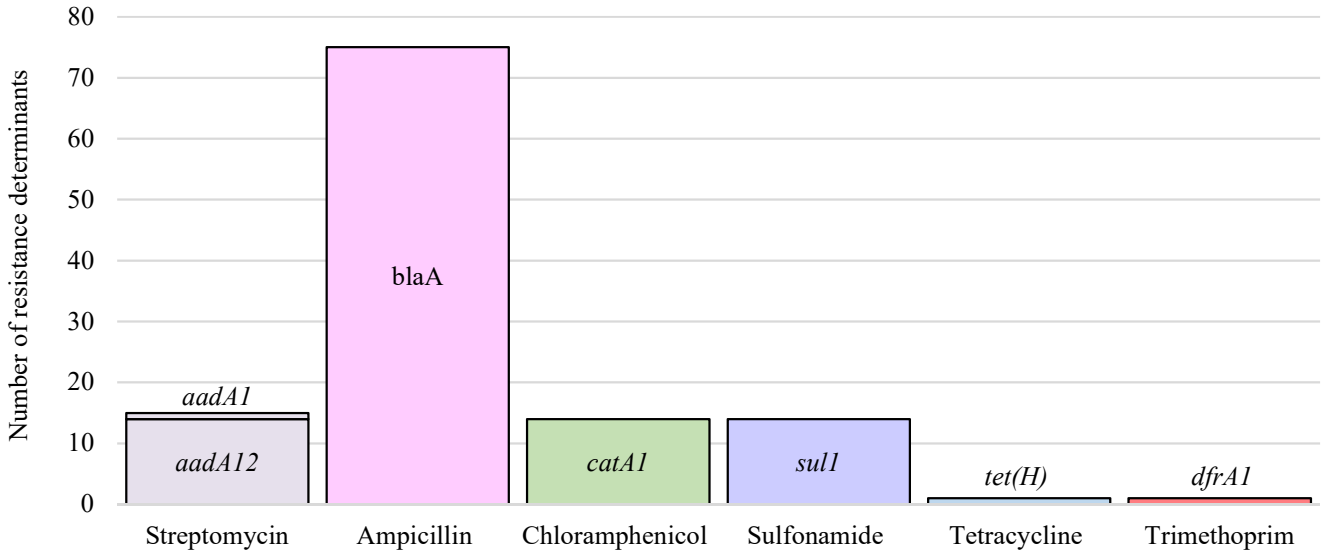

FIGURE 86. Identified resistance determinants in *Yersinia enterocolitica* O:3 and O:9 (n=75) to selected antimicrobial agents in Norway 2023.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN YERSINIA

TABLE 54. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Yersinia enterocolitica* O:3 and O:9 isolates identified in Norway 2023.

Antibiotic categories	Tested	Phenotype WT[1]		Phenotype NWT[1]		Sensitivity (%)	Specificity (%)
		Genotype R	Genotype S	Genotype R	Genotype S		
Penicillins	70	70	0	0	0	-	-
ESC[2]	70	0	70	0	0	-	100.0
Carbapenems	70	0	70	0	0	-	100.0
Fluoroquinolones	70	0	70	0	0	-	100.0
Tetracycline	70	0	68	1	1	100.0	98.6
Phenicols	70	0	57	12	1	100.0	98.3

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Yersinia enterocolitica* (v.14.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins (ESC).

RESULTS AND COMMENTS

The NRL annually performs antimicrobial susceptibility testing on all pathogenic *Yersinia enterocolitica* isolates. Additionally, 2020 onwards the NRL has screened all isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance.

In 2023 the NRL identified one outbreak cluster of *Y. enterocolitica* O:3 (n=3), including a total of eight isolates. Antimicrobial resistance results from only a single isolate from this cluster is included in this report.

Antimicrobial resistance for *Yersinia enterocolitica* serotypes O:3 and O:9 has been combined and presented without distinction of place of acquisition. We observed a stable trend in resistance to all tested antibiotics. All isolates expressed intrinsic resistance to ampicillin, attributed to the *blaA* gene. In addition, resistance to chloramphenicol and sulfonamide was identified in 18.6% of the isolates, attributed to the *catA1* and *sul1* genes, respectively.

The overall correlation between phenotypic and predicted genotypic resistance was high, both sensitivity and specificity were above 97% for the tested and screened antibiotics.

Shigella spp. from human clinical specimens

In 2023, 129 human cases of shigellosis were notified to MSIS. Most cases were infected abroad (61%). The National Reference Laboratory (NRL) for Entero-pathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 128 *Shigella* spp. isolates from primary diagnostic laboratories. Twelve isolates were linked to 2 clusters. One-hundred eighteen unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 114 *Shigella* isolates (Table 55). Isolates were susceptibility tested against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chlor-amphenicol. The results are presented in Tables 56-61, Figures 87-91, and in the text.

TABLE 55. Number of *Shigella* spp. isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2023, by species and place of acquisition.

Shigella spp.	No. of isolates tested in 2023		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. sonnei	59	63	11	11	40	42	8	10
S. flexneri	43	43	8	8	24	24	11	11
S. boydii	11	11	1	1	8	8	2	2
S. dysenteriae	1	1	1	1	0	0	0	0
Total	**114**	**118**	**21**	**21**	**72**	**74**	**21**	**23**

ANTIMICROBIAL RESISTANCE IN SHIGELLA SONNEI

TABLE 56. Percentage distributions of antimicrobial susceptibility categories in *Shigella sonnei* (n=59) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	42.4	-	57.6
Cefotaxime	≤ 1	> 2	50.8	0.0	49.2
Ceftazidime	≤ 1	> 4	93.2	6.8	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	27.1	-	72.9
Tetracycline[2]	≥ 17 mm	< 17 mm	23.7	-	76.3
Chloramphenicol[3]	≤ 16	> 16	100.0	-	0.0

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0) [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

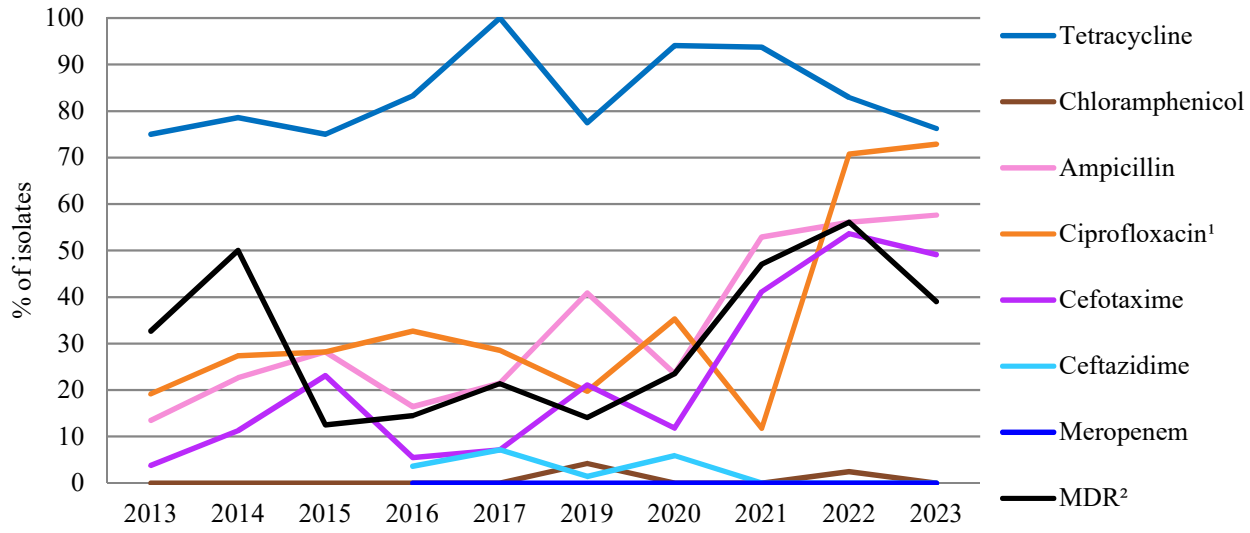

FIGURE 87. Trend 2013-2023. Percentage of *Shigella sonnei* resistant to selected antimicrobial agents from all human clinical specimens tested in Norway 2023. [1]Resistance to ciprofloxacin inferred from pefloxacin disk diffusion 2022 onwards to align with observed genotypic resistance. [2]MDR defined as acquired non-susceptibility to antimicrobials from ≥ 3 categories.

TABLE 57. Percentage distributions of genotypic resistant *Shigella sonnei* (n=63) compared to phenotypic wild type/non-wild type distribution (n=59) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	14.3	85.7
Ampicillin	42.4	57.6	44.4	55.6
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	50.8	49.2	54.0	46.0
Ceftazidime[3]	93.2	6.8		
Colistin	-	-	100.0	0.0
Chloramphenicol	100.0	0.0	100.0	0.0
Ciprofloxacin	28.8	71.2	28.6	71.4
Sulfonamide	-	-	11.1	88.9
Tetracycline	23.7	76.3	23.8	76.2
Trimethoprim	-	-	0.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella sonnei* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

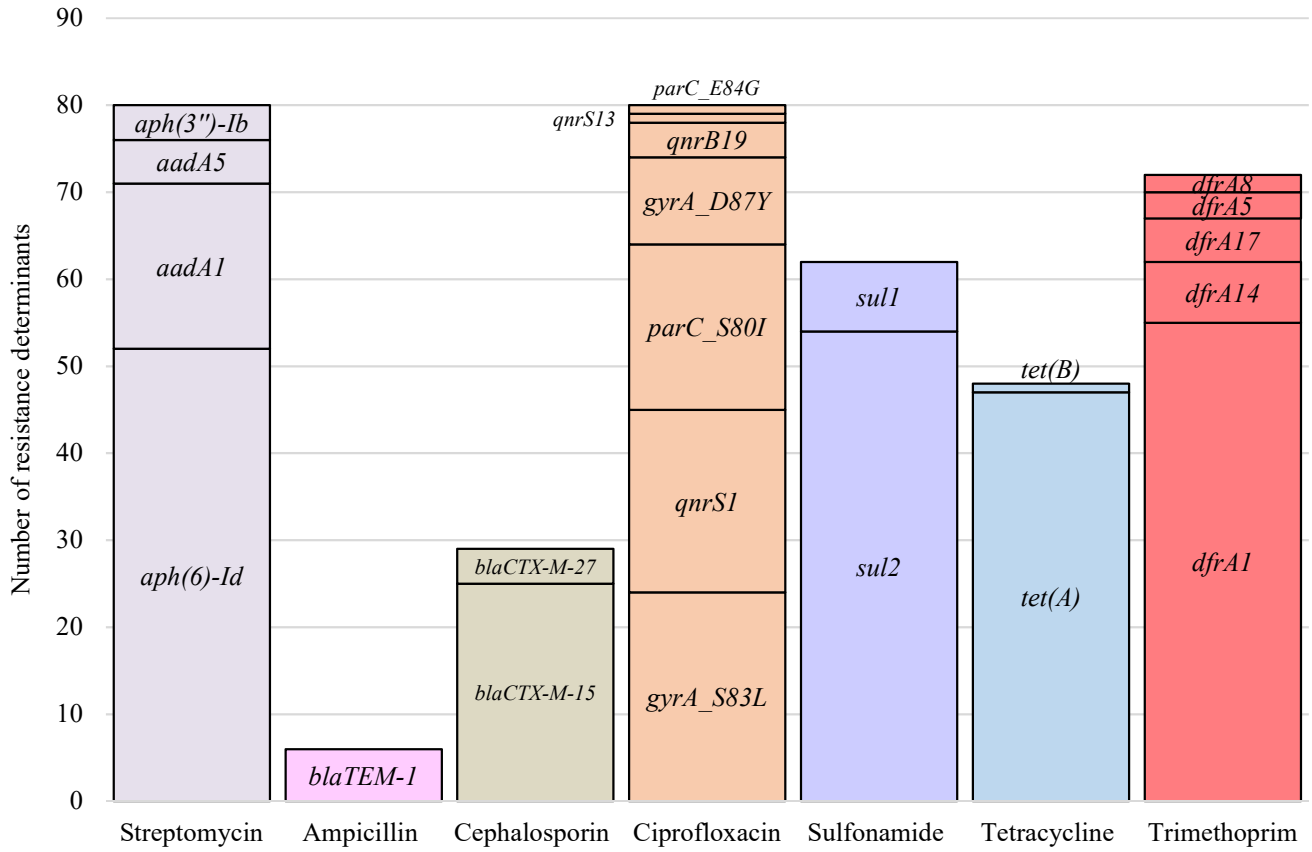

FIGURE 88. Identified resistance determinants in *Shigella sonnei* (n=63) to selected antimicrobial agents in Norway 2023.

ANTIMICROBIAL RESISTANCE IN SHIGELLA FLEXNERI

TABLE 58. Percentage distributions of antimicrobial susceptibility categories in *Shigella flexneri* (n=43) from all human clinical specimens tested in Norway 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	27.9	-	72.1
Cefotaxime	≤ 1	> 2	86.0	0.0	14.0
Ceftazidime	≤ 1	> 4	93.0	7.0	0.0
Meropenem	≤ 2	> 8	97.7	2.3	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	55.8	-	44.2
Tetracycline[2]	≥ 17 mm	< 17 mm	27.9	-	72.1
Chloramphenicol[3]	≤ 16	> 16	60.5	-	39.5

[1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.14.0) [2]Breakpoints according to national zone distributions. [3]Breakpoint according to epidemiological cut-off value (ECOFF) for wild type distribution by EUCAST.

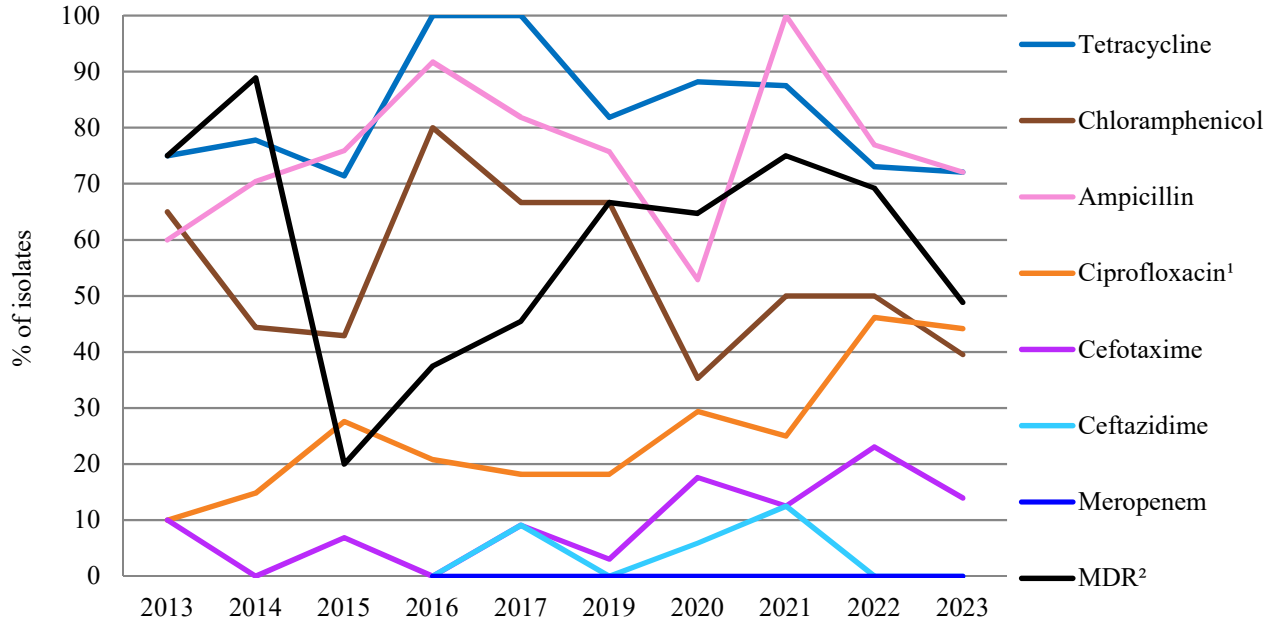

FIGURE 89. Trend 2013-2023. Percentage of *Shigella flexneri* resistant to selected antimicrobial agents from all human clinical specimens tested in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2022 onwards to better align with observed genotypic resistance. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 59. Percentage distributions of genotypic resistance in *Shigella flexneri* (n=43) compared to phenotypic wild type/non-wild type distribution (n=43) from human clinical specimens in Norway 2023.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	39.5	60.5
Ampicillin	27.9	72.1	27.9	72.1
Meropenem	97.7	2.3	100.0	0.0
Cefotaxime[3]	86.0	14.0	86.0	14.0
Ceftazidime[3]	93.0	7.0		
Colistin	-	-	0.0	100.0
Chloramphenicol	60.5	39.5	60.5	39.5
Ciprofloxacin	55.8	44.2	48.8	51.2
Sulfonamide	-	-	53.5	46.5
Tetracycline	27.9	72.1	32.6	67.4
Trimethoprim	-	-	16.3	83.7

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella flexneri* (v.14.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined to predict genotypic resistance against extended-spectrum cephalosporins.

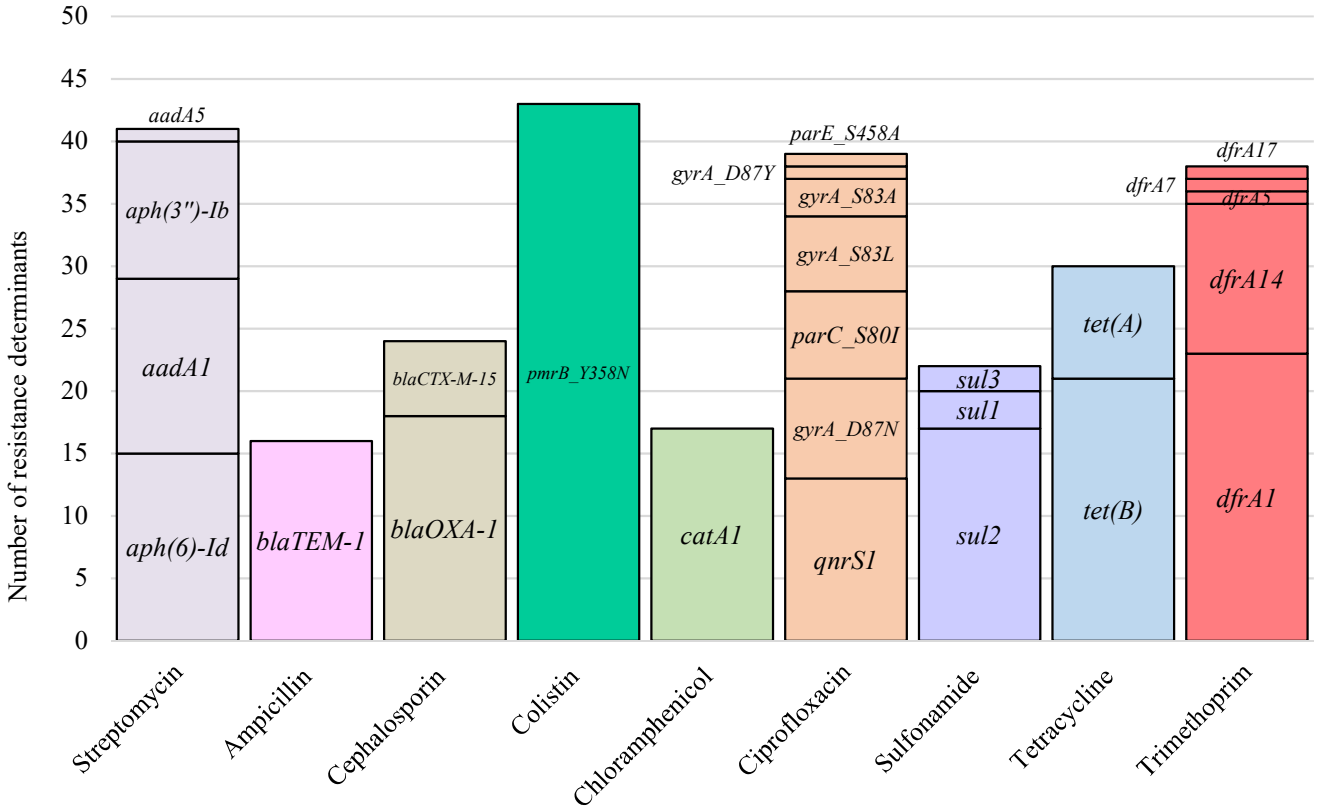

FIGURE 90. Identified resistance determinants in Shigella flexneri (n=43) to selected antimicrobial agents in Norway 2023.

MULTI-DRUG RESISTANCE IN SHIGELLA

TABLE 60. Number of predicted genotypic multi-drug resistance in (MDR) *Shigella* spp. isolates identified in Norway 2023, stratified according to species and resistance to different antibiotic categories.

Shigella spp.	MDR[1]	Antibiotic categories[2]							
		STR	AMP	ESP	CHL	CIP	SUL	TET	TMP
Shigella sonnei	62	54	35	29	0	44	56	48	62
Shigella flexneri	36	26	31	6	17	22	20	28	31
Shigella boydii	8	5	4	3	0	6	4	4	6
Shigella dysenteriae	1	1	1	1	0	1	1	1	1
Total no. of MDR isolates	**107**	**86**	**71**	**39**	**17**	**73**	**81**	**81**	**100**

[1]Multi-drug resistance (MDR) defined as predicted genotypic resistance to 3 ≥ antibiotic categories. [2]Antibiotic category: STR: Streptomycin, AMP: Ampicillin, ESP: Extended-Spectrum Cephalosporin, CHL: Chloramphenicol, CIP: Ciprofloxacin, SUL: Sulfonamide, TET: Tetracycline, TMP: Trimethoprim.

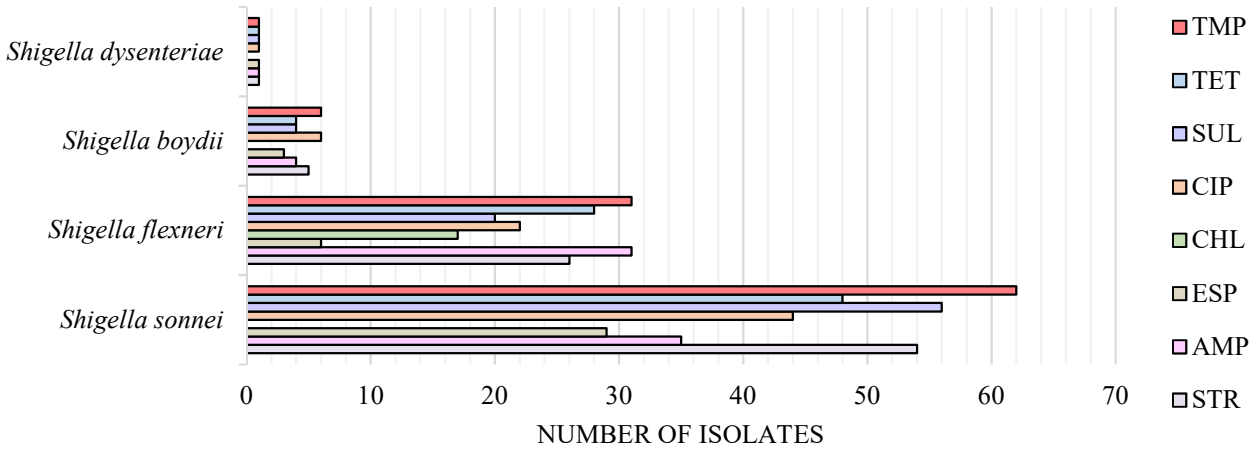

FIGURE 91. Number of predicted genotypically multi-drug resistant (MDR) *Shigella* spp. isolates (n=107) identified in Norway 2023, stratified according to species and resistance to different antibiotic categories; STR: Streptomycin, AMP: Ampicillin, ESP: Extended-Spectrum Cephalosporin, CHL: Chloramphenicol, CIP: Ciprofloxacin, SUL: Sulfonamide, TET: Tetracycline, TMP: Trimethoprim.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN SHIGELLA

TABLE 61. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Shigella* spp. (n=114) isolates identified in Norway 2023.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	114	1	43	69	1	98.6	97.7
ESC[2]	114	0	75	39	0	100.0	100.0
Carbapenems	114	0	113	0	1	-	99.1
Fluoroquinolones	114	0	46	68	0	100.0	100.0
Tetracycline	114	0	32	80	2	100.0	94.1
Phenicols	113	0	96	17	0	100.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Shigella spp.* (v.14.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins (ESC).

RESULTS AND COMMENTS

The NRL annually performs antimicrobial susceptibility testing on all *Shigella* spp. isolates. Since 2020, the NRL has screened all isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance. From 2022 onwards, ciprofloxacin resistance is inferred from susceptibility to pefloxacin, as low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion, and to better align phenotypic resistance with predicted genotypic resistance.

In 2023, the NRL identified two clusters: *S. sonnei* (n=9), and *S. flexneri* (n=3). The *S. sonnei* cluster was linked to the international spread of an extensively drug-resistant strain among men who have sex with men.

A stable and large proportion of *S. sonnei* are recorded resistant to tetracycline over the last decade. In addition, since 2020 an increasing trend of resistance towards ciprofloxacin and extended-spectrum cephalosporins is recorded. The observed increase in resistance to ciprofloxacin from 30% in 2020 to over 70% in 2023 is attributed in part by the change in antibiotic used for screening (ciprofloxacin vs. pefloxacin), and in part by an increase in identification of resistant strains. This is confirmed by the presence of resistance determinants against ciprofloxacin in 53% of the isolates in 2020 and in 71% in 2023. When screening for genotypic resistance determinants, the presence of various mutations in the quinolone resistance-determining regions (QRDRs) of *gyrA* and *parC,* as well as the presence of different *qnr* variants was confirmed. A total of 29 ESBL producing strains (46%) were identified, of which 25 encoded the $bla_{\text{CTX-M-15}}$ gene, and four encoded the $bla_{\text{CTX-M-27}}$ gene. Phenotypically, the strain encoding $bla_{\text{OXA-1}}$ was not identified as an ESBL producer. An MDR genotype was identified for 87.3% of the isolates, largely attributed to resistance against streptomycin, ciprofloxacin, sulfonamide, tetracycline, and trimethoprim.

For *S. flexneri* a stable and large proportion of isolates were recorded resistant to tetracycline and ampicillin over the last decade. In addition, an increasing trend of resistance to ciprofloxacin and extended-spectrum cephalosporins was observed. The observed increase in resistance to ciprofloxacin from around 30% in 2020 to 44% in 2022 is largely attributed to the change in the antibiotic used for screening. When screening for genotypic resistance determinants, the presence of various mutations in the quinolone resistance-determining regions (QRDRs) of *gyrA* and *parC,* as well as the presence of different *qnrS1* was confirmed. A total of six ESBL producing strains (14%) were identified, all of which encoded the $bla_{\text{CTX-M-15}}$ gene. In addition, 16 isolates encoded the $bla_{\text{OXA-1}}$ gene, that is predicted to confer resistance to penicillin and cephalosporins. Interestingly, all *S. flexneri* isolates (n=43) harboured the *pmrB*_Y358N mutation, which has been associated with colistin resistance. Mutations in the *pmrB* can lead to modifications in the lipopolysaccharides on the bacterial cell surface and thus reduce the accessibility of colistin to bacterial membranes. None of the isolates were susceptibility tested for colistin. An MDR genotype was identified in 80% of the isolates, largely attributed to resistance against streptomycin, ampicillin, tetracycline, and trimethoprim.

In addition to the ESBL encoding strains identified from *S. sonnei* and *S. flexneri*, a single strain of *S. dysenteriae* also encoded the $bla_{\text{CTX-M-15}}$ gene. Overall correlation between phenotypic resistance and predicted genotypic resistance was high.

Increasing resistance to quinolones and extended-spectrum cephalosporins among *Shigella* spp. in Norway from 2018 to 2023

Shigella spp. is one of the most frequently reported drug-resistant bacteria worldwide (1). Patients with mild symptoms are usually treated symptomatically. However, according to recommended treatment guidelines, patients with severe symptoms and those at risk of developing serious complications require antimicrobial treatment. The increasing global trend of resistance in *Shigella* spp. is a major public health concern, as treatment options for moderate and severe cases become limited. Resistance to quinolones and extended-spectrum cephalosporins (ESCs) is of particular concern, as these are the current first- and second-line antimicrobials for treatment (1, 2). Additionally, we are observing an increase of multi-drug resistant strains (3). In Norway, resistant *Shigella* strains are typically acquired through travel to endemic areas, however also in domestically acquired strains resistance to quinolones and ESCs is increasing.

Between 2018 and 2023, a total of 514 cases of shigellosis were reported to MSIS. Except for years during the COVID-19 pandemic, most of these cases were associated with travel (Figure 92). However, since 2021 we have observed an increasing number of non-travel-associated cases, which by 2023 reached levels beyond the pre-pandemic era.

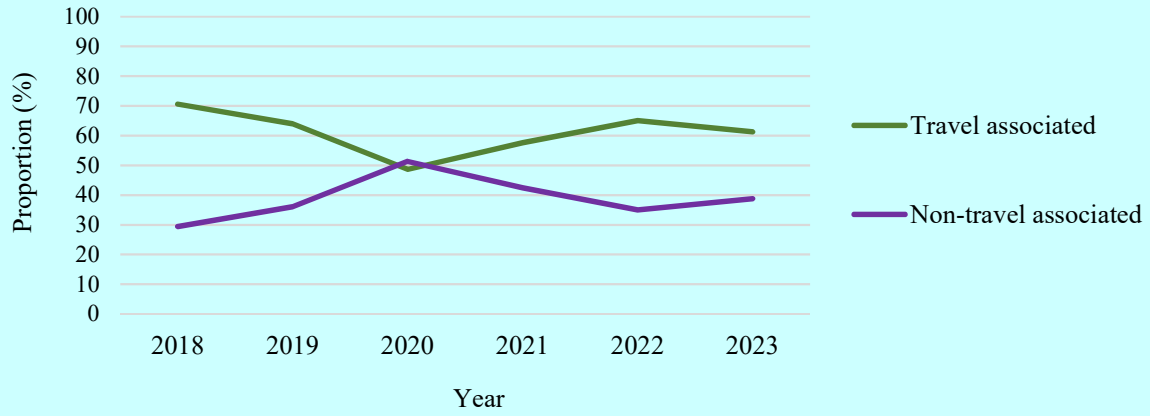

FIGURE 92. Proportion of travel and non-travel associated shigellosis reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) between 01/2018 and 12/2023 (n=514).

Of the 514 cases reported to MSIS since 2018, 505 isolates have been sequenced at the National Reference Laboratory for Enteropathogenic Bacteria. Results show that *S. sonnei* (56.2%, n=284) and *S. flexneri* (34.7%, n=175) are the most predominant species. A genotype resistant to quinolone was seen in 46.6% of the isolates and to ESCs in 26.8% of the isolates. The most common quinolone resistance determinant was *qnrS1* (39.3%), followed by the acquisition of double mutations in *gyrA* (D87G and S83L) (24.8%), and the combination of *qnrS1* with the mutation *gyrA*-D87Y (11.2%). Among those resistant to ESCs, $bla_{\text{CTX-M15}}$ was the most frequent resistance gene identified (79.7%) (Table 62).

When analysing the trend of genotypic resistance from 2018 and 2023, we observed that the occurrence of $bla_{\text{CTX-M15}}$ increased from 15.6% to 46.5% in *S. sonnei* and from 4.5% to 13.3% in *S. flexneri*. Similarly, occurrence of *qnrS1* increased from 15.6% to 29.6% in *S. sonnei*. Worryingly, 24.2% of isolates were resistant to both quinolones and ESCs. The most common resistance combinations observed were $bla_{\text{CTX-M15}}$ with *qnrS1* (24.3%) and $bla_{\text{CTX-M15}}$, *qnrS1* and *gyrA*-D87G (11.2%).

TABLE 62. Antimicrobial resistance determinants (ARDs) relevant for resistance to quinolones and extended-spectrum cephalosporins (ESCs), displayed for all *S. sonnei* and *S. flexneri* isolates tested at the Norwegian National Reference Laboratory between 01/2018 and 12/2023. *N indicates the total number of all *S. sonnei* and *S. flexneri* isolates showing resistance to ESCs and quinolones.

Antimicrobial agents	ARDs	Tested isolates		*S. flexneri*	*S. sonnei*
		%	n/N*	%	%
ESCs	$bla_{\text{CTX-M-15}}$	79.7	22/123	16.3	63.4
	$bla_{\text{CTX-M-27}}$	12.2	91/123	1.6	10.6
	$bla_{\text{CTX-M-3}}$	8.1	10/123	8.1	-
Quinolones	*qnrS1*	39.3	84/214	21.5	17.8
	*gyrA*_D87G, *gyrA*-S83L	24.8	53/214	0.9	23.8
	qnrS1, *gyrA*-D87Y	11.2	24/214	-	11.2
	gyrA-D87N, *gyrA*-S83L	10.3	22/214	9.3	0.9
	gyrA-S83L	8.9	19/214	-	8.9
	qnrS1, *gyrA*-D87N, *gyrA*-S83L	2.3	5/214	1.9	0.5
	gyrA-D87Y	1.4	3/214	0.9	0.5
	gyrA-D87N	0.9	2/214	-	-
	qnrS1, *gyrA*-D87G, *gyrA*-S83L	0.9	2/214	0.9	-

Phylogenetic analyses of the sequenced strains identified several interesting clusters of related isolates. From historical clusters spanning the entire study period to recently emerging clusters. For *S. sonnei*, we did not find that the non-travel associated isolates formed distinct clusters, suggesting that most of the domestically acquired cases in Norway are linked to international strains or clusters (Figure 93). As such, the increase of resistant strains internationally is reflected in the domestically acquired cases.

We identified three clades, which seem to have evolved to acquire and harbour different genotypic resistance profiles. Clade 1 largely included isolates that harboured the $bla_{\text{CTX-M-15}}$ and *qnrS1* genes. However, within this subclade we identified a distinct historical cluster of eight isolates, mostly travel-associated, from 2018 and 2019 that displayed genotypic resistance to only ESC attributed to $bla_{\text{CTX-M-3}}$. This cluster may represent the derivation of $bla_{\text{CTX-M-15}}$ and quinolone resistant strains seen in the more recent strain within this clade.

Also, clade 2 largely included isolates that harboured the $bla_{\text{CTX-M-15}}$ and *qnrS1* genes, but in addition to these genes harboured the *gyrA*-D87Y mutation. The *gyrA*-D87Y is a common mutation often reported in combination with *qnrS1* to confer high level resistance to ciprofloxacin (4). Isolates within this clade were both travel associated and domestically acquired from 2018 to 2023, however the domestically acquired isolates were predominantly from 2023 and largely identified within two smaller clusters indicating a more recent dissemination.

Clade 3 could further be divided into four subclades with distinct genotypic resistance profiles. Common to all the isolates within this clade was that presence of the *gyrA*-S83L mutation and in addition to this, two subclades also harboured the *gyrA*-D87G mutation in combination with either $bla_{\text{CTX-M-15}}$ or the $bla_{\text{CTX-M-27}}$ gene. This clade included isolates that were associated with travel as well as domestically acquired isolated from the entire study period 2018-2023.

Subclades:

i. *gyrA*-S83L
ii. *gyrA*-S83L, *gyrA*-D87G, $bla_{\text{CTX-M-15}}$
iii. *gyrA*-S83L
iv. *gyrA*-S83L, *gyrA*-D87G, $bla_{\text{CTX-M-27}}$

In addition to these clades, we identified a small cluster of three recent travel associated isolates that were identified with the *gyrA*-D87N mutation. The *gyrA*-D87N mutation in combination with *gyrA*-S83L has been reported to yield high-level resistance to ciprofloxacin (5).

The phylogenetic analyses of these *S. sonnei* strains recovered in Norway indicate that the increased resistance seen in domestically acquired *S. sonnei* mirrors the increased resistance seen in the travel associated isolates. Furthermore, the different clades seem to represent the different evolutionary paths taken by *S. sonnei* to acquire a broader resistance genotype, including both the acquisition of novel resistance genes and combinations of mutations within the quinolone resistance-determining regions of *gyrA*.

For *S. flexneri*, many clusters harboured double mutations in *gyrA* (D87G and S83L). Several smaller clusters displayed a genotypic resistance to quinolones as well as ESCs, with identification of the *qnrS1* and $bla_{\text{CTX-M-15}}$ genes (results not shown). These clusters included both travel associated and non-travel associated isolates.

In summary, our results show an increasing number of isolates carrying double or triple ARDs, which confer resistance to first- and second-line antimicrobials simultaneously. While most shigellosis cases in Norway have traditionally been acquired during international travel, there has been a noticeable increase in non-travel associated cases harbouring resistant strains from 2018 to 2023.

Isolates from 2022 and 2023 show considerable changes in the circulating genotypic profiles. These results highlight the crucial role of robust laboratory-based surveillance of shigellosis and the need to closely monitor resistance in *Shigella* spp. in both domestic cases and in returning travellers. Such information is essential for informed decision making, enabling public health authorities to implement appropriate interventions and targeted responses.

Physicians and public health professionals should be aware of the risks related to vulnerable populations, and the potential for transmission of *Shigella* spp. also through non-food routes such as sexual contact. The latter has been the cause of several outbreaks in Europe, mainly among men who have sex with men, harbouring extensively drug-resistant *S. sonnei* lineages (6). Developments in 2023 also highlight the importance of susceptibility testing in cases of non-travel associated diarrhoea to guide antimicrobial treatment and avoid treatment failure.

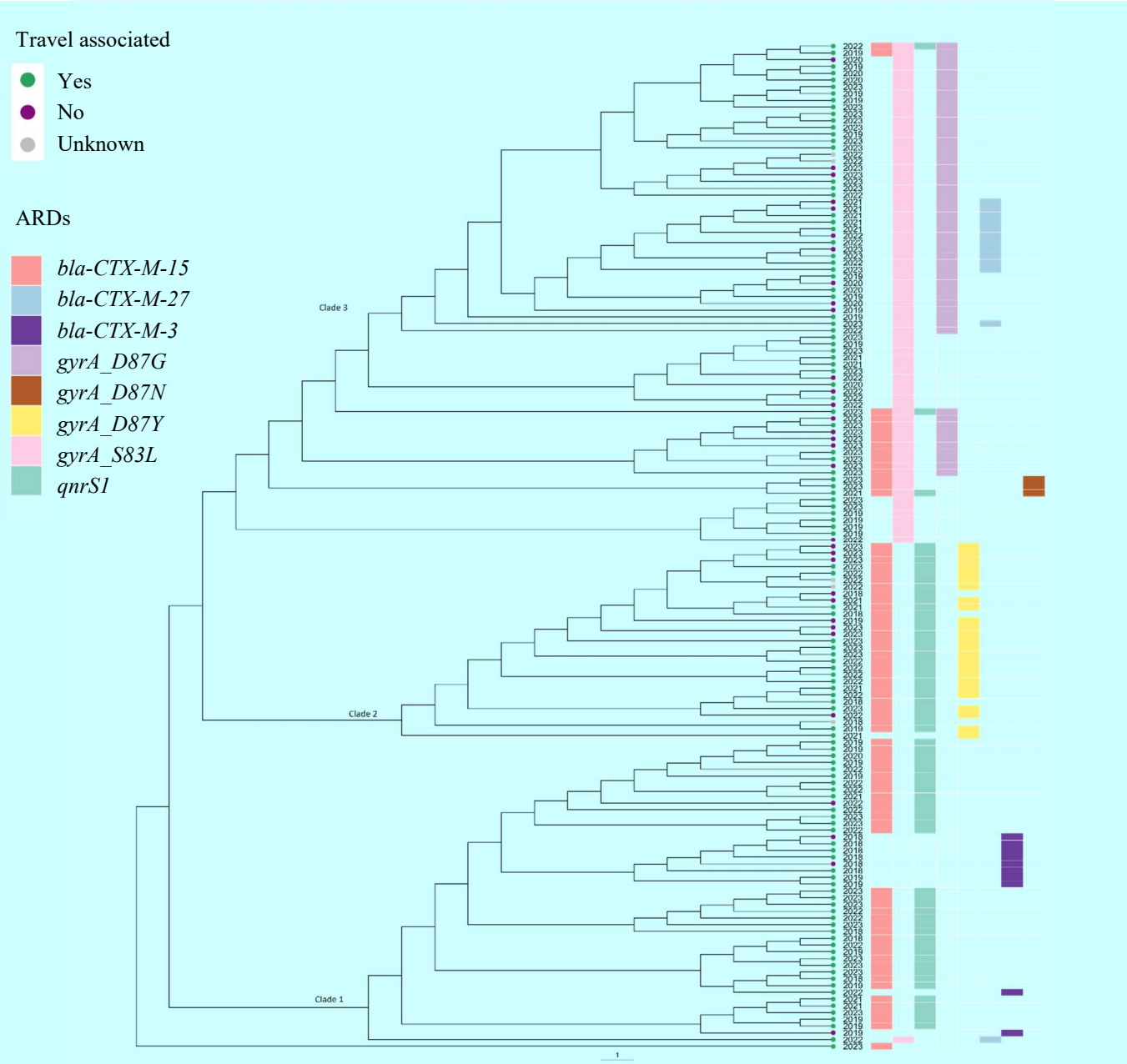

FIGURE 93. Phylogenetic tree created using core genome MLST (cgMLST) of *S. sonnei* isolates sequences at the National Reference Laboratory between 01/2018 and 12/2023, highlighting antimicrobial resistance determinants (ARDs) which are relevant for resistance to quinolones and extended-spectrum cephalosporins (ESCs), by travel history and year of isolation. The coloured round tips indicate the travel association (green) and non-travel association (purple). The different ARDs are indicated by the coloured squares.

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HUMAN CLINICAL ISOLATES

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Distribution of bacterial species in blood cultures

Surveillance of antimicrobial resistance is usually based on prevalences of reduced susceptibility and resistance to certain combinations of antimicrobials and bacterial species in clinical samples. The NORM surveillance programme generally follows this approach. However, there is a serious limitation to the model because a transition in the distribution from susceptible bacterial species to inherently more resistant ones will represent de facto emergence of resistance which is not easily detected. In order to complement the surveillance of individual species, NORM collects data on all positive blood cultures from the laboratory information systems of the participating institutions. A patient with a given microbial isolate was excluded from registration with a new isolate of the same species within a month from the first entry. This rule was applied irrespectively of changes in the organism´s susceptibility pattern. Isolates of a different species from the same patient were included in the surveillance. It proved difficult to systematically evaluate the clinical significance of species which are commonly part of the normal skin flora. In Table 63, proportions are therefore estimated for all isolates and for all isolates excluding species considered to be common skin contaminants such as coagulase negative staphylococci, *Micrococcus* spp., *Corynebacterium* spp., *Bacillus* spp. and *Cutibacterium* spp. This does not imply that such isolates cannot cause infections, but only that it was not possible to enforce a standardised protocol for inclusion of the clinically significant isolates. Similarly, all isolates were registered as individual findings although polymicrobial bloodstream infections are regularly detected in some patients. Limitations in the data extraction procedure prohibited in-depth analysis of these parameters.

TABLE 63. Number of blood culture isolates in 2023, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) 2019-2023. The table is based on data from the information systems of all laboratories in Norway (n=19).

Species	No. of isolates 2023	% of all isolates					% of all isolates excluding skin flora				
		2019	2020	2021	2022	2023	2019	2020	2021	2022	2023
Staphylococcus aureus	2,184	11.0	10.6	10.5	10.7	10.2	13.9	13.7	13.8	14.1	13.4
Coagulase negative staphylococci	4,632	18.7	20.4	21.1	21.3	21.6	-	-	-	-	-
Streptococcus pneumoniae	567	3.1	1.6	1.6	2.5	2.6	4.0	2.1	2.1	3.4	3.5
Streptococcus pyogenes	380	1.0	0.8	0.4	0.6	1.8	1.2	1.0	0.5	0.8	2.3
Streptococcus agalactiae	267	1.8	1.7	1.6	1.5	1.2	2.2	2.1	2.0	2.0	1.6
Beta-haemolytic streptococci group C and G	459	2.0	2.3	2.4	2.0	2.1	2.5	2.9	3.1	2.6	2.8
Viridans- and non-haemolytic streptococci	1,108	5.0	5.4	5.1	5.8	5.2	6.4	7.0	6.7	7.7	6.8
Enterococcus faecalis	704	3.4	3.5	3.7	3.5	3.3	4.3	4.5	4.9	4.7	4.3
Enterococcus faecium	293	1.3	1.1	1.4	1.4	1.4	1.7	1.4	1.8	1.8	1.8
Other Gram-positive aerobic and facultative anaerobic bacteria	901	3.7	3.5	4.2	4.3	4.2	2.3	2.4	2.7	2.5	2.7
Escherichia coli	4,688	25.4	24.7	23.2	21.7	21.8	32.2	32.0	30.7	28.4	28.8
Klebsiella spp.	1,586	7.4	7.5	7.7	7.8	7.4	9.4	9.6	10.1	10.3	9.8
Enterobacter spp.	354	1.7	1.7	1.9	1.7	1.6	2.1	2.2	2.4	2.3	2.2
Proteus spp.	277	1.6	1.6	1.4	1.3	1.3	2.0	2.1	1.8	1.7	1.7
Other *Enterobacterales*	515	2.2	2.3	1.9	2.4	2.4	2.7	3.0	2.5	3.2	3.2
Pseudomonas spp.	368	1.8	1.9	1.9	1.9	1.7	2.3	2.4	2.5	2.5	2.3
Other Gram-negative aerobic and facultative anaerobic bacteria	519	2.1	1.8	2.0	2.1	2.4	2.6	2.3	2.6	2.8	3.2
Bacteroides spp.	449	1.9	2.2	2.3	2.0	2.1	2.4	2.9	3.0	2.6	2.8
Other anaerobic bacteria	972	3.8	4.2	4.6	4.3	4.5	4.4	4.9	5.4	5.0	5.3
Yeasts	251	1.1	1.2	1.1	1.2	1.2	1.4	1.5	1.4	1.6	1.5
Total	**21,474**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 63 and Figure 94, aerobic and facultative Gram-positive and Gram-negative bacteria represented 53.6% and 38.6% of all isolates, respectively. The predominance of Gram-positives among all isolates was at the same level as in previous years. The most common Gram-positive species were coagulase negative staphylococci, which represented 21.6%. This is practically unchanged from 21.3% in 2022. The difference between aerobic Gram-positives and Gram-negatives was reversed when species of the skin flora (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) were excluded, with 39.2% aerobic Gram-positives and 51.2% aerobic Gram-negatives.

Among aerobic Gram-positives, the prevalence of *S. pneumoniae* steadily declined from 12.1% in 2005 to 4.0% in 2019 (skin contaminants excluded), following the introduction of the conjugate pneumococcal vaccine in the national childhood immunisation programme in June 2006. The prevalence was even lower in the pandemic years 2020-2021 (2.1%), but has now increased again to 3.5%. The occurrence of *Streptococcus pyogenes* (n=380) has increased sharply from previous years (n=138 in 2022), which is in accordance with other surveillance systems. Their proportion of invasive isolates now exceeds pre-pandemic levels. The rates for other aerobic Gram-positives have remained relatively stable over many years.

E. coli (28.8%) and other *Enterobacterales* (16.9%) accounted for the vast majority of aerobic Gram-negative isolates. The proportion of *E. coli* is still lower than in previous years, but further surveillance is needed to confirm this trend. *Pseudomonas* spp. remained stable at 2.3%, all figures excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 6.6% (8.1% excluding skin flora). Yeasts accounted for 1.2% (1.5% excluding skin flora). The major pathogens among anaerobes were members of *Bacteroides* spp. (2.1%/2.8%) and among yeasts *Candida albicans* (0.7%/0.9%). However, a multitude of other species were also represented.

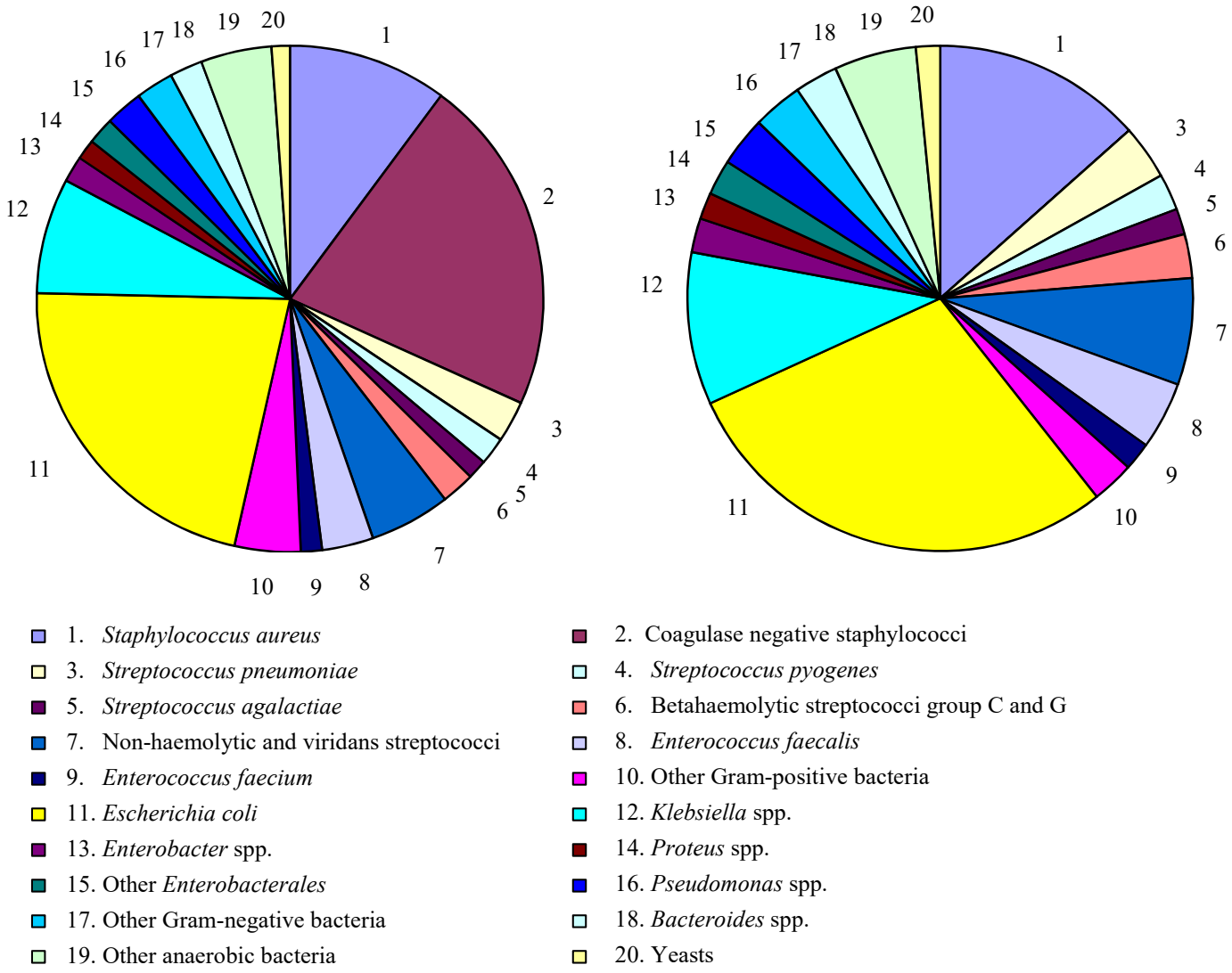

FIGURE 94. Distribution of all blood culture isolates (left, n=21,474) and blood culture isolates excluding common skin contaminants (right, n=16,263) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp. Data for 2023 were retrieved from the information systems of all Norwegian laboratories (n=19).

Escherichia coli in blood cultures

TABLE 64. *Escherichia coli* blood culture isolates in 2023 (n=2,240). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	62.1	-	37.9
Amoxicillin-clavulanic acid*	≤ 8	> 8	77.4	-	22.6
Piperacillin-tazobactam	≤ 8	> 8	94.6	-	5.4
Cefotaxime**	≤ 1	> 2	94.0	0.5	5.5
Ceftazidime	≤ 1	> 4	93.4	1.5	5.1
Cefepime	≤ 1	> 4	92.8	2.1	5.1
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	93.2	1.7	5.1
Gentamicin***	≤ 2	> 2	94.6	-	5.4
Ciprofloxacin**	≤ 0.25	> 0.5	87.4	2.6	10.0
Tigecycline	≤ 0.5	> 0.5	99.8	-	0.2
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	77.8	0.3	21.9
ESBL	Negative	Positive	94.2	-	5.8

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for intravenous administration. **Breakpoints for indications other than meningitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

NORM results are interpreted according to NordicAST/ EUCAST clinical breakpoints at the time of analysis and categorised as susceptible with standard exposure (S), susceptible with increased exposure (I), or resistant (R). The vast majority of isolates were fully susceptible (S) to broad-spectrum agents such as cefotaxime (94.0%), ceftazidime (93.4%), gentamicin (94.6%), cefepime (92.8%), piperacillin-tazobactam (94.6%), tigecycline (99.8%) and meropenem (100.0%) (Table 64). There were no significant changes in resistance rates from 2022-2023. The monobactam aztreonam was surveyed for the first time in 2023 and 93.2% of the isolates were susceptible to standard exposure. Aztreonam has been suggested as an alternative for treatment of multi-resistant Gram-negative strains.

The prevalence of resistance to gentamicin at 5.4% was at the same level as 5.6% in 2021 and 5.1% in 2022 (Figure 95). Data were interpreted according to the breakpoints for systemic urinary tract infections, although NordicAST/ EUCAST no longer consider aminoglycosides sufficient for monotherapy in infections originating from other sources. A high proportion of gentamicin resistant isolates (38/121, 31.4%) also produced extended-spectrum beta-lactamase (ESBL) enzymes. The prevalence at individual laboratories varied due to relatively small numbers. When aggregated by region there were only minor geographical variations (North 4.8%, West 5.1%, South-East 5.4% and Middle 6.4%).

The prevalence of resistance to ciprofloxacin was 10.0% in 2023 compared to 10.4% in 2021 and 10.0% in 2022. The breakpoint for ciprofloxacin resistance has been changed many times over the years, most recently in 2017 with a reduction from R > 1 mg/L to R > 0.5 mg/L and from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L. The long-term trend for ciprofloxacin resistance cannot be precisely determined due to changes in susceptibility test methodology, but it appears that the increase seen during 2006-2017 has stabilised when using the present breakpoint. The temporal association between ciprofloxacin resistance and ciprofloxacin usage is depicted in Figure 96. A similar association between quinolone use and resistance in systemic *E. coli* isolates is also reported internationally. The resistance rates for ampicillin (37.0% in 2021, 36.6% in 2022 and 37.9% in 2023) and trimethoprim-sulfamethoxazole (21.7% in 2021, 20.2% in 2022 and 21.9% in 2023) remain unchanged.

Detection of ESBL was based on reduced zone diameters for cefotaxime and/or ceftazidime. All isolates with reduced susceptibility were further characterised by combination disks or MIC gradient tests. A total of 129 isolates (5.8%) were reported as ESBL positive, which is at the same level as in 2021 (5.8%) and 2022 (6.0%) (Figure 98). The isolates originated from laboratories across the country, and estimates at local level are uncertain due to small numbers. When aggregated at regional level there were only minor geographical differences in the prevalence of ESBL production; Middle (4.4%), West (5.3%), North (5.2%) and South-East (6.4%). Most of the ESBL isolates were phenotypically resistant to cefotaxime (n=119), ceftazidime (n=106), aztreonam (n=106) and cefepime (n=105), whereas many were susceptible to piperacillin-tazobactam (n=99) and/or gentamicin (n=91). Fourty-seven isolates were susceptible to amoxicillin-clavulanic acid using breakpoints for non-urinary tract infections, whereas 82 were resistant. The ESBL isolates displayed high rates of co-resistance to ciprofloxacin (n=79) and trimethoprim-sulfamethoxazole (n=74). A single isolate was clinically resistant to meropenem and contained both ESBL-A and NDM enzymes. Another isolate was clinically susceptible to meropenem, but had a zone diameter below the screening breakpoint. It harboured an OXA-48 like sequence.

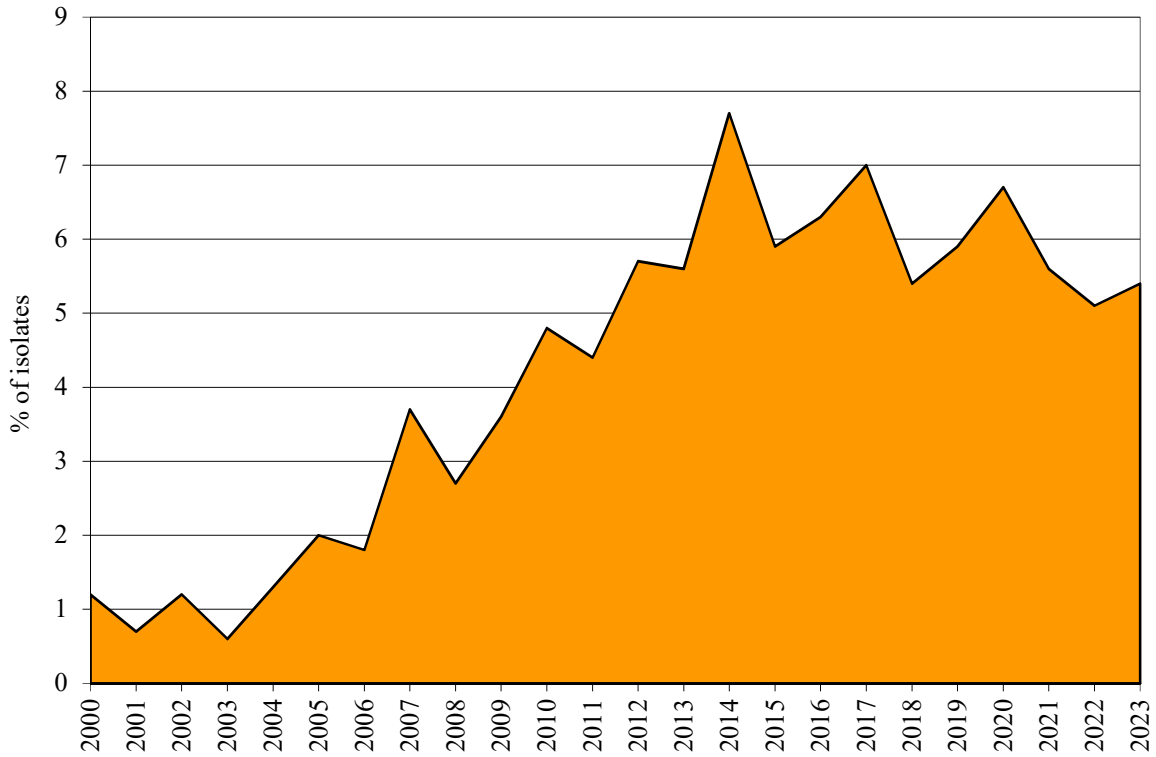

FIGURE 95. Prevalence of resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2023.

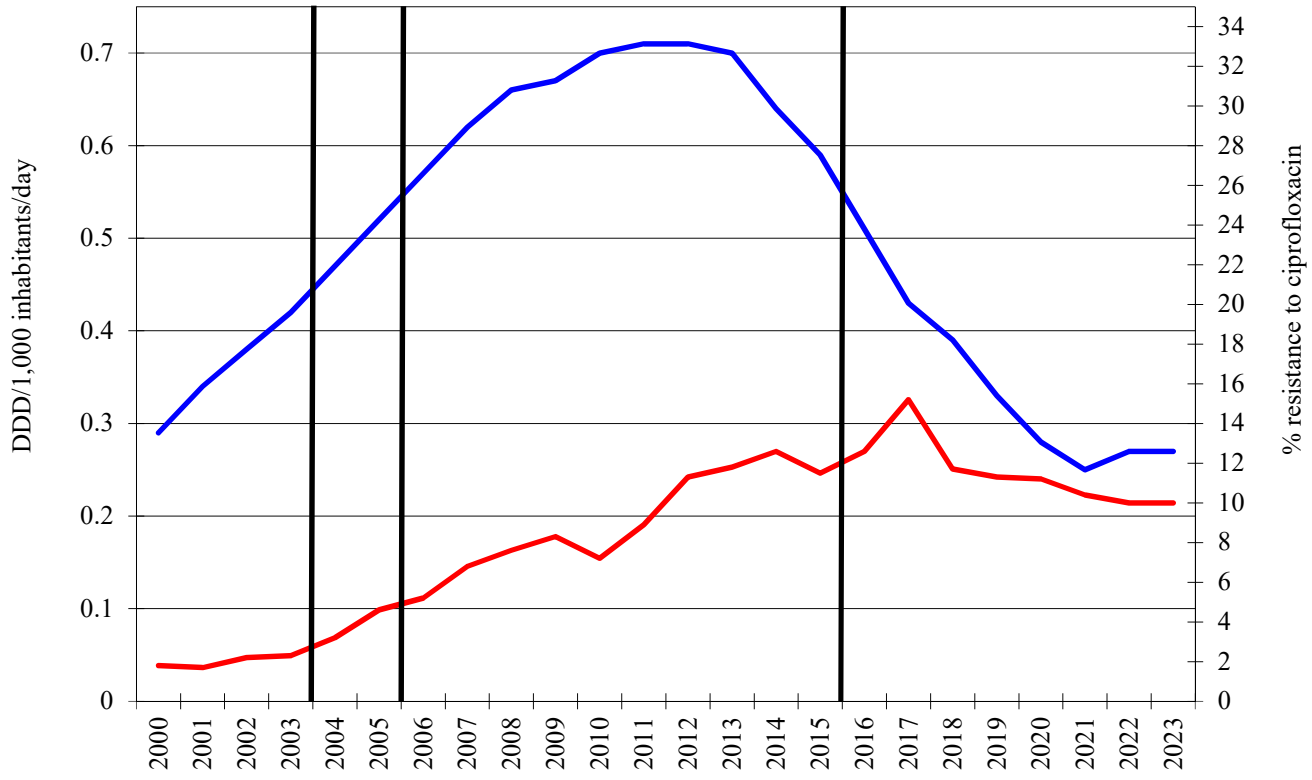

FIGURE 96. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates (red) as defined by MIC > 4 mg/L (2000-2003), MIC > 2 mg/L (2004-2005), MIC > 1 mg/L (2006-2015), and MIC > 0.5 mg/L (2016-2023). The breakpoints cannot be calibrated over the entire time period due to changes in susceptibility test methodology.

Escherichia coli in urine

TABLE 65. *Escherichia coli* urinary tract isolates in 2022 (n=1,478). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	67.3	-	32.7
Mecillinam	≤ 8	> 8	95.6	-	4.4
Amoxicillin-clavulanic acid*	≤ 32	> 32	92.4	-	7.6
Piperacillin-tazobactam	≤ 8	> 8	96.4	-	3.6
Cefalexin	≤ 16	> 16	94.0	-	6.0
Cefotaxime**	≤ 1	> 2	96.2	0.1	3.7
Ceftazidime	≤ 1	> 4	96.1	0.7	3.2
Meropenem**	≤ 2	> 8	99.9	0.0	0.1
Aztreonam	≤ 1	> 4	95.6	1.4	3.0
Gentamicin***	≤ 2	> 2	95.2	-	4.8
Ciprofloxacin**	≤ 0.25	> 0.5	89.3	2.2	8.5
Nitrofurantoin	≤ 64	> 64	99.0	-	1.0
Fosfomycin*	≤ 8	> 8	97.5	-	2.5
Trimethoprim	≤ 4	> 4	79.4	-	20.6
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	81.3	0.4	18.3
ESBL	Negative	Positive	96.1	-	3.9

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for oral administration in uncomplicated urinary tract infections. **Breakpoints for indications other than meningitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Urinary tract isolates of *E. coli* have been included in the surveillance programme every year since NORM was established in 2000. The prevalence of resistance for 2023 is shown in Table 65 and the rates of resistance for 2000-2023 are shown in Figure 97. The footnotes denote where EUCAST/NordicAST breakpoints specific for urinary tract infections have been applied.

The prevalence of resistance among urinary tract isolates has remained relatively stable over the last 20 years. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to around 35% (32.7% in 2023). Resistance to trimethoprim and trimethoprim-sulfamethoxazole has remained stable around 20-25% and was determined to be 20.6% and 18.3%, respectively, in 2023. The prevalence of resistance to mecillinam remained unchanged at 4.4%. Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. When adjusting for changes in breakpoint (see legend Figure 96), the prevalence of resistance has remained remarkably stable around 8-9% over the last five years. In 2023, 8.5% of the isolates were resistant to ciprofloxacin in addition to 2.2% that were only susceptible to increased exposure through adjustment of dosage or higher concentration at the site of infection. The corresponding rates for blood culture isolates were 10.0% resistance and 2.6% susceptibility to increased exposure. The persistent discrepancy between urinary tract isolates and isolates from bloodstream infections suggests that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and/or topoisomerase genes, whereas urinary tract isolates may be more representative of the wild type normal flora.

The prevalence of resistance to amoxicillin-clavulanic acid was 7.6% in 2023 compared to 4.4% in 2022, but this phenotype is technically challenging to determine and therefore prone to fluctuations. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (99.0%) remained fully susceptible to nitrofurantoin. Fosfomycin has been included in NORM since 2017. The vast majority of isolates was categorised as susceptible (97.5%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Fifty-seven isolates (3.9%) were reported as ESBL producers. This is at the same level as 3.1% in 2021 and 3.8% in 2022. As seen in Figure 98, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (5.8%). ESBL positive strains were isolated in all parts of the country. Thirty-one isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=13), or in patients from outpatient clinics (n=10) or nursing homes (n=3). The ESBL isolates were all resistant to ampicillin, and the majority were also resistant to cefalexin (56/57), cefotaxime (54/57), ceftazidime (45/57) and aztreonam (42/57). Almost all ESBL isolates were *in vitro* susceptible to mecillinam (55/57). This agent may be a viable treatment option in uncomplicated UTI provided a dosage of 400 mg x 3. Many ESBL isolates were resistant to trimethoprim (32/57), trimethoprim-sulfamethoxazole (32/57) and ciprofloxacin (40/57), but remained susceptible to nitrofurantoin (55/57), fosfomycin (53/57) and gentamicin (43/57). All isolates were clinically susceptible to meropenem, and no zone diameters below the screening breakpoint for carbapenemase producers were detected.

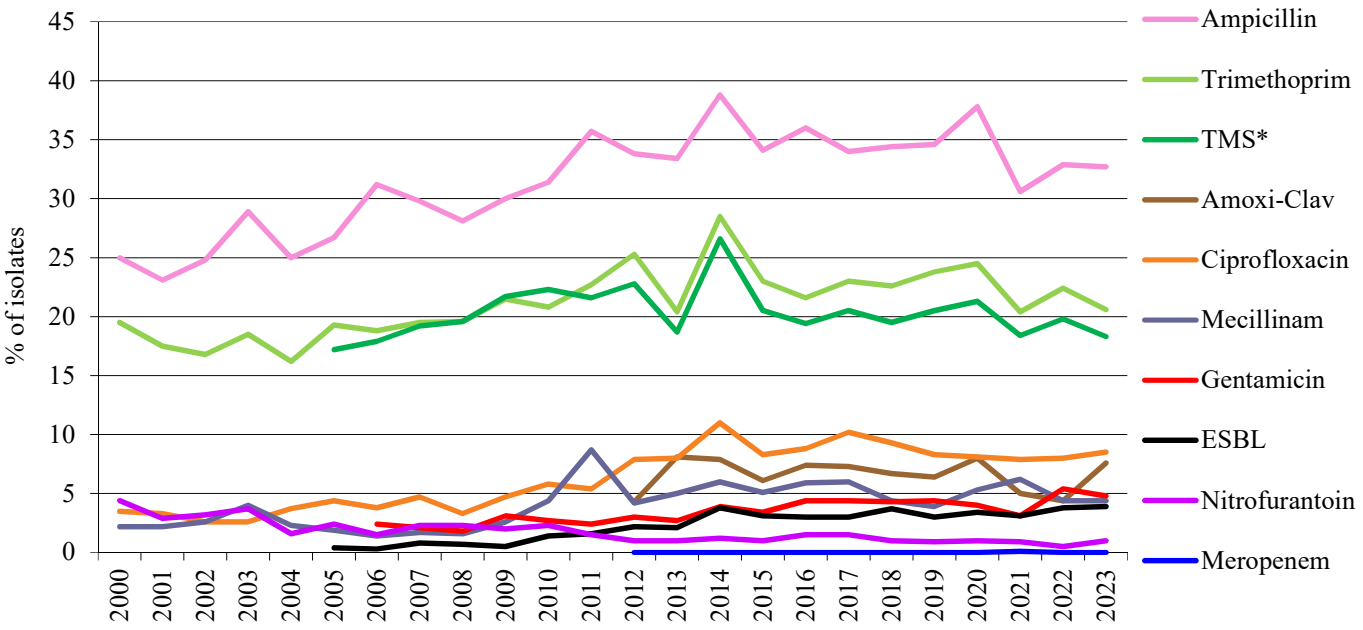

FIGURE 97. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2023. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

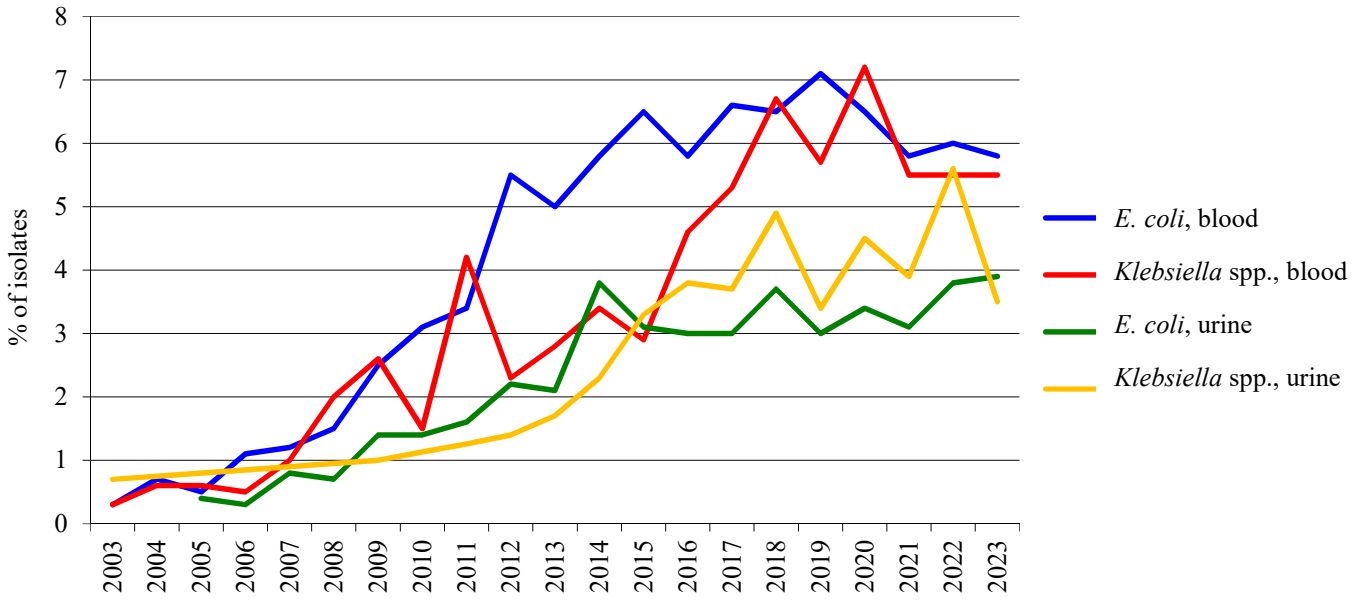

FIGURE 98. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2023.

Enterobacterales and the risk of selection for AmpC hyperproduction during antibiotic treatment resistant

Resistance against 3rd generation cephalosporins (3GC) in *Enterobacterales* is increasing and is most often caused by acquired beta-lactamases (extended-spectrum beta-lactamase; ESBL) or an elevated expression of an intrinsic chromosomal AmpC beta-lactamase. The latter mechanism is particularly relevant for the *Enterobacter cloacae* complex, *Klebsiella aerogenes*, *Citrobacter freundii* complex, *Hafnia alvei*, *Providencia* spp., *Serratia* spp., and *Morganella morganii* (1-3). The expression of the chromosomal AmpC beta-lactamase is normally low (basal level) and can be induced (increased expression level) by certain beta-lactam antibiotics causing resistance towards ampicillin, amoxicillin-clavulanic acid and 1st generation cephalosporins. The induced expression state is transient and returns to a basal level when the inducer is removed. However, pre-existing mutants with stable high-level expression (constitutive hyperproduction) of chromosomal AmpC can be selected mediating resistance to all penicillins, 1st – 3rd generation cephalosporins and aztreonam (1-4).

The occurrence of spontaneous mutants with stably elevated AmpC expression varies between different *Enterobacterales*. An extensive *in vitro* study of the mutation rate for AmpC hyperproduction in *Enterobacterales* (n=237) shows clear species-specific differences (5). While the mutation rate was high to moderate (average 3 x 10^{-8}) in the *E. cloacae* complex (n=40), *K. aerogenes* (n=26), *C. freundii* complex (n=41), and *H. alvei* (n=25) strains, the rate was significantly lower (15- to 600-fold) in *Providencia* spp. (n=29), *Serratia* spp. (n=51), and *M. morganii* (n=25) strains. This is also reflected in the relative occurrence of such mutants between different species in clinical samples (6, 7). In the NORM-2022 report the prevalence of resistance towards 3GC in blood culture isolates of *Enterobacter* spp. (n=259), *Citrobacter* spp. (n=77), and S*erratia* spp. (n=124), were 21.4%, 24.7%, and 9.7%, respectively (8). In a prospective single-centre study of patients with infections caused by *Enterobacterales* with chromosomal AmpC, the overall incidence of the emergence of resistance to 3GC during extended-spectrum cephalosporin therapy was a total of 5% (11/218), represented by the *E. cloacae* complex (12.3%; 8/65), *K. aerogenes* (2.9%; 2/51), and *C. freundii* (2.6%; 1/39), whereas no resistance development was observed in *S. marcescens* (0%; 0/37) , *M. morganii* (0%; 0/21), and other *Enterobacter* spp. (0%;0/5) (7).

Cases of resistance development due to selection of spontaneous mutants with AmpC hyperproduction were reported to occur during treatment with 3GC in the 1980s. The first systematic report and subsequent studies indicated that this could be a significant problem in treating infections caused by *Enterobacterales* with inducible AmpC, especially for *Enterobacter* spp. (9, 10). Consequently, the Norwegian Working Group on Antibiotics (NWGA) has recommended that susceptibility testing of AmpC harbouring *Enterobacterales* should include a warning against the use of piperacillin-tazobactam, 3GC, and aztreonam in monotherapy due to risk of resistance development. This has likely led to an increased use of carbapenems.

A recent review article has highlighted major methodological weaknesses in the clinical observational studies that form the basis for this recommendation (6). These include bias in patient selection, methodological uncertainties related to antimicrobial susceptibility testing and resistance determination, and failure to stratify by the site of infection. The article summarises several studies which support the argument that the danger of selection of mutants with AmpC hyperproduction is significantly exaggerated and must be stratified based on the bacterial species, the severity of the infection, the site of infection and the expected inoculum of infection (5, 6).

Collectively, this provides a solid basis for adjusting NWGA's recommendation as a carbapenem-saving measure without underestimating the danger of selection of pre-existing mutants with AmpC hyperproduction. The recommendation should accompany antimicrobial susceptibility results of all relevant species (*E. cloacae* complex, *K. aerogenes*, *C. freundii* complex, *H. alvei*, *Providencia* spp., *Serratia* spp., and *M. morganii*) in case of susceptibility to piperacillin-tazobactam, broad-spectrum cephalosporins and/or aztreonam, although the risk of stable AmpC overproduction differs between different species. The appearance of resistance towards 3GC during therapy with 3GC for *Enterobacter cloacae* and *Citrobacter freundii* species complex infections has been reported to occur on average after 7-9 days (range 3-28) (7,9). When assessing the risk for selection of spontaneous AmpC-hyperproducing strains and subsequent therapeutic failure, one should in particular consider the species involved, duration of treatment, severity of disease, and infections with high-level inoculum and limited source control (11, 12). Taking this into consideration, NWGA proposes a standard recommended comment that should follow antimicrobial susceptibility testing for severe infections caused by these bacterial species.

Recommended comment

In case of susceptibility, piperacillin-tazobactam, broad-spectrum cephalosporins or aztreonam can be used. Due to the risk for selection of resistance, the course should be monitored for treatment failure. This applies in particular to critical illness, long treatment duration and infections with high bacterial burden and limited source control.

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Klebsiella spp. in blood cultures

TABLE 66. *Klebsiella* spp. blood culture isolates in 2023 (n=1,028), except for amoxicillin-clavulanic acid (n=992) where 36 *K. aerogenes* isolates are excluded due to lack of breakpoints. Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	88.1	-	11.9
Piperacillin-tazobactam	≤ 8	> 8	89.3	-	10.7
Cefotaxime**	≤ 1	> 2	92.8	0.6	6.6
Ceftazidime	≤ 1	> 4	92.0	2.0	6.0
Cefepime	≤ 1	> 4	91.0	3.4	5.6
Meropenem**	≤ 2	> 8	99.2	0.5	0.3
Aztreonam	≤ 1	> 4	90.2	2.8	7.0
Gentamicin***	≤ 2	> 2	95.7	-	4.3
Ciprofloxacin**	≤ 0.25	> 0.5	87.7	4.2	8.1
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	87.9	0.2	11.9
ESBL	Negative	Positive	94.5	-	5.5

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for intravenous administration. **Breakpoints for indications other than menigitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 67. *Klebsiella pneumoniae* blood culture isolates in 2023 (n=729). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	88.5	-	11.5
Piperacillin-tazobactam	≤ 8	> 8	90.4	-	9.6
Cefotaxime**	≤ 1	> 2	93.3	0.1	6.6
Ceftazidime	≤ 1	> 4	91.9	2.3	5.8
Cefepime	≤ 1	> 4	90.8	3.2	6.0
Meropenem**	≤ 2	> 8	99.3	0.3	0.4
Aztreonam	≤ 1	> 4	92.4	2.1	5.5
Gentamicin***	≤ 2	> 2	95.5	-	4.5
Ciprofloxacin**	≤ 0.25	> 0.5	84.5	5.2	10.3
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	85.4	0.3	14.3
ESBL	Negative	Positive	93.7	-	6.3

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for intravenous administration. **Breakpoints for indications other than menigitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 68. *Klebsiella oxytoca* blood culture isolates in 2023 (n=239). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	89.1	-	10.9
Piperacillin-tazobactam	≤ 8	> 8	88.7	-	11.3
Cefotaxime**	≤ 1	> 2	94.5	1.7	3.8
Ceftazidime	≤ 1	> 4	94.9	1.3	3.8
Cefepime	≤ 1	> 4	92.5	3.3	4.2
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	86.7	5.4	7.9
Gentamicin***	≤ 2	> 2	96.2	-	3.8
Ciprofloxacin**	≤ 0.25	> 0.5	95.4	1.7	2.9
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	94.1	0.0	5.9
ESBL	Negative	Positive	96.2	-	3.8

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for intravenous administration. **Breakpoints for indications other than menigitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 69. *Klebsiella aerogenes* blood culture isolates in 2023 (n=36). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Piperacillin-tazobactam	≤ 8	> 8	69.4	-	30.6
Cefotaxime*	≤ 1	> 2	69.4	2.8	27.8
Ceftazidime	≤ 1	> 4	69.4	2.8	27.8
Cefepime	≤ 1	> 4	77.8	11.1	11.1
Meropenem*	≤ 2	> 8	91.7	8.3	0.0
Aztreonam	≤ 1	> 4	72.2	2.8	25.0
Gentamicin**	≤ 2	> 2	94.4	-	5.6
Ciprofloxacin*	≤ 0.25	> 0.5	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	97.2	0.0	2.8
ESBL	Negative	Positive	94.4	-	5.6

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for indications other than menigitis. **Breakpoints for infections originating from the urinary tract. ***Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Klebsiella spp. isolates in blood cultures were speciated as follows: 729 (71.0%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola* and *K. africana*); 239 (23.2%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis* and *K. spallanzanii*): 36 (3.5%) *K. aerogens*; and 24 unspecified *Klebsiella* isolates (2.3%), giving a total of 1,028 *Klebsiella* spp. (Tables 66-69).

The majority of *Klebsiella* spp. isolates were susceptible to aminoglycosides, and the prevalence of gentamicin resistance remained stable at 4.3% in 2023 compared to 4.2% in 2021 and 4.5% in 2022. Gentamicin resistance was slightly more common in *K. pneumoniae* (4.5%) than in *K. oxytoca* (3.8%), and appeared for the first time also in *K. aerogenes* (5.6%). Aminoglycoside resistance in common *Enterobacterales* species is a cause for great concern as these antimicrobials have traditionally been used in the empirical regimen for treatment of sepsis in Norway.

As for *E. coli*, the breakpoints for ciprofloxacin were reduced from R > 1 mg/L to R > 0.5 mg/L and from S ≤ 0.5 to S ≤ 0.25 in 2017. The prevalence of resistance to ciprofloxacin peaked at 11-12% in 2016-2017, but has now stabilised at 8.3% in 2022 and 8.1% in 2023. Resistance to ciprofloxacin was much more common in *K. pneumoniae* (10.3%) than in *K. oxytoca* (2.9%), and this phenotype was not seen at all in *K. aerogenes* in 2023. Overall resistance to trimethoprim-sulfamethoxazole remained unchanged at 11.9% compared to 11.8% in 2022. The prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (5.9%) and *K. aerogenes* (2.8%) than in *K. pneumoniae* (14.3%).

Comparison of resistance to beta-lactam antibiotics between *Klebsiella* species is complicated by the chromosomal K1 beta-lactamase in *K. oxytoca* and chromosomal AmpC in *K. aerogenes*. Most *Klebsiella* spp. isolates were susceptible (S+I) to cefotaxime (93.4%), ceftazidime (94.0%), cefepime (94.4%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (89.3%), see Figure 99. The prevalence of resistance to 3rd generation cephalosporins has remained essentially unchanged 2018-2024. The increased resistance rate to piperacillin-tazobactam over the last years (4.4% in 2019, 11.2% in 2020) was due to a reduction of the breakpoint for resistance from R > 16 mg/L to R > 8 mg/L. The rate did not change from 2022 (11.0%) to 2023 (10.7%).

As for *E. coli*, the detection of extended-spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidime disks. Isolates with reduced zone diameters were further characterised by combination disks or MIC gradient tests. The prevalence of phenotypically confirmed ESBL isolates remained stable from 2022 (5.5% in *Klebsiella* spp.; 6.8% in *K. pneumoniae*) to 2023 (5.5% in *Klebsiella* spp.; 6.3% in *K. pneumoniae*), see Figure 98. The 57 ESBL isolates originated from 14 different laboratories and were identified as *K. pneumoniae* (n=46, 81%), *K. oxytoca* (n=9, 16%) and *Klebsiella* spp. (n=2). ESBL isolates were often resistant to cefotaxime (55/57), cefepime (50/57), ceftazidime (48/57) and aztreonam (44/57), and co-resistance was frequently seen for trimethoprim-sulfamethoxazole (49/57), ciprofloxacin (35/57) and gentamicin (30/57). Many isolates remained susceptible to piperacillin-tazobactam (26/57). A total of six meropenem resistant isolates (0.6%) were verified as carbapenemase producers (CPE). Five *K. pneumoniae* isolates (0.7%) contained OXA-48-like (n=1), OXA-48-like + NDM (n=3) or KPC (n=1) enzymes. A single *K. aerogenes* isolate contained KPC. Additional isolates were only susceptible to increased meropenem exposure (I) or had zone diameters below the screening breakpoint, but did not contain any known carbapenemase genes.

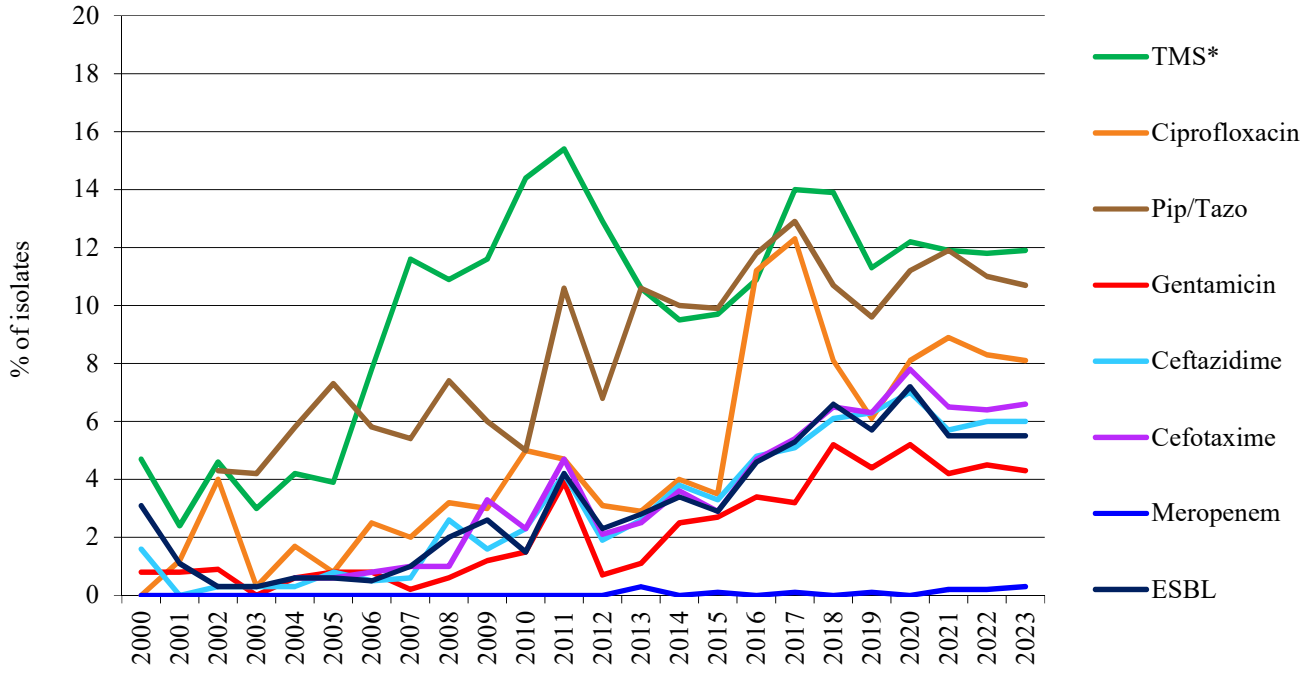

FIGURE 99. Prevalence of resistance to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2023. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 70. *Klebsiella* spp. urinary tract isolates in 2023 (n=1,101), except for amoxicillin-clavulanic acid and cefalexin (n=1,041) where 60 *K. aerogenes* isolates are excluded due to lack of breakpoints. Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	93.2	-	6.8
Amoxicillin-clavulanic acid*	≤ 32	> 32	95.0	-	5.0
Piperacillin-tazobactam	≤ 8	> 8	91.8	-	8.2
Cefalexin	≤ 16	> 16	94.8	-	5.2
Cefotaxime**	≤ 1	> 2	95.5	0.4	4.1
Ceftazidime	≤ 1	> 4	95.4	1.1	3.5
Cefepime	≤ 1	> 4	94.8	1.3	3.9
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	94.0	1.6	4.4
Gentamicin***	≤ 2	> 2	97.4	-	2.6
Ciprofloxacin**	≤ 0.25	> 0.5	90.1	3.5	6.4
Trimethoprim	≤ 4	> 4	87.7	-	16.3
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	86.7	1.1	12.2
ESBL	Negative	Positive	96.5	-	3.5

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for oral administration in uncomplicated urinary tract infections. **Breakpoints for indications other than meningitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 71. *Klebsiella pneumoniae* urinary tract isolates in 2023 (n=775). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	94.7	-	5.3
Amoxicillin-clavulanic acid*	≤ 32	> 32	96.1	-	3.9
Piperacillin-tazobactam	≤ 8	> 8	92.9	-	7.1
Cefalexin	≤ 16	> 16	95.7	-	4.3
Cefotaxime**	≤ 1	> 2	96.0	0.1	3.9
Ceftazidime	≤ 1	> 4	95.3	1.3	3.4
Cefepime	≤ 1	> 4	94.8	1.2	4.0
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	95.6	1.3	3.1
Gentamicin***	≤ 2	> 2	97.5	-	2.5
Ciprofloxacin**	≤ 0.25	> 0.5	87.5	4.4	8.1
Trimethoprim	≤ 4	> 4	80.6	-	19.4
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	84.0	1.5	14.5
ESBL	Negative	Positive	96.3	-	3.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for oral administration in uncomplicated urinary tract infections. **Breakpoints for indications other than meningitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 72. *Klebsiella oxytoca* urinary tract isolates in 2023 (n=238). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	89.9	-	10.1
Amoxicillin-clavulanic acid*	≤ 32	> 32	91.2	-	8.8
Piperacillin-tazobactam	≤ 8	> 8	87.8	-	12.2
Cefalexin	≤ 16	> 16	92.4	-	7.6
Cefotaxime**	≤ 1	> 2	95.8	1.3	2.9
Ceftazidime	≤ 1	> 4	97.1	0.4	2.5
Cefepime	≤ 1	> 4	94.1	2.1	3.8
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	89.0	3.4	7.6
Gentamicin***	≤ 2	> 2	96.6	-	3.4
Ciprofloxacin**	≤ 0.25	> 0.5	96.2	1.3	2.5
Trimethoprim	≤ 4	> 4	91.2	-	8.8
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	92.4	0.0	7.6
ESBL	Negative	Positive	97.9	-	2.1

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for oral administration in uncomplicated urinary tract infections. **Breakpoints for indications other than meningitis. ***Breakpoints for infections originating from the urinary tract. ****Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 73. *Klebsiella aerogenes* urinary tract isolates in 2023 (n=60). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	90.0	-	10.0
Piperacillin-tazobactam	≤ 8	> 8	93.3	-	6.7
Cefotaxime*	≤ 1	> 2	91.7	0.0	8.3
Ceftazidime	≤ 1	> 4	91.6	1.7	6.7
Cefepime	≤ 1	> 4	100.0	0.0	0.0
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 4	95.0	0.0	5.0
Gentamicin**	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.25	> 0.5	98.3	0.0	1.7
Trimethoprim	≤ 4	> 4	96.7	-	3.3
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	100.0	0.0	0.0
ESBL	Negative	Positive	98.3	-	1.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for indications other than meningitis. **Breakpoints for infections originating from the urinary tract. ***Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Klebsiella spp. urinary tract isolates have previously been included in the NORM surveillance programme in 2001, 2003, 2009 and 2012-2022. Due to methodological changes it is not possible to directly compare the results from 2001 and 2003 with the ones from later surveys. There are no *Klebsiella* spp. disk diffusion breakpoints for fosfomycin or nitrofurantoin, and *K. aerogenes* is not included in the breakpoints for oral administration of cefalexin and amoxicillin-clavulanic. The urinary tract isolates in NORM 2023 were speciated as follows: 775 (70.5%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola* and *K. africana*); 238 (21.6%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis* and *K. spallanzanii*); 60 (5.4%) *K. aerogens*; and 28 isolates (2.5%) not identified to the species level, giving a total of 1,101 *Klebsiella* spp. isolates (Tables 70-73).

The prevalence of resistance to urinary tract antibiotics was slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Table 65). The majority of isolates remained susceptible to gentamicin at 97.4% compared to 98.0% in 2021 and 95.7% in 2022. Among urinary tract *E. coli*, 95.2% were gentamicin susceptible in 2023. The rates of resistance to ciprofloxacin in *Klebsiella* spp. decreased from 7.4% in 2022 to 6.4% in 2023. The comparable rate for urinary tract *E. coli* in 2023 was 8.5%. Susceptibility to trimethoprim (82.4% in 2022; 87.7% in 2023) and trimethoprim-sulfamethoxazole (84.9% in 2022; 86.7% in 2023) was higher than in *E. coli* (79.4% and 81.3% in 2023, respectively).

All *Klebsiella* isolates are inherently resistant to ampicillin due to the chromosomal SHV beta-lactamase. As for *Klebsiella* spp. blood culture isolates, ESBL detection in urinary tract isolates was based on resistance to cefotaxime and/or ceftazidime and subsequent confirmatory ESBL combination disk or MIC gradient tests. Thirty-eight isolates (3.5%) were reported as ESBL, of which 29 were *K. pneumoniae*, five were *K. aerogenes*, three were *K. oxytoca*, and one was unspeciated. They were retrieved from 15 different laboratories and originated from hospital inpatients (n=17), outpatient clinics (n=4), general practices (n=15) and nursing homes (n=2). The 3.5% ESBL rate (3.7% in *K. pneumoniae*) was a decrease from 2022 (5.6% for all *Klebsiella*, 6.0% for *K. pneumoniae*) but at the same level as in 2021 (3.9% for all *Klebsiella*, 4.5% in *K. pneumoniae*). As expected, the 38 ESBL isolates were generally resistant to broad-spectrum beta-lactam antibiotics (cefalexin, cefotaxime, ceftazidime, cefepime, aztreonam). There was also widespread co-resistance to trimethoprim (n=36), trimethoprim-sulfamethoxazole (n=36), ciprofloxacin (n=21) and gentamicin (n=18), but many isolates remained susceptible to mecillinam (n=29), amoxicillin-clavulanic acid (n=19) and/or piperacillin-tazobactam (n=22). No isolates were clinically resistant to meropenem, and carbapenemase production was not detected by the screening procedure.

Cefiderocol – a siderophore cephalosporin for treatment of infections with multi-drug resistant Gram-negative bacteria

Infections with multi-drug resistant (MDR) Gram-negative bacteria, in particular carbapenemase-producers, is a clinical challenge due to limited treatment options. Carbapenemase-producing organisms often express resistance to all beta-lactam antibiotics including carbapenems and co-resistance to other clinically important classes of antibiotics. The recent development and approval of new beta-lactam-beta-lactamase inhibitor combinations such as ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam and aztreonam-avibactam has provided treatment options (1). Another alternative is the siderophore-cephalosporin cefiderocol (2, 3).

Chemistry and mechanism of action

The most distinctive feature of cefiderocol is the catechol side-chain that can chelate ferric iron (4). This side-chain binds iron in the extracellular environment enabling active transport across the outer membrane via the bacterial iron transport systems enhancing the periplasmic concentration (4). Once in the periplasmic space, iron is released and cefiderocol binds to penicillin-binding proteins (mainly PBP3) inhibiting peptidoglycan synthesis (5). In addition, cefiderocol contain C3- and C7-side-chains which are similar to cefepime and ceftazidime, respectively. Along with the catechol side-chain they provide enhanced stability against both serine- and metallo-beta-lactamases (MBLs) including carbapenemase variants (6, 7).

Antibacterial spectrum and clinical applications

Cefiderocol is approved for treatment of infections caused by aerobic Gram-negative bacteria with limited treatment options (https://www.ema.europa.eu/en/medicines/human/EPAR/fetcroja). In the current European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for treatment of infections caused by MDR Gram-negative bacilli, cefiderocol is conditionally recommended for severe infections due to carbapenem resistant *Enterobacterales* carrying MBL and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam (8). For severe infections with carbapenem resistant *Pseudomonas aeruginosa* there is insufficient evidence for recommending cefiderocol, and for carbapenem resistant *Acinetobacter baumannii* ESCMID conditionally recommends against cefiderocol use (8). The Infectious Disease Society of America (IDSA) has included cefiderocol in their specific recommendations for the treatment of infections caused by carbapenemase-producing *Enterobacterales* and difficult-to-treat *P. aeruginosa* as well as *A. baumannii* and *Stenotrophomonas maltophilia* (https://www.idsociety.org/practice-guideline/amr-guidance/). This is a dynamic field and IDSA has issued the need for yearly updates in their recommendations.

Cefiderocol shows potent and broad-spectrum *in vitro* activity against Gram-negative bacteria (2, 3, 9, 10). In a systematic review and meta-analysis including 78 worldwide studies and 82,035 clinical isolates, 97% of *Enterobacterales* and 98.6% of *P. aeruginosa* were cefiderocol susceptible according to EUCAST clinical breakpoints (10). No clinical breakpoints are available from EUCAST for *A. baumannii* and *S. maltophilia*, but using CLSI breakpoints the study found that 96.2% of *A. baumannii* and 99.9% of *Stenotrophomonas maltophilia* were susceptible (10). Despite the overall potent activity and stability of cefiderocol against beta-lactamases it is clear that susceptibility is decreased in carbapenem resistant Gram-negatives and in particular MBL-producing *Enterobacterales* and *P. aeruginosa* (10). Analysis of carbapenemase-producing *Enterobacterales* identified in Norway in 2023 shows that 52% (160/306) of the isolates were resistant to cefiderocol using disc diffusion (see pages 130-138), but it is worth noting that 26% (79/306) of all isolates and 49% (79/160) of those interpreted as resistant had a zone diameter within the area of technical uncertainty (ATU) and were interpreted as resistant.

Resistance mechanisms

Like other beta-lactams, mechanisms of resistance to cefiderocol include beta-lactamase activity, changes in porins, expression of efflux pumps and mutations in PBPs (specifically PBP3). In addition, mutations in iron transport systems has been shown to affect cefiderocol susceptibility. For an overview of different resistance mechanisms see e.g. (9, 11). All these mechanisms contribute to reduced susceptibility to cefiderocol, but a combination of mechanisms is frequently required to obtain clinical resistance.

Despite its increased stability against beta-lactamases, some beta-lactamase families have intrinsically a comparatively higher ability to hydrolyse cefiderocol (12). This includes MBLs such as NDM and SPM-1 and the PER ESBLs (12). The reduced stability against NDM is reflected in the higher proportion of resistance in NDM-producing isolates (10). In addition, specific variants within some important beta-lactamase families have been shown to have increased activity against cefiderocol. This has particularly been described for KPC carbapenemases where variants such as KPC-31, KPC-41 and yet not designated variants lead to resistance or show significant increases in MIC compared to the ancestral variants such as KPC-2 and KPC-3 which have limited activity against cefiderocol (13-15). Worryingly, some of these variants confer cross-resistance to ceftazidime-avibactam and have been shown to evolve during ceftazidime-avibactam therapy (13). A similar scenario is described in patients exposed to cefepime, where changes in the chromosomal AmpC beta-lactamase of *Enterobacter cloacae* resulted in ceftazidime-avibactam resistance and reduced susceptibility to cefiderocol (16). Thus, there is evolutionary space among some beta-lactamases to evolve the ability of hydrolysing cefiderocol and that exposure to the chemically similar beta-lactams might promote this. The evolutionary space has been shown using a directed evolutionary approach where the acquisition of only one to two non-synonymous mutations in different beta-lactamases caused further reduced susceptibility to cefiderocol (17).

As expected, a range of mutations in, reduced expression of, or loss of genes involved in iron transport systems have been implicated in causing reduced susceptibility to cefiderocol. These include *pirA* in *A. baumannii* (18), *cirA* in *Klebsiella pneumoniae* (19) and *E. cloacae* (20), *cirA* and *fiu* in *Escherichia coli* (5), as well as *piuA* in *P. aeruginosa* (5). There is not much evidence on the contribution of porin alterations and efflux to cefiderocol resistance and the data are somewhat contradictory (5, 21, 22). Mutations in PBP3 have been identified and described in cefiderocol resistant isolates or in isolates with reduced susceptibility and may contribute to cefiderocol resistance (18, 23). However, more in-depth studies are required to understand the role and contribution of these mechanisms to clinical cefiderocol resistance. Overall, this shows that a combination of heterogenous resistance mechanisms is involved. In addition, a high level of cefiderocol heteroresistance has been observed and suggested to be implicated in treatment failures during clinical trials (24, 25)

Antimicrobial susceptibility testing

The iron chelating properties of cefiderocol and uptake through iron transport systems has challenged antimicrobial susceptibility testing (26). Consequently, iron concentrations need to be taken into consideration and iron-depleted Mueller-Hinton broth must be used. This has particularly challenged the development of commercial MIC methods as well as the reference broth microdilution method (ISO 20776-1:2019). Thus, there is currently uncertainties in MIC determination of cefiderocol and EUCAST has (still valid as of June 2024) a warning that commercially available MIC tests have problems with various aspects (e.g. reproducibility and accuracy) (https://www.eucast.org/ast-of-bacteria/warnings). However, there are available MIC tests that show relatively good correlation with the reference method (27), but more validation is required. An additional challenge of broth microdilution-based MIC methods is the reading of MICs due to trailing endpoints and hazy growth. In contrast to MIC determinations, iron-depleted media is not required for the EUCAST disk diffusion method and this is currently the only EUCAST recommended method.

Summary

Overall, cefiderocol offers an alternative treatment option for serious infections with MDR Gram-negatives and in particular carbapenemase-producers. However, there are concerns about the high level of resistance particularly observed among MBL-producers, continued resistance development and challenges with methods for cefiderocol susceptibility testing.

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Pseudomonas aeruginosa in blood cultures

TABLE 74. *Pseudomonas aeruginosa* blood culture isolates in 2023 (n=339). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Piperacillin-tazobactam	≤ 0.001	> 16	0.0	93.8	6.2
Ceftazidime	≤ 0.001	> 8	0.0	94.1	5.9
Cefepime	≤ 0.001	> 8	0.0	91.7	8.3
Ceftolozane-tazobactam	≤ 4	> 4	98.2	-	1.8
Aztreonam	≤ 0.001	> 16	0.0	92.6	7.4
Imipenem	≤ 0.001	> 4	0.0	90.6	9.4
Meropenem*	≤ 2	> 8	94.4	2.9	2.7
Amikacin**	≤ 16	> 16	99.4	-	0.6
Tobramycin**	≤ 2	> 2	99.4	-	0.6
Ciprofloxacin	≤ 0.001	> 0.5	0.0	91.4	8.6

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for indications other than meningitis. **Breakpoints for infections originating from the urinary tract.

RESULTS AND COMMENTS

NORM has previously reported on *Pseudomonas aeruginosa* blood culture isolates in 2005, 2010, 2015 and 2019. The first two surveys were based on MIC determination, whereas the isolates from 2015 onwards have been examined by disk diffusion. Moreover, Nordic-AST/EUCAST performed a major revision of clinical breakpoints in 2019 where wild type strains were defined as susceptible only to increased exposure of many antibiotics including piperacillin-tazobactam, ceftazidime, aztreonam, imipenem and ciprofloxacin. Comparison of data from different years should therefore be done with caution.

Most isolates were susceptible to all relevant antimicrobials, and very few were resistant to multiple antibiotic classes as commonly seen in other countries (Table 74). The prevalence of resistance has increased over the last decade for all beta-lactam antibiotics as seen in Figure 100. Meropenem resistance is of special concern (5.7% in 2019, 2.7% in 2023) as this substance is often the drug of choice for invasive infections. Many of these isolates were concomitantly resistant to other beta-lactam antibiotics normally active against *P. aeruginosa*, including imipenem (8/9), aztreonam (7/9), ceftazidime (5/9), piperacillin-tazobactam (4/9) and cefepime (3/9). The molecular basis for meropenem resistance was not determined, but may include carbapenemase production, upregulation of chromosomally encoded AmpC, efflux pumps and/or porin mutations. The prevalence of resistance to aminoglycosides is still very low, whereas resistance to ciprofloxacin has increased from 6.6% in 2019 to 8.6% in 2023.

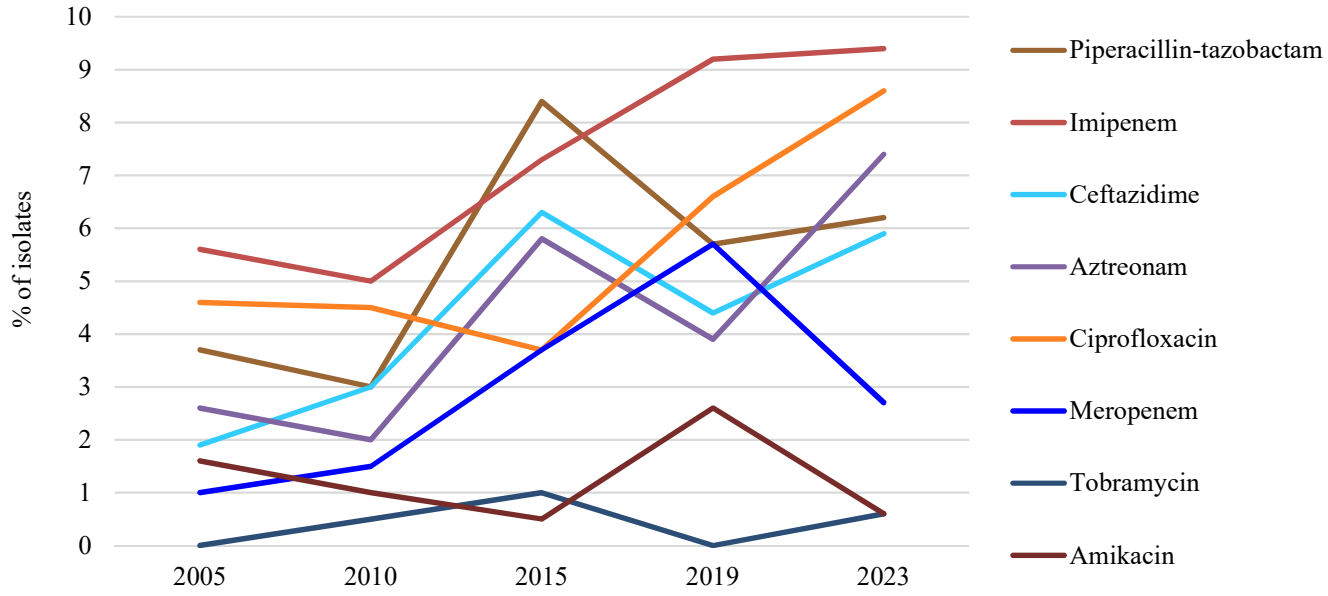

FIGURE 100. Prevalence of resistance to various antimicrobial agents in *Pseudomonas aeruginosa* blood culture isolates 2005-2023. The breakpoint for resistance to ciprofloxacin was reduced from R > 1 mg/L to R > 0.5 mg/L, for imipenem from R > 8 mg/L to R > 4 mg/L, and for tobramicin from R > 4 mg/L to R > 2 mg/L, all in 2019. Please note that the X axis is not to scale.

Acinetobacter spp. in blood cultures

TABLE 75. *Acinetobacter* spp. blood culture isolates in 2023 (n=68). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Imipenem	≤ 2	> 4	98.5	0.0	1.5
Meropenem*	≤ 2	> 8	98.5	0.0	1.5
Amikacin**	≤ 8	> 8	94.1	-	5.9
Gentamicinn**	≤ 4	> 4	95.6	-	4.4
Tobramycin**	≤ 4	> 4	97.1	-	2.9
Ciprofloxacin	≤ 0.001	> 1	0.0	98.5	1.5
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	98.5	0.0	1.5

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended-spectrum beta-lactamase. *Breakpoints for indications other than meningitis. **Breakpoints for infections originating from the urinary tract. ***Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Acinetobacter spp. blood culture isolates have previously only been surveyed in NORM in 2007/2008. Due to later revisions of breakpoints, direct comparison of results over time should be done with caution. In 2023, a total of 68 *Acinetobacter* spp. blood culture isolates were included. Thirty-six were assigned to the *Acinetobacter baumannii/calcoaceticus* complex, five isolates were speciated as *Acinetobacter lwoffii*, whereas the remaning 27 remained unspeciated. A majority of this latter group presumably also belongs to the *Acinetobacter baumannii/calcoaceticus* complex, and all isolates were therefore analysed at the genus level as *Acinetobacter* spp.

The isolates were generally susceptible to all relevant antibiotics (Table 75). A single isolate was resistant to both meropenem and imipenem. Four isolates were resistant to the broad-spectrum aminoglycoside amikacin, and among these, three and two isolates were also resistant to gentamicin and tobramycin, respectively. Further details about multi-resistant *P. aeruginosa* and *Acinetobacter* spp. reported to the Norwegian Notification System for Communicable Diseases (MSIS) are presented on pages 135-138.

Carbapenemase-producing Gram-negative bacteria in Norway 2023

Gram-negative bacteria with acquired carbapenemases represent a major public health burden due to multi-drug resistance and consequently difficult-to-treat infections (1, 2). Thus, surveillance is essential for infection control and prevention. In Norway, infection and colonisation with carbapenemase-producing Gram-negative bacteria is notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) and confirmed at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance. Here, we summarise the findings for 2023.

Carbapenemase-producing *Enterobacterales* (CPE)

In 2023, 237 cases/patients were identified with CPE (Figure 101). This is an increase from 152 in 2022 and represents an increase in the incidence from 2.8 to 4.3 per 100,000 person-years. Association to import from 35 different countries was linked to 77% (61% in 2022) of the cases. For 11% there was no association to import (8% in 2022) and for 12% data on import was missing. Import from Ukraine represented 29% overall and 38% of all cases associated with import.

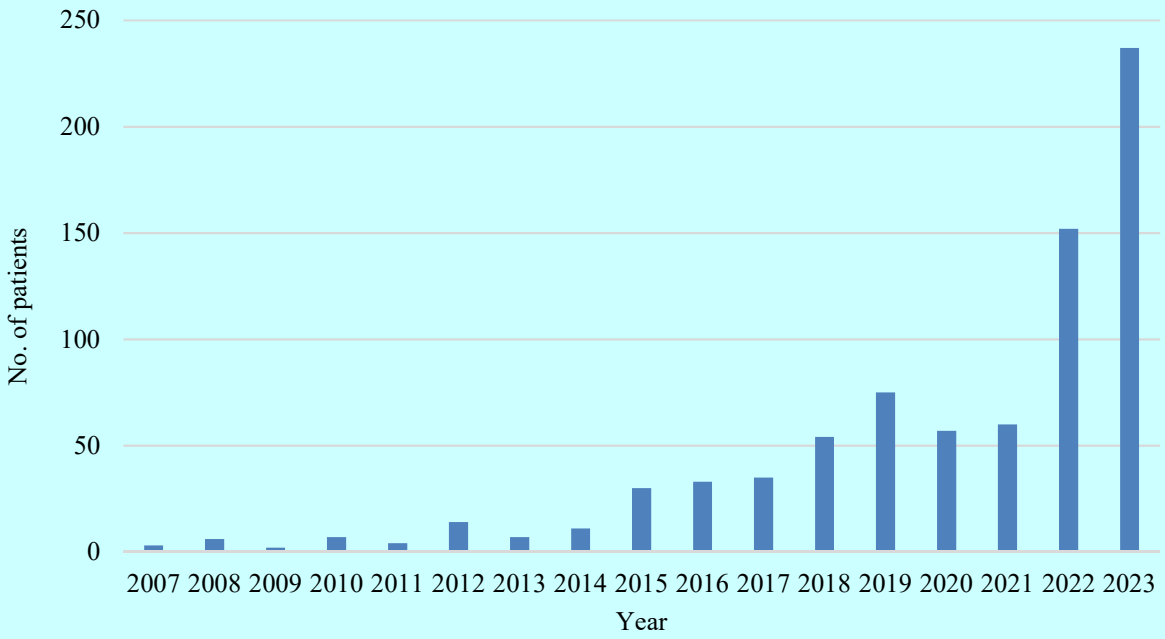

FIGURE 101. Number of cases with CPE in Norway 2007-2023.

A total of 306 CPE isolates were identified from the 237 patients compared to 196 isolates from 152 patients in 2022 (56% increase). Forty-three patients harboured 2-5 CPE isolates of different species/carbapenemase genes or same species, but different sequence type (ST). Sixty-five percent of the isolates were identified through screening, while 3% and 14% were identified in blood or urine culture, respectively. Eighteen percent were from other sample materials.

Similar to previous years, *Escherichia coli* and *Klebsiella pneumoniae* were the dominant species (Figure 102A). The number of *E. coli* increased from 80 isolates in 2022 to 133 in 2023 (66% increase) while the number of *K. pneumoniae* increased by 36% (89 in 2022; 121 in 2023). One *K. pneumoniae* isolate was typed as *Klebsiella quasipneumoniae* subsp. *quasipneumoniae*. The number of other *Enterobacterales* species also increased by 93% (27 in 2022; 52 in 2023). Two isolates of carbapenemase-producing (OXA-181) *Klebsiella planticola* (formerly *Raoultella planticola*) were for the first time identified in 2023 from different patients, both associated with screening and import from Türkiye.

NDM (n=116), OXA-48-like (n=113) and NDM+OXA-48-like (n=37) were dominant as in previous years (Figure 102B). One *Citrobacter sedlakii* isolate was identified harbouring three carbapenemases (NDM-5, OXA-48 and OXA-181).

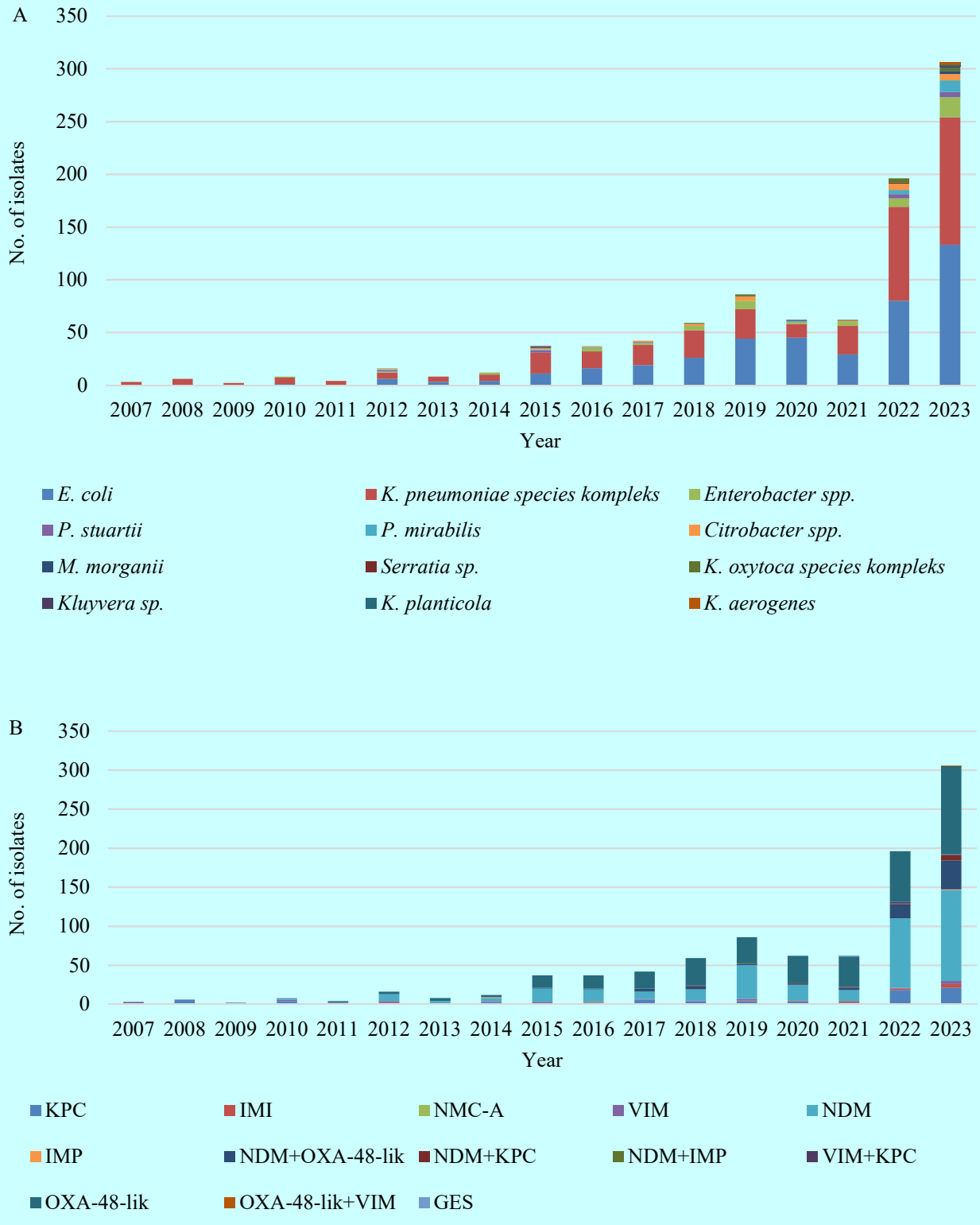

FIGURE 102. Number of CPE isolates according to species (A) and distribution of carbapenemase variants (B) in Norway 2007-2023.

All isolates were typed with whole genome sequencing (WGS), which revealed a large diversity of genetic backgrounds and carbapenemase variants. A minimum of 40 different STs were identified among the 133 *E. coli* isolates (Figure 103). Two isolates belonged to novel yet unassigned STs. The combinations ST167-NDM-5 (n=12), ST69-OXA-244 (n=9) and ST648-NDM-5 (n=8) were the most common. NDM-5 (n=51) and OXA-244 (n=21) were the most commonly identified carbapenemase variants found in 17 and 8 different genetic backgrounds, respectively. The dominant genetic backgrounds (ST167, ST38, ST69, ST361, ST648 and ST410) are considered global high-risk clones (3, 4).

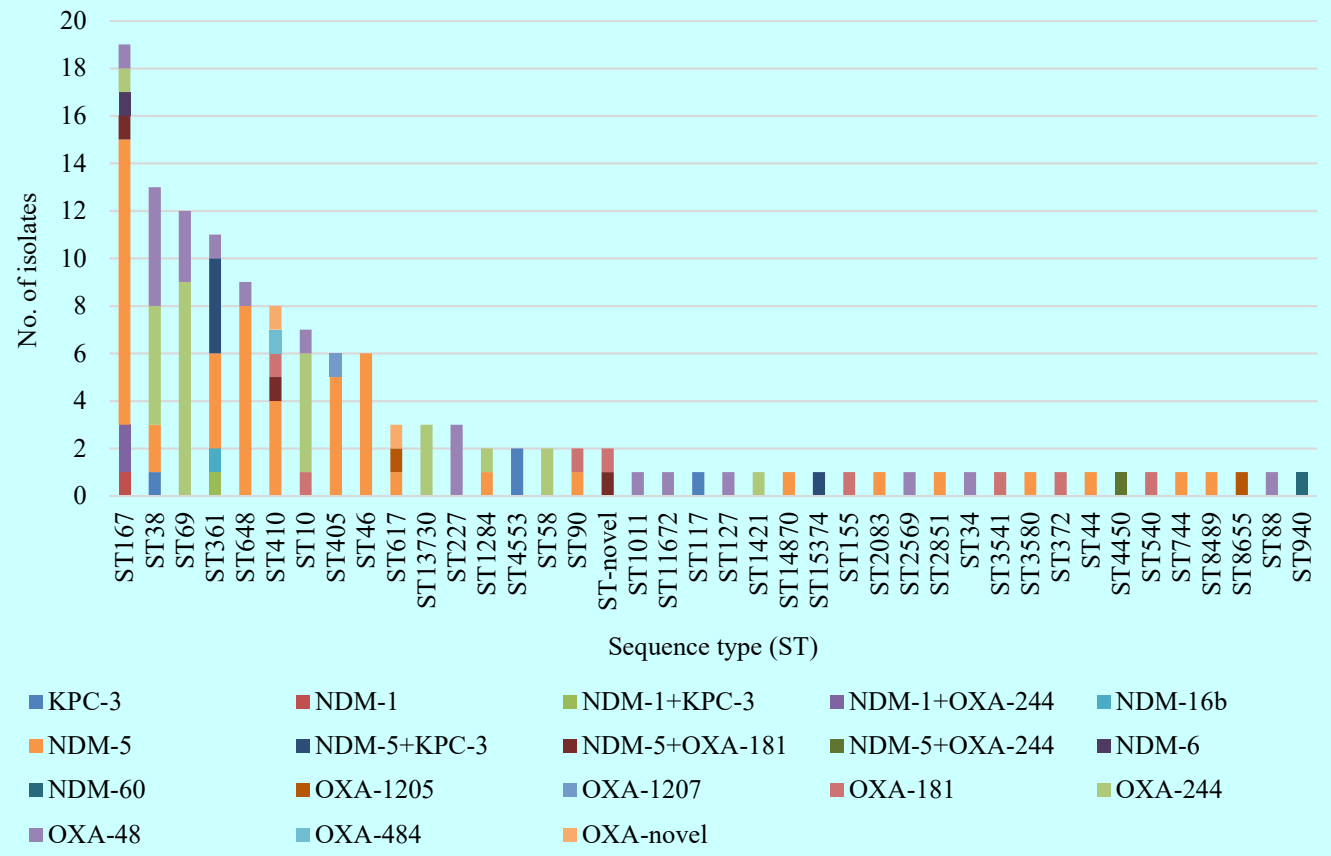

FIGURE 103. Carbapenemase variant distribution by STs among carbapenemase-producing *E. coli* identified in 2023 (n=133).

Phylogenetic analysis (core-genome multilocus sequence typing, cgMLST) of carbapenemase-producing *E. coli,* identified 11 clusters of 2-5 closely related isolates (Figure 104). Eight clusters consisted only of isolates associated with import. Isolates in four clusters were associated with import from Ukraine only (clusters 1, 4, 8 and 11). Two clusters consisted of isolates associated with import from Ukraine and one other country (clusters 2 and 3). Clusters 7 and 9 consisted of isolates associated with import from other countries than Ukraine. For these clusters the spread is anticipated to have occurred before import to Norway.

In cluster 10 consisting of three ST69-OXA-244 isolates, one isolate was associated with import from Ukraine, one not associated with import, and one with unclear import status. The isolates were identified within a time-frame of approximately seven months, at three different laboratories and no clear epidemiological links were identified between the isolates.

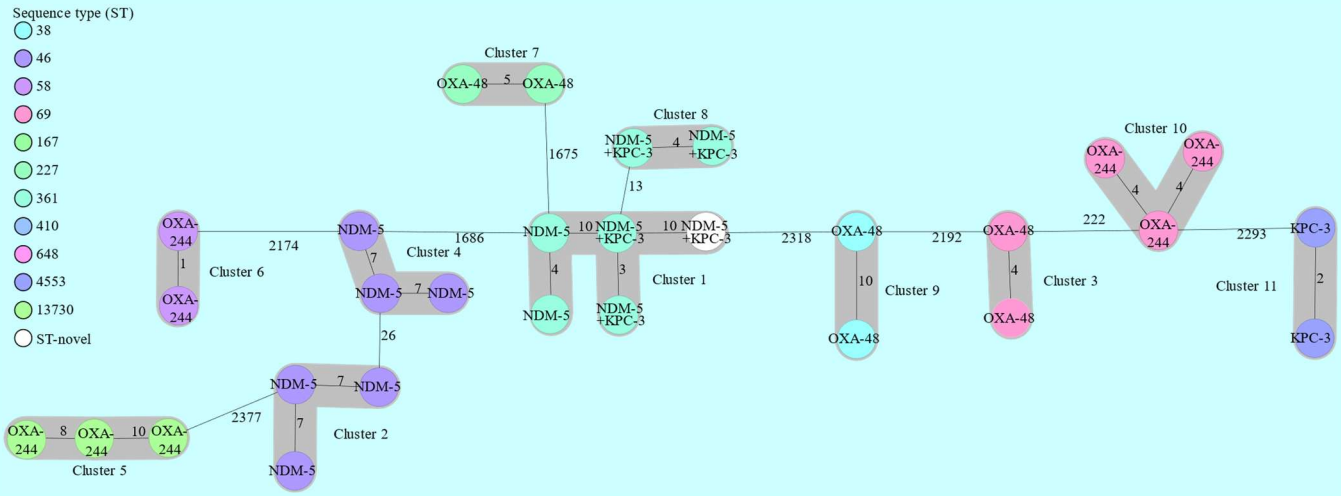

FIGURE 104. Minimum spanning network of closely related carbapenemase-producing *E. coli* identified in Norway 2023. The analysis is based on 2,513 core genome alleles using SeqSphere+ and *E. coli* K12 as reference genome. The isolates are represented by circles and coloured according to ST. Specific carbapenemase variants are indicated within each circle and number of allelic differences along the connecting lines. Grey shading between isolates indicate close relationship (≤10 allelic differences).

Two clusters, clusters 5 and cluster 6, consisted of isolates with no association to import. The three ST13730-OXA-244 isolates in cluster 5 were identified at two different laboratories approximately eight months apart. The two ST58-OXA-244 isolates in cluster 6 were also identified at different laboratories approximately six months apart. For both clusters no clear epidemiological links were identified.

A high level of diversity was also observed among the carbapenemase-producing *K. pneumoniae* isolates (n=121) with a minimum of 31 identified STs (Figure 105). One isolate belonged to a novel yet unassigned ST. As in previous years, the population was dominated by three global high-risk clones (5, 6); ST147 (n=38), ST395 (n=16) and ST307 (n=11). These represented 54% of the isolates. NDM-1 (n=31), OXA-48 (n=24) and NDM-1+OXA-48 (n=23) were the most common carbapenemase variants/combinations. NDM-9, associated with resistance to taniborbactam, a novel metallo-beta-lactamase (MBL) inhibitor under development in combination with cefepime (7, 8), was for the first time identified in Norway in three ST307 isolates. Three isolates associated to import from Ukraine belonged to ST23 (two with NDM-1+OXA-48 and one with OXA-48). ST23 is a known hypervirulent genomic background (5, 9) and the spread of carbapenemase-producing ST23 has been subject to a risk assessment by ECDC (10).

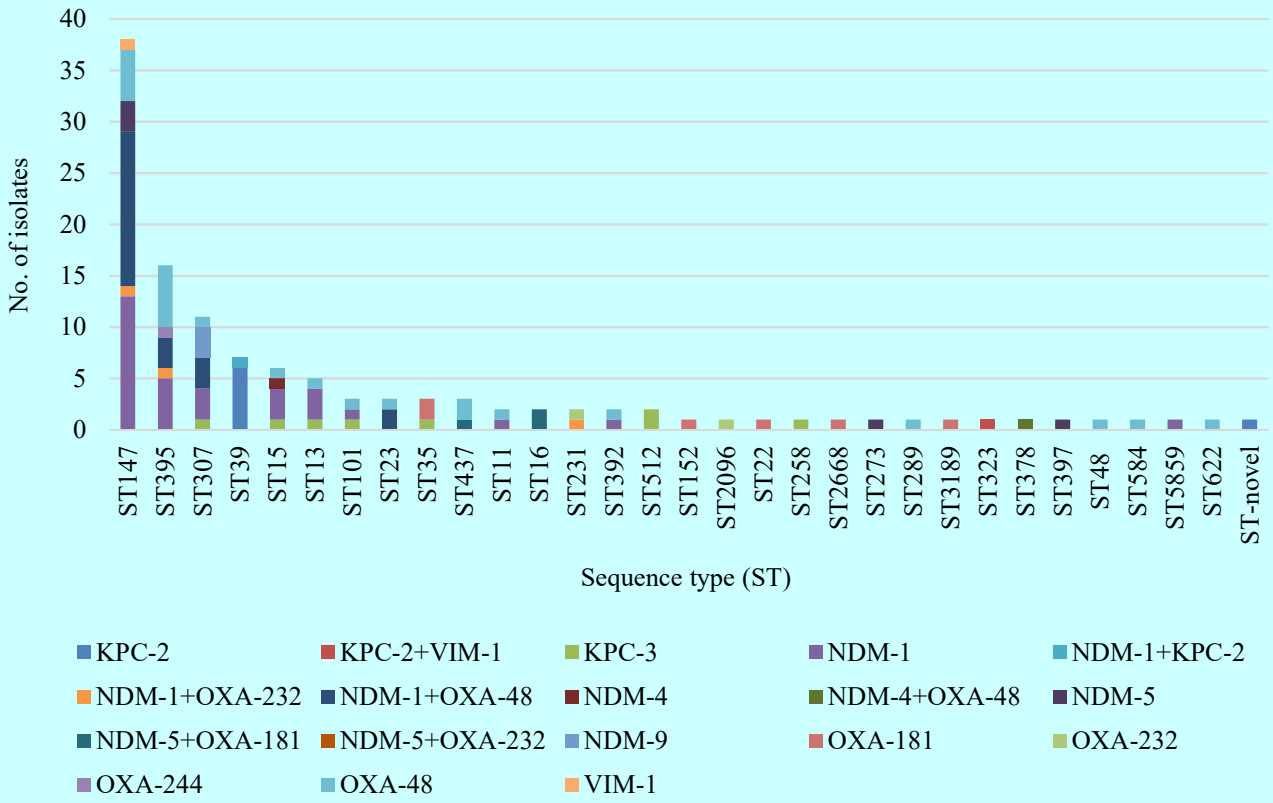

FIGURE 105. Carbapenemase variant by STs among the carbapenemase-producing *K. pneumoniae* isolates in 2023 (n=121).

Phylogenetic analysis of carbapenemase-producing *K. pneumoniae* revealed 13 clusters of 2-20 closely related isolates (Figure 106). Eleven clusters consisted exclusively of isolates associated with import. In ten of these, all isolates were associated with import from Ukraine (clusters 2, 3, 5, 6, 7, 8, 9, 10, 12 and 13), while in the additional cluster (cluster 11) the isolates were associated with import from Croatia. The isolates in several of these clusters were identified at different laboratories and over a long time-span.

The largest cluster (cluster 1), consisted of 20 ST147 isolates with either NDM-1+OXA-48 (n=15), OXA-48 (n=4) or NDM-1 (n=1). The isolates were identified at seven laboratories and from 19 patients. Association to import from Ukraine was identified for 17 patients. For one patient with ST147-OXA-48, association to import was suspected, but the country unknown. For one patient with ST147-NDM-1+OXA-48, association with import was unclear. These isolates came from two different laboratories within a 7.5-month period. Potential epidemiological links between the cases were not revealed.

One cluster (cluster 4) consisting of three ST307-NDM-9 isolates from three patients were identified at two laboratories within a 2.5-month period. The first isolate was associated with import from Ukraine while for the other two, no import was suspected. Epidemiological investigations confirmed possible connection as the patients had been admitted to the same hospital.

Finally, one ST22-OXA-181 isolate was identified in 2023 connected to a known long-term outbreak at one hospital in Norway.

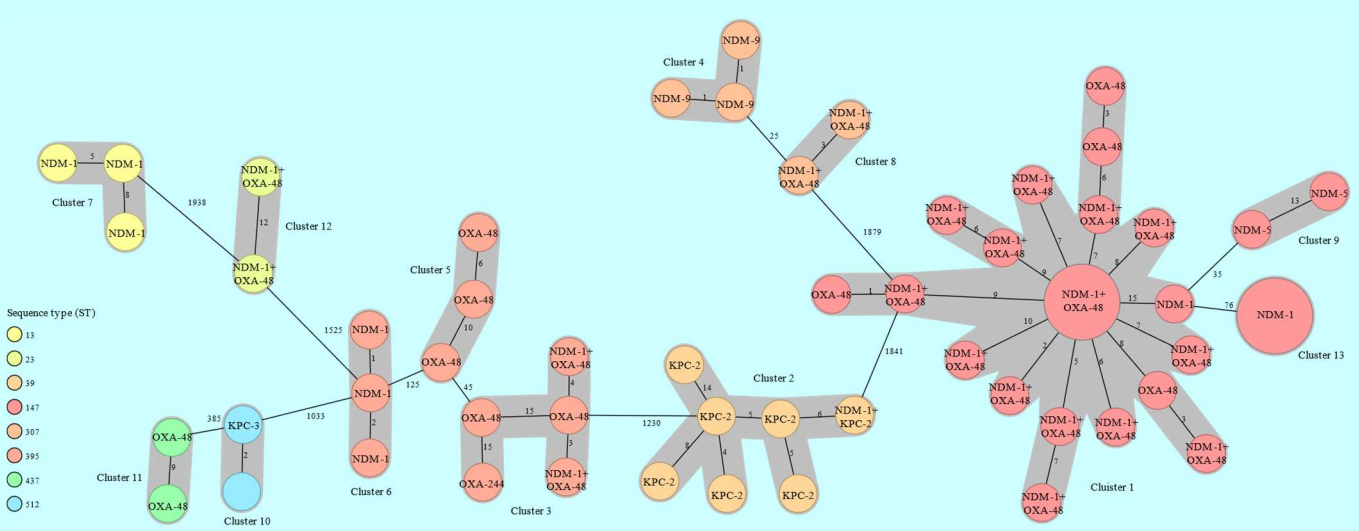

FIGURE 106. Minimum spanning network of closely related carbapenemase-producing *K. pneumoniae* identified in Norway 2023. The analysis is based on 2,358 core genome alleles using SeqSphere+ and *K. pneumoniae* NTUH-K2044 as reference genome. The isolates are represented by circles and coloured according to ST. Specific carbapenemase variants are indicated within each circle and number of allelic differences along the connecting lines. Grey shading between isolates indicate close relationship (≤15 allelic differences).

In total, 52 carbapenemase-producing non-*E. coli*/*K. pneumoniae* were identified in 2023 (Table 76) compared to 27 in 2022 (93% increase). The isolates were identified in 42 patients and 79% were associated with import. The genetic and epidemiological data do not indicate internal spread in Norway. Isolates with no or an unclear association with import, were of different species, ST or harboured different carbapenemase variants.

OXA-23-producing *Proteus mirabilis* was for the first time identified in Norway in 2023. OXA-23 is normally found in *Acinetobacter* spp. and rarely identified in *Enterobacterales.* However, there are several reports of *Acinetobacter* associated OXA-carbapenemases (e.g. OXA-23-like, OXA-24/-40-like and OXA-58-like) in *P. mirabilis* (11-13). Phenotypic identification in *Enterobacterales* is challenging due to the relatively low carbapenemase activity of these enzymes (11, 12). Analysis of a limited collection of OXA-23-producing *P. mirabilis* at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance and the EUCAST development laboratory showed that in some cases the meropenem zone diameter was higher than the current screening breakpoint dependent on producer of disks and media (unpublished data). In contrast to isolates with OXA-48-like carbapenemases, temocillin cannot be used as an indicator for carbapenemase-production. Resistance to amoxicillin-clavulanic acid has be suggested as an indicator for subsequent molecular analysis (11, 12).

TABLE 76. Sequence type (ST) and carbapenemase variants identified among other *Enterobacterales* species than *E. coli* and *K. pneumoniae* in Norway 2023 (n=52).

Species	ST-carbapenemase variant combination
C. freundii (*n*=3)	ST18-OXA-48+VIM-78 (*n*=1), ST22-OXA-48 (*n*=1), ST62-KPC-2 (*n*=1)
C. sedlakii (*n*=1)	ST682-NDM-5+OXA-48+OXA-181 (*n*=1)
C. werkmanii (*n*=1)	ST-novel-OXA-181 (*n*=1)
Citrobacter spp. (*n*=1)	ST-novel-OXA-48 (*n*=1)
E. asburiae (*n*=1)	ST252-NDM-7 (*n*=1)
E. bugandensis (*n*=3)	ST499-IMI-1 (*n*=1), ST901-IMI-1 (*n*=1), ST2528-IMI-1 (*n*=1)
E. cloacae (*n*=2)	ST373-IMI-1 (*n*=1), ST477.IMI-1 (*n*=1)
E. hormaechei (*n*=8)	ST90-VIM-1 (*n*=2), ST171-NDM-1 (*n*=1), ST231-NDM-1 (*n*=1), ST1483-OXA-48 (*n*=1), ST2942-NDM-1 (*n*=2), ST-novel-OXA-48 (*n*=1)
E. ludwigii (*n*=1)	ST-novel-OXA-48 (*n*=1)
E. mori (*n*=1)	ST-novel-IMP-1 (*n*=1)
Enterobacter spp. (*n*=3)	ST-novel-OXA-48 (*n*=2), ST487-OXA-48 (*n*=1)
K. aerogenes (*n*=2)	ST-novel-NDM-5 (*n*=1), ST-novel-KPC-2 (*n*=1)
K. michiganensis (*n*=2)	ST376-OXA-181 (*n*=1), ST-novel-VIM-1 (*n*=1)
K. oxytoca (*n*=1)	ST364-OXA-48 (*n*=1)
K. planticola (*n*=2)[1]	OXA-181 (*n*=2)
Kluyvera spp. (*n*=1)[1]	OXA-181 (*n*=1)
M. morganii (*n*=3)[1]	NDM-1 (*n*=1), OXA-48 (*n*=1), OXA-244 (*n*=1)
P. mirabilis (*n*=11)[1]	NDM-1 (*n*=10), OXA-23 (*n*=1)
P. stuartii (*n*=5)[1]	NDM-5 (*n*=3), NDM-1 (*n*=1), OXA-48 (*n*=1)

[1] MLST scheme not established

The antimicrobial susceptibility profile of all CPE isolates was determined with broth microdilution, except for cefiderocol that was analysed using disk diffusion (Figure 107). No marked changes were observed compared to the last two years. The results illustrate the limited treatment options available for infections with CPE. The level of resistance to meropenem and imipenem is similar to meropenem-vaborbactam and imipenem-relebactam. This is due to the large proportion of NDM and OXA-48-like that these inhibitors have no activity against (14). The level of resistance to ceftazidime-avibactam is also high (54%) which is due to the lack of activity of avibactam against MBLs (14). All isolates with class A (e.g. KPC, IMI) or class D (e.g. OXA-48-like) carbapenemases were susceptible to ceftazidime-avibactam. The combination aztreonam-avibactam has recently been approved and offers an alternative treatment option for infections with MBL-producing *Enterobacterales* since aztreonam is not affected by MBLs and that avibactam inhibits class A and D carbapenemases as well as ESBLs and AmpC enzymes. A high level of resistance (52%, 160/306 isolates) to cefiderocol is observed, but it is worth noting that 26% (79/306) of all isolates and 49% (79/160) of those interpreted as resistant had a zone diameter in the area of technical uncertainty (ATU) and were interpreted as resistant.

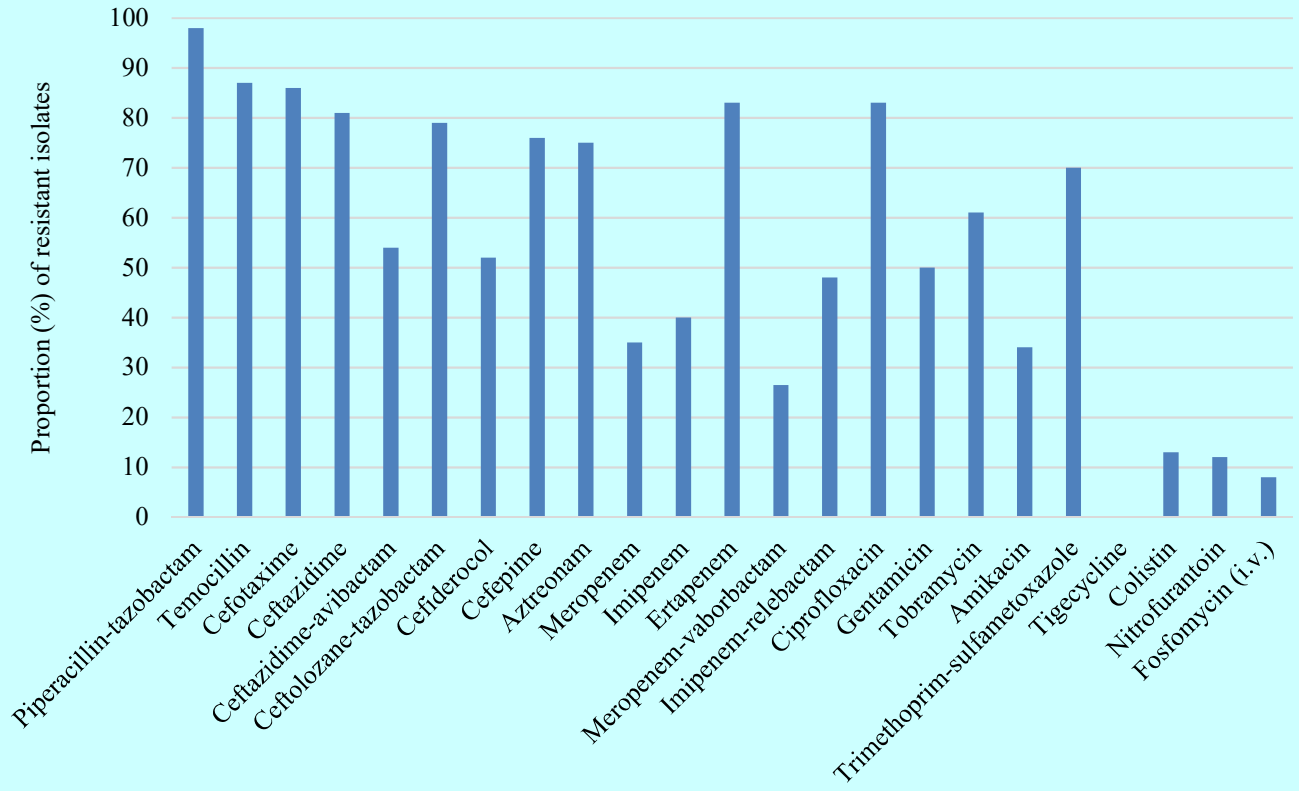

FIGURE 107. Proportion (%) of resistant isolates among CPE in 2023. Categorisation was done according to NordicAST breakpoint table v. 14. Cefiderocol data are based on disk diffusion and a zone diameter in the ATU (21-23 mm) was interpreted as resistant. Data for imipenem-relebactam relates to *Enterobacterales* except *Morganellaceae*. Piperacillin-tazobactam MIC (16 mg/L) and ciprofloxacin MIC (0.5 mg/L) in the ATU were interpreted as resistant. Data for temocillin are related to *E. coli*, *Klebsiella* spp. (except *K. aerogenes*) and *P. mirabilis*. Data for tigecycline, nitrofurantoin and fosfomycin (i.v.) are for *E. coli* only. Fosfomycin results must be interpreted with caution as the reference method is agar dilution.

***Pseudomonas* spp.**

In 2023, a total of 28 carbapenemase-producing *Pseudomonas* isolates were identified from 27 patients compared to 18 isolates in 2022 and four in 2021 (Figure 108). The majority of isolates were linked to import (n=24), primarily from Ukraine (n=16). Nine isolates were detected through screening, while nineteen were from clinical samples, with 5% from blood cultures and 21% from urine. One isolate was identified as *P. putida,* while the rest were *P. aeruginosa*. Two unrelated *P. aeruginosa* isolates with different carbapenemases were found in one of the patients.

The *P. aeruginosa* population was relatively heterogeneous, comprising ten different STs, including one unknown (Figure 109). The dominant clones were ST773 (n=8) and ST1047 (n=6), both primarily associated with known import from Ukraine, while six belonged to known global epidemic clones (ST111, ST235 and ST654) (15). NDM-1 was the most prevalent carbapenemase variant, present in all ST773-isolates. Except for one (VIM-2), all ST1047 isolates were positive for IMP-1. Overall, the following carbapenemases were detected: NDM-1 (n=10); IMP-1 (n=7); VIM-2 (n=6); GES-5 (n=2); VIM-1 (n=1); NDM-1+VIM-5 (n=1), and in *P. putida* (ST114): VIM-2.

Phylogenetic analysis based on cgMLST (Figure 109) showed close relatedness among all ST773 isolates (cluster 1; 1-10 allele differences), two clusters of closely related ST1047 isolates (clusters 2 and 3; 1 allele difference), and two other clusters (4 and 5). These closely related isolates were detected at various laboratories in Norway and were mainly associated with the same import country. Based on epidemiological data, there was no evidence of transmission between patients in Norwegian hospitals.

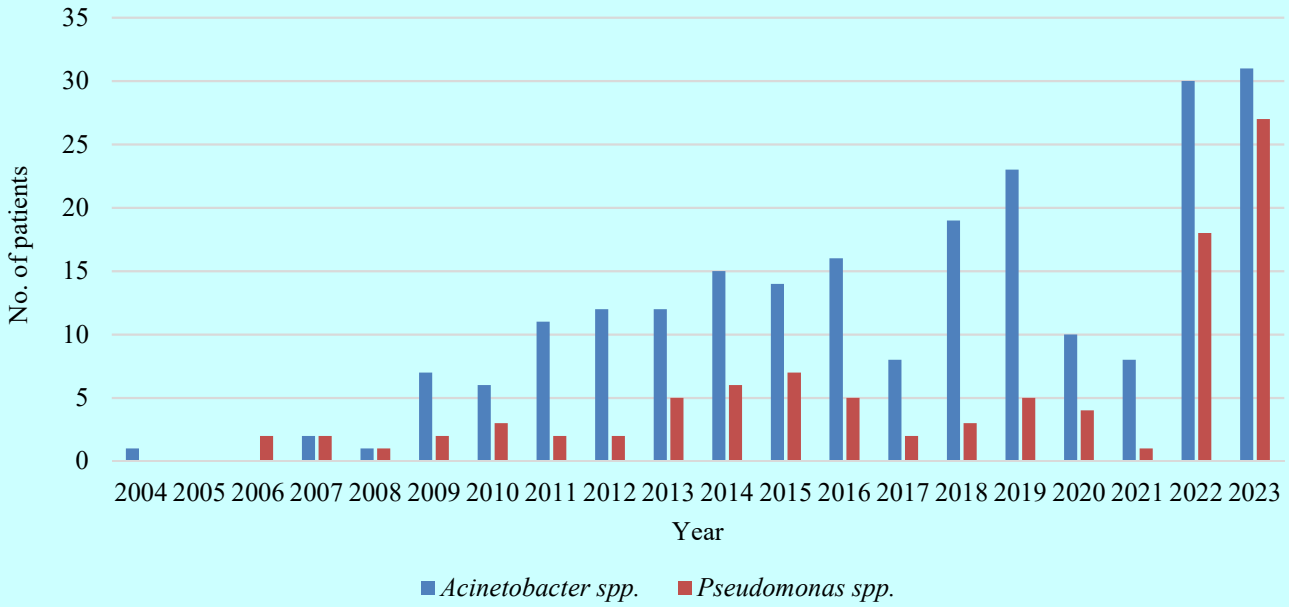

FIGURE 108. Number of patients with carbapenemase-producing *Pseudomonas* spp. and *Acinetobacter* spp. identified in Norway 2004-2023.

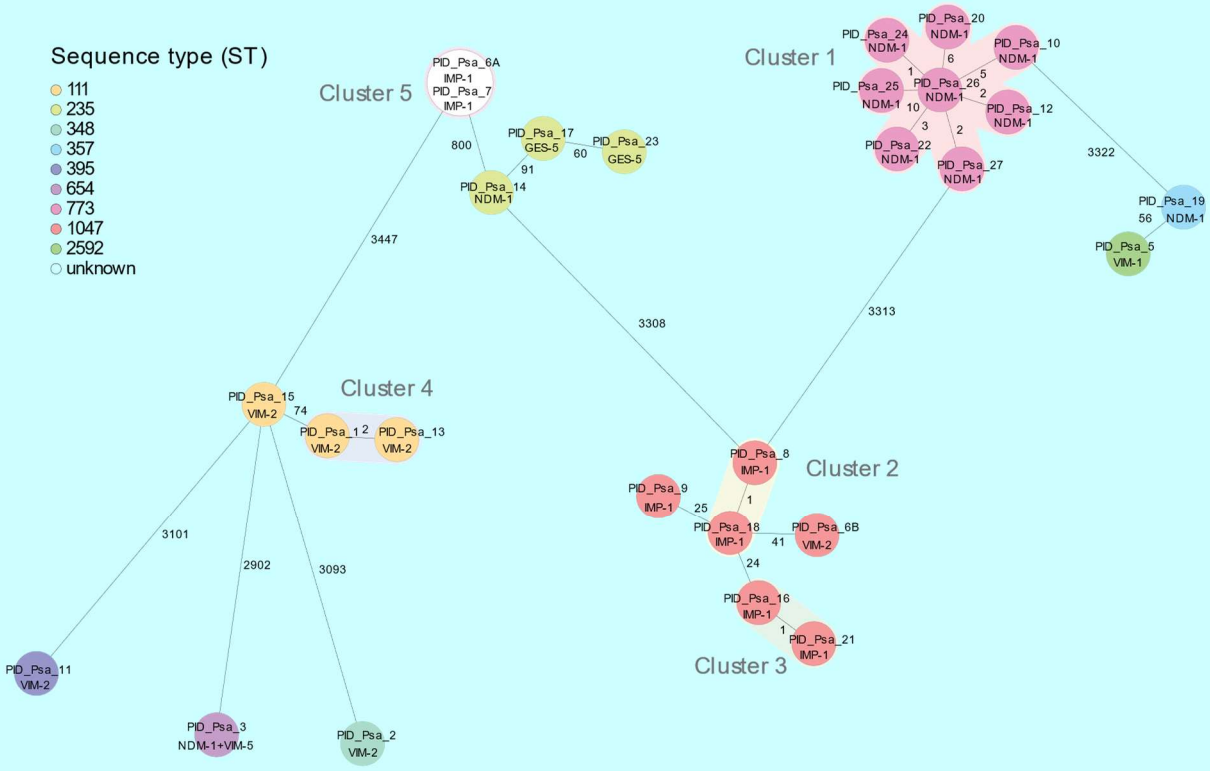

FIGURE 109. Minimum spanning network of carbapenemase-producing *P. aeruginosa* identified in Norway 2023 (n=26). The analysis is based on 3,867 core genome alleles using SeqSphere+ and *P. aeruginosa* PAO1 as a reference genome. The isolates are represented by circles with sizes corresponding to the number of isolates. Colouring indicates ST and specific carbapenemase variants shown within each circle. Clusters (1 to 5) of closely related isolates (≤12 allelic differences) are highlighted, and the number of allelic differences is given along the connecting lines.

***Acinetobacter* spp.**

Thirty-one patients with carbapenemase-producing *Acinetobacter* spp. were identified in 2023 compared to 30 patients in 2022 (Figure 108). Twenty-nine (94%) were associated with import of whom 17 (55%) from Ukraine. No link to import was found for one patient and for one the association to import was unknown. Thirteen of the isolates were identified through screening. One isolate was from blood culture.

Acinetobacter baumannii was the dominant species (n=30). One isolate was identified as *Acinetobacter pittii* and was not associated with import. The *A. baumannii* population was dominated by three clones; ST2 (n=14), ST19 (n=7) and ST78 (n=4) (Table 77). All three STs belong to global high-risk clones (16,17). OXA-23 was the dominant carbapenemase variant identified in 19 isolates. All ST78 isolates and the *A. pittii* isolate harboured OXA-72 (OXA-24/-40 variant). NDM-1 alone or in combination with OXA-72 was identified in three isolates.

TABLE 77. Sequence type (ST) and carbapenemase variant combination among *A. baumannii* (n=30) in Norway 2023.

ST	Carbapenemase variant
ST2 (n=14)	OXA-23 (n=12), NDM-1+OXA-72 (n=1), OXA-23+OXA-72 (n=1)
ST19 (n=7)	OXA-23 (n=5), OXA-72 (n=2)
ST78 (n=4)	OXA-72 (n=4)
ST15 (n=1)	NDM-1 (n=1)
ST46 (n=1)	OXA-72 (n=1)
ST164 (n=1)	OXA-23+OXA-58 (n=1)
ST492 (n=1)	NDM-1+OXA-72 (n=1)
ST1077 (n=1)	OXA-72 (n=1)

Phylogenetic analysis identified two clusters of closely related isolates (Figure 110). Cluster 1 consisted of four ST2-OXA-23 isolates identified at three laboratories and all were associated with import from Ukraine. Cluster 2 consisted of three ST19-OXA-23 isolates identified at the same laboratory and associated with import from Ukraine. Domestic spread was not identified in 2023.

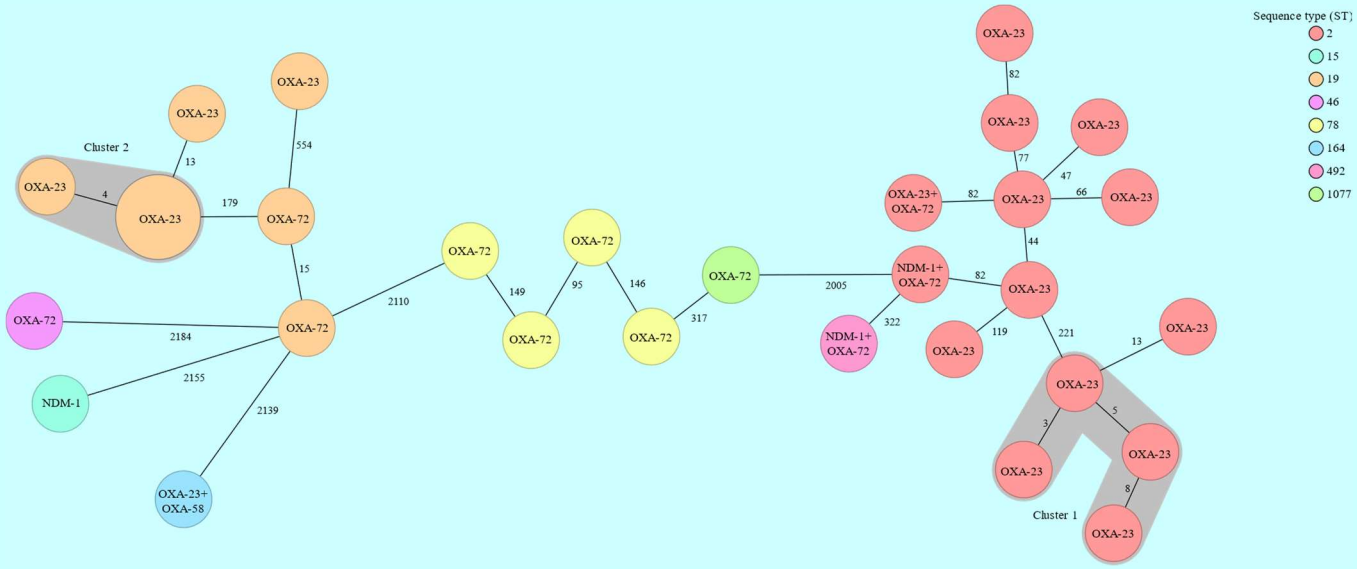

FIGURE 110. Minimum spanning network of carbapenemase-producing *A. baumannii* identified in Norway 2023. The analysis is based on 2,390 core genome alleles using SeqSphere+ and *A. baumannii* ACICU as reference genome. The isolates are represented by circles and coloured according to ST. Specific carbapenemase variants are indicated within each circle and number of allelic differences along the connecting lines. Grey shading between isolates indicates close relationship (≤9 allelic differences).

All *Acinetobacter* spp. isolates were resistant to meropenem and imipenem and the level of resistance to other relevant antibiotics was high (Table 78).

TABLE 78. Proportion (%) resistant isolates among the carbapenemase-producing *Acinetobacter* spp. (n=31).

Antibiotic	Proportion of resistant isolates
Meropenem	100 %
Imipenem	100 %
Ciprofloxacin	97 %
Amikacin	90 %
Gentamicin	74 %
Tobramycin	65 %
Trimethoprim-sulfamethoxazole	81 %
Colistin	10 %

Conclusion

The prevalence of carbapenemase-producing Gram-negative bacteria continues to increase in Norway. In particular the incidence of CPE increased from 2.8 per 100,000 person-years in 2022 to 4.3 in 2023. The number of patients with carbapenemase-producing *Pseudomonas* spp. also increased from 18 in 2022 to 27 in 2023 (50% increase). The number of patients with carbapenemase-producing *Acinetobacter* spp. was stable. The increase is largely associated to import particularly from Ukraine. No link to import or unknown import association were revealed for 20% of the patients with carbapenemase-producing organisms. The genomic analysis shows that the diversity of genetic backgrounds and carbapenemase variants increases. Clusters of closely related isolates were identified mainly consisting of isolates associated with import from Ukraine. It is anticipated that the dissemination the Ukrainian-related clones occurred before arrival in Norway. Domestic spread was identified, but it is so far limited. However, the increasing prevalence should raise the awareness for domestic spread. Interregional transmission was not observed.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 79. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2023 (n=121). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin*	≤ 1	> 1	78.5	-	21.5
Amoxicillin-clavulanic acid**	≤ 2	> 2	95.9	-	4.1
Cefuroxime**	≤ 1	> 2	76.9	12.4	10.7
Cefotaxime	≤ 0.125	> 0.125	98.3	-	1.7
Ceftriaxone	≤ 0.125	> 0.125	98.3	-	1.7
Meropenem*	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.06	> 0.06	99.2	-	0.8
Chloramphenicol	≤ 2	> 2	99.2	-	0.8
Tetracycline	≤ 2	> 2	98.3	-	1.7
Trimethoprim-sulfamethoxazole***	≤ 0.5	> 1	86.0	4.1	9.9
Beta-lactamase	Negative	Positive	84.3	-	15.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis. **Breakpoints for intravenous administration. ***Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 80. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2023 (n=121). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Ampicillin*			0.8		0.8	5.0	20.7	44.6	6.6	5.0	0.8	1.7	3.3	2.5	2.5	5.8
Amoxi-clav**			0.8		0.8	3.3	5.0	35.5	39.7	10.7	2.5	0.8	0.8			
Cefuroxime**			0.8			0.8	3.3	9.9	62.0	12.4	4.1	1.7	2.5	0.8	0.8	0.8
Cefotaxime	1.7	4.1	18.2	48.8	18.2	7.4			0.8	0.8						
Ceftriaxone			90.1	7.4	0.8			1.7								
Meropenem*	0.8		3.3	7.4	36.4	40.5	9.9	1.7								
Ciprofloxacin*	14.0	35.5	49.6				0.8									
Chloramp.							2.5	41.3	54.5	0.8			0.8			
Tetracycline			0.8		0.8	1.7	17.4	73.6	4.1				1.7			
TMS***	2.5	5.8	25.6	38.0	8.3	2.5	0.8	2.5	4.1		1.7	1.7	0.8	5.8		

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *Breakpoints for indications other than meningitis. **Breakpoints for intravenous administration. ***Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Systemic *H. influenzae* isolates were first included in the NORM surveillance programme in 2013. Resistance data are provided on an annual basis by the Reference Laboratory at the Norwegian Institute of Public Health. The number of isolates was limited in 2021 due to the pandemic (n=63), but the occurrence has returned to pre-pandemic levels in 2022 (n=130) and 2023 (n=121). Only a single isolate was retrieved from a cerebrospinal fluid, and all isolates represented unique patients (Tables 79-80). The EUCAST/NordicAST breakpoints remained unchanged.

Different substrates have been suggested for screening of beta-lactam resistance in *H. influenzae*. The penicillin G 1U disk (PCG1) successfully identified almost all ampicillin (26/26) and cefuroxime (12/13) resistant isolates. Twenty-two out of 102 (21.6%) beta-lactamase negative isolates were resistant to PCG1. Seven and ten of these isolates were resistant to ampicillin and cefuroxime, respectively, and only nine remained fully susceptible to both agents. The rate of ampicillin resistance increased from 14.6% in 2022 to 21.5% in 2023, but this is in line with the 20.6% rate of resistance in 2021. Beta-lactamase production was detected in 19/121 (15.7%), which is higher than in 2021 (12.7%) and 2022 (10.8%), but at the same level as in the pre-pandemic years 2016 (17.3%) and 2017 (17.8%).

A cefuroxime MIC > 2 mg/L has been suggested as the most accurate indicator for chromosomal beta-lactam resistance encoded by alterations in the PBP3 sequence. Thirteen isolates (10.7%) displayed this phenotype as compared to 9.5% in 2021 and 10.0% in 2022. Eight of these isolates were also resistant to ampicillin and five were resistant to amoxicillin-clavulanic acid. Most (11/13) cefuroxime resistant isolates were beta-lactamase negative. Two isolates were resistant to cefotaxime (MIC 1-2 mg/L) and ceftriaxone (MIC 0.5 mg/L), but all isolates remained susceptible to meropenem. As observed in previous surveys of systemic *H. influenzae* isolates, resistance rates to ciprofloxacin (0.8%), tetracycline (1.7%) and chloramphenicol (0.8%) were very low. The 9.9% resistance rate to trimethoprim-sulfamethoxazole was lower than in 2021 (15.9%) and 2022 (13.1%).

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 81. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2023 (n=13). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G*	≤ 0.25	> 0.25	92.3	-	7.7
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Ciprofloxacin	≤ 0.016	> 0.016	100.0	-	0.0
Chloramphenicol	≤ 2	> 2	100.0	-	0.0
Rifampicin	≤ 0.25	> 0.25	100.0	-	0.0
Tetracycline	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Penicillin G=Benzylpenicillin.

TABLE 82. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2023 (n=13). Distribution (n) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*					4	6	2	1								
Ceftriaxone			13													
Ciprofloxacin	13															
Chloramph.								3	10							
Rifampicin	3	3	6			1										
Tetracycline					1	5	3	4								
Azithromycin								1	6	6						

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *Penicillin G=Benzylpenicillin.

RESULTS AND COMMENTS

N. meningitidis from blood cultures and cerebrospinal fluids were first included in NORM in 2013. The Reference Laboratory at the Norwegian Institute of Public Health provides data for *N. meningitidis* on an annual basis. The EUCAST/NordicAST breakpoint remained unchanged from the previous year. Results are presented in Tables 81-82.

Thirteen isolates were received from the 16 reported cases of systemic infections caused by *N. meningitidis* in 2023. Two isolates were recovered from cerebrospinal fluids (CSF), and one of these patients also had *N. meningitidis* in blood culture. One isolate from a throat swab was also included, as it was recovered from a patient who died of invasive meningococcal disease. The throat isolate had the same characteristics as the meningococcal DNA found in the CSF of the patient.

There were no known associations between the cases. The number of isolates is a slight increase from four, five and nine isolates in the pandemic years 2020-2022, respectively. The isolates belonged to serogroups B (n=4), Y (n=4), W (n=2), W/Y (n=1), C (n=1) and A (n=1). While serogroup A cases had not been seen in Norway after 2006, one first case occurred in 2022 and another one in 2023. This last case was a patient returning from travel in Central Asia.

The four serogroup B isolates belonged to four different sequence types (STs) while the four serogroup Y isolates were ST-23. The serogroup A isolate was genetically related but somewhat different from the one identified in 2022. The serogroup C isolate belonged to the ST-11 clonal complex.

A single meningococcal isolate had an MIC of 0.5 mg/L to penicillin G and was thus resistant to this agent. No resistance according to clinical breakpoints was detected for any of the other antimicrobials tested. EUCAST/NordicAST has not established breakpoints for azithromycin, but the MIC distribution does not indicate the presence of acquired macrolide resistance (Table 82).

Neisseria gonorrhoeae

TABLE 83. *Neisseria gonorrhoeae* from all specimen types in 2023 (n=1,500). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G*	≤ 0.06	> 1	4.2	80.1	15.7
Ceftriaxone	≤ 0.125	> 0.125	99.9	-	0.1
Cefixime	≤ 0.125	> 0.125	99.9	-	0.1
Ciprofloxacin	≤ 0.03	> 0.06	48.5	0.2	51.3
Tetracycline	≤ 0.5	> 0.5	65.1	-	34.9
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	86.3	-	13.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Penicillin G=Benzylpenicillin.

TABLE 84. *Neisseria gonorrhoeae* from all specimen types in 2023 (n=1,500) Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*		0.1	1.0	0.9	2.3	13.1	30.3	27.3	9.5	6.9	2.5	4.2	0.9	1.1		
Ceftriaxone	33.1	7.8	52.1	6.3	0.6	0.1	0.1	0.1								
Cefixime			71.8	14.7	12.1	1.3			0.1	0.1						
Ciprofloxacin	30.4	14.3	2.9	0.9	0.2	1.1	0.8	2.1	7.2	14.9	12.7	8.0	2.2	2.4		
Tetracycline	0.1			0.5	1.7	8.9	24.1	29.7	19.4	2.4	0.9	2.5	6.9	2.5	0.3	0.1
Spectinomycin									0.1	0.1	0.5	14.5	58.4	25.8	0.7	
Azithromycin			0.3	2.7	7.1	10.3	20.8	16.9	17.5	16.4	4.7	0.6	0.3	0.4	0.4	1.5

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *Penicillin G=Benzylpenicillin.

RESULTS AND COMMENTS

Neisseria gonorrhoeae was surveyed in NORM in 2003 and 2010, and then yearly since 2013 by the Reference Laboratory at the Norwegian Institute of Public Health in collaboration with Oslo University Hospital. In 2023, a total of 1,500 gonococcal isolates were available for further analyses. This is a further dramatic increase from 2021 (n=220) and 2022 (n=827). The proportion of cases with positive culture among all reported cases (including PCR-only positives) has gradually increased from 39.6% (220/555) in 2021 and 44.5% (827/1,857) in 2022, to 50.3% (1,500/2,985) in 2023. This may suggest a combination of an increased culture positivity rate and true epidemiological changes in the population.

From some patients several isolates were collected from different clinical sites at the same point of time. Thus, the Reference Laboratory received in 2023 isolates from 1,411 unique episodes of infection. The isolates in 2023 were recovered from urethra (n=504), cervix uteri/vagina (n=311), anus (n=247), throat (n=232), eye (n=10) or "others/unknown" (n=196). A total of 931 (62.1%) isolates were from men and 569 (37.9%) from women. The predominance of men has decreased as the corresponding figures for 2022 were 75.9% men and 24.1% women. The geographical location where the infections were acquired was in most cases unknown to the laboratory. From MSIS it is reported that gonococcal infections often are acquired abroad, but with increasing secondary transmission in sexual networks within Norway.

The dominant sequence type (ST), ST-1580, continued to increase in proportion from 16% in 2022 to 28% in 2023. Two-third (66%) of these ST-1580 infections were in women.

The results from susceptibility testing are presented in Tables 83-84. A majority of isolates were either susceptible only to increased exposure (80.1%) or resistant (15.7%) to penicillin G. The corresponding figures for 2022 were 78.2% and 17.8%, respectively. A total of 206 isolates (13.7%) produced beta-lactamase, which is a slight decrease from 2021 (17.3%) and 2022 (16.4%). Practically all beta-lactamase positive isolates (193/206, 93.7%) were also resistant to ciprofloxacin. Fifty-five isolates (4.3%) were resistant and 1,176 (90.9%) were only susceptible to increased exposure to penicillin G in spite of being beta-lactamase negative. This illustrates the complex mechanisms for penicillin resistance in this species.

Two isolates were resistant to ceftriaxone (MIC 0.25 and 0.5 mg/L, respectively) and cefixime (MIC 1 and 2 mg/L, respectively). Ceftriaxone resistant isolates from Norway have previously been linked to treatment failure. The oral cephalosporin cefixime is no longer recommended for empirical treatment in Europe. The results confirm the emergence of cephalosporin resistant gonococci in Norway. The standard treatment for gonorrhoeae is now ceftriaxone alone. Azithromycin was previously used in a combination with ceftriaxone, but 24.4% of the isolates displayed azithromycin MIC values above the EUCAST screening breakpoint for acquired resistance of 1 mg/L. The corresponding figure for 2022 was 21.2%. The prevalence of ciprofloxacin resistance persisted at a high level (51.3%) in 2023. Ciprofloxacin is consequently not a viable alternative except in cases where susceptibility has been documented. All strains were susceptible to spectinomycin.

Staphylococcus aureus in blood cultures

TABLE 85. *Staphylococcus aureus* blood culture isolates in 2023 (n=1,695). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 1	93.2	-	6.8
Clindamycin	≤ 0.25	> 0.25	98.9	-	1.1
Fusidic acid	≤ 1	> 1	96.3	-	3.7
Ciprofloxacin	≤ 0.001	> 2	0.0	96.9	3.1
Gentamicin	≤ 2	> 2	98.8	-	1.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	99.1	-	0.9
Tetracycline	≤ 1	> 1	97.1	-	2.9
Tigecycline	≤ 0.5	> 0.5	99.6	-	0.4
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.5	0.0	0.5
Beta-lactamase	Negative	Positive	32.0	-	68.0
Cefoxitin screen	≥ 22	< 22	98.2	-	1.8
MRSA** (*mecA*)	Negative	Positive	98.2	-	1.8

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. **MRSA=Methicillin resistant *Staphylococcus aureus*.

RESULTS AND COMMENTS

S. aureus blood culture isolates have been included in the NORM surveillance programme since it was initiated in 2000. For the 2023 data, the most recent EUCAST/ NordicAST breakpoint protocol was applied. The breakpoints for resistance to erythromycin and tetracycline have both been reduced from R > 2 mg/L to R > 1 mg/L, thus eliminating the I category of susceptible to increased exposure. For historical comparison, the present R categories correspond to the combined I+R categories in previous years. The breakpoint for resistance to ciprofloxacin was increased from R > 1 mg/L to R > 2 mg/L from 2024 onwards.

Thirty-one methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2023, corresponding to a prevalence of 1.8% (Table 85). This is a slight increase from 0.8% in 2021 and 1.0% in 2022. The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from 13 different hospitals, and there was no significant clustering among institutions. Laboratory screening for MRSA in NORM is performed using cefoxitin disks and there was full concordance between cefoxitin and *mecA* PCR results. Some MRSA isolates were concomitantly resistant to ciprofloxacin (15/31), erythromycin (11/31), tetracycline (9/31), gentamicin (7/31), clindamycin (3/31), rifampicin (1/31), trimethoprim-sulfamethoxazole (1/31) and/or fusidic acid (1/31). All MRSA isolates were susceptible to linezolid. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 88 on page 146. The NORM findings are at the same level as reported from the databases of the participating laboratories where 39 out of 2,182 (1.8%) *S. aureus* blood culture isolates were MRSA. None of the 14 *S. aureus* isolates recovered from cerebrospinal fluid were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 39/2,196 (1.8%). This is an increase from 1.0% in 2022.

One hundred sixteen *S. aureus* isolates (6.8%) were resistant to erythromycin. This is at the same level as 6.0% in 2021 and 5.5% in 2022. The macrolide resistance phenotypes of erythromycin resistant isolates were determined by the double disk diffusion (DDD) test. Three isolates (3%) were constitutively MLS_B resistant, 91 (78%) were inducibly MLS_B resistant, and 22 (19%) displayed efflux mediated M-type resistance. These figures represent 0.2%, 5.4% and 1.3% of all *S. aureus* isolates from blood cultures, respectively. The proportion with M-type resistance was lower and the proportion with inducible MLS_B resistance was higher than in 2022.

The prevalence of resistance to fusidic acid (3.7%) was at the same level as 3.8% in 2022 and 4.4% in 2022. The 3.1% prevalence of ciprofloxacin resistance is a further decline from 8.8% in 2021 and 4.9% in 2022, but this may in part be explained by an adjustment of the resistance breakpoint (see above). It should be noted that the wild type population of *S. aureus* is defined as susceptible only to increased exposure to this agent. There were no significant changes for gentamicin, rifampicin, tigecycline or trimethoprim-sulfamethoxazole. All isolates were fully susceptible to linezolid. The general test panel for *S. aureus* did not include vancomycin in 2023.

Figure 111 shows the prevalence of resistance to various antimicrobials. A total of 68.0% of the isolates were beta-lactamase positive, which is unchanged from 68.2% in 2021 and 68.5% in 2022. There were no significant differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

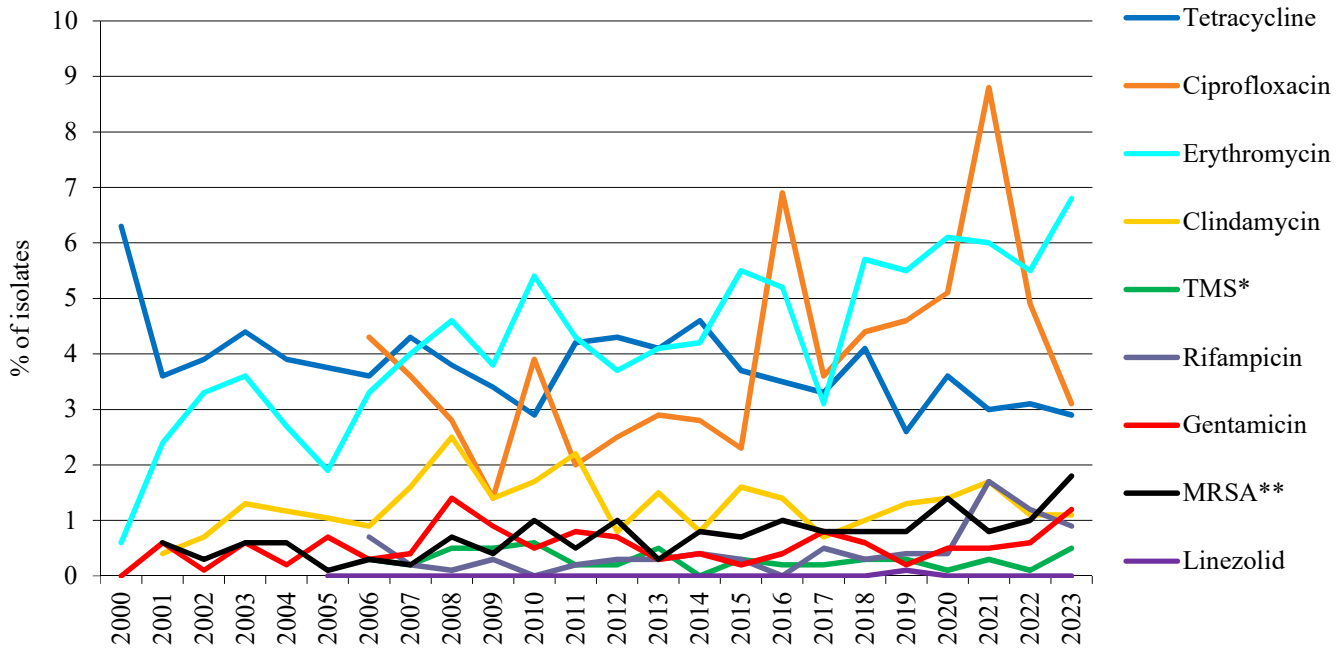

FIGURE 111. Prevalences of antimicrobial resistance among *Staphylococcus aureus* blood culture isolates 2000-2023. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Staphylococcus aureus in wound specimens

TABLE 86. *Staphylococcus aureus* isolates in wound specimens in 2023 (n=898). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 1	92.8	-	7.2
Clindamycin	≤ 0.25	> 0.25	98.2	-	1.8
Fusidic acid	≤ 1	> 1	94.1	-	5.9
Ciprofloxacin	≤ 0.001	> 2	0.0	98.0	2.0
Gentamicin	≤ 2	> 2	99.1	-	0.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	98.6	-	1.4
Tetracycline	≤ 1	> 1	96.8	-	3.2
Tigecycline	≤ 0.5	> 0.5	99.2	-	0.8
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.8	0.1	0.1
Beta-lactamase	Negative	Positive	31.0	-	69.0
Cefoxitin screen	≥ 22	< 22	98.7	-	1.3
MRSA** (*mecA*)	Negative	Positive	98.7	-	1.3

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. **MRSA=Methicillin resistant *Staphylococcus aureus*.

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Twelve out of 898 (1.3%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at the same level as in 2021 (1.5%) and 2022 (1.6%). The MRSA isolates originated from patients visiting general practitioners (n=5), hospital wards (n=4), outpatient clinics (n=2) and a nursing home (n=1) in different parts of the country. Most MRSA isolates (8/12) were co-resistant to erythromycin (3/12), ciprofloxacin (2/12), tetracycline (3/12), fusidic acid (3/12), clindamycin (n=2) and/or gentamicin (2/12) in different combinations. All MRSA isolates were susceptible to tigecycline, rifampicin, trimethoprim-sulfamethoxazole and linezolid. No isolates were reported with zone diameters below the cefoxitin screening breakpoint without being confirmed as MRSA by *mecA* PCR. This indicates high specificity of the cefoxitin screen as well as a low prevalence of *mecC* MRSA (see page 147).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates decreased from 7.1% in 2022 to 5.9% in 2023 (Table 86 and Figure 112). The prevalence of this phenotype has thus stabilised after the previous epidemic which peaked at 25.0% in 2004. The prevalence of resistance to fusidic acid is still lower in blood culture isolates (3.7%) than in wound isolates (5.9%). For other antimicrobial agents such as gentamicin, rifampicin, trimethoprim-sulfamethoxazole and tetracycline there were only minor changes from 2022-2023, and the prevalence of resistance was in general similar for blood culture isolates and isolates from wound specimens. All isolates were phenotypically susceptible to linezolid.

Sixty-five (7.2%) isolates were resistant to erythromycin. This is an increase from 5.8% in 2022, but lower than 8.5% in 2021. The rates include the former I category due to a change of the breakpoint for resistance (see above). All erythromycin resistant isolates were further examined to determine the macrolide resistance phenotype. The majority were either inducibly (53/65; 82% of erythromycin resistant isolates) or constitutively (4/65; 6% of erythromycin resistant isolates) resistant to clindamycin, thus representing the $iMLS_B$ and $cMLS_B$ phenotypes, respectively. A minor proportion of the isolates displayed low-level resistance to erythromycin only (8/65; 12% of erythromycin resistant isolates) which is compatible with efflux mediated M-type resistance. The findings are in accordance with the results from previous years.

A total of 69.0% of the isolates were beta-lactamase positive compared to 69.7% in 2021 and 69.8% in 2022. There were no significant differences in non-betalactam resistance rates between beta-lactamase negative and positive isolates.

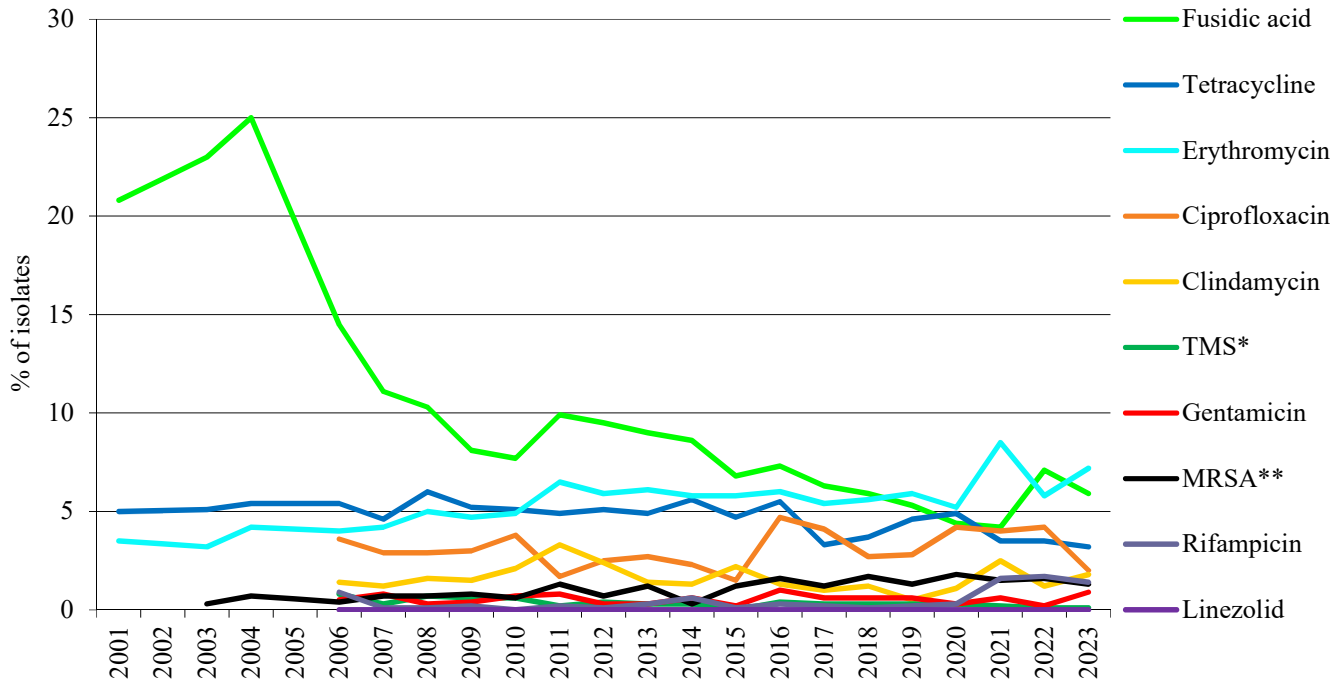

FIGURE 112. Prevalence of antimicrobial resistance among *Staphylococcus aureus* wound isolates 2001-2023. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2023

The number of persons reported with MRSA in Norway was 2,544 in 2023, a 27% increase compared to 2022 (2,008 persons). After a decrease in notified cases during the COVID-19 pandemic (1,659 people in 2021), MRSA cases increased and are now back to the level of the peak year 2016 (2,424 people). The decrease in MRSA cases in 2020 and 2021 was probably influenced by prevention and control of COVID-19. Of the people who were reported diagnosed with MRSA to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2023, 1,109 (44%) persons were reported with MRSA infection and 1,435 (56%) with colonisation. The incidence rate in the form of all MRSA cases per 100,000 person-years was 46, and 20 and 26 for infections and colonisations respectively (Figure 113).

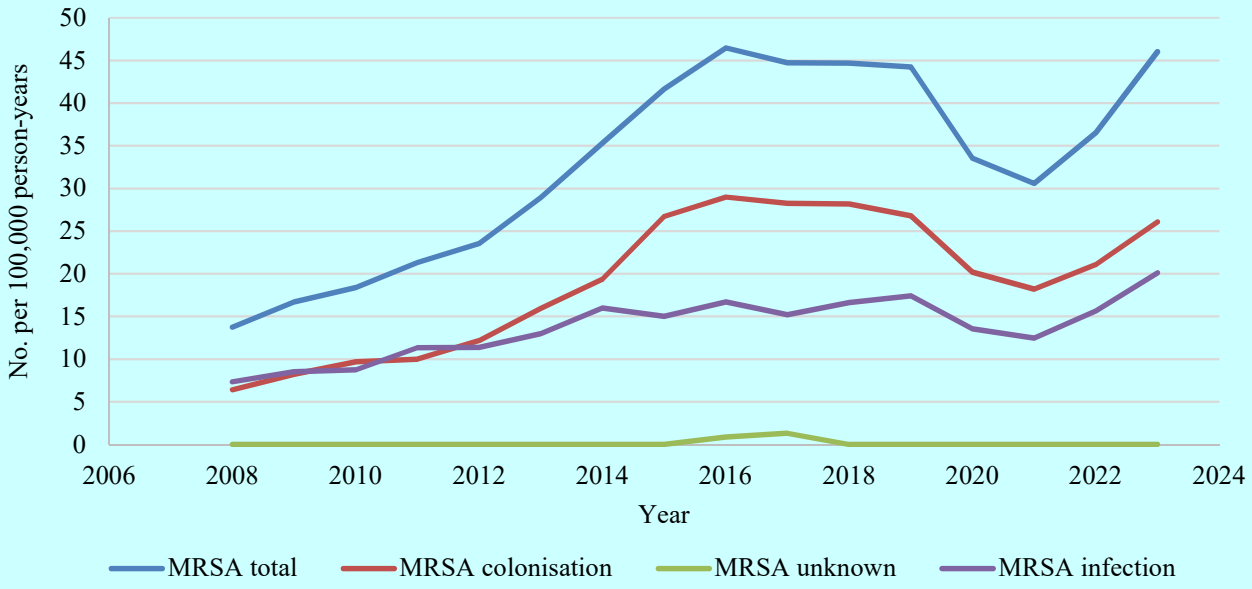

FIGURE 113. Number of persons notified with MRSA per 100,000 person-years in Norway 2008-2023, by infection and colonisation.

In 2023, a total of 670 (26 %) persons were reported to have acquired MRSA during travel abroad or prior to coming to Norway, while 799 (31 %) persons were reported to have acquired MRSA in Norway. It is important to note that 43% of all reported cases lack information about possible place of infection (Figure 114).

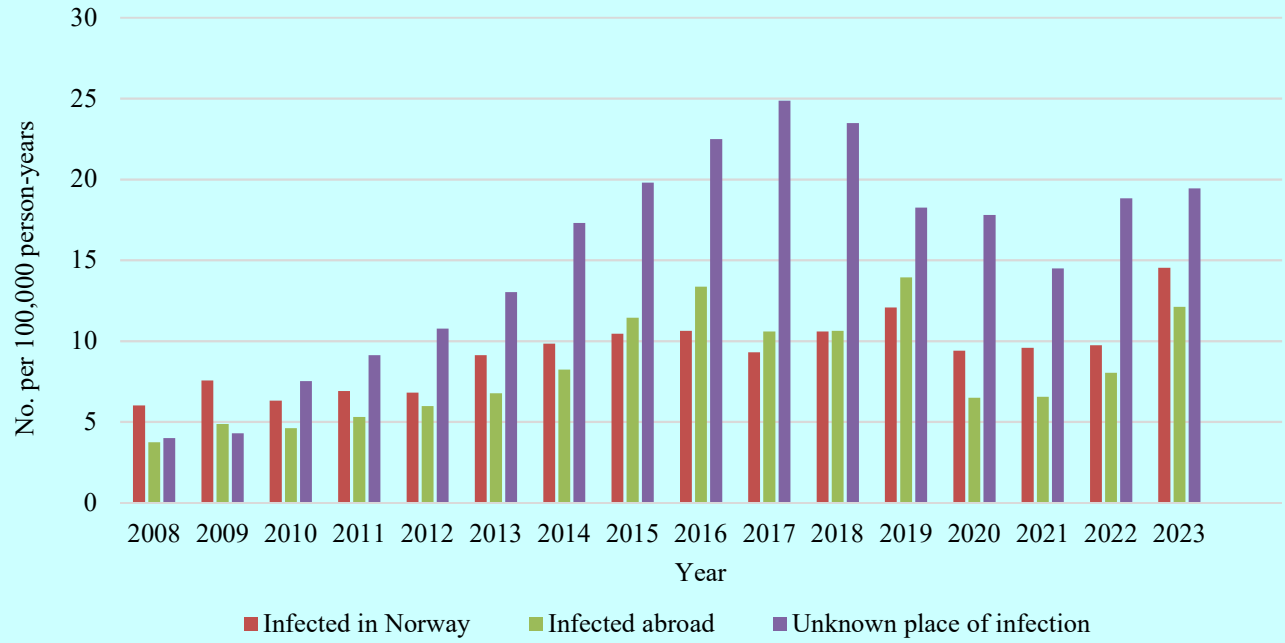

FIGURE 114. Number of persons notified with MRSA per 100,000 person-years in Norway 2008-2023, by assumed place of infection.

The Norwegian Reference Laboratory for Methicillin-Resistant *Staphylococcus aureus* (MRSA) at St. Olavs hospital, Trondheim University Hospital, received 2,834 MRSA isolates from 2,509 persons in 2023, including both MRSA carriage and infections. The MRSA incidence continued to increase compared to the pandemic years 2020-2021. Staphylococcal protein A (*spa*)-typing was the main genotyping method and was performed on all isolates, while whole genome sequencing was performed on selected isolates.

In 2023, 354 different *spa*-types were identified of which 287 *spa*-types (81.1 %) were reported less than five times, displaying the significant diversity which is typical for Norway and the other Nordic countries. Table 87 shows the ten most common *spa*-types in Norway in 2023 with associated clonal complexes (CC). The top five most common *spa*-types were the same in 2023 as in 2022. Previously there has been an increase of the multi-drug resistant *spa*-types t3841 and t1476, but no further increase was seen from 2022 to 2023.

TABLE 87. The ten most common MRSA *spa*-types in Norway in 2023.

spa-type	CC	No. of isolates	% of isolates
t304	CC6	297	10.4 %
t127	CC1	210	7.4 %
t002	CC5	159	5.6 %
t008	CC8	154	5.4 %
t223	CC22	128	4.5 %
t355	CC152	120	4.2 %
t021	CC30	108	3.8 %
t3841	CC672	74	2.6 %
t1476	CC8	60	2.1 %
t688	CC5	55	1.9 %

Antimicrobial susceptibility testing was performed with the EUCAST disc diffusion method by the referring laboratories, and interpreted according to the 2024 NordicAST breakpoints (Table 88). Ceftaroline is included in this report for the first time in spite of limited data. The highest proportion of co-resistance was found for erythromycin (40.9%), followed by tetracycline (31.2%) and ciprofloxacin (29.2%). Moderate levels of resistance were observed for gentamicin (16.5%) and fusidic acid (15.7%). Low rates of resistance were found for rifampicin (1.8%), trimethoprim-sulfamethoxazole (1.9%) and mupirocin (0.8%). No isolates showed decreased susceptibility to linezolid or vancomycin.

TABLE 88. Antibiotic susceptibility results from human MRSA cases in 2023.

	Breakpoints (mg/L)		Proportion of isolates (%)			Isolates (n)
	S	R	S	I	R	
Erytromycin	≤1	>1	59.1	-	40.9	2,832
Clindamycin*	≤0.25	>0.25	74.9	-	25.1	2,830
Fusidic acid	≤1	>1	84.3	-	15.7	2,832
TMS**	≤2	>4	96.5	1.6	1.9	2,832
Tetracycline	≤1	>1	68.8	-	31.2	2,815
Ceftaroline	≤1	>2	90.9	6.9	2.2	549
Gentamicin	≤2	>2	83.5	-	16.5	2,832
Ciprofloxacin	≤0.001	>2	-	70.8	29.2	2,818
Mupirocin	≤1	>256	99.2	-	0.8	2,832
Rifamipicin	≤0.06	>0.06	98.2	-	1.8	2,832
Linezolid	≤4	>4	100.0	-	-	2,832
Vancomycin	≤2	>2	100.0	-	-	2,832

S=Susceptible with standard exposure. I=Susceptible with increased exposure. R=Resistant. *Total clindamycin resistance including inducibly resistant MRSA cases (18.2%). **Breakpoints for the TMS (trimethoprim-sulfamehoxazole) combination are given for the trimethoprim component only.

The prevalence of resistance for erythromycin, tetracycline, ciprofloxacin and fusidic acid seems to have been slightly increasing over the last years (Figure 115), potentially because of the changing epidemiology of the most frequent *spa*-types. For ciprofloxacin there were many isolates with zone diameters close to the breakpoint, which may have contributed to different interpretation of the result by different laboratories. Antimicrobial resistance to mupirocin increased in 2022, but decreased from 2022 to 2023.

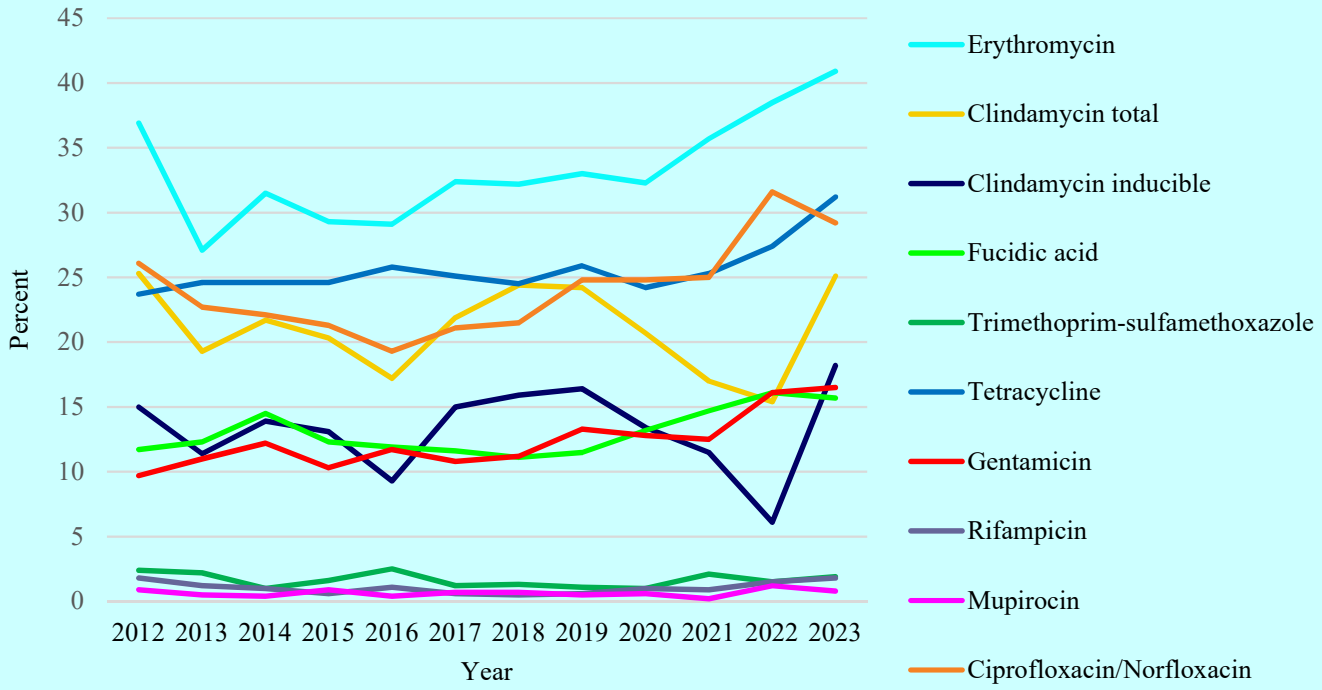

FIGURE 115. Prevalence of antimicrobial resistance in all MRSA isolates from 2012-2023. Isolates are categorised according to the breakpoints at the time of testing. Results for cefoxitin are not shown.

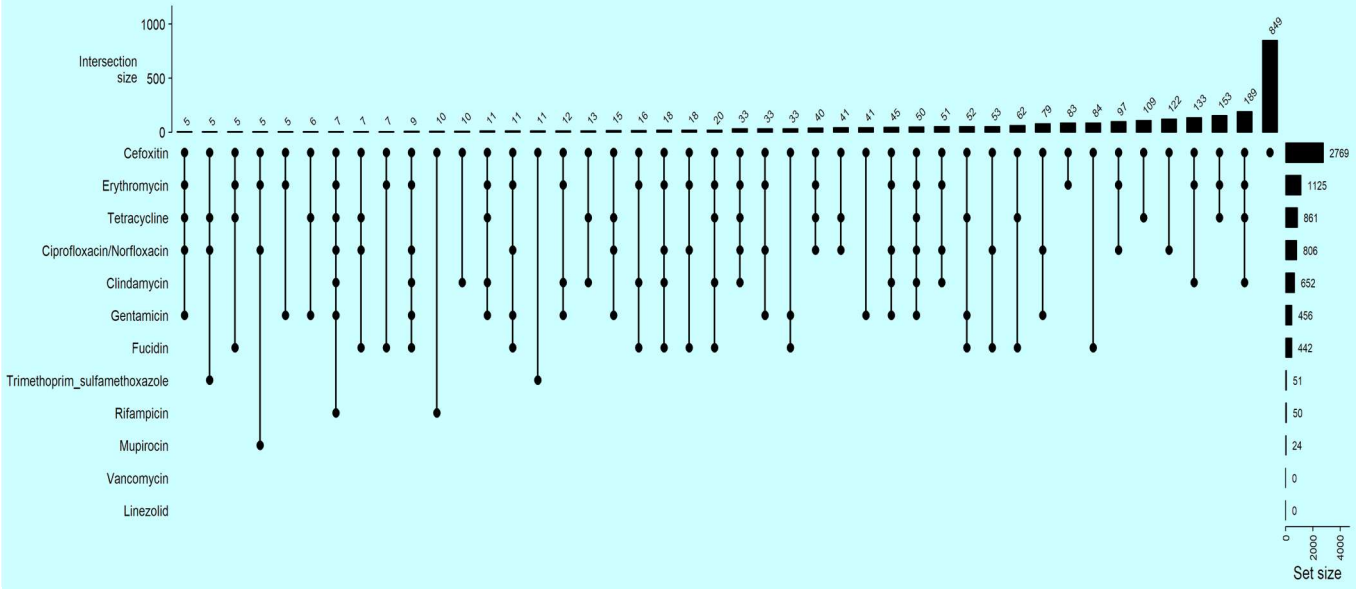

FIGURE 116. Combinations of resistance to the most common antibiotics relevant for MRSA in 2023. Cefoxitin resistance alone was by far the most common profile for Norwegian MRSA isolates (30.7%), followed by resistance to cefoxitin, erythromycin, tetracycline and clindamycin (6.8 %) and the combination of resistance to cefoxitin, erythromycin and tetracycline (5.5%).

The MRSA Reference Laboratory identified 25 livestock-associated MRSA (LA-MRSA) in humans, defined as PVL-negative MRSA belonging to CC398. Their *spa*-types were t034, t011, t571, and t1255. PVL-positive MRSA CC398 counted 46 human isolates, of *spa*-types t034, t011, and t571. Two human isolates were positive for *mecC* (t6220 (CC130, n=1) and t843 (CC130, n=1)). The laboratory received 39 *mecA*-positive *Staphylococcus argenteus* and 34 *mecA*-positive *Staphylococcus lugdunensis* isolates.

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Easier access to epidemiological AMR data

To make surveillance more efficient and meet the different needs of those using monitoring data, the Norwegian Institute of Public Health (NIPH) has created a tool that provides easier access to epidemiological data on microbes exhibiting unusual resistance patterns. The goal is to make real-time data available in figures that are easy to understand and contain information based on preferences and needs of healthcare workers within the field of infection prevention and control (IPC), microbiologists and physicians.

Microbes exhibiting unusual resistance patterns in MSIS

The Norwegian Surveillance System for Communicable Diseases (MSIS) tracks carriage and infections caused by bacteria and fungi exhibiting unusual resistance patterns. MSIS receives data from primary and reference laboratories, as well as epidemiological data about patients from treating physicians. The monitored microbes include:

- Carbapenemase-producing organisms (CPO), which include:
  - Carbapenemase-producing *Enterobacterales* (CPE)
  - Carbapenemase-producing *Pseudomonas* spp.
  - Carbapenemase-producing *Acinetobacter* spp.
- Methicillin resistant *Staphylococcus aureus* (MRSA)
- Vancomycin resistant and/or linezolid resistant enterococci (VRE and/or LRE)
- *Candida auris* (regardless of resistance pattern)
- *Clostridioides difficile* infection (CDI). CDI is reportable regardless of resistance pattern, but since CDI is often induced by antibiotic therapy it is a possible marker for tracking the impact of antibiotic use.
- Penicillin resistant pneumococci (PRP)

Unlocking the potential of MSIS

MSIS gives detailed information on both carriage and infection of selected resistant microbes. Besides age and gender, it contains details like the likely country where the patient was infected, the healthcare region of the patient, and whether the sample was taken from primary or specialised healthcare settings. These details are important for understanding the dynamics of resistance and driving evidence-based interventions.

The advantages of the new tool are that data from MSIS are carefully reviewed by doctors with expertise in microbiology, infection prevention and control, and epidemiology, along with data coders, ensuring the data are reliable and presented in user-friendly figures and tables. Additionally, there will be an accompanying method description for transparency and better understanding of the data foundation. These features have been previously partially lacking in the MSIS statistics database (statistikk.fhi.no) and therefore represent an improvement over the data that were previously available.

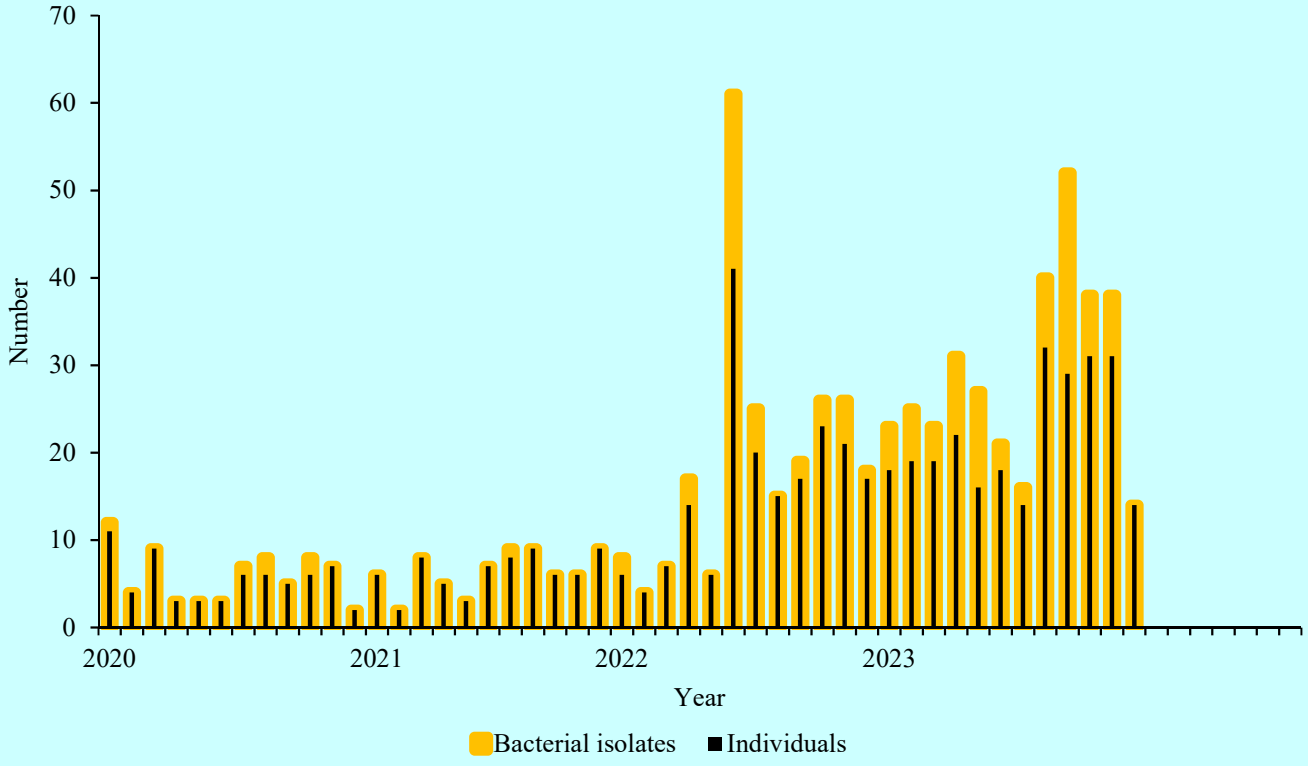

FIGURE 117. Monthly Number of Bacterial Isolates and Individuals with CPO Notified to MSIS (2020-2023).

Real-time data sharing in the future
We are committed to making health data accessible for analysis and research in the most timely and efficient way possible. Our new tool is just one step towards achieving this goal. Currently, the full version of the interactive tool is only available for internal use at NIPH, but we publish the data on our website in the form text, figures and tables. We are also actively working on integrating the full version into new digital solutions for real-time data sharing in the future. Our goal is to ensure that healthcare professionals have access to the latest information at their fingertips so they can utilise national data for risk assessments, trend analysis, benchmarking, and communication with healthcare workers through lectures and training sessions.

Where to find the new data
Data on incidence of antimicrobial resistant bacteria and fungi with particular importance for infection prevention and control in the health services in Norway are available at
https://www.fhi.no/sm/antibiotikaresistens/forekomst-av-antibiotikaresistente-bakterier-og-sopp/?term=

About MSIS
Information about The Norwegian Surveillance System for Communicable Diseases (MSIS) is available at
https://www.fhi.no/ut/msis/meldesystemet-for-smittsomme-sykdommer/

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Staphylococcus lugdunensis in blood cultures

TABLE 89. *Staphylococcus lugdunensis* blood culture isolates in 2023 (n=60). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 1	96.7	-	3.3
Clindamycin	≤ 0.25	> 0.25	96.7	-	3.3
Fusidic acid	≤ 1	> 1	95.0	-	5.0
Ciprofloxacin	≤ 0.001	> 2	0.0	100.0	0.0
Gentamicin	≤ 2	> 2	98.3	-	1.7
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	100.0	-	0.0
Tetracycline	≤ 1	> 1	98.3	-	1.7
Tigecycline	≤ 0.5	> 0.5	100.0	-	0.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	100.0	0.0	0.0
Beta-lactamase	Negative	Positive	53.3	-	46.7
Cefoxitin screen	≥ 27	< 27	100.0	-	0.0
MRSL** (*mecA*)	Negative	Positive	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. **MRSL=Methicillin resistant *Staphylococcus lugdunensis*.

RESULTS AND COMMENTS

S. lugdunensis is a coagulase-negative staphylococcal species which is increasingly recognised as a cause of native and prosthetic valve endocarditis, osteomyelitis, prosthetic and native joint infections, skin and soft-tissue infections, infections of the central nervous system, peritonitis and urinary tract infections. *S. lugdunensis* has never been surveyed in NORM before 2023.

S. lugdunensis isolates were screened for methicillin resistance (MRSL) with the cefoxitin disk test, but the breakpoint (R < 27 mm) is higher for *S. lugdunensis* and *S. epidermidis* than for *S. aureus* and other coagulase-negative staphylococcal species (R < 22 mm). No MRSL isolates were detected among the 60 blood culture isolates included in the survey. Only seven isolates (11.7%) displayed acquired resistance to fucidic acid (n=3), erythromycin (n=2), clindamycin (n=2), gentamicin (n=1) and tetracycline (n=1) in various combinations. About half of the isolates (46.7%) were beta-lactamase positive.

Staphylococcus lugdunensis in wound specimens

TABLE 90. *Staphylococcus lugdunensis* in wound specimens in 2023 (n=824). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 1	96.0	-	4.0
Clindamycin	≤ 0.25	> 0.25	96.4	-	3.6
Fusidic acid	≤ 1	> 1	90.3	-	9.7
Ciprofloxacin	≤ 0.001	> 2	0.0	99.8	0.2
Gentamicin	≤ 2	> 2	99.2	-	0.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	96.5	-	3.5
Tetracycline	≤ 1	> 1	96.2	-	3.8
Tigecycline	≤ 0.5	> 0.5	100.0	-	0.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.9	0.0	0.1
Beta-lactamase	Negative	Positive	59.2	-	40.8
Cefoxitin screen	≥ 27	< 27	98.8	-	1.2
MRSL** (*mecA*)	Negative	Positive	98.9	-	1.1

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. **MRSL=Methicillin resistant *Staphylococcus lugdunensis*.

RESULTS AND COMMENTS

The survey of *S. lugdunensis* in wound samples included 824 isolates. Nine isolates were verified as methicillin resistant *S. lugdunensis* (MRSL) by *mecA* PCR, and eight were also identified by the cefoxitin screening test (88.9% sensitivity). The last *mecA* positive isolate was tested repeatedly with a cefoxitin zone diameter of 32 mm, which suggests that the gene was not expressed. Conversely, a positive cefoxitin screening test could not be confirmed by *mecA* PCR in two isolates, thus giving a test specificity of 99.8%. Both isolates had borderline zone diameters of 26 mm.

Resistance to non-beta-lactam antibiotics was more common in wound isolates than in blood culture isolates, but a majority were still fully susceptible to relevant antibiotics. The association between resistance to erythromycin and clindamycin was less clear than commonly seen in *S. aureus*. Among the 33 erythromycin resistant isolates (4.0%), 18 were also resistant to clindamycin whereas 15 were susceptible to this agent. However, clindamycin resistance (3.6%) was seen without erythromycin resistance in 10/30 isolates. This may sugest the presence of resistance mechanisms in addition to traditional MLS_B determinants such as *erm* and *mef*.

The prevalence of resistance to fusidic acid (9.7%) was higher than in *S. aureus* (5.9%) wound isolates, whereas resistance to tetracycline was at the same level in the two species (3.8% in *S. lugdunensis*; 3.2% in *S. aureus*). Acquired resistance to gentamicin (n=7), ciprofloxacin (n=2) and trimethoprim-sulfamethoxazole (n=1) was only seen in individual isolates, and all strains were fully susceptible to linezolid and tigecycline. Beta-lactamase production was less frequent in wound isolates (40.8%) than in blood culture isolates (46.7%).

Outbreaks of resistant microbes in Norway 2023

Outbreaks of infectious diseases in Norway are mandatory to report to the Norwegian Institute of Public Health (NIPH). According to the Norwegian Surveillance System for Communicable Diseases (MSIS) regulation (1), the following outbreaks should be reported: 1) Outbreaks of diseases that are notifiable to MSIS, 2) suspected food- and waterborne outbreaks, 3) outbreaks of particularly severe diseases (e.g. high mortality or complication rates or serious clinical picture) 4) particularly extensive outbreaks and 5) outbreaks in health care institutions.

The aims of outbreak reporting include alerting and sharing information with relevant authorities and asking for assistance if needed. Reported local outbreaks can be seen in connection and reveal larger national outbreaks. The reporting contributes to get an overview of the epidemiological situation, both at local and national level. The data is also used as basis for recommendations on infection control measures and outbreak management, and for national and international reporting.

Outbreaks are reported by municipal medical officers, hospitals and food safety authorities through a web-based outbreak reporting system, called Vesuv. Data collected in Vesuv include information on the time and place of the outbreak, number of cases, main symptoms, suspected or confirmed pathogen and transmission route, etc. No individual patient data is registered in Vesuv. Although mandatory, it is suspected that there is a certain level of underreporting of outbreaks. This may be because some outbreaks are not detected, or because detected outbreaks are not reported. Because outbreaks should be reported once they are suspected, Vesuv may not be updated in terms of e.g. the number of cases involved in an outbreak.

Definition of an outbreak
An outbreak can be defined as two or more cases of the same infectious disease where a common source is suspected, or a number of cases that exceeds the expected level within a given area and time (2).

Reported outbreaks in 2023
The following data are obtained from Vesuv and the annual report of infectious disease outbreaks (3). A total of 528 outbreaks were reported to Vesuv in 2023. Of those, 91 % were reported from health care institutions. Of the 482 nosocomial outbreaks, SARS-CoV-2 and norovirus account for 88 % of the outbreaks, and 23 outbreaks were caused by antimicrobial resistant microbes, with a total of 142 cases. Three community outbreaks of antimicrobial resistant microbes were reported in 2023; two caused by methicillin resistant *Staphylococcus aureus* (MRSA) involving home-based care and assisted living facility, and one caused by *Mycobacterium tuberculosis.* Table 91 shows the outbreaks of resistant microbes in health care institutions in 2023 and the four previous years, and Table 92 shows the outbreaks in 2023 by type of health care institution.

TABLE 91. Outbreaks of antimicrobial resistant microbes in health care institutions, Vesuv 2019-2023.

Pathogen	2023		2019	2020	2021	2022
	Outbreaks (n)	Cases (n)	Outbreaks (n)			
Carbapenemase-producing *Enterobacterales*	8	19	1			2
Methicillin resistant *Staphylococcus aureus* (MRSA)	5	30	6	8	3	2
Vancomycin resistant enterococci (VRE)	5	53	4	5		1
E. coli (ESBL-producing)	2	10		2		
Linezolid resistant enterococci (LRE)	2	28	1		1	1
Klebsiella spp. (ESBL-producing)	1	2	3			1
Citrobacter (ESBL-producing)						1
Total	23	142	15	15	4	8

TABLE 92. Outbreaks of antimicrobial resistant microbes by type of health care institution, Vesuv 2023.

Pathogen	Long-term care facility	Hospital
Carbapenemase-producing *Enterobacterales*		8
Methicillin resistant *Staphylococcus aureus* (MRSA)	3	2
Vancomycin resistant enterococci (VRE)		5
E. coli (ESBL-producing)	1	1
Linezolid resistant enterococci (LRE)		2
Klebsiella spp. (ESBL-producing)	1	
Total	5	18

There were 2-3 cases in each of the carbapenemase-producing *Enterobacterales* (CPE) outbreaks, and six of the outbreaks were caused by *E. coli* and two by *Klebsiella pneumoniae*. The increase of CPE outbreaks in 2023 compared to previous years, is mainly due to a new routine, where NIPH is informed by The Norwegian National Advisory Unit on Detection of Antimicrobial Resistance about genetically linked clusters of CPE. NIPH reports these outbreaks in Vesuv and starts further investigations to identify possible epidemiological links.

Three of the five vancomycin resistant enterococci (VRE) outbreaks are linked to a larger outbreak that involves several hospitals and long-term care facilities.

Outbreaks of methicillin resistant *Staphylococcus aureus* (MRSA) are affecting both hospitals and long-term care facilities. The number of outbreaks per year has varied between two and eight the last five years. The size of the MRSA outbreaks normally varies between two and ten cases. In 2023 there was one larger outbreak reported from a nursing home with 18 cases, whereof four were health care workers. No outbreak of *Candida auris* has ever been reported in Norway.

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Enterococcus spp. in blood cultures

TABLE 93. *Enterococcus* spp. blood culture isolates in 2023 (n=753). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	78.3	0.1	21.6
Imipenem	≤ 0.001	> 4	0.0	76.5	23.5
Gentamicin HLR*	≤ 128	> 128	81.4	-	18.6
Linezolid	≤ 4	> 4	99.5	-	0.5
Tigecycline**	≤ 0.25	> 0.25	98.6	-	1.4
Vancomycin***	≤ 4	> 4	99.7	-	0.3
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.7	-	0.3

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *HLR=High Level Resistance. **Breakpoints only for *E. faecalis* and *E. faecium*. ***Breakpoints for enterococci other than *E. casseliflavus* and *E. gallinarum*.

TABLE 94. *Enterococcus faecalis* blood culture isolates in 2023 (n=515). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Imipenem	≤ 0.001	> 4	0.0	98.8	1.2
Gentamicin HLR*	≤ 128	> 128	93.6	-	6.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	98.8	-	1.2
Vancomycin	≤ 4	> 4	100.0	-	0.0
Vancomycin (*vanA* or *vanB*)	Negative	Positive	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *HLR=High Level Resistance.

TABLE 95. *Enterococcus faecium* blood culture isolates in 2023 (n=209). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	23.0	0.5	76.5
Imipenem	≤ 0.001	> 4	0.0	19.6	80.4
Gentamicin HLR*	≤ 128	> 128	49.3	-	50.7
Linezolid	≤ 4	> 4	98.1	-	1.9
Tigecycline	≤ 0.25	> 0.25	98.1	-	1.9
Vancomycin	≤ 4	> 4	99.0	-	1.0
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.0	-	1.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *HLR=High Level Resistance.

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a genus and separately for *E. faecalis* and *E. faecium*. The results for each species are microbiologically more valid as resistance rates differ significantly between *E. faecalis* and *E. faecium*. However, overall rates of resistance are of interest when formulating empirical treatment strategies because they include the probability of systemic infections with each enterococcal species. The overall results for enterococci are presented in Table 93. The surveillance in NORM 2023 included 515 (68.4%) *E. faecalis* isolates (70.6% in 2022), 209 (27.8%) *E. faecium* isolates (26.0% in 2022), and 29 (3.9%) unspeciated or belonging to other species (3.3% in 2022). The ratio of *E. faecalis* to *E. faecium* isolates has declined in many countries as the incidence of *E. faecium* bacteremia has increased. In Norway, this ratio has gradually decreased from 3.3 in 2020, 2.7 in 2021 and 2022, and now 2.5 in 2023. The panel of antimicrobial agents examined was unchanged from 2022-2023.

E. faecalis was universally susceptible to ampicillin (Table 94). The prevalence of resistance to ampicillin in *E. faecium* was 76.5% in 2023 compared to 72.0% in 2021 and 83.3%

in 2022 (Table 95). As expected, the results for imipenem closely mirrored those of ampicillin. The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 6.4%, which is a further decrease from 8.5% in 2021 and 6.9% in 2022 (Figure 118). The prevalence of HLGR in *E. faecium* increased to 50.7% compared to 44.3% in 2022. Almost all HLGR *E. faecium* isolates (103/106) were also resistant to ampicillin and imipenem. Conversely, 103/160 (64.4%) ampicillin resistant *E. faecium* displayed HLGR. High-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and beta-lactams often used for treatment of severe enterococcal infections.

Transferrable vancomycin resistance has not yet become endemically established in clinical enterococcal isolates in Norway, but recent outbreaks have occurred in different parts of the country. Two blood culture isolates (0.3%) were reported as vancomycin resistant in NORM 2023 and both were confirmed by PCR to harbour transferrable vancomycin resistance (1 *vanA* and 1 *vanB E. faecium)*. Four *E. faecium* isolates (0.5%) were phenotypically resistant to linezolid, and relevant genetic features were detected in all of them.

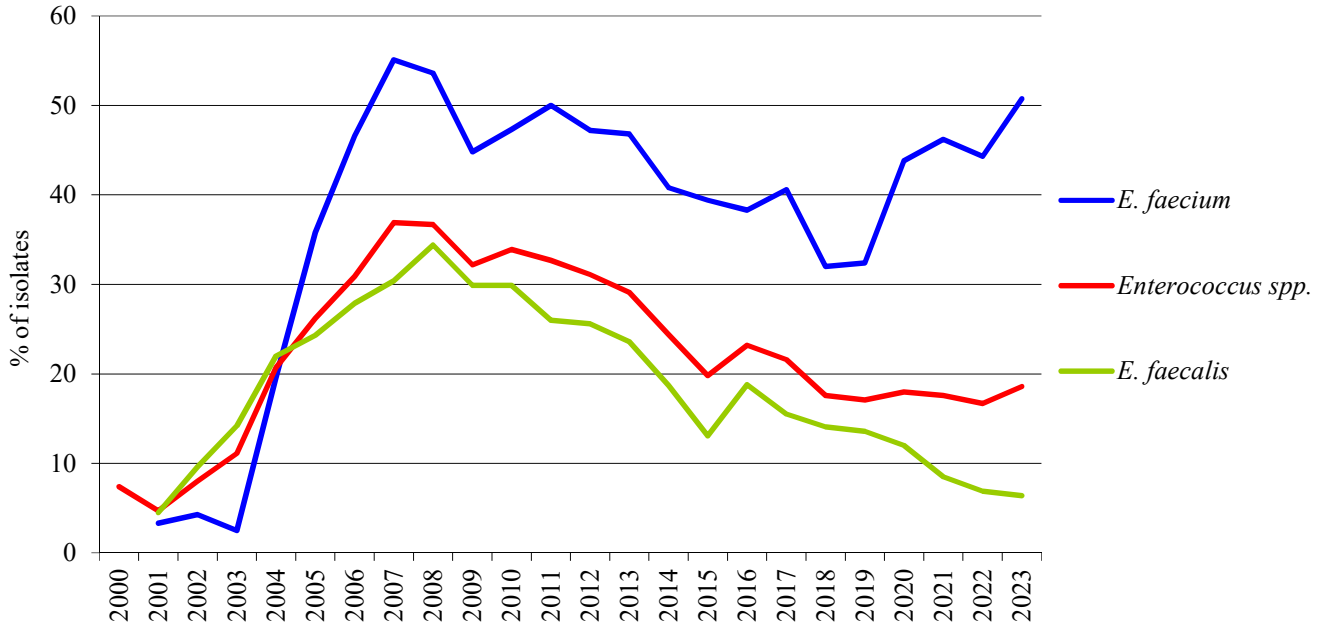

FIGURE 118. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2023. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Vancomycin resistant enterococci and linezolid resistant enterococci in Norway 2023

Vancomycin resistant enterococci

Enterococci are the sixth most common cause of hospital associated bacterial infections in Europe (1) and the fifth most common bacterial genus in blood culture isolates in Norway. They are intrinsically resistant to many antimicrobial agents and readily acquire resistance towards clinically important antimicrobials including vancomycin.

Vancomycin resistance in enterococci is due to changes in the peptide sidechain that prevent vancomycin from inhibiting crosslinking in the peptidoglycan cell wall (2). Currently, ten gene clusters are known to encode vancomycin resistance (*vanA*, *vanB*, *vanC*, *vanD*, *vanE*, *vanG*, *vanL*, *vanM, vanN* and *vanP*), including *vanC* gene clusters that are intrinsic to *Enterococcus casseliflavus* and *Enterococcus gallinarum.* The other gene clusters are acquired by horizontal gene transfer, occur mostly in *Enterococcus faecium* and/or *Enterococcus faecalis*, and are to varying degrees associated with successful mobile genetic elements such as plasmids and integrative conjugative elements (3).

Vancomycin resistant enterococci (VRE) are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) with national reference functions located at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-res). K-res confirms the resistance phenotype when there is discrepancy between pheno- and genotype with the reference method (microbroth dilution) and performs genetic characterisation with PCR and whole genome sequencing (WGS) on selected isolates to clarify resistance mechanisms and potential genetic relatedness indicating regional/national spread.

In Europe, a worrying increase in invasive vancomycin resistant *E. faecium* has been reported from 2016 to 2020 (4). In Norway, the incidence of VRE infection/colonisation has varied during the last decades (from 0.12 per 100,000 inhabitants in 2009 to 7.07 in 2017). In 2023, 89 persons with VRE (including linezolid resistant VRE (LVRE)) were registered in MSIS which is an increase of 14 (19%) since 2022, representing an increase in annual incidence of VRE (including LVRE) from 0.6 in 2021, 1.4 in 2022 to 1.6 per 100,000 persons in 2023. Three of the isolates from 2023 were linezolid resistant (LVRE) (Figure 119). K-res has received isolates and/or WGS data on the majority (84/91; 95%) of the VRE from 2023. Thus, the overview of the molecular epidemiology of VRE in Norway in 2023 is not complete.

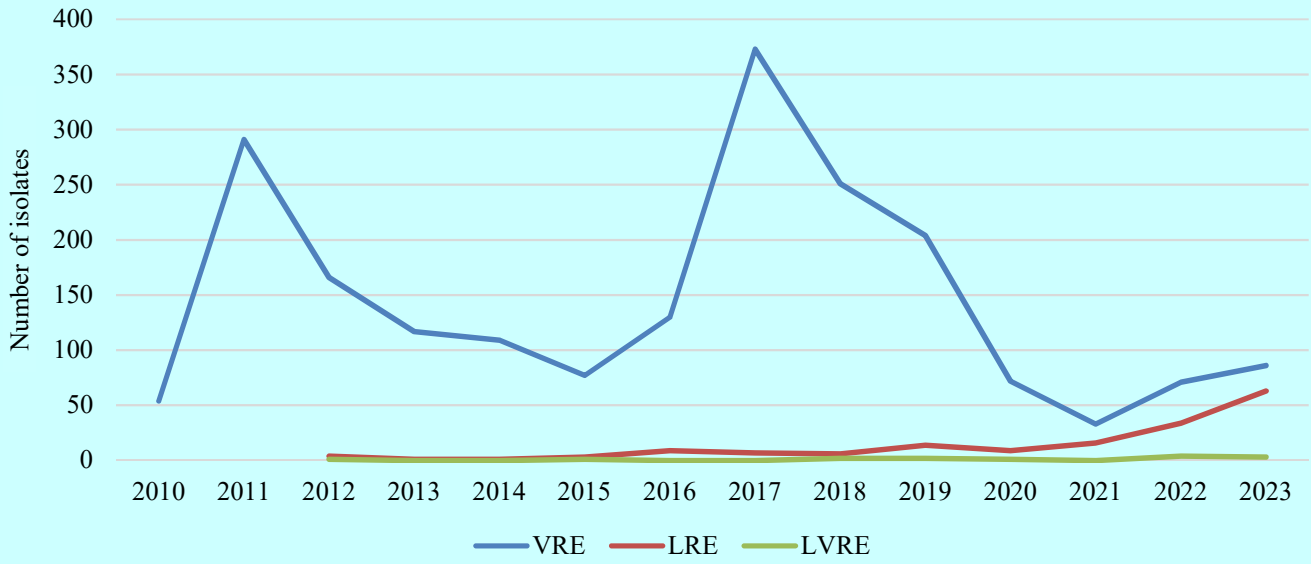

FIGURE 119. The number of vancomycin resistant (VRE), linezolid resistant (LRE) and both vancomycin and linezolid resistant (LVRE) enterococci in Norway 2010-2023. VRE data are from MSIS and LRE+LVRE data from K-res.

Among the 84 WGS VRE isolates from 2023, we mainly identified *E. faecium* with *vanA* (n=68) and *vanB* (n=10), but also *vanA* (n=2) and *vanB* (n=4) *E. faecalis* (Figure 120). Globally vancomycin resistance is also much more prevalent in *E. faecium* than *E. faecalis*, and *vanA* is more frequent than *vanB* (3).

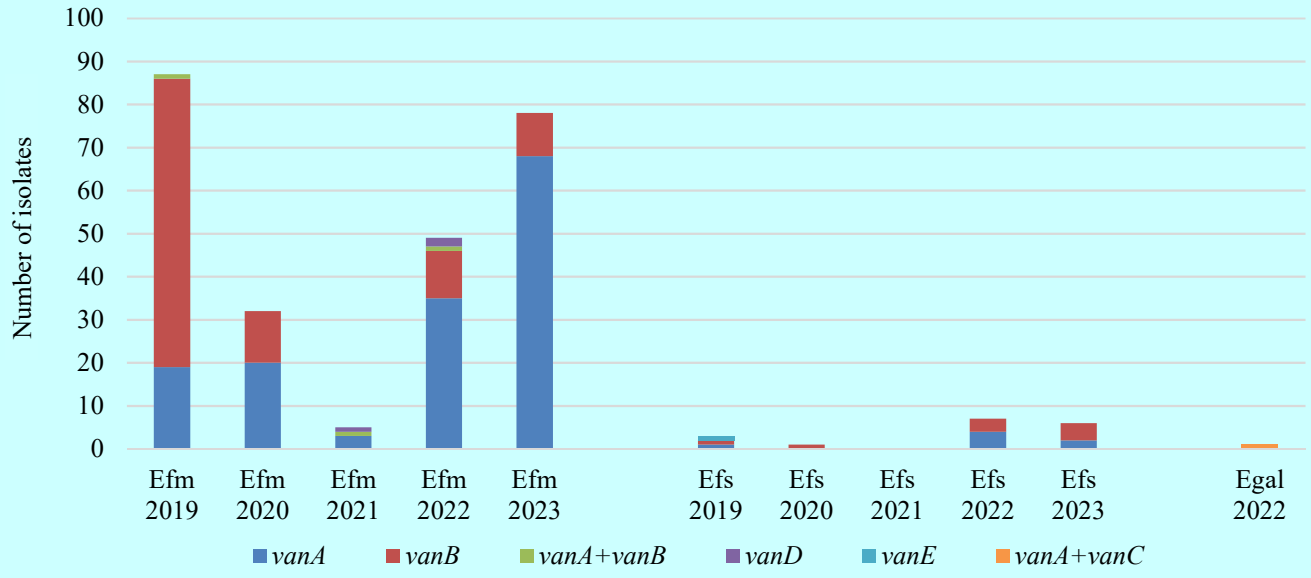

FIGURE 120. Species and genotype distribution of Norwegian VRE isolates that K-res has WGS data on for 2019-2023. This also includes linezolid resistant VRE. *Efm = E. faecium*, *Efs = E. faecalis*, *Egal = E. gallinarum.*

We registered 13 different sequence types (STs) of *E. faecium* (Figure 121). The majority (n=72/78; 92 %) of the *E. faecium* belong to known pandemic hospital adapted STs (ST17, ST18, ST78, ST80, ST117 and ST203). Two different STs of *E. faecalis* occurred (Figure 122) of which ST6 is often linked to clinical isolates and hospitals (5).

Eight clusters with two to 26 isolates of ST80 and ST117 *E. faecium* (Figure 121) and one cluster with two ST6 isolates of *E. faecalis* (Figure 122) were identified. Six of the clusters contained isolates with possible epidemiological connection (*E. faecium vanA* ST117 cluster 1 (n=23), *vanA* ST80 cluster 2 (n=5), tigecycline resistant *vanA* ST80 cluster 5 (n=2), *vanA* ST80 cluster 6 (n=2) and *vanA* ST80 cluster 7 (n=2) in Figure 121 as well as *E. faecalis vanB* ST6 cluster 2 (n=2) in Figure 122 and were thus considered outbreaks. Five of these clusters contained isolates from the South-Eastern health region, while *E. faecium* cluster 7 (n=2) was from the Central health region of Norway. *E. faecium* cluster 1 belongs to the same cluster that was associated with import mainly from Ukraine in 2022. Two of the *E. faecium* clusters contained two isolates associated with import that are also not related in time and/or place, and one cluster contained two isolates of different genotype from the same person. Thus, these were not considered as outbreaks. However, known hospital associated clones of *E. faecium* can typically survive for a long time and move with the patients between hospitals, which makes it difficult to determine which isolates belong to an outbreak. Studies from the Public Health Laboratory in Melbourne, Australia (6), support the use of a three-month sliding window for genomic outbreak analyses of *E. faecium,* which we have implemented at K-res.

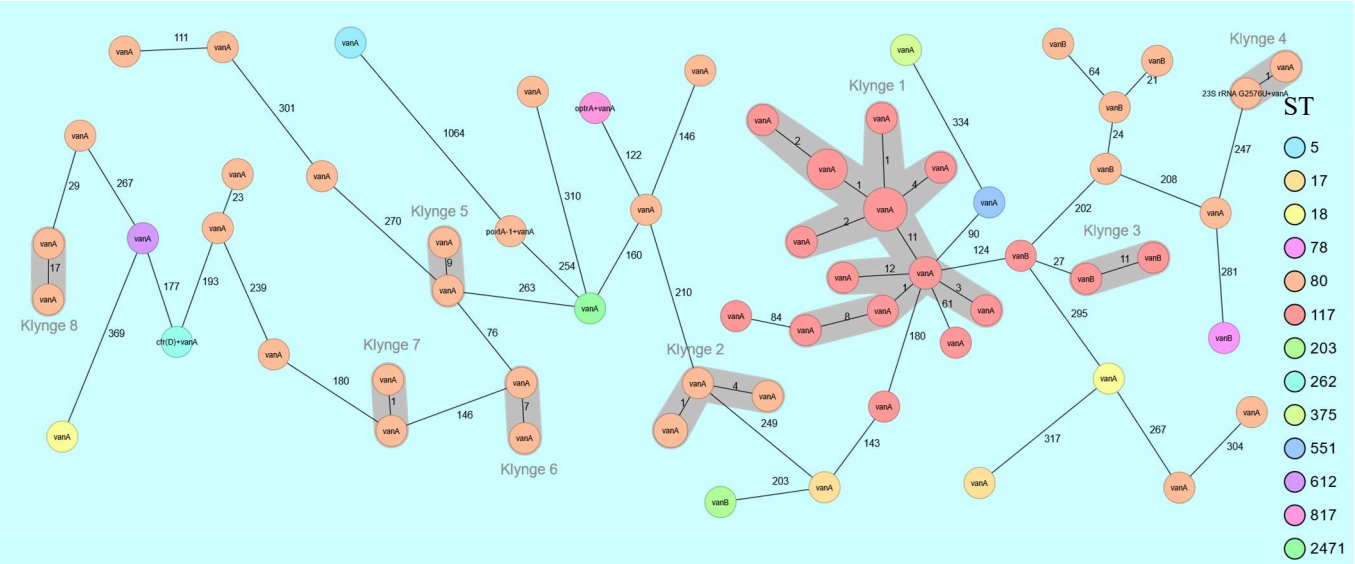

FIGURE 121. Minimum spanning network built from core genome allelic profile of 78 Norwegian VRE *E. faecium* 2023 isolates using Ridom-SeqSphere+ software with integrated core genome (cg) MLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour coded according to sequence type (ST). VRE and LRE mechanisms are indicated in the circles. Isolates with zero allelic differences end up in the same circle. The number of allelic differences between the isolates is indicated on the lines between the circles. Clusters (≤20 allelic differences) are highlighted with grey markings.

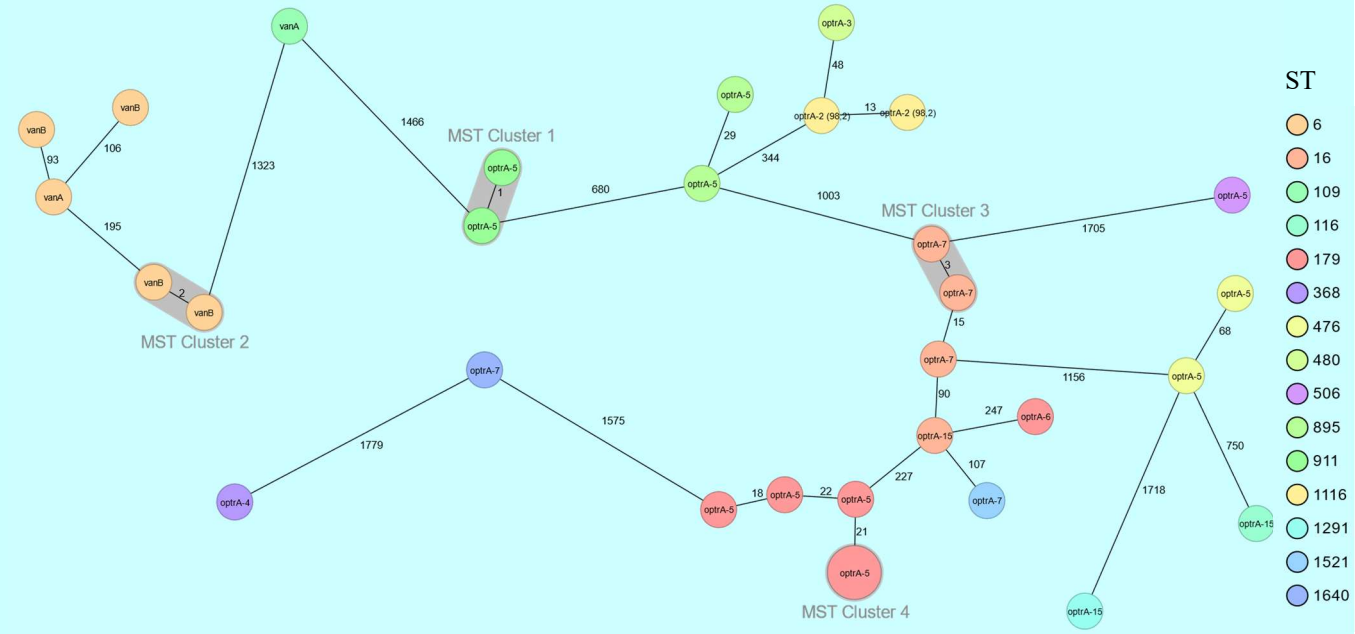

FIGURE 122. Minimum spanning network built from core genome allelic profile of 31 Norwegian *E. faecalis* isolates (VRE (n=6) and LRE (n=25)) from 2023 using Ridom-SeqSphere+ software with integrated cgMLST scheme with *E. faecalis* OG1RF as reference strain. The isolates are colour coded according to ST. VRE and LRE genotypes are indicated in the circle, and number of allelic differences between the isolates is indicated on the lines between the circles. Isolates with zero allelic differences end up in the same circle. Clusters (≤7 allelic differences) are highlighted with grey marking.

Conclusion

In 2023, 89 persons with vancomycin resistant enterococci (VRE) (including linezolid resistant VRE) were reported to MSIS, a 19% increase from 2022, representing an increase in annual incidence from 0.6 in 2021, 1.4 in 2022 to 1.6 per 100,000 persons in 2023. The majority (80%) of VRE cases in 2023 were from screening samples. In this report, we present genomic data for 84 of 91 VRE. Most of these isolates were *E. faecium* (n=78) with *vanA* (n=68) or *vanB* (n=10). The VRE isolates are mainly sporadic isolates, but clusters of variable sizes were identified mainly in the South-Eastern health region. Five outbreaks with *vanA E. faecium* (ST117 and ST80) and one with *vanB E. faecalis* (ST6) were registered. Most (92%) of the VRE *E. faecium* belonged to widespread hospital adapted clones that have been reported worldwide. 45% of the isolates were related to possible outbreaks. Interregional spread of VRE was not suspected.

Linezolid resistant enterococci

The oxazolidinone linezolid is considered an antibiotic of last resort in the treatment of infections caused by multi-resistant enterococci, and particularly VRE. The prevalence of linezolid resistance in enterococci is still low (<1%) worldwide (7) but is increasing in many countries (8).

Linezolid binds to the ribosome and inhibits bacterial protein synthesis. Acquired resistance to linezolid may be due to structural changes in the ribosome based on mutations in the ribosomal RNA and/or ribosomal proteins as well as through gene products that chemically modify (methylate) the ribosome (*cfr*). Another type of resistance mechanism is due to proteins (encoded by *optrA* and *poxtA*) that protect the ribosome against binding of linezolid (8). The *cfr*, *optrA* and *poxtA* genes can all be localised on mobile genetic elements (8-10). The *cfr* gene that confers resistance against oxazolidinones, phenicols, lincosamides, pleuromutilins and streptogramin A in *E. coli* and staphylococci does not seem to mediate linezolid resistance in enterococci although expressed. This is probably due to specific ribosomal structures in enterococci (8,11). Mutation-based resistance is associated with treatment with oxazolidinones. The most common chromosomal mutation that causes linezolid resistance is G2576U mutation in the 23S rRNA V domain. Most species have more than one copy of the 23S rRNA gene in their genome and the resistance level correlates with the number of mutated copies (12).

Linezolid resistant enterococci (LRE) are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) after confirmation at the national reference laboratory for LRE, the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-res). K-res confirms the resistance phenotype with the reference method (microbroth dilution) and performs genetic characterisation with PCR and whole genome sequencing to find resistance mechanisms and monitor genetic relatedness between the isolates. The Norwegian working group on antibiotics and methods for antimicrobial susceptibility testing (AFA) recommend routinely susceptibility testing for linezolid of clinical isolates of *Enterococcus* in Norway. A survey carried out by K-res in 2020 shows that most laboratories follow these recommendations. In the NORM report from 2022, 0.5 % of the invasive *Enterococcus* isolates (n=780) were categorised as resistant, while none of the isolates from previous years have been categorised as resistant. Also, globally there is a small increase of reported LRE which indicates that the recommendations from AFA should be followed.

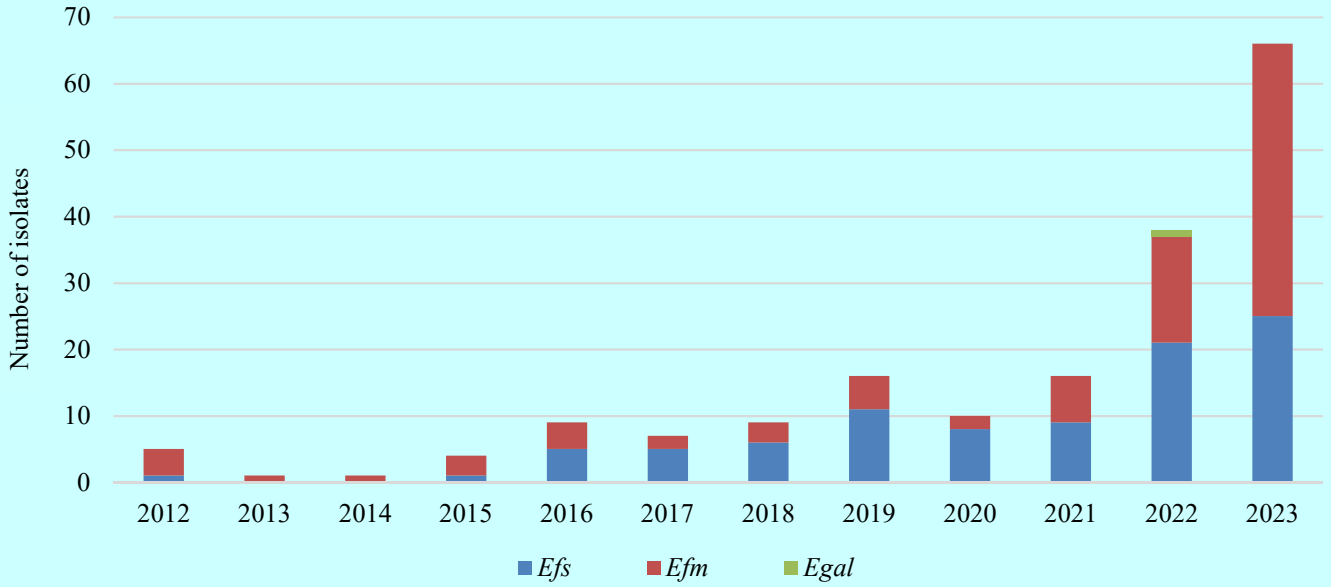

FIGURE 123. The number of linezolid resistant *E. faecium* (*Efm*), *E. faecalis* (*Efs*) and *E. gallinarum* (*Egal*) in Norway 2012-2023, including LRE that are vancomycin resistant.

In 2023, 66 persons with LRE (including LVRE) were detected in Norway. This is 28 more persons (74 % increase) compared to 2022 (Figure 123). We have observed an annual increase in incidence from 0.3 in 2021, 0.7 in 2022 to 1.2 per 100,000 persons in 2023. Most (n=47/66; 71 %) of the LRE isolates from 2023 were from infections. The predominant species has changed from *E. faecium* towards *E. faecalis* the last years, but in 2023 the majority was again *E. faecium* which is mainly due to several outbreaks (see below).

Linezolid resistance in enterococci has traditionally mostly been mediated by point mutations in the chromosomal 23S rRNA regions, mainly the G2576U mutation, which is known to occur during long time exposure to linezolid. In 2023, 41 LRE were *E. faecium*, of which 30 had mutational based linezolid resistance, nine *poxtA*, one *optrA* and one isolate had both *poxtA og optrA*. In the *E. faecalis* isolates (n=25), all had *optrA* (Figure 124). The LRE isolates from 2023 were mainly from infections (n=47), and 22 of these had *optrA E. faecalis* and 22 *E. faecium* with mutational based resistance. Nineteen of the isolates were carrier isolates dominated by *E. faecium* with mutational based resistance (n=8) and *poxtA* (n=6). Only six of the LRE isolates were associated with known import, but information about import is lacking for 44 isolates. Most of the *E. faecium* isolates (n=38) belonged to well-known pandemic hospital associated sequence types (ST17, ST18, ST117 and ST80). The *E. faecalis* isolates (n=21) belonged to 13 different STs of which ST16, ST179, ST476, ST895, ST911 and ST1116 were found in two or more isolates (Table 96).

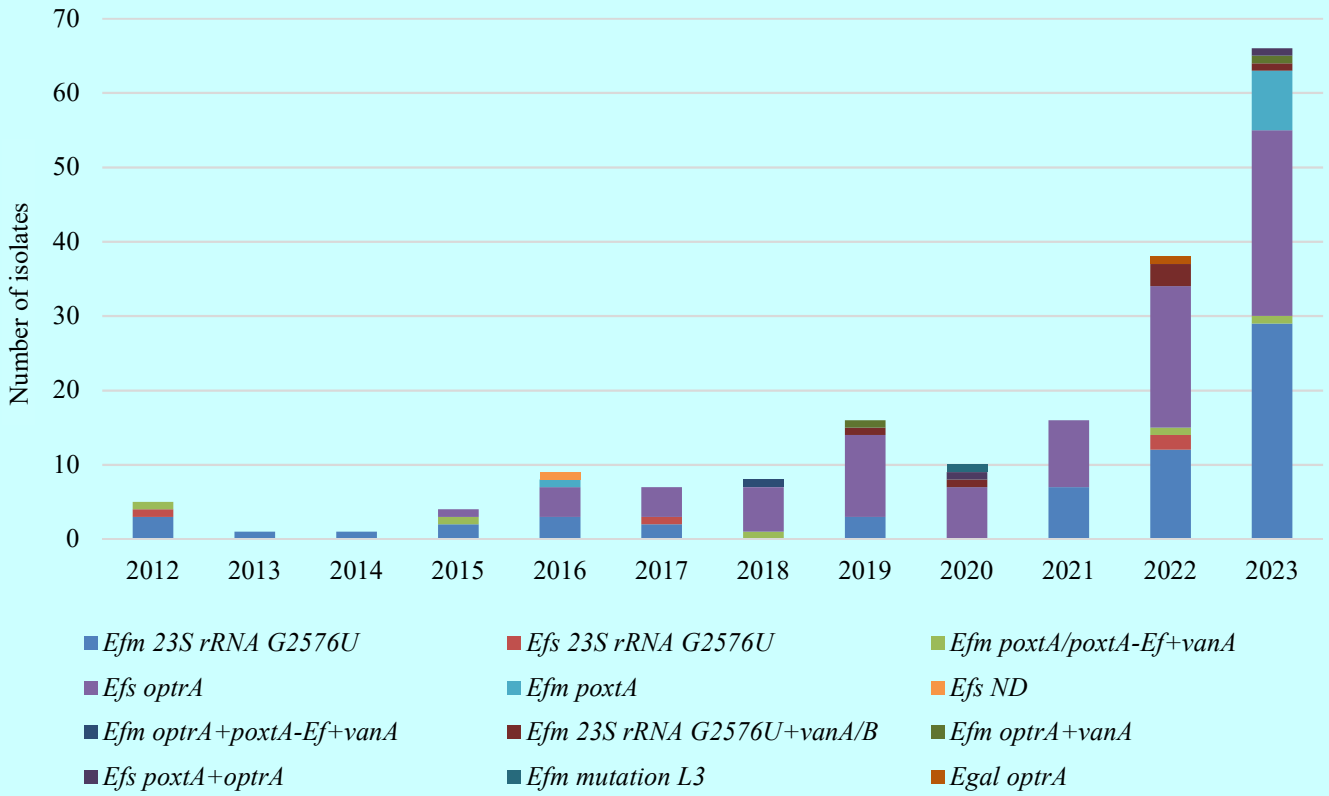

FIGURE 124. Number of LRE according to resistance mechanisms per year. *Efm=E. faecium. Efs=E. faecalis*. *Egal=E. gallinarum.* ND=not determined genotype. This isolate was not sent to K-res or archived at the primary laboratory.

In 2023 we have observed several clusters/outbreaks with LRE. Whole genome analyses showed that two ST16, two ST179 and two ST911 *optrA E. faecalis* from 2023, respectively, belonged to the same clusters (Figure 122). The ST179 *optrA E. faecalis* was considered a possible outbreak since both isolates had identical allelic profile and were isolated within the same timeframe in two different health regions (Figure 122 cluster 4). Phylogenetic analyses also showed three clusters of *E. faecium* with the G2576U mutation in the 23S rRNA V domain (ST17 n=19 cluster 1, ST80 n=6 cluster 3 and ST17 n=4 cluster 4) as well as a cluster of *E. faecium* with *poxtA* (ST117 n=7 cluster 2) (Figure 125). An epidemiological link was also demonstrated for these four *E. faecium* clusters from the South-Eastern health region. Thus, they were considered outbreaks and the first outbreak with *poxtA* LRE was registered in Norway.

TABLE 96. Species, resistance mechanism and sequence type among LRE in Norway 2023.

Species	Resistance mechanism	ST
E. faecalis (n=25)	*optrA* (n=25)	ST179 (n=6); ST16 (n=4); ST476 (n=2); ST895 (n=2); ST911 (n=2); ST1116 (n=2); ST116 (n=1); ST368 (n=1); ST480 (n=1); ST506 (n=1); ST1291 (n=1); ST1521 (n=1); ST1640 (n=1)
E. faecium (n=41)	*23S rRNA G2576U mutation* (n=30)	ST17 (n=23); ST80 (n=6); ST18 (n=1)
	poxtA (n=9)	ST117 (n=7); ST80 (n=1); ST56 (n=1)
	optrA (n=1)	ST817 (n=1)
	poxtA+optrA (n=1)	ST868 (n=1)
E. faecalis (n=25)	*optrA* (n=25)	ST179 (n=6); ST16 (n=4); ST476 (n=2); ST895 (n=2); ST911 (n=2); ST1116 (n=2); ST116 (n=1); ST368 (n=1); ST480 (n=1); ST506 (n=1); ST1291 (n=1); ST1521 (n=1); ST1640 (n=1)

Conclusion

The number of persons (n=66) reported with linezolid resistant enterococci (LRE) (including vancomycin resistant LRE) in Norway increased by 74% from 2022 to 2023, representing an increase in annual incidence from 0.3 in 2021, 0.7 in 2022 to 1.2 per 100,000 persons in 2023. The majority (71%) of the LRE are clinical isolates. *E. faecium* with 23S rRNA mutations (n=30) and *E. faecalis* with transferable resistance (*optrA*, n=25) were the dominant LRE variants. Phylogenetic and epidemiological analyses confirmed four outbreaks of *E. faecium* resistant to linezolid in the South-Eastern health region. Three of these clusters were due to *E. faecium* with a mutation (G2576T) in the 23S rRNA gene and one due to *E. faecium* with *poxtA*. This is the first registered outbreak in Norway with *poxtA*. One possible interregional spread of *optrA E. faecalis* was also noted. The increase in LRE can largely (58%) be linked to domestic spread.

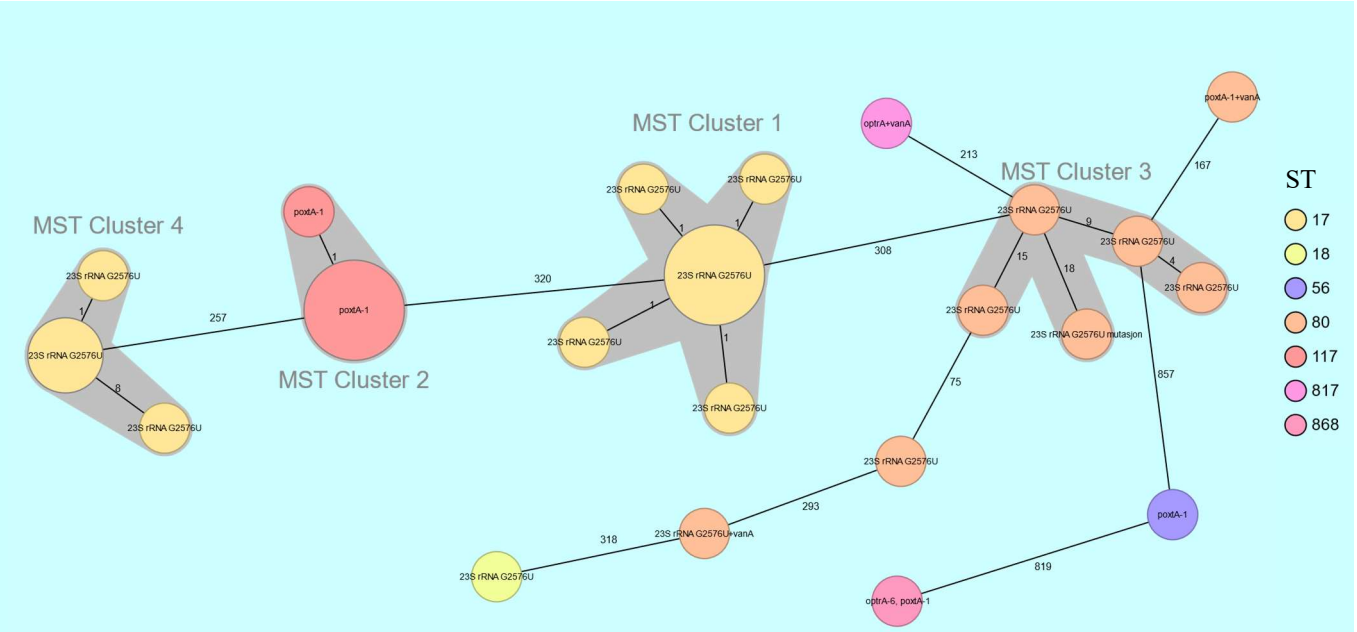

FIGURE 125. Minimum spanning network built from core genome allelic profile of the 41 Norwegian LRE *E. faecium* 2023 isolates using Ridom-SeqSphere+ software with integrated cgMLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour coded according to ST. VRE and LRE mechanisms are indicated in the circle. Isolates with zero allelic differences end up in the same circle. Number of allelic distances between the isolates are given at the lines between the circles. Clusters with ≤20 allelic distances are highlighted with grey marking.

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Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 97. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2023 (n=611). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G*	≤ 0.06	> 2	91.8	7.9	0.3
Cefotaxime*	≤ 0.5	> 2	99.5	0.5	0.0
Ceftriaxone*	≤ 0.5	> 2	99.3	0.7	0.0
Erythromycin	≤ 0.25	> 0.25	93.5	-	6.5
Clindamycin	≤ 0.5	> 0.5	95.3	-	4.7
Tetracycline	≤ 1	> 1	92.3	-	7.7
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	90.8	1.8	7.4

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 98. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2023 (n=611). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*		5.1	61.5	21.9	3.3	0.8	3.9	2.3	0.3	0.5	0.3					
Cefotaxime*		0.8	43.7	45.0	4.3	2.5	2.5	0.8	0.5							
Ceftriaxone*		0.2	12.4	74.8	3.9	4.3	2.1	1.6	0.3	0.3						
Erythromycin				17.0	74.3	2.1				0.7	0.3	0.7	0.5			4.4
Clindamycin				6.1	79.2	10.0					0.2	0.2			0.3	4.1
Tetracycline			0.2	0.2		7.2	61.4	22.4	1.0	0.8	1.0	0.3	0.5	2.8	2.1	
TMS**				0.2	0.3	35.2	47.1	5.2	2.8	1.8	3.8	3.6				
Chloramph.								0.2	0.8	55.2	43.2	0.2	0.5			
Norfloxacin										1.1	11.8	58.3	27.0	1.8		

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method and antibiotics without defined breakpoints. S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis, see text. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

All systemic *S. pneumoniae* isolates in Norway are submitted to the National Reference Laboratory for Pneumococci at the Norwegian Institute of Public Health. The EUCAST/NordicAST breakpoints were unchanged 2023-2024. Breakpoints for chloramphenicol are no longer valid, and norfloxacin screening for quinolone resistance is only validated using disk diffusion. The oxacillin screening disk was not applied in the NORM 2023 protocol. The number of pneumococcal isolates was significantly reduced during the pandemic years 2020-2021, but has now returned to pre-pandemic levels.

The results are summarised in Tables 97-98 and Figures 126-127. Twenty-four strains were isolated from cerebrospinal fluids. Five of these were only isolated from this specimen type, whereas the remaining 19 were concomitantly retrieved from blood cultures. Both blood culture isolates and isolates from cerebrospinal fluids were included from patients with positive cultures from both specimen type. The results for penicillin G, cefotaxime and ceftriaxone were interpreted according to the general breakpoints for pneumococci. The isolates from cerebrospinal fluids were in addition categorised according to the breakpoints for meningitis (penicillin G R > 0.064, cefotaxime and ceftriaxone both R > 0.5 mg/L).

A total of 7.9% (48/611) of *S. pneumoniae* isolates were only susceptible to increased penicillin G exposure (MIC 0.125-2 mg/L), and two isolates (0.3%) were classified as resistant (MIC > 2 mg/L). The rates of susceptibility only to increased penicillin G exposure (I) have fluctuated over the years and this may in part be due to technical issues. The 7.9% recorded in 2023 is lower than 9.7% in 2022, but above the level in 2021 (6.3%). The two penicillin G resistant blood culture isolates (MIC 4 mg/) were both susceptible only to increased cefotaxime (MIC 1 mg/L) and ceftriaxone (MIC 1-2 mg/L) exposure. Two additional isolates susceptible to increased penicillin G exposure (MIC 2 mg/L) were also categorised as I to ceftriaxone (n=2) and cefotaxime (n=1). Two of the isolates in the penicillin G I category originated from cerebrospinal fluids and were thus resistant according to the clinical breakpoints for this specimen type. These two isolates were both susceptible to cephalosporins.

The prevalence of erythromycin resistance increased from 4.6% in 2022 to 6.5% in 2023 (Figure 126). Most of these isolates (29/40) were resistant to both erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining eleven isolates displayed low-level resistance to erythromycin and were susceptible to clindamycin, as seen in efflux-mediated M-type resistance.

Double disk diffusion tests were not performed. The distribution of MLS phenotypes was not significantly altered from previous years. The results may suggest a continuing predominance of *erm*-encoded macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 127).

The 7.4% resistance rate to trimethoprim-sulfamethoxazole was essentially unchanged from 2022. The prevalence of tetracycline resistance increased from 5.7% in 2022 to 7.7% in 2023, but this was at the same level as 7.9% in 2021 (Figure 126). The vast majority of isolates (99.5%) apparently belonged to the wild type distribution for chloramphenicol, but clinical breakpoints for this antibiotic are no longer available. The low prevalence of high-level norfloxacin resistance (Table 98) may reflect the limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

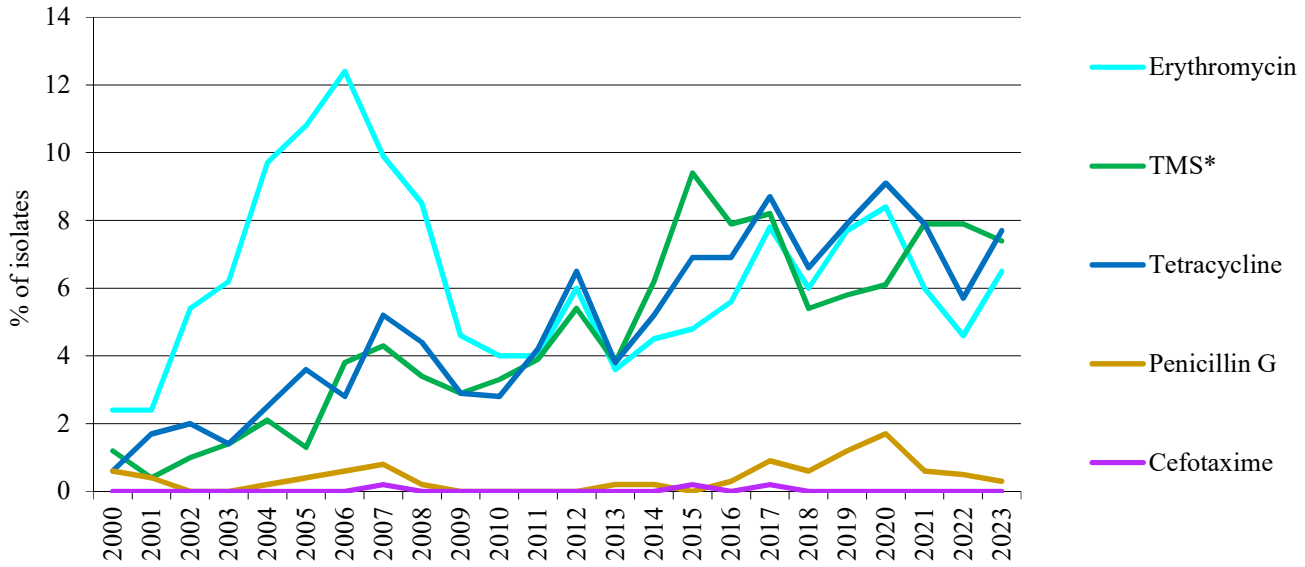

FIGURE 126. Prevalence (%) of resistance to antimicrobial agents in *Streptococcus pneumoniae* blood culture and cerebrospinal fluid isolates during 2000-2023. Doxycycline was substituted by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole.

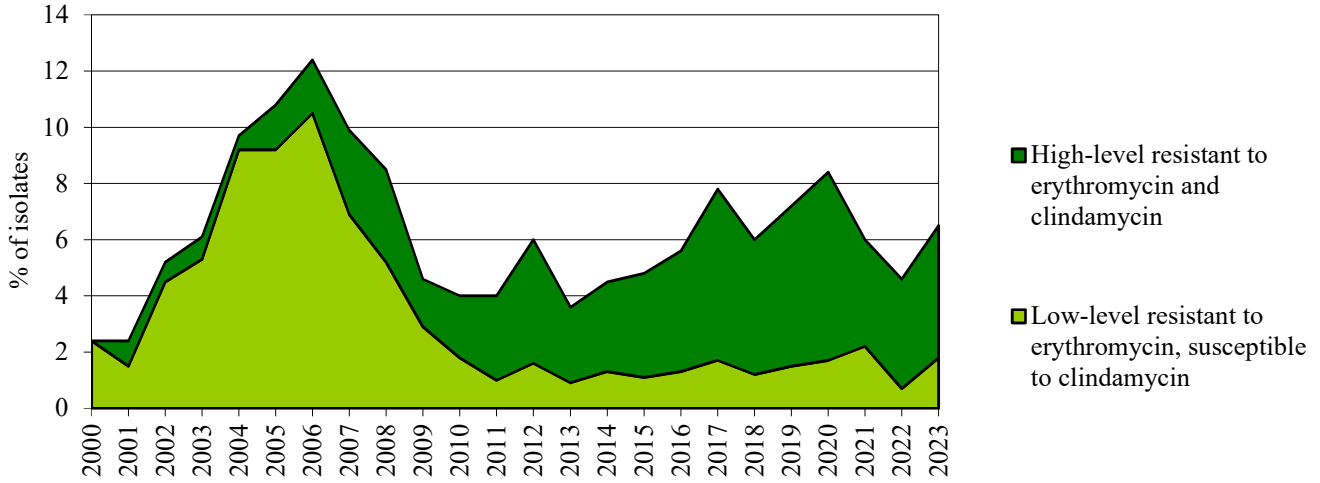

FIGURE 127. Prevalence of resistance (%) to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2023.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 99. *Streptococcus pneumoniae* in respiratory tract specimens in 2023 (n=180). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G*	≤ 0.06	> 2	85.0	15.0	0.0
Cefotaxime*	≤ 0.5	> 2	98.9	1.1	0.0
Ceftriaxone*	≤ 0.5	> 2	99.4	0.6	0.0
Erythromycin	≤ 0.25	> 0.25	90.0	-	10.0
Clindamycin	≤ 0.5	> 0.5	94.4	-	5.6
Tetracycline	≤ 1	> 1	91.7	-	8.3
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	83.3	4.4	12.2
Norfloxacin screen	≥ 10 mm	< 10 mm	95.8	-	4.2

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 100. *Streptococcus pneumoniae* in respiratory tract specimens in 2023 (n=180). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*	3.9	17.2	37.8	21.7	4.4	3.3	6.1	2.8	2.8							
Cefotaxime*	3.3	18.9	51.7	7.2	7.8	5.6	2.2	2.2	1.1							
Ceftriaxone*	11.7	32.8	33.9	6.7	9.4	1.1	2.2	1.7	0.6							
Erythromycin		0.6		1.7	8.9	40.6	38.3	0.6		0.6	0.6	2.8	0.6			5.0
Clindamycin			1.1	1.7	12.8	40.6	35.6	2.8			0.6					5.0
Tetracycline		1.1	1.1	7.2	37.2	38.3	5.0	1.1	0.6	0.6	0.6	0.6	3.9	2.8		
TMS**					2.8	16.1	36.1	23.9	4.4	4.4	2.2	6.1		3.9		
Chloramph.			0.6				0.6		9.4	39.4	46.1	3.3		0.6		

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method and antibiotics without defined breakpoints. S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis, see text. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

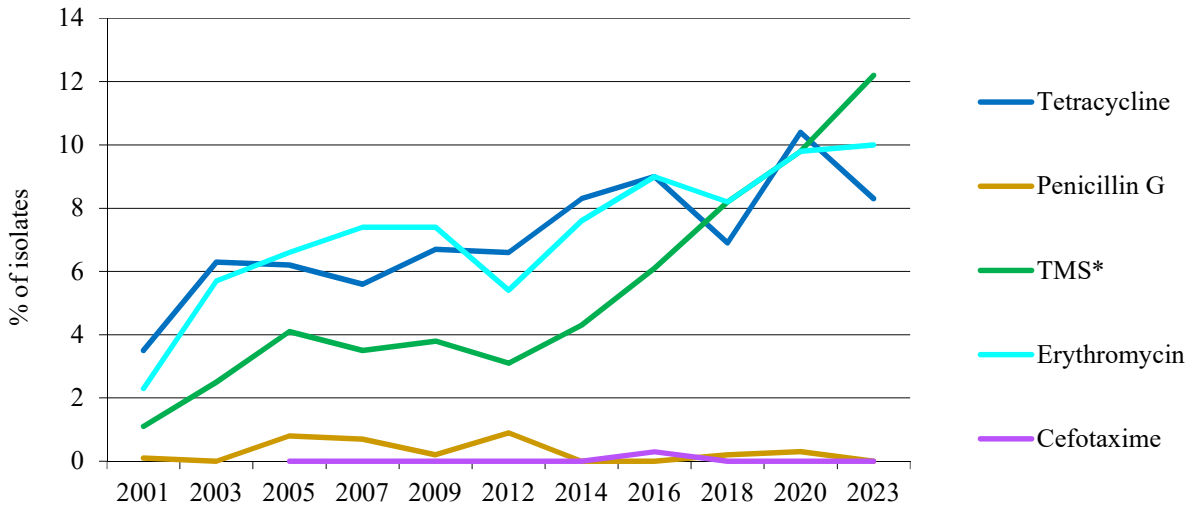

FIGURE 128. Prevalence of antimicrobial resistance in *Streptococcus pneumoniae* from respiratory tract samples 2001-2023. Isolates are categorised according to the breakpoints at the time of analysis for each year. Doxycycline was replaced by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole. Please note that the x-axis is not to scale.

RESULTS AND COMMENTS

S. pneumoniae isolates from respiratory tract specimens were last surveyed in NORM in 2020. The rates of resistance to various antimicrobials are shown in Tables 99-100 and Figure 128.

There were no penicillin G resistant isolates according to the non-meningitis breakpoint of R > 2 mg/L. A considerable proportion of isolates (8.3% in 2020, 15.0% in 2023) would require increased exposure for treatment with penicillin G as they had MICs in the 0.125-2 mg/L range.

These 27 isolates should be categorised as penicillin G resistant in the context of clinical meningitis, and two of them would have required increased exposure to cefotaxime (n=2) and ceftriaxone (n=1). Almost all (25/27) isolates with penicillin G MIC > 0.06 mg/L were detected by the oxacillin screening test (sensitivity 92.6%), whereas seven fully penicillin susceptible isolates were classified as oxacillin resistant (specificity 95.4%). Isolates with elevated penicillin G MICs were often cross-resistant to other antimicrobial agents such as trimethoprim-sulfamethoxazole (13/27), erythromycin (11/27), tetracycline (8/27) and/or clindamycin (7/27).

The rate of resistance to erythromycin was 10.0% in 2023 compared to 8.2% in 2018 and 9.8% in 2020. Macrolide resistance was thus higher in respiratory tract isolates than in isolates from blood cultures and sterile sites (6.5%). The MLS fenotype of 17/18 erythromycin resistant isolates was determined by double disk diffusion. Five isolates (29% of erythromycin resistant isolates, 2.9% of all isolates) displayed constitutive MLS_B resistance to erythromycin and clindamycin, whereas one isolate was inducibly resistant to clindamycin. Low-level M-type resistance was detected in 11 isolates (65% of erythromycin resistant isolates, 6.5% of all isolates).

Tetracycline resistance decreased from 10.4% in 2020 to 8.3% in 2023, whereas trimethoprim-sulfamethoxazole resistance increased from 9.8% in 2020 to 12.2% in 2023. Resistance to fluoroquinolones was examined by the norfloxacin disk test and 4.2% of isolates had zone diameters below the screening breakpoint. It should be noted that this test may be challenging to interpret in the laboratory.

Streptococcus pyogenes in blood cultures

TABLE 101. *Streptococcus pyogenes* in blood cultures in 2023 (n=382). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.25	93.5	-	6.5
Clindamycin	≤ 0.5	> 0.5	97.1	-	2.9
Tetracycline	≤ 1	> 1	89.8	-	10.2
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	99.7	0.0	0.3

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 102. *Streptococcus pyogenes* in blood cultures in 2023 (n=382). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G		6.5	89.8	2.4		1.3										
Erythromycin				1.8	23.6	60.5	7.6		0.5	1.0	0.3	0.5	1.0		0.3	2.9
Clindamycin			1.0	18.1	66.7	12.0	0.3					0.3				2.6
Tetracycline					3.4	57.9	27.7	0.8			0.5	1.6	2.9	3.9	1.3	
TMS*			1.8	32.5	55.0	9.2	0.5	0.8				0.3				

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *TMS=Trimethoprim-sulfamethoxazole. Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

The Reference Laboratory at the Norwegian Institute of Public Health provides resistance data for systemic *S. pyogenes* isolates on an annual basis. The number of isolates was reduced during the pandemic years 2020-2022, but a sharp increase in both localised and systemic *S. pyogenes* infections was seen in 2023. The results were categorised according to the most recent EUCAST/ NordicAST clinical breakpoint protocol. There were no changes in breakpoints in 2024.

As expected, all isolates were fully susceptible to penicillin G (Tables 101-102). The rate of resistance to erythromycin remained unchanged at 6.5%. The prevalence of clindamycin resistance decreased from 11.5% in 2021 and 4.2% in 2022, to 2.9% in 2023. High-level resistance to erythromycin was in most cases (10/11) linked to clindamycin resistance, presumably due to *erm*-encoded constitutive expression of MLS_B resistance. A single isolate was high-level erythromycin resistant but clindamycin susceptible, as seen in inducible MLS_B resistance. The remaining 14 isolates displayed low-level erythromycin resistance combined with clindamycin susceptibility, thus suggesting a *mef*-encoded efflux mechanism. Phenotypic MLS testing was not performed.

The prevalence of tetracycline resistance decreased from 39.7% in 2021 to 17.1% in 2022 and now 10.2% in 2023. One may suspect that the changing rates of tetracycline resistance is linked to shifts in the distribution of *S. pyogenes* clones in the population. The prevalence of resistance to trimethoprim-sulfamethoxazole has been stable at very low levels (1.3% in 2021; 0.0% in 2022), and only a single isolate (0.3%) with this phenotype was detected in 2023.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 103. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2023 (n=282). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G*	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.25	77.3	-	22.7
Clindamycin	≤ 0.5	> 0.5	85.1	-	14.9
Tetracycline	≤ 1	> 1	28.0	-	72.0
Vancomycin	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for indications other than meningitis, see text.

TABLE 104. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2023 (n=282). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*			2.1	48.2	49.3	0.4										
Erythromycin				1.1	6.4	50.4	19.5	0.4	1.4	3.9	4.6	2.5	2.1	0.4		7.4
Clindamycin				1.4	10.3	65.2	3.9	4.3	3.9	0.4	0.4					10.3
Tetracycline			0.4	3.5	22.0	1.8			0.4	0.4	1.1	14.9	40.8	14.2	0.7	
Vancomycin					2.5	48.2	48.6	0.7								
Gentamicin										0.4			3.2	25.9	58.2	12.4

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method or antibiotics without defined breakpoints. *Breakpoints for indications other than meningitis, see text.

RESULTS AND COMMENTS

All systemic isolates of *Streptococcus agalactiae* (beta-haemolytic group B streptococci) in Norway are referred to the National Reference Laboratory at St. Olavs Hospital, Trondheim University Hospital, where confirmatory identification and susceptibility testing is performed. Since 2014, the Reference Laboratory has provided resistance data for invasive *S. agalactiae* isolates to NORM on a yearly basis. As for *Streptococcus pyogenes*, there were no changes in EUCAST/NordicAST breakpoints for *S. agalactiae* in 2024.

A total of 282 isolates were retrieved from invasive infections in 2023 compared to 311 in 2022. Twenty-nine isolates (10.3%) originated from neonates and small children < 1 year of age. Most isolates (276/282; 99.4%) were recovered from blood cultures, but there were also six isolates from cerebrospinal fluids. Three patients had isolates from both specimen types. All isolates were included in the analysis.

As seen in Tables 103-104 there were no isolates with reduced susceptibility to penicillin G or vancomycin. A total of 22.7% (64 isolates) were resistant to erythromycin compared to 21.2% in 2022. All were analysed by double disk diffusion for MLS_B resistance phenotype. Constitutive MLS_B resistance was found in 45/64 isolates (71%), while inducible MLS_B resistance was detected in 6/64 isolates (9%). The remaining 13/64 isolates (20%) had results in accordance with the efflux-mediated M phenotype encoded by *mef* genes. Six isolates were recorded as clindamycin resistant (MIC 1 mg/L) in spite of being susceptible to erythromycin (MIC 0.016-0.064 mg/L). This phenotype may reflect mutations in ribosomal proteins.

There are no clinical breakpoints for aminoglycosides in *S. agalactiae*, but combination therapy with a beta-lactam is often used in clinical practice for treatment of sepsis of unknown origin. High-level resistance to gentamicin (MIC ≥ 128 mg/L) was detected in 12.4% of the isolates compared to 10.3% in 2022. The prevalence of resistance to tetracycline (72.0%) was at the same level as in 2022 (74.6%) with a majority of isolates displaying MIC values of 8-32 mg/L (Table 104).

Antimicrobial resistance in the *Bacteroides fragilis* group

The reference method for antimicrobial susceptibility testing (AST) of anaerobic bacteria is MIC determination by agar dilution. For many years, routine AST of anaerobes has primarily been carried out by the use of MIC gradient strips. However, in 2021, a disk diffusion method for *Bacteroides* spp. was published by EUCAST (1), and has since been extended to cover other anaerobic species (*Prevotella* spp., *Fusobacterium necrophorum*, *Clostridium perfringens*, *Cutibacterium acnes* and *Clostridioides difficile*), with breakpoints last being updated in 2024 (2).

Bacteroides spp. are the most commonly isolated anaerobic bacteria from human infections, and may harbour resistance mechanisms to commonly used antimicrobials (3). In regard to beta-lactam antibiotics, *Bacteroides* spp. are generally resistant to cephalosporins due to the production of cephalosporinases, such as those encoded by the *cepA* or *cfxA* genes (4). For carbapenems, the most common resistance mechanism is production of a metallo-beta-lactamase encoded by the *cfiA* gene, which is chromosomal in a subset of *B. fragilis* designated as division II (3). Further studies have shown that division II of *B. fragilis* is sufficiently different from division I that it represents a different species (5, 6); however, this change has not yet been implemented in routine clinical microbiology. Carbapenem resistance in other *Bacteroides* species is rare and the mechanisms poorly elucidated, but certain beta-lactamase-mediated mechanisms have been described (7). For piperacillin/tazobactam, resistance in *B. fragilis* is usually associated with the *cfiA*-encoded metallo-beta-lactamase of division II, whereas other species in the *B. fragilis* group have inherently higher MICs and are often resistant, in particular *B. thetaiotaomicron*, *B. ovatus* and *B. vulgatus* (5).

Metronidazole resistance is still rare, but emerging (8). A multitude of mechanisms can give rise to metronidazole resistance (9), but the most common transferable mechanism is the production of nitroimidazole reductases encoded by *nim* genes. Several such genes exist (*nimA-nimJ*), encoding enzymes that inactivate metronidazole by reduction to an amine. Some *nim* genes are exclusively chromosomal, whereas others, such as *nimA*, *nimC*, *nimD* and *nimE*, can be plasmid-borne (9). Clindamycin resistance is mainly caused by rRNA methylase genes, primarily *ermB* and *ermF (10)*.

In 2019, a Nordic multi-centre study recruiting 45 laboratories evaluated the new EUCAST disk diffusion method on 30 *Bacteroides* spp. strains (11). In general, the results were satisfying, with 43/45 laboratories completing testing per protocol, and good interlaboratory agreement. A particular finding was difficulties with piperacillin-tazobactam testing for *B. fragilis* division II strains (*cfiA* positive), in the form of lower interlaboratory agreement, a higher error rate and reported subjective difficulty in interpreting the zones; piperacillin-tazobactam in division II strains was the only bug-drug combination where numerous participants reported false susceptible results. Many of the same effects were also seen with MIC gradient strips (unpublished data). These findings indicate that piperacillin-tazobactam AST in *B. fragilis* division II strains is inherently challenging. In 2023, the EUCAST MIC breakpoint for piperacillin-tazobactam in *Bacteroides* was lowered to R > 2 mg/L, and the disk diffusion breakpoint to R < 24 mm (2). This change results in a larger proportion of strains being characterised as resistant, and may reduce the occurrence of false susceptible results in division II strains.

Bacteroides and other anaerobes isolated from blood were part of the NORM surveillance in Norway in 2020 (12). For the *B. fragilis* group, the rates of resistance according to today's breakpoints were 7.4% for meropenem, 27.6% for piperacillin-tazobactam and 0% for metronidazole. The high number for piperacillin-tazobactam is likely due to the breakpoint revision to R > 2 mg/L and to the inclusion of *B. thetaiotaomicron*, *B. ovatus* and *B. vulgatus*. A recent study from the United Kingdom reported similar numbers, but found an increasing trend of resistance in *Bacteroides* to all tested antimicrobials, including meropenem, piperacillin-tazobactam and metronidazole, which is worrying (13). Similar numbers have also been confirmed from other countries (14).

In conclusion, resistance to carbapenems and metronidazole in *B. fragilis* is still rare, but increasing, and can be characterised as an emerging resistance threat. Resistance to piperacillin-tazobactam is common in some *Bacteroides* species such as *B. thetaiotaomicron* and *B. ovatus*, whereas in *B. fragilis* it is mainly associated with division II strains and often co-occurs with meropenem resistance.

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Resistance to empiric antibiotic combinations used to treat bloodstream infections – Is ´no news´ good news?

The resistance to empiric antibiotic combinations among significant bloodstream infection (BSI) pathogens (Table 105) has remained largely unchanged since 2022 (1). Among significant Gram-positives, resistance rates have remained stable over the last decade, giving no real cause for concern.

In the dominant Gram-negative species *E. coli* and *Klebsiella* spp., both ESBL-rates and gentamicin resistance have remained around the 5% mark, continuing the promising trends from 2022. Furthermore, despite the yearly increase in clinical and carrier cases with carbapenem-resistant Gram-negatives (Samuelsen *et. al.* in this report), the occurrence of these in BSIs in 2023 was still only a handful of cases.

TABLE 105. Resistance (%) to broad-spectrum antibiotics and antibiotic combinations in key bloodstream infection pathogens.

Antibiotic drug combiantions[1]		Proportion of invasive isolates resistant (%)												
		E. coli (n=2,240)	*Klebsiella* spp. (n=1,028)	ESBL *Enterobacterales** (n=186)	*Pseudomonas aeruginosa* (n=339)	*Acinetobacter* spp. (n=77)	*H. influenzae* (n=121)	*Enterococcus* spp. (n=753)	*Streptococcus pneumoniae* (n=611)	*Sterptococcus pyogenes* (n=382)	*Streptococcus agalactiae* (n=282)	*Stapylococcus aureus* (n=1,695)	MRSA** (n=2,832)	*Staphylococcus lugdunensis* (n=60)
PEN	GEN	5.4	4.3	36.6	-	4.4	33.9[2]	-	0.3	0.0	0.0	1.2	16.5	1.7
PEN	CIP	10.0	8.1	61.3	8.6	1.5	0.0	-	0.3	0.0	0.0	3.1	29.2	0.0
CLI	GEN	5.4	4.3	36.6	-	4.4	100.0	100.0	4.7	2.9	14.9	0.2	5.4	0.0
AMP	GEN	5.0	4.3	36.6	-	4.4	21.5	21.6[4]	X	0.0[5]	0.0[5]	1.1	16.5	1.7
PTZ	GEN	0.8	2.3	16.7	6.2	4.4	4.1[3]	21.6[4]	X	0.0[5]	0.0[5]	0.4[6]	16.5	0.0
CTX		5.8	5.5	93.5	-	-	1.7	100.0	0.0	0.0[5]	0.0[5]	1.8[7]	100.0	0.0
PTZ		5.4	10.7	32.8	6.2	-	4.1[3]	21.6[4]	X	0.0[5]	0.0[5]	1.8[7]	100.0	0.0
MER		0.0	0.3	1.6	2.7	1.5	0.0	100.0	X	0.0[5]	0.0[5]	1.8[7]	100.0	0.0

[1]Antibiotic abbreviations: PEN=penicillin G, GEN=gentamicin, CIP=ciprofloxacin, CLI=clindamycin, AMP=ampicillin, PTZ=piperacillin-tazobactam, CTX=cefotaxime, MER=meropenem. [2]Inferred from benzylpenicillin 1 unit (PCG1). [3]Inferred from amoxicillin-clavulanate. [4]Inferred from ampicillin only. [5]Inferred from penicillin only. [6]Piperacillin-tazobactam inferred from cefoxitin. [7]Inferred from cefoxitin. X: No data available. -: No breakpoint/susceptibility testing not recommended. **Escherichia coli* and *Klebsiella* spp. **Includes MRSA from all sources.

In conclusion, if resistance levels among *E. coli* and *Klebsiella* spp. continue to stabilise, this should be cause for cautious optimism regarding the continued use of first-line empiric combinations with beta-lactams and gentamicin. ´No news´ should be considered good news.

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1. NORM/NORM-VET 2022. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway.

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Mycobacterium tuberculosis

In 2023 (2022 in parenthesis), 152 (173) persons were reported with tuberculosis disease (TB) to the Norwegian Surveillance System for Communicable Diseases (MSIS). Of these, 18 (17) were born in Norway. In addition to these 152 persons in 2023, seven came to Norway under TB treatment.

124 (138) cases were confirmed with *M. tuberculosis* complex (MTBC) by culture and 11 (22) cases were confirmed by genotypic test only (culture negative). Of the culture positive cases, 3 (2) were identified as *M. bovis*, *M. africanum* or *M. orygis*, the rest were *M. tuberculosis*. Resistance results reported to MSIS are shown in Table 106. Results from testing of both isolates and direct samples are included. There were 16 (11) rifampicin resistant (RR)-TB cases including 15 (10) multi-drug resistant (MDR)-TB cases (resistant to both rifampicin and isoniazid). All the RR-TB cases in 2022 and 2023 were culture positive. Four (2) of the MDR cases had resistance to fluoroquinolones, so-called pre-XDR (extensively drug resistant) TB. All RR-TB cases had TB for the first time, except 2 (1) MDR-TB cases who had received chemotherapy in the past (including one case of pre-XDR), 5 (0) with unknown category and 1 (1) previously on preventive treatment.

In addition to the MDR-TB cases, 14 (6) TB cases had strains resistant to isoniazid (sensitive to rifampicin), 4 (2) of them only with low-level resistance.

TABLE 106. Antimicrobial resistance for MTBC reported to MSIS (not *M. bovis* BCG) in 2023 from isolates or direct samples. Figures from 2022 in parentheses.

Origin of birth	No. of cases	Resistance to antimicrobial agents				
		Isoniazid 127 (139)	Rifampicin 133 (150)	Ethambutol 121 (130)	Pyrazinamide 119 (130)	MDR-TB 127 (139)
Norway	18 (17)	1 (1)	0 (1)	0 (0)	1 (1)	0 (1)
Europe excluding Norway	59 (44)	20 (8)	13 (6)	12 (4)	7 (3)	12 (6)
Asia	39 (66)	6 (4)	2 (2)	1 (1)	4 (2)	2 (1)
Africa	34 (46)	2 (3)	1 (2)	0 (1)	0 (1)	1 (2)
America	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	152 (173)	29 (16)	16 (11)	13 (6)	12 (7)	15 (10)
Proportion resistant isolates (%)		22.8 (11.5)	12.0 (7.3)	10.7 (4.6)	10.1 (5.4)	11.8 (7.2)

MDR-TB: Multi-drug resistant tuberculosis, resistant to at least rifampicin and isoniazid.

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Candida spp. in blood cultures

TABLE 107. Antimicrobial susceptibility of *Candida albicans* blood culture isolates in 2023 (n=134). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	98.5	1.5	0.0
Voriconazole	≤ 0.06	> 0.25	100.0	0.0	0.0
Anidulafungin	≤ 0.03	> 0.03	99.3	-	0.7
Micafungin	≤ 0.016	> 0.016	99.3	-	0.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 108. *Candida albicans* blood culture isolates in 2023 (n=134). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B				2.2	11.2	30.6	53.7	2.2									
Fluconazole				1.5	0.7	5.2	52.2	36.6	2.2		1.5						
Voriconazole	9.7	63.4	24.6		2.2												
Anidulafungin	30.6	50.0	17.9	0.7			0.7										
Micafungin	0.7	19.4	65.7	13.4				0.7									
Caspofungin			2.2	9.0	41.8	35.8	9.7	0.7	0.7								

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 109. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates in 2023 (n=39). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 0.001	> 16	0.0	87.2	12.8
Anidulafungin	≤ 0.06	> 0.06	89.7	-	10.3
Micafungin	≤ 0.03	> 0.03	97.4	-	2.6

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 110. *Candida glabrata* blood culture isolates in 2023 (n=39). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Ampho. B					2.6	5.1	35.9	56.4									
Fluconazole									5.1	10.3	23.1	30.8	17.9		2.6		10.3
Voriconazole				5.1	10.3	20.5	38.5	12.8		2.6		2.6		7.7			
Anidulafungin		7.7	46.2	20.5	15.4	5.1	2.6				2.6						
Micafungin		5.1	48.7	43.6						2.6							
Caspofungin					2.6	41.0	51.3	5.1									

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 111. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates in 2023 (n=14). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	100.0	0.0	0.0
Voriconazole	≤ 0.125	> 0.25	100.0	0.0	0.0
Anidulafungin	≤ 0.06	> 0.06	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 112. *Candida tropicalis* blood culture isolates in 2023 (n=14). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B						7.1	21.4	64.3	7.1								
Fluconazole								42.9	50.0	7.1							
Voriconazole				50.0	21.4	28.6											
Anidulafungin			35.7	50.0	14.3												
Micafungin			14.3	64.3	21.4												
Caspofungin					7.1	50.0	35.7	7.1									

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 113. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates in 2023 (n=25). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	92.0	4.0	4.0
Voriconazole	≤ 0.125	> 0.25	92.0	8.0	0.0
Anidulafungin	≤ 4	> 4	100.0	-	0.0
Micafungin	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 114. *Candida parapsilosis* blood culture isolates in 2023 (n=25). Distribution (%) of MICs (mg/l).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B					12.0		28.0	52.0	8.0								
Fluconazole							12.0	24.0	36.0	20.0	4.0		4.0				
Voriconazole		16.0	16.0	32.0	16.0	12.0	8.0										
Anidulafungin							4.0	16.0	16.0	32.0	32.0						
Micafungin						4.0		20.0	56.0	20.0							
Caspofungin							8.0	84.0	8.0								

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 115. Antimicrobial susceptibility of *Candida dubliniensis* blood culture isolates in 2023 (n=11). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	100.0	0.0	0.0
Voriconazole	≤ 0.06	> 0.25	100.0	0.0	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 116. *Candida dubliniensis* blood culture isolates in 2023 (n=11). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Ampho. B			9.1	27.3	27.3	27.3	9.1										
Fluconazole						63.6	27.3	9.1									
Voriconazole	9.1	72.7	9.1	9.1													
Anidulafungin	10.5		18.2	63.6	18.2												
Micafungin			54.5	36.4	9.1												
Caspofungin					36.4	36.4	18.2							9.1			

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

RESULTS AND COMMENTS

All *Candida* isolates from blood culture from Norwegian patients are included in the NORM surveillance. The National Reference Laboratory of Medical Mycology at Oslo University Hospital performs confirmatory identification and susceptibility testing. Isolates from the same episode, defined as cultures less than four weeks apart without changes in the susceptibility pattern, are counted as one in this survey.

The number of unique candidemias has been about 200 for years, but has increased to 246 isolates (231 patients) in 2022 and 250 isolates (226 patients) in 2023. Nine infections in six patients were reinfections with the same species more than four weeks apart, and three patients had a new episode with another species. There were twelve mixed infections with more than one *Candida* spp. In one patient, acquired fluconazole resistance in *C. glabrata* within the same episode occurred.

Candida albicans is still the most common species (n=134; 53.6%). The proportion of *C. albicans* has declined from 66% in 2020 to 56.5% in 2023. The proportion of *C. glabrata* isolates remains low, at 15.6% (n=39). The number of other species reported with susceptibility data is low and the proportion change from year to year: *C. parapsilosis* species complex (n=25; 10%), *C. tropicalis* (n=14; 5.6% and *C. dubliniensis* (n=11; 4.4%). In 2023 the number of more infrequent species was in total 27 (10.8%) compared to 18 (7.3%) last year. *Candida auris,* the only notifiable fungal pathogen, was not detected in blood cultures in Norway in 2023.

All isolates were susceptibility tested to amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin. All but voriconazole are tested by E-test according to the manufacturer's instructions (AB bioMérieux), voriconazole by MTS (Liofilchem), and interpreted according to EUCAST clinical breakpoints version 10.0 (2020). Unexpected susceptibility patterns were confirmed by EUCAST standardised broth microdilution method and for some isolates *fks* sequencing at Statens Serum Institut in Copenhagen. The results are presented in Tables 107-116.

All, but three *C. albicans* isolates, were susceptible to all antifungal agents. There was one echinocandin resistant strain with mutations in the hot spot region of the *fks* gene (F641S) and two isolates with reduced sensitivity to fluconazole with a MIC of 4 mg/L. Eighteen anidulafungin sensitive *C. albicans* isolates with micafungin MIC of 0.03 mg/L were all regarded micafungin susceptible according to the evaluation of ATU algoritm.

Acquired fluconazole resistance was also observed in five *C. glabrata* isolates (MIC 64-256 mg/L), and four *C. glabrata* isolates in three patients were echinocandin resistant. In one patient the isolate developed fluconazole resistance in addition to echinocandin resistance (see above) and was counted twice within four weeks.

Two *C. parapsilosis* isolates showed reduced sensitivity to azoles. The fluconazole resistant isolate was from a patient previously hospitalised in Greece. Both isolates showed reduced sensitivity to voriconazole (MIC 0.25 mg/L). The other *C. parapsilosis sensu stricto* isolates and two siblings belonging to the *C. parapsilosis* complex were all susceptible to all antifungal agents, as were all *C. tropicalis* and *C. dubliniensis* isolates.

Except from the two *C. parapsilosis* isolates, all isolates with defined breakpoints were susceptible to voriconazole. There is still insufficient evidence that *Candida* spp. is a good target for therapy with isavuconazole and breakpoints have not been set.

Of the 27 isolates not shown in the tables, more than half are regarded fluconazole resistant. *C. krusei* (n=10) is inherently resistant to fluconazole. There are no breakpoints defined for *C. guillermondii,* but this species is often regarded as multi-drug resistant, and all isolates (n=6) displayed fluconazole MIC values of 256 mg/L. With exception of five *C. lusitaniae,* all isolates were susceptible to amphotericin B.

In conclusion, acquired resistance in *Candida* spp. is rare in Norway. The proportion of *C. albicans* is further declining and it seems to be a trend towards relatively fewer *C. albicans* isolates and an increase in fluconazole resistant species like in other European countries. In accordance, echinocandins are now recommended as first line treatment in Norwegian guidelines due to fungicidal effect, with de-escalation to fluconazole in stable patients infected with susceptible *Candida* spp.

Appendix 1: Collection and analysis of data on usage of antimicrobial agents in animals

Sales data – terrestrial animals

Wholesalers and feed mills in Norway are mandated to provide sales statistics for all veterinary medicinal products (VMPs), including when supplied as medicated feed, to the Norwegian Institute of Public Health (NIPH). Data on sales of each product presentation (name, form, strength and pack size) for terrestrial animals of the included VMPs (see table next chapter) were obtained from the NIPH.

Use data – farmed fish and terrestrial food-producing animals

The Norwegian Food Safety Authority established the Veterinary Prescription Register (VetReg) for farmed fish 1 January 2011 and for terrestrial animals 1 January 2012. The veterinarians are mandated to report any administration and deliveries of VMPs and human medicinal products (HMPs) to VetReg for all terrestrial food-producing animals and horses while it is voluntary for all other animal species such as companion animals. Pharmacies and feed mills have to report all deliveries, i.e. for all terrestrial animals and farmed fish, to veterinarians or animal owners, including medicines prescribed for companion animals and HMPs.

For farmed fish the reporting of use (kg active substance) of antibacterials, calculated from prescription data reported to VetReg, was shown to be in the same magnitude as the sales of the same VMPs reported by NIPH for the years 2013-2018 (1) and this is also the case also for the years 2019-2023 (unpublished data). For the period 2013-2023, VetReg data are used for reporting of use of antibacterials for farmed fish.

For terrestrial food-producing animals the annual reporting of use (kg active substance) calculated from prescription data reported to VetReg was considerably lower by form and antibacterial substance when compared to the sales data from NIPH for the corresponding year (unpublished data). This is thought to be partly due to underreporting by pharmacies and veterinarians, but also due to several data-quality issues (2). Therefore, use data are not presented in this report in terms of kg used.

It could not be identified whether the VetReg data are representative for the prescribing of VMPs by animal species, but as the prescribing patterns were relatively stable across this period the data is believed to give a rough picture of the prescription patterns of antibacterial classes by animal species. VetReg data have therefore been used as an additional souce in order to assess changes in the sales of antibacterial VMPs for the main food-producing terrestrial animals (cattle, pigs, sheep, goats and poultry) according to targets set in the National Strategy against Antibiotic Resistance (2015-2020) (3).

Antibacterials included in the data set

The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to identify the VMPs to be included in the data. Sales of VMPs belonging to the ATCvet codes shown in the below table were collected from the NIPH for terrestrial animals, for farmed fish data for QJ01 was collected from VetReg. This is identical to the inclusion criteria by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (4). For the estimation of prescription of HMP antibacterials belonging to the ATC codes J01 and J04AB are included (extracted from VetReg data).

Antibacterial veterinary medicinal products included in the data set

Categories	ATCvet codes
Intestinal use	QA07AA; QA07AB
Intrauterine use	QG01AA; QG01AE, G01BA; QG01BE; QG51AA; QG51AG
Systemic use	QJ01
Intramammary use	QJ51
Antiparasitic agents[1]	QP51AG

[1] Only sulfonamides

Antibacterial veterinary medicinal products belonging to the ATCvet categories shown in the table, however, sold on special exemption from market authorisation are included in the sales data and prescription data. Dermatological preparations (QD) and preparations for sensory organs (QS) are not included in the data which is in accordance with the ESVAC protocol (4).

Data source animal population data - Denominator

A population correction unit (PCU) has been established as a denominator for the reporting of ESVAC sales data. In this report, PCU has been used as denominator for sales of antibacterial VMPs. It is emphasised that the PCU is purely a surrogate for the animal population at risk.

The animal categories included in the PCU as well as the calculation methodology are identical to ESVAC and is detailed in the ESVAC 2016 report. The PCU for each terrestrial animal category is calculated by multiplying numbers of livestock animals (dairy cows, sows, sheep and horses) and slaughtered animals (cattle, pigs, sheep, goats, poultry, rabbits and turkeys) by the theoretical weight at the most likely time for treatment.

The PCU is calculated for each species, weight class and/or production type, as follows:

- Number of animals slaughtered × estimated weight at treatment
- Number of livestock × estimated weight at treatment

The total PCU is calculated according to the above data.

1 PCU = 1 kg of animal biomass.

For farmed fish, biomass slaughtered fish is used as PCU in ESVAC reports.

Data on animal population used to calculate PCU were obtained from Statistics Norway (https://www.ssb.no/jord-skog-jakt-og-fiskeri/jordbruk)[1] and from a report (https://ruralis.brage.unit.no/ruralis-xmlui/handle/11250/2367791) for horses; for farmed fish data on slaughtered biomass was obtained from the Norwegian Fish Directorate (https://www.fiskeridir.no/Akvakultur/Tall-og-analyse/Akvakulturstatistikk-tidsserier).

[1] Living cows and sows are as reported pr 1st of October, living sheep are as reported pr 1st of March.

Indicators

It is not specified in the National Strategy against Antibiotic Resistance (2015-2020) which indicators to be used in order to measure progress in terms of reduction of sales of antibacterials in animals (3). In 2017, ECDC, EFSA and EMA jointly established a list of harmonised outcome indicators to measure progress in reducing the usage of antimicrobials and antimicrobial resistance both in humans and food-producing animals. In order to measure the overall effect of policy interventions/management measure to reduce the consumption for food-producing animals the proposed main indicator is overall sales in mg/PCU (mg active substance/population correction unit) (4, 5). Therefore, the indicator used to report the sales of antibacterials in the current report are sales, in kg active substance, and for food-producing animals also sales in mg/PCU.

Analysis of the overall sales data

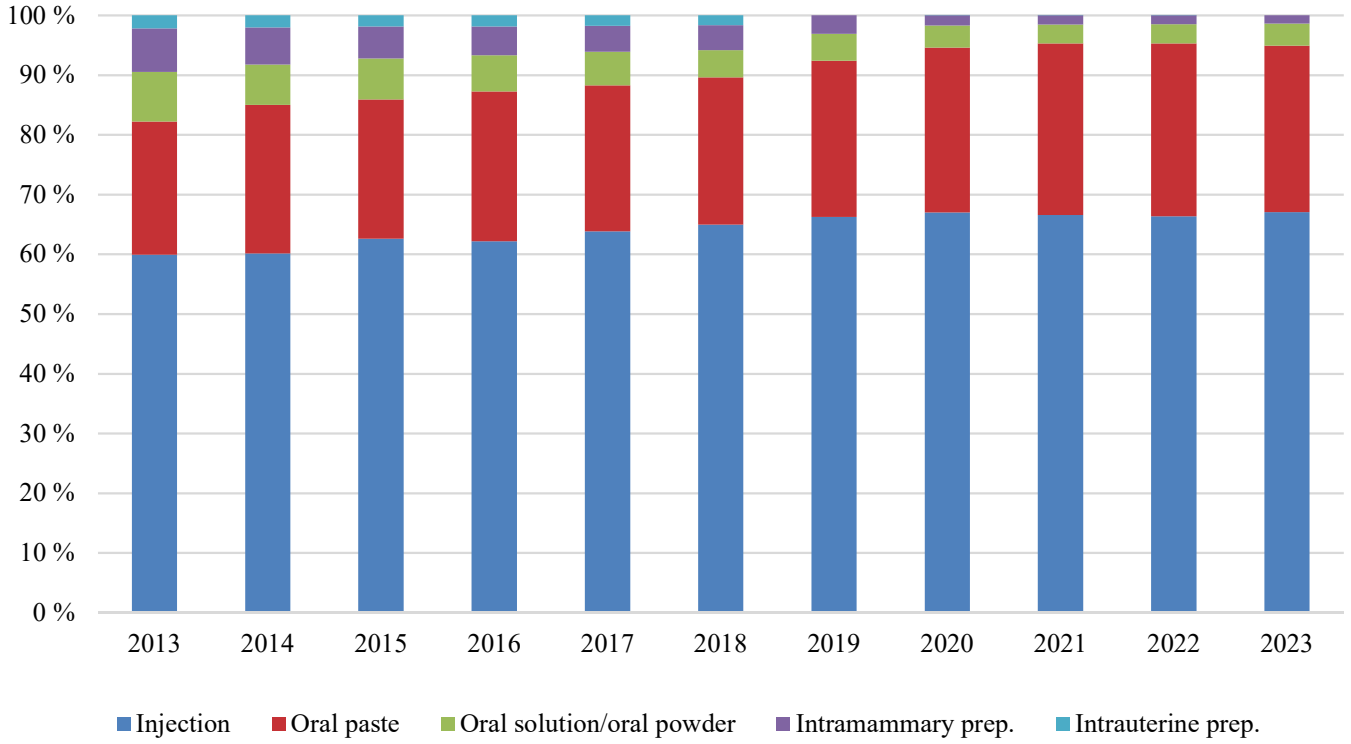
The sales data for each antibacterial VMP presentation were calculated to express weight of active substance. In order to comply with the ESVAC protocol (4), sales of derivatives (in previous report referred to as prodrugs) - e.g. procaine benzylpenicillin and penethamate hydriodide - have been calculated to the corresponding values for the active ingredient, here benzylpenicillin by use of standardised conversion factors (4). For VMPs where the strength is given in international units (IU), the weight of active substance has been calculated by use of ESVAC conversion facors for IUs (4).

The sales data of antibacterial VMPs for terrestrial animals have been split into sales for food-producing animals (including horses) and companion animals. Sales of antibacterial VMPs for companion animals refer to sales of tablets, injectables, oral solution and oral paste that are approved solely for companion animals; in addition, dihydrostreptomycin tablets of pack size 10 pieces have been included in the data on sales for companion animals (no sales after 2004). The other antibacterial VMPs are assumed sold for use only in food-producing animals (including horses). There is some use of injectable antibacterial VMPs in companion animals; thus, the usage for this animal category is slightly underestimated and thus slightly overestimated for food-producing animals. Sales of VMPs for food-producing animals have been further stratified into VMPs for treatment of individual food-producing animals – i.e. bolus, oral paste injectables, intramammary preparations, intrauterine preparations and some tablets (dihydrostreptomycin pack size 20 and 100) and for group treatment – i.e. oral solution, which includes oral powder intended for solution, and oral powder.

Estimation of sales for cattle, pigs, sheep, goats and poultry

The national strategy does not specify for which food-producing terrestrial animals the reduction should cover. Because cattle, pigs, sheep, and poultry accounted for approximately 99% of the Norwegian meat production in 2023 (https://www.ssb.no/slakt). These species as well as goats were selected to evaluate the goals set down in the national strategy (3).

The sales data for 2013-2022 have been refined in order to obtain estimates on the usage in cattle, pigs, sheep, goats and poultry to identify changes across time. Data on prescriptions per animal species obtained from the VetReg have been used as supportive information to the sales data for this refinement. VetReg data show that for the years 2016-2023, more than 95% of the prescriptions of antibacterial oral paste VMPs were for horses showing that off-label use for other animal species of oral paste was negligible. Of note is that the total annual sales of antibacterial VMPs for terrestrial food-producing animals, oral paste approved for horses accounted for 22% in 2013; this figure increased to 28% in 2023 (Figure). Oral paste (numerator) and PCU for horses (denominator) have therefore been excluded from the analysis of data for the estimation of usage of antibacterial VMPs for cattle, pigs, sheep, goats and poultry.



Proportion of kg sold in Norway of antibacterial veterinary medicinal products (VMPs) approved for one or more of the food-producing animal species, including horses, by pharmaceutical forms in the period 2013-2023. Of note, there have been no sales of antibacterial VMP intrauterine devices since 2018.

The usage of HMPs for cattle, pigs, sheep, goats and poultry was estimated by use of the following data from VetReg:

- Delivery to animal owners from pharmacies of antibacterial HMPs for use in these species plus
- Veterinarians' use/delivery of antibacterial HMP for these species. Note that due to underreporting by veterinarians the data represents an underestimate

Estimation of sales of HMPs for dogs and cats

Veterinarians reported almost no use of HMPs for companion animals to VetReg; this is due to the fact that veterinarians are not mandated to report use of medicines for companion animals to VetReg. It should be noted that the sales from pharmacies to veterinarians of antibacterial HMPs applicable for use in dogs and cats were negligible. The amounts, in kg active substance, of usage of antibacterial HMPs for companion animals were estimated by use of the following data from VetReg:

- Delivery from pharmacies to animal owners of antibacterial HMPs for use in dogs and cats
- Delivery from pharmacies to veterinarians of antibacterial HMP tablets and of oral solution and oral powder for solution suitable for companion animals

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5. EMA, 2017. Joint ECDC, EFSA and EMA scientific opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals (https://www.ecdc.europa.eu/sites/default/files/documents/AMR-indicators-joint-report-Oct-2017.pdf).

Appendix 2:
Collection and analysis of data on usage of antimicrobial agents in humans

Data sources
In Norway, antimicrobials are prescription only medicines, and only allowed sold through pharmacies. These data are collected from three databases: the Norwegian drug wholesales statistics database, the hospital pharmacies drug statistics database and the Norwegian Prescribed Drug Registry (NorPD).

The Norwegian Institute of Public Health collects data on drug use from wholesalers. The wholesales database covers total sales of antimicrobials to humans and animals in Norway and is based on sales of medicaments from drug wholesalers to pharmacies and health institutions in Norway. The figures presented should be regarded as maximum figures based on the assumption that all medicaments sold are actually consumed. The actual drug consumption will probably be somewhat lower. Data are available since the beginning of the seventies.

Data on antibacterial use in hospitals are retrieved from *Sykehusapotekenes Legemiddelstatistikk* (the hospital pharmacies drug statistics database) which is a cooperation of the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. *Sykehusapotekenes Legemiddelstatistikk* collects sales data from each pharmacy delivering drugs to hospitals. Data are collected as sales from the pharmacy to hospital wards. Data have been available since 2006. The National Centre for the use of antibiotics in hospitals (*Nasjonal kompetansetjeneste for antibiotikabruk i spesialisthelsetjenesten*) have analysed the data according to activity (bed days).

Population statistics per 1 January are collected from Statistics Norway. Information on bed days and admissions are collected from the Norwegian Patient Register. The definition of bed days is: "*the number of whole days an admitted patient disposes a bed*". An admission is defined as: "*admission of patient where the medical interventions usually are complex and require hospitalisation for one or more days*" (1).

Data on the use in nursing homes is not presented. However, the data is included in total sales data from the Norwegian drug wholesales statistics database and volume of use can be estimated. Antibiotics can be sold through pharmacies or directly from wholesalers and the shares of the two may vary from one year to another. Due to this it is difficult to get exact sales and it hamper the ability to provide aggregated statistics in Norwegian nursing homes.

Data on the use in ambulatory care are retrieved from NorPD, a nation-wide prescription database situated at the Norwegian Institute of Public Health. This database includes all prescriptions being prescribed to out-patients in Norway. For analyses on prescriptions and DDDs, all prescriptions and DDDs to outpatients are included. For the results on annual prevalence (number of individuals per population group being prescribed antibiotics within a year) only prescriptions to individuals with national ID numbers are included. The data give us the exact population prevalence of antibacterial use in the total population in ambulatory care. More information is available at www.fhi.no. Data are available from 2004.

Drug Classification
The data are categorised according to the ATC classification system (2). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2024 is used for all years.

Unit of measurement
The ATC/DDD system is recommended by the WHO to serve as a tool for drug utilisation research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels.

The use of defined daily dose – DDD – as a unit of measurement, simplifies and improves the evaluation of drug consumption over time, nationally and internationally. The DDD is a theoretical unit of measurement, and does not necessarily reflect the recommended or Prescribed Daily Dose.

The basic **definition** of the unit is:
The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

The DDDs for the antibacterials are as a main rule based on the use in infections of moderate severity. Some antibacterials are only used in severe infections and their DDDs are assigned accordingly. The DDDs assigned are based on daily treatment.

Inclusion criteria
The antibacterials for human use included in this report belong to ATC group J01 *antibacterials for systemic use*. Oral vancomycin (A07AA09), fidaxomycin (A07AA12) and oral and rectal metronidazole (P01AB01) are also included in some figures. Antibacterials used in dermatological preparations (ATC group D) and preparations intended for sensory organs (ATC group S) are not included in the material.

References
1. Definitions Norwegian Directorate of Health https://volven.helsedirektoratet.no/begrep.asp?id=452&catID=12
2. WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs 2024. WHO Collaborating Centre, Oslo

Appendix 3: Sampling, microbiological methods and data processing in NORM-VET

Sampling strategy

The clinical isolates included in NORM-VET 2023 were *Escherichia coli* and *Staphylococcus pseudintermedius* from infections in dogs. The isolates were retrieved through submissions to the Norwegian Veterinary Institute. The *E. coli* isolates (n=65) were primarily from urinary tract infections collected in the years 2020-2023. The *S. pseudintermedius* isolates (n=195) were primarily from ear and skin infections collected in the years 2018-2023. Clinical isolates of *Pasteurella canis* and *Pasteurella multocida* from infections in various animals were also included. The *P. canis* isolates (n=62) were primarily from ear and skin infections in dogs collected in the years 2017-2023. *P. multocida* isolates from clinical infections in various animals (primarily cats (~80), cattle (~30), dogs (~15) and pigs (~12)) were also included. The *P. multocida* isolates (n=143) were primarily from lung infections collected in the years 2017-2023.

Caecal samples from cattle and fattening pigs were collected at slaughter throughout the year by the Norwegian Food Safety Authority (NFSA), following the specifications set by the European Food Safety Authority (EFSA; EFSA Journal 2019;17(6):5709) with one exception; EFSA specifications requires caeal samples from cattles under one year, and this is not required in NORM-VET. One individual caecal sample was included per herd, in total 277 and 333 samples from cattle and pigs, respectively, except from one pig herd where samples were collected twice.

All the caecal and meat samples were used for selective isolation of *E. coli* resistant to extended-spectrum cephalosporins (ESC) and carbapenemase-producing *Enterobacterales* (CPE). The included indicator bacteria *E. coli*, *Enterococcus faecalis* and *Enterococcus faecium* were also retrieved from the caecal samples. In addition, the caecal samples were used for selective isolation of linezolid resistant *Enterococcus* spp. (LRE) and for isolation of *Campylobacter coli* and *Campylobacter jejuni* (see Appendix 4).

All food samples were collected by the NFSA. Beef and pork samples, 286 and 283, respectively, were collected at retail in all regions of Norway following the specifications set by EFSA (EFSA Journal 2019;17(6):5709). Samples were collected without taking place of origin into account. All the food samples were analysed using selective isolation for *E. coli* resistant to ESC and CPE.

Faecal and oral/nasal/perineum swab samples from a total of 251 dogs were collected by practicing veterinarians throughout the year. The sampled dogs were between a few months and 17 years of age and from all over the country. A total of 25 dogs had been out of the country last six months, though only two of these had been outside Scandinavia. Clinical symptoms from ear or skin were reported from 31 dogs and ten of these had been treated with antimicrobials last six months, while clinical symptoms from ingestinal tract were reported from seven dogs of which three had received antimicrobials last six months. The included indicator *E. coli* were retrieved from the faecal swab samples. The same samples were also used for selective isolation of *E. coli* resistant to ESC and CPE. The nasal/perineum swabs were used for retrieving *S. pseudintermedius* and for selective isolation of methicillin resistant *S. pseudintermedius* (MRSP) and/or *S. aureus* (MRSA).

Indicator isolates of *E. coli*

Sample material, i.e. faecal content from dog and caecal content from one cattle and one fattening pig per herd were plated directly onto MacConkey agar (Difco) and incubated at 44±0.5°C for 20±2h. Typical colonies were subcultured on blood agar and incubated at 37±1°C for 20±2h. Colonies were identified as *E. coli* by typical colony appearance and a positive indole reaction.

Indicator isolates of *E. faecalis* and *E. faecium*

Sample material, i.e. caecal content from one cattle and one fattening pig per herd were plated directly onto Slanetz and Bartley agar (Oxoid) and incubated at 44±0.5°C for 24-48h. Typical colonies were subcultured on blood agar incubated at 37±1°C for 20±2h. Colonies were identified as *E. faecalis* or *E. faecium* using MALDI-TOF MS.

Linezolid resistant *Enterococcus* spp. (LRE)

Sample material, i.e. caecal content from one cattle and one fattening pig per herd were plated directly onto Slanetz and Bartley agar containing 4 mg/L linezolid (Oxoid) and incubated at 44±0.5°C for 24-48h. Typical colonies were subcultured on Slanetz and Bartley agar containing 4 mg/L linezolid and blood agar containing 5% bovine blood and incubated at 37±1°C for 20±2h. Presumptive colonies were identified as *E. faecalis* or *E. faecium* by typical colony appearance and verified using MALDI-TOF MS.

Indicator isolates of *Staphylococcus pseudintermedius*

Sample material, i.e. nasal/perineum swabs from dogs were enriched in 5 mL Mueller Hinton broth with 6.5% NaCl and incubated at 37±1°C for 18-24 h. Aliquots from the overnight broth were plated onto blood agar and mannitol-salt agar (MAST, Oxoid) and incubated at 37±1°C for 20±2h. Typical colonies were subcultured on blood agar incubated at 37±1°C for 20±2h. Colonies were identified as *S. pseudintermedius* using MALDI-TOF MS.

Enrichment of samples before selective isolation

All samples were enriched prior to plating onto selective media. A total of 1±0.1 g caecal sample material was homogenised with 9 mL of BPW-ISO. Faecal swab samples from dogs were inoculated in 5 mL of BPW-ISO. A total of 25±0.5 g sample material of beef and pork were homogenised with 225 mL of BPW-ISO. Samples were incubated at 37±1°C for 20±2h according to the protocol from the EURL-AR (https://www.eurl-ar.eu/protocols.aspx). After incubation, 10 µL aliquots of the enrichment broth were plated onto selective media as described in the sections below.

***E. coli* resistant to extended-spectrum cephalosporins (ESC)**

Aliquots from the overnight BPW-ISO broth from all faecal, caecal and meat samples were plated onto MacConkey agar containing 1 mg/L cefotaxime and

MacConkey agar containing 2 mg/L ceftazidime. The agar plates were incubated at 44±0.5°C for 18-24h. Presumptive ESC-resistant *E. coli* were subcultured on MacConkey agar containing 1 mg/L cefotaxime and blood agar, and confirmed as *E. coli* using MALDI-TOF MS before further testing for cephalosporinase production.

Carbapenemase-producing *Enterobacterales* (CPE)
Aliquots from the overnight BPW-ISO broth from all caecal, faecal, and meat samples were plated onto CHROMID® CARBA and CHROMID® OXA-48 agar (bioMérieux, Marcy l'Etoile, France). The plates were incubated at 35±2°C for 18-24h. Presumptive CPE were subcultured on MacConkey agar and blood agar, and species confirmed using MALDI-TOF MS before further phenotypical testing.

Methicillin resistant *Staphylococcus aureus* (MRSA) and/or *Staphylococcus pseudintermedius* (MRSP)
Nasal/perineum swabs were incubated in 5 mL Mueller-Hinton broth containing 6.5% NaCl at 37±1°C for 18-24 hours. A loopful of the overnight broth (10 µL) was plated onto Brilliance™ MRSA2 agar plate (Oxoid). The plates were incubated at 37±1°C for 24±2 hours. Suspected colonies were subjected to species identification using MALDI-TOF MS before further phenotypical testing.

Genotyping
For genotyping of presumptive antimicrobial resistant isolates, whole genome sequencing (WGS) was performed on an illumina® MiSeq or illumina® NextSeq (illumina, San Diego, California, USA). Paired end reads were subjected for analysis for both aquired genes and chromosomal point mutations using the ResPointFinder3 pipeline (equals ResFinder_EFSA2023, http://genepi.food.dtu.dk/resfinder) which the NVI have implemented on the IRIDA platform (www.irida.ca).

Susceptibility testing
Isolates were tested for antimicrobial susceptibility using a broth microdilution method. Minimum inhibitory concentration (MIC) values were obtained using panels from Sensititre® (TREK Diagnostic LTD) or Micronaut (MERLIN Diagnistika GmbH, Bruker) with different panels depending on the bacteria to be tested as recommended by Decision 2020/1729/EU. Epidemiological cut-off values (ECOFF) recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 08.03.2024 and 23.04.2024 for *Pasteurella* spp.) were used with some exceptions as explained further in Appendix 7. See Appendix 6 for definitions of cut-off values. The table below gives an overview of which panel was used for which clinical isolate.

S. pseudintermedius isolates from dogs were also investigated for penicillinase (beta-lactamase) production using the clover leaf test and for methicillin resistance using oxacillin disk.

Overview of which panel was used for which clinical isolate:

Clinical isolate tested	Panel
E. coli	Sensititre® TREK EUVSEC3
S. pseudintermedius	Sensititre® TREK EUST2
Pasteurella multocida	MICRONAUT E1-319-100
Pasteurella canis	MICRONAUT E1-319-100

Quality assurance systems
The following susceptible bacteria were included as quality control on a regular basis: *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213 and *Haemophilus influenzae* ATCC 49766. In addition to the regular susceptible bacteria, the following bacteria received from EURL-AR were included: *Acinetobacter baumannii* 2012-70-100-69 (EUVSEC3 and EUVSEC2 panel), and *E. faecium* 2012-70-76-8 and *E. faecalis* 2012-70-103-3 (EUVENC panel). The results were approved according to reference values given by EUCAST or EURL-AR when available. Additional control strains were included when necessary. The laboratories at the NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in quality assurance programmes for veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit. Loughborough. UK) and for resistance monitoring (EURL for Antimicrobial Resistance in Denmark).

Data processing
Susceptibility data were recorded and stored in the sample registration system at the NVI as discrete values (MIC). Data management was performed both in SAS-PC System® v 9.4 for Windows (SAS Institute Inc. Cary. NC. USA) and in R version 4.2.2 Copyright (C) 2023 (The R Foundation for Statistical Computing Platform), while the statistical analysis was performed in R. All changes and differences yielding a p-value <0.05 were considered as statistically significant. The 95% confidence intervals were calculated using the exact binomial test.

Appendix 4:
Sampling, microbiological methods and data processing of zoonotic and non-zoonotic enteropathogenic bacteria in NORM and NORM-VET

NORM-VET enteropathogenic bacteria
Sampling strategy – animals and food

***Salmonella* spp.**
Isolates of *Salmonella* spp. were retrieved from the Norwegian *Salmonella* control programme for live animals, and from the surveillance of wild boar. Additional isolates were obtained from submissions to the National Reference Laboratory for Salmonella, and from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). One isolate of each serovar per incident was included for susceptibility testing.

Campylobacter jejuni* and *Campylobacter coli
Caecal samples from cattle and fattening pigs decribed in Appendix 3, were used for isolation of *Campylobacter coli* and *Campylobacter jejuni*. Sample material, i.e. caecal content from one fattening pig and one cattle per herd as described in Appendix 3, were plated directly onto mCCDA agar and Bützler agar and incubated under microaerophilic conditions at 41.5±0.5°C for 48h. Typical colonies were subcultured on blood agar and confirmed as *C. jejuni* or *C. coli* using Matrix Assisted Laser Desorption/Ionization - Time of Flight Mass Spectrometry (MALDI-TOF MS; Bruker Daltonics GmbH).

Susceptibility testing animal isolates
Isolates were tested for antimicrobial susceptibility. MIC values were obtained using panels from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacteria to be tested as recommended by Decision 2020/1729/EU, see table below. For animal isolates, epidemiological cut-off (ECOFF) values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 08.03.2024) were used, with some exceptions as explained further in Appendix 7.

Overview of Sensititre® TREK panels used:

Bacteria tested	Sensititre® TREK panel
Salmonella spp.	EUVSEC3
Campylobacter jejuni/coli	EUCAMP3

Quality assurance systems NORM-VET
The following susceptible bacteria were included as quality controls on a regular basis: *E. coli* ATCC 25922 and *C. jejuni* ATCC 33560. In addition to the regular susceptible bacteria, the following bacteria received from EURL-AR were included: *C. coli* 2012-70-443-2 (EUCAMP3 panel) and *Acinetobacter baumannii* 2012-70-100-69 (EUVSEC3). The NVI and the Reference Laboratory for Enteropathogenic Bacteria/NIPH have a quality assurance system according to the requirements of NS-EN ISO/IEC 17025. The participating laboratories at the NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in external quality assurance programmes for veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit Loughborough, United Kingdom) and for resistance monitoring (EURL for Antimicrobial Resistance, Denmark).

Data processing animal isolates
Susceptibility data were recorded and stored in the sample registration system at NVI as discrete values (MIC). Data management was performed both in SAS-PC System® v 9.4 for Windows (SAS Institute Inc. Cary. NC. USA) and in R version 4.2.2 Copyright (C) 2023 (The R Foundation for Statistical Computing Platform), while the statistical analysis was performed in R. All changes and differences yielding a p-value <0.05 were considered as statistically significant. The 95% confidence intervals were calculated using the exact binomial test.

NORM - enteropathogenic bacteria
Sampling strategy - humans

All human isolates of *Salmonella, Yersinia enterocolitica* and *Shigella* were obtained from clinical cases. One isolate per patient or one isolate per recognised outbreak was included for susceptibility testing. *Campylobacter* isolates from a selection of a little less than 10% of registered campylobacteriosis cases were submitted in the following way: Two regional laboratories submitted the first ten and two submitted the first five isolates each month to the NRL for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Identification of bacteria - human isolates
The reference analyses on human clinical isolates of enteropathogenic bacteria were performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th edition ASM-Press, Washington 2003 and Ewing WH: Edwards and Ewing's Identification of *Enterobacteriaceae*, 4. edition, Elsevier, New York 1986).

Susceptibility testing - human isolates
Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the NRL for Enteropathogenic Bacteria at the NIPH by agar disk diffusion tests according to the EUCAST standardised method for AMR testing of non-fastidious bacteria. *Campylobacter* isolates from humans were tested for antimicrobial susceptibility using MIC Test Strips.

For human isolates, EUCAST clinical breakpoints for *Enterobacteriaceae* v.14.0 2024 were used if defined. In absence of clinical breakpoints, ECOFFs or national zone distributions were used (e.g. tetracycline) as detailed in Apendix 8. Pefloxacin was used to infer ciprofloxacin resistance in *Salmonella* and *Shigella*.

Isolates with reduced susceptibility to cefotaxime or ceftazidime were tested for the presence of $ESBL_A$ by a double disk approximation test, and for the presence of $ESBL_M$ by an AmpC detection test. Isolates with reduced susceptibility to meropenem were forwarded to the Norwegian National Advisory Unit on Detection of Antimicobial Resistance (K-Res) for further analyses.

Genotyping - human isolates
All *Enterobacterales* isolates received at NRL from primary diagnostic laboratories in Norway were screened for antimicrobial resistance determinants using NCBI AMRFinderPlus following whole genome sequencing (paired end, Illumina) and *de novo* assembly (SKESA 2.4.0) in Ridom SeqSphere+ (v.10.0.1).

Quality assurance systems - human isolates
The NRL for Enteropathogenic Bacteria at the NIPH is accredited according to the requirements of NS-EN ISO/IEC 17025. *E. coli* ATCC 25922 was used as quality control strain for AMR testing of non-fastidious *Enterobacteriaceae.* The NRL participated in the external quality assessment programme of ECDC for *Salmonella* spp. and *Campylobacter* for antimicrobial susceptibility testing.

Data processing - human isolates
The NRL at the NIPH stores susceptibility data of human isolates as either millimeter zone diameters or MIC values. The results were further analysed by WHONET 5.6 with the aid of the BacLink programme, both developed by Dr. John Stelling.

Appendix 5: Sampling, microbiological methods and data processing in NORM

General considerations and sampling

NORM is based on a combination of periodic sampling and testing in primary diagnostic laboratories, and annual results from national reference laboratories for specific microoganisms. Isolates are included from defined clinical conditions such as respiratory tract infections, wound infections, urinary tract infections, and sepsis. Surveillance schemes 2000-2023 are presented in the table below, for enteric infections see Appendix 4. In 2023, all 21 diagnostic laboratories in Norway participated in the surveillance system in addition to eleven reference laboratories. All diagnostic laboratories followed the same sampling strategy and used identical criteria for the inclusion of microbial strains. Only one isolate per patient and infectious episode was included unless otherwise stated. All microbes were identified using conventional methods as described in the ASM Manual of Clinical Microbiology. The surveillance period started in the beginning of January, and consecutive isolates were included for defined time periods for each surveillance category. The surveillance categories and sampling periods in 2023 were as follows: *E. coli* from blood cultures (6 months); *Klebsiella* spp., *Enterococcus* spp., and *Staphylococcus aureus* from blood cultures (9 months); *Staphylococcus lugdunensis* and *Candida* spp. from blood cultures (12 months); *Streptococcus pneumoniae*, *Streptococcus pyogenes, Streptococcus agalactiae, Haemophilus influenzae* and *Neisseria meningitidis* from blood cultures and cerebrospinal fluids (12 months); *S. aureus* (1 week) and *S. lugdunensis* (3 months) from wound specimens; *S. pneumoniae* from respiratory tract specimens (3 weeks); *E. coli* (3 days) and *Klebsiella* spp. (3 weeks) from urinary tract infections; and *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* from all specimen types (12 months). *S. pneumoniae*, *S. pyogenes*, *N. meningitidis* and *H. influenzae* from blood cultures and cerebrospinal fluids were analysed at the the Norwegian Institute of Public Health (NIPH) in Oslo. *N. gonorrhoeae* was analysed at NIPH and Oslo University Hospital (OUS)/Ullevål. *Candida* spp. isolates were analysed at OUS/ Rikshospitalet. MRSA and *S. agalactiae* isolates were analysed at St. Olav University Hospital in Trondheim. *M. tuberculosis* isolates were analysed at NIPH, OUS/Ullevål and Rikshospitalet.

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp., *S. aureus* and *S. lugdunensis* isolates were examined according to the EUCAST disk diffusion method using antibiotic disks and Mueller Hinton II agar from either Oxoid or Beckton Dickinson. Suitable antibiotics were selected for each bacterial species, and the results were interpreted according to the most recent breakpoints from NordicAST, which are harmonised with EUCAST. Beta-lactamase production in *S. aureus, S. lugdunensis* and *N. gonorrhoeae* was examined by nitrocefin disks, acidometric agar plates (3.6 mg/L penicillin G and phenol red) or clover leaf test. *Enterococcus* strains were screened for glycopeptide resistance using vancomycin 6 mg/L BHI agar. *H. influenzae*, *S. pyogenes*, *S. agalactiae*, *N. meningitidis* and *N. gonorrhoeae* were susceptibility tested using MIC gradient tests (bioMerieux or Liofilchem) on MH II agar supplemented with 5% lysed horse blood, GC agar with 1% haemoglobin and Isovitalex (*N. gonorrhoeae*), whereas *S. pneumoniae* was examined using Sensititre microdilution plates from Thermo Fisher Scientific (systemic isolates) or MIC gradient tests (respiratory tract isolates). Susceptibility testing of *Candida* spp. isolates was performed by MIC gradient tests using RPMI agar containing 2% glucose and MOPS. Resistance values were recorded as inhibition zone sizes or MIC values in order to monitor trends in the occurrence of resistance. *M. tuberculosis* isolates were tested using BACTEC MGIT 960 systems. All three test laboratories for *M. tuberculosis* participate in the WHO external DST quality control programme. They were also tested for mutations in the *rpoB* gene to detect rifampicin resistance.

Confirmation of resistance phenotypes

E. coli and *Klebsiella* spp. with reduced susceptibility to 3rd generation cephalosporins were examined for ESBL production using ESBL combination MIC gradient tests (Liofilchem), disks (BD) or tablets (Rosco) according to the instructions of the manufacturer. *S. aureus* and *S. lugdunensis* isolates with reduced susceptibility to cefoxitin were examined by *mecA* PCR for confirmation of methicillin resistance (MRSA). *Enterococcus faealis* and *E. faecium* isolates displaying growth on the vancomycin screening agar were examined by *van* PCRs. The MLS phenotype of erythromycin resistant *S. aureus, S. lugdunensis, S. pneumoniae, S. pyogenes* and *S. agalactiae* isolates were analysed using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

Molecular typing and characterisation of isolates

The NORM report includes specific molecular analyses of carbapenemase-producing Gram-negatives, vancomycin resistant enterococci (VRE) and linezolid resistant enterococci (LRE). These microbes are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) and characterised by the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-res). The analyses include whole genome sequencing of the isolates followed by analysis for resistance genes/mutations and molecular typing. Presence of resistance genes/mutations is analysed using AMR-FinderPlus combined with the Bacterial Antimicrobial Resistance Reference Gene Database (1) plus LRE-Finder specifically for linezolid resistance markers (2). Molecular typing of the isolates was performed at two hierarchal levels using species-specific multilocus sequence typing (MLST) schemes, standard MLST and core genome MLST (cgMLST). Standard MLST includes comparison of the sequence of seven defined species-specific house-keeping genes (alleles) where each allele is assigned an arbitrary number. The standard MLST scheme enables definition of a specific sequence type (ST) (see e.g. https://pubmlst.org/). In contrast, cgMLST includes a defined set of ~1400-3800 alleles depending on the species allowing for analysis at a higher resolution (see e.g. references 3 and 4). For each cgMLST scheme a defined reference genome is applied and

the analysis includes an allele-by-allele comparison with defined thresholds for cluster analysis (https://www.cgmlst.org/ncs). A comparison table is used for distance calculation and enables creation of a minimum spanning tree (MST) (5). In the MST, isolates are visualised as circles and lines are created between the closest related isolates. This creates a network of the population. The length of the line is not proportional to the evolutionary distance. However, the number of allele differences between samples are indicated in the MST. Using species-specific defined cut-offs of allele differences for cluster determination, clusters of closely related isolates can be determined and visualised.

References

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Quality control

The following strains were used for quality control: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 (ESBL positive), *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299 (*vanB* positive), *S. pneumoniae* ATCC 49619, *S. pneumoniae* TIGR4, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. aureus* ATCC 43300 (heterogeneous MRSA), *S. aureus* CCUG 35600 (homogeneous MRSA), *H. influenzae* ATCC 49766, *N. gonorrhoeae* CCUG 26213/ ATCC 49266, *N. gonorrhoeae* WHO L, *C. albicans* ATCC 90028, *C. krusei* ATCC 6258 and *C. parapsillosis* ATCC 22019.

Data processing

The specially designed web-based eNORM computer programme was used for registration and storage of patient data, sample data and resistance data. The results were further analysed by WHONET 5.6 with the aid of the BacLink programme, both developed by Dr. John Stelling. The distribution of microbial species in blood culture was based on extraction of routine data from the laboratory information systems of the participants. Additional isolates of the same species from the same patient recovered within one month after the initial finding were considered duplicates and omitted from the survey. No attempts were made to evaluate the clinical significance of each finding.

	Microbe	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Respiratory tract	*S. pneumoniae*	50	50		50		50		3 w		3 u			3 w		3 w		3 w		3 w		3 w			3 w
	H. influenzae	50	50			25			3 w				3 w			3 w			3 w					3 w	
	S. pyogenes			50		25		25		2 w					3 w						3 w				
	M. catarrhalis				50					4 w															
Urine	*E. coli*	50	50	50	50	50	50	50	1 w	2 d	2 d	2 d	2 w	2 d	2 d	3 d	3 d	3 d	3 d	3 d	3 d	1 w	3 d	3 d	3 d
	Klebsiella spp.	50	50		50						3 u			3 w	3 w	3 w	3 w	3 w	3 w	3 w	3 w	3 w	3 w	3 w	3 w
	Enterococcus spp.	50	50									2 w					3 w			3 w					
	Enterobacter spp.						50											3 w						3 w	
	Citrobacter spp.																							3 w	
	Serratia spp.																							3 w	
	Proteus spp.							25											3 w						
	P. aeruginosa																				3 w				
Wounds	*S. aureus*		50		50	50		50	2 w	2 w	2 u	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w
	S. lugdunensis			50		25		25		4 w					3 w						3 w				3 m
	S. pyogenes			50		25		25		4 w					3 w						3 w				
	GCS/GGS																			4 w					
Blood	*E. coli*	50	50	50	50	50	50	50	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m	6 m
	Klebsiella spp.	25	25	25	25	25	25	25	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m
	Enterobacter spp.							12 m	12 m	9 m								9 m						9 m	
	Citrobacter spp.																							9 m	
	Serratia spp.																							9 m	
	Proteus spp.																		9 m						
	P. aeruginosa			12 m	12 m				12 m			12 m					9 m				9 m				12 m
	Acinetobacter spp.								12 m	12 m															12 m
	H. influenzae														12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	N. menigitidis														12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	S. aureus	50	50	50	50	50	50	50	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m
	S. lugdunensis																								12 m
	Enterococcus spp.	20	20	20	20	20	20	20	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m	9 m
	S. pneumoniae	50	50	50	50	50	50	50	9 m	9 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	S. pyogenes (GAS)						12 m	12 m							12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	S. agalactiae (GBS)							50		12 m			12 m			12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	GCS/GGS																			12 m					
	Obligate anaerober			12 m	12 m	12 m				12 m	12 m	12 m				12 m						12 m			
	Candida spp.							12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
All locations	*N. gonorrhoeae*				12 m			12 m				12 m			12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m
	M. tuberculosis	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m	12 m

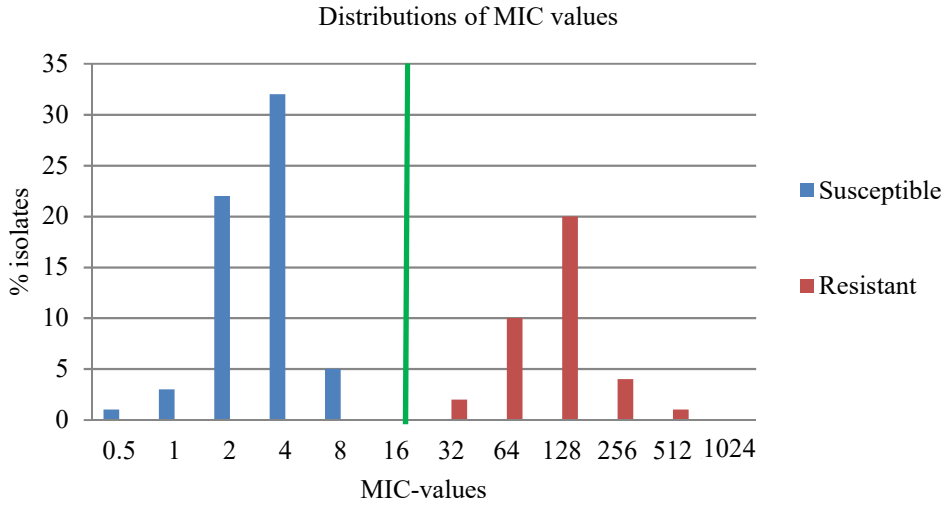
Surveillance at reference laboratories in red. d=days; w=weeks; m=months.

Appendix 6:
Definitions and classification of resistances used in this report

General guidelines for the reader of this report

The results presented in the NORM and NORM-VET programmes are not directly comparable. This is because the sampling and also the classification of resistance differ between the programmes. Clinical breakpoints are used for the classification within NORM, while epidemiological cut-off values (ECOFF) are used for the classification of resistance within NORM-VET.

The terms and usage of these two ways of classification of resistance are further explained below. The ECOFF would normally be lower for minimum inhibitory concentration (MIC) values and higher for disk diameters than the clinical breakpoints. However, this is not always the case.



Epidemiological cut-off values

Based on the distribution of the MIC values, or the inhibition zone diameter distribution, each bacterial population could (in an ideal case) be divided into two sub-populations by a biphasic curve as shown in the example above. The curve to the left (blue) shows the susceptible or wild type distribution, whereas the curve to the right (red) shows the resistant or non-wild type distribution. In NORM-VET we have chosen to define the non-wild type distribution as resistant. The green line indicates a possible ECOFF value applicable to the distributions in the example. ECOFF may be used to detect emerging resistance in the bacterial populations.

However, for several bacterial populations and corresponding tested antimicrobial substances these distributions may be overlapping. A part of the population within the overlapping area may carry resistance mechanisms and others not. In the area with the non-wild type distribution, new resistance mechanisms are responsible for the resistance either alone or in addition to the resistance mechanisms present at lower MIC values. In order to establish MIC values for each specific bacterial population and antimicrobial agent, large amounts of data are collected and assessed. In the NORM-VET part of this report, we have mainly used the ECOFF values recommended by EUCAST.

Clinical breakpoints

Clinical breakpoints are defined in order to indicate if treatment of a specific pathogen is likely to succeed or not. Other factors like dosage and formulations also affect the clinical result. The MIC values are ideally obtained for the pathogen *in vitro*, and this is compared with the pre-determined clinical breakpoint to determine whether the organism is likely to respond *in vivo*.

Term used to describe antimicrobial resistance levels

In this report the levels of resistance (i.e. the percentage of resistant isolates among the tested isolates) in the NORM-VET programme have been classified according to the levels presented in the EFSA and ECDC Summary Report from 2021 and 2022, as follows:

Rare:	< 0.1%
Very Low:	0.1% to 1%
Low:	> 1% to 10%
Moderate:	> 10% to 20%
High:	> 20% to 50%
Very high:	> 50% to 70%
Extremely high:	> 70%

Appendix 7:
Cut-off values NORM-VET

Epidemiological cut-off (ECOFF) values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 08.03.2024 and 23.04.2024 for *Pasteurella* spp.) were used. For additional antimicrobial agents not defined in the EUCAST recommendations, EFSA recommended cut-off values were used.

In the NORM-VET figures; the penicillins are grouped together in the class beta-lactams/penicillins; trimethoprim and sulfonamides are grouped together in the class Sulfonamides and trimethoprim; macrolides, lincosamides and streptogramins are grouped together in the class Macrolides/lincosamides/streptogramins and the streptomycins are grouped together with other.

Overview of the antimicrobial classes and agents tested for with corresponding epidemiological cut-off values (mg/L) used in NORM-VET 2023:

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella enterica*	*Campylobacter coli / C. jejuni*	*Enterococcus faecalis / E. faecium*	*Staphylococcus pseudintermedius*	*Pasteurella multocida / P. canis*
Tetracyclines	Doxycycline						>1
	Tetracycline	>8	>8	>2 / >1	>4	>1	>2
	Tigecycline	>0.5	ND		>0.25		
Amphenicols	Chloramphenicol	>16	>16	>16	>32	>16¤	>1
	Florfenicol						>1
Penicillins with extended spectrum	Ampicillin	>8	>4		>4		>0.5
	Temocillin	(>16)					
Beta-lactamase sensitive penicillins	Benzylpenicillin					ψ	>0.5
Beta-lactamase resistent penicillins	Oxacillin						ND
Combinations of penicillins, incl. beta-lactamase inhibitors	Amoxicillin/clavulanate						>0.5
1st generation cephalosporins	Cephalexin						>8
2nd generation cephalosporins	Cefoxitin	(>16)				>4¤	
3rd generation cephalosporins	Cefotaxime	>0.25	>0.5				
	Ceftazidime	>1	>2				
	Cefovecin						ND
Combinations of 3rd generation cephalosporins and clavulanic acid	Cefotaxime/clavulanate	(>0.25)					
	Ceftazidime/clavulanate	(>1)					
4th generation cephalosporins	Cefepime	(>0.125)					
Monobactams	Aztreonam						
Carbapenems	Meropenem	>0.06	ND				
	Ertapenem	(>0.03)		ND/>0.125			
	Imipenem	(ND)					
Trimethoprim and derivatives	Trimethoprim	>2	>2			>2¤	
Sulfonamides	Sulfamethoxazole	>64#	ND			ND	
Combinations of sulfonamides and trimethoprim, incl. derivates	Sulfamethoxazole and trimethoprim						>0.125
Macrolides	Erythromycin			>8 / >4	>4	>0.5	>16
	Azithromycin	>16	>16				

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella enterica*	*Campylobacter coli / C. jejuni*	*Enterococcus faecalis / E. faecium*	*Staphylococcus pseudintermedius*	*Pasteurella multocida / P. canis*
Lincosamides	Clindamycin					>0.25	ND
Streptogramins	Quinupristin and dalfopristin				>32 / >2	>1¤	
Streptomycins	Streptomycin					>16¤	
Other aminoglycosides	Gentamicin	>2	>2	>2	>64 / >32	>0.25	>8
	Amikacin	>8	>4				
	Kanamycin					>8¤	
Fluoroquinolones	Ciprofloxacin	>0.064	>0.125	>0.5	>4 / >8	>2¤	
	Enrofloxacin						>0.06
	Pradofloxacin						ND
Other quinolones	Nalidixic acid	>8	>8				
Glycopeptid antibacterials	Vancomycin				>4	>2¤	
	Teicoplanin				>2		
Polymyxins	Colistin	>2	ND				
Other antibacterials	Fusidic acid					>0.5¤	
	Tiamulin					>2¤	
	Linezolid				>4	>4¤	
	Mupirocin					>1¤	
	Daptomycin				>4 / >8		
	Rifampicin					>0.03¤	

ND = not defined, ( ) = only ESBL/AmpC suspected isolates tested as described in Commission Implementing Decision of 17. Nov 2020 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2020/1729/EU), data not shown in the report tables. #Cut-offs defined by EFSA. ¤Cut-off defined by ECOFF for *S. aureus*. ᵠBenzylpenicillin, resistance was deduced from beta-lactamase production analysis.

Appendix 8: Breakpoints NORM

NORM data are categorised according to the breakpoints of the Nordic Committee on Antimicrobial Susceptibility Testing (NordicAST) which are harmonised with EUCAST breakpoints. NordicAST breakpoints are available at www.nordicast.org.

Zoonotic and non-zoonotic enteropathogenic bacteria are also categorised based on EUCAST epidemiological cut-off values (ECOFF) as specified below.

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*	*Acinetobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Staphylococcus lugdunensis*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Amikacin	≤ 8	> 8				■																			
	≤ 16	> 16			■																				
Amphotericin B	≤ 1	> 1																			■	■	■	■	■
Ampicillin	≤ 1	> 1					■																		
	≤ 4	> 4								■[1]															
	≤ 4	> 8															■								
	≤ 8	> 8	■							■	■[2]	■[2]													
Amoxi-Clav*	≤ 2	> 2					■																		
	≤ 8	> 8	■	■																					
	≤ 32	> 32	■	■																					
Anidulafungin	≤ 0.03	> 0.03																			■				
	≤ 0.06	> 0.06																				■	■		
	≤ 4	> 4																						■	
Aztreonam	≤ 0.001	> 16			■																				
	≤ 1	> 4	■	■																					
Cefalexin	≤ 16	> 16	■	■																					
Cefepime	≤ 0.001	> 8			■																				
	≤ 1	> 4	■	■																					
Cefixime	≤ 0.125	> 0.125							■																
Cefoxitin	≥ 22 mm	< 22 mm													■										
	≥ 27 mm	< 27 mm														■									
Cefotaxime	≤ 0.125	> 0.125					■																		
	≤ 0.25	> 0.25										■[1]													
	≤ 0.5	> 0.5								■[1]															
	≤ 0.5	> 2																■							
	≤ 1	> 2	■	■						■	■[2]	■													
Ceftaroline	≤ 1	> 2													■										
Ceftazidime	≤ 0.001	> 8			■																				
	≤ 1	> 4	■	■						■	■[2]	■[2]													
	≤ 2	> 2								■[1]															
Ceftolozane-Tazobactam	≤ 4	> 4			■																				
Ceftriaxone	≤ 0.125	> 0.125					■	■	■																
	≤ 0.5	> 2																■							
Cefuroxime	≤ 1	> 2					■																		
Chloramphenicol	≤ 2	> 2					■	■																	
	≤ 16	> 16								■[1]	■[1]	■[1]													

Antimicrobials	MIC (ml/L) S	MIC (ml/L) R	*Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*	*Acinetobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Staphylococcus lugdunensis*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Ciprofloxacin	≤ 0.001	> 0.5			■								■	■											
	≤ 0.001	> 1				■																			
	≤ 0.001	> 2													■	■									
	≤ 0.016	> 0.016						■																	
	≤ 0.03	> 0.06							■																
	≤ 0.06	> 0.06					■			■[2]	■[2]														
	≤ 0.125	> 0.125										■[1]													
	≤ 0.25	> 0.5	■	■								■													
Clindamycin	≤ 0.25	> 0.25													■	■									
	≤ 0.5	> 0.5																■	■	■					
	≤ 4	> 4																							
Erythromycin	≤ 0.25	> 0.25																■	■	■					
	≤ 1	> 1													■	■									
	≤ 4	> 4											■												
	≤ 8	> 8												■											
Fluconazole	≤ 0.001	> 16																				■			
	≤ 2	> 4																			■		■	■	■
Fosfomycin	≤ 8	> 8	■																						
Fusidic acid	≤ 1	> 1													■	■									
Gentamicin	≤ 2	> 2	■	■									■[1]	■[1]	■	■									
	≤ 4	> 4				■																			
	≤ 128	> 128															■								
Imipenem	≤ 0.001	> 4			■												■								
	≤ 2	> 4				■																			
Linezolid	≤ 4	> 4													■	■	■								
Mecillinam	≤ 8	> 8	■	■																					
Meropenem	≤ 0.06	> 0.06																							
	≤ 2	> 2					■																		
	≤ 2	> 8	■	■	■	■				■[2]	■[2]	■[2]													
Micafungin	≤ 0.016	> 0.016																			■				
	≤ 0.03	> 0.03																				■			
	≤ 2	> 2																							■
Mupirocin	≤ 1	> 256													■										
Nitrofurantoin	≤ 64	> 64	■																						
Norfloxacin	≥ 10 mm	< 10 mm																■							
Oxacillin	≥ 20 mm	< 20 mm																■							
Pefloxacin	≥ 23 mm	< 23 mm								■[1]															
	≥ 24 mm	< 24 mm								■	■[2]														

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*	*Acinetobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Staphylococcus lugdunensis*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Penicillin G	≤ 0.06	> 1							■																
	≤ 0.06	> 2																■							
	≤ 0.25	> 0.25						■											■	■					
	≤ 0.25	> 0.5																							
Piperacillin-Tazobactam	≤ 0.001	> 16			■																				
	≤ 8	> 8	■	■																					
Rifampicin	≤ 0.06	> 0.06													■	■									
	≤ 0.25	> 0.25						■																	
Spectinomycin	≤ 64	> 64							■																
Tetracycline	≤ 0.5	> 1							■																
	≤ 1	> 1													■	■		■	■	■					
	≤ 2	> 2					■	■					■	■											
	≤ 4	> 4										■[1]													
	≤ 8	> 8								■[1]															
	≥ 17 mm	< 17 mm								■[3]	■[3]	■[3]													
Tigecycline	≤ 0.25	> 0.25															■								
	≤ 0.5	> 0.5	■												■	■									
Tobramycin	≤ 2	> 2			■																				
	≤ 4	> 4				■																			
Trimethoprim	≤ 4	> 4	■	■		■																			
TMS**	≤ 0.5	> 1					■																		
	≤ 1	> 2																■	■						
	≤ 2	> 4	■	■		■									■	■									
Vancomycin	≤ 2	> 2													■	■				■					
	≤ 4	> 4															■								
Voriconazole	≤ 0.06	> 0.25																			■				■
	≤ 0.125	> 0.25																					■	■	

*Amoxi-Clav=Amoxicillin-clavulanic acid. **TMS Trimethoprim-sulfamethoxazole. Breakpoints for the combination are given for the trimethoprim component only. [1]Epidemiological cut-off value (ECOFF) based on wild type distribution by EUCAST applied to separate between wild type and non-wild type populations. [2]EUCAST clinical breakpoint also applied to separate between wild type and non-wild type populations. [3]There are no clinical breakpoints for tetracycline for *Salmonella*, *Shigella* and *Yersinia*. A clinical breakpoint of R < 17 mm based on national data was applied for all three species, and also as screening breakpoint for *Shigella*.

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