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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. Anti-microbial 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 a 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 June 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 are that livestock associated MRSA will not be established in the Norwegian pig population, and that ESBL in the poultry production will be reduced to a minimum. Also, the action plan states 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-second annual joint report from NORM and NORM-VET, presents data on resistance and usage for 2022. The editors would like to thank all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Oslo / Ås, September 2023

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 2022. 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 2022 utgjorde salget av antibakterielle veterinærpreparater til landdyr totalt 4 623 kg som er 257 kg lavere enn i 2021 og det laveste salget rapportert (data tilgjengelig fra 1993).

Salget av antibakterielle veterinærpreparater til matproduserende landdyr, inkludert hest, var på 4 241 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-laktamaseømfindtlige penicilliner (benzylpenicillinprokain) som ble benyttet. Fra 2013 til 2022 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 30 % målt i kg aktivt stoff. Når salget relateres til dyrepopulasjonen, var nedgangen i forbruket 26 %. Til hest ble det i hovedsak brukt trimetoprim-sulfa som oralpasta.

Salget av antibakterielle veterinærpreparater til flokkbehandling er fortsatt lavt; i 2022 representerte salg av slike preparater 2,7 % av totalsalget til matproduserende landdyr, inkludert hest.

Forbruket av veterinære antibakterielle midler til oppdrettsfisk (forbruk til rensefisk inkludert) var fortsatt svært lavt i 2022 og utgjorde 425 kg. Dette representerer en nedgang på over 99 % sammenlignet med 1987 da forbruket var på sitt høyeste. I 2022 ble det foretatt behandling med antibiotika i 1,9 % av sjølokalitetene for laks og regnbueørret.

Til kjæledyr (hund og katt) ble det i 2022 solgt 382 kg veterinære antibakterielle midler. Dette er en nedgang på 28 % sammenlignet med 2013. Data rapportert til VetReg for perioden 2015-2022 viser en reduksjon på totalt 39 % i forskrivningen av antibakterielle humanpreparater til hund og katt, noe som indikerer at redusert salg av veterinære antibakterielle midler 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 (0,8 %) av totalsalget av veterinære antibakterielle midler til dyr (inkludert fisk) i 2022. 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 2022 ble kun 3 slaktekyllingflokker behandlet med antibiotika.

Forbruk av antibiotika hos mennesker

I 2022 var det totale salget av antibakterielle midler til systemisk bruk hos mennesker (J01 unntatt metenamin) 12,7 definerte døgndoser (DDD)/1 000 innbyggere/dag. Siden 2012 har det vært en markant nedgang i total antibiotikabruk, i alt en reduksjon på 25 %. 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 85 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. Penicilliner (J01C) er oftest forskrevet i primærhelsetjenesten og representerte i 2022; 41 % av all DDD og 57 % av reseptene i ATC-gruppe J01, ekskl. metenamin, etterfulgt av tetracykliner, J01A (19 % av all DDD og 10 % av alle resepter). De fem hyppigst forskrevne antibiotika i 2022 var fenoxymetylpenicillin, pivmecillinam, metenamin, dicloxacillin og doxycyklin. Disse fem utgjorde 65 % av alle resepter og 73 % av all antibiotika DDD brukt i primærhelsetjenesten. I Norge er luftveisinfeksjoner den vanligste indikasjonen for smalspektret penicillin, og i 2022 ble fenoxymetylpenicillin forskrevet på 27 % av alle antibiotikaresepter og utgjorde 22 % av all DDD mens metenamin representerte 9 % av antibiotikareseptene og 26 % av alle DDD i primærhelsetjenesten. Metenamin brukes som forebyggende medisin mot urinveisinfeksjoner og utgjorde 24 % av totalt antall DDD i J01 antibakterielle midler til systemisk bruk. Den jevne nedgangen i antibiotikabruk i primærhelsetjenesten de siste årene kan skyldes økt oppmerksomhet om antimikrobiell resistens, både blant helsepersonell og i befolkningen generelt. Etter innføringen av regjeringens handlingsplan mot 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. ved å unngå antibiotikaforskrivning til virusinfeksjoner, velge riktig antibiotika, individualisere doser eller varighet av kur, så det bør være mulig å oppnå en ytterligere reduksjon i antibiotikaforbruket og en enda mer smalspektret terapiprofil.

Antibiotikasalg (i DDD) til sykehus utgjorde 7,5 % av totalt salg av antibakterielle midler til mennesker i 2022. Salget er redusert med 5 % i DDD/1 000 innbygger/dag sammenliknet med 2019 og økt med 7 % siden 2021. I norske sykehus ble det gjennomsnittlig brukt 77 DDD/100 liggedøgn i 2022. Dette er en økning siden 2021, og en økning på 15 % siden 2012. 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 som er anbefalt i retningslinjene. Bruken av bredspektret antibiotika er redusert siden 2012. De utgjorde 21 % av bruken

målt i DDD/100 liggedøgn i 2022 og 26 % i 2012. I sykehus ble penicilliner (J01C) mest brukt (nesten halvparten av bruken målt i DDD), mens cefalosporiner er den nest største antibiotikagruppen; 19 % av all DDD. Det er store variasjoner mellom sykehus, både målt i volum (i DDD/100 liggedøgn) og i terapiprofil. Variasjonene kan ikke forklares med forskjeller i aktivitet eller pasientsammensetning alene.

Resistens hos kliniske isolater fra dyr

I 2022 ble det undersøkt *Staphylococcus aureus* og koagulase-negative *Staphylococcus* spp. (CoNS) fra mastitt hos storfe, samt *Pseudomonas aeruginosa* fra forskjellige infeksjoner hos hund. Av 191 undersøkte *S. aureus* isolater var 86,9 % fullt følsomme for alle de antibiotika de ble testet for. Ingen av isolatene var multiresistente (dvs. resistente mot tre eller flere antibakterielle klasser), og ingen ble identifisert som meticillinresistente *S. aureus* (MRSA). Tilsvarende var 44,2 % av 190 undersøkte CoNS isolater fullt følsomme, mens 2,1 % var multiresistente.

Totalt 78,8 % av 118 undersøkte *P. aeruginosa* isolater var fullt følsomme for de antibiotika som var inkludert i testpanelet. Multiresistens ble påvist hos 4,2 % av isolatene. Noen isolater viste nedsatt følsomhet for karbapenemer, og blir videre undersøkt med helgenomsekvensering. Karbapenemresistens forårsaket av mutasjoner har imidlertid blitt beskrevet tidligere hos *P. aeruginosa* fra hund.

Resistens hos indikatorbakterier fra dyr og mat

Resultatene fra 2022 bekrefter at situasjonen i Norge er god med tanke på antibiotikaresistens hos bakterier fra dyr og mat. Forekomsten av multiresistens (resistens mot tre eller flere antibakterielle klasser) og spesielle resistente bakterier/resistensmekanismer av særlig interesse, slik som ekstendert-spektrum cefalosporin (ESC)-resistente *Escherichia coli*, er fremdeles lav. Karbapenemresistente *Enterobacterales* (CRE) har ikke blitt påvist fra produksjonsdyr eller mat i Norge.

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*, CRE, vankomycinresistente *Enterococcus* spp. (VRE), linezolidresistente *Enterococcus* spp. (LRE), 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 2022 ble det undersøkt blindtarmsprøver fra flokker av slaktekylling og kalkun for isolering og sensitivitetsundersøkelse av *E. coli* og *Enterococcus* spp., samt isolering av ESC-resistente *E. coli*, CRE, VRE og LRE. Svaberprøver fra katt var også inkludert for sensitivitetsundersøkelse av *E. coli*, samt for undersøkelser for forekomst av ESC-resistente *E. coli* og CRE. Fra katt ble det videre undersøkt svaberprøver fra munnhule/perineum for isolering og sensitivitetstesting av *Staphylococcus felis* og *S. aureus*, samt for påvisning av MRSA og MRSP. Prøvene av mat i 2022 var kylling- og kalkunkjøtt, og disse ble undersøkt for forekomst av ESC-resistente *E. coli* og CRE.

I prøvene fra slaktekylling var majoriteten (79,3 %) av de 363 *E. coli* isolatene fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for, og kun 1,4 % av isolatene var multiresistente. Andelen fullt følsomme isolater har vært relativt stabil rundt 80 % de siste årene (2014-2022). Den tidligere meldte økningen i kinolonresistens fra 3,4 % i 2014 til 12,6 % i 2020, ser nå ut til å ha stagnert med 9,4 % av isolatene resistente mot kinoloner i 2022. ESC-resistente *E. coli* ble kun påvist i to av blindtarmprøvene, og ikke fra noen av kjøttprøvene fra slaktekylling. Resistensmekanismen i de to isolatene var henholdsvis kromosomale mutasjoner og et $bla_{\text{CTX-M-55}}$ gen. Den lave forekomsten er i samsvar med resultatene fra 2018 og 2020, og bekrefter at tiltakene iverksatt av fjørfenæringen for å redusere forekomsten av ESC-resistente *E. coli* hos slaktekylling har vært vellykket. Av *Enterococcus faecalis* isolatene (n=84) fra slaktekyllingflokkene var 32,1 % fullt følsomme for de antibakterielle midlene de ble testet for, mens tilsvarende tall for *Enterococcus faecium* (n=358) var 58,1 %. Andelen fullt følsomme isolater har vært relativt stabil i årene 2014-2022. Ingen av isolatene var multiresistente. Hverken LRE eller VRE ble påvist i den selektive screeningen. VRE har ikke vært påvist de siste årene.

Majoriteten (79,1 %) av *E. coli* (n=110) fra kalkun var fullt følsomme for de antibakterielle midlene som var inkludert i testpanelet. Denne situasjonen ser ut til å ha vært relativt stabil de siste årene (2016-2022). Totalt 2,7 % av isolatene var multiresistente. ESC-resistente *E. coli* ble påvist fra elleve (10 %) av kalkunprøvene. Hos ni av disse var resistensen forårsaket av kromosomale mutasjoner, mens den hos de to siste isolatene var forårsaket av $bla_{\text{CTX-M-15}}$ genet. ESC-resistente *E. coli* ble ikke påvist fra noen av de 122 undersøkte prøvene av kalkunkjøtt. Av 24 undersøkte *E. faecalis* isolater og 115 undersøkte *E. faecium* isolater var henholdsvis 50 % og 21,1 %, fullt følsomme for alle de antibakterielle midlene det ble testet for. Multiresistens ble påvist hos 2,8 % av *E. faecium* isolatene. Det har vært en reduksjon i resistens mot narasin hos *E. faecium* fra kalkun sammenliknet med tidligere år, fra ca. 80 % til 60 % i 2022. Monensin har vært benyttet til kalkun, og ikke narasin. Monensin ble imidlertid faset ut i løpet av 2022, og kalkun blir nå alet opp uten bruk av koksidiostatika. Det er ingen kjent kryssresistens mellom narasin og monensin, og årsaken til nedgangen i narasinresistens er derfor uklar. Hverken LRE eller VRE ble påvist i de selektive undersøkelsene, og dette samsvarer med resultatene fra 2018 og 2020.

I prøvene fra katt var majoriteten (79,2 %) av 211 *E. coli* isolater fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for. Multiresistens ble påvist hos kun 0,5 % av isolatene. Seks isolater var resistente mot ESC, og kromosomale mutasjoner ble påvist som bakenforliggende årsak. Ett av isolatene (også påvist ved selektive metoder) hadde i tillegg genet $bla_{\text{CTX-M-1}}$. Fire av 250 undersøkte katteprøver (1,6 %) var positive for ESC-resistente *E. coli* i den selektive screeningen. Kromosomale mutasjoner ble påvist hos to av dem, hvorav ett også hadde $bla_{\text{CTX-M-1}}$ genet

og det andre *bla*$_{CTX-M-14}$ genet. De to siste isolatene ble genotypet som henholdsvis *bla*$_{CTX-M-15}$ og *bla*$_{CTX-M-55}$. Ingen CRE ble påvist fra katt. Av 160 *Staphylococcus felis* isolater fra 263 katteprøver fra munnhule/perineum, var 73,1 % fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for. To isolater ble videre undersøkt med helgenomsekvensering, og *blaZ* ble påvist i ett av isolatene. Hverken MRSA eller MRSP ble påvist ved selektive metoder.

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 2022 sensitivitetstestet 49 *Salmonella* spp. isolater fra dyr (fire fra gris, åtte fra storfe, ett fra sau, to fra hund, 31 fra katt og tre fra villsvin). 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, monophasic (4,[5],12:i:-), og ett *Salmonella* Oranienburg isolat var resistent mot kinoloner. I tillegg til isolatene fra dyr, ble det undersøkt fire *Salmonella* spp. isolater fra kjøtt eller andre matvarer som ikke var av norsk opprinnelse. Disse kom fra Nasjonalt referanselaboratorium for *Salmonella*. Alle fire isolatene var fullt følsomme for de antibiotika som var inkludert i testpanelet.

Campylobacter spp. fra flokker med slaktekylling var inkludert i 2022. Kun to isolater av *C. coli* ble påvist, og disse ble ikke undersøkt videre. Av 91 *C. jejuni* isolater var 89,0 % fullt følsomme for de antibakterielle midlene de ble sensitivitetstestet for. Multiresistens ble påvist hos 1,1 % av isolatene.

Kliniske isolater av tarmpatogene bakterier fra mennesker

Referanselaboratoriet 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 sammenlignet med innenlandservervede stammer. Genet *mcr-3.1,* som koder for kolistinresistens ble identifisert for første gang fra en reiseassosiert monofasisk *Salmonella* Typhimurium infeksjon. En økende trend av resistens mot cefalosporiner med utvidet spektrum, spesielt ved reiseassosierte infeksjoner med monofasisk *Salmonella* Typhimurium ble identifisert. Multiresistens (MDR) var en karakteristisk egenskap for et betydelig antall monofasiske *Salmonella* Typhimurium (76,1 %) og *Salmonella* Typhi isolater (57,1 %). Elleve isolater ble karakterisert som ESBL-produserende og genotypet til *bla*$_{CTX-M}$ (n=7), *bla*$_{OXA-10}$ (n=2), *bla*$_{CMY-2}$ (n=1) og *bla*$_{DHA}$ (n=1).

For *Campylobacter jejuni* var det generelle resistensnivået for ciprofloksacin og tetracyklin høyere for stammer fra reiseassosierte infeksjoner sammenlignet med innenlandservervede stammer. Antibiotikaresistens i *Yersinia enterocolitica* er fortsatt lav. En økende trend av resistens mot ciprofloksacin og utvidet spektrum cefalosporiner ble observert både hos *Shigella sonnei* og *Shigella flexneri*. Tjuefem og sytten ESBL-produserende stammer ble identifisert fra henholdsvis *Shigella sonnei* og *Shigella flexneri* isolater, og karakterisert med *bla*$_{CTX-M}$ and *bla*$_{OXA}$ gener.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2022. Det ble påvist 16 tilfeller av meticillinresistente *Staphylococcus aureus* (MRSA) blant 1 601 blodkulturisolater (1,0 %). Resultatene samsvarer med tall fra laboratorienes datasystemer som rapporterte 23 MRSA isolater blant 2 246 *S. aureus* (1,0 %) fra blodkultur og spinalvæske i 2022. Dette er på samme nivå som 0,8 % i 2021. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 843 tilfeller av MRSA infeksjon i 2022 sammenliknet med 734 i 2020 og 701 i 2021. De fleste tilfellene var fra pasienter med overfladiske sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (13 av 807; 1,6 %) slik de også har gjort i tidligere år (1,8 % i 2020; 1,5 % i 2022). MSIS registrerte videre 1 091 tilfeller av MRSA kolonisering i 2022 mot 1 148 i 2020 og 1 050 i 2021. I alt ble det meldt funn av MRSA hos 1 934 personer i 2022. Dette utgjør en insidensrate på 38/100 000 personår mot 35/100 000 i 2020 og 32/100 000 i 2021. 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. Det årlige antall koloniserte personer hadde en topp i 2017 og gikk betydelig ned i de følgende år, men det var igjen en svak økning i 2022. Endringene i forekomst av MRSA kan delvis skyldes smitteverntiltakene som ble satt i verk under Covid-19 pandemien. En høy andel av tilfellene blir fortsatt smittet i utlandet. 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 2022. Andelen av gentamicinresistente isolater var 5,1 % i 2022 sammenliknet med 6,7 % i 2020 og 5,6 % i 2021, mens forekomsten av resistens mot ciprofloxacin var stabil med 10,0 % i 2022 mot 10,4 % i 2021. *Klebsiella* spp. har omtrent samme forekomst av resistens mot gentamicin (4,5 %) og ciprofloxacin (8,3 %) som *E. coli*. Produksjon av bredspektrede beta-laktamaser (ESBL) er blitt et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 133 av 2 229 (6,0 %) *E. coli* og 61 av 1 114 (5,5 %) *Klebsiella* spp. fra blodkultur ble rapportert som ESBL-positive i 2022. Forekomsten er stabil både for *E. coli* (6,5 % i 2020; 5,8 % i 2021) og *Klebsiella* spp. (7,2 % i 2020; 5,5 % i 2021). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (6,0 %) enn fra urinprøver (3,8 %). Som forventet var det høy forekomst av resistens mot beta-laktam antibiotika hos isolater av *Enterobacter* spp., *Citrobacter* spp. og *Serratia* spp. fra blodkultur og urin. Dette skyldes at disse bakterieartene er bærere av kromosomale AmpC-enzymer. Forekomsten av resistens mot andre typer

antibiotika var imidlertid generelt lavere enn hos *E. coli* og *Klebsiella* spp..

Kolonisering/infeksjon med 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 antall pasienter med karbapenemase-produserende *P. aeruginosa* (n=18) og *Acinetobacter* spp. (n=30) økte også dramatisk (henholdsvis n=1 og n=8 i 2021). Multiresistente Gram-negative bakterier kan ofte knyttes til import fra land med høy forekomst av slike mikrober. I 2022 utgjorde isolater fra ukrainske pasienter ved norske sykehus en betydelig andel av totalen.

Antallet systemiske isolater av *Haemophilus influenzae* og *Neisseria meningitidis* økte i 2022, men var fortsatt på et historisk lavt nivå etter pandemien. Både systemiske isolater og luftveisisolater av *H. influenzae* viste synkende andel med produksjon av beta-laktamase (henholdsvis 10,8 % og 10,7 %) men økende forekomst av kromosomal beta-laktamresistens (henholdsvis 10,7 % og 19,3 %). Som tidligere rapportert fra MSIS så man en bratt økning av antallet *Neisseria gonorrhoeae* isolater fra 2021 (n=220) til 2022 (n=830). Det ble påvist utbredt resistens mot penicillin G (17,8 %), og bare 4,0 % var følsomme for standard dosering av penicillin G svarende til villtype-populasjonen. Hele 59,9 % var resistente mot ciprofloxacin. Alle isolater var følsomme for ceftriaxon, men tre isolater (1,4 %) var resistente mot det perorale cefalosporinet cefixim. Alle isolater var fullt følsomme for spectinomycin.

Det ble påvist tre enterokokkisolater fra blodkultur med klinisk signifikant vankomycinresistens i 2022 (en *vanA* og to *vanB E. faecium*). Forekomsten av resistens mot ampicillin i *E. faecium* ligger stabilt rundt 70-80 %. Høygradig gentamicinresistens ble redusert hos både *E. faecalis* (8,5 % i 2021; 6,9 % i 2022) og *E. faecium* (46,2 % i 2021; 44,3 % i 2022). Nesten alle *E. faecium* med høygradig gentamicin-resistens var også resistente mot ampicillin. Det ble funnet tre enterokokkisolater med genetisk verifisert linezolid-resistens (en *E. faecalis* med *optrA* og to *E. faecium* med rDNA mutasjoner). Både VRE og LRE er meldepliktige til MSIS, og det ble bekreftet funn av 74 VRE (75 i 2020; 34 i 2021) og 38 LRE (10 i 2020; 16 i 2021) på referanse-laboratoriet ved Nasjonal kompetansetjeneste for påvisning av antibiotikaresistens (K-res) på UNN i 2022. 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 økende fokus på slike mikrober i laboratoriene.

Overvåkingen av resistens hos systemiske isolater av *Streptococcus pneumoniae* (pneumokokker) og *Streptococcus pyogenes* (beta-hemolytiske streptokokker gruppe A) viste at bare 0,5 % av pneumokokkisolatene fra blod og spinalvæske var resistente mot penicillin G. I tillegg var 9,7 % kun følsomme for økt eksponering av dette middelet. Andelen kategorisert som I+R økte dermed fra 6,9 % i 2021 til 10,2 % i 2022, men forekomsten i 2022 tilsvarer at det ble påvist 12,8 % I+R i 2020. Syv isolater (1,3 %) ble kategorisert som I for ett eller flere 3.-generasjons cefalosporiner. Forekomsten av makrolidresistens blant pneumokokker var 4,6 % i 2022 sammenliknet med 6,0 % i 2021. Alle isolater av *S. pyogenes* fra blodkultur var følsomme for penicillin G. Forekomsten av erytromycin-resistens (6,5 %) var på samme nivå som før pandemien (6,7 % i 2020). Systemiske isolater av *Streptococcus agalactiae* (beta-hemolytiske streptokokker gruppe B) var også følsomme for penicillin G, men hadde høyere forekomst av resistens mot erytromycin (22,7 % i 2021; 21,2 % i 2022) og tetracyklin (80,0 % i 2021; 74,6 % i 2022).

I alt 174 pasienter med tuberkulose ble meldt til MSIS i 2022. Ti isolater (7,2 %) ble definert som multiresistente (MDR) mot både rifampicin og isoniazid sammenliknet med 8,8 % i 2021. Pasientene hadde ervervet sine infeksjoner i Europa utenom Norge (n=6), Afrika (n=2), Asia (n=1) og Norge (n=1).

Det ble utført resistensbestemmelse av 246 *Candida* blodkulturisolater fra 231 ulike pasienter. De vanligste artene var *C. albicans* (n=139), *C. glabrata* (n=41), *C. parapsilosis* complex (n=17), *C. dubliniensis* (n=19) og *C. tropicalis* (n=12). Alle *C. albicans* var følsomme for de undersøkte midlene med unntak av et enkelt echinocandinresistent isolat. Det ble kun påvist enkelte non-*albicans* isolater med ervervet resistens mot flukonazol, men som forventet var det høy forekomst av resistens mot azoler hos *C. glabrata* (17,0 %). Nøyaktig speciesbestemmelse er avgjørende 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 husdyrholdet 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 2022. 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 4,623 kg antibacterial ingredients in 2022, which is 257 kg lower than in 2021 and the lowest annual level reported (data available since 1993).

Sales of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,241 kg in 2022. Penicillins continued to be the most-selling antibacterial class for the major species – i.e. cattle, pigs, goats, sheep and poultry - and were almost exclusively accounted for by beta-lactamase sensitive penicillins. From 2013-2022, the estimated sales of antibacterial VMPs for cattle, pigs, sheep, goats and poultry declined by 30% when measured in kg and 26% 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 2022 such products accounted for only 2.7% of the total sales.

In 2022, the sales (kg) of antibacterial VMPs for farmed fish (cleaner fish included) were 425 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 1.9% of the on-grower locations were subjected to antibacterial treatment in 2022.

The sales (kg) of antibacterial VMPs marketed for companion animals were 382 kg in 2022. From 2013-2022 the sales of such VMPs for use in companion animals have been reduced by 28%. Prescriptions of human antibacterial medicinal products reported to the Veterinary Prescription Register declined by 39% (kg) from 2015 to 2022. This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substituted by prescribing of human antibacterial products.

The European Medicines Agency (EMA) has suggested to restrict the use of some antbacterial 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 of quinolones of the total sales of antibacterial VMPs was very low (0.8%) 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 continue to be very low; in 2022 three broiler flocks were subjected to such treatment.

Usage of antimicrobial agents in humans

In 2022, the total sales of antibacterial agents for systemic use in humans (J01 excl. methenamine) was 12.7 defined daily doses (DDD)/1,000 inhabitants/day. Since 2012 there has been a marked decline in total antibiotic use, a reduction of 25%. 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 85% of the total human sales of antibacterials are used in primary care, i.e. outside health institutions. For ambulatory care, the most important antibiotic group in 2022 was penicillins, J01C; 41% of DDDs and 57% of prescriptions in ATC group J01, excl. methenamine, followed by tetracyclines, J01A (19% of DDDs and 10% of prescriptions). The five antibiotic substances most often prescribed for outpatients in 2022 were phenoxymethylpenicillin, pivmecillinam, methenamine, dicloxacillin and doxycycline. These five antibiotics represented 65% of all prescriptions and 73% of all DDD of the antibacterial group J01. In Norway, the main indication for narrow-spectrum penicillins in primary care is respiratory tract infections, and in 2022, phenoxymethylpenicillin was prescribed in 27% of the prescriptions representing 22% of DDDs while the urinary antiseptic methenamine represented 9% of the J01 prescriptions and 26% of the DDDs. In total use, methenamine accounted for 24% of all DDDs in the antibacterial J01 group. The steady decrease in primary care the latest years 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 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, shortening duration of courses and individualisation of doses. One should expect that it is possible to achieve a further reduction of consumption rate and a better narrow-spectrum profile.

In 2022, the antibacterial sales (in DDDs) to hospitals represented 7.5% of total sales of antibacterials for human use in the country. There has been a decrease of 5% in DDD/1,000 inhibitants/day since 2019 (i.e. before the pandemic) and an increase by 7% compared to 2012. In 2022, a mean use of 77 DDD/100 bed days was observed, an increase since 2021 and an increase by 15% since 2012. Therapy patterns of antibacterials in hospitals do 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 21% of total DDDs for hospitals in 2022 compared to 26% in 2012 (measured in DDD/100 bed days). In hospitals, around half of the use,

measured in DDDs, is penicillins (J01C). The second largest group is the cephalosporins; 19% 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 composition alone.

Resistance in animal clinical isolates

The clinical isolates included in 2022 were *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp. (CoNS) from mastitis in cattle, and *Pseudomonas aeruginosa* from various infections in dogs.

In total, 86.9% of the 191 *S. aureus* isolates were susceptible to all antimicrobial agents included in the test panel. None of the isolates were multi-drug resistant (MDR), and no methicillin resistant *S. aureus* (MRSA) were identified. Among the 190 CoNS, 44.2% were susceptible to all antimicrobial agents included in the test panel. MDR was detected in 2.1% of the isolates.

Of the 118 *P. aeruginosa* isolates, 78.8% were susceptible to all antimicrobial agents included in the test panel, while 4.2% were MDR. A few isolates showed reduced susceptibility to carbapenems and will be further investigated by whole genome sequencing. Resistance to carbapenems due to mutations has previously been described in *P. aeruginosa* from dogs.

Resistance in indicator bacteria from animals and food

The 2022 data confirm that the situation regarding antimicrobial resistance in bacteria from animals and food in Norway is good. The occurrence of multi-drug resistance (MDR), i.e. resistance to three or more antimicrobial classes, and specific emerging resistant bacteria/ mechanisms, such as resistance to extended-spectrum cephalosporins (ESC), are low. Carbapenem resistant *Enterobacterales* (CRE) have never been isolated in samples from production animals or food in Norway.

NORM-VET is following the requirements set in the Commission implementing 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 act may be 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 family animals. Selective methods are used for detection of ESC resistant *E. coli*, CRE, vancomycin resistant *Enterococcus* spp. (VRE), linezolid resistant *Enterococcus* spp. (LRE), MRSA and methicillin resistant *Staphylococcus 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 2022, animal samples included caecal samples from broiler and turkey flocks for susceptibility testing of *E. coli* and *Enterococcus* spp. and detection of emerging resistant bacteria/resistance mechanisms such as ESC resistant *E. coli* and CRE. Faecal swab samples from cats were included for susceptibility testing of *E. coli*, and for detection of ESC resistant *E. coli* and CRE. Oral/perineal swabs from cats were included for susceptibility testing of *Staphylococcus* spp. and selective isolation of MRSA and MRSP. Food samples consisted of broiler and turkey meat, and were used for the detection of ESC resistant *E. coli* and CRE.

In samples from broiler flocks, the majority (79.3%) of *E. coli* (n=363) were fully susceptible to the antimicrobial classes in the test panel, and 1.4% were MDR. The proportion of fully susceptible isolates has been relatively stable around 80% in the last years (2014-2022). The previously reported increase in resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) from 3.4% in 2014 to 12.6% in 2020 seems to have reversed with resistance in 9.4% of the isolates in 2022. ESC resistant *E. coli* were found in only two of the 363 broiler caecal samples and not in any of the 303 broiler meat samples. Resistance in the two detected isolates was due to presence of the $bla_{\text{CTX-M-55}}$ gene and chromosomal mutations, respectively. This low occurrence is in concordance with the results from 2018 and 2020, and confirms that the measures implemented by the industry to reduce the occurrence of ESC resistant *E. coli* in broilers have been successful. Full susceptibility to all antimicrobial classes included in the test panel was present in 32.1% of *Enterococcus faecalis* (n=84) and 58.1% of *Enterococcus faecium* (n=358) isolates from broilers. The proportion of susceptible isolates has been relatively stable over the years 2014-2022. None of the isolates were MDR. Neither LRE nor VRE were detected in the selective screening, and this latter is in concordance with the 2018 and 2020 results.

In turkey, the majority (79.1%) of *E. coli* isolates (n=110) were fully susceptible to the antimicrobial agents in the test panel, and this seems to have been relatively stable over the last years (i.e. 2016-2022). Altogether, 2.7% of the isolates were MDR. ESC resistant *E. coli* were found in 11 of the samples (10%). Nine of these were due to chromosomal mutations, and the latter two were due to the presence of the $bla_{\text{CTX-M-15}}$ gene. ESC resistant *E. coli* were not detected in the 122 turkey meat samples. A total of 50.0% of *E. faecalis* (n=24) and 21.1% of *E. faecium* (n=109) isolates were susceptible to all antimicrobial classes included in the test panel. MDR was detected in 2.8% of *E. faecium* isolates. There has been a reduction in resistance to narasin in turkey *E. faecium* isolates compared to previous years from about 80% to about 60% in 2022. In turkey production, monensin and not narasin has been used. The use of monensin was, however, phased out during 2022, and has not been replaced by any other coccidiostats. There is no known cross-resistance between narasin and monensin, and the reason behind the occurrence of narasin resistance in *E. faecium* from turkey is thus not clear. Neither LRE nor VRE were detected in the selective screening, and this latter is in concordance with the 2018 and 2020 results.

In faecal samples from cats, the majority (79.2%) of *E. coli* isolates (n=211) were fully susceptible to the antimicrobial agents in the test panel. MDR was detected in only 0.5% of the isolates. Six isolates displayed resistance to ESC, and chromosomal mutations were identified. One isolate, also identified through the selective method, additionally carried the $bla_{\text{CTX-M-1}}$ gene. Four (1.6%) of 250 investigated cats were positive for ESC resistant *E. coli* in the selective screening. Chromosomal mutations were identified in two

of these, where one isolate also carried the *bla*$_{\text{CTX-M-1}}$ and the other carried the *bla*$_{\text{CTX-M-14}}$ gene. The two last isolates were genotyped as *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{CTX-M-55}}$, respectively. No CRE were detected among the cat samples. In total, 73.1% of 160 *Staphylococcus felis* isolates from 263 oral/perineal samples were susceptible to all antimicrobial agents included in the test panel. Two isolates were whole genome sequenced, and the *blaZ* gene conferring resistance to beta-lactams was detected in one of them. Neither MRSA nor MRSP were detected in the selective screening method.

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 2022, a total of 49 *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: four pigs, eight cattle, one sheep, two dogs, 31 cats and three wild hogs). One isolate was resistant to tetracyclines and ampicillin (*Salmonella* Typhimurium, monophasic (4,[5], 12:i:-)), and one isolate (*Salmonella* Oranienburg) was resistant to quinolones. Additionally, four *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 four isolates were fully susceptible.

Campylobacter spp. from broiler flocks were included in 2022. Only two isolates of *C. coli* were identified, and these were not further analysed. In total, 89.0% of the 91 *C. jejuni* isolates from broilers tested were susceptible to all antimicrobial agents included in the test panel. MDR was detected in 1.1% of the isolates.

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 rates were higher in strains from travel associated infections compared to domestically acquired infections. The *mcr-3.1* gene encoding colistin resistance was identified for the first time in a travel associated monophasic *Salmonella* Typhimurium infection. An increasing trend for resistance against extended-spectrum cephalosporins was recorded, especially in travel associated infections with monophasic *Salmonella* Typhimurium. Multi-drug resistance (MDR) was a characteristic trait for a considerable number of monophasic *Salmonella* Typhimurium (76.1%) and *Salmonella* Typhi isolates (57.1%). Eleven isolates were characterised as ESBL producers and genotyped with *bla*$_{\text{CTX-M}}$ (n=7), *bla*$_{\text{OXA-10}}$ (n=2), *bla*$_{\text{CMY-2}}$ (n=1) and *bla*$_{\text{DHA}}$ (n=1) genes.

For *Campylobacter jejuni*, overall resistance rates for ciprofloxacin and tetracycline were higher in travel associated infections compared to domestically acquired. 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-five and seventeen ESBL-producing strains were identified among *Shigella sonnei* and *Shigella flexneri* isolates, respectively, harbouring *bla*$_{\text{CTX-M}}$ and *bla*$_{\text{OXA}}$ genes.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2022. Only 16 methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,601 strains included in NORM in 2022 (1.0%). The total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 2,246 including 23 MRSA strains (1.0%). This is at the same level as 0.8% in 2021. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 843 cases of MRSA infections in 2022 compared to 734 in 2020 and 701 in 2021. 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 1.6% (13/807) and comparable to previous years (1.8% in 2020; 1.5% in 2021). Furthermore, MSIS registered 1,091 MRSA colonisations in 2022 compared to 1,148 in 2020 and 1,050 in 2021. A total of 1,934 persons were thus reported with MRSA in 2022, corresponding to an incidence rate of 38/100,000 person years (35/100,000 in 2020; 32/100,000 in 2021). 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. The annual number of newly colonised persons reached a peak in 2017 and declined significantly in the following years, but a slight increase was observed in 2022. The changes in MRSA incidence may in part be explained by the infection control measures implemented during the Covid-19 pandemic. A large proportion of MRSA cases are still infected abroad. 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 2022. The prevalence of gentamicin resistance was 5.1% in 2022 compared to 6.7% in 2020 and 5.6% in 2021, while the prevalence of ciprofloxacin resistance remained stable at 10.0% in 2022 compared to 10.4% in 2021. *Klebsiella* spp. isolates now demonstrate approximately the same rates of resistance to gentamicin (4.5%) and ciprofloxacin (8.3%) as *E. coli*. Extended-spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 133/2,229 (6.0%) *E. coli* and 61/1,114 (5.5%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2022. The prevalence has remained stable for both *E. coli* (6.5% in 2020; 5.8% in 2021) and *Klebsiella* spp. (7.2% in 2020; 5.5% in 2021). The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (6.0%) than in urinary tract isolates (3.8%). As expected, *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp. isolates from blood cultures and urines displayed high rates of beta-lactam resistance due to chromosomal AmpC enzymes. However, these bacterial species were in general

less resistant to non-beta-lactam antibiotics than *E. coli* and *Klebsiella* spp..

Colonisation or infection with carbapenemase-producing *Enterobacterales* (CPE), *P. aeruginosa* and *Acinetobacter* spp. has been notifiable to MSIS since 2012. The number of CPE patients increased sharply from 60 in 2021 to 152 in 2022. The number of patient notifications with carbapenemase-producing *P. aeruginosa* (n=18) and *Acinetobacter* spp. notifications (n=30) has also increased dramatically since 2021 (n=1 and n=8, respectively). Many multi-drug resistant Gram-negative isolates can be linked to import from countries with high prevalence of these organisms. In 2022, isolates from Norwegian hospital patient transferred from Ukraine represented a significant proportion of the total number.

The incidences of *Haemophilus influenzae* and *Neisseria meningitidis* isolates from blood cultures and cerebrospinal fluids increased in 2022, but were still at historically low levels in the aftermath of the coronavirus pandemic. Both systemic and respiratory tract *H. influenzae* isolates demonstrated declining rates of beta-lactamase production (10.8% and 10.7%, respectively) but increased frequencies of chromosomally encoded beta-lactam resistance (10.7% and 19.3%, respectively). As reported by MSIS, the number of *Neisseria gonorrhoeae* isolates (n=830) increased sharply in 2022 compared to 2021 (n=220). Many isolates displayed resistance to penicillin G (17.8%), and only 4.0% were susceptible to standard penicillin G dosage corresponding to the wild type population. Ciprofloxacin resistance was detected in 59.9% of isolates. Three isolates (0.4%) were resistant to cefixime, but were sensitive to ceftriaxone. All isolates were susceptible to spectinomycin.

Three enterococcal blood culture isolates with clinically significant vancomycin resistance were detected in 2022 (one *vanA* and two *vanB E. faecium*). The prevalence of ampicillin resistance in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) was further reduced in *E. faecalis* (8.5% in 2021; 6.9% in 2022) and *E. faecium* (46.2% in 2021; 44.3% in 2022). Almost all HLGR *E. faecium* isolates were also resistant to ampicillin. There were three genetically confirmed linezolid resistant isolates (LRE) in the NORM surveillance programme in 2022 (one *E. faecalis* harbouring *optrA* and two *E. faecium* with rDNA mutations). Both vancomycin resistant enterococci (VRE) and LRE should be reported to the national notification system (MSIS), and 74 VRE (75 in 2020; 34 in 2021) and 38 LRE (10 in 2020; 16 in 2021) were verified at the National Reference Laboratory at K-res/UNN in 2022. 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 systemic *Streptococcus pneumoniae* (pneumococci) and *Streptococcus pyogenes* (beta-haemolytic group A streptococci) isolates at the NIPH reference laboratory revealed that only 0.5% of *S. pneumoniae* isolates from blood cultures and cerebrospinal fluids were resistant to penicillin G. Another 9.7% would require increased exposure to be susceptible to this agent. The I+R categories thus increased from 6.9% in 2021 to 10.2% in 2022, but this is comparable to the 12.8% recorded in 2020. Seven isolates (1.3%) were categorised as I for one or more 3rd generation cephalosporins. The prevalence of macrolide resistance was 4.6% in 2022 compared to 6.0% in 2021. All *S. pyogenes* blood culture isolates were susceptible to penicillin G. The prevalence of erythromycin resistance (6.5%) was at the same level as before the pandemic (6.7% in 2020). Systemic *Streptococcus agalactiae* isolates (beta-haemolytic group B streptococci) isolates were also susceptible to penicillin G, but often resistant to erythromycin (22.7% in 2021; 21.2% in 2022) and tetracycline (80.0% in 2021; 74.6% in 2022).

A total of 174 patients with tuberculosis were reported to MSIS in 2022. Ten isolates (7.2%) were defined as multidrug resistant (MDR) to both rifampicin and isoniazid compared to 8.8% in 2021. The patients had acquired their infections in Europe outside Norway (n=6), Africa (n=2), Asia (n=1) and Norway (n=1).

Susceptibility testing was performed on 246 *Candida* spp. blood culture isolates from 231 unique patients. The most common species were *C. albicans* (n=139), *C. glabrata* (n=41), *C. parapsilosis* complex (n=17), *C. dubliniensis* (n=19) and *C. tropicals* (n=12). All *C. albicans* were susceptible to the substances examined with the exception of a single echinocandin resistant isolate. Only single non-*albicans* isolates with acquired fluconazole resistance were detected, but as expected there was a high prevalence of resistance to azoles among *C. glabrata* (17.0%). 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 antibacterials 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 01.01.2023. Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	277,785	142,460	135,325
5 to 14 years	638,282	328,061	310,221
15 to 24 years	659,326	338,761	320,565
25 to 44 years	1,490,776	762,386	728,390
45 to 64 years	1,411,354	718,812	692,542
65 years and older	1,011,461	474,990	536,471
All age groups	5,488,984	2,765,470	2,723,514

TABLE 2. Livestock population in Norway in 2022. Data provided by the Register of Production Subsidies as of 01.03.2022.

	Number* of	
Animal category	Herds	Animals
Cattle	13,500	893,200
Dairy cows only**	5,900	453,000
Suckling cow only**	5,000	260,600
Combined production (cow)**	1000	150,000
Goats	1400	75,200
Dairy goats**	400	35,500
Sheep	13,200	930,000
Breeding sheep > 1 year**	13,200	930,000
Swine	1,700	724,000
Breeding animal > 6 months**	990	40,100
Fattening pigs for slaughter**	1,700	412,000
Laying hen flocks > 50 birds	600	4,100,000
Broilers	600[1]	75,000,000[2]
Turkey, ducks, geese for slaughter (flock > 250 birds)	38	353,000

*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 1992-2022. Data provided by the Norwegian Directorate of Fisheries updated by 05.06.2023.

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[3]	1,559,972	84,928	5,116	638	2,291	2,612	18	16

[1]From the wild population. [2]After 2001 in numbers of 1,000 individuals. [3]Preliminary numbers.

Import of live animals

Import of live animals (excluding fish and companion animals) to Norway in 2022 was one camelide and 14, 765 day old chicks of 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 1993-2022 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 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 analysis, 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 veterinary 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 2022 were 4,623 kg. A decline of the annual sales of such VMPs of 49% in the period 1993-2022 is observed (Figure 1).

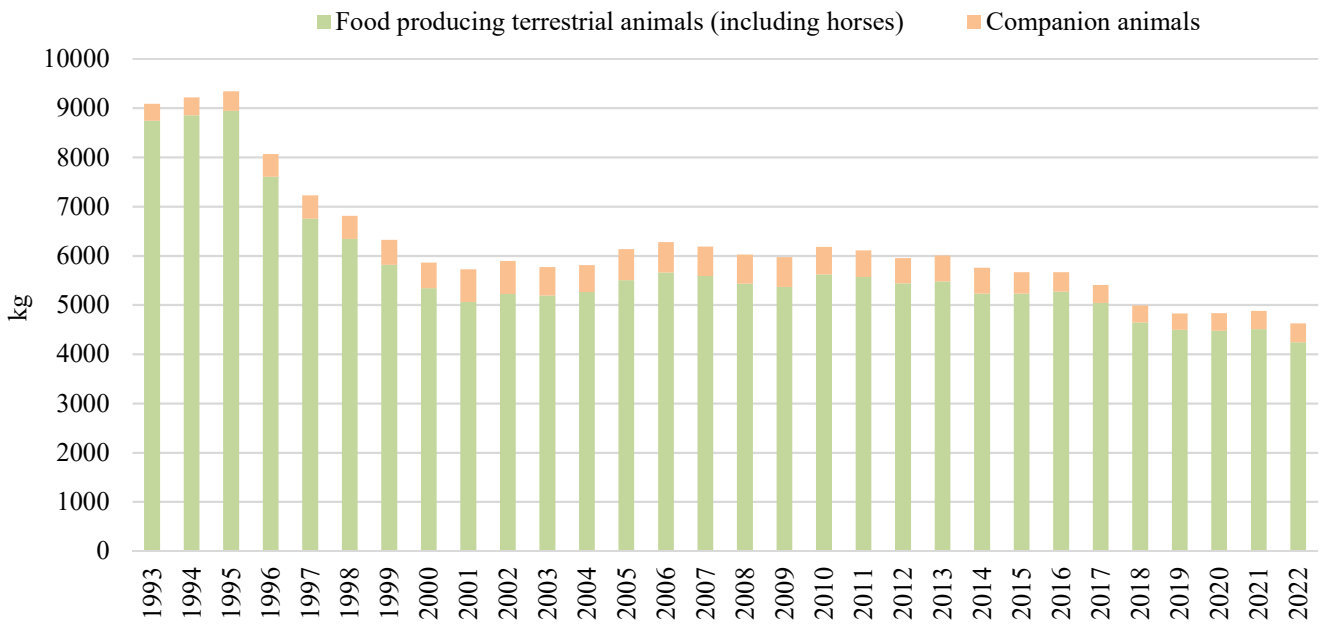


FIGURE 1. Total sales, in kg active substance, for food-producing terrestrial animals (including horses) and companion animals, of antibacterial veterinary medicinal products for therapeutic use in Norway in 1993-2022.

Food-producing terrestrial animals, including horses

In 2022 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,241 kg and compared to 1993 a decrease in the sales of such VMPs of 51% is observed (Figure 2). In total, 61% of the sales (kg) of antibacterial VMPs for this animal category in 2022 contained penicillins only, of which 96% was beta-lactamase sensitive penicillins. Of the total sales for use in terrestrial food-producing animals in 2022, 29% was sold as oral trimethoprim-sulfa paste for horses.

The proportion of sales of VMPs containing only penicillins for terrestrial food-producing animals increased from 18% to 61% during the period 1993-2022. This is mainly due to reduced sales of injectable and intramammary combination VMPs of penicillins and an aminoglycoside (dihydrostreptomycin) that has been gradually replaced by VMPs containing penicillins as the sole antibacterial agents.

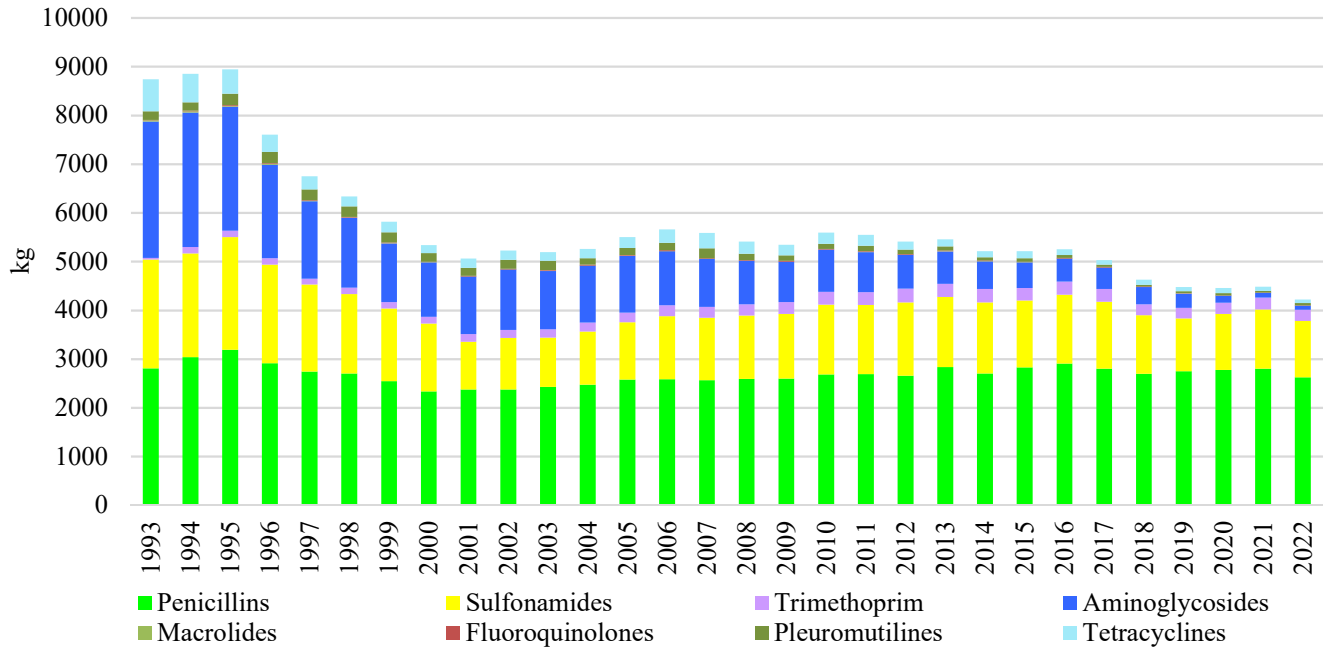


FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals (including horses) in Norway in 1993-2022. In addition, minor amounts of amphenicols VMPs were sold in 2008-2022 (range 16-27 kg) and of baquiloprim in 1994-2000 (range 0.2-1.8 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 2022, 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 4-6). During 1993-2022 no VMPs containing 3rd or higher generations of cephalosporins have been approved for food-producing animals in Norway via national procedures. One 3rd generation product has been approved via community procedures, but it is 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 an approval would only be given for specific animals if sensitivity testing precludes all other options. This is the case also for polymyxins (Knud Torjesen, Norwegian Medicines Agency, personal communication). Glycopeptides are not allowed for food-producing animals in EU/EEA countries; this is the case also for carbapenems.

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 therapeutic traditions. In 2022, only 2.7% of the sales of antibiotic VMPs for food-producing terrestrial animals was for VMPs applicable for group treatment (oral treatment).

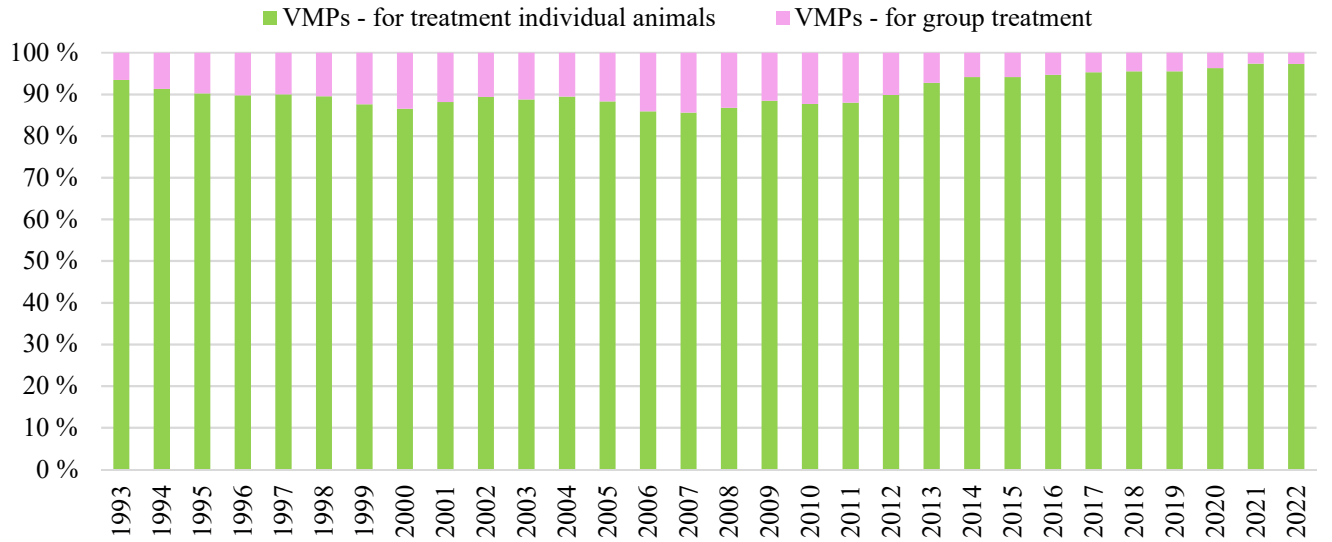


FIGURE 3. Proportion of sales in Norway (in kg active substance), of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals, including horses (bolus, injectables, intramammary preparations, intrauterine preparations, oral paste and some tablet VMP presentations – see Appendix 1) and applicable for group treatment through feed or drinking water (oral solution and oral powder. No premixes are marketed 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 2022. The data were extracted from the VetReg database 27 March 2023. 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 proportion accounted for by for cattle, pigs and sheep was 0.2%, 0.1% and 0.03%, respectively. Only fluoroquinolones were used (Figures 4-6).

Cattle

Of the prescriptions (VetReg data) of antibacterial veterinary and human medicinal products for cattle in 2022, 90.2% was for penicillins (kg active substance); 88.1% was beta-lactamse sensitive penicillins (intramammaries not included) (Figure 4) and this proportion has increased gradually from 79% in 2016.

Of the prescriptions of intramammaries reported to VetReg, 99% (kg and number of prescription) was for cattle. For intramammaries the sales data obtained from wholesalers are used to document the prescribing patterns for cattle (see explanation Appendix 1); the sales of intramammaries in kg active substance contaning penicillins only were 97% in 2022 and for combinations of penicillins and aminoglycosides it was 3%.

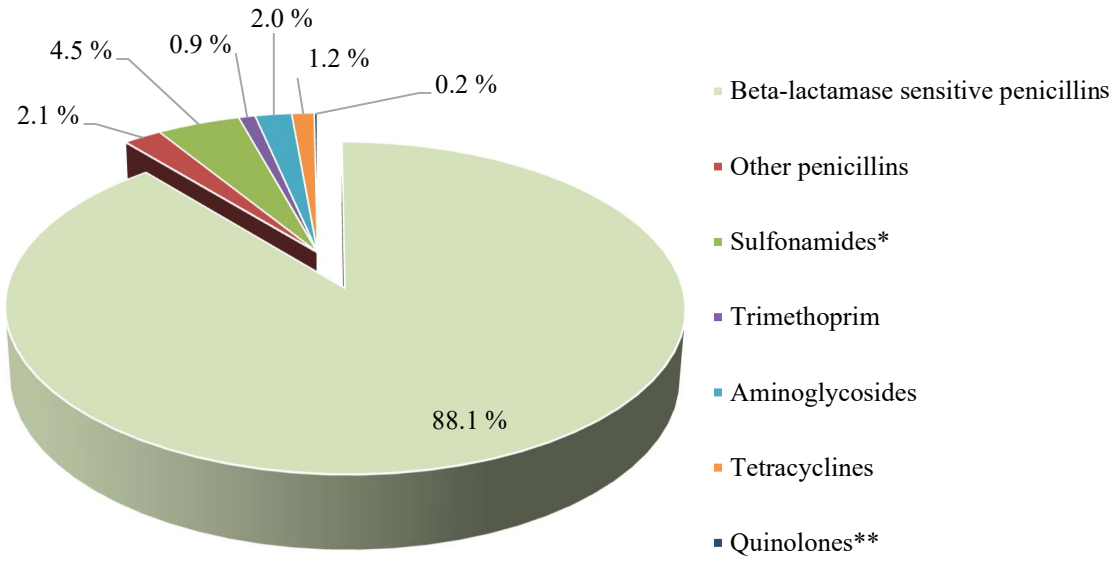


FIGURE 4. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for cattle in Norway in 2022. Data were obtained from the Veterinary Prescription Register (intramammaries and products for topical treatment not included in data in the figure); *In combination with trimethoprim only; **Fluoroquinolones only. In addition, 1.1% of the prescribed amounts was 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 (Figure 5), 85.4% of the total amount reported to VetReg was penicillins; 75.8% was for beta-lactamse sensitive penicillins only and this proportion has increased from 65% in 2016.

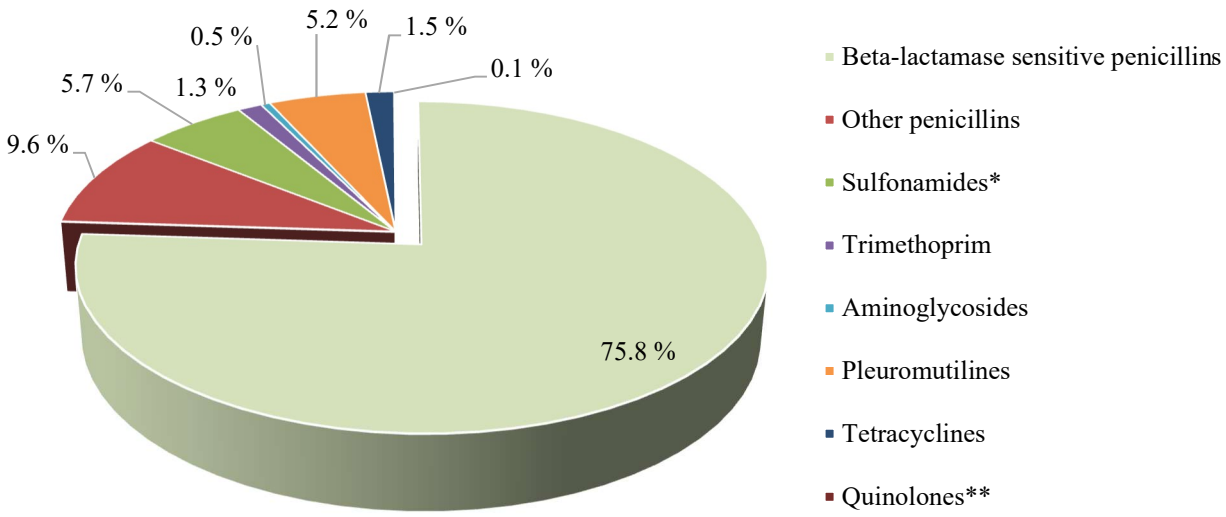


FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for pigs in Norway in 2022 (preparations for topical treatment not included). Data are obtained from the Veterinary Prescription Register. *In combination with trimethoprim only; **Fluoroquinolones only. In addition, 0.3% of the prescribed amounts was for macrolides and lincosamides.

Sheep

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of sheep (Figure 6), 78.7% of the toal amount reported to VetReg was penicillins; 77.6% was for beta-lactamase sensitive penicillins only and this proportion has increased gradually from 69.8% in 2016.

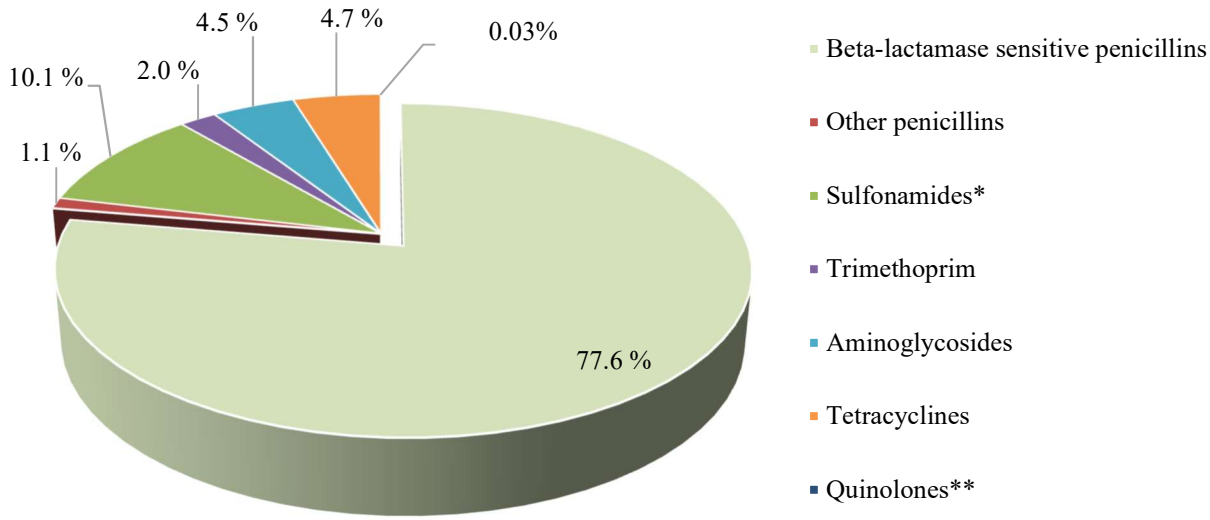


FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for sheep in Norway in 2022. Data are obtained from the Veterinary Prescription Register (intramammaries and preparations for topical treatment not included in data in the figure). *In combination with trimethoprim only; **Fluoroquinolones only. In addition, 0.03% of kg active substance prescribed was for amphenicols, macrolides and pleuromutilines.

Farmed fish

In 2022, the total amouns of antibacterials prescribed for use in aquaculture in Norway was 425 kg (Table 4); of this 423 kg was prescribed for farmed fish intended for human consumption (i.e. cleaner fish excluded).

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 the group of "other quinolones" is used for farmed fish. From 2011 to 2022, the proportion of sales of quinolones has fluctuated; in 2022 this proportion was 7 % (28 kg) (Table 4).

TABLE 4. Usage, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2013-2022. Data represent prescription data obtained from the Veterinary Prescription Register (see Appendix 1). Note that data include antibacterials for use in cleaner fish.

Active substance	2013	2014	2015[1]	2016[1]	2017	2018[1]	2019	2020[2]	2021[2]	2022
Tetracyclines										
Oxytetracycline	0	0	0	0	0	20	0	0.019	0	0
Amphenicols										
Florfenicol	236	399	188	136	269	858	156	113	536	397
Quinolones										
Flumequine	25	25	0	0	0	0	0	0	0	0
Oxolinic acid	599	99	84	66	343	54	66	107	57	28
Enrofloxacin			0.02	0.05	0.01		0.01	0.12	0.44	0.1
Total	**860**	**523**	**273**	**201**	**612**	**931**	**222**	**220**	**593**	**425**

[1]The total amounts (kg) given are deviating due to rounding of each single value. [2]Difference in figures from NORM/NORM-VET 2021 is due to updates of VetReg data and updated routines to identify errors in VetReg-reports.

In 2022 the major proportion of prescriptions was for fish in the ongrowing phase. This discontinued a yearly trend where the major proportion of prescriptions previously was for fish in the pre-ongrower phase (Figure 7). The number of prescriptions of antibacterial VMPs for Atlantic salmon ongrowers were, however, low during the period 2013-2022, despite that Atlantic salmon represents more than 95% of the farmed fish produced in Norway in this period. This is a strong indication that the vaccines used 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 2022 is observed (Figure 7); from 13 in 2021 to 32 in 2022. Of the 32 prescriptions for this group of fish, 24 of the prescriptions were for the treatment of halibut (eight for cod). However, total consumption, in kilograms, of antibacterial agents for marine species was only 20 kg of the total consumption of 425 kg.

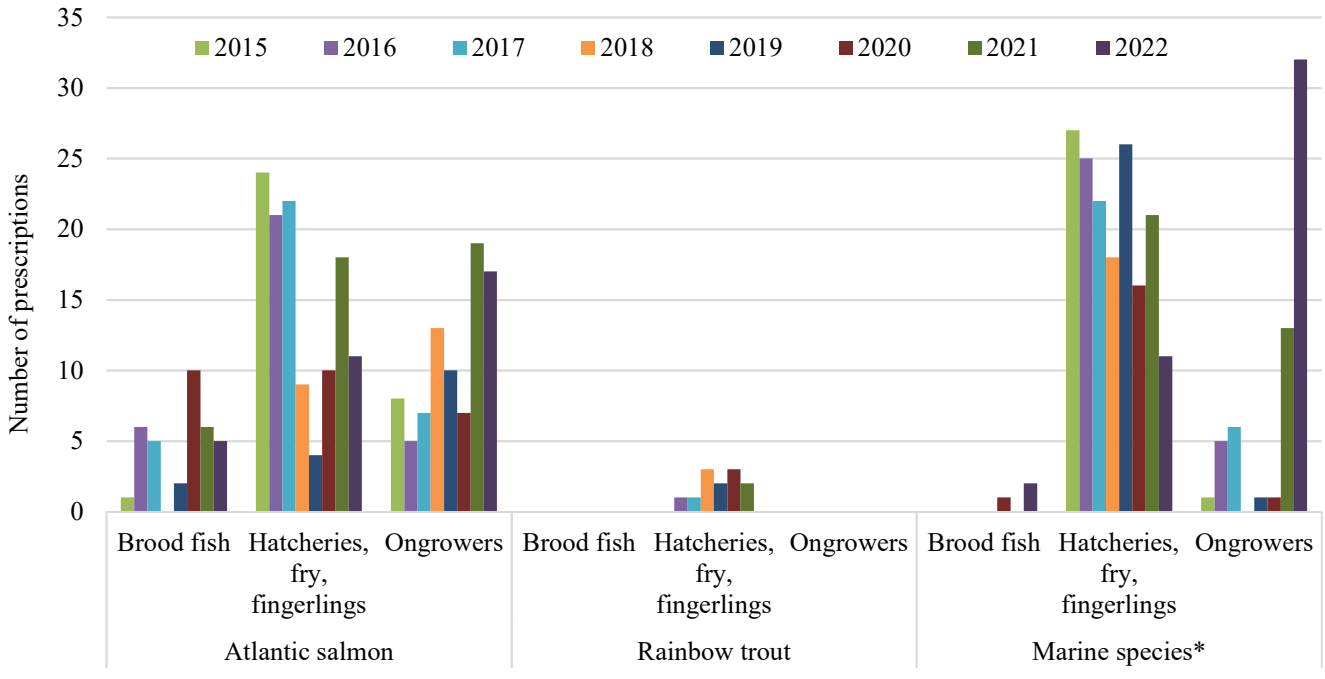


FIGURE 7. Number of prescriptions of antibiotics by fish species, split into production stages/types, in Norway in 2015-2022. Data were obtained from the Veterinary Prescription Register. *Cod, halibut, pollack, turbot and/or wolffish. Note that cleaner fish are not included.

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 2022 was 0.27 mg/PCU. Thus, the sales in mg/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.

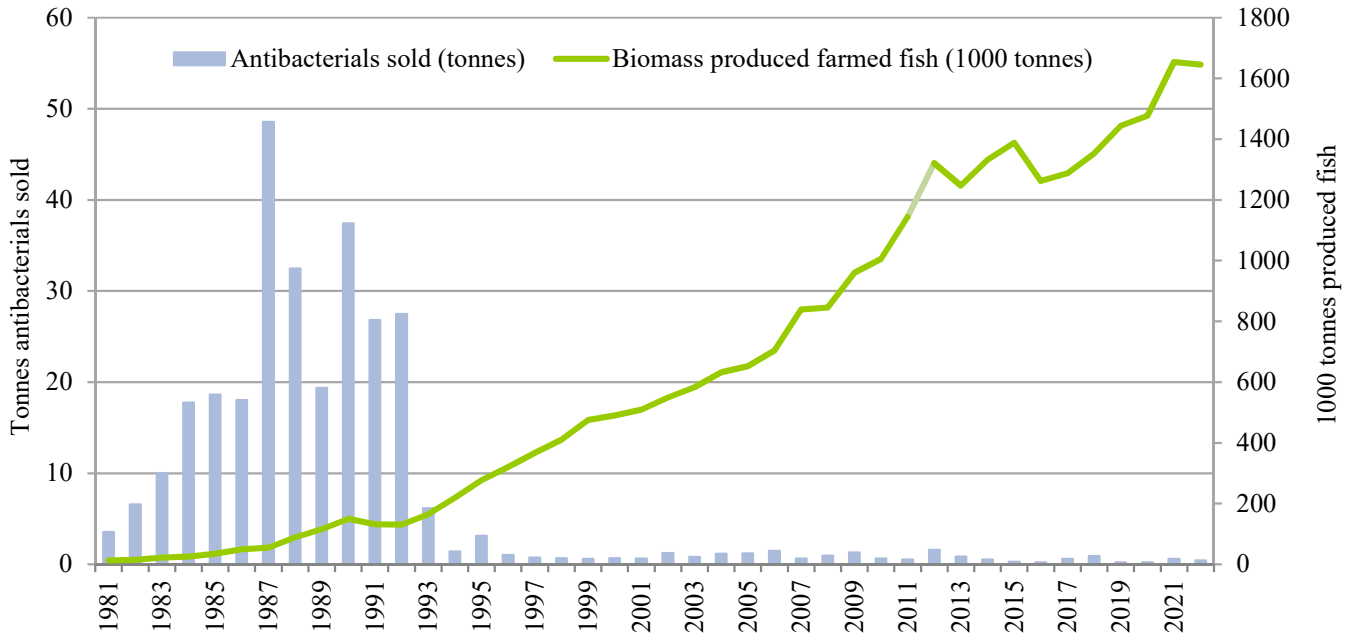


FIGURE 8. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish (including cleaner fish) in Norway in 1981-2022 versus tonnes produced (slaughtered) farmed fish. For the years 1981-2012 the data represent sales data provided by the Norwegian Institute of Public Health; for 2013-2022 data represent prescription data obtained form the Veterinary Prescription Register. Data on slaughtered biomass farmed fish were obtained from the Norwegian Directorate of Fisheries (Akvakulturstatistikk (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 was subjected to treatment with antibiotics (range 0.6% – 1.4%). This was also the case for the years 2018-2022; these figures were 1.6%, 1.2%, 0.8%, 2.2% and 1.9%, respectively.

Companion animals (dogs and cats)

The sales in 2022 of antibacterial VMPs approved solely for companion animals (includes VMPs formulated as tablets, oral solution, injectable and oral paste) was 382 kg; in 2021 this figure was 375 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 changes in the number 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 sold in Norway for dogs and cats, while in 2001 the corresponding number was 26. The number of VMP presentations for dogs and cats amounted to 49 in 2015; in 2022 this figure had decreased to 38.

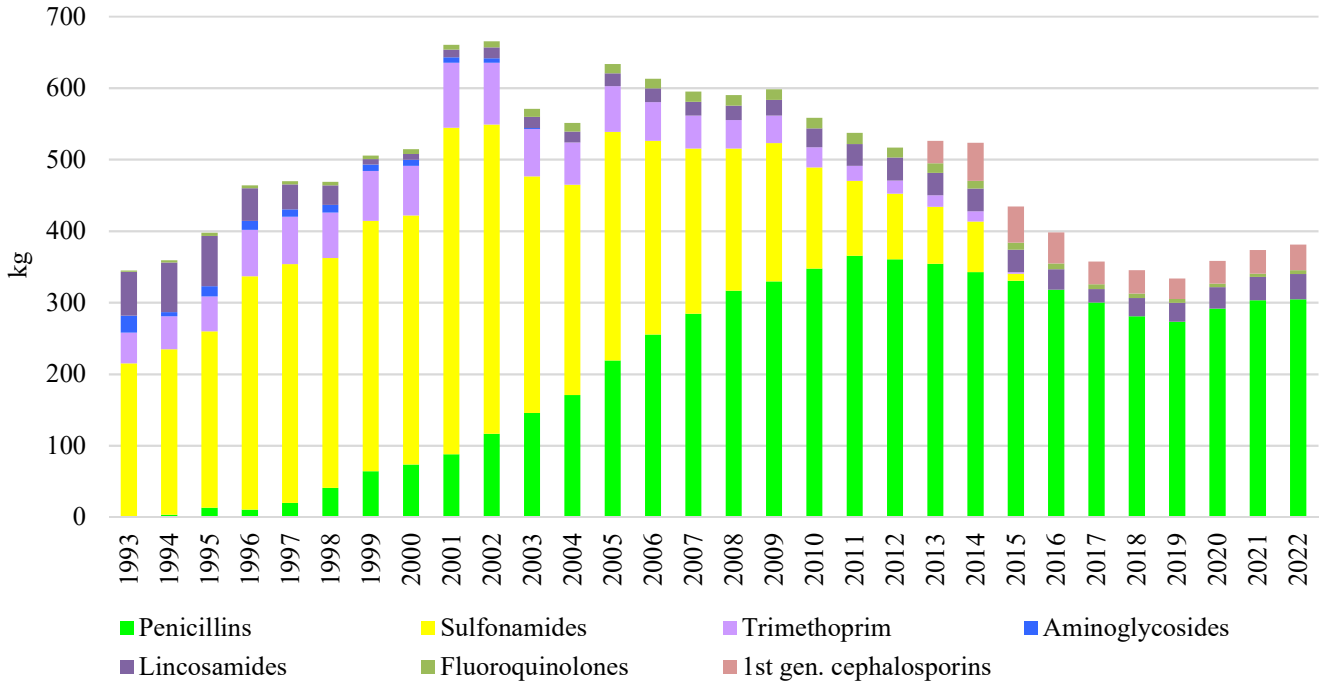


FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables, oral paste, oral solution and tablets; note the exceptions for tablets: see Appendix 1) in Norway for the period 1993-2022. Minor annual sales of a 3rd generation cephalosporin injectable VMP (range 0.4-1.1 kg) during 2008-2022 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 1993-2022 (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). In 1997, a VMP with amoxicillin in combination with clavulanic acid was marketed for dogs and cats and from then the proportion of the combination amoxicillin and clavulanic acid increased steadily (Figure 10) peaking in the period 2009 to 2012 when it was 88% of the sales of aminopenicillins. In 2022 this figure was 83% (Figure 10).

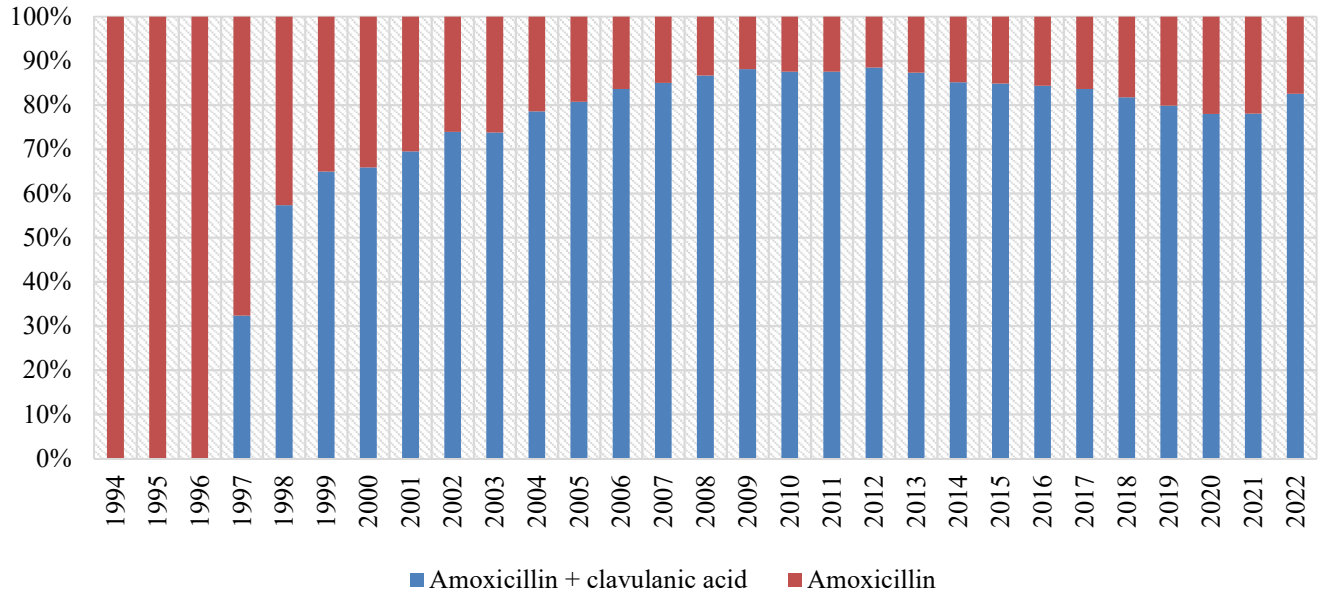


FIGURE 10. Proportions of sales (in kg active substance), of VMPs with amoxicillin combined with clavulanic acid versus amoxicillin for dogs and cats in Norway during 1994-2022.

From 1993 to 2022 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 to 2.8% in 2011 and since then this proportion has decreased to 1.4% in 2022 (Figures 9 and 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; this figure was 0.2% in 2008 and 0.1% in 2022 (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 antibacterial classes which the AMEG advices to restrict the use of compared to the total sales of antibacterial VMPs, stratified by animal categories. In total, 0.8% of the total sales of antibacterial VMPs in 2022 belonged to the AMEG category that EMA has adviced to restrict the use of, and that was primarily accounted for by use in farmed fish. Of note is that apart from one VMP for local ear treatment, other pharmaceutical forms of VMPs containing polymyxins are not marketed in Norway.

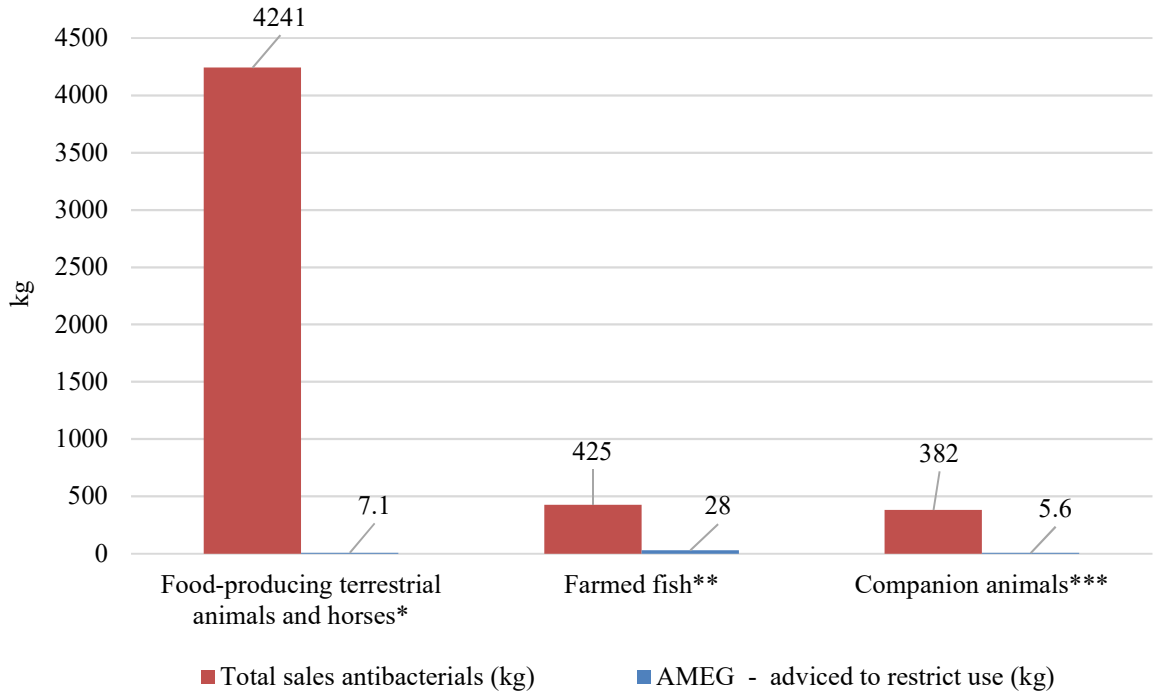


FIGURE 11. Total sales and sales of antibacterial veterinary medicinal products (VMPs) in 2022, for which the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency advises to restrict the use, stratified by animal category (1, 2). Of note – VMPs for topical treatment are not 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).
2. EMA. Categorisation of antibiotics for use in animals for prudent and responsible use. 2019 (https://www.ema.europa.eu/en/documents/report/infographic-categorisation-antibiotics-use-animals-prudent-responsible-use_en.pdf).
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, 2019.

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 to 2012 was 39% lower than in 1995 (Figures 2 and 12).

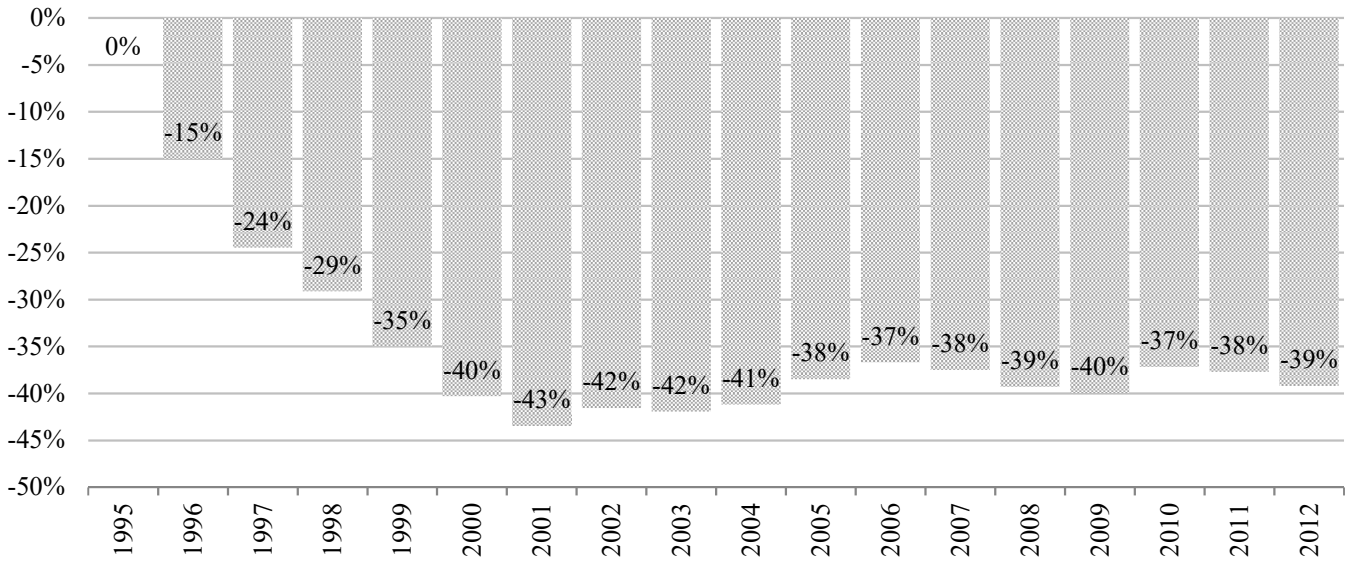


FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMP) approved for use in food-producing terrestrial animals, including horses, 1995 being the reference year.

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 2013-2022 have been further refined in order to obtain estimates 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) has 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 results of this analysis show that the reduction in the usage of antibacterial VMPs for cattle, pigs, sheep, goats and poultry from 2013 to 2022 was 30% and 26%, 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 2022, both in terms of the proportion by antibacterial classes and by phamaceutical forms. The figures are therefore assumed not being 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 (VetReg data) was relatively stable (and very low) across 2015-2022. 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 an 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.

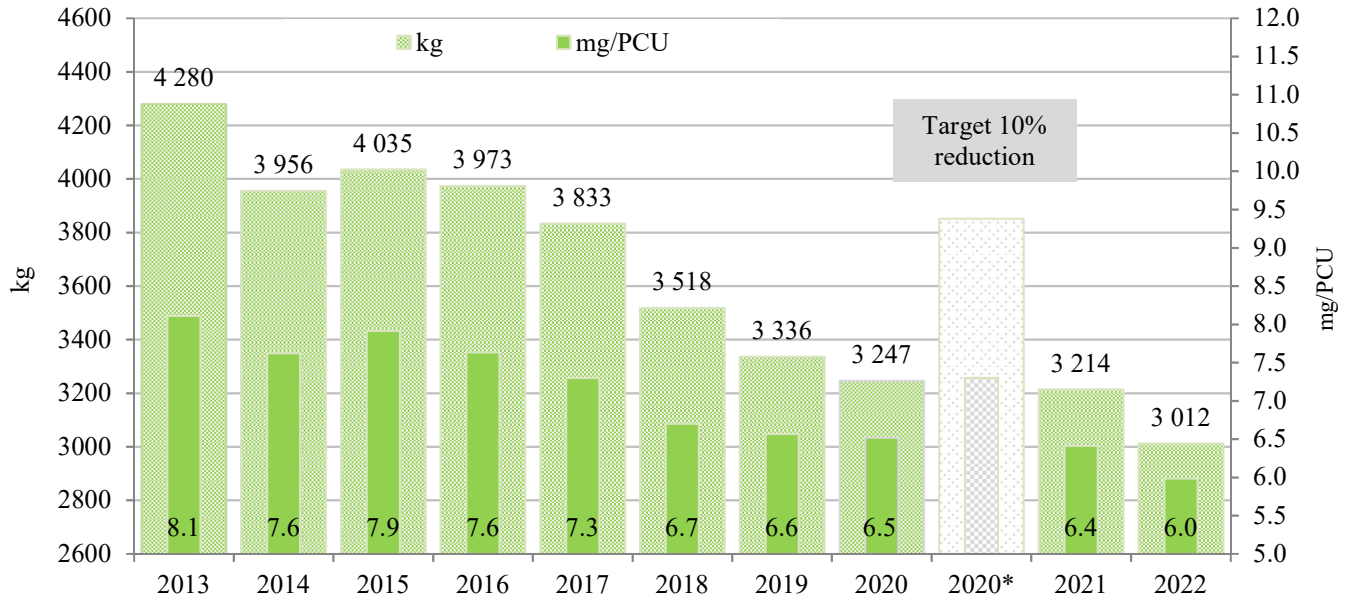


FIGURE 13. Estimated sales, in kg active substance and in mg/PCU (PCU =1 kg and represents the population correction unit for cattle, pigs, sheep, goats and poultry), of antibacterial veterinary medicinal products for cattle, pigs, sheep, goats and poultry in Norway in 2013 to 2022 and the target (2020*) according to the National Strategy. Sales data 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 is that the usage of antibacterials should be at the same level or lower in 2020 than the average for the period 2004 to 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 2015-2022.

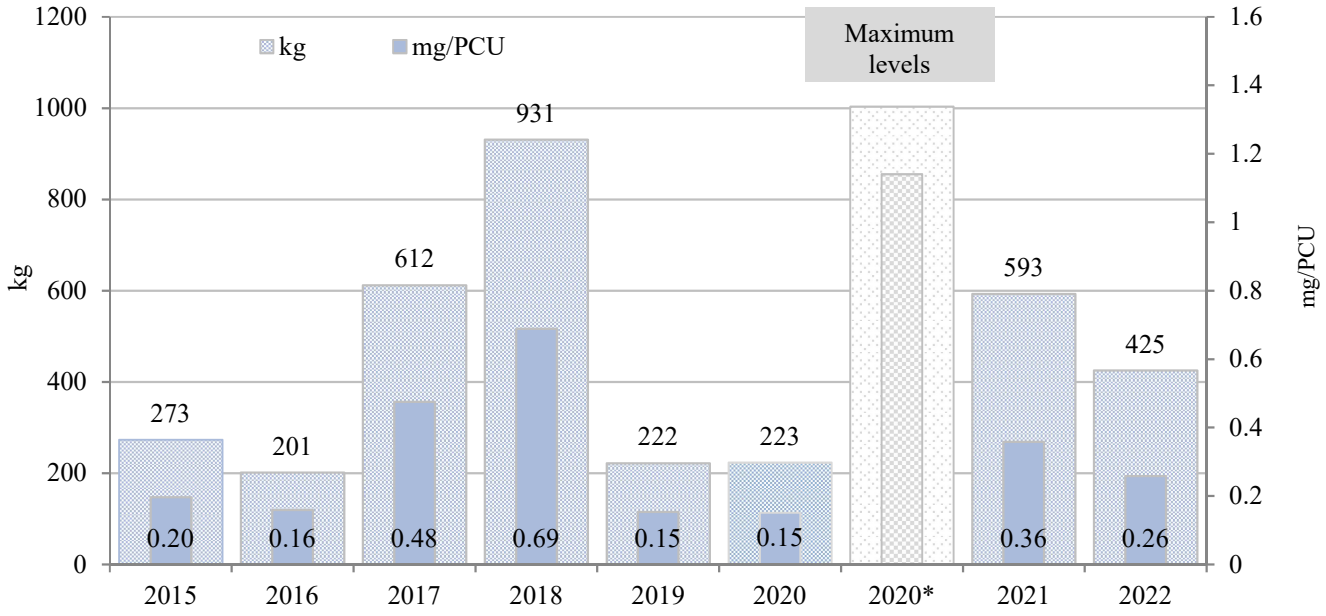


FIGURE 14. Prescription, in kg active substance and in mg/PCU (PCU =1 kg biomass farmed fish slaughtered), of antibacterial VMPs for farmed fish, in Norway in the period 2015 to 2020 and the maximum levels (2020*) according to the National Strategy. Maximum levels are based on the average for the period 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.

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 2022 a reduction in the sales of such antibacterial VMPs for companion animals of 28% is observed (Figure 15). If use of human antibacterial products (HMPs) for dogs and cats, reported to VetReg are included in the data, a 31% reduction of antibacterials in the period 2013-2022 is observed. As shown in Figure 15, the sales of antibacterial VMPs for companion animals declined gradually from 2013 to 2019 while for the following three years a slight increase is observed. Data for more years are needed in order to see if this is a trend.

Of note is that the prescribing (kg) of human antibacterial products (HMPs) for dogs and cats, reported to VetReg, declined by 39% from 2015 to 2022. This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substituted by prescribing antibacterial HMPs.

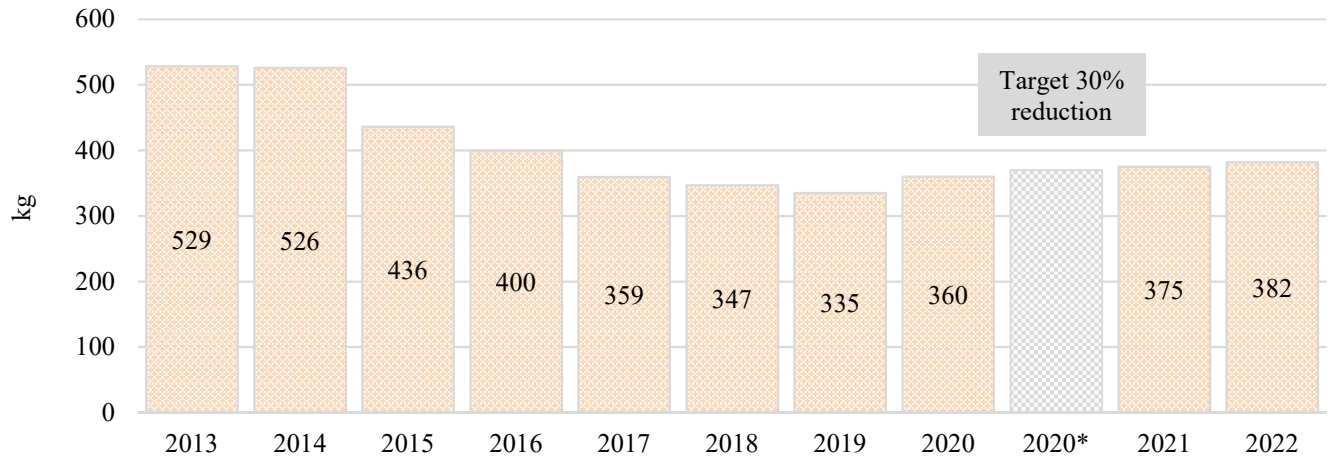


FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (injectables, oral paste, oral solution and tablets; exceptions for tablets - see Appendix 1) in the period 2013-2022 and the target (2020*) 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 period February 2015 to June 2016 (see NORM-VET 2019, Table 5). One of the targets stated in the National Strategy against Antibiotic Resistance is phasing out use of narasin as coccidiostat feed additive in the Norwegian broiler industry, without increasing of 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 2022. Concurrent with and in the years subsequent to discontinuation of 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 report 2021).

TABLE 5. Number of broiler flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs)[1] in Norway in the period 2013-2022. Data were obtained from HelseFjørfe, Animalia.

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

[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 in a few cases therapeutically against necrotic enteritis 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).

USAGE IN HUMANS

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

Overall antibiotic sales

In 2022, the total sales of antibacterials for systemic use in humans (J01, excl. methenamine) increased by 13% compared to 2021; from 11.2 to 12.7 DDD/1,000 inhabitants/day (Table 6). The use has decreased every year since 2012 except for a small increase from 2018 to 2019. The overall consumption (J01, excl. methenamine) has decreased by 25% since 2012, when a *Mycoplasma pneumoniae* epidemic caused a very high prescription rate of macrolides and tetracyclines. During the Covid-19 pandemic there was a significant reduction in the use of antibiotics, mainly due to reduced use of antibiotics indicated for respiratory tract infections (RTI-AB), but consumption is now back to approximately the same level as before the pandemic, Figure 16. Although a lot has been achieved there are still areas for improvement, e.g. in avoiding antibiotics for viral infections, choosing narrow-spectrum antibiotics where indicated, shortening duration of courses and individualisation of doses. One should expect that it is possible to achieve a further lowering of consumption rates 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 in primary care, hospitals and long-term care institutions. Around 85% of the human use of antibacterials is used by patients outside health institutions. In 2022, hospitals covered 7.5% 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 17). Over the years the proportion of narrow-spectrum penicillins (J01CE) of the total sales (J01, excl. methenamine) has been quite stable (around 27%), but it was lower in 2020 and 2021 (24%). In 2022, the proportion was 28%. In Norway, narrow-spectrum penicillins are recommended as first line treatment when antibiotics are warranted for respiratory tract infections. During the Covid-19 pandemic, the closing down of society and the higher threshold for consulting general practitioners, combined with infection control measures such as social distancing and the use of face masks, led to lower incidence of infections handled by healthcare. Especially respiratory tract infections have been reported more seldom during the Covid-19 pandemic.

During 2022 there have been several shortage situations for antibiotics, but most often generics have been put available for the market and although none of the shortage situations in 2022 were serious enough to impact the antibiotic consumption pattern, however, the lack of formulations for pediatric use has been of concern.

TABLE 6. Human usage of antibacterial agents in Norway 2012, 2014, 2016, 2018, 2020 and 2022 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2021-2022 and 2012-2022. Data from the Norwegian drug wholesales statistics database. Methodology for collection of data on human usage of antimicrobial agents is presented in Appendix 2.

		Year						Change (%)	
ATC	Groups of substances	2012	2014	2016	2018	2020	2022	2021-2022	2012-2022
J01A	Tetracyclines	3.87	3.46	3.16	2.86	2.65	2.82	+5	-27
J01B	Amphenicols	<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	+7	-16
J01CE	Beta-lactamase sensitive penicillins	4.31	3.88	3.73	3.43	2.77	3.50	+30	-19
J01CF	Beta-lactamase resistant penicillins	0.90	0.91	0.90	0.90	0.95	1.04	+9	+15
J01CR	Combination of penicillins, incl. beta-lactamase inhibitors	0.04	0.07	0.10	0.08	0.11	0.15	+20	+330
J01D	Cephalosporins, monobactams, carbapenems	0.53	0.46	0.42	0.39	0.37	0.37	+10	-30
J01E	Sulfonamides and trimethoprim	0.87	0.88	0.85	0.88	0.90	0.92	+2	+6
J01F	Macrolides, lincosamides and streptogramins	2.26	1.68	1.33	1.05	0.80	0.75	+12	-67
J01G	Aminoglycosides	0.08	0.08	0.08	0.09	0.10	0.10	+41	+33
J01M	Quinolones	0.74	0.67	0.53	0.42	0.30	0.29	+5	-61
J01X*	Other antibacterials	0.47	0.43	0.38	0.32	0.34	0.37	+16	-22
J01	**Total excluding methenamine**	**16.9**	**15.4**	**14.1**	**12.9**	**11.5**	**12.7**	**+13**	**-25**
J01XX05	Methenamine	3.57	3.86	4.09	4.08	3.85	3.96	0	+11
J01	**Total all antimicrobial agents**	**20.4**	**19.3**	**18.2**	**15.3**	**15.2**	**16.6**	**+10**	**-19**

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

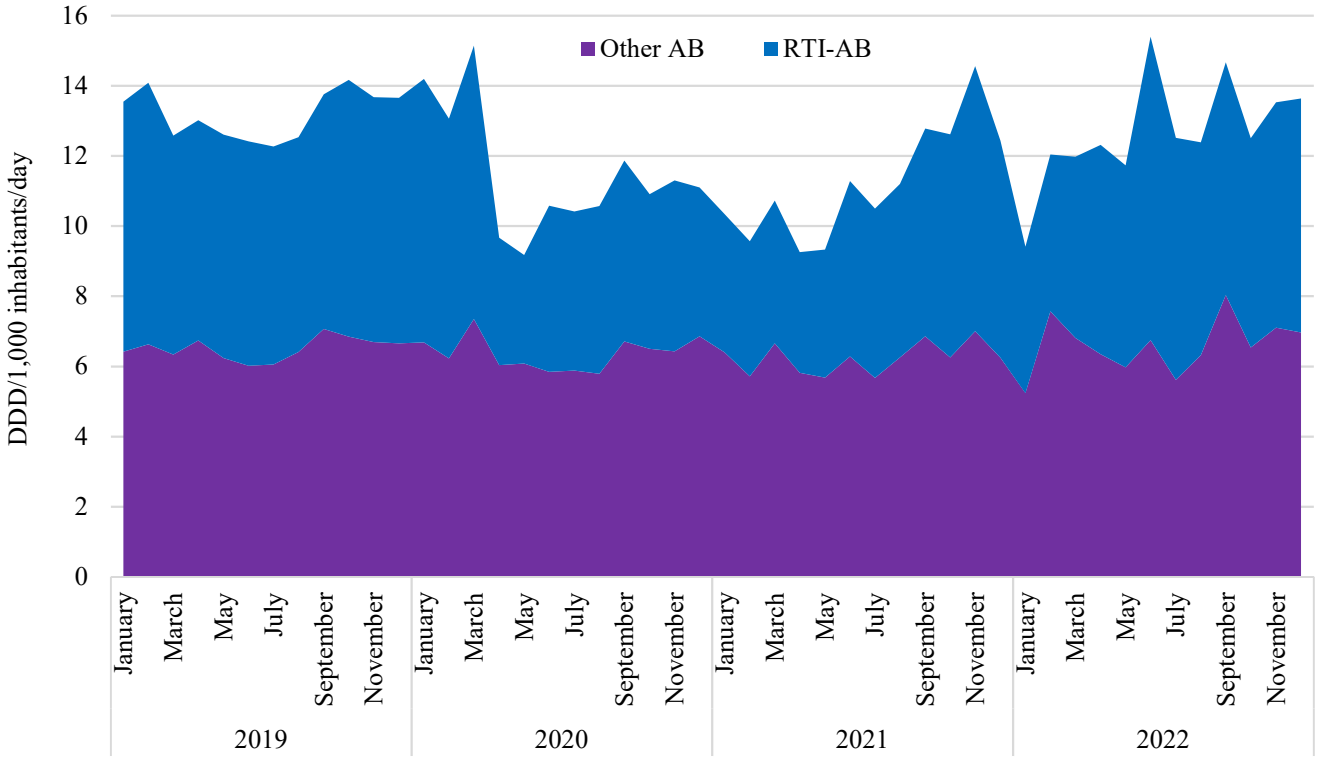


FIGURE 16. Monthly sales of antibiotics in 2019, 2020, 2021 and 2022 measured in DDD/1,000 inhabitants/day. Antibiotics for respiratory tract infections (RTI-AB) are defined as amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline. Other antibiotics (AB) are defined as all other antibiotics in ATC group J01, excl. methenamine. Data from the Norwegian drug wholesales statistics database.

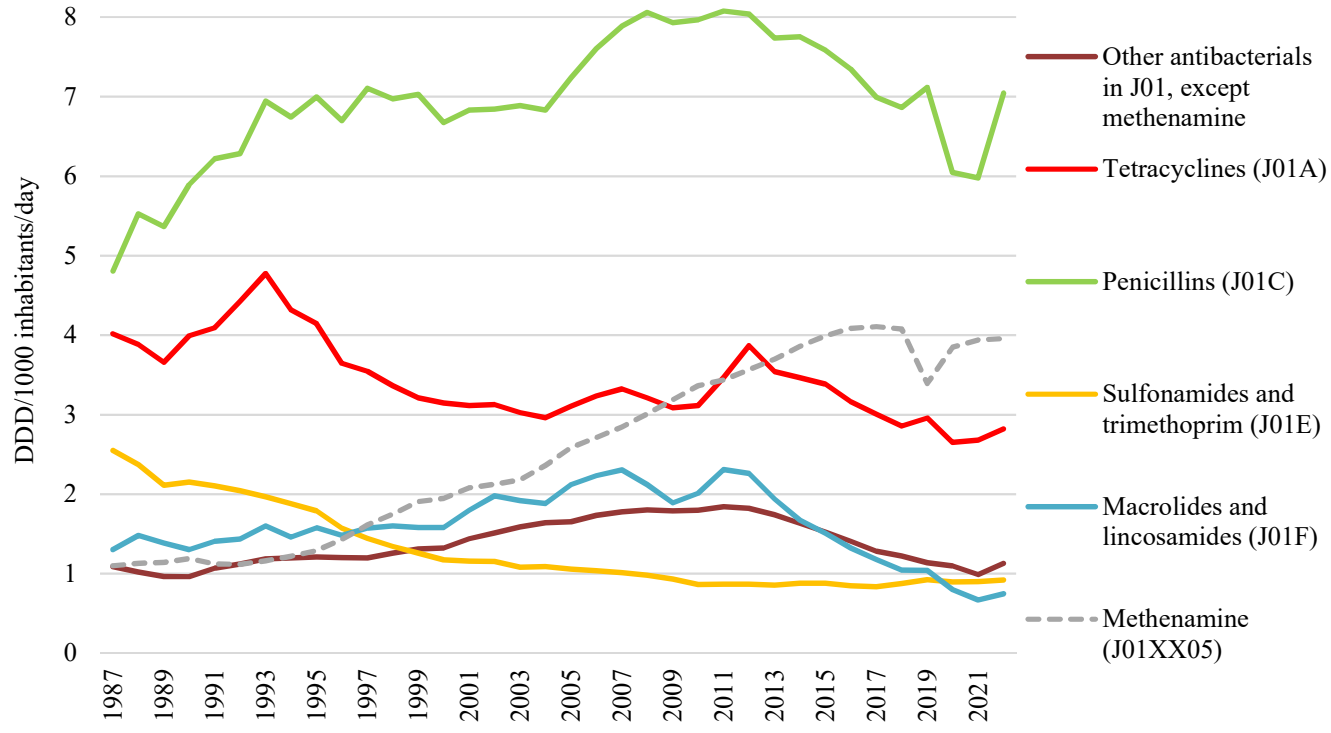


FIGURE 17. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine and other antibacterials in Norway 1987-2022. Other antibacterials include all other antibacterials in ATC group J01, except methenamine (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 commonly used antibacterial groups in Norway in 2022. After years of increased use, the urinary prophylactic agent methenamine reached a stable level in 2016. In spring 2019 we experienced a major shortage, and in 2022 the use was still lower than in 2015 (Figure 17, Table 6). Methenamine has the largest amounts of DDDs of all antibiotics used in Norway and accounted for 23% of total antibacterial use in 2022. Among the tetracyclines (J01A), doxycycline is the most frequently used antibacterial, followed by lymecycline, a drug indicated for acne (Table 7).

In 2022, the penicillins (ATC group J01C) accounted for 42% of the total antibacterial use in Norway (Figure 18). In 2022, beta-lactamase sensitive penicillins accounted for half of the penicillin group (50% share) measured in DDDs. Over the years there has been increasing use of broad-spectrum penicillins. Penicillins with extended spectrum (J01CA) represent 33% of the J01C group compared to 23% in 1999. 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 6). A significant increase in the use of oral co-amoxiclav is observed, following the Norwegian approval in May 2017. Pivmecillinam is the main antibiotic used for urinary tract infections, although pivmecillinam, trimethoprim and nitrofurantoin are all equivalental recommendations for acute cystitis in national guidelines.

The subgroup of sulfonamides and trimethoprim has decreased over the years due to a decreased use of trimethoprim. Use of the combination - co-trimoxazole - is increasing (Figures 17-18, Table 7).

Since 2012 the use of macrolides has dropped markedly, (Tables 6-7, Figure 17-18). Use of 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, doxycyline 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, sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased, mainly due to decreased use of 1st and 2nd gen. cephalosporins (Tables 6-7, Figure 18). Since 2019 there has been a slight reduction in the sales of cefotaxime. One reason may be that reducing the use of cefotaxime and other 3rd generation cephalosporins was a specific target 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 in Norway.

The quinolones represent only a small fraction (2%) of the total antibacterial sales (Tables 6-7, Figure 18) 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 93% of the quinolone group in 2022.

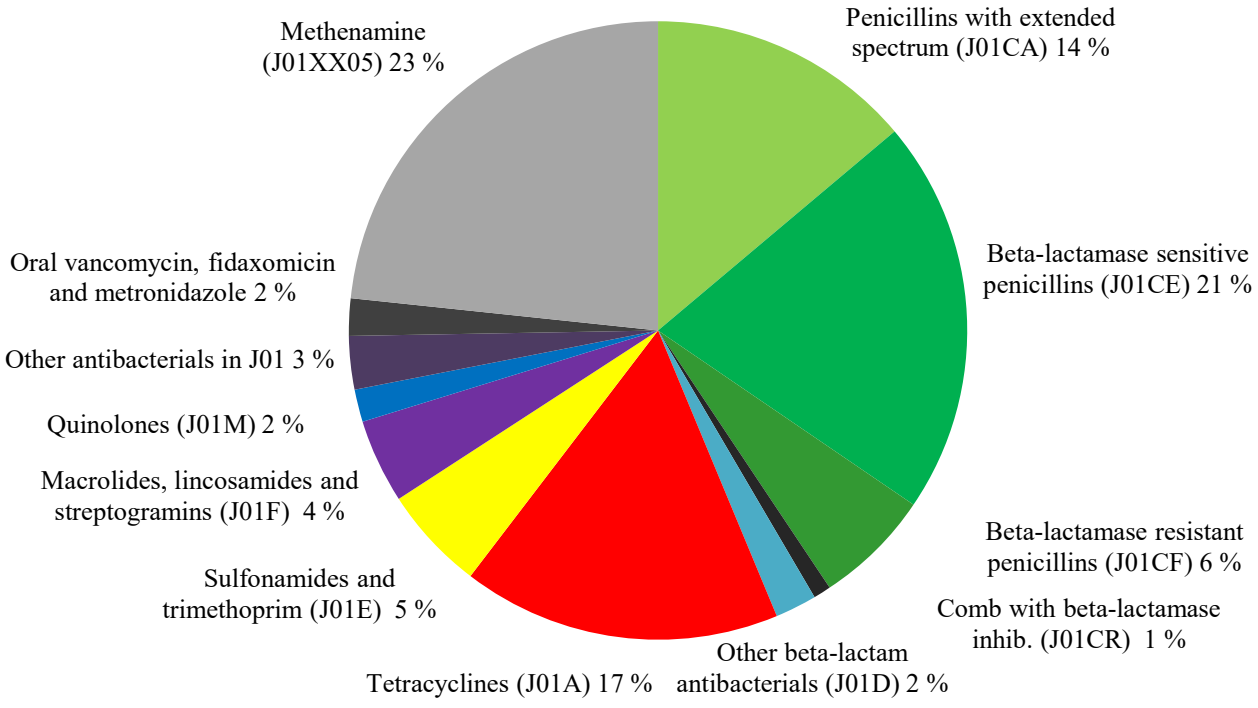


FIGURE 18. Relative amounts of antibacterial agents for systemic use in 2022 in Defined Daily Doses (DDD) (total sales in the country). Data from the Norwegian drug wholesales statistics database.

TABLE 7. 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. 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
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	1.99	1.82	1.60	1.38	1.51
	J01A A04	Lymecycline	0.90	0.96	0.94	0.93	1.08	1.12
	J01A A06*	Oxytetracycline		<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
	J01A A08*	Minocycline	0.006	0.003	0.002	0.001	0.001	0.001
	J01A A12	Tigecycline	<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
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.03	0.04	0.04	0.05	0.05	0.05
	J01C A04	Amoxicillin	0.97	0.97	0.88	0.84	0.65	0.74
	J01C A08	Pivmecillinam	1.78	1.87	1.69	1.57	1.52	1.56
	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
	J01C E02	Phenoxymethyl-penicillin	4.07	3.64	3.50	3.18	2.53	3.32
	J01C E08*	Benzathine benzylpenicillin	<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
	J01C F02	Cloxacillin	0.14	0.19	0.17	0.16	0.16	0.19
	J01C F05*	Flucloxacillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CR - Combination of penicillins, incl. beta-lactamase inhibitors	J01C R02	Amoxicillin and enzyme inhibitor	0.00	0.01	0.01	0.03	0.05	0.09
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.07	0.09	0.05	0.06	0.07
J01DB – 1st generation cephalosporins	J01D B01	Cefalexin	0.18	0.14	0.10	0.09	0.07	0.06
	J01D B03	Cefalotin	0.08	0.09	0.09	0.07	0.02	0.02
	J01D B04	Cefazolin				0.03	0.08	0.09
J01DC – 2nd generation cephalosporins	J01D C02	Cefuroxime	0.08	0.06	0.04	0.03	0.03	0.02
J01DD – 3rd generation cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	0.11	0.13
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.008	0.006	0.004
	J01D D04	Ceftriaxone	0.03	0.02	0.02	0.02	0.03	0.02
	J01D D08*	Cefixime			<0.001	<0.001	<0.001	<0.001
	J01D D52	Ceftazidime and avibactam				<0.001	<0.001	<0.001
J01DF - Monobactams	J01D F01	Aztreonam	<0.001	0.001	0.001	<0.001	<0.001	0.001
J01DH - Carbapenems	J01D H02	Meropenem	0.03	0.03	0.03	0.02	0.03	0.03
	J01D H03	Ertapenem	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
J01DI – Other cephalo-sporins and penems	J01D I02	Ceftaroline fosamil		<0.001	<0.001	<0.001	<0.001	<0.001
	J01D I04	Cefiderocol						<0.001
	J01DI54	Ceftolozane and enzyme inhibitor			<0.001	<0.001	0.001	<0.001

ATC group	ATC code	Substance	2012	2014	2016	2018	2020	2022
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.46	0.38	0.34	0.33	0.29
	J01E B02*	Sulfamethizole					<0.001	<0.001
	J01E C02*	Sulfadiazine			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
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.75	0.60	0.44	0.29	0.21
	J01F A02	Spiramycin	0.01	0.005	0.003	0.002	0.002	0.001
	J01F A06*	Roxithromycin		<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
	J01F A10	Azithromycin	0.48	0.35	0.30	0.24	0.19	0.21
	J01FS15	Telithromycin	<0.001	<0.001	<0.001			
	J01F G01*	Pristinamycin						
	J01F F01	Clindamycin	0.33	0.34	0.28	0.25	0.23	0.23
J01G - Aminoglycosides	J01GA01*	Streptomycin	<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
	J01G B03	Gentamicin	0.05	0.05	0.06	0.08	0.09	0.09
	J01G B06	Amikacin	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
	J01M A02	Ciprofloxacin	0.71	0.64	0.51	0.39	0.28	0.27
	J01MA12	Levofloxacin	0.002	0.002	0.003	0.004	0.005	0.006
	J01MA14*	Moxifloxacin	0.004	0.007	0.009	0.011	0.009	0.01
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.02	0.02	0.02	0.02	0.02
	J01X A02	Teicoplanin	0.001	<0.001	<0.001	<0.001		<0.001
	J01X B01	Colistin	0.004	0.005	0.006	0.006	0.008	0.01
	J01X C01	Fusidic acid	0.005	0.004	0.003	0.003	<0.001	<0.001
	J01X D01	Metronidazole	0.07	0.05	0.03	0.04	0.04	0.04
	J01X E01	Nitrofurantoin	0.37	0.35	0.31	0.25	0.26	0.29
	J01XX01	Fosfomycin	<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
	J01XX08	Linezolid	0.01	0.007	0.010	0.009	0.009	0.009
	J01XX09	Daptomycin	0.001	<0.001	0.001	0.001	0.001	0.001
	J01X X11	Tedizolid			<0.001	<0.001	0.001	0.002
Antibiotics in other ATC groups	A07A A09	Vancomycin	0.002	0.002	0.002	0.002	0.003	0.004
	A07A A11	Rifaximin	0.004	0.012	0.043	0.076	0.10	0.13
	A07A A12	Fidaxomicin	<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
	D06A X09*/ R01A X06*	Mupirocin (grams)[1]	145	174	186	247	288	248

*Drugs not licensed in Norway in 2022. [1]Given as the total amount grams (g) mupirocin per year.

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 Prescription Database (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 2022, the use of antibacterials (J01 excl. methenamine) in primary care was 10.3 DDD/1,000 inhabitants, i.e. at the same level as in 2018 and 2019. For primary care, the most important antibiotic group in 2022 was the penicillins, J01C (41% of DDDs and 57% of prescriptions in ATC group J01). Tetracyclines, J01A was the second most commonly used group (19% of DDDs and 10% of prescriptions) followed by sulfonamides and trimethoprim, J01E (5% of DDDs and 10% of prescriptions). The five antibiotic substances most often prescribed for outpatients in 2022 were phenoxymethylpenicillin, pivmecillinam, methenamine, dicloxacillin and doxycycline. These five antibiotics represented 65% of all prescriptions and 73% of all DDD in the antibacterial group J01. Phenoxymethylpenicillin was prescribed in 27% of prescriptions representing 22% of DDDs while methenamine represented 9% of prescriptions and 26% of the DDDs.

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 since 2012 will continue is currently difficult to predict, however, there is an increased attention towards antimicrobial resistance, both among the public and health personnel. A large proportion of general practitioners has completed quality improvement courses after the introduction of the Government's Action plan against AMR in 2016.

Geographical variation

The usage of antibacterials varies among the Norwegian regions, Table 8. The county using the least is using around 84% in DDDs and 81% in prescriptions of the highest use county (Figures 19-20). Over the years, and measured in DDDs, some counties are consistently high-use or low-use counties. Antibiotic use has decreased in all counties over the latest years, but with certain differences between the counties.

Females use more antibiotics than males; 23% of females purchased at least one antibiotic prescription (methenamine excluded) in 2022 compared to 15% of males. This is at the same level as in 2019. The prevalence of antibiotic use has decreased over the years, more so in young children than in the elderly. The gender pattern is similar in all regions of the country. Young children, young women and the elderly are high users of antibiotics (Figure 21). Among those who use antibacterials, the elderly population uses 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), see Figure 22. The mean number of antibacterial prescriptions delivered from pharmacies is reduced since 2012 for men and women and in all age groups, more so for men and younger age groups (Figure 23). The target of 250 prescriptions/1,000 inhabitants 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.

TABLE 8. Human usage of the 10 single antibacterial agents for systemic use most often prescribed by doctors in ambulatory care in the four health regions in Norway in 2022. Sales are given in DDD/1,000 inhabitants/day. Data from the Norwegian prescription Database.

	Health region			
	Mid	North	South-East	West
Methenamine	4.28	3.99	3.57	3.50
Phenoxymethylpenicillin	2.92	2.37	3.18	3.14
Doxycycline	1.41	1.24	1.37	1.36
Pivmecillinam	1.46	1.33	1.27	1.33
Lymecycline	0.99	0.94	1.06	1.21
Dicloxacillin	0.70	0.72	0.75	0.68
Amoxicillin	0.59	0.55	0.62	0.56
Sulfamethoxazole and trimethoprim	0.50	0.54	0.45	0.49
Trimethoprim	0.32	0.30	0.23	0.21
Nitrofurantoin	0.30	0.34	0.23	0.30

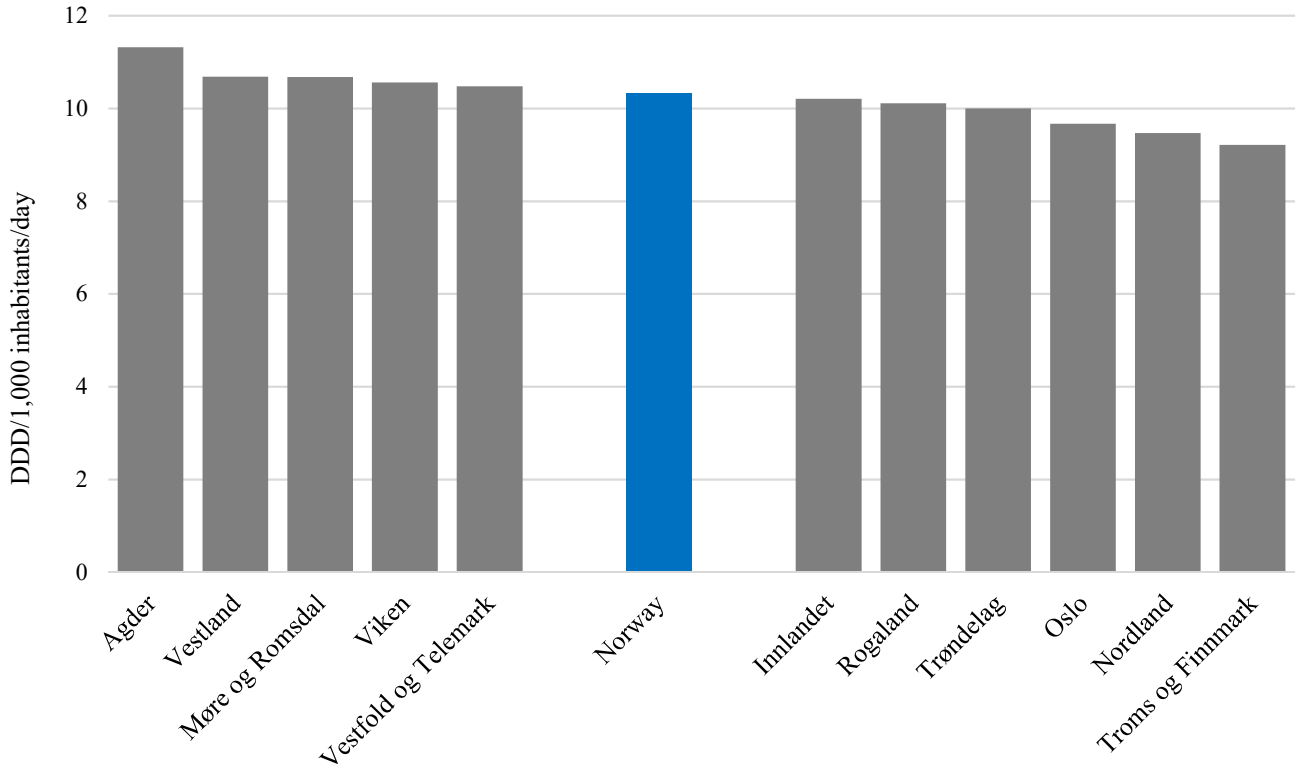


FIGURE 19. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2022. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

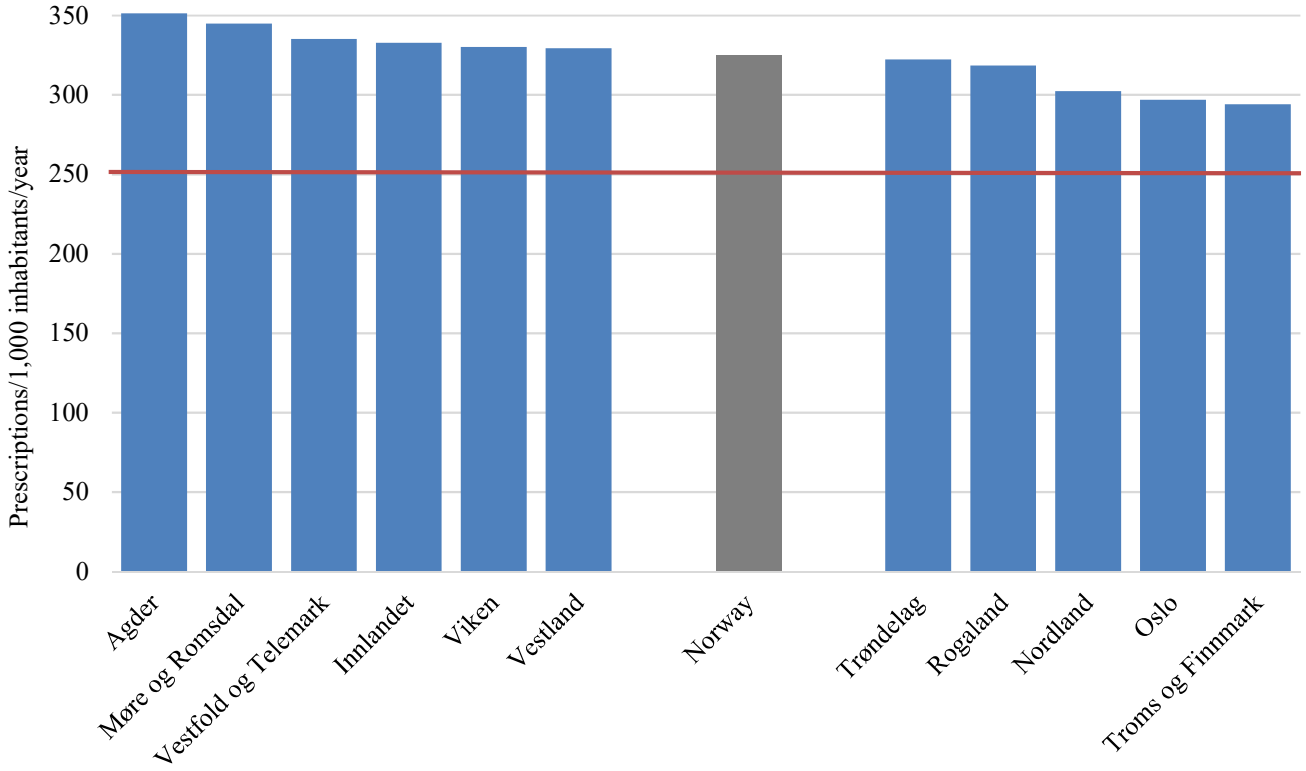


FIGURE 20. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2022. Measured as number of prescriptions/1,000 inhabitants. Data from NorPD (excl. health institutions). Red line; goal set by the National Strategy against Antibiotic Resistance 2015-2020.

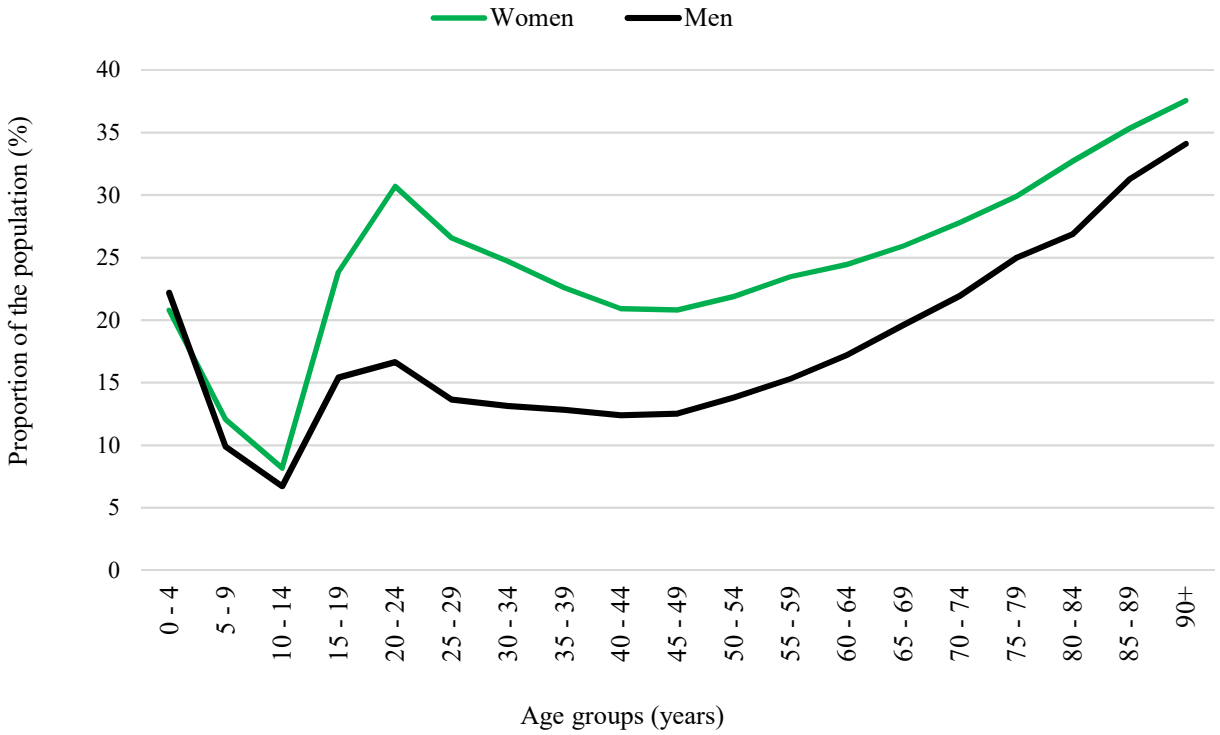


FIGURE 21. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care by gender and age in Norway in 2022. Antibacterials included are antibacterials for systemic use (ATC group J01), vancomycin (A07AA09), fidaxomicin (A07AA12) and metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions.

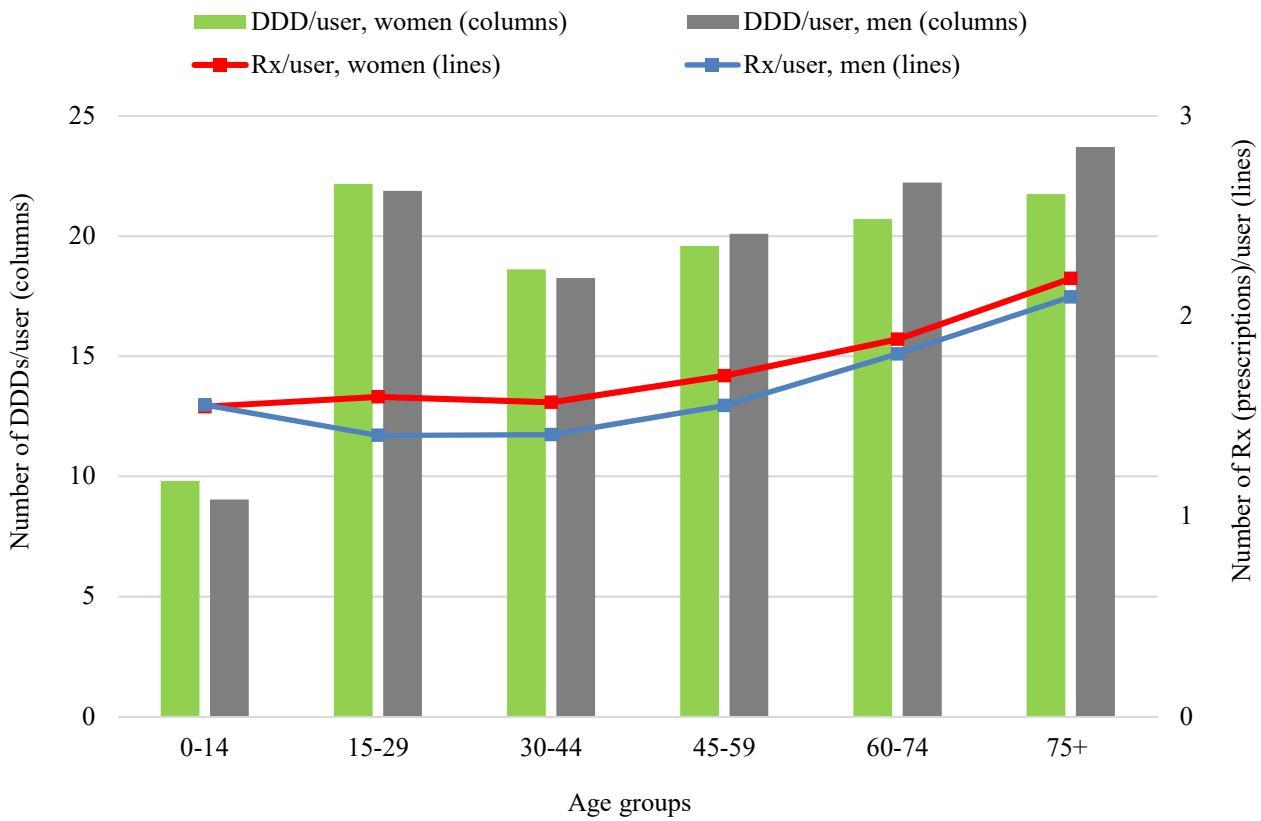


FIGURE 22. Mean number of prescriptions (Rx) per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway in 2022. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

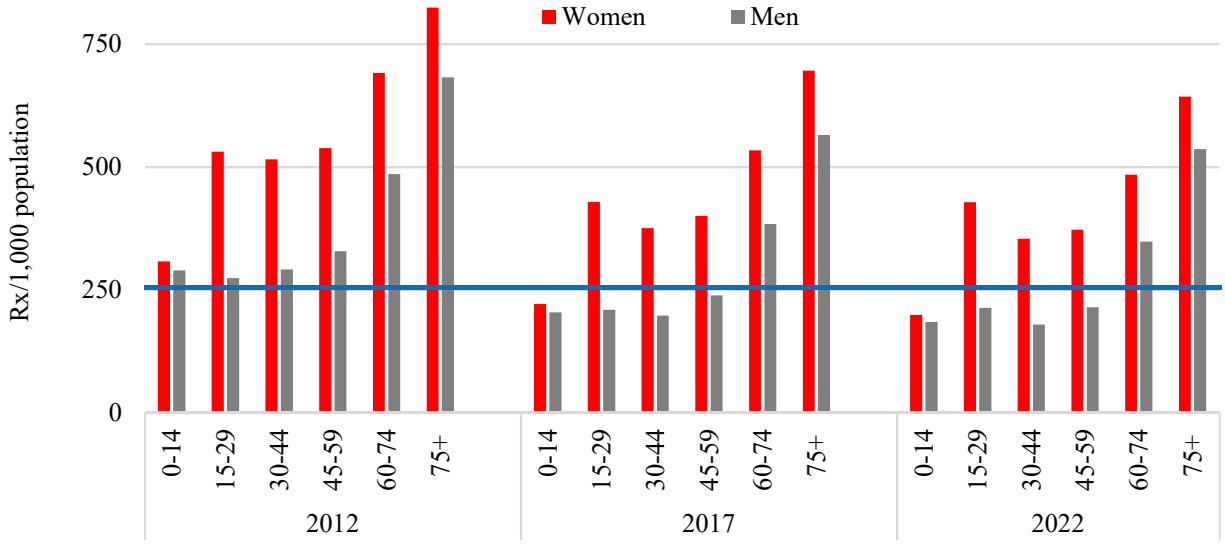


FIGURE 23. Mean number of prescriptions (Rx)/1,000 population of antibacterials (J01, excluding methenamine) in ambulatory care by gender and age groups and changes pr 5th year; 2012, 2017 and 2022. The blue line indicates the un-official target of 250 prescriptions/1,000 population/year.

Antibiotic consumption in hospital care

In 2022, the antibacterial sales (in DDDs) to hospitals represented around 7.5% of total sales of antibacterials for human use in the country. The consumption has decreased by 5% in DDD/1,000 inhibitants/day compared to 2019 and increased by 7% since 2021 (Figure 24). The decrease in 2020 and 2021 is related to the Covid-19 pandemic. 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 pandemic the total sales of antibiotics to hospitals were stable with regard to DDD/1,000 inhabitants/day, but a change in pattern of use has occurred with increased use of narrow-spectrum antibiotics. Narrow-spectrum penicillins are highly utilised, for this group the theoretical value of DDDs is lower than the therapeutic doses most commonly prescribed in Norway. Furthermore, a narrow-spectrum penicillin combination regimen with an aminoglycoside will account for more DDDs than monotherapy with a cephalosporin or a carbapenem. This implies that the total count of DDDs will show higher values for volume when combination regimens are used instead of 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 22% of total DDDs for hospitals in 2022 compared to 26% in 2012. The share of beta-lactamase sensitive penicillins in 2022 was 16% of the total.

Penicillins (J01C) represent 48% of the use measured in DDDs in hospitals (J01CE 16%, J01CA 10% and J01CF 16%, J01CR 6%). The second largest group is the cephalosporins; 19% of all DDDs, the dominant subgroup being 3rd generation cephalosporins (J01DD). In 2022, six substances accounted for 51% of all DDDs used in hospitals. These were cloxacillin, benzylpenicillin, cefotaxime, cefazolin, gentamicin and doxycycline. Three single substances accounted for 33% of all antibacterial DDDs in hospitals; cloxacillin (13%), benzylpenicillin (12%), and cefotaxime (8%).

Figure 26 shows annual trends in national antibiotic use in hospitals, wih hospital activity data presented as DDD/100 bed days, instead of population statistics. The average length of stay (LOS) in Norwegian hospitals in the latest years is relatively stable according to national statistics, but the 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 adjust for activity, in order to make comparisons between hospitals possible. For 2022, data on admissions were not accessible, hence in this report the data are only presented in DDD/100 bed days. The reduced number of bed days in Norway over 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. Figur 27 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 28. 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 again observed. In 2022, there was increased use of penicillins with beta-lactamase inhibitors, 1st and 3rd generation cephalosporins and carbapenems, compared to the use in 2020 and 2021. Moreover, a decrease in the use of beta-lactamase sensitive penicillins and aminoglycosides has been observed in 2022, compared to 2019 (i.e. before the pandemic). The use of aminoglycosides increased by

39% from 2016 to 2019, probably due to implementation of antibiotic stewardship programs in Norwegian hospitals from 2016. The use of carbapenems peaked in 2014, after many years of increasing use, and seems to have reached a stable level (if we exclude the pandemic years). Only parenteral formulations of 2nd, 3rd and higher generation cephalosporins, as well as carbapenems, are licensed in Norway, and these are mainly used in hospitals. Figure 29 shows the distribution between "Preferred antibiotics" (which largely reflect standard recommended treatment regimens in national guidelines), and resistance driving antibiotics, for the different Norwegian hospitals. The proportions of preferred antibiotics vary among hospitals, between 80% and 54%, respectively.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between the hospitals. Figure 30 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 patient composition alone but are probably related to different prescribing practices between the hospitals.

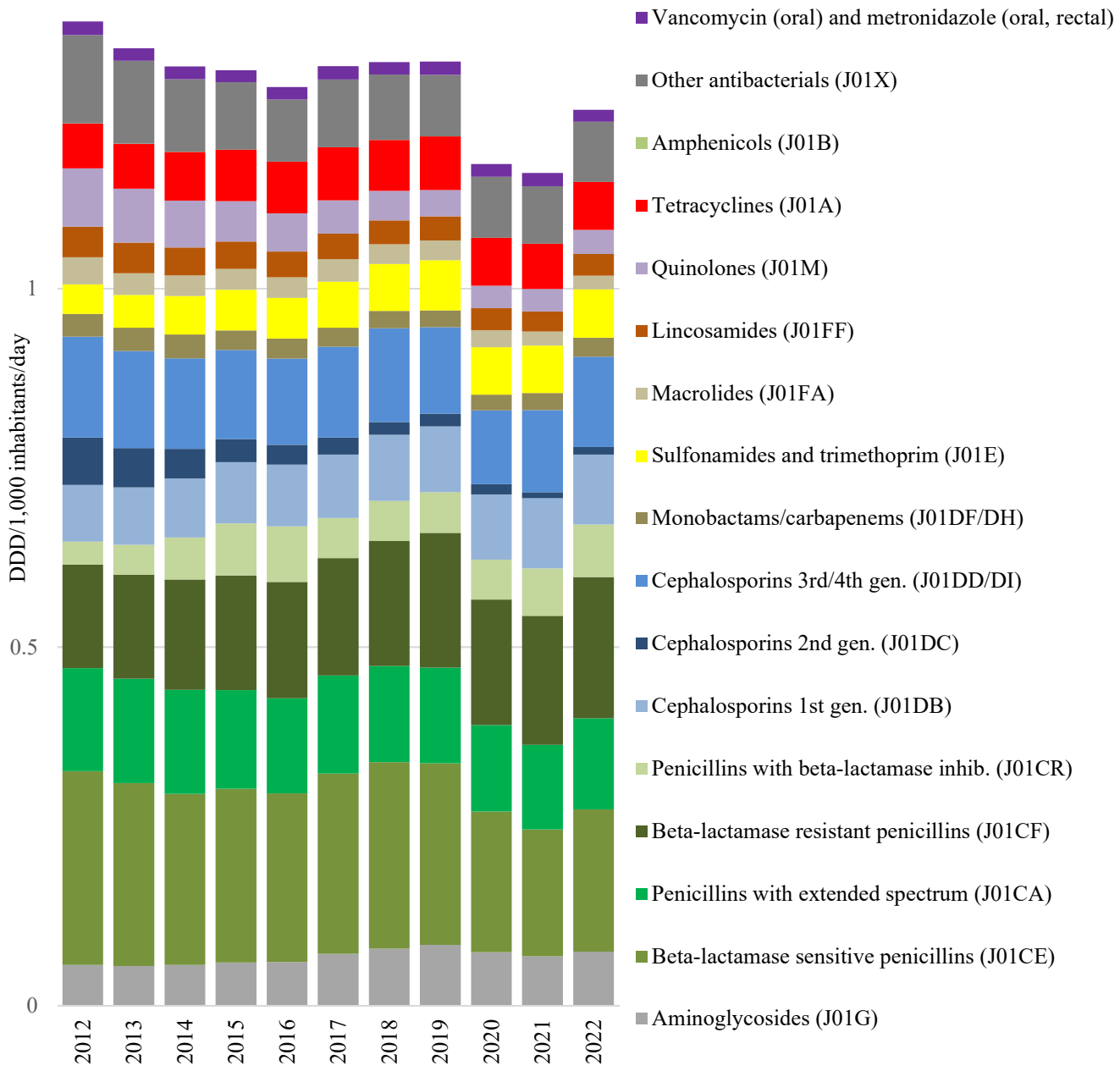


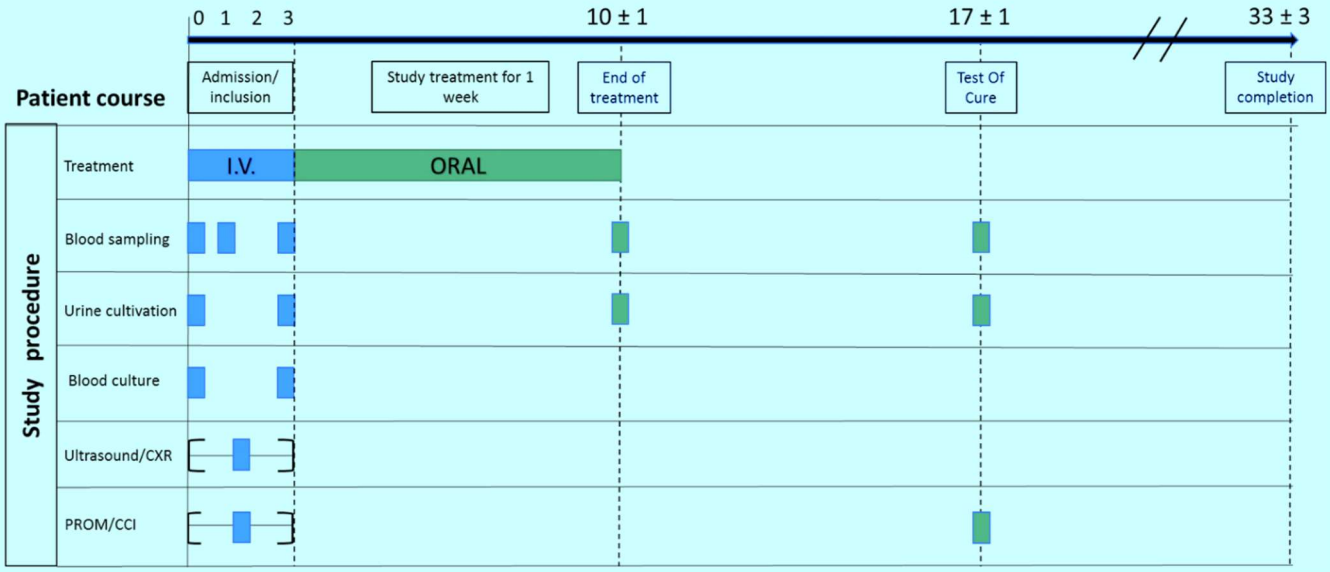
FIGURE 24. Proportions of antibacterial agents for systemic use (J01), vancomycin (A07AA09), and metronidazole (P01AB01) in Norwegian hospitals 2012-2022, measured in DDD/1,000 inhabitants/day.

The role of pivmecillinam in treating pyelonephritis

The alternatives to oral antibiotic treatment of pyelonephritis have traditionally been limited to trimethoprim-sulfamethoxazole and quinolones (1). In Scandinavian countries a third option – pivmecillinam (P-MEC) has been used to a certain extent on an empirical basis, not only in primary care, but also in hospitals, and is now included in the Norwegian guidelines as an alternative for uncomplicated pyelonephritis (2). The drug mecillinam (MEC) is an antimicrobial agent from the amidinopenicillin group with effect primarily against Gram-negative microbes. Orally formulated, the drug is modified with pivalic acid to P-MEC for better bioavailability. In the Scandinavian countries where mecillinam has been distributed for decades, the resistance rates in the community are still low (~5%) (3).

The documentation for the use of P-MEC for treatment of pyelonephritis is still limited. In 2017 a Danish review summarised the documented efficacy of MEC/P-MEC in treating pyelonephritis and bacteraemia caused by *Enterobacterales* (4). The authors commented that several of the studies were of older age with low number of participants and often designed with MEC/P-MEC given together with a second antibiotic. In addition, comparing different trial end-points like clinical- and bacteriological cure rates are difficult to interpret. They concluded that P-MEC is a responsible alternative treating acute uncomplicated pyelonephritis but emphasised the need for further research on MEC/P-MEC in well-designed studies with adequate sample size and modern trial design with a comparator.

In the hospital setting, it is desired to discharge patients with pyelonephritis for further ambulant oral treatment following a few days of intravenous antibiotics. In 2022, a Norwegian trial investigated the efficacy of P-MEC as step-down treatment in hospitalised patients with bacteriemic pyelonephritis caused by *E. coli* (5). The population was adult men and women suffering from a variety of comorbidities. This, together with the low grade of trial intervention was meant to make the results applicable to daily clinical practice. After three days of intravenous treatment, participants were discharged with P-MEC for another 7 days. Test of cure was one week after completed treatment, and the primary end point was a composite of afebrility, no need for re-treatment and patient-reported improvement in health status (Figure 25). The results were promising and indicated that P-MEC is a responsible choice in oral step-down treatment following three days of intravenous antibiotic treatment (Table 9).



CXR = Chest X-ray. PROM = Patient Reported Outcome Measure. CCI = Charlson Comorbidity Index.

FIGURE 25. Patient course from admission to study completion.

TABLE 9. Outcome measures at Test of Cure – TOC day 17 ± 1. Per-protocol population N=50.

Primary outcome – TOC – day 17 ± 1	n/N	%
Clinical efficacy		
Afebrile	49/49	100.0
No need for re-treatment	45/50	90.0
Improved health status	46/49	93.9
Composite primary end-point (all three above)	44/50	88.0 (95% CI: 75.7- 95.5)

Some of the strengths of the study were the patient characteristics with a number of 50 participants equally distributed between both genders, and median age of 67 years. This is in contrast to other studies often dominated by younger females. Two major objections to the study have been highlighted; the dose of P-MEC (400mg four times daily) and the inclusion of patients infected with non-wild type *E. coli*. According to the Summary of Product Characteristics (SPC) the maximum dose of P-MEC is 400 mg three times daily. There is, however, documentation that doses of P-MEC exceeding 1200 mg daily is well-tolerated, and in a recent poster from the Statens Serum Institut (SSI) (6) it is postulated that doses of 60 mg/kg is tolerated in mature humans. Susceptibility determination for MEC is performed in the laboratory by standardised disk diffusion test, showing the minimal inhibition concentration (MIC) value. Wild type *E. coli* will normally show MIC < 1 mg/L. *E. coli* is categorised as resistant at MIC values > 8 mg/L. Non-wild type isolates may have MIC values between 1-8 mg/L. In such cases, P-MEC given as 400 mg times four daily will not give adequate serum concentration levels (7). The authors have argued that treating patients suffering from bacteriemic pyelonephritis with *E. coli* with P-MEC as oral step-down treatment will depend on more than theoretical laboratory breakpoint values. In real life, factors like gender, body weight, polypharmacy, renal function, urinary tract abnormalities and other co-morbidities also affect the success rate of antibiotic treatment. Hence, clinical studies performed in daily practise settings might give complementary knowledge.

In the struggle for finding antibiotic alternatives in treating febrile urinary tract infections, MEC/P-MEC seems to be a responsible choice but clinical trials with modern design, adequate sample size and drug comparator are still highly desirable.

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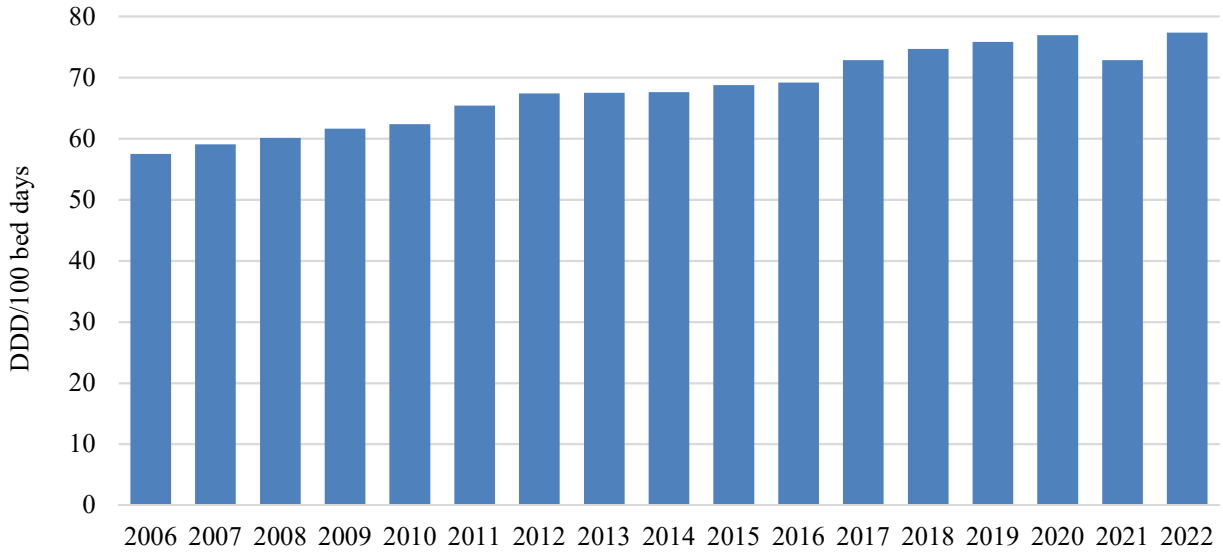

FIGURE 26. Total use of antibiotics in Norwegian hospitals (somatic) 2006-2022, measured in DDD/100 bed days. Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

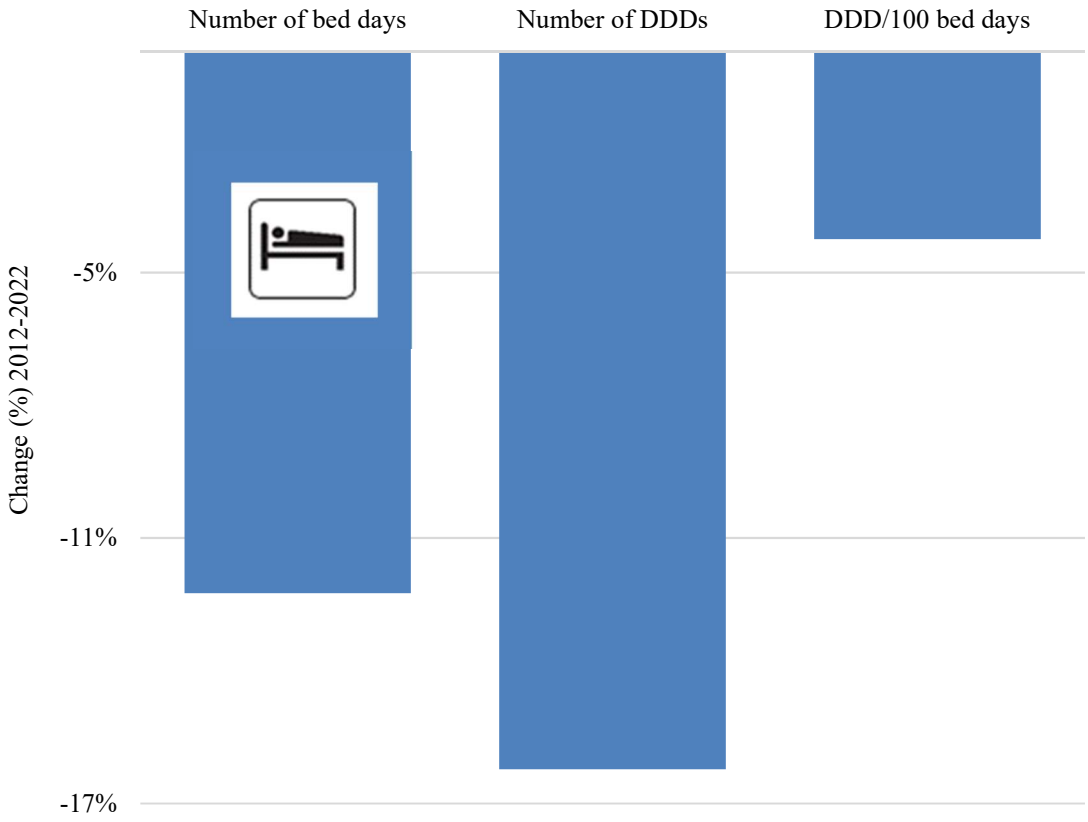

FIGURE 27. Proportional change will vary according to the measures used. Antibiotic usage in hospitals are often presented in DDD/100 bed days, but total number of DDDs may also be used as a measure. The number of bed days has been reduced by 12% since 2012. The figure visualises the impact of the reduction in bed days on antibiotic consumption statistics of broad-spectrum antibacterial agents for systemic use (ATC J01CR, J01DC, J01DD, J01DH, and J01MA) in Norwegian hospitals 2012-2022, measured as % change either as change of total DDDs (16% reduction) or change of DDD/100 bed days (4 % reduction).

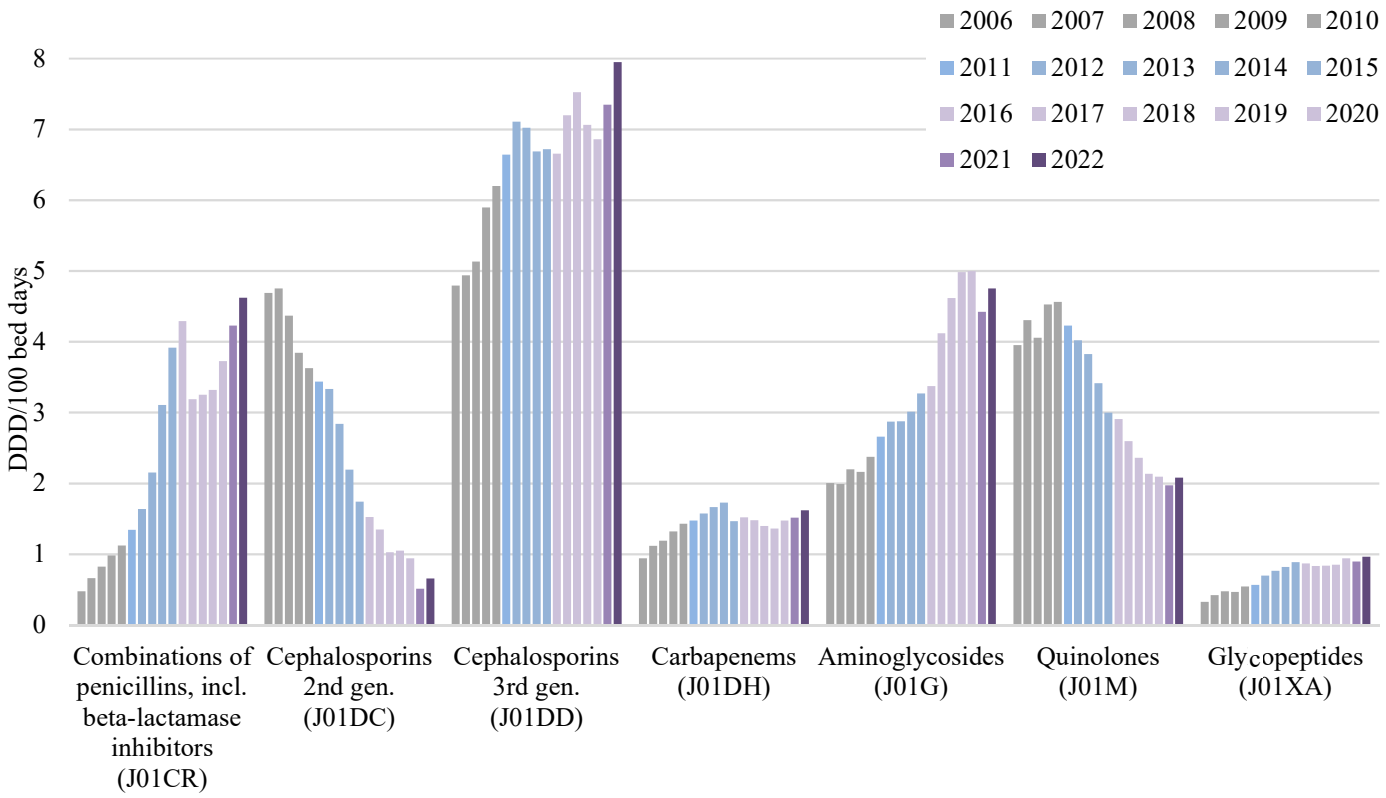

FIGURE 28. Consumption of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2022, measured in DDD/100 bed days.

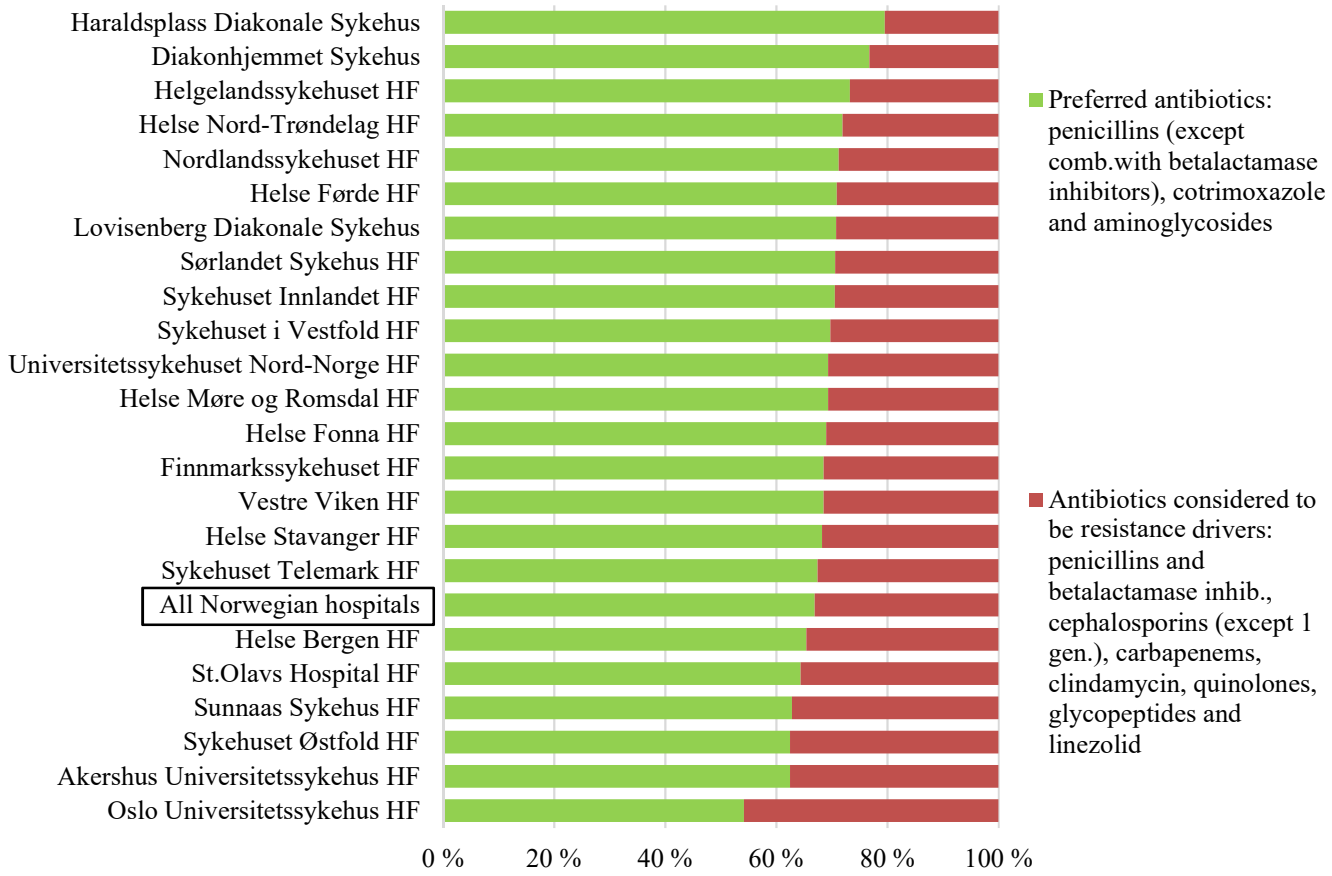

FIGURE 29. Proportions (% of DDDs) of preferred antibiotics (green part of the column) and antibiotics that are considered to be drivers of antibiotic resistance (red part i.e. belonging to ATC groups J01CR, J01DC, J01DD, J01DE, J01DI, J01DH, J01M, J01XA and J01XX08) in Norway, presented per hospital/health trust in 2022. 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.

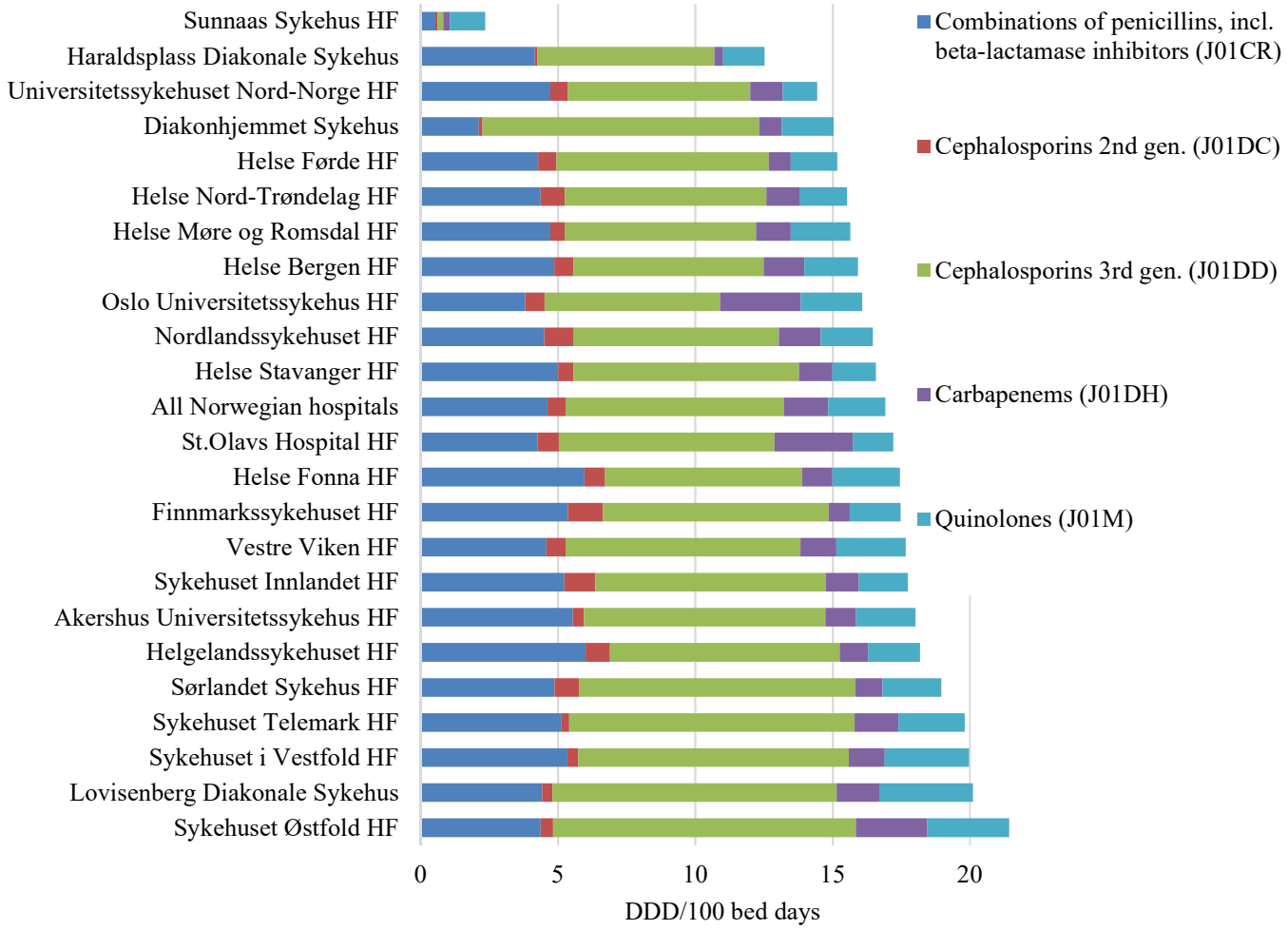

FIGURE 30. Consumption of selected antibacterial agents for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2022, measured in DDD/100 bed days. All hospitals, except one (Sunnaas Sykehus) are acute care hospitals.

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

In 2015, the government published its National Strategy against Antibiotic Resistance, aiming to reduce the total volume of antibiotics by 30%, as compared to 2012, by the end of 2020. This was followed by a National Action Plan, in 2016, with suggested measures. The overall target for total human consumption was reduction of DDDs by 30%. In addition, two sector specific goals in ambulatory care were introduced; reduction of the average number of prescriptions (target; 250 precriptions per 1,000 inhabitants per year) and the reduction of antibiotics for respiratory tract infections by 20% (in DDD/1,000 inhabitants/day). Figure 31 shows the total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to the National targets. The number of DDD/1,000 inhabitants/day for J01 is reduced by 19% since 2012. When excluding methenamine the reduction in use is 25% (Table 6). Over the years there are differences in the use of antibiotics recommended in Guidelines (i.e. narrow-spectrum antibiotics), indicating a higher adherence rate to the National Guideline for Antibiotic Use in Primary Care, and possibly also increased awareness of antibiotics as drivers of AMR (Figure 32). Precriptions (Rx) per 1,000 inhabitants per year (J01, excl. methenamine) is reduced by 29% since 2012 and in 2022 the number was 325 Rx/1,000 inhabitants/year for the general population.

Between 2012 and 2019, there has been a reduced prevalence of use in all age groups. The largest reduction is seen 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 is mainly due to lower prescribing of antibiotics for respiratory tract infections (Figure 33). The largest reduction in prescriptions per 1,000 during the first year of the pandemic was observed in children 0-9 years olds, but in 2022 the prescription patterns had returned to approximately the same levels as in 2019. A small reduction in the prevalence of use in the elderly compared to the pre-pandemic times, was observed. Whether this is due to more rational prescribing to elderly, or less actual infections, is not known.

For hospitals, the main target was 30% reduction in combined use of five selected groups of broad-spectrum antibiotics. To reach this goal, the National Action Plan also made antibiotic stewardship programs mandatory in Norwegian hospitals. Figure 34 shows the annual variation of total hospital use of these groups in the years 2006-2022 according to the national target. Figure 35 shows how the use of these five groups has changed in different Norwegian hospitals/health trusts in relation to the national target; a reduction by 30% (marked by a black dotted line in the figure). For all hospitals in Norway together there was 4.3% reduction in use of the five selected groups of broad-spectrum antibiotics from 2012 to 2022 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 indicator of clinical activity, confounds the drug use data, and it it likely that the use of other activity indicators would produce different results (see text box on page 47). Unadjusted sales data measured in DDDs, show a reduction of 16% for the same period (Figure 27).

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 – formerly KAS). These advisory units have been strenghtened and appointed key roles in promoting and supporting rational use of antibiotics in primary care and hospitals, respectively. The Directorate of Health has in collaboration with the advisory units, issued National Antibiotic Treatment Guidelines for antibiotic use in ambulatory care, nursing homes, dentistry and hospitals.

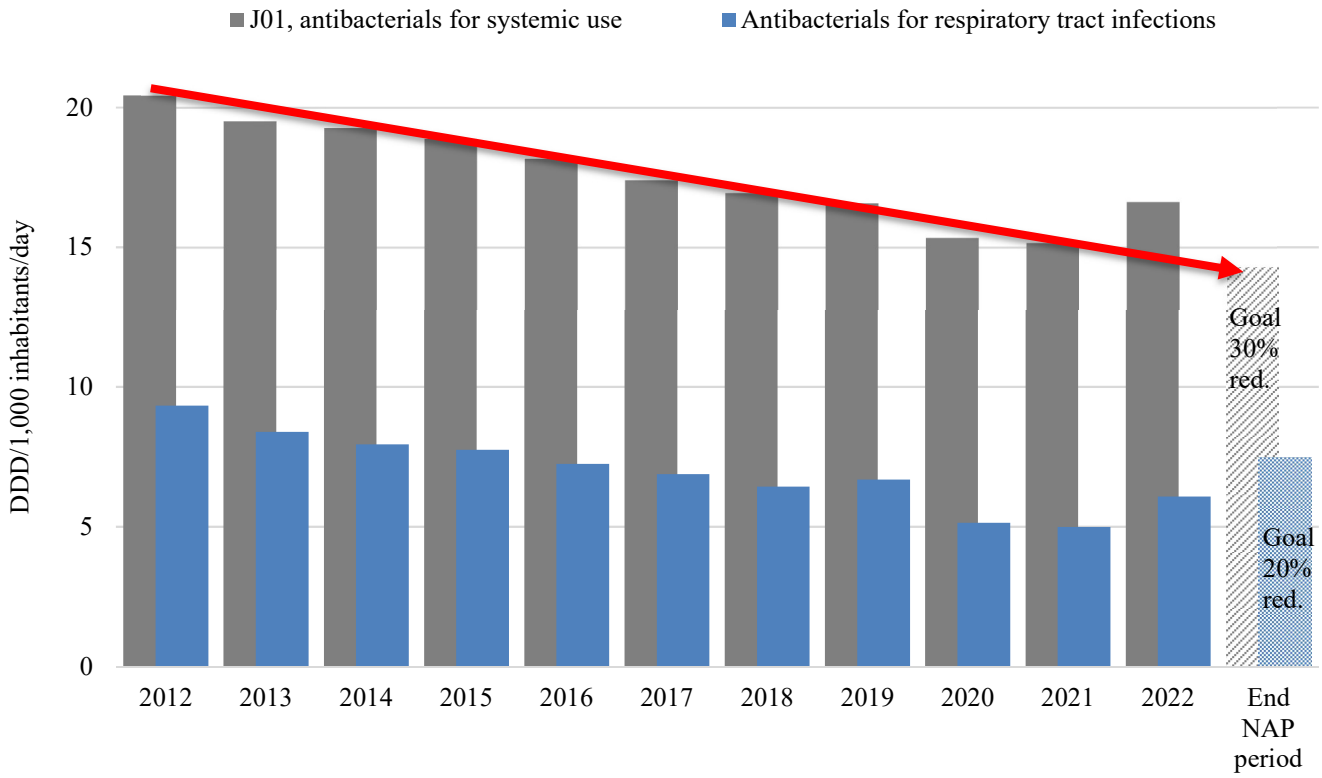

FIGURE 31. Total human sales of antibacterial agents for systemic use (ATC group J01) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2022 measured in DDD/1,000 inhabitants/day. According to the National Action Plan (NAP), the target for 2020 was 30% reduction of total use since 2012, measured in DDDs. Bars show measured use 2012-2022 (grey; J01, blue; antibiotics for respiratory tract infections), red line and bars with pattern; targets set in the National Strategy against Antibiotic Resistance.

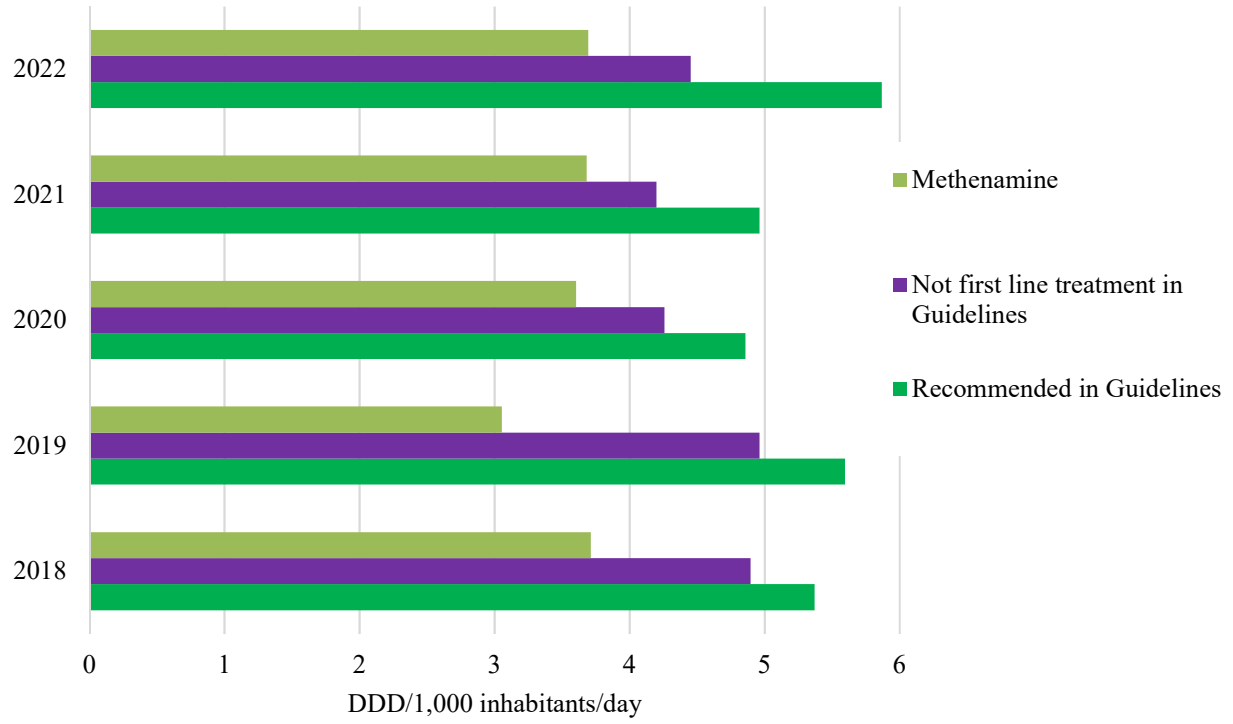

FIGURE 32. Consumption of antibacterial agents for systemic use (ATC group J01) in outpatients. Aggregated in three groups; a) recommended as first line treatment in the Guidelines for primary care (phenoxymethylpenicillin for respiratory tract infections, pivmecillinam, trimethoprim and nitrofurantoin 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).

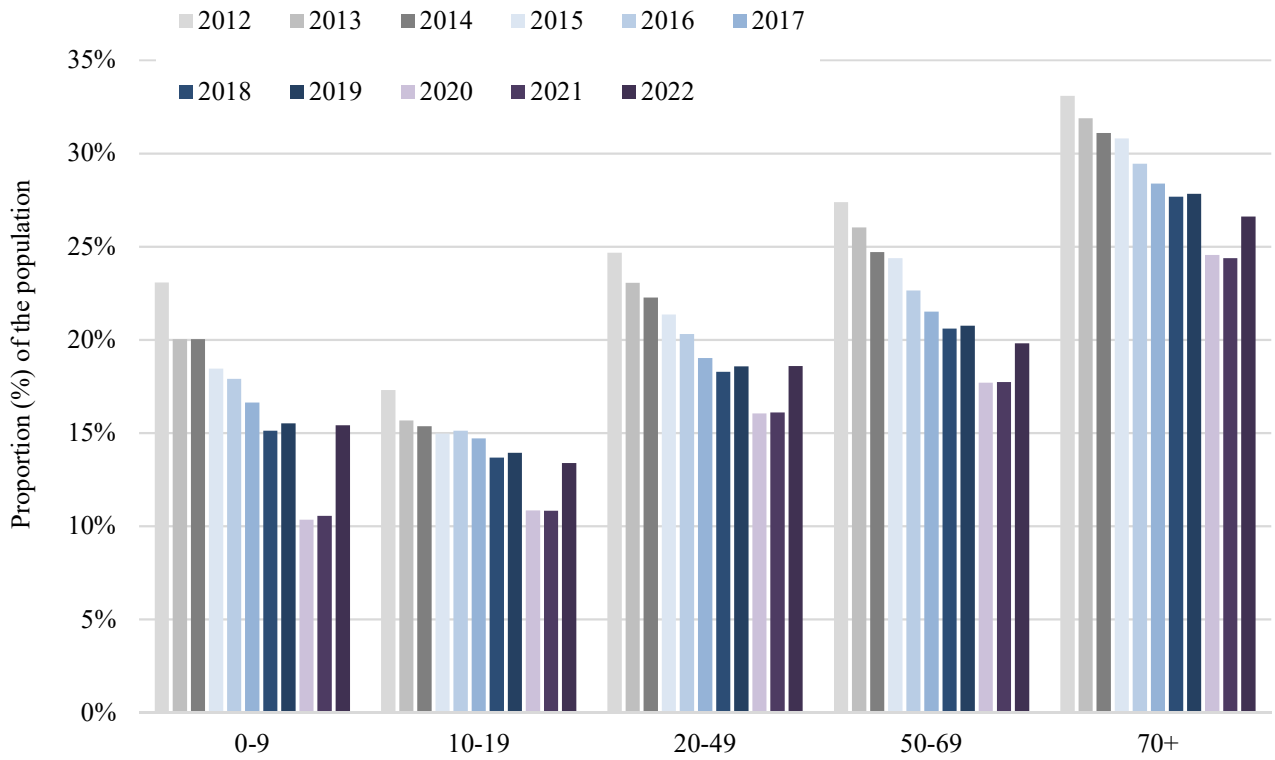

FIGURE 33. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care in Norway, 2012-2022. Antibiotics included are antibacterials for systemic use (ATC group J01, excl. methenamine).

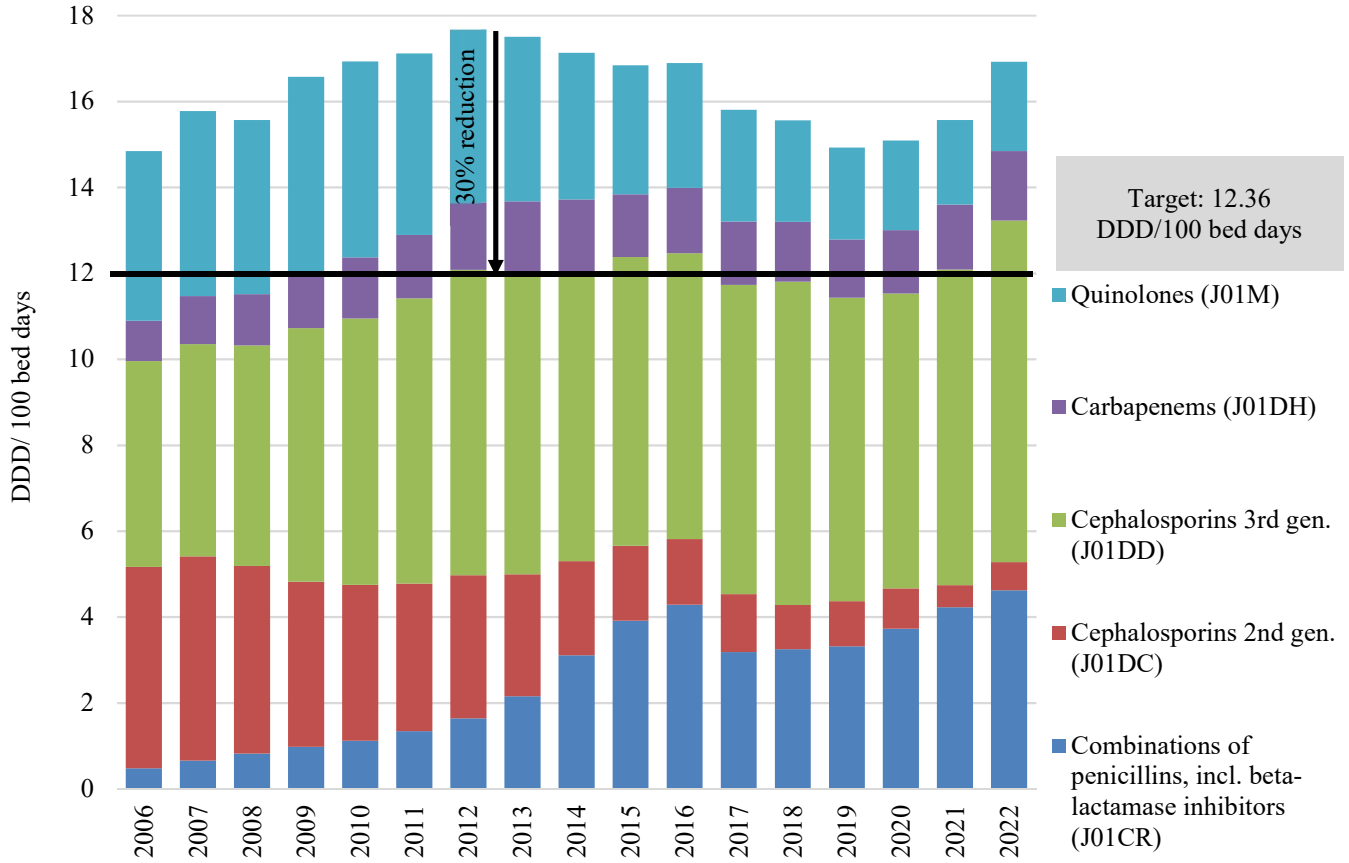

FIGURE 34. Consumption of selected antibacterial agents for systemic use (belonging to ATC-groups J01CR, J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2022, measured in DDD/100 bed days.

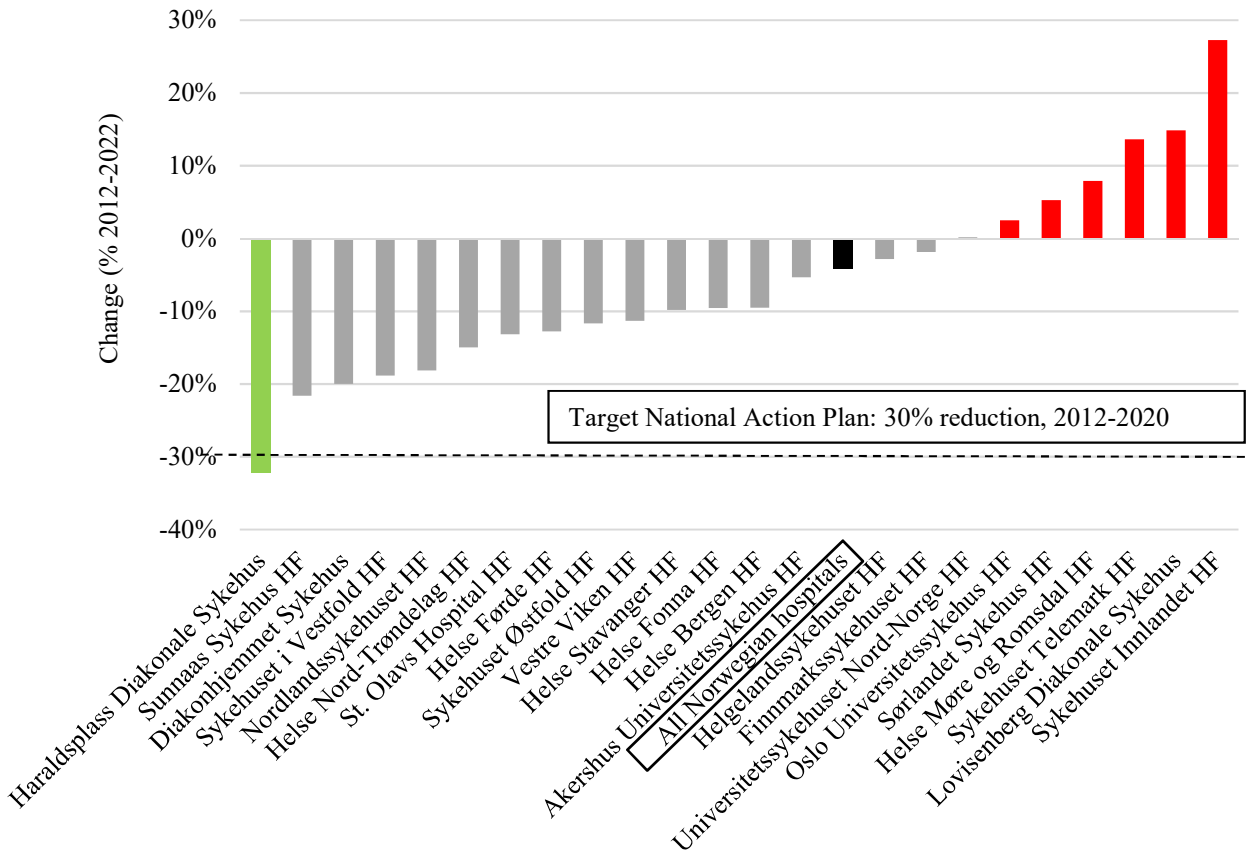

FIGURE 35. Change in consumption of selected antibacterials for systemic use (belonging to ATC-groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, 2012-2022. The data are presented per hospital/health trust as measured in DDD/100 bed days.

Which indicator is best suited for surveillance and benchmarking of antibiotic usage in hospitals?

Lord Kelvin's famous statement 'If you cannot measure it, you cannot improve it' (1) also applies to antibiotic consumption. But how should we measure antibiotic usage in hospitals, if the goal is to improve prescription?

Measurement of consumption, in order to identify and correct suboptimal prescription patterns, is a key component of antibiotic stewardship programs in hospitals (2). Most indicators are constructed as fractions, with the total amount of antibiotics in the numerator, and one or more adjustment factors in the denominator, to facilitate comparison over time and across entities (3, 4). A much used numerator is the 'Defined Daily Dose' (DDD), which is the international gold standard unit of measurement for antibiotics and other drugs (5). One DDD is the 'assumed average maintenance dose per day for a drug used for its main indication in adults'. For antibiotics, this translates to the recommended daily dose for treatment of moderately severe infections (3). Although the DDD often differs from the 'prescribed daily dose' (PDD), conversion of kilograms to DDDs provides a rough estimate of how many 'days of therapy' (DOT) a certain amount of antibiotics represents.

Adjustment for population size

Adjustment for population size is prerequisite for assessment of changes in antibiotic consumption in a population over time ('surveillance') or differences in usage between populations ('benchmarking'). The approach makes sense for quantification of antibiotic consumption at the international, national, and (perhaps) regional level, but not at hospital level, where the 'true' underlying population may be more difficult to define (3). Accordingly, the preferred indicator of antibiotic usage in hospitals at the international level is DDD per 1,000 inhabitants per day (DID) (3). The European Centre for Disease Prevention and Control (ECDC) uses DID to quantify total and sector wise (community and hospital) antibiotic usage in EU/EEA countries (6). A similar indicator, DOT per 1,000 inhabitants per day, is used to quantify hospital usage in the United States (3). Because DDD may be regarded as a proxy for DOT, the two indicators are to a certain degree comparable. Both estimate the average proportion (‰) of the population that is treated daily with antibiotics. A notable difference is that DID can be calculated from aggregate data, while calculation of DOT per 1,000 inhabitants requires individual prescription data.

Adjustment for hospital activity

Comparison of antibiotic usage across hospitals, e.g. in the shape of a national quality indicator (7), requires adjustment for differences in activity. Commonly used parameters are number of bed days, admissions, or patients (4). Indicators with bed days or admissions in the denominator are inherently vulnerable to variability in the average number of bed days per admission ('length of stay', LOS). A number of factors may influence LOS, including low efficiency or quality of health services. Another example is the Norwegian Care Coordination Reform (2012), which led to a reduction in LOS of 0.1 days per year (8). The reform contributed to an 11.5% reduction in overall LOS during 2012-2020, with regional reductions ranging from 3.4% in North to 15.8% in West (9). In 2020, average LOS was 4.5 days in the Northern region, compared to 4.0 days in all other regions. The variability likely reflects demographic differences, such as median travel time to an acute care hospital, which varies from nine minutes in central parts of the South-Eastern region to 138 minutes in parts of the Northern region (10).

Travel distances may also influence the proportion of day cases vs. inpatients. Day cases (hospitalised patients with zero bed days) accounted for 29.7% of all hospital admissions in Norway in 2020 (9). The proportions ranged from 26.6% in the Northern region to 31.2% in the Central region. This has relevance for calculation of antibiotic usage. No currently used indicators include day cases in the denominator, despite that administration of antibiotics to day cases contributes to the number of DDDs in the numerator. Thus, a low proportion of day cases 'inflates' the denominator, leading to (apparently) lower antibiotic consumption.

Adjustment for patient composition

Calculation of antibiotic usage should also take into account qualitative factors influencing prescription. The case mix index (CMI) (diagnosis-related group (DRG) weight per admission) has been suggested as a proxy for patient composition (4, 11, 12). The index is calculated from diagnosis coding and is part of the activity-based funding system for hospitals in Norway (13). A Swiss study found significant correlation between CMI and total hospital antibiotic usage, expressed as DDD per 100 bed days or admission (11). Similarly, CMI correlated significantly with hospital usage of broad-spectrum antibiotics, expressed as DDD per admission or patient, but not per 100 bed days, in a Norwegian study (12). Irrespective of indicator, the correlation increased in strength between 2012 and 2019, possibly reflecting improved prescription after implementation of a national guideline (2). Although CMI has limitations related to coding quality and differences between DRG systems in different countries, the index appears to detect patient complexity associated with need for antibiotic treatment. The index may therefore be a useful smoothing factor to provide a stronger basis for benchmarking of hospital antibiotic usage.

Valid indicators

ECDC claim that bed days is 'the recommended denominator' for calculation of hospital usage (6), but this is not supported by the cited reference (4). On the contrary, the authors of the cited paper propose no less than 12 indicators of hospital antibiotic usage as a 'global standard'. The indicators were consensually validated by an international expert panel, assessing the suitability of 74 unique numerator/denominator combinations identified through a literature review. The 12 valid indicators were based on five numerators (DDD, DOT, PDD, exposed patients, or length of therapy) and four denominators (bed days, admissions, patients, and/or CMI). The proposal illustrates 1) the variety of accepted numerators and denominators, 2) the lack of a gold standard, and 3) the lack of objective methods for assessment and validation of indicators.

A Norwegian evaluation of indicators of hospital antibiotic usage (12) utilised the well-described, dose-dependent association between consumption and resistance (3, 14, 15) to develop a model for objective comparison and validation of indicators. In theory, 'the perfect indicator' would under optimal conditions show perfect correlation between antibiotic usage and resistance. Such conditions include the absence of confounders (i.e. drug A is the only driver of resistance to drug A) and that usage is stable or increasing, because resistance declines slowly when the antibiotic pressure is reduced (14). In the lack of a perfect indicator, the activity-neutral indicator DID was used to establish a plausible and statistically significant reference correlation from surveillance data. Conditions were optimised by selecting antibiotics predominantly used in hospitals (piperacillin-tazobactam and 3rd generation cephalosporins) during a period with increasing use (2010-2015), and an associated resistance marker robust against variations in diagnostic procedures (ESBL-producing *E. coli* in blood cultures).

Ten DDD-based indicators (five established and five novel) were included in the evaluation (Table 10). Denominators (bed days, admissions, patients, and/or CMI) were selected from consensually validated indicators (4). Using the same raw data as the reference correlation, five indicators gave statistically significant correlations between antibiotic usage and resistance. All indicators met the validation criterion of showing a correlation at least as strong as DDD per 100 bed days.

TABLE 10. Validation of DDD-based indicators of antibiotic usage in hospital. Adapted from (12).

Indicator	Numerator	Denominator (hospital activity)	Denominator (patient composition)	Day cases included	Correlation between usage and resistance[1]	Valid[2]	Previous assessment (consensual) (4)
DID	DDD	NA	NA	NA	$r = 1.000$, $p = 0.008$*	Reference	NA
A1	DDD	100 bed days	None	No	$r = 0.981$, $p = 0.124$	Standard	Valid
B1	DDD	Admissions	None	No	$r = 0.999$, $p = 0.027$*	Yes	Valid
C1	DDD	Patients	None	No	$r = 0.995$, $p = 0.063$	Yes	'For discussion'
B2	DDD	Admissions	None	Yes	$r = 0.989$, $p = 0.096$	Yes	None (novel indicator)
C2	DDD	Patients	None	Yes	$r = 0.999$, $p = 0.033$*	Yes	None (novel indicator)
A1p	DDD	100 bed days	CMI	No	$r = 1.000$, $p = 0.013$*	Yes	Valid
B1p[3]	DDD	Admissions	CMI	No	$r = 0.994$, $p = 0.069$	Yes	'For discussion'
C1p	DDD	Patients	CMI	No	$r = 0.998$, $p = 0.043$*	Yes	None (novel indicator)
B2p[3]	DDD	Admissions	CMI	Yes	$r = 0.992$, $p = 0.079$	Yes	None (novel indicator)
C2p	DDD	Patients	CMI	Yes	$r = 0.999$, $p = 0.023$*	Yes	None (novel indicator)

DID, DDD per 1,000 inhabitants per day. NA, not applicable. CMI, case mix index (average diagnosis-related group (DRG) weights per admission). [1] Regional hospital usage of piperacillin-tazobactam and 3rd generation cephalosporins vs. incidence rate of ESBL-producing *E. coli* in blood cultures (Norway, 2010-2015). *, statistically significant ($p < 0.05$); [2] Correlation with resistance at least as strong as DDD per 100 bed days; [3] Equals DDD per DRG weights.

Choice of indicator: does it matter?

Parallel use of at least two indicators has been suggested, to compensate for flaws and weaknesses (4, 16). This may complicate interpretation when the selected indicators produce dissimilar results. For instance, the reduction in hospital usage of broad-spectrum antibiotics in Norway (2012-2020) calculated with ten valid indicators ranged from 14.5% with DDD per 100 bed days to 29.3% with the novel indicator 'DDD per patient per CMI, day cases included', as compared to 35.6% with DID (12). This suggests that the goal of 30% reduction actually was achieved, in contrast to official conclusions (2, 7).

'DDD per patient per CMI, day cases included' corresponded best with DID in three of four regions, narrowly beaten in Central Norway by another novel indicator, 'DDD per admission per CMI, day cases included' (equals 'DDD per DRG weight', i.e. antibiotic usage adjusted for the total hospital 'production'). This suggests that the novel concept of including day cases in the denominator may have some advantages compared to the traditional approach. Finally, the ten indicators ranked health regions and hospitals differently by usage of broad-spectrum antibiotics (2020), but there were only minor differences between the four indicators with combined adjustment for admissions or patients and CMI (Table 11).

TABLE 11. Health regions (A) and acute care hospitals (B) ranked by usage of selected broad-spectrum antibiotics (ATC groups J01CR, J01DC, J01DD, J01DH, and J01M) in 2020, calculated with valid indicators (Table 10). Adapted from (12).

A. Health regions	A1	B1	C1	B2	C2	A1p	B1p	C1p	B2p	C2p	DID
Northern region	1	4	4	4	4	1	4	4	4	4	4
Central region	2	1	2	2	2	2	2	2	2	2	3
Western region	3	2	1	1	1	4	3	3	3	3	2
South-Eastern region	4	3	3	3	3	3	1	1	1	1	1
B. Acute care hospitals	**A1**	**B1**	**C1**	**B2**	**C2**	**A1p**	**B1p**	**C1p**	**B2p**	**C2p**	**DID**
Haraldsplass Diakonale Sykehus	1	4	1	3	1	6	8	7	8	5	-
Helse Møre og Romsdal HF	2	1	2	1	2	4	4	4	1	2	-
Universitetssykehuset Nord-Norge HF	3	14	16	16	17	2	6	8	7	8	-
Diakonhjemmet Sykehus	4	3	3	6	6	5	3	3	4	4	-
Helse Nord-Trøndelag HF	5	2	4	4	5	8	5	6	5	7	-
Finnmarkssykehuset HF	6	5	6	7	8	18	14	14	16	15	-
Sykehuset Telemark HF	7	8	8	10	7	9	11	10	12	10	-
Helse Bergen HF	8	9	9	11	11	3	1	2	2	3	-
Helgelandssykehuset HF	9	12	12	12	12	17	19	19	18	19	-
Sykehuset Innlandet HF	10	7	7	8	9	10	9	9	9	9	-
Lovisenberg Diakonale Sykehus	11	11	10	2	3	12	13	12	10	11	-
Oslo Universitetssykehus HF	12	20	15	18	16	1	2	1	3	1	-
Sørlandet sykehus HF	13	6	5	5	4	13	7	5	6	6	-
Vestre Viken HF	14	10	11	9	10	11	10	11	11	12	-
Helse Førde HF	15	13	13	13	14	19	20	20	21	21	-
Nordlandssykehuset HF	16	17	18	19	19	14	18	18	17	18	-
St. Olavs Hospital HF	17	22	21	21	22	7	12	13	13	13	-
Helse Stavanger HF	18	15	14	14	13	16	15	16	14	14	-
Akershus Universitetssykehus HF	19	19	17	22	20	15	17	15	19	17	-
Helse Fonna HF	20	18	20	20	21	22	22	22	22	22	-
Sykehuset Østfold HF	21	16	19	15	15	20	16	17	15	16	-
Sykehuset i Vestfold HF	22	21	22	17	18	21	21	21	20	20	-

Conclusions

Adjustment for both quantitative and qualitative differences is required for meaningful comparison of antibiotic usage over time and across hospitals. Adjustment for activity should be robust against differences in factors influencing LOS or the proportion of day cases. In addition, indicators of antibiotic usage should reflect the adverse effects of antibiotics as drivers of resistance. Novel indicators with combined adjustment for (all) admissions or patients and CMI tick all these boxes. At national and regional level, they also correspond well with DID, which is the preferred indicator of hospital antibiotic usage at the international level.

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OCCURRENCE OF ANTIMICROBIAL RESISTANCE

ANIMAL CLINICAL ISOLATES

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The clinical isolates included in NORM-VET 2022 were *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp. (CoNS) from mastitis in cattle, and *Pseudomonas aeruginosa* from various infections in dogs. Sampling, laboratory methods and data processing are described in Appendix 3.

Staphylococcus aureus from cattle

A total of 191 isolates of *Staphylococcus aureus* from mastitis in cattle were susceptibility tested. The isolates were collected in 2021. The results are presented in Table 12, Figure 36 and the text.

TABLE 12. Antimicrobial resistance in *Staphylococcus aureus* from mastitis in cattle (n=191) collected in 2021.

			Distribution (%) of MIC values (mg/L)*																
Substance	Resistance (%)	[95% CI]	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256
Oxytetracycline	7.3	[4.1 – 12.0]							53.9	38.7	7.3								
Amoxicillin	2.6	[0.9 – 6.0]					0.5	15.2	74.9	6.8	1.1	0.5	0.5		0.5				
Benzylpenicillin	3.1	[1.2 – 6.7]		1.6	18.9	55.0	20.4	1.1	0.5	0.5	1.1	0.5		0.5					
Cloxacillin	0.0	[0.0 – 1.9]							39.3	59.2	1.6								
Cephalexin	0.5	[0.0 – 2.9]									6.8	53.4	37.7	1.6		0.5			
Cephapirin	2.1	[0.6 – 5.3]					1.6	25.1	71.2	2.1									
Trimethoprim-sulfamethoxazole	0.0	[0.0 – 1.9]				5.2	60.2	33.5	1.1										
Tylosin tartrate	0.0	[0.0 – 1.9]								2.6	38.7	57.6	1.1						
Lincomycin	0.0	[0.0 – 1.9]							1.1	7.9	86.4	4.7							
Streptomycin	0.5	[0.0 – 2.9]										0.5	61.3	36.7	1.1		0.5		

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-offs not defined. CI=confidence interval. White fields show range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for 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 are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFF, only ECOFFs are shown (i.e. for benzylpenicillin and for the CLSI clinical breakpoint for cephalexin). Clinical breakpoints are not defined for oxytetracycline, cloxacillin, amoxicillin, cephalexin, cephapirin, tylosin tartrate, lincomycin and streptomycin.

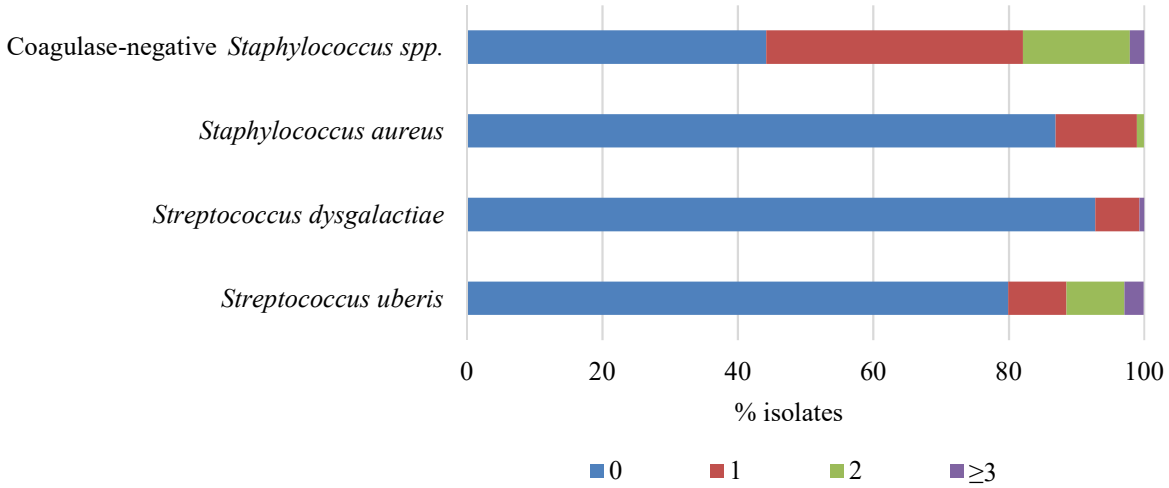

FIGURE 36. Antimicrobial resistance profile for *Staphylococcus aureus* and coagulase-negative *Staphylococcus* spp. (CoNS) from mastitis in cattle collected in 2021, as well as *Streptococcus dysgalactiae* and *Streptococcus uberis* in cattle collected in 2020 (NORM-VET 2021). Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 86.9% of the *S. aureus* isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to oxytetracycline was the most frequently identified resistance phenotype, followed by resistance to benzylpenicillin and the 1st generation cephalosporin cephapirin. The following proportions of isolates were resistant to one or more antimicrobial classes: 12.0% were resistant to one, and 1.0% to two antimicrobial classes, respectively (Figure 36).

One of the isolates showed reduced susceptibility to cephalexin. The isolate was subjected to cefoxitin sensitivity testing using disk diffusion to identify possible methicillin resistance. The isolate was susceptible to cefoxitin and therefore not defined as an MRSA.

S. aureus from mastitis in cattle has been included in previous NORM-VET reports, the last time in 2010. The rate of resistance to benzylpenicillin is still low at 3.1% [95% CI: 1.2-6.7]. The antimicrobial agents included in the test panel have changed over the years, complicating comparisons to previous results. Clinical breakpoints are shown in dotted blue lines in Table 12. 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 result.

Coagulase-negative *Staphylococcus* spp. from cattle

A total of 190 isolates of coagulase-negative *Staphylococcus* spp. (CoNS) from mastitis in cattle were susceptibility tested. Table 13 shows the number of isolates per species of CoNS. The isolates were collected in 2021. The results are presented in Table 14, Figure 36 and the text.

TABLE 13. Number of isolates per species of coagulase-negative *Staphylococcus* spp. from clinical mastitis in cattle (n=190).

Species	Number of isolates
Staphylococcus capitis	1
Staphylococcus caprae	1
Staphylococcus chromogenes	40
Staphylococcus cohnii	1
Staphylococcus condimenti	1
Staphylococcus epidermidis	65
Staphylococcus haemolyticus	22
Staphylococcus hyicus	6
Staphylococcus pasteuri	1
Staphylococcus simulans	49
Staphylococcus warneri	3

TABLE 14. Antimicrobial resistance in coagulase-negative *Staphylococcus* spp. from clinical mastitis in cattle (n=190) collected in 2021.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*																
Substance		[95% CI]	0.002	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256
Oxytetracycline	2.2	[0.6 – 5.3]							4.7	73.2	20.0	1.1	1.1							
Amoxicillin	5.8	[2.9 – 10.1]					1.1	13.2	42.6	29.5	7.9	5.3				0.5				
Benzylpenicillin	27.9	[21.6 – 34.8]		0.5	4.2	33.2	27.9	6.3	3.7	9.5	10.0	3.2	1.1		0.5					
Cloxacillin	0.0	[0.1 – 3.8]							2.1	17.4	66.8	12.6	1.1							
Cephalexin	0.5	[0.0 – 2.9]									2.6	14.2	64.2	16.3	2.1	0.5				
Cephapirin	0.0	[0.0 – 1.9]					2.1	34.7	39.5	20.5	3.2									
Trimethoprim-sulfamethoxazole	27.4	[21.2 – 34.4]				8.4	29.5	23.7	11.1	21.1	3.7	0.5	1.1	1.1						
Tylosin tartrate	0.5	[0.0 – 1.9]								0.5	12.6	64.7	21.6	0.5						
Lincomycin	2.6	[0.9 – 6.0]								23.2	40.5	31.6	2.1	1.6	0.5	0.5				
Streptomycin	15.3	[10.5 – 21.2]										6.8	47.4	27.9	2.6		2.6	1.6	1.1	10.0

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-offs not defined. CI=confidence interval. White fields show range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for 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 are not defined for oxytetracycline, amoxicillin, benzylpenicillin, cloxacillin, cephalexin, cephapirin, tylosin tartrate, lincomycin and streptomycin.

RESULTS AND COMMENTS

In total, 44.2% of the isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to the penicillins benzylpenicillin and amoxicillin was the most frequently identified resistance phenotype, followed by resistance to sulfonamides/trimethoprim and the amino-glycoside streptomycin.

The following proportions of isolates were resistant to one or more antimicrobial classes: 37.9% were resistant to one, 15.8% to two and 2.1% to three or more antimicrobial classes, respectively (Figure 36).

CoNS from clinical mastitis in cattle have been included in NORM-VET previously, last time in 2005. The overall level of resistance to benzylpenicillin in CoNS as a group is stable at around 25%, but varies among the most commonly identified species, from very low in *S. simulans*, to relatively high in *S. epidermidis* and *S. haemolyticus* (Smistad *et. al*. 2019, Taponen *et. al*. 2015, Waller *et. al.* 2011). The antimicrobial agents included in the test panel have changed over the years, complicating comparisons to previous results. 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 result. The general recommendation in Norway is to not treat subclinical mastitis caused by CoNS, whilst clinical mastitis is treated before the bacterial diagnosis is set.

Antimicrobial resistance testing in the routine mastitis diagnostics in Norway in 2022

Background

The Norwegian dairy co-operative TINE SA operates the TINE Mastitis Laboratory in Molde that analyses milk samples from dairy cows and goats across the country. Approximately 80,000 quarter milk samples from dairy cows, and 6,000 udder half samples from goats are analysed at the laboratory per year. The laboratory performs antimicrobial resistance testing of selected isolates, which may serve as an important surveillance of the level of AMR in the milk-producing animals. The laboratory records the results in a central database, the Norwegian Dairy Herd Recording System (NDHRS) (1). Statistics from the mastitis diagnostics in dairy cows have been published yearly since 2000 (2).

Methods

Results from AMR testing of isolates/samples from dairy cows from 2022 were retrieved from the NDHRS. Since benzyl-penicillin procaine is the first choice for treatment of mastitis in Norwegian dairy cows, *Staphylococcus aureus* (all reasons for sampling) and non-*aureus* staphylococci (NAS) (from clinical mastitis only) are routinely tested for beta-lactamase production by the clover leaf assay (3). Penicillin resistant *S. aureus* and *Enterobacteriaceae* from clinical mastitis are tested by disk diffusion for amoxicillin-clavulanic acid, ampicillin, cefoxitin (*S. aureus*) and trimethoprim-sulphamethoxazole (*Enterobacteriaceae*). Other bacterial species from clinical mastitis may also be tested. Streptococci are considered sensitive to penicillin and are therefore not routinely tested.

Results and discussion

In total, 7,114 isolates from 4,977 cows in 2,137 farms were tested. The tested isolates were *S. aureus* (n=5,716; 80%), *Enterobacteriacae* (n=772; 11%), NAS (n=587; 8%) and other bacteria (n=39; 1%).

Among the *S. aureus* tested by clover leaf, 97 isolates (1.7%) had beta-lactamase production. In the subset of samples from clinical mastitis, 17 of 1,543 (1.1 %) *S. aureus* had beta-lactamase production. Two *S. aureus* (resistant to penicillin) were resistant to cefoxitin and were verified as MRSA at the Veterinary Institute. The isolates came from one cow. Among the *S. aureus* tested for amoxicillin-clavulanic acid, 99/99 (100%) were sensitive.

S. aureus is the most common cause of clinical mastitis in Norway, and has been the major target for udder health control programs. Despite this, the prevalence of *S. aureus* remains high (1). However, the proportion of *S. aureus* isolates with beta-lactamase production has been reduced since 2015 (Table 15).

TABLE 15. Proportion of *S. aureus* mastitis isolates with beta-lactamase production in Norwegian dairy cows 2015-2022.

Year	No. of tested isolates	Occurrence of *S. aureus* with beta-lactamase production (%)
2015	6,658	3.0
2018	7,158	2.6
2022	5,716	1.7

NAS as a group is the most common bacterial finding in milk samples from Norwegian dairy cows (1). They are considered minor pathogens since they rarely cause clinical mastitis and give mild elevations in the somatic cell count (inflammation marker used as a quality and payment parameter). Because of the high prevalence in some herds, however, NAS may in sum contribute to reduced milk quality and increasing antibiotic use if the farmer requests treatment. The general recommendation is to not treat mild or subclinical mastitis caused by NAS, because of the limited cost-benefit, as well as the relatively high proportion of resistance to the first-choice drug in mastitis, benzylpenicillin. Table 16 gives an overview of the different NAS species tested and the proportion of isolates with beta-lactamase production.

Table 17 shows the results of the susceptibility testing for amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole of *E. coli* in 2022. A majority of the isolates were susceptible to trimethoprim-sulfamethoxazole, while they showed reduced susceptibility to amoxicillin-clavulanic acid.

The traditional mastitis control programmes have focused on targeting infected udders with antibiotics (4). The udder pathogen panorama is shifting towards opportunistic (like NAS) or environmental bacteria (like *E. coli*) in many countries (5). These infections have less effect of antibiotic treatments as well as higher self-cure rate representing a potential for further reduction of antibiotic use in mastitis control strategies also in Norwegian dairy farming.

TABLE 16. Number of tested non-*aureus* staphylococci (NAS) from mastitis in Norwegian dairy cows in 2022, and their proportion of isolates with beta-lactamase production.

Species	n	Occurrence of beta-lactamase production (%)
Staphyloccus epidermidis	211	77
Staphyloccus chromogenes	106	17
Staphyloccus simulans	134	1
Staphyloccus haemolyticus	44	73
Staphyloccus warneri	21	29
Other NAS	71	44
Total	587	31

TABLE 17. Susceptibility testing of *E. coli* from mastitis in Norwegian dairy cows in 2022. Number of isolates (%) is given for each category susceptible (S), susceptible with increased exposure (I), and resistant (R).

Species	Amoxicillin-clavulanic acid			Trimethoprim-sulfamethoxazole		
	S	I	R	S	I	R
E. coli	2 (0.3%)	669 (93.6%)	44 (6.2%)	651 (91%)	1 (0.1%)	68 (9.5%)

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Pilot testing the EARS-Vet surveillance network for antibiotic resistance in bacterial pathogens from animals in the EU/EEA

As part of the EU Joint Action on Antimicrobial Resistance (AMR) and Healthcare-Associated Infections an initiative was launched to build the European AMR Surveillance Network in Veterinary Medicine (EARS-Vet) (1). Activities included mapping national systems for AMR surveillance in animal bacterial pathogens (2), and defining EARS-Vet objectives, scope and standards (3). In a follow-up publication the EARS-Vet network pilot tested the suggested EARS-Vet surveillance, namely by i) assessing available data, ii) performing cross-country analyses, and iii) identifying potential challenges and developing recommendations to improve future data collection and analysis (4). Eleven partners from nine EU/EEA countries participated and shared available data for the time period 2016-2020. The data included a total of 140,110 bacterial isolates and 1,302,389 entries (isolate-antibiotic agent combinations). Collected data were highly diverse and fragmented. A joint analysis was performed on AMR trends of 53 combinations of animal host-bacteria-antibiotic categories of interest to EARS-Vet with a standardised approach and interpretation using epidemiological cut-offs. Substantial variations of resistance levels were demonstrated, both among and within countries (e.g., between animal host species). Key issues included the lack of harmonisation of antimicrobial susceptibility testing methods used in European surveillance systems and veterinary diagnostic laboratories, the absence of interpretation criteria for many bacteria–antibiotic combinations, and the lack of data from EU/EEA countries where little or no surveillance currently exists (4). Still, this pilot study provides a proof-of-concept of what EARS-Vet can achieve. The results form an important basis to shape future systematic data collection and analysis.

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Pseudomonas aeruginosa from dogs

A total of 118 isolates of *Pseudomonas aeruginosa* from infections in dogs were susceptibility tested. The isolates were collected in the years 2018 to 2022. The results are presented in Table 18, Figure 37 and in the text.

TABLE 18. Antimicrobial resistance in *Pseudomonas aeruginosa* from clinical infections in dogs (n=118) collected from 2018 to 2022.

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
Piperacillin-tazobactam	3.4	[0.9 – 8.5]							66.9	23.7	5.9	3.4			
Ceftazidime	2.5	[0.5 – 7.3]					13.6	61.9	19.5	2.5	2.5				
Cefepime	1.7	[0.2 – 6.0]					15.3	51.7	17.8	13.6	1.7				
Aztreonam	3.4	[0.9 – 8.5]						8.5	66.1	16.1	5.9	3.4			
Meropenem	5.1	[1.9 – 10.7]				48.3	28.8	17.8	5.1						
Doripenem	1.7	[0.2 – 6.0]			32.2	36.4	16.9	12.7	1.7						
Imipenem	0.8	[0.0 – 4.6]					11.0	27.1	29.7	28.0	2.5	0.8	0.8		
Tobramycin	1.7	[0.2 – 6.0]				76.3	16.9	5.1	1.7						
Gentamicin	3.4	[0.9 – 8.5]					27.1	50.8	16.1	2.5	2.5	0.8			
Amikacin	2.5	[0.5 – 7.3]						25.4	54.2	11.9	5.9	2.5			
Ciprofloxacin	15.3	[9.3 – 23]		70.3	10.2	4.2	8.5	1.7	5.1						
Levofloxacin	10.2	[5.4 – 17.1]		1.7	15.3	55.9	9.3	7.6	5.1	5.1					
Colistin	0.8	[0.0 – 4.6]				2.5	50	44.1	2.5		0.8				
Ceftolozane-tazobactam	0.0	[0.0 – 3.1]				59.3	35.6	4.2	0.8						

*Bold vertical lines denote cut-off values for resistance. ND=cut-offs not defined. CI=confidence interval. White fields show range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for 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 are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFF, only ECOFFs are shown. A clinical breakpoint is not defined for gentamicin.

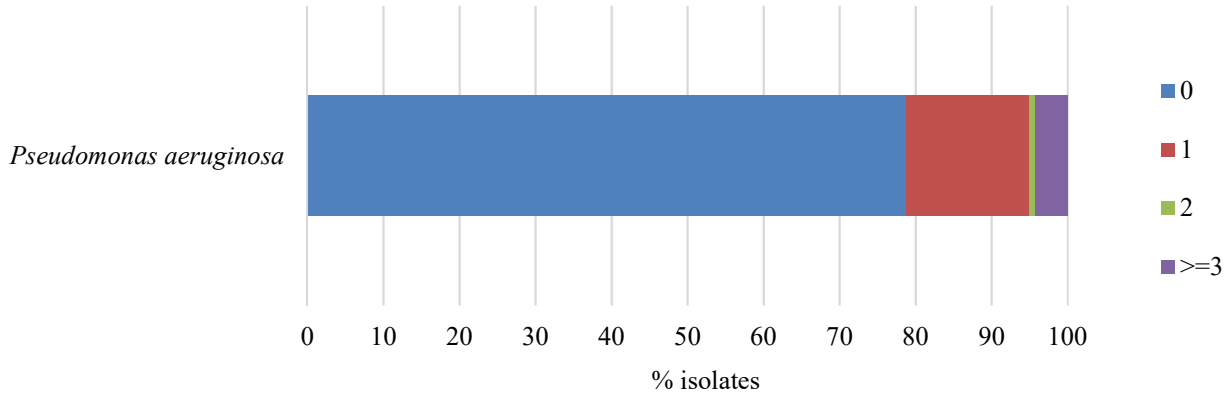

FIGURE 37. Antimicrobial resistance profile for *Pseudomonas aeruginosa* from dogs collected from 2018 to 2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

P. aeruginosa is naturally resistant to a wide range of antibacterial agents. In total, 78.8% of the isolates were susceptible to all antimicrobial agents included in the test panel. The following proportions of isolates were resistant to one or more antimicrobial classes: 16.1% were resistant to one, 0.8% to two and 4.2% to three or more antimicrobial classes, respectively (Figure 37).

Resistance to the quinolones ciprofloxacin and levofloxacin were the most frequently identified resistance phenotypes, followed by resistance to beta-lactams/penicillins and the carbapenems meropenem, imipenem and/or doripenem. Resistance to the carbapenems in *P. aeruginosa* from dogs has been described previously, with mutations in membrane proteins of efflux pumps identified as causative mechanism (Haenni *et al.* 2017). The six isolates showing decreased sensitivity to carbapenems will be further investigated by whole genome sequencing to determine the presence of carbapenem resistance mechanisms.

P. aeruginosa is an opportunistic pathogen in many animal species and can cause infections in dogs such as otitis, ulcerative keratitis, urinary tract infections, and skin and wound infections. The most common *P. aeruginosa*-associated infection in dogs is otitis externa. *P. aeruginosa* has not been included in NORM-VET previously.

Available clinical breakpoints are shown in dotted blue lines in Table 18. 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 result.

Antimicrobial resistance testing of clinical isolates from dogs and cats at AniCura Diagnostic Laboratory in 2022

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.

ADL retrieves and analyses samples from veterinary clinics all around Norway. The laboratory carries out bacteriological examinations, including sensitivity 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 for 2022.

The data consisted of susceptibility testing results for a total of 122 *Escherichia coli*, 41 *Staphylococcus aureus* and 208 *Staphylococcus pseudintermedius* isolates. The *E. coli* were retrieved from urinary infections from a total of 93 dogs and 25 cats. The *S. aureus* were from skin and ear infections, abscesses etc. from 25 dogs and 16 cats, while the *S. pseudintermedius* were from skin and ear infections, abscesses and surgical wounds, of which 77 were from skin/abscesses/wounds and 127 from ear infections in dogs and two in each category from cats. The data were cleaned for duplication of samples (i.e. samples from the same dog or cat considered to be from the same infection). We also excluded isolates where MIC-values were missing for one or more antimicrobial substances.

All isolates were identified using VITEK ® MS from BioMerieux. 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 4.2.3 Copyright (C) 2023 (The R Foundation for Statistical Computing Platform). We applied Clinical Breakpoint values (BP) for defining an isolate as resistant or susceptible. The BPs applied were mainly defined by EUCAST, but if these were not defined the CLSI BPs were applied. There were no clinical BPs available for chloramphenicol in *S. aureus* and *S. pseudintermedius*, and epidemiological cut-off (ECOFF) values for *S. aureus* were therefore applied. In the tables we have included both the ECOFFs and the BPs as far as these have been defined; either by EUCAST or CLSI.

Results and comments

Escherichia coli from urinary infections in dogs and cats

In total, susceptibility results for *E. coli* from 84 dogs and 20 cats were included. Table 19 and Figure 38 show the results from the susceptibility testing.

In total 53.6% of the *E. coli* isolates from dogs were susceptible to all antimicrobial agents included. Resistance to amphenicols (i.e. chloramphenicol) were the most frequently identified resistance determinants, followed by resistance to beta-lactams/penicillins (i.e. ampicillin and amoxicillin-clavulanic acid). Altogether, 33.3% of the isolates were resistant to one antimicrobial class, 9.5% to two and 3.6% to three or more antimicrobial classes, respectively (Figure 39).

Among the 20 *E. coli* isolates from cats, 13 isolates were susceptible to all antimicrobial agents included, five isolates were resistant to one antimicrobial class, and two to two antimicrobial classes. The number of isolates from cats was low and any comparison between the two animal species therefore has to be made with caution.

Two isolates from dog showed reduced susceptibility to the extended-spectrum cefalosporins cefpodoxime and cefovecin (2.4% [95% CI: 0.3-8.3]), and were additionally resistant to beta-lactams/penicillins and 1st generation cephalosporins. Both isolates were susceptible to the carbapenem imipenem (data not shown).

TABLE 19. Antimicrobial resistance in *Escherichia coli* from urine samples of dogs (n=84) and cats (n=20) in 2022.

			Distribution (n) of MIC values (mg/L)*													
Substance	Animal	Resistance (n)	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Doxycycline	Dog	1				6	69	7		1	1					
	Cat	0				8	10		1	1						
Tetracycline	Dog	2					64	16	2		2					
	Cat	1					17	1	1		1					
Chloramphenicol	Dog	30						9	22	23	30					
	Cat	4						3	11	2	4					
Ampicillin	Dog	14						27	24	19	3	11				
	Cat	4						9	5	2		4				
Amoxicillin-clavulanic acid	Dog	7						52	20	5	5	2				
	Cat	1						15	3	1	1					
Cefalexin	Dog	3							3	75	3		3			
	Cat	0							4	14	2					
Cefpodoxime	Dog	2			53	22	5	2		2						
	Cat	0			18	2										
Cefovecin	Dog	2				54	23	4		2						
	Cat	0				18	1	1								
Trimethoprim-sulfamethoxazole	Dog	2					82				2					
	Cat	0					20									
Gentamicin	Dog	0					83	1								
	Cat	0					20									
Neomycin	Dog	0						84								
	Cat	0						20								
Amikacin	Dog	0						82	2							
	Cat	0						20								
Enrofloxacin	Dog	1		78		4	1		1							
	Cat	0		20												
Marbofloxacin	Dog	1				82	1		1							
	Cat	0				20										
Nitrofurantoin	Dog	1									80	2	1	1		
	Cat	0									19	1				

*Bold vertical lines denote epidemiological cut-off 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 are marked in blue dotted lines. Clinical cut-offs for doxycycline, tetracycline, ampicillin, amoxicillin-clavulanic acid and nitrofurantoin are the same as the ECOFFs and only ECOFFs are shown in the table.

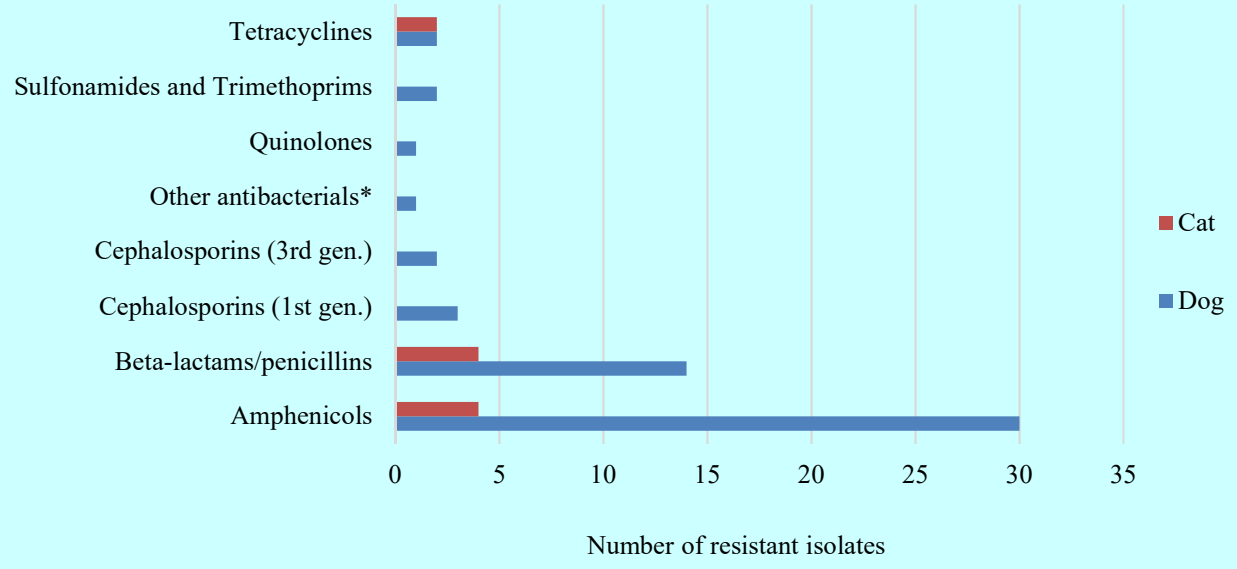

FIGURE 38. Antimicrobial resistance (number of isolates) in *Escherichia coli* from urine samples of dogs (n=84) and cats (n=20) in 2022. *i.e. nitrofurantoin.

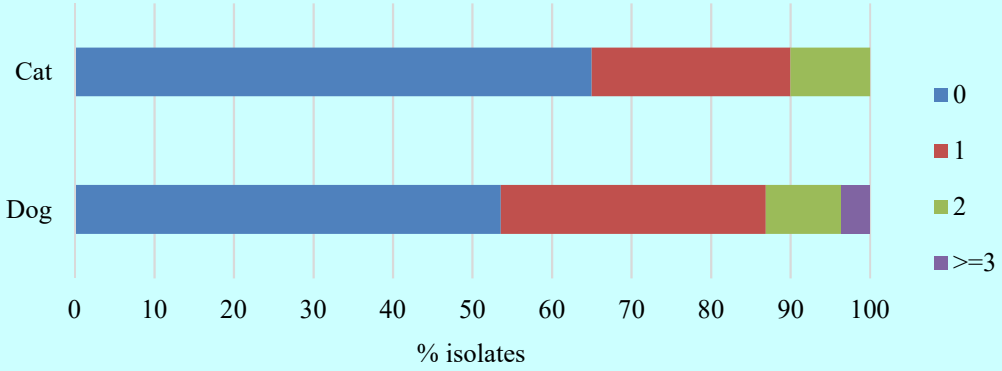

FIGURE 39. Antimicrobial resistance profile for *Escherichia coli* from urinary infections in dogs (n=84) and cats (n=20) in 2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

For trimethoprim-sulfamethoxazole the ranges tested were not compliable with the epidemiological cut-off (ECOFF) value, as the ECOFFs were lower than tested range areas (Table 19). 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 ECOFF. With use of clinical BP, only two dog isolates were defined as resistant to trimethoprim-sulfamethoxazole.

Comparison to previous data included in NORM-VET is difficult as the methodology for susceptibility testing differs, as well as the included antimicrobial substances. However, for the substances that were included in both panels (i.e. for tetracycline, chloramphenicol and ampicillin) the ADL results from 2022 were rather similar to the results from NORM-VET in 2019, which was the last year *E. coli* isolates from dogs were included.

Staphylococcus aureus from skin and ear infections in dogs and cats

In total, susceptibility results for *S. aureus* from 25 dogs and 14 cats were included. Table 20 and Figure 40 show the results from the susceptibility testing. In total, 20 and nine of the 25 and 14 isolates from dogs and cats, respectively, were resistant to one antimicrobial class (mainly beta-lactam/penicillins). No methicillin resistant *S. aureus* (MRSA) were identified among these 39 isolates.

For several antimicrobial substances (i.e. amoxicillin-clavulanic acid, cefalotin, trimethoprim-sulfamethoxazole and neomycin) the ranges tested were not compliable with the corresponding ECOFF values (Table 20), as the ECOFFs were lower than the tested range areas. 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 these ECOFFs. The BP for amoxicillin-clavulanic acid in *S. aureus* was also outside of the tested range, and resistant isolates could therefore not be defined for this substance. For chloramphenicol there are no clinical BPs defined and the ECOFF was therefore applied for this substance.

Susceptibility testing of *S. aureus* from dogs has not been included in NORM-VET, and comparison to previous surveillance data is therefore not possible.

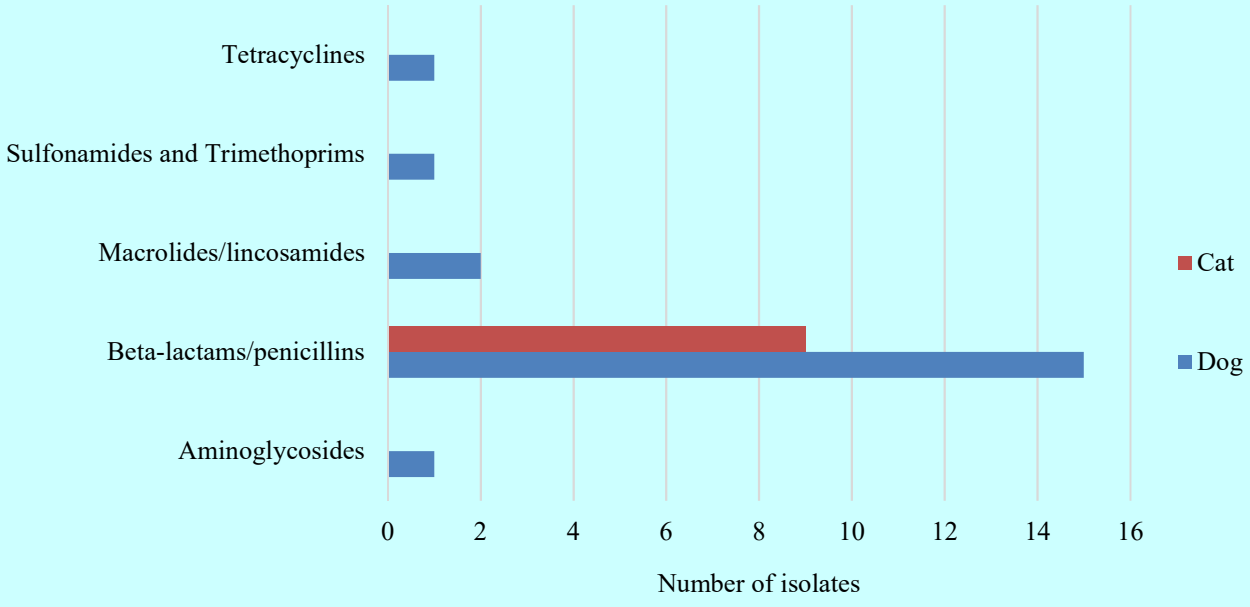

FIGURE 40. Antimicrobial resistance in *Staphylococcus aureus* from skin and ear infections in dogs (n=25) and cats (n=14) in 2022.

TABLE 20. Antimicrobial resistance in *Staphylococcus aureus* from skin and ear infections in dogs (n=25) and cats (n=14) in 2022.

			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	0					25									
	Cat	0					14									
Tetracycline	Dog	1						24			1					
	Cat	0						14								
Chloramphenicol	Dog	0								15	10					
	Cat	0								7	7					
Benzylpenicillin	Dog	15	7	2	1	1	14									
	Cat	9	3		2		9									
Oxacillin	Dog	0				20	5									
	Cat	0				10	4									
Amoxicillin/	Dog	ND							25							
Clavulanic acid	Cat	ND							14							
Cefalotin	Dog	0							25							
	Cat	0							14							
Cefovecin	Dog	0					1	18	6							
	Cat	0						13	1							
Trimethoprim-	Dog	1					24					1				
sulfamethoxazole	Cat	0					14									
Erythromycin	Dog	1				24				1						
	Cat	0				14										
Clindamycin	Dog	0			1	23				1						
	Cat	0			2	12										
Gentamicin	Dog	0					25									
	Cat	0					14									
Neomycin	Dog	1							24				1			
	Cat	0							14							
Enrofloxacin	Dog	0					25									
	Cat	0					14									
Marbofloxacin	Dog	0					25									
	Cat	0					13	1								
Nitrofurantoin	Dog	0										15	10			
	Cat	0										4	9	1		

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=not defined. 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 are marked in blue dotted lines. Clinical breakpoints for tetracycline, benzylpenicillin oxacillin, amoxicillin-clavulanic acid and etrythromycin are the same as the ECOFFs and only ECOFFs are shown in the table for these substances. For chloramphenicol, no current clinical breakpoints exist.

Staphylococcus pseudintermedius from skin and ear infections in dogs

In total, susceptibility results for *S. pseudintermedius* from 173 dogs were included, 71 from skin infections and 102 from ear infections. Table 21 and Figures 41-42 show the results of the susceptibility testing. Among the *S. pseudintermedius*, 25.0% of the isolates from ear infections and 21.0% 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, 37.0% and 41.0% of the isolates from skin and ear, respectively, were resistant to one antimicrobial class, 21.0% and 24.0% to two, and 17.0% and 14.0% to three or more antimicrobial classes (Figure 42). One isolate was resistant to oxacillin, and presence of the *mec*A gene was confirmed by Real-time PCR. The isolate was further investigated by whole genome sequencing at the NVI, belonged to sequence type (ST) 2647 amd genes encoding resistance to beta-lactams and aminoglycosides were identified.

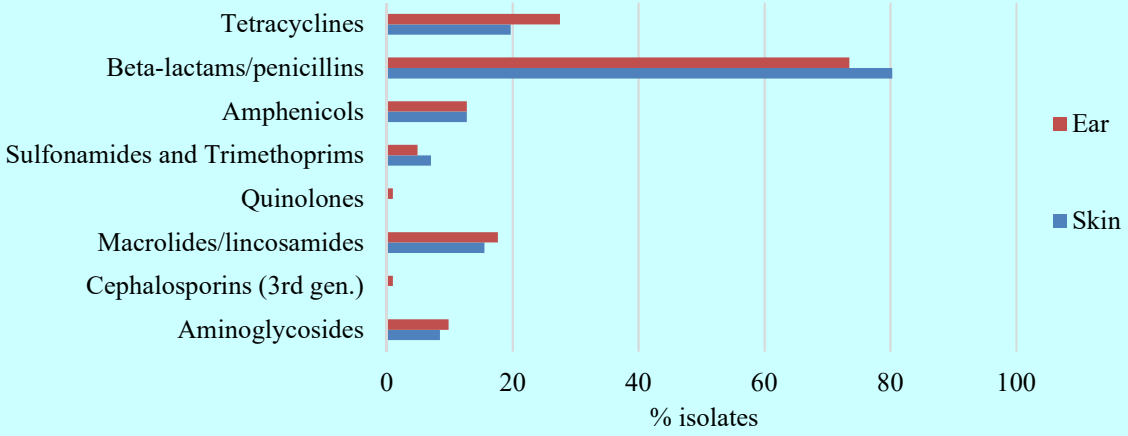

FIGURE 41. Antimicrobial resistance (percentages) in *Staphylococcus pseudintermedius* from skin (n=71) and ear (n=102) infections in dogs in 2022.

TABLE 21. Antimicrobial resistance in *Staphylococcus pseudintermedius* from skin (including abcesses and postoperative wound infections) (n=71) and ear (n=102) infections in dogs.

				Distribution (%) of MIC values (mg/L)*												
Substance	Sample	Resistance (%)	[95% CI]	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Doxycycline	Ear	28.4	[19.9-38.2]					71.6	2.9	11.8	6.9	6.9				
	Skin	18.3	[10.1- 29. 3					81.7	2.8	11.3	1.4	2.8				
Tetracycline	Ear	27.5	[19.1-37.2]						72.5				27.5			
	Skin	19.7	[11.2-30.9]						80.3	1.4			18.3			
Chloramphenicol	Ear	12.7	[7.0 20.8]								50.0	37.3			12.7	
	Skin	12.7	[6.0-22.7]								53.5	33.8			12.7	
Benzylpenicillin	Ear	73.5	[63.9 -81.8]	26.5			8.8	64.7								
	Skin	80.2	[69.1-88.8]	19.7			7.0	73.2								
Oxacillin	Ear	1.0	[0.0-5.3]				99.0				1.0					
	Skin	0.0	[0.0-5.1]				100									
Amoxicillin/	Ear	0.0	[0.0-3.6]							100						
Clavulanic acid	Skin	0.0	[0.0-5.1]							100						
Cefalotin	Ear	0.0	[0.0-3.6]							100						
	Skin	0.0	[0.0-5.1]							100						
Cefovecin	Ear	1.0	[0.0-5.3]					97.1	1.0	1.0		1.0				
	Skin	0.0	[0.0-5.1]					97.2	2.8							
Trimethoprim-	Ear	4.9	[1.6-11.1]					95.1			1.0		3.9			
sulfamethoxazole	Skin	7.0	[2.3-15.7]					91.6		1.4			7.0			
Erythromycin	Ear	16.8	[10.0-25.3]				68.6	11.9	2.9			16.8				
	Skin	15.5	[8.0-26.0]				74.6	9.9				15.5				
Clindamycin	Ear	9.8	[4.8-17.3]				81.4	2.0			9.8					
	Skin	14.1	[7.0-24.4]			7.0	77.5	1.4			14.1					
Gentamicin	Ear	2.9	[0.6-8.4]					94.1			2.0	2.9				
	Skin	2.8	[0.3-9.8]					97.2				2.8				
Neomycin	Ear	7.8	[3.4 - 14.9]							81.4		1.0	9.8	7.8		
	Skin	5.6	[1.6-13.8]							84.5		2.8	7.0	5.6		
Enrofloxacin	Ear	1.0	[0.0-5.3]					99.0			1.0					
	Skin	0.0	[0.0-5.1]					100								
Marbofloxacin	Ear	1.0	[0.0-5.3]					97.1	2.0		1.0					
	Skin	0.0	[0.0-5.1]					97.2	2.8							
Nitrofurantoin	Ear	0.0	[0.0-3.6]										99.0	1.0		
	Skin	0.0	[0.0-5.1]										100			

*Bold vertical lines denote epidemiological cut-off 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 are marked in blue dotted lines. For chloramphenicol, no current clinical breakpoints exist.

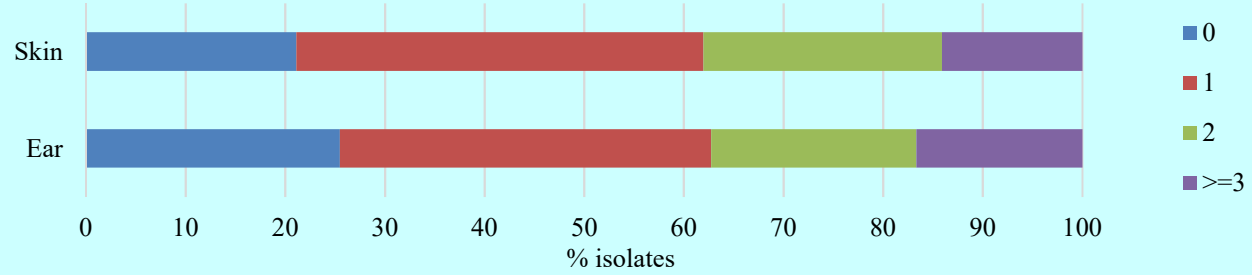

FIGURE 42. Antimicrobial resistance profile for *Staphylococcus pseudintermedius* from skin (n=71) and ear (n=102) infections in dogs in 2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

For several antimicrobial substances (i.e. doxycycline, amoxicillin-clavulanic acid, gentamicin and neomycin) the ranges tested were not compliable with ECOFF values, as the ECOFFs were lower than tested range areas. 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 these ECOFFs. Also, ECOFFs have not been defined for many of the substances. The BPs for amoxicillin-clavulanic acid in *S. pseudintermedius* were, however, also outside of the range tested, and resistant isolates could therefore not be defined for this antimicrobial substance. For tetracycline, the BP was outside the tested range area, while the ECOFF was within the tested range and ECOFF was therefore applied. Since neither ECOFF nor clinical BP have been defined for chloramphenicol in *S. pseudintermedius*, the ECOFF for *S. aureus* was used for this substance. Comparison to previous data included in NORM-VET is difficult as the methodology for susceptibility testing differs, as well as the included antimicrobial substances. However, for the substances that were included in both panels (i.e. for tetracycline, benzylpenicillin, erythromycin, clindamycin and gentamicin) the ADL results from 2022 were rather similar to the results from NORM-VET in 2019, which was the last year *S. pseudintermedius* isolates from dogs were included.

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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 enabling the spread of antimicrobial resistance to other bacteria, including those responsible for infections in animals or humans. Thus, resistance monitoring among indicator bacteria from microbiota of 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 attention over the last years. These are defined by the WHO as critically important for antimicrobial treatment of human infections (WHO 2019). Monitoring the resistance to these substances in the bacterial population is thus 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 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 uses of selective methods targeting specific antimicrobial resistant bacteria. The application 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 antimicrobial resistance surveillance in animals. In addition, selective methods are used for detection of *E. coli* resistant to ESC, carbapenem resistant *Enterobacterales* (CRE), vancomycin resistant *Enterococcus* spp. (VRE), linezolid resistant *Enterococcus* spp. (LRE), methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus pseudintermedius* (MRSP).

INDICATOR BACTERIA FROM ANIMALS

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

In 2022, samples from animals included caecal samples from broiler and turkey flocks, and faecal swabs from cats, for isolation of indicator bacteria and some emerging resistant bacteria. In addition, swabs from oral mucosa and perineum of cats were included for detecting *Staphylococcus* spp., methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus pseudintermedius* (MRSP). Results from the surveillance programme for MRSA in pigs are described as well (see page 75).

Some of the cut-off values defining resistance applied in NORM-VET have been changed over the years. Data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2022 to facilitate comparisons in this report. Only data retrieved following the requirements set in decision 2013/652/EU and 2020/1729/EU are shown for broiler and turkey. For previous data, please see the respective annual reports.

Sampling, laboratory methods and data processing are described in Appendix 3.

PRODUCTION ANIMALS

Escherichia coli from broiler and turkey

Caecal samples from 363 broiler flocks and 110 turkey flocks were examined and *E. coli* isolates were obtained from 363 (100%) and 110 (100%) samples, respectively. One isolate per positive sample was susceptibility tested. The results are presented in the text, in Table 22 and Figures 43-45.

TABLE 22. Antimicrobial resistance in *Escherichia coli* isolates from caecal samples of broiler (n=363) and turkey (n=110) flocks in 2022.

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	Broiler	5.5	[3.4 – 8.4]								86.2	7.7	0.6		0.6	5.0			
	Turkey	5.5	[2.0 – 11.5]								87.3	7.3			0.9	4.5			
Tigecycline	Broiler	0.3	[0.0 – 1.5]					99.4	0.3	0.3									
	Turkey	0.0	[0.0 – 3.3]					100											
Chloramphenicol	Broiler	0.6	[0.1 – 2.0]										97.5	1.9	0.6				
	Turkey	0.9	[0.0 – 5.0]										95.5	3.6			0.9		
Ampicillin	Broiler	7.4	[5.0 – 10.6]							1.4	30.6	56.2	4.4	0.3		7.2			
	Turkey	14.5	[8.5 – 22.5]							15.5	65.5	4.5				14.5			
Cefotaxime	Broiler	0.0	[0.0 – 1.0]					100											
	Turkey	0.9	[0.0 – 5.0]					99.1		0.9									
Ceftazidime	Broiler	0.0	[0.0 – 1.0]					96.1	3.9										
	Turkey	0.9	[0.0 – 5.0]					95.5	3.6			0.9							
Meropenem	Broiler	0.0	[0.0 – 1.0]		100														
	Turkey	0.0	[0.0 – 3.3]		100														
Trimethoprim	Broiler	3.3	[1.7 – 5.7]					85.7	10.7	0.3					3.3				
	Turkey	3.6	[1.0 – 9.0]					91.8	4.5						3.6				
Sulfamethoxazole	Broiler	4.1	[2.3 – 6.7]										84.3	5.8	5.0	0.8	0.3		3.8
	Turkey	3.6	[1.0 – 9.0]										86.4	7.3	2.7				3.6
Azithromycin	Broiler	0.0	[0.0 – 1.0]								1.1	30.9	66.4	1.7					
	Turkey	0.0	[0.0 – 3.3]								9.1	40.9	49.1	0.9					
Gentamicin	Broiler	0.0	[0.0 – 1.0]						69.7	29.2	1.1								
	Turkey	0.0	[0.0 – 3.3]						52.7	44.5	2.7								
Amikacin	Broiler	0.0	[0.0 – 1.0]									98.9	1.1						
	Turkey	1.8	[0.2 – 6.4]									95.6	2.7	1.8					
Ciprofloxacin	Broiler	9.1	[6.3 – 12.5]	69.1	21.2	0.6		2.8	1.9	3.6	0.3		0.6						
	Turkey	0.9	[0.0 – 5.0]	71.8	27.3			0.9											
Nalidixic acid	Broiler	8.0	[5.4 – 11.3]									90.4	1.7	0.6		1.4	6.0		
	Turkey	0.9	[0.0 – 5.0]									99.1					0.9		
Colistin	Broiler	0.0	[0.0 – 1.0]							100									
	Turkey	0.0	[0.0 – 3.3]							99.1	0.9								

*Bold vertical lines denote epidemiological cut-off values for resistance. CI=confidence interval. 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.

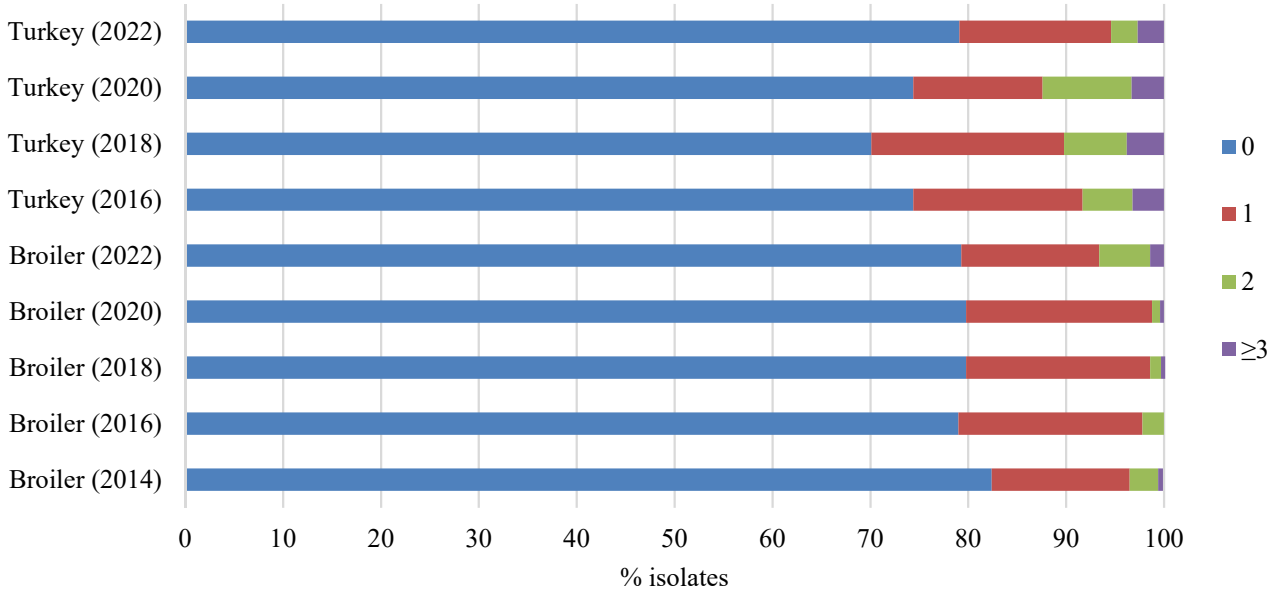

FIGURE 43. Antimicrobial resistance profile for *Escherichia coli* from caecal samples from broiler and turkey flocks in 2014-2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

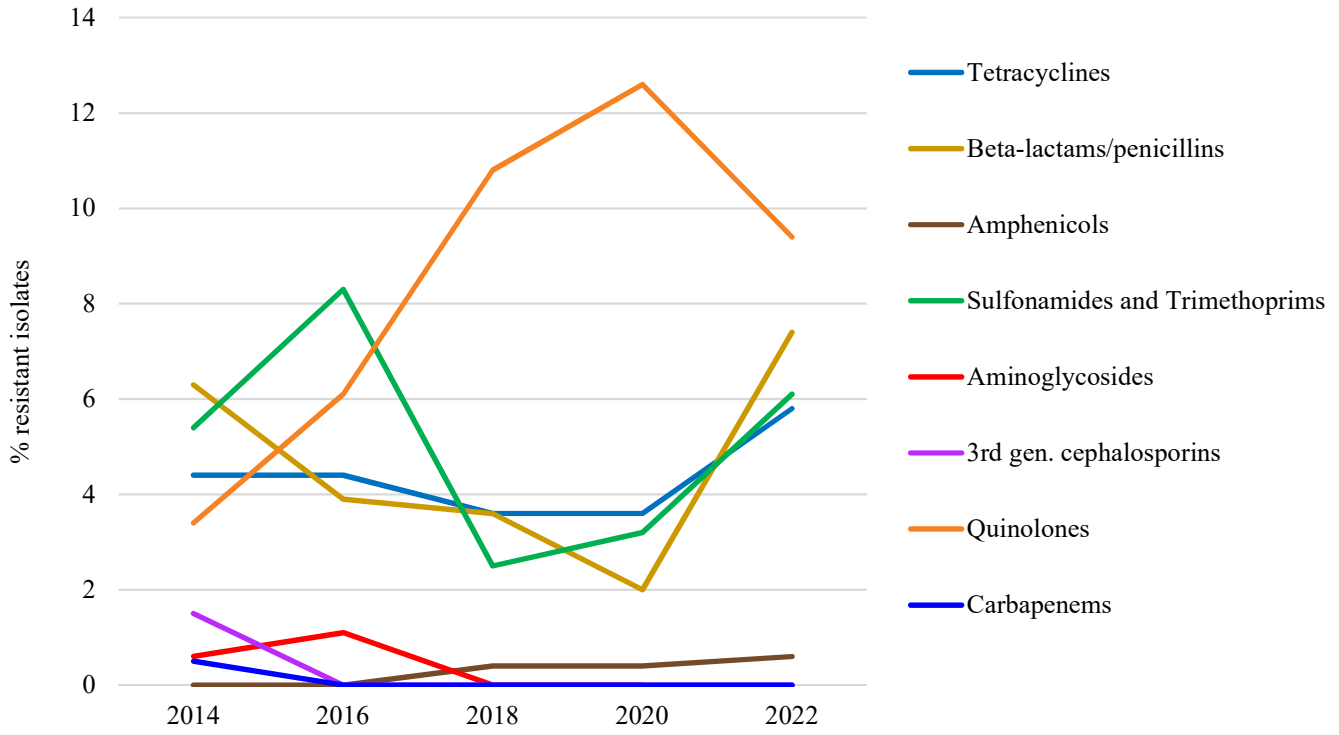

FIGURE 44. Prevalence of resistance to various antimicrobial agents in *Escherichia coli* from caecal samples from broilers collected in 2014-2022. The breakpoints used in NORM-VET 2022 were applied.

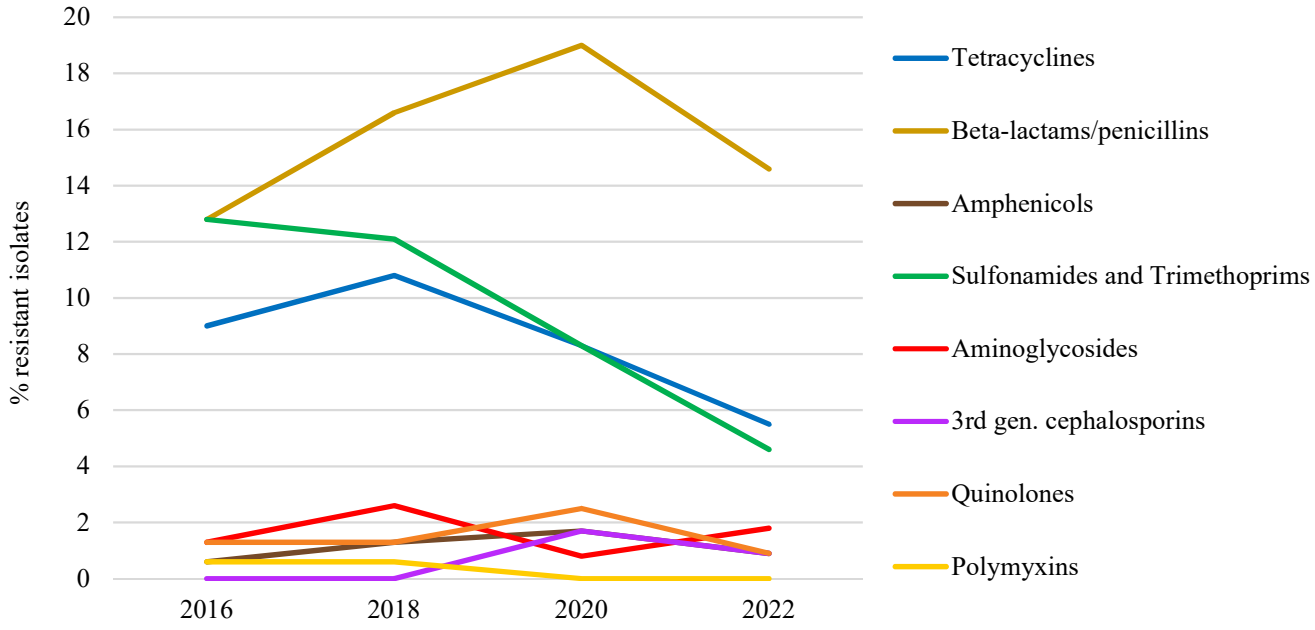

FIGURE 45. Prevalence of resistance to various antimicrobial agents in *Escherichia coli* from caecal samples from turkey collected in 2016-2022. The breakpoints used in NORM-VET 2022 were applied.

RESULTS AND COMMENTS

BROILER

The 2022 data showed that 79.3% of the *E. coli* isolates from broiler caecal samples were susceptible to all antimicrobial agents included. Altogether, 14.0% of the isolates were resistant to one antimicrobial class (predominantly quinolones), 5.2% to two and 1.4% to three antimicrobial classes (Figure 43). In total, 20.6% of the isolates were resistant to at least one antimicrobial, indicating a high occurrence of resistance in broilers according to the EFSA classification described in Appendix 6. Resistance to ciprofloxacin and nalidixic acid were the most frequently identified resistance determinants, followed by resistance to ampicillin, tetracycline, sulfamethoxazole and trimethoprim.

As shown in Figure 43, the number of isolates being fully susceptible has been relatively stable around 80% over the

years 2014-2022. The antimicrobial classes for which the isolates showed resistance have changed over these years (Figure 44). There was an increase in resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) from 2014-2020 (p=0.002) (NORM-VET 2021). However, in 2022, a decrease was registered with 9.4% [95% CI: 6.6 – 12.8] of the isolates resistant to quinolones. The decrease in resistance indicated for sulfonamides and penicillins with extended-spectrum (i.e. sulfamethoxazole and ampicillin, respectively) in 2020, seems to have been reversed as indicated in Figure 44.

None of the *E. coli* isolates from broilers displayed resistance to the extended-spectrum cephalosporins (ESC) cefotaxime or ceftazidime [95% CI: 0.0 – 1.0]. This is in concordance with the results from previous years. In addition, a selective method was used to investigate the occurrence of ESC resistant *E. coli* in the same broiler caecal sample material (see below).

The occurrence of resistance among *E. coli* varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance rates (EFSA and ECDC European Union Summary Report 2020/2021). This favorable situation in Norway is probably due to the very limited use of antibiotics in Norwegian broiler production (Table 5).

TURKEY

The 2022 data showed that 79.1% of the *E. coli* isolates were susceptible to all antimicrobial agents included. Altogether, 15.5% of the isolates were resistant to one antimicrobial class, 2.7% to two and 2.7% to three or more antimicrobial classes (Figure 43). In total, 20.8% of the isolates were resistant to at least one antimicrobial agent, indicating a high occurrence of resistance in turkey according to the EFSA classification described in Appendix 6. Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to tetracycline, trimethoprim and sulfamethoxazole.

As shown in Figure 43, the number of isolates being fully susceptible has been relatively stable between 70-80% over the years 2016-2022. However, the antimicrobial classes for which the isolates show resistance have changed over these years (Figure 45). The indicated increase in resistance to penicillins with extended-spectrum (i.e. ampicillin) in 2016-2020, seems to have reversed in 2022. Resistance to tetracyclines and sulfonamides declined from about 10% in the years up to 2018, to 5.5% in 2020 and 3.6% in 2022. These observed changes are, however, not statistically significant and further monitoring is needed to assess whether these are truly decreasing trends.

One of the isolates displayed resistance to ESC (i.e. cefotaxime and ceftazidime) (0.9% [95% CI: 0.02 – 5.0]). This isolate had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and genotyping showed that the resistance was due to mutations in the promotor and attenuator regions (n.-42C>T) of the chromosomally located *ampC* gene resulting in *ampC* overexpression. This strain was not detected using the selective method to investigate the occurrence of ESC resistant *E. coli* in the same turkey caecal sample material (see below).

The occurrence of resistance among *E. coli* varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance levels (EFSA and ECDC European Union Summary Report 2020/2021).

Extended-spectrum cephalosporin resistant *E. coli* from broiler and turkey

A total of 363 broiler flocks and 110 turkey flocks were investigated for the presence of *E. coli* resistant to extended-spectrum cephalosporins (ESC). The results are presented in the text and in Figures 46-47.

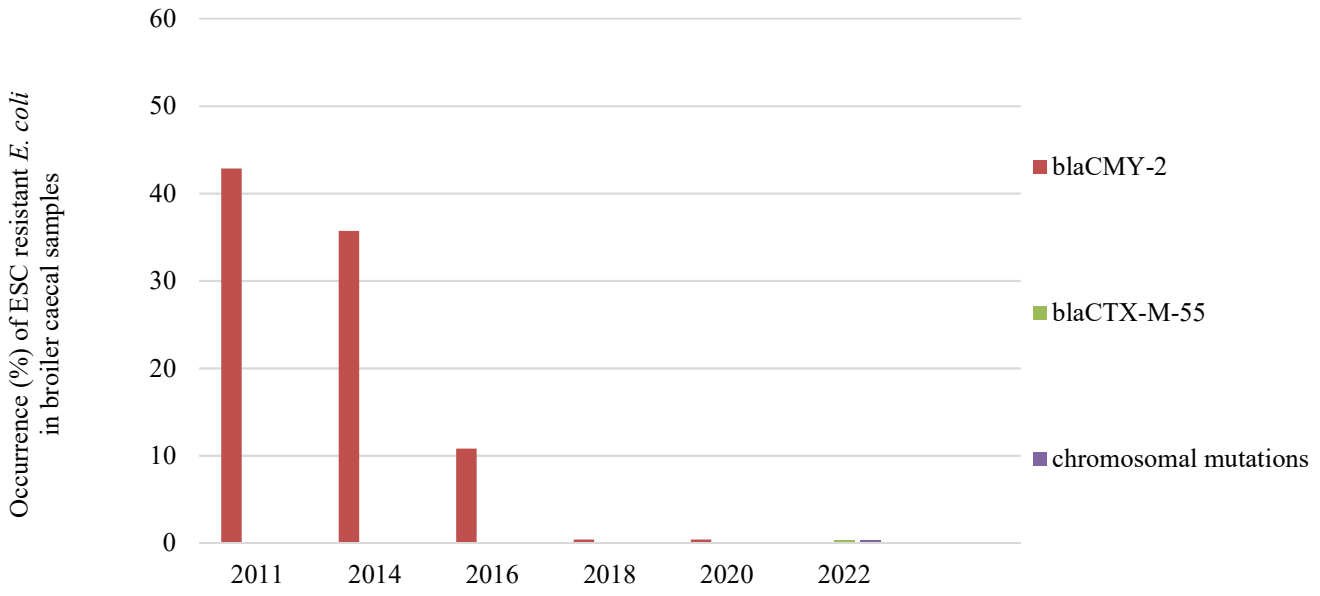

FIGURE 46. Occurrence (%) of ESC resistant *Escherichia coli* in caecal samples from broiler flocks in 2011-2022.

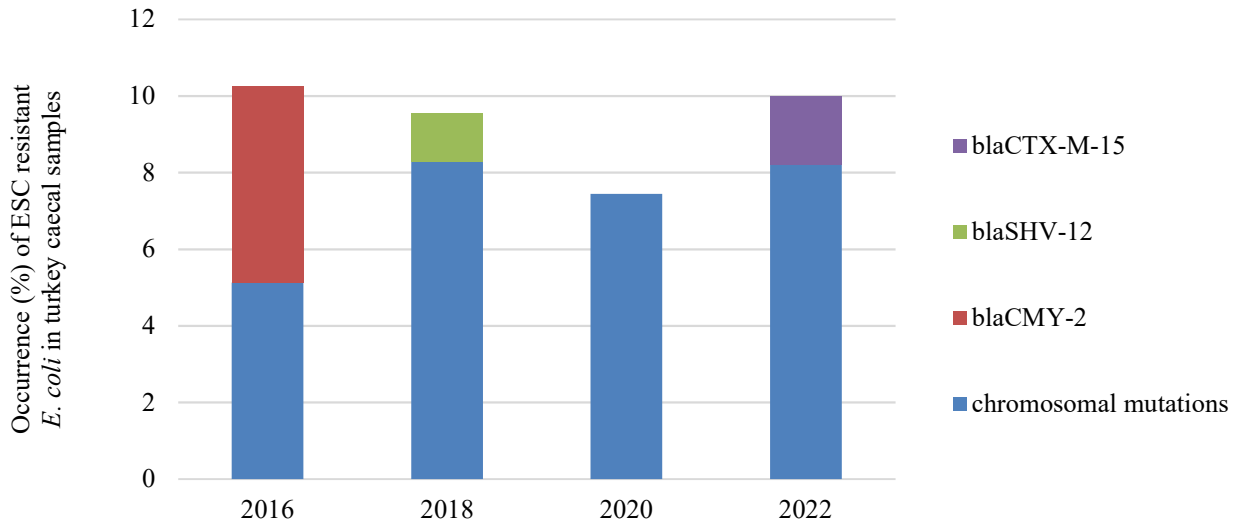

FIGURE 47. Occurrence (%) of ESC resistant *Escherichia coli* in caecal samples from turkey flocks 2016-2022.

RESULTS AND COMMENTS

BROILER

ESC resistant *E. coli* were found in two (0.55% [95% CI: 0.07 – 1.98]) of the 363 broiler flock samples. As described above, no cephalosporin resistant isolates were found using the standard non-selective procedure, indicating a low within-flock prevalence.

One of the isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and whole genome sequencing showed that resistance was due to mutations (n.-42C>T) in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. The other isolate had a cephalosporin resistance profile corresponding to an ESBL phenotype, and whole genome sequencing showed that the resistance was due to the gene $bla_{\text{CTX-M-55}}$. The isolates did not show reduced susceptibility to meropenem, the preferred carbapenem used for detecting carbapenem resistance.

As shown in Figure 46, these results are in concordance with the results from 2018 and 2020, and confirm that the measures implemented by the industry to reduce the occurrence of ESC resistant *E. coli* in broilers have been successful.

Also, in a European perspective, this prevalence of ESC resistant *E. coli* in Norwegian broilers is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC European Union Summary Report 2020/2021). There are also variations in prevalence between the Nordic countries, with Norway having the lowest reported prevalence.

TURKEY

ESC resistant *E. coli* were found in 11 of the 110 turkey flock samples (10% [95% CI: 5.1 – 17.2]). As described above, only one ESC resistant isolate was found using the non-selective procedure, though not from the same sample as detected by this selective screening method, indicating a low within-flock prevalence. In addition to being resistant to beta-lactams, i.e. ampicillin and the ESCs cefotaxime and ceftazidime, one isolate was resistant to sulfamethoxazole and two were resistant to ciprofloxacin. None of the isolates showed reduced susceptibility to meropenem, the preferred carbapenem used for detecting carbapenem resistance.

Nine of the isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and whole genome sequencing showed that resistance was due to mutations (n.-42C>T) in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. The two last isolates had a cephalosporin resistance profile corresponding to an ESBL phenotype, and whole genome sequencing showed that the resistance was due to $bla_{\text{CTX-M-15}}$.

Compared to previous results, it appears to have been a decrease in the occurrence of ESC resistant *E. coli* due to presence of the plasmid-mediated $bla_{\text{CMY-2}}$ gene from 5.1% [95% CI: 2.2 – 9.9] in 2016 to 0% in 2018 [95% CI: 0.0 – 2.3], 2020 [95% CI: 0.0 – 3.0] and 2022 [95% CI: 0.0 – 3.3] (Figure 47). This change is, however, statistically non-significant. ESC resistance due to chromosomal mutations in the promoter region of the chromosomal *ampC* gene appears to be relatively stable between 5-8% (Figure 47). Further monitoring is necessary to follow this situation in the future.

In an international perspective, the occurrence of ESC resistant *E. coli* in Norwegian turkey is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC European Union Summary Report 2020/2021).

Carbapenem resistant *Enterobacterales* from broiler and turkey

Selective screening for carbapenem resistant *Enterobacterales* (CRE) was performed on caecal samples from a total of 363 broiler and 110 turkey flocks. No CRE were detected. Carbapenems are not approved for use in food-producing animals in 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.

Escherichia coli multilocus sequence type 38 from humans and broiler production represents distinct monophyletic groups

Escherichia coli belonging to multilocus sequence type 38 (ST38) is a well-known cause of extra-intestinal infections in humans, and is frequently associated with resistance to extended-spectrum cephalosporins (ESCs) (1). Resistance to carbapenems, mediated by *bla*$_{OXA}$-genes has also been reported in this ST. The European Centre for Disease Prevention and Control (ECDC) recently released a rapid risk assessment on the increased detection of OXA-244 producing *E. coli* ST38 in humans, requesting further knowledge in order to determine the source (2,3). ST38 has also been predominant among ESC resistant *E. coli* from Norwegian and Nordic broiler production (4-6). We used whole genome sequencing (WGS) to compare *E. coli* ST38 from broiler production and humans. Our aim was to investigate the genetic characteristics and relationship between *E. coli* ST38 from these two sources, and to examine if there has been potential spillover between them.

In total, 288 *E. coli* ST38 genomes isolated from humans in Europe (n=153, collected 2009–2019) and from Nordic broiler production (n=135, collected 2011–2014) were analysed. *In silico* characterisation of all genomes was done using the plasmid, gene identification and annotation pipeline Ellipsis v 0.5.2 (7). In addition, a core SNP based phylogenetic analysis was performed with the ALPPACA pipeline (8) to investigate the genetic relatedness within the ST38 group.

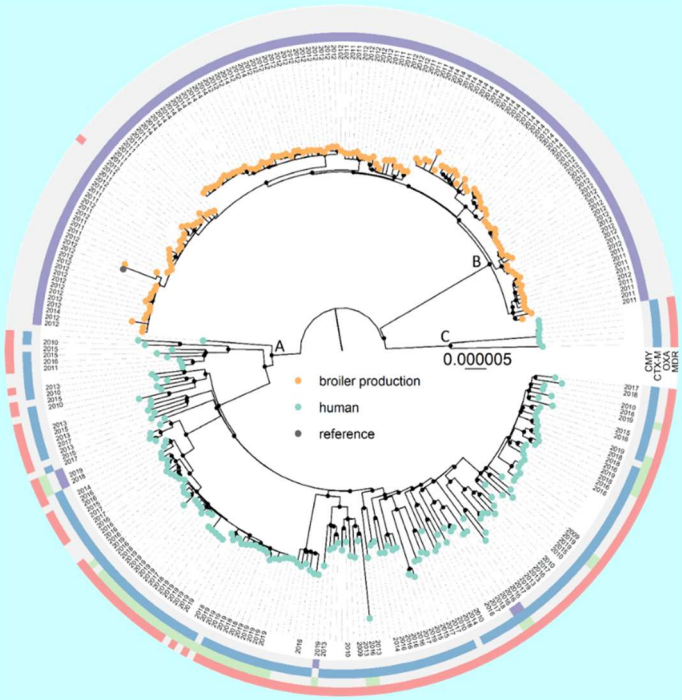

FIGURE 47X. Maximum likelihood core genome SNP tree of 288 *E. coli* multilocus sequence type 38 originating from humans (n=153) and broiler production (n=135). Presence (CMY = purple, CTX-M = blue, OXA = green, MDR = red) and absence (light grey) of relevant antimicrobial resistance genes and multidrug resistance is displayed in the outer circles. Only *bla*$_{OXA-48}$, *bla*$_{OXA-181}$ and *bla*$_{OXA-244}$ are included in the OXA-group. Both *bla*$_{CMY-2}$ and *bla*$_{CMY-16}$ are included in the CMY-group, and *bla*$_{CTX-M-1}$, -3, -9, -14, -14b, -15 and -27 are included in the CTX-M group. Black circles on nodes represent bootstrap values >95%. Colour on tip-points indicate origin of the ST38 genomes. The tree is rooted with *E. coli* ST115 as outgroup.

The phylogenetic analysis revealed that *E. coli* ST38 from humans and broiler production belong to distinct monophyletic groups (Figure 47X). Furthermore, we detected large differences in the presence of acquired AMR genes. *bla*$_{CMY-2}$ was the only ESC encoding gene detected in *E. coli* ST38 from broiler production. In ST38 from humans, a diverse set of ESC resistance genes was present, with genes in the *bla*$_{CTX-M}$ group most frequently detected. Four ST38 from humans carried *bla*$_{CMY-2}$ in association with IncF plasmid replicons. In *E. coli* ST38 from broiler production, *bla*$_{CMY-2}$ is known to be associated with IncK or IncI1 plasmids (4). Thus, there is no indication of common *bla*$_{CMY-2}$–carrying plasmids in ST38 from humans and broiler production. *bla*$_{OXA}$-genes, including *bla*$_{OXA-244}$, were not present in *E. coli* ST38 from broiler production.

In conclusion, our results show that ST38 from humans and broiler production belong to well-separated clades, and suggest that increased detection of OXA-244-producing *E. coli* ST38 in humans is not associated with spillover from broiler production. The present work was performed in the NoResist project and financed by the Research Council of Norway (project number 250212) and the Norwegian Veterinary Institute.

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Enterococcus spp. from broiler and turkey

Caecal samples from 363 broiler flocks and 110 turkey flocks were investigated. *E. faecalis* was obtained from 84 (23.1%) and *E. faecium* from 358 (98.6%) of the broiler samples. From turkey, *E. faecalis* was obtained from 10 (9.1%) and *E. faecium* from 109 (99.1%) of the samples. All these *E. faecalis* and *E. faecium* isolates were susceptibility tested. The results are presented in Tables 23-24, Figures 48-52, and in the text.

TABLE 23. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from broiler flocks (n=84) in 2022.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	63.1	[51.9 – 73.4]						36.9			2.4	1.2	38.1	17.9	3.6		
Tigecycline	1.2	[0.0 – 6.5]		36.9	58.3	3.6			1.2								
Chloramphenicol	2.4	[0.3 – 8.3]								8.3	89.3			1.2	1.2		
Ampicillin	0.0	[0.0 – 4.3]					4.8	41.7	53.6								
Erythromycin	8.3	[3.4 – 16.4]						35.7	52.4	3.6	1.2	2.4	2.4	1.2		1.2	
Quinupristin - Dalfopristin	0.0	[0.0 – 4.3]					1.2			7.1	58.3	33.3					
Gentamicin	0.0	[0.0 – 4.3]									70.2	29.8					
Ciprofloxacin	0.0	[0.0 – 4.3]					10.7	71.4	17.9								
Vancomycin	0.0	[0.0 – 4.3]						59.5	38.1	2.4							
Teicoplanin	0.0	[0.0 – 4.3]					100										
Linezolid	0.0	[0.0 – 4.3]						11.9	88.1								
Daptomycin	0.0	[0.0 – 4.3]					3.6	58.3	34.5	3.6							

*Bold vertical lines denote microbiological cut-off values for resistance. CI=confidence interval. 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 24. Antimicrobial resistance in *Enterococcus faecium* from caecal samples from broiler (n=358) and turkey (n=109) flocks in 2022.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Broiler	9.8	[6.9 – 13.3]						89.1	0.8	0.3	0.3	0.3	0.8	5.6	2.8		
	Turkey	22.0	[14.6 – 31.0]						76.1	1.8			1.8	0.9	13.8	5.5		
Tigecycline	Broiler	0.0	[0.0 – 1.0]	10.6	59.2	29.6	0.6											
	Turkey	0.0	[0.0 – 3.3]	21.1	45.0	33.9												
Chloramphenicol	Broiler	0.0	[0.0 – 1.0]								9.2	89.7		1.1				
	Turkey	0.9	[0.0 – 5.0]								9.1	89.9				0.9		
Ampicillin	Broiler	0.0	[0.0 – 1.0]					30.2	30.2	33.0	5.0	1.7						
	Turkey	6.4	[2.6 – 12.8]					8.3	19.3	15.6	31.2	19.3		0.9		5.5		
Erythromycin	Broiler	5.3	[3.2 – 8.2]						71.2	19.0	4.5	3.4	1.4	0.3			0.3	
	Turkey	18.4	[11.6 – 26.9]						57.8	11.0	12.8	12.8	3.7	0.9			0.9	
Quinupristin –	Broiler	37.7	[32.7 – 43.0]					1.7	21.8	38.8	35.8	2.0						
Dalfopristin	Turkey	68.8	[59.2 – 77.3]					3.7	11.0	16.6	68.8							
Gentamicin	Broiler	0.0	[0.0 – 1.0]									96.1	3.9					
	Turkey	0.9	[0.0 – 5.0]									90.8	6.4	1.8				0.9
Ciprofloxacin	Broiler	0.6	[0.1 – 2.0]				0.8	3.4	11.7	37.4	36.6	9.5	0.6					
	Turkey	1.8	[0.2 – 6.5]				1.8	0.9	17.4	28.4	40.4	9.2		1.8				
Vancomycin	Broiler	0.3	[0.0 – 1.5]						84.1	14.5	1.1	0.3						
	Turkey	0.0	[0.0 – 3.3]						86.2	13.8								
Teicoplanin	Broiler	0.0	[0.0 – 1.0]					98.9	1.1									
	Turkey	0.0	[0.0 – 3.3]					99.1	0.9									
Linezolid	Broiler	0.0	[0.0 – 1.0]						4.5	94.4	1.1							
	Turkey	0.0	[0.0 – 3.3]						4.6	91.7	3.7							
Daptomycin	Broiler	0.0	[0.0 – 1.0]				0.3	1.7	10.9	58.9	27.7	0.6						
	Turkey	0.0	[0.0 – 3.3]				0.9	3.7	11.9	50.5	32.1	0.9						

*Bold vertical lines denote microbiological cut-off values for resistance. CI=confidence interval. 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.

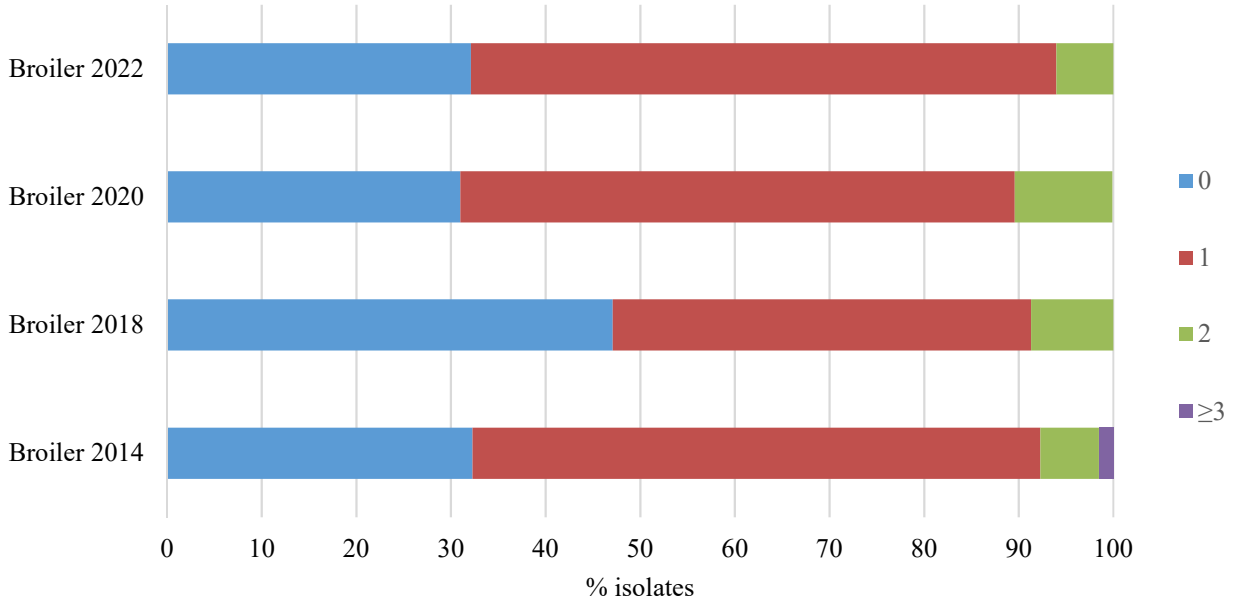

FIGURE 48. Antimicrobial resistance profile for *Enterococcus faecalis* caecal isolates from broiler in 2014-2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated. The epidemiological cut-offs used in NORM-VET 2022 were applied.

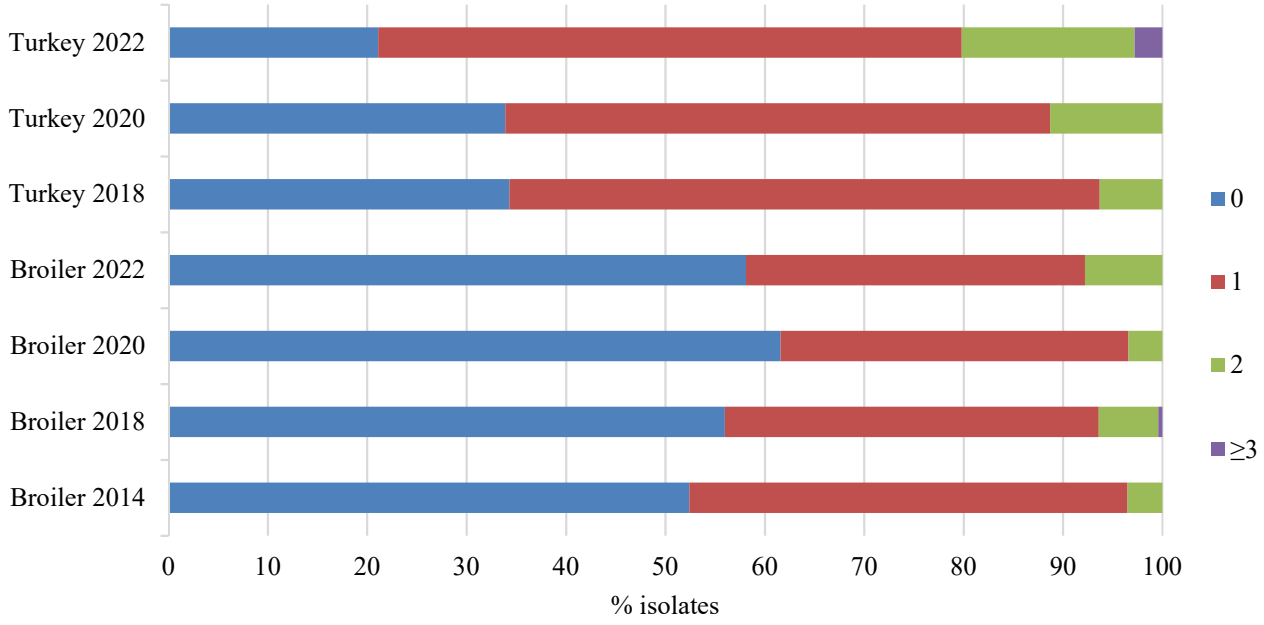

FIGURE 49. Antimicrobial resistance profile for *Enterococcus faecium* caecal isolates from broiler in 2014-2022 and turkey in 2018-2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated. The epidemiological cut-offs used in NORM-VET 2022 were applied. Resistance to narasin is not included.

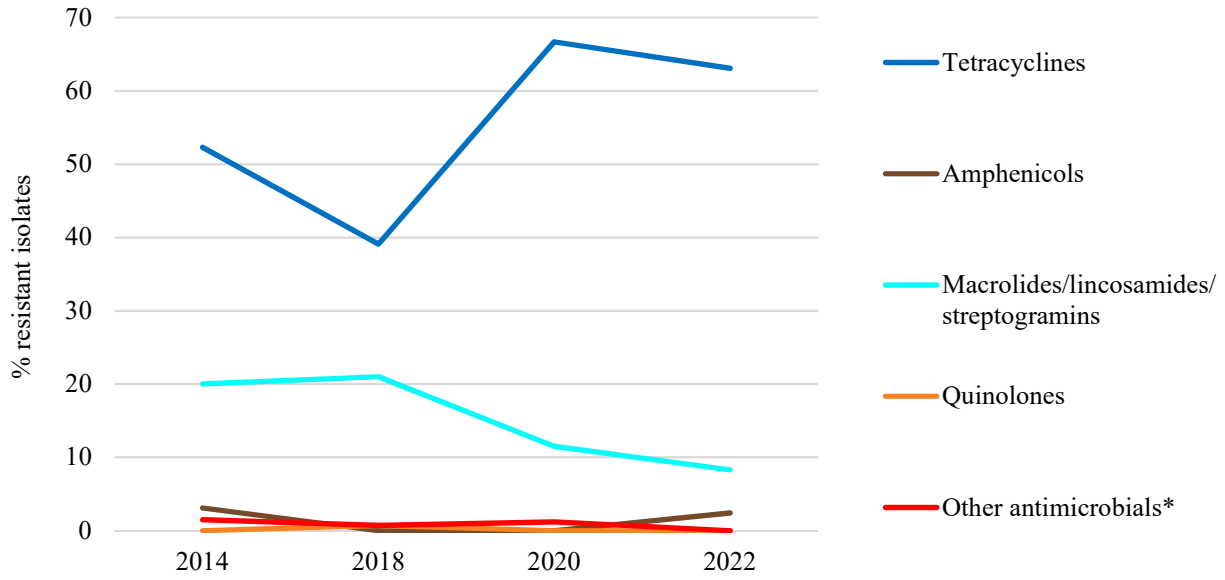

FIGURE 50. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecalis* isolates from caecal samples from broiler 2014-2022. The epidemiological cut-off values used in NORM-VET 2022 were applied. *i.e. daptomycin.

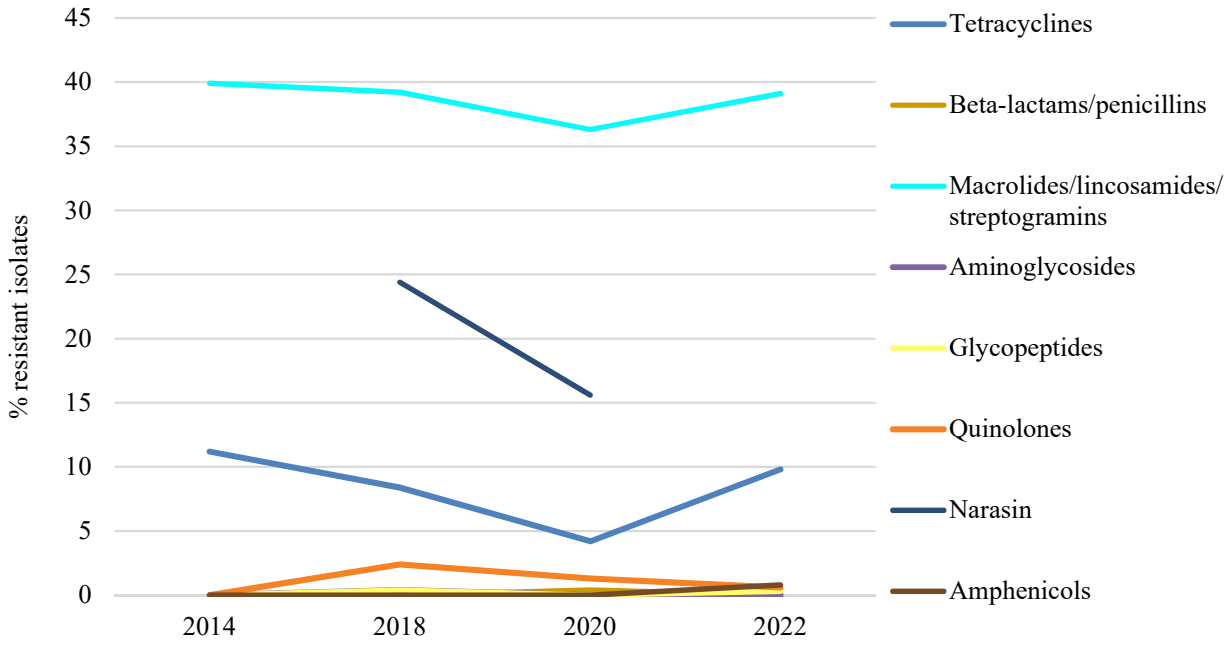

FIGURE 51. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* isolates from caecal samples from broiler 2014-2022. The epidemiological cut-off values used in NORM-VET 2022 were applied.

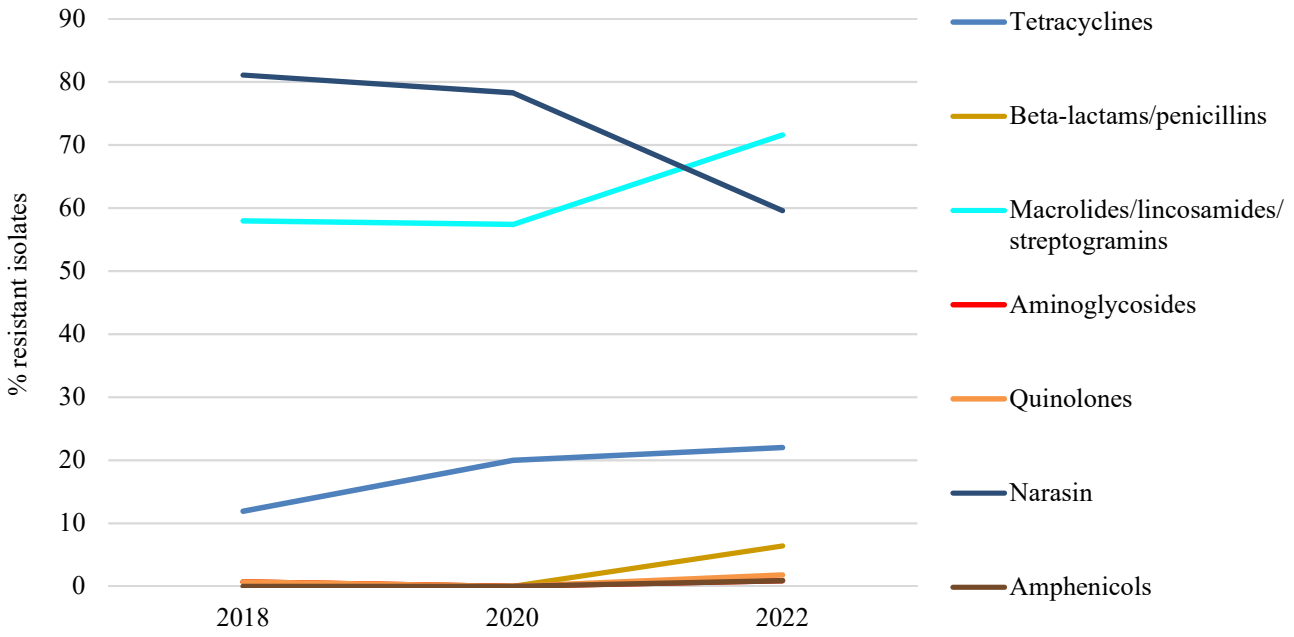

FIGURE 52. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* isolates from caecal samples from turkey 2018-2022. The epidemiological cut-offs used in NORM-VET 2022 were applied.

RESULTS AND COMMENTS

BROILER

The 2022 data showed that 32.1% of the *E. faecalis* and 58.1% of the *E. faecium* isolates from broiler caecal samples were susceptible to all antimicrobial classes included in the test panel.

E. faecalis: Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to the macrolide erythromycin. Altogether, 61.9% of the isolates were resistant to one and 6.0% to two antimicrobial classes (Figure 48).

E. faecium: Resistance to quinupristin-dalfopristin was the most frequently identified resistance determinant, followed by resistance to tetracycline and erythromycin. Altogether, 34.1% of the *E. faecium* isolates were resistant to one and 7.8% to two antimicrobial classes (Figure 49).

In total, 67.9% of the *E. faecalis* isolates and 41.9% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a very high and high occurrence of resistance, respectively, according to the EFSA classification described in Appendix 6.

As shown in Figure 48, the number of *E. faecalis* isolates being fully susceptible has been relatively stable between 30-40% over the years 2014-2022. There has, however, been an increase in the occurrence of tetracycline resistance compared to 2018 (Figure 50). From 36.7% [95% CI: 28.7 – 45.3] in 2018, to 66.7% [95% CI: 55.7 – 76.4] in 2020 and 63.1% [95% CI: 51.9 – 73.4] in 2022. However, the occurrence in 2014 was more similar to the occurrences in 2020-2022 with 52.3% [95% CI: 39.5 – 64.9]. This high prevalence of tetracycline resistance among *E. faecalis* is surprising, as there is insignificant use of oxytetracycline for clinical purposes in Norwegian broiler production.

The number of *E. faecium* isolates being fully susceptible has been relatively stable around 55-65% over the years 2014-2022 (Figure 49).

In 2020, a decreasing trend of resistance to narasin was indicated in both *E. faecalis* and *E. faecium* from broilers. Unfortunately, this was not possible to follow up in 2022 due to lack of narasin sensitivity panels. The decrease found in 2020 was expected as the use of narasin as coccidiostat to broilers was phased out in Norway in 2015-2016, and since then Norwegian broilers have been raised without the use of coccidiostats.

Reduced susceptibility to linezolid was not observed in any of the *E. faecalis* nor the *E. faecium* isolates. This is in concordance with the results from previous years. In addition, a selective method was applied to screen the same broiler caecal sample material for the occurrence of linezolid resistant *Enterococcus* spp. (LRE) (see next page).

One of the *E. faecium* isolates displayed reduced susceptibility to vancomycin. Whole genome sequencing of the isolate displayed no resistance genes to explain this reduced susceptibility. This strain was not detected by the selective method applied to investigate the occurrence of vancomycin resistant *Enterococcus* spp. (VRE) in the same caecal sample material (next page). The result is in concordance with results from 2014, 2018 and 2020. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. The use selected for a reservoir of VRE in Norwegian broiler production that persisted for many years after the ban was implemented.

TURKEY

The 2022 data showed that 50.0% of the *E. faecalis* and 21.1% of the *E. faecium* isolates from turkey caecal samples were susceptible to all antimicrobial classes included in the test panel. Narasin was not included in these calculations, and is commented on separately below.

E. faecalis: Three of the ten isolates were resistant to one antimicrobial class (tetracycline or erythromycin), and two isolates to two (tetracyclines and erythromycin) antimicrobial classes.

E. faecium: Resistance to quinupristin-dalfopristin was the most frequently identified resistance determinant, followed by resistance to tetracycline and erythromycin. Altogether, 58.7% of the isolates were resistant to one antimicrobial class, 17.4% to two, and 2.8% to three or more antimicrobial classes (Figure 49).

In total, 78.9% of the *E. faecium* isolates were resistant to at least one antimicrobial class (narasin not included), indicating an extremely high occurrence of resistance, according to the EFSA classification described in Appendix 6.

There seems to have been a decrease in *E. faecium* isolates being fully susceptible in 2022 compared to 2020 and 2018 (Figure 49). This change is, however, not statistically significant. That is mainly due to an increase in resistance to the streptogramin quinupristin-dalfopristin from 54.8% [95% CI: 42.2 – 64.1%] in 2020 to 68.8% [95% CI: 59.2 – 77.3] in 2022, but also to a slight increase in resistance to erythromycin, tetracyclines and penicillins as shown in Figure 52. None of these changes were statistically significant, and further monitoring is needed to follow the situation in the years to come. Note that resistance to quinupristin-dalfopristin has not been included in previous reports as ECOFF was first defined by EUCAST in 2023. Data from previous years have therefore been recalculated for the present report.

Resistance to narasin was identified in one of the ten *E. faecalis* and 59.6% [95% CI: 49.3 – 68.4] of the *E. faecium* isolates (data not shown). There has been a decrease in resistance to narasin in turkey isolates compared to previous years from about 80% to about 60% in 2022. However, the change in occurrence is not statistically significant, and further monitoring is needed to see whether this is a true trend. Due to high toxicity in turkeys, narasin has never been used in the turkey production. Instead the coccidiostat monensin has been used. The use of monensin was phased out during 2022, and has not been replaced by any other coccidiostats. There is no known cross-resistance between narasin and monensin, and the reason behind the occurrence of narasin resistance in *E. faecium* from turkey is thus not clear.

None of the *E. faecalis* or *E. faecium* isolates showed reduced susceptibility to vancomycin or linezolid. This is in concordance with results from the previous years. In addition, a selective method was applied to screen the same caecal sample material for the occurrence of linezolid resistant *Enterococcus* spp. (LRE) and vancomycin resistant *Enterococcus* spp. (VRE) (see below).

Vancomycin resistant *Enterococcus* spp. (VRE) from broiler and turkey

A total of 363 broiler flocks and 110 turkey flocks were screened for the presence of vancomycin resistant *Enterococcus* spp. (VRE). No VRE were detected (broiler [95% CI: 0.0 – 1.0], turkey [95% CI: 0.0 – 3.3]). This is in concordance with the result from 2018 and 2020. For broilers, there has been a statistically significant decrease from 2014 when 6.7% [95% CI: 3.7 – 10.9] of the flocks were VRE positive.

Linezolid resistant *Enterococcus* spp. (LRE) from broiler and turkey

A total of 363 broiler flocks and 110 turkey flocks were screened for the presence of linezolid resistant *Enterococcus* spp. (LRE). No LRE were detected (broiler [95% CI: 0.0 – 1.0], turkey [95% CI: 0.0 – 3.3]). This is the first time samples from broiler and turkey flocks have been screened for the presence of LRE.

SPORTS AND FAMILY ANIMALS

Escherichia coli from cats

Faecal swab samples from a total of 250 cats were examined. The majority of theses cats had no symptoms from the intestines, as only ten cats were reported to have such symptoms. *E. coli* isolates were obtained from 211 samples (84.4%) and were further susceptibility tested (one isolate per positive sample). The results are presented in Table 25, Figure 53, and in the text.

TABLE 25. Antimicrobial resistance in *Escherichia coli* isolates (n=211) from faecal samples from cats in 2022.

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	≥1024
Tetracycline	1.4	[0.3 – 4.1]								97.2	1.4				1.4				
Tigecycline	0.0	[0.0 – 1.7]					99.1	0.9											
Chloramphenicol	0.0	[0.0 – 1.7]										98.1	1.9						
Ampicillin	17.5	[12.7 – 23.4]							0.9	20.9	57.3	3.3	0.5	1.4	15.6				
Cefotaxime	3.3	[1.3 – 6.7]					96.7	2.8				0.5							
Ceftazidime	1.4	[0.3 – 4.1]					94.3	4.3	0.9	0.5									
Meropenem	0.0	[0.0 – 1.7]		100															
Trimethoprim	1.4	[0.3 – 4.1]					85.8	12.8						1.4					
Sulfamethoxazole	2.8	[1.1 – 6.1]										81.5	8.5	3.3	3.8	0.5			2.4
Azithromycin	0.0	[0.0 – 1.7]								9.0	73.9	16.6	0.5						
Gentamicin	0.0	[0.0 – 1.7]						78.2	19.9	1.9									
Amikacin	0.0	[0.0 – 1.7]									99.1	0.9							
Ciprofloxacin	2.8	[1.1 – 6.1]	68.2	28.4	0.5	0.5	2.4												
Nalidixic acid	2.4	[0.8 – 5.4]									97.2	0.5			0.9	1.4			
Colistin	0.0	[0.0 – 1.7]							99.5	0.5									

*Bold vertical lines denote epidemiological cut-off values for resistance. CI=confidence interval. 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.

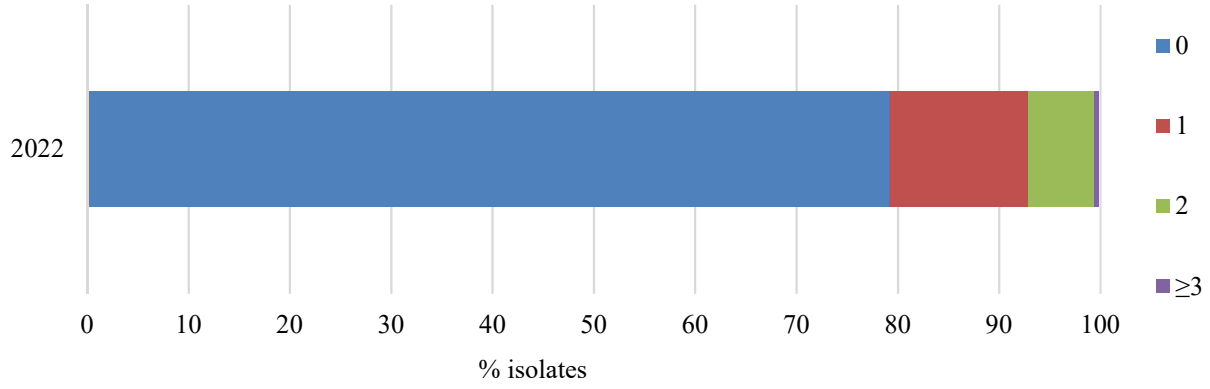

FIGURE 53. Antimicrobial resistance profile for *Escherichia coli* from faecal samples from cats in 2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 79.2% of the isolates were susceptible to all antimicrobial agents included. Altogether, 13.7% of the isolates were resistant to one antimicrobial class (predominantly ampicillin), 6.6% to two, and 0.5% to three or more antimicrobial classes (Figure 53). In total, 20.8% of the isolates were resistant to at least one of the tested antimicrobial agents, indicating a high occurrence of resistance among *E. coli* from faecal samples of cats according to the EFSA classification described in Appendix 6.

Six of the isolates displayed resistance to the extended-spectrum cephalosporins (ESC) cefotaxime or ceftazidime. Five of these isolates displayed an AmpC beta-lactamase phenotype due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene (n.-32T>A). One isolate displayed an ESBL/AmpC beta-lactamase phenotype due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene (p.n.-32T>A) while simultaneously carrying $bla_{\text{CTX-M-1}}$. The last isolate was also detected by the selective methods. Selective methods were applied to screen the same sample material for the occurrence of ESC resistant *E. coli* and of carbapenem resistant *Enterobacterales*.

Samples from cats have not been included in NORM-VET previously.

Extended-spectrum cephalosporin resistant *Escherichia coli* from cats

Selective screening for *E. coli* resistant to extended-spectrum cephalosporins (ESC) was performed on the faecal swab samples from cats. A total of 250 samples were screened. *E. coli* resistant to ESC were detected in four of the samples (1.6% [95% CI: 0.4 – 4.0]). Two of these isolates displayed an ESBL/AmpC beta-lactamase phenotype due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene (p.n.-32T>A), where one isolate also carried the $bla_{\text{CTX-M-1}}$ and the other isolate carried the $bla_{\text{CTX-M-14}}$ gene. The two last isolates displayed an ESBL phenotype and were genotyped as $bla_{\text{CTX-M-15}}$ and $bla_{\text{CTX-M-55}}$, respectively.

Selective methods for detection of ESC resistant *E. coli* from cat samples have not been included in NORM-VET previously.

Carbapenem resistant *Enterobacterales* from cats

A total of 250 faecal swab samples from cats were screened for the presence of carbapenem resistant *Enterobacterales* (CRE). No CRE were detected [95% CI: 0.0 – 1.5].

Selective methods for detection of CRE from cat samples have not been included in NORM-VET previously.

Staphylococcus felis from cats

A total of 263 oral/perineal samples from cats were investigated for the presence of *Staphylococcus felis*. The majority of theses cats had no symptoms from skin or ears, as only ten cats were reported to have such symptoms.

Staphylococcus felis was detected from 159 of these samples (60.5%). One isolate per cat was susceptibility tested. The results are presented in Table 26, Figure 54 and in the text.

TABLE 26. Antimicrobial resistance in *Staphylococcus felis* isolates (n=159) from oral/perineal samples in cats 2022.

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	1.9	[0.4 – 5.4]						96.9	1.3					1.9				
Chloramphenicol	0.6	[0 – 3.4]									95.6	3.8		0.6				
Benzylpenicillin[ψ]	19.5	[13.6 – 26.5]			79.9	0.6	2.5	2.5	3.1	11.3								
Cefoxitin	0.6	[0.0 – 3.4]						99.4				0.6						
Trimethoprim	1.3	[0.2 – 4.5]							71.1	27.7	1.3							
Sulfamethoxazole	9.4	[5.4 – 15.1]													74.8	15.7	5.0	4.4
Erythromycin	8.8	[4.9 – 14.3]					52.8	38.4			0.6		8.2					
Clindamycin	6.9	[3.5 – 12.0]				77.4	15.7	1.3		0.6		5.0						
Quinupristin-dalfopristin	1.3	[0.2 – 4.5]						98.7		1.3								
Streptomycin	0.0	[0.0 – 2.3]									91.8	5.7	2.5					
Gentamicin	0.6	[0.0 – 3.4]						98.7	0.6				0.6					
Kanamycin	1.3	[0.2 – 4.5]									98.7		0.6		0.6			
Ciprofloxacin	0.0	[0.0 – 2.3]					98.1	0.6	1.3									
Vancomycin	0.0	[0.0 – 2.3]							98.8	1.3								
Fusidic acid	3.8	[1.4 – 8.0]					96.2		0.6	1.3	1.3	0.6						
Tiamulin	0.6	[0.0 – 3.4]						96.9	2.5			0.6						
Linezolid	0.0	[0.0 – 2.3]							98.7	0.6	0.6							
Mupirocin	0.0	[0.0 – 2.3]						100										
Rifampicin	0.6	[0.0 – 3.4]	99.4			0.6												

Bold vertical lines denote microbiological cut-off values for resistance. CI=confidence interval. 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.

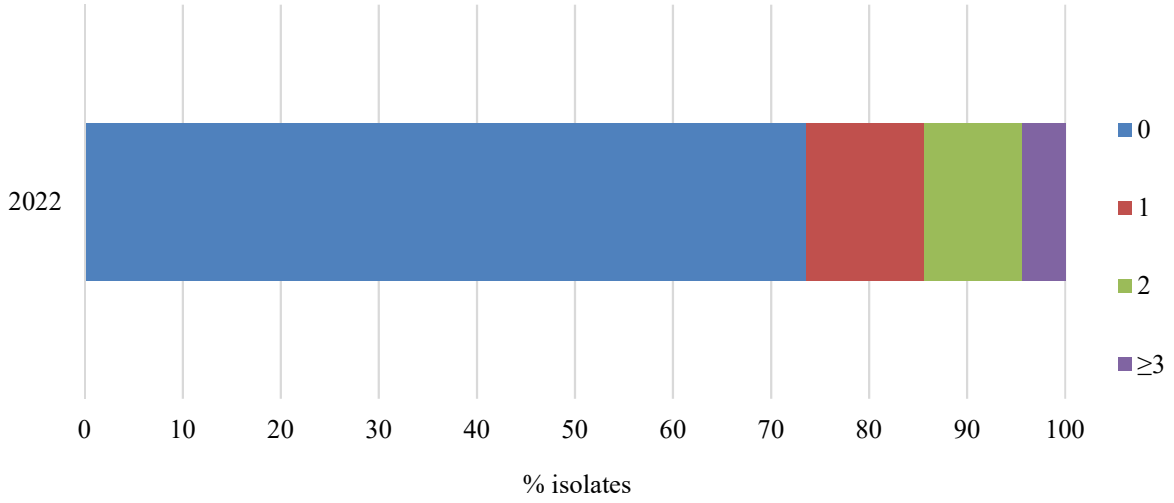

FIGURE 54. Antimicrobial resistance profile for *Staphylococcus felis* (n=159) from oral/perineal samples in cats in 2022. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 73.6% of the 159 *S. felis* isolates were susceptible to all antimicrobial agents included in the test panel. Altogether, 12% of the isolates were resistant to one antimicrobial class, 10% to two, and 4.4% to three or more antimicrobial classes (Figure 54). Resistance to benzyl-penicillin was the most frequently identified resistance determinant, followed by resistance to sulfamethoxazole, erythromycin and fusidic acid.

All isolates were subjected to the clover leaf test for detection of beta-lactamase production. The majority of isolates with a positive beta-lactamase test had penicillin MIC values > 0.125 mg/L, and the majority of beta-lactamase negative isolates had penicillin MIC-values ≤ 0.125 mg/L, overall confirming the results from the sensitivity testing.

The *S. felis* isolates were also subjected to oxacillin sensitivity testing using disk diffusion to identify possible methicillin resistant isolates. In total 98.8% [95% CI: 95.6 – 99.8] of the 160 isolates were susceptible and 1.3% [95% CI: 0.2 – 4.4] were resistant. One of these isolates was also resistant to cefoxitin and nine other antimicrobials agents. Both isolates were subjected to whole genome sequencing. The *blaZ* gene conferring resistance to beta-lactams was detected in one isolate. In the other isolate, no genetic reason for the possible methicillin resistance was detected.

Isolation and susceptibility testing of carrier *S. felis* has not previously been performed in NORM-VET.

Staphylococcus aureus from cats

A total of 263 samples from cats were investigated for the presence of *Staphylococcus aureus*. *S. aureus* was detected from nine of the samples (3.4%). Resistance to benzylpenicillin was identified in four isolates (all with a positive beta-lactamase test), followed by resistance to erythromycin in one, fucidic acid in one and sulfa-methoxazole in one isolate which also was resistant to benzylpenicillin. Isolation and susceptibility testing of carrier *S. aureus* has not previously been performed in NORM-VET on cat samples.

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

A total of 250 samples from cats were investigated for the presence of methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant *Staphylococcus pseudintermedius* (MRSP). Neither MRSA nor MRSP was detected from the samples [95% CI: 0.0 – 1.5]. Selective methods for detection of MRSA and MRSP from cat samples have not been included in NORM-VET previously.

Methicillin resistant *Staphylococcus aureus* (MRSA) in pig in Norway in 2022

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 2022, 591 herds were included, of which 82 were genetic nucleus or multiplier herds, 11 herds were central units of the sow pool herds, 16 were of the largest farrow to grower or farrow to finish herds, and the remaining 482 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 2022" (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 27 shows the number of herds identified by the MRSA surveillance programme and the total number of detected MRSA positive herds from 2013-2022, 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 27. Pig herds positive for methicillin resistant *Staphylococcus aureus* 2013-2022. Total number of MRSA positive herds detected by the MRSA surveillance programme, total number of MRSA positive herds, as well as results from MRSA typing.

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	
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.

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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 2022. *Surveillance programmes for terrestrial and aquatic animals in Norway. Annual report 2021*. Oslo: Norwegian Veterinary Institute 2023.
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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Evaluation of the One Health-ness of 20 Years of antimicrobial resistance surveillance in Norway

We evaluated the One Health-ness (OH-ness) of the surveillance system for antimicrobial resistance (AMR) in Norway by using the recently developed "Evaluation tool for One Health epidemiological surveillance capacities and capabilities" (OH-EpiCap tool).

First, we defined the OH system of AMR surveillance in Norway to include the Norwegian AMR monitoring programmes in the human (NORM) and veterinary sectors (NORM-VET), the surveillance programme for LA-MRSA in swine, parts of MSIS, as well as the AMR mapping surveys performed in different niches of the Norwegian environment. The OH–EpiCap tool was applied by a group of stakeholders (key persons in the Norwegian AMR surveillance programmes) in a digital meeting and questions related to the three so-called dimensions: 1. Organisation, 2. Operation and 3. Impact. Within these dimensions, four target areas were included and four questions per target were given, resulting in 48 questions. The obtained answers resulted in a score ranging from one (1, no compliance) to four (4, full compliance). A consensus was agreed on, and only one score was given for each question.

The tool produced a report on the OH-EpiCap website, with dimension indices representing mean scores for all questions, expressed as percentages. The OH-EpiCap tool can be found at https://freddietafreeth.shinyapps.io/OH-EpiCap/, accessed on 25 April 2023. A link to the user guide is provided within the tool itself.

The evaluation resulted in an overall OH-ness score at 68% across all three dimensions included in the tool (Figure 55). The tool provided suggestions for improvement. These were only indicated within the areas of internal evaluation and operational costs, whereas most of the indicators included in the tool showed good adherence to the One Health principles.

By performing this internal evaluation, we recognised that AMR surveillance in the environment needs to be included in a more systematic and standardised way to improve the OH-ness as defined by the quadripartite organisations. Last but not least, it was beneficial to bring key stakeholders together to conduct the evaluation. It increased a joint perception of the OH-ness of AMR surveillance in Norway and encouraged further collaboration in the future.

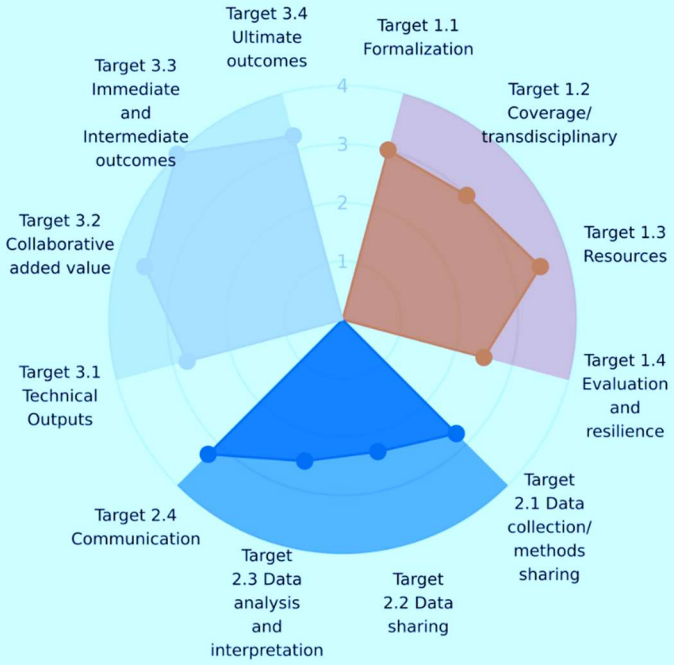

FIGURE 55. The average scores of the target areas attributed to three dimensions; Organisation (orange), Operation (blue), and Impact (grey), in the evaluation performed on the surveillance of antimicrobial resistance in Norway using the OH-EpiCap tool.

The text is a summary of the main findings in the publication "Evaluation of the One Health-Ness of 20 Years of Antimicrobial Resistance Surveillance in Norway" published in Antibiotics 2023, 12(7), 1080; https://doi.org/10.3390/ antibiotics12071080.

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INDICATOR BACTERIA FROM FOOD

Gro Johannessen, Madelaine Norström, Jannice Schau Slettemeås and Anne Margrete Urdahl

In 2022, food samples included broiler and turkey meat. One isolate of interest 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, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2022. Sampling, laboratory methods and data processing are described in Appendix 3.

MEAT

Extended-spectrum cephalosporin resistant *Escherichia coli* from broiler and turkey meat

In total, 303 broiler and 122 turkey meat samples were examined for the presence of *E. coli* resistant to extended-spectrum cephalosporins (ESC), i.e. cefotaxime and/or ceftazidime. Results are presented in the text and in Figures 56-57.

RESULTS AND COMMENTS

BROILER MEAT

ESC resistant *E. coli* were not detected in any of the 303 [95% CI: 0.0 – 1.2] broiler meat samples. The result from 2022 is in concordance with results from 2018 and 2020 where ECS resistant *E. coli* were detected in one and three samples, respectively. There was a significant reduction of ESC resistant *E. coli* in broiler meat in 2018 ($p<0.001$) as compared to previous years (Figure 56).

In a European perspective, the occurrence of ESC resistant *E. coli* detected in Norwegian broiler meat is very low, although the occurrence varied markedly between countries reporting to EFSA in 2020 (EFSA and ECDC Summary report 2020/2021). While the Nordic countries tend to report a lower prevalence of ESC resistant *E. coli* in broiler meat, a decrease in prevalence has also been observed in several other European countries. There are also variations in prevalence between the Nordic countries, with Norway having a very low prevalence.

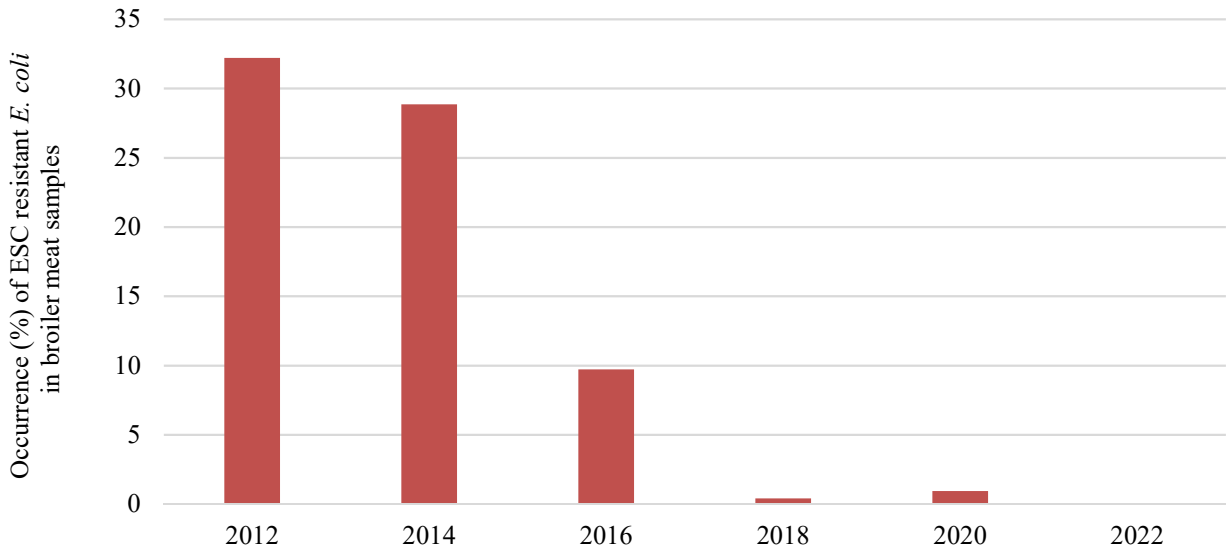

FIGURE 56. Occurrence (%) of ESC resistant *E. coli* in broiler meat samples 2012-2022. All isolates had genotype bla_{CMY-2}.

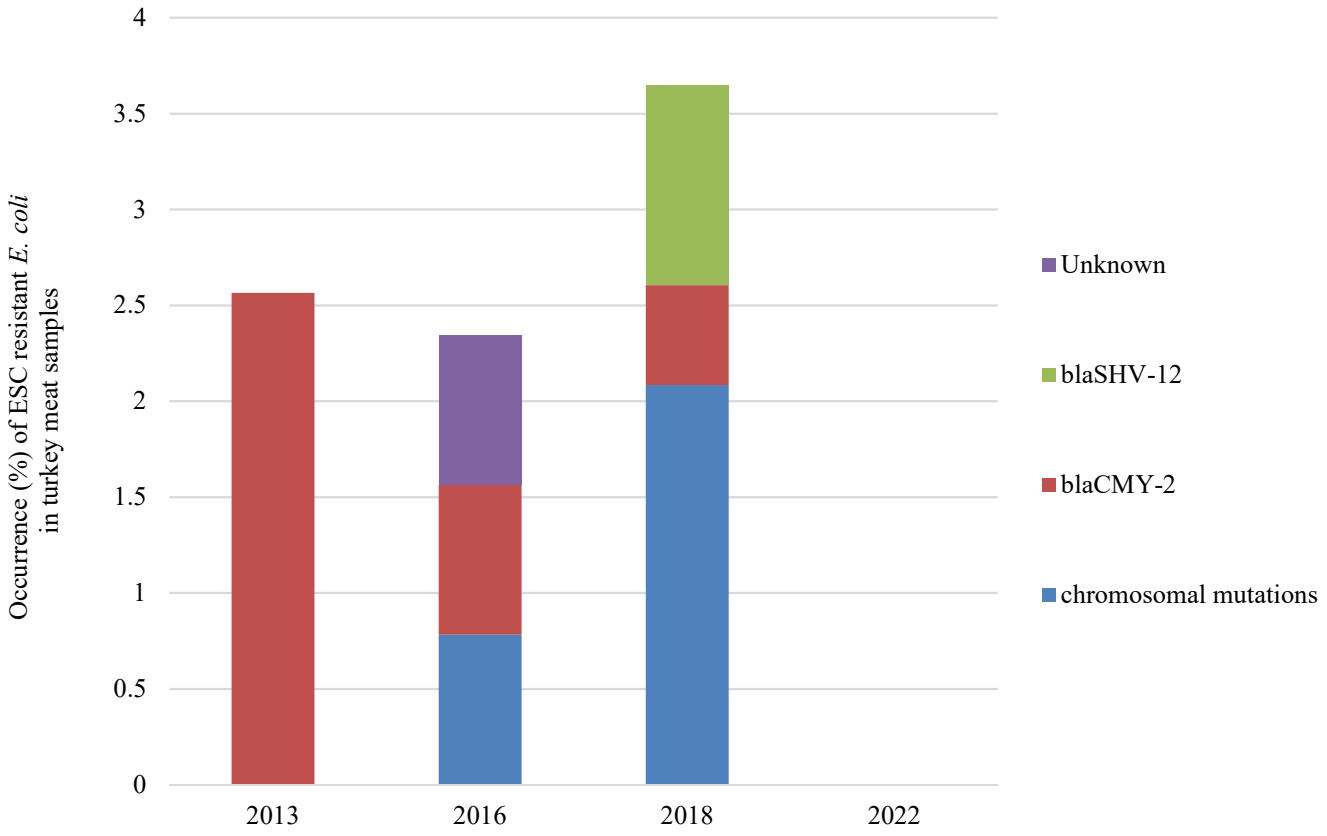

FIGURE 57. Occurrence (%) of resistance genes in ESC resistant *E. coli* in turkey meat samples in 2013-2022.

TURKEY MEAT

ESC resistant *E. coli* were not detected in any of the 122 [95% CI: 0.0 – 3.0] turkey meat samples.

Similar to the findings in broiler meat, the occurrence of ESC resistant *E. coli* in turkey meat has been reduced from 35.3% in 2013 to 2.3% in 2016, 3.6% in 2018, and none in 2022. Turkey meat was not included in 2020. Figure 57 gives an overview of the resistance genes detected through the years 2013-2022.

Carbapenem resistant *Enterobacterales* from broiler and turkey meat

A total of 303 broiler and 122 turkey meat samples were examined for the presence of carbapenem resistant *Enterobacterales* (CRE). No CRE were detected (broiler meat: [95% CI: 0.0 – 1.2] and turkey meat: [95% CI: 0.0 – 3.0]). This is in concordance with the results from 2020 where no CRE were detected. 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 such 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. Regarding human isolates, 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 2022 included those that were detected in the Salmonella surveillance programmes, as well as isolates obtained from submissions to the National Reference Laboratory (NRL) 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.The data are presented in Table 28 and in the text.

TABLE 28. Antimicrobial resistance in *Salmonella* spp. (n=49) from animals (four pigs, eight cattle, one sheep, two dogs, 31 cats and three wild hogs); *S.* Typhimurium (n=39) and other *Salmonella* spp. (n=10) in 2022.

Substance	n (resistance)	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	1								48					1			
Tigecycline	ND					46	3										
Chloramphenicol	0										48	1					
Ampicillin	1							15	32	1				1			
Cefotaxime	0					48	1										
Ceftazidime	0					28	20	1									
Meropenem	ND		9	40													
Trimethoprim	0					35	14										
Sulfamethoxazole	ND												1	16	18	9	5
Azithromycin	0									41	7	1					
Gentamicin	0						47	2									
Amikacin	0									49							
Ciprofloxacin	1	8	39	1			1										
Nalidixic acid	1									46	2		1				
Colistin	ND							21	13	15							

*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, 49 *Salmonella* spp. isolates from animals isolated through the Salmonella surveillance programmes, from clinical submissions or necropsies were susceptibility tested. The animal isolates included one from sheep, eight from cattle, four from pigs, two from dogs, 31 from cats and three from wild hogs. In total, 39 isolates were *S.* Typhimurium, whereof one was monophasic (4,[5],12:i:-), one was *S. enterica* subsp. *diarizonae*, four isolates were of *S.* Dublin, one was *S.* Senftenberg, and one *S.* Oranienburg. One isolate was resistant to tetracyclines and ampicillin (*S.* Typhimurium, monophasic (4,[5],12:i:-)), and one isolate (*S.* Oranienburg) was resistant to quinolones.

Additionally, four *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. Two isolates were of *S. Senftenberg* and two were of *S.* Dublin. These four isolates were fully susceptible to all antimicrobial agents included in the panel.

Salmonella from human clinical specimens

In 2022, 712 human cases of nontyphoidal salmonellosis and 7 cases of typhoid fever were notified to the Norwegian Surveillance System for Communicable Disease (MSIS). Most of the cases were domestically acquired (64%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 645 *Salmonella* isolates from the primary diagnostic laboratories for further characterisation. One hundred twenty-five isolates were linked to seven clusters/outbreaks, and 529 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 403 isolates, including all *Salmonella* Typhimurium, *Salmonella* Typhi and *Salmonella* Paratyphi A and B isolates, 98% of the monophasic *Salmonella* Typhimurium isolates, and 95% of the domestically acquired isolates of *Salmonella* Enteritidis and 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 2022, by serovar and place of acquisition.

Salmonella serovars	No. of isolates tested in 2022		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. Typhimurium	56	56	29	29	18	18	9	9
S. Typhimurium monophasic	45	46	26	27	13	13	6	6
S. Enteritidis	122	194	42	44	51	121	29	29
S. Typhi	7	7	1	1	6	6	0	0
S. Paratyphi A and B	16	16	0	0	16	16	0	0
Other *Salmonella*	157	210	90	99	41	83	26	28
Total	**403**	**529**	**188**	**200**	**145**	**257**	**70**	**72**

A total of 74 isolates were recovered from blood cultures representing 18% of all *Salmonella* isolates, including all *S.* Typhi, 9 *S.* Paratyphi A (90%), 1 Paratyphi B (16.7%), 17 *S.* Enteritidis (13.9%), 4 monophasic *S.* Typhimurium (8.9%), 3 *S.* Typhimurium (5.4%), and 33 *Salmonella* isolates of other serovars (21%). The results from the antimicrobial susceptibility testing and genomic resistance screening for *Salmonella* are presented in Tables 30-44, Figures 58-69 and in the related text.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHIMURIUM

TABLE 30. Percentage distributions of antimicrobial susceptibility categories in domestically acquired *Salmonella* Typhimurium (n=29) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	82.8	-	17.2
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	93.1	-	6.9
Tetracycline[2]	≥ 17 mm	< 17 mm	82.8	-	17.2
Chloramphenicol	≤ 8	> 8	86.2	-	13.8

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. [1]Low-level resistance to 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.13.0).[2]Breakpoints according to national zone distributions.

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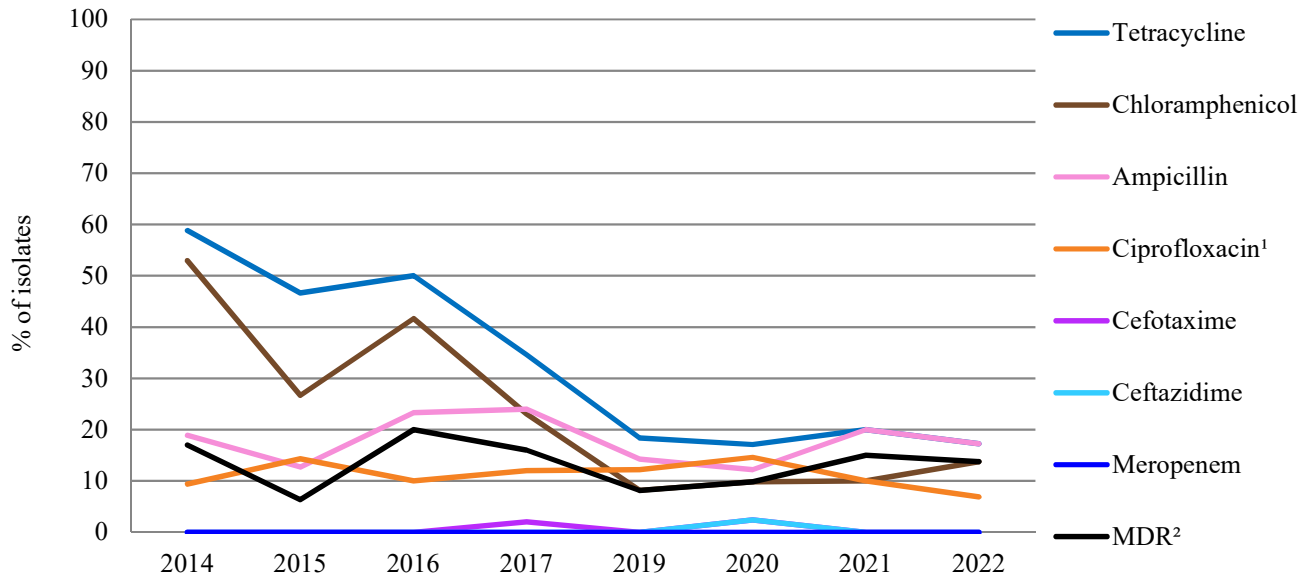

FIGURE 58. Trend 2014-2022. Percentage of domestically acquired *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 31. Percentage distributions of predicted genotypic resistance in domestically acquired *Salmonella* Typhimurium (n=29) compared to phenotypic wild type/non-wild type distribution (n=29) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	82.8	17.2
Ampicillin	82.8	17.2	82.8	17.2
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	86.2	13.8	86.2	13.8
Ciprofloxacin	93.1	6.9	93.1	6.9
Sulfonamide	-	-	93.1	6.9
Tetracycline	82.8	17.2	82.8	17.2
Trimethoprim	-	-	93.1	6.9

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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=18) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	83.3	-	16.7
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	88.9	-	11.1
Tetracycline[2]	≥ 17 mm	< 17 mm	77.8	-	22.2
Chloramphenicol	≤ 8	> 8	94.4	-	5.6

[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.13.0).[2]Breakpoints according to national zone distributions.

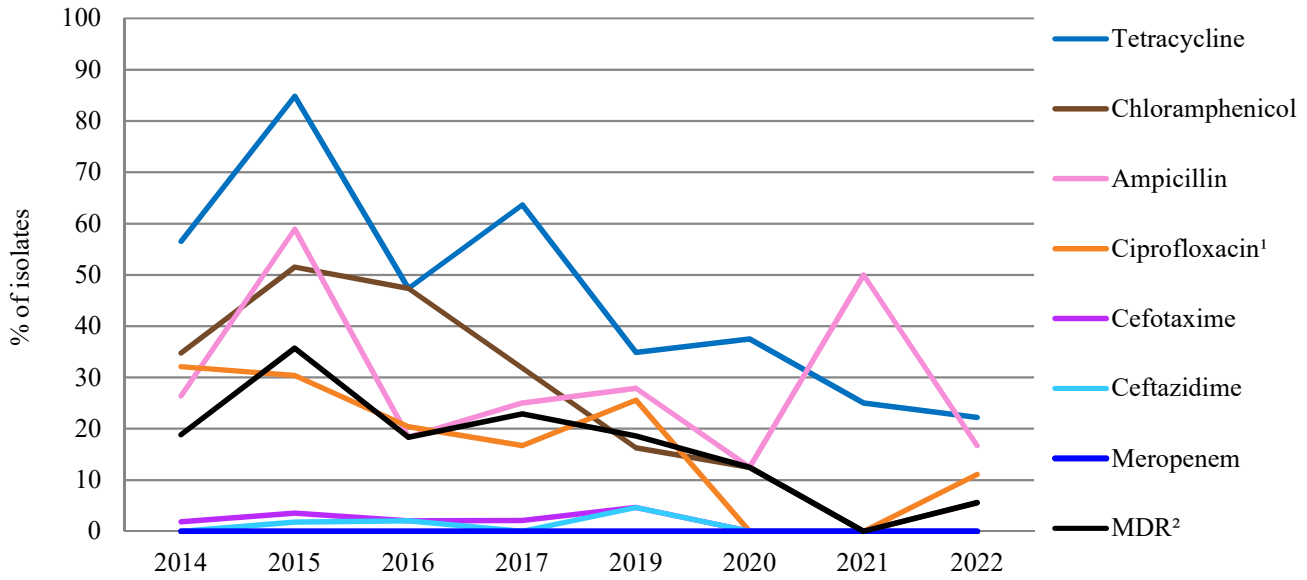

FIGURE 59. Trend 2014-2022. Percentage of travel associated *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 33. Percentage distributions of predicted genotypic resistance in travel associated *Salmonella* Typhimurium (n=18) compared to phenotypic wild type/non-wild type distribution (n=18) from human clinical specimens in Norway 2022.

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

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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.

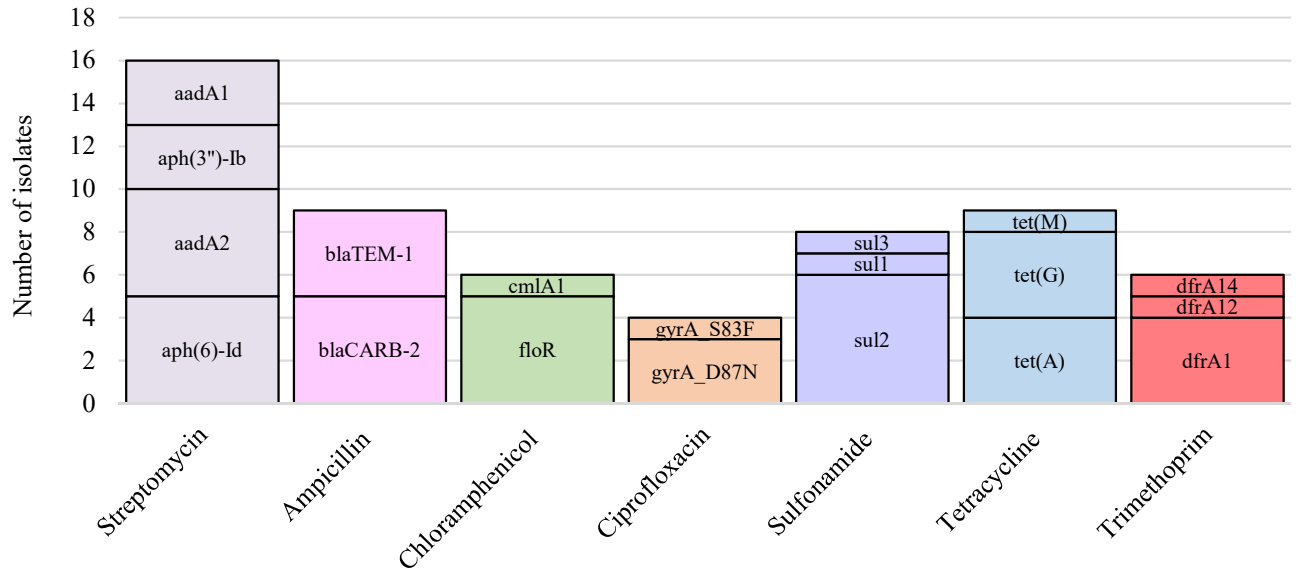

FIGURE 60. Identified resistance determinants in *Salmonella* Typhimurium (n=56) to selected antimicrobial agents in Norway 2022.

ANTIMICROBIAL RESISTANCE IN MONOPHASIC SALMONELLA TYPHIMURIUM

TABLE 34. Percentage distributions of antimicrobial susceptibility categories in domestically acquired monophasic *Salmonella* Typhimurium (n=26) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	26.9	-	73.1
Cefotaxime	≤ 1	> 2	96.2	0.0	3.8
Ceftazidime	≤ 1	> 4	96.2	0.0	3.8
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	96.2	-	3.8
Tetracycline[2]	≥ 17 mm	< 17 mm	26.9	-	73.1
Chloramphenicol	≤ 8	> 8	92.3	-	7.7

[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.13.0).[2]Breakpoints according to national zone distributions.

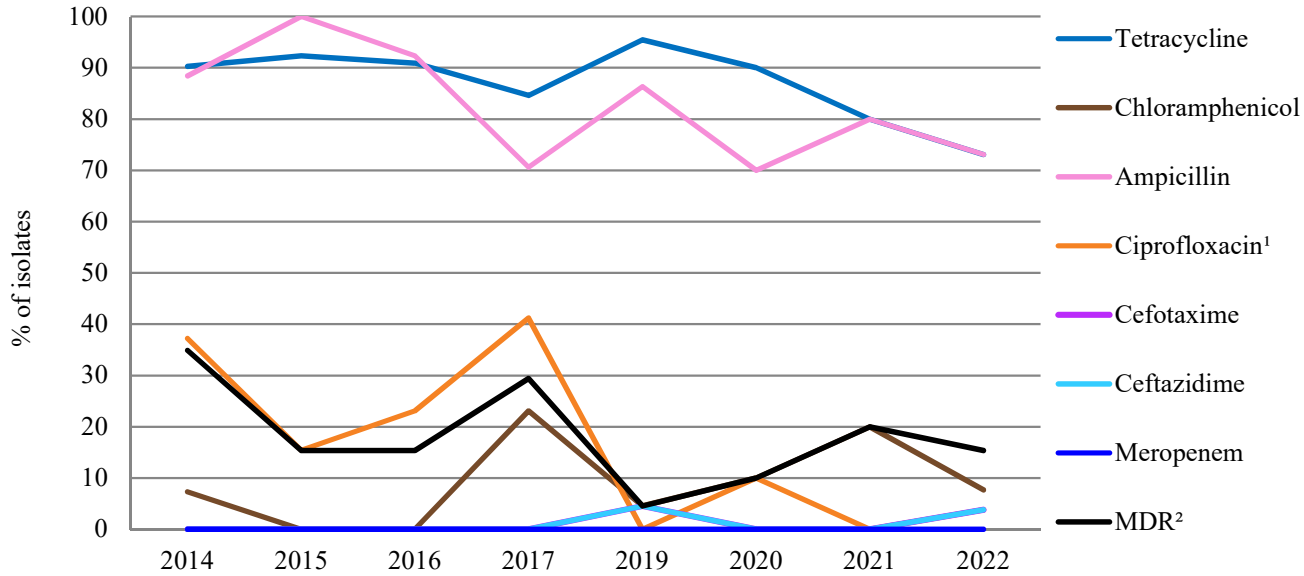

FIGURE 61. Trend 2014-2022. Percentage of domestically acquired monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 35. Percentage distributions of predicted genotypic resistance in domestically acquired monophasic *Salmonella* Typhimurium (n=27) compared to phenotypic wild type/non-wild type distribution (n=26) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	92.6	7.4
Streptomycin	-	-	25.9	74.1
Ampicillin	26.9	73.1	25.9	74.1
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	96.2	3.8	96.3	3.7
Ceftazidime[3]	96.2	3.8		
Colistin	-	-	100.0	0.0
Chloramphenicol	92.3	7.7	92.6	7.4
Ciprofloxacin	96.2	3.8	100.0	0.0
Sulfonamide	-	-	29.6	70.4
Tetracycline	26.9	73.1	29.6	70.4
Trimethoprim	-	-	92.6	7.4

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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=13) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	23.1	-	76.9
Cefotaxime	≤ 1	> 2	92.3	0.0	7.7
Ceftazidime	≤ 1	> 4	92.3	0.0	7.7
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	76.9	-	23.1
Tetracycline[2]	≥ 17 mm	< 17 mm	7.7	-	92.3
Chloramphenicol	≤ 8	> 8	53.8	-	46.2

[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.13.0). [2]Breakpoints according to national zone distributions.

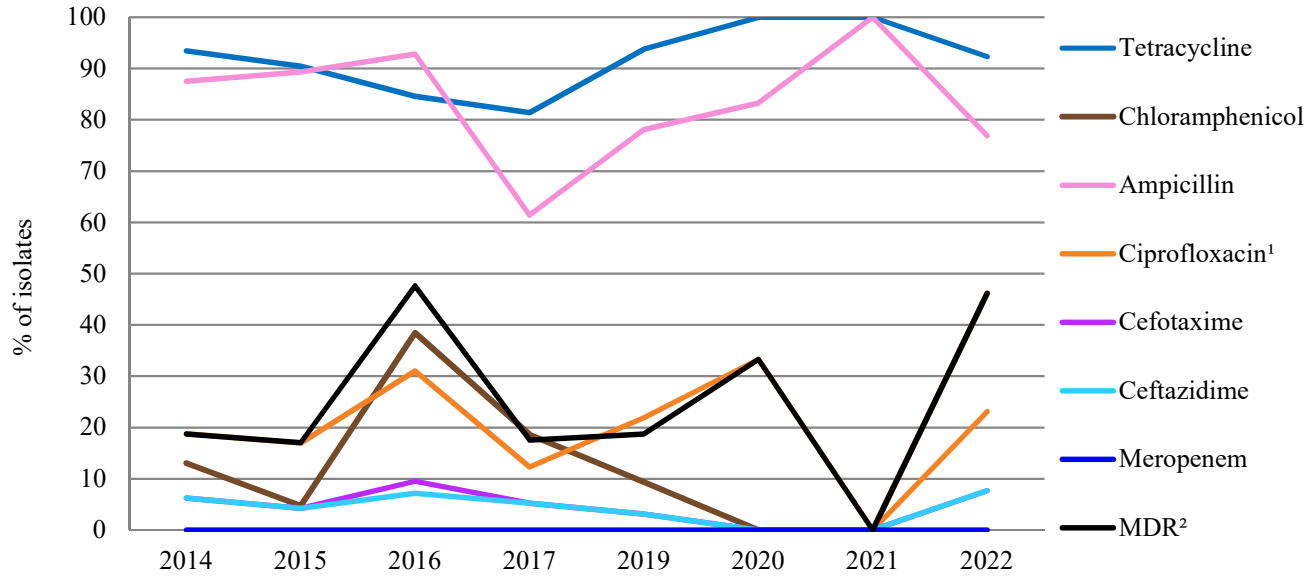

FIGURE 62. Trend 2014-2022. Percentage of travel associated monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 37. Percentage distributions of predicted genotypic resistance in travel associated monophasic *Salmonella* Typhimurium (n=13) compared to phenotypic wild type/non-wild type distribution (n=13) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	84.6	15.4
Streptomycin	-	-	15.4	84.6
Ampicillin	23.1	76.9	23.1	76.9
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	92.3	7.7	92.3	7.7
Ceftazidime[3]	92.3	7.7		
Colistin	-	-	92.3	7.7
Chloramphenicol	53.8	46.2	53.8	46.2
Ciprofloxacin	76.9	23.1	76.9	23.1
Sulfonamide	-	-	46.2	53.8
Tetracycline	7.7	92.3	15.4	84.6
Trimethoprim	-	-	84.6	15.4

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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.

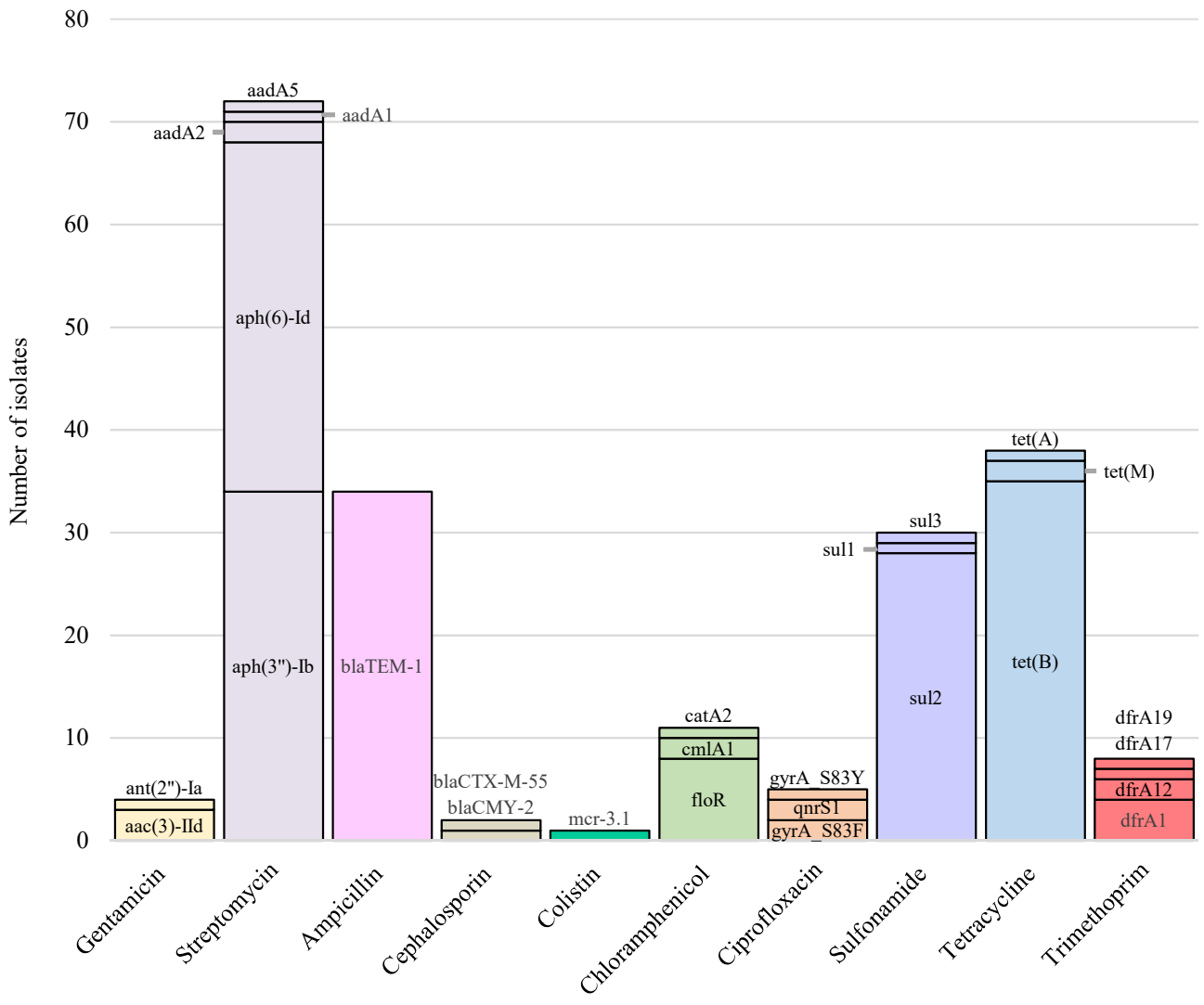

FIGURE 63. Identified resistance determinants in monophasic *Salmonella* Typhimurium (n=46) to selected antimicrobial agents in Norway 2022.

ANTIMICROBIAL RESISTANCE IN SALMONELLA ENTERITIDIS

TABLE 38. Percentage distributions of antimicrobial susceptibility categories in *Salmonella* Enteritidis (n=122) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	93.4	-	6.6
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	72.1	-	27.9
Tetracycline[2]	≥ 17 mm	< 17 mm	93.4	-	6.6
Chloramphenicol	≤ 8	> 8	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.13.0). [2]Breakpoints according to national zone distributions.

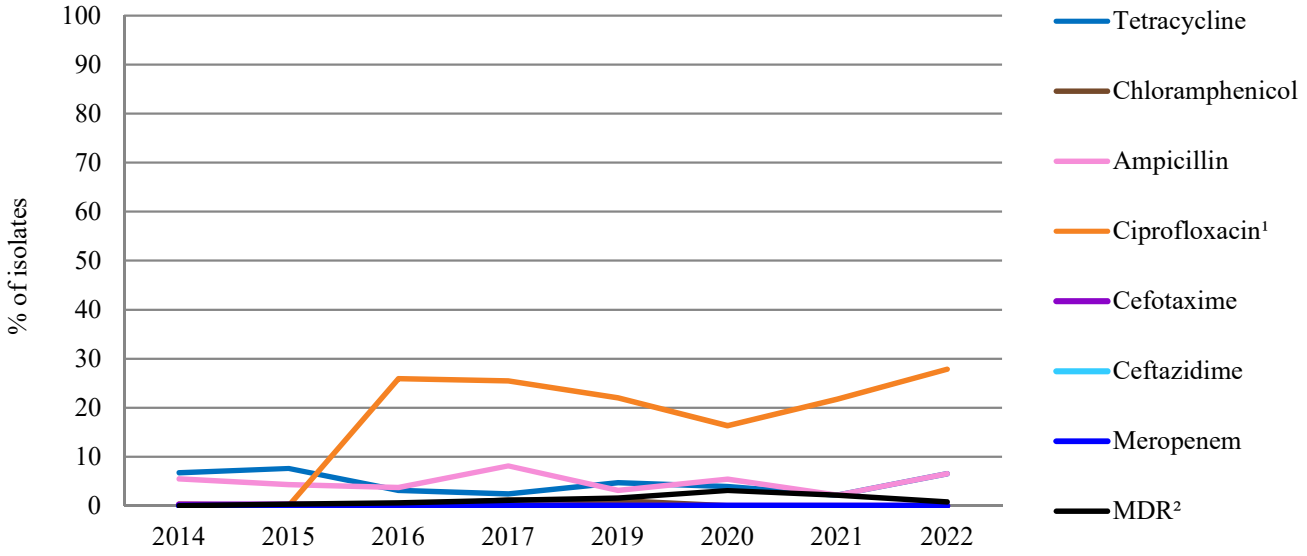

FIGURE 64. Trend 2014-2022. Percentage of *Salmonella* Enteritidis resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 39. Percentage distributions of predicted genotypic resistance in *Salmonella* Enteritidis (n=194) compared to phenotypic wild type/non-wild type distribution (n=122) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	99.5	0.5
Ampicillin	92.6	7.4	93.5	6.7
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	100.0	0.0	99.5	0.5
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	100.0	0.0	99.5	0.5
Ciprofloxacin	72.1	27.9	74.2	25.8
Sulfonamide	-	-	99.5	0.5
Tetracycline	93.4	6.6	94.3	5.7
Trimethoprim	-	-	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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.

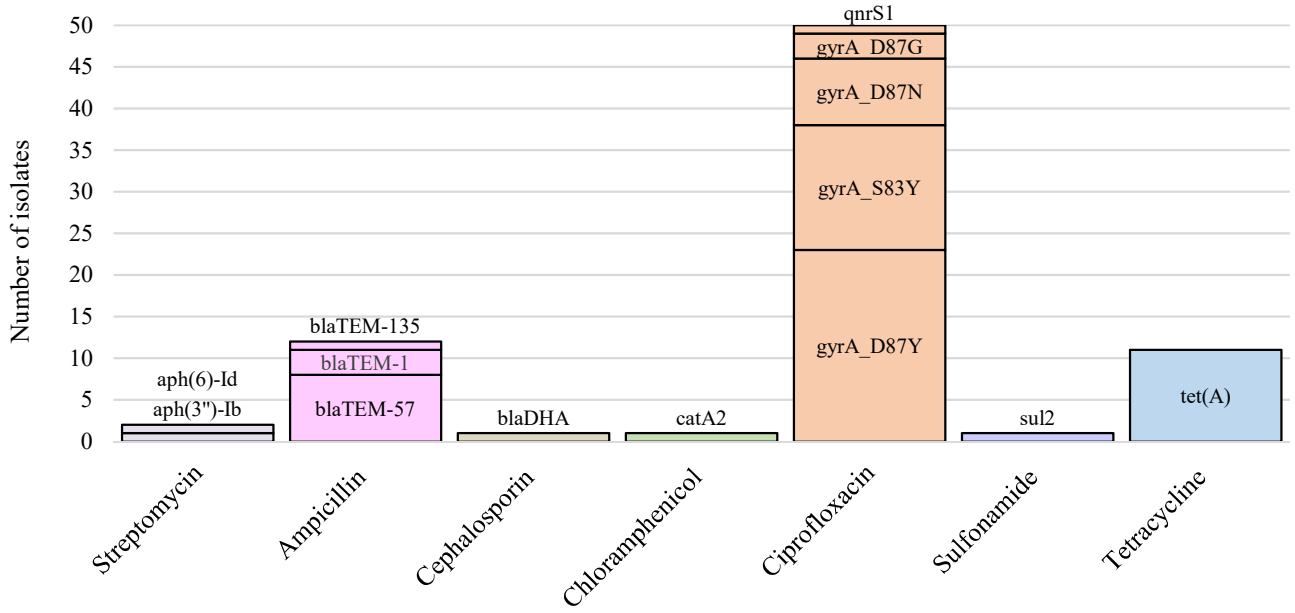

FIGURE 65. Identified resistance determinants in *Salmonella* Enteritidis (n=194) to selected antimicrobial agents in Norway 2022.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHI

TABLE 40. Percentage distributions of antimicrobial susceptibility categories in *Salmonella* Typhi (n=7) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	42.9	-	57.1
Cefotaxime	≤ 1	> 2	71.4	0.0	28.6
Ceftazidime	≤ 1	> 4	71.4	0.0	28.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	0.0	-	100.0
Tetracycline[2]	≥ 17 mm	< 17 mm	85.7	-	14.3
Chloramphenicol	≤ 8	> 8	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.13.0). [2]Breakpoints according to national zone distributions.

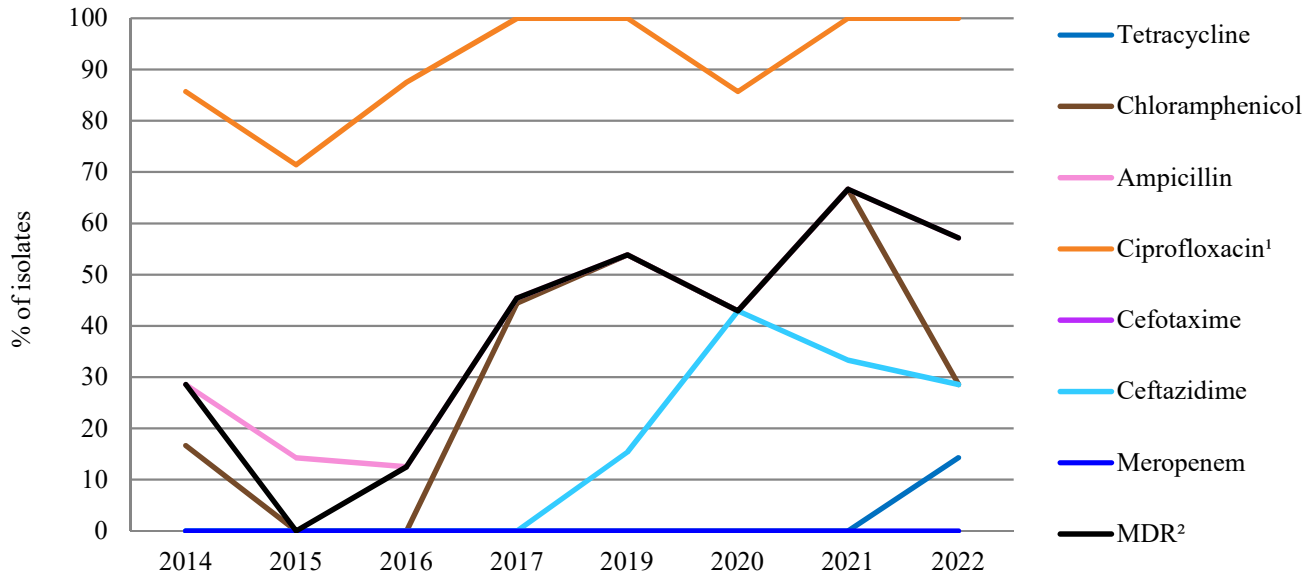

FIGURE 66. Trend 2014-2022. Percentage of *Salmonella* Typhi resistant to selected antimicrobial agents irrespective of place of acquisition in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 41. Percentage distributions of predicted genotypic resistance in Salmonella Typhi (n=7) compared to phenotypic wild type/non-wild type distribution (n=7) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	57.1	42.9
Ampicillin	42.9	57.1	42.9	57.1
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	71.4	28.6	71.4	28.6
Ceftazidime[3]	71.4	28.6		
Colistin[4]	-	-	100.0	0.0
Chloramphenicol	71.4	28.6	71.4	28.6
Ciprofloxacin	0.0	100.0	0.0	100.0
Sulfonamide	-	-	42.9	57.1
Tetracycline	85.7	14.3	85.7	14.3
Trimethoprim	-	-	57.1	42.9

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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.

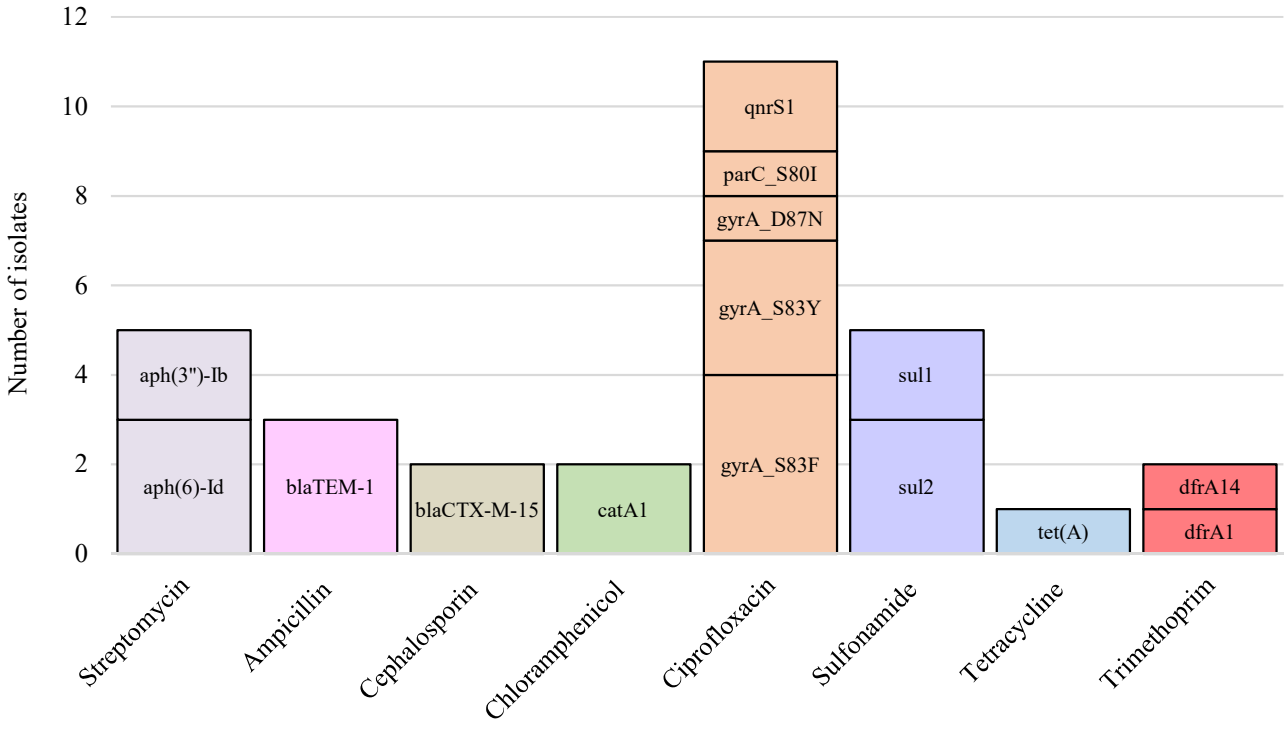

FIGURE 67. Identified resistance determinants in *Salmonella* Typhi (n=7) to selected antimicrobial agents in Norway 2022.

ANTIMICROBIAL RESISTANCE IN OTHER SALMONELLA SEROTYPES

TABLE 42. Percentage distributions of predicted genotypic resistance in other *Salmonella* serotypes (n=210) compared to phenotypic wild type/non-wild type distribution (n=160) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	98.1	1.9
Streptomycin	-	-	93.3	6.7
Ampicillin	92.5	7.5	91.4	8.6
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	98.8	1.2	97.1	2.9
Ceftazidime[3]	99.4	0.6		
Colistin	-	-	100.0	0.0
Chloramphenicol	97.5	2.5	94.8	5.2
Ciprofloxacin	95.0	5.0	88.6	11.4
Sulfonamide	-	-	94.3	5.7
Tetracycline	95.6	4.4	90.0	10.0
Trimethoprim	-	-	94.8	5.2

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [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.

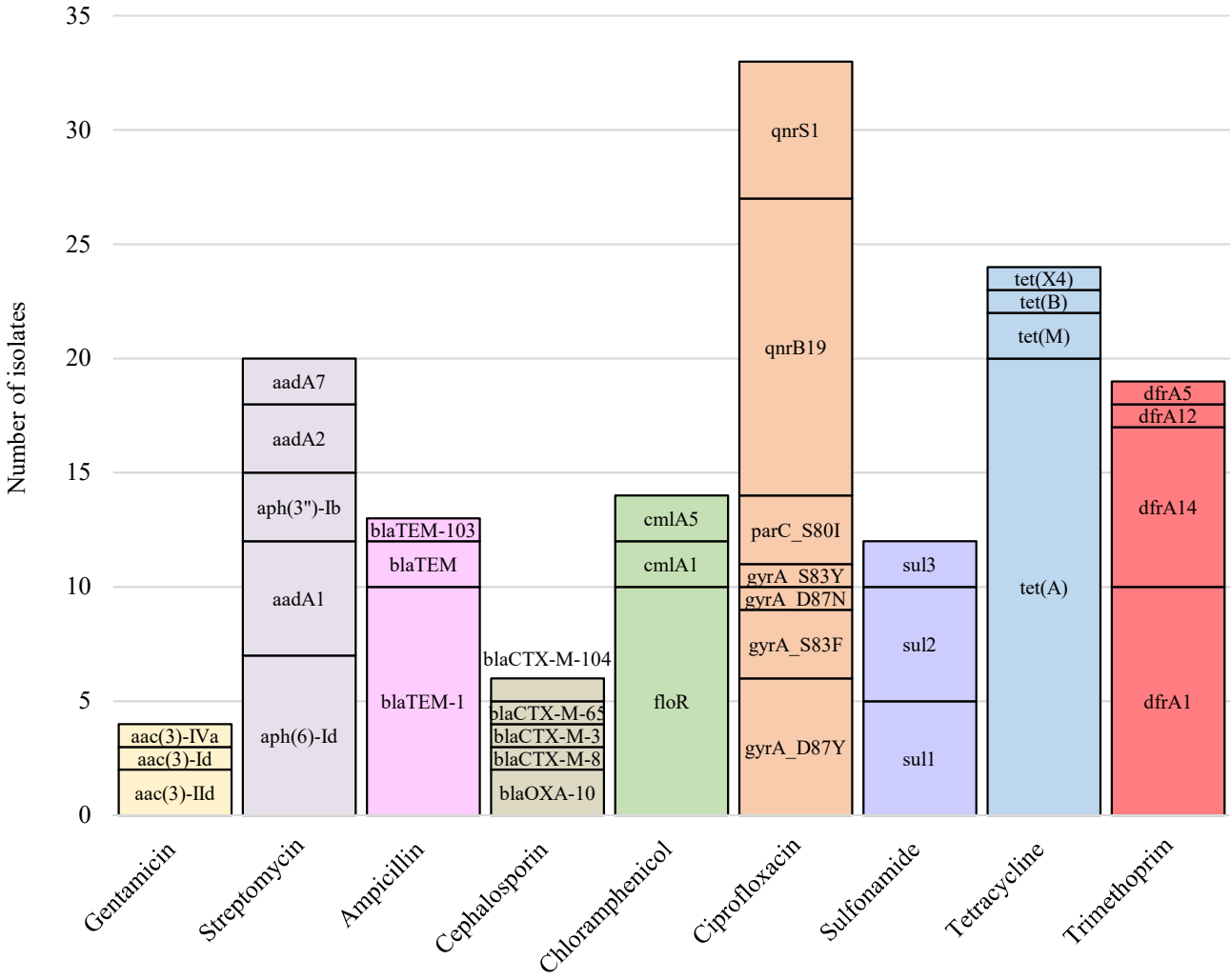

FIGURE 68. Identified resistance determinants in other *Salmonella* serotypes (n=210) to selected antimicrobial agents in Norway 2022.

MULTI-DRUG RESISTANCE IN SALMONELLA

TABLE 43. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates identified in Norway 2022, 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	35	35	34	2	9	4	29	30	4
Salmonella Typhimurium	10	9	9	0	5	3	6	7	4
Salmonella Typhi	4	3	4	2	2	4	4	1	3
Salmonella Enteritidis	2	1	2	0	0	2	1	1	0
Other *Salmonella*	20	14	11	4	11	13	12	17	10
Total no. of MDR isolates	**71**	**62**	**60**	**8**	**27**	**26**	**52**	**56**	**21**

[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.

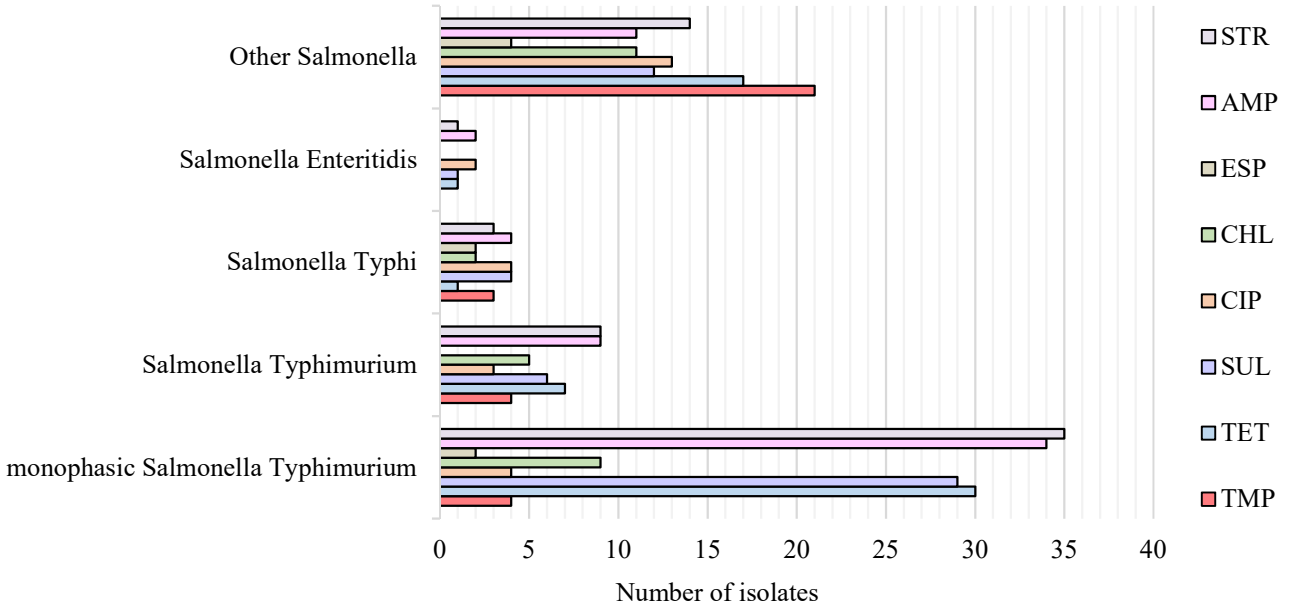

FIGURE 69. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates (n=71) identified in Norway 2022, stratified according to serotype and resistance to different antibiotic categories; STR: Streptomycin, AMP; Ampicillin, ESP; Extended-Spectrum Cephalosporin, CHL; Chloramphenicol, 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 2022.

Antibiotic categories	Tested	Phenotype WT[1]		Phenotype NWT[1]		Sensitivity (%)	Spesificity (%)
		Genotype R	Genotype S	Genotype R	Genotype S		
Penicillins	403	0	331	65	7	100.0	97.9
Extended-spectrum cephalosporins[2]	403	1	396	6	0	85.7	100.0
Carbapenems	403	0	403	0	0	-	100.0
Fluoroquinolones	403	0	334	65	4	100.0	98.8
Tetracycline	403	0	341	60	2	100.0	99.4
Phenicols	403	0	383	19	1	100.0	99.7

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.13.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

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, from 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, the government enforced infection control measures which included travel restrictions that substantially reduced travel associated *Salmonella* infections. Analysis of trends in antimicrobial resistance must be interpreted accordingly.

In 2022, the NRL identified a total of 6 outbreak clusters: *S.* Agona (n=78), monophasic *S.* Typhimurium (n=21), *S.* Enteritidis (n=9), *S.* Blockley (n=7), *S.* Infantis (n=5), and *S.* Braenderup (n=5). Antimicrobial resistance results from only a single isolate from each of these clusters 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 a reducing trend in tetracycline resistance for strains from infections associated with travel. No ESBL producers were identified. Mutations in the *gyrA*-gene were identified as probable mediators for the observed ciprofloxacin resistance. An MDR genotype was assigned to 17.9% of the isolates, attributed to resistance against streptomycin, ampicillin, 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. Two ESBL-producing isolates were identified, encoding $bla_{\text{CTX-M-55}}$ and $bla_{\text{CMY-2}}$, respectively. The mobilised colistin resistance gene variant *mcr-3.1* was identified in one isolate, however, susceptibility testing against colistin was not performed to confirm this phenotype. The strain was recovered from a travel associated infection. This is the first report of a *mcr-3.1* gene identified from *Salmonella* in Norway. The strain was genotypically multi-drug resistant to aminoglycoside (*aac(3)-IId*), macrolide (*mph*), ampicillin ($bla_{\text{TEM-1}}$), tetracycline (*tet*), chloramphenicol (*floR*), sulfonamide (*sul2*), and quinolone (*qnrS1)*. The replicon for an IncQ1 plasmid was identified in the strain and assumed probable carrier of *mcr-3.1* and *qnrS1* genes. *Salmonella* strains carrying *mcr-3.1*, co-existing with *qnrS1* and $bla_{\text{CTX-M-55}}$ have previously been documented in the scientific literature. An MDR genotype was identified for 76.1% of the isolates, largely attributed to resistance against streptomycin, ampicillin, tetracycline, and sulfonamide.

Antibiotic resistance in *S.* Enteritidis is generally low. An apparently sudden emergence of ciprofloxacin resistance in 2016 was linked to the change in antibiotic used for testing fluoroquinolone resistance (from ciprofloxacin to pefloxacin). When screening for genotypic resistance determinants, the presence of mutations in *gyrA*-gene as well as the presence of *qnr*-genes were confirmed. One ESBL-producing isolate was identified encoding bla_{DHA}. An MDR genotype was identified for 1.0% of the isolates, attributed to resistance against ampicillin, ciprofloxacin, and tetracycline.

The overall rate of antibiotic resistance in *S.* Typhi is high with an observed increasing trend of resistance against extended-spectrum cephalosporins over the last five years. Two ESBL-producing isolates were identified, both encoding $bla_{\text{CTX-M-15}}$. MDR was a characteristic feature of a considerable proportion of the *S.* Typhi isolates (4/7, 57.1%). An MDR genotype in *S.* Typhi was attributed to resistance towards streptomycin, ampicillin, chloramphenicol, ciprofloxacin, sulfonamide, trimethoprim and in two isolates also extended-spectrum cephalosporins.

Among other *Salmonella* serotypes (n=210), the most common serotypes identified were *S.* Newport (n=13), *S.* Stanley (n=13), *S.* Chester (n=11), *S.* Paratyphi B variant Java (n=10) and *S.* Paratyphi A (n=10). Overall predicted genotypic resistance was low (<11%) across all screened antibiotics, except for quinolones (11.4%). Six ESBL-producing isolates were identified. Two *S.* Agona, both encoding $bla_{\text{OXA-10}}$, harboured *qnrS1* in addition to a *gyrA* mutation (D87Y). Two *S.* Infantis and single isolates of *S.* Heidelberg and *S.* Minnesota encoded different variants of the $bla_{\text{CTX-M}}$-gene. OXA-10 enzymes are weak hydrolysers of cefotaxime and ceftazidime and strains encoding $bla_{\text{OXA-10}}$ were not phenotypically detected as ESBLs. An MDR genotype was identified in 8.8% 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, eleven isolates were predicted as genotypically resistant to extended-spectrum cephalosporins: *S.* Typhi (n=2), *S.* Agona (n=2), *S.* Infantis (n=2), monophasic *S.* Typhimurium (n=2), *S.* Enteritidis (n=1), *S.* Heidelberg (n=1) and *S.* Minnesota (n=1). Resistance was mediated by different variants of $bla_{\text{CTX-M}}$ (n=7) and $bla_{\text{OXA-10}}$ (n=2), $bla_{\text{CMY-2}}$ (n=1) and bla_{DHA} (n=1) genes. The overall correlation between phenotypic resistance and predicted genotypic resistance was high, both sensitivity and specificity were generally above 97% for all tested and screened antibiotics.

CAMPYLOBACTER SPP.

Campylobacter jejuni and *Campylobacter coli* from broilers

Caecal samples from 106 broiler flocks were examined. These were flocks identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks in Norway in 2022, or flocks that for some reasons had not been tested in the *Campylobacter* surveillance programme. The *Campylobacter* surveillance programme examined 2,189 flocks from 515 producers (Pettersen *et al.* 2023). *C. jejuni* isolates were obtained from 95 of the 106 flocks, and 91 of these were susceptibility tested. Only two *Campylobacter coli* were identified and these were not further analysed. The results are presented in Table 45, Figures 70-71, and in the text.

TABLE 45. Antimicrobial resistance in *Campylobacter jejuni* from broiler (n=91) in 2022.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
			0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	7.7	[3.1 – 15.2]				92.3						5.5	2.2				
Chloramphenicol	0.0	[0.0 – 4.0]						100									
Ertapenem	1.1	[0.0 – 6.0]		98.9			1.1										
Erythromycin	0.0	[0.0 – 4.0]					100										
Gentamicin	0.0	[0.0 – 4.0]			3.3	85.7	11										
Ciprofloxacin	5.5	[1.8 – 12.4]		93.4	1.1						5.5						

*Bold vertical lines denote epidemiological cut-off values. CI=confidence interval. 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.

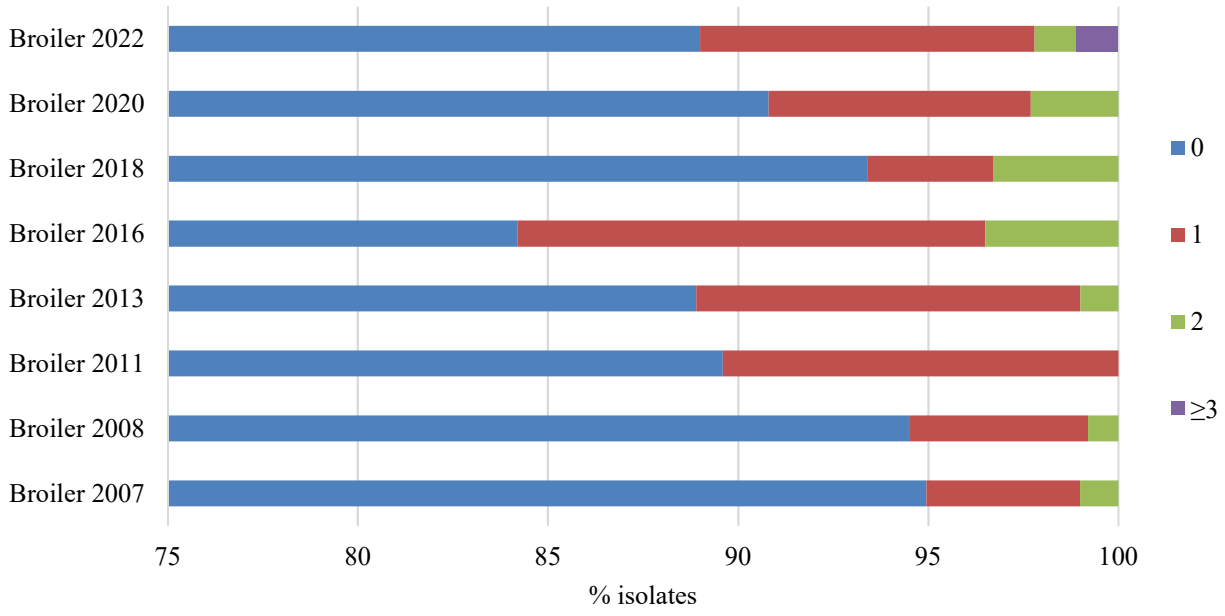

FIGURE 70. Antimicrobial resistance profiles for *Campylobacter jejuni* isolates from broilers in 2007-2022. Proportions of isolates susceptible to all (blue), or resistant to one (red), two (green) or three and more (purple) antimicrobial classes are illustrated.

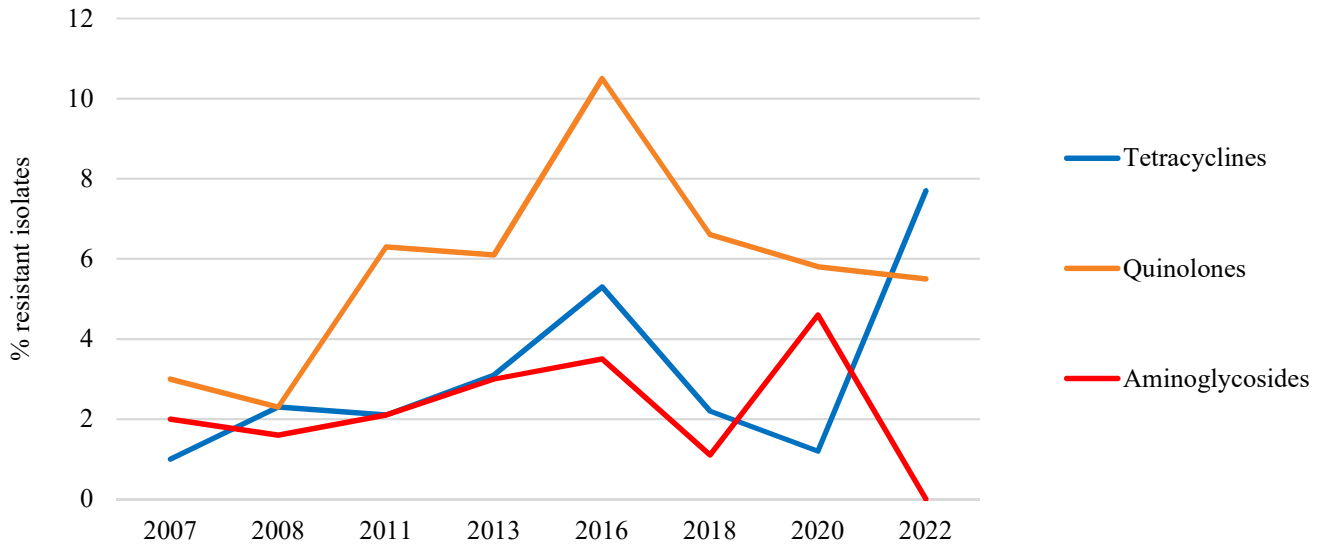

FIGURE 71. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers in 2007-2022. The cut-off values used in NORM-VET 2022 were applied.

RESULTS AND COMMENTS

BROILER

A total of 89.0% of the *C. jejuni* isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to one antimicrobial class was detected in 8.8% of the isolates, while resistance to two antimicrobial classes was detected in 1.1% of the isolates and resistance to three or more antimicrobial classes was detected in 1.1% of the isolates (Figure 70). According to the EFSA classification described in Appendix 6, this corresponds to a low occurrence of antimicrobial resistance among *C. jejuni* isolates from broilers.

Since the last time *Campylobacter* from broilers were included in NORM-VET, i.e. in 2020, the antimicrobial agents included in the panel for susceptibility testing have changed. Streptomycin and the quinolone nalidixic acid have been replaced by chloramphenicol and the carbapenem ertapenem. This has to be taken into account when evaluating the trends in Figures 70 and 71. Aminoglycoside resistance has previously been due to reduced susceptibility to streptomycin, thereby dropping to zero in 2022 when streptomycin is no longer included.

One isolate showed decreased susceptibility to the carbapenem ertapenem. Whole genome sequencing did not reveal any reasons for this decreased susceptibility to ertapenem.

Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to the quinolone ciprofloxacin.

As shown in Figure 71, there has been an increase in quinolone resistance since 2007. An increase in resistance to quinolones in *C. jejuni* from broilers has also been observed in several of the countries reporting to EFSA (EFSA and ECDC Summary Report 2020/2021). Resistance to the quinolone ciprofloxacin was also the most frequently identified resistance determinant in cattle isolates in 2021, and in the domestically acquired human clinical isolates (NORM/NORM-VET 2021).

In a European perspective, the occurrence of resistance in *C. jejuni* (including quinolone resistance) from Norwegian broilers is quite low, although the occurrence varies between countries reporting to EFSA with the Nordic countries having the lowest resistance rates (EFSA and ECDC Summary Report 2018/2019). Further monitoring is needed to follow the situation in Norway in the years to come.

Campylobacter spp. from human clinical cases

In 2022, 2,983 human campylobacteriosis cases were notified to MSIS. Most cases with known place of acquisition were infected in Norway (58%). Surveillance data suggested that the vast majority of cases were sporadic. The first five *Campylobacter* isolates each month from five 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 355 isolates were received at NRL, of which six were linked to a cluster and antimicrobial susceptibility testing was performed on 350 unique *Campylobacter jejuni* and *Campylobacter coli* isolates (Table 46) against four different antibiotic groups: macrolides (erythromycin), aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin), and tetracycline. The results from the antimicrobial susceptibility testing are presented in Tables 47-49, Figures 72-74, and in the related text.

TABLE 46. Number of *Campylobacter* spp. isolates tested for phenotypic antimicrobial susceptibility (AST) recoved from human clinical specimens in Norway 2022, by species and place of acquisition.

Campylobacter spp.	No. of isolates tested in 2022	Place of acquistion		
		Norway	Abroad	Unknown
Campylobacter jejuni	341	162	108	71
Campylobacter coli	9	5	3	1
Total	**350**	**167**	**111**	**72**

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER JEJUNI

TABLE 47. Percentage distributions of antimicrobial susceptibility categories in domestically acquired *Campylobacter jejuni* (n=162) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	91.4	-	8.6
Erythromycin	≤ 4	> 4	98.8	-	1.2
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.13.0)

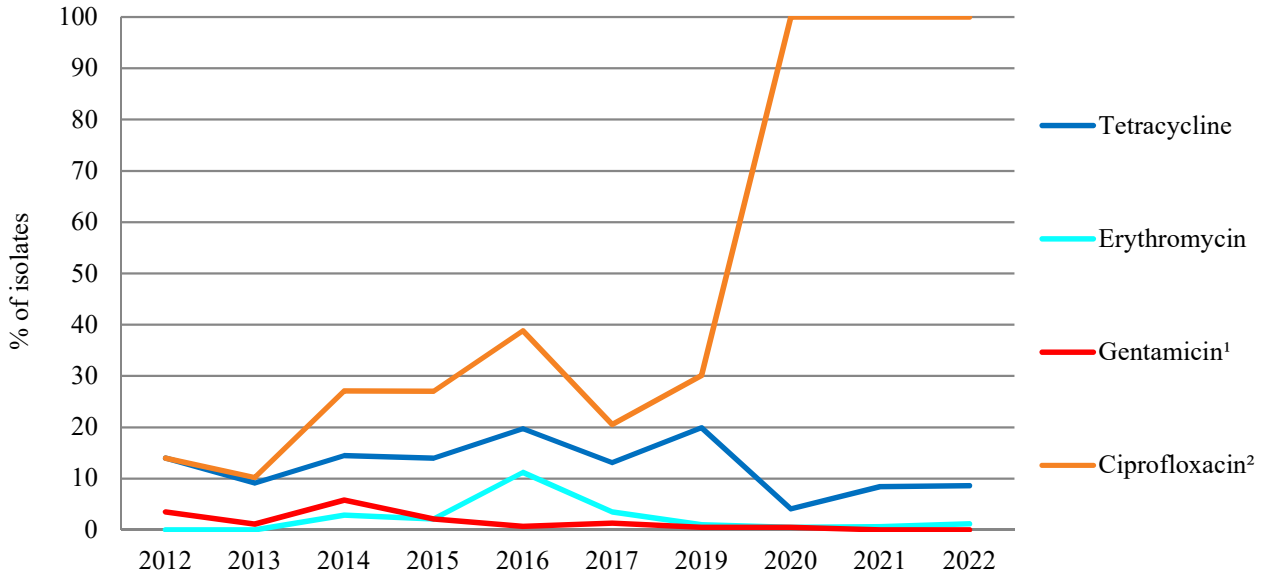

FIGURE 72. Trend 2012-2022. Percentage of domestically acquired *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.13.0).

TABLE 48. Percentage distributions of antimicrobial susceptibility categories in travel associated *Campylobacter jejuni* (n=108) from human clinical specimens in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	30.6	-	69.4
Erythromycin	≤ 4	> 4	99.1	-	0.9
Gentamicin[1]	≤ 2	> 2	99.1	-	0.9
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.13.0)

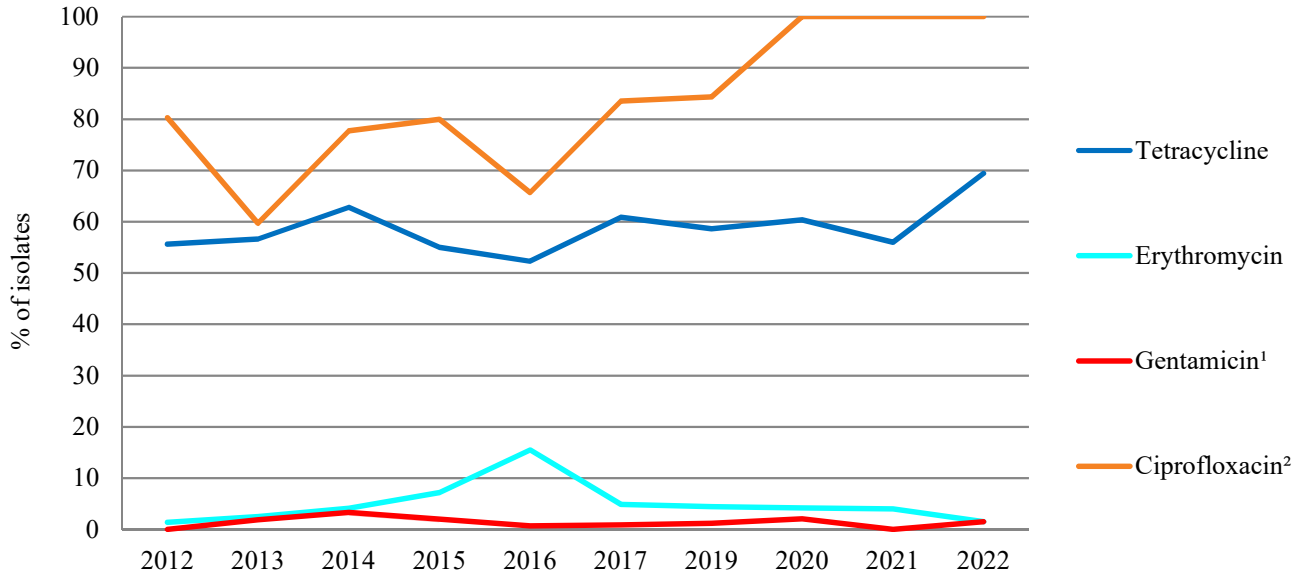

FIGURE 73. Trend 2012-2022. Percentage of travel associated *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.13.0).

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER COLI

TABLE 49. Percentage distributions of antimicrobial susceptibility categories in *Campylobacter coli* (n=9) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	44.4	-	55.6
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.13.0).

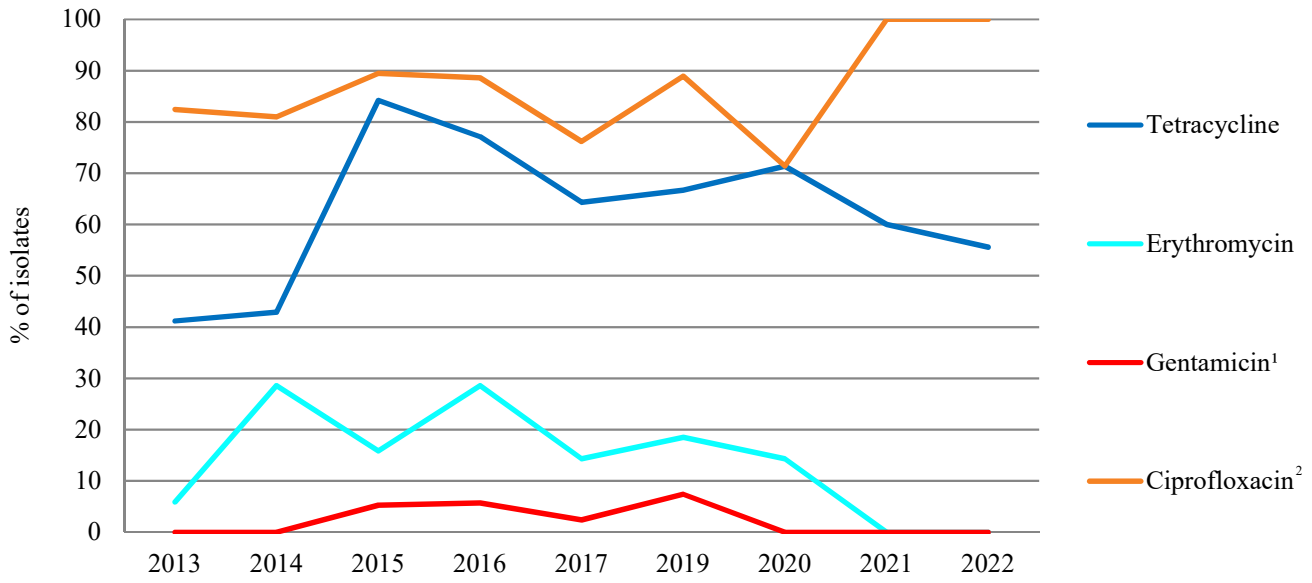

FIGURE 74. Trend 2013-2022. Percentage of *Campylobacter coli* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.13.0).

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 fluroquinolones for both *C. jejuni* and *C. coli* from ≤0.5 mg/L to ≤0.001mg/L.

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

We identified an MDR phenotype in two *C. jejuni* strains, both from travel associated infections. One strain displayed resistance to ciprofloxacin, tetracycline and erythromycin, and the other displayed resistance to ciprofloxacin, tetracycline, and gentamicin.

YERSINIA ENTEROCOLITICA

Yersinia enterocolitica from human clinical specimens

In 2022, 118 human yersiniosis cases were notified to MSIS. Most cases were domestically acquired (71%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 118 isolates of pathogenic *Yersinia* from the primary diagnostic laboratories. Thirty-four isolates were linked to four clusters/outbreaks, and 89 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 89 isolates (Table 50) against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chloramphenicol. The results are presented in Tables 51-53, Figures 75-76, and in the related text.

TABLE 50. Number of *Yersinia enterocolitica* isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2022, by serotype and place of acquisition.

Yersinia enterocolitica	No. of isolates tested in 2022		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	65	65	40	40	12	12	13	13
Y. enterocolitica O:9	13	13	12	12	0	0	1	1
Y. entericolitica (other serotypes)	11	11	5	5	1	1	5	5
Total	**89**	**89**	**57**	**57**	**13**	**13**	**19**	**19**

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

TABLE 51. Percentage distributions of antimicrobial susceptibility categories in *Yersinia enterocolitica* O:3 and O:9 (n=78) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	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	92.3	1.3	6.4
Tetracycline[1]	≥ 17 mm	< 17 mm	98.7	-	1.3
Chloramphenicol	≤ 8	> 8	88.5	-	11.5

[1]Breakpoints according to national zone distributions.

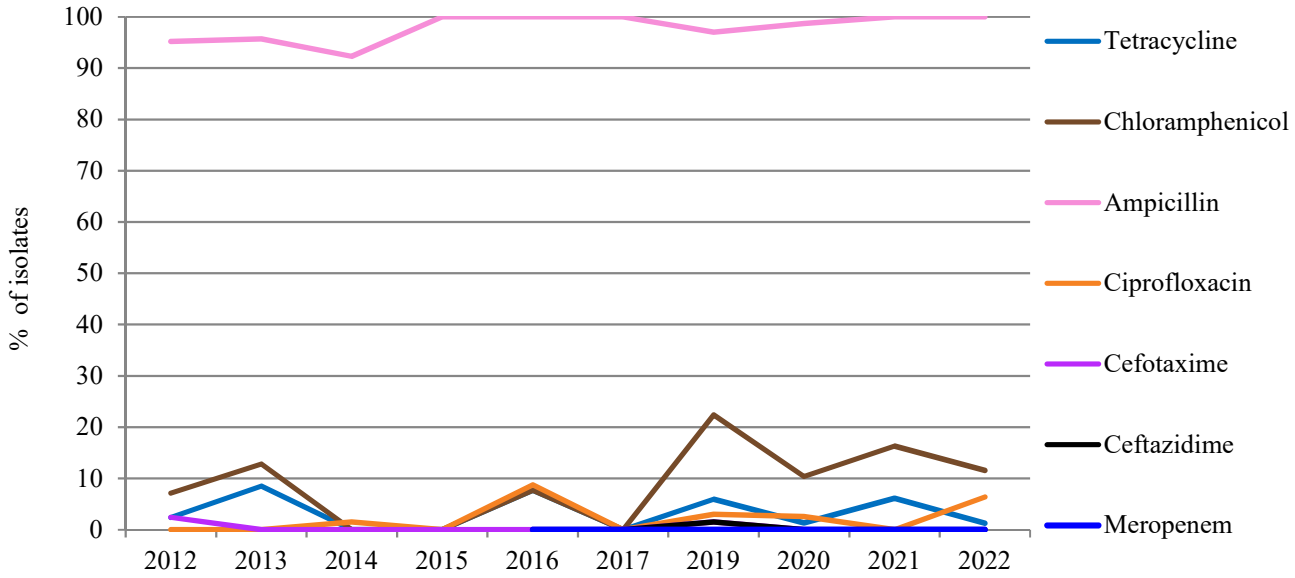

FIGURE 75. Trend 2012-2022. Percentage of *Yersinia enterocolitica* O:3 and O:9 resistant to selected antimicrobial agents irrespective of place of acquisition in Norway.

TABLE 52. Percentage distributions of genotypic resistance in *Yersinia enterocolitica* O:3 and O:9 (n=78) compared to phenotypic wild type/non-wild type distribution (n=78) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	87.2	12.8
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	88.5	11.5	88.5	11.5
Ciprofloxacin	98.7	1.3	100.0	0.0
Sulfonamide	-	-	87.2	12.8
Tetracycline	98.7	1.3	98.7	1.3
Trimethoprim	-	-	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Yersinia enterocolitica* (v.13.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

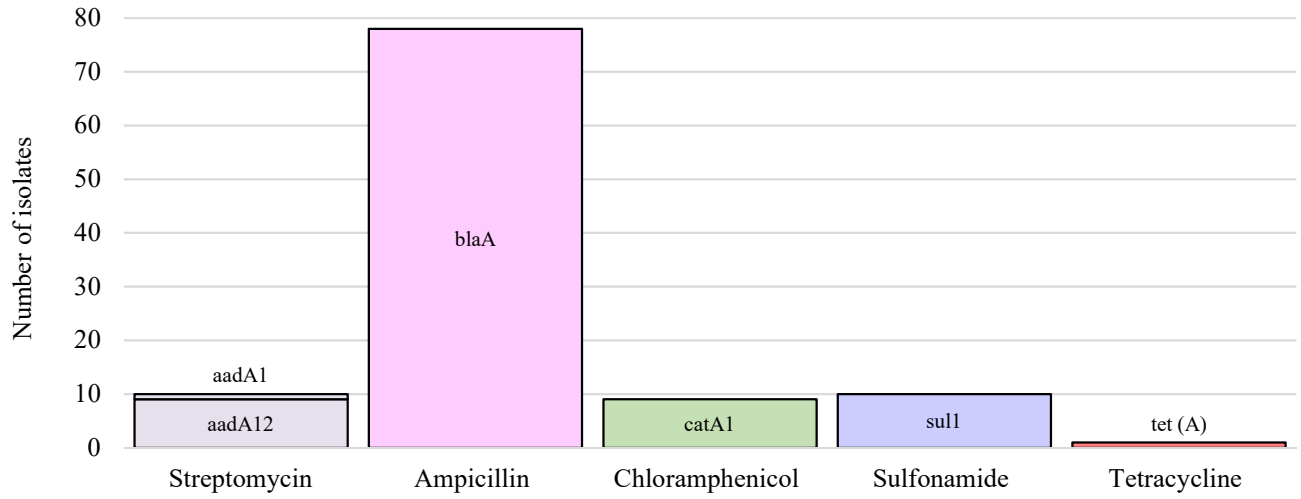

FIGURE 76. Identified resistance determinants in *Yersinia enterocolitica* O:3 and O:9 (n=78) to selected antimicrobial agents in Norway 2022.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN YERSINIA

TABLE 53. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Yersinia enterocolitica* O:3 and O:9 isolates identified in Norway 2022.

Antibiotic categories	Tested	Phenotype WT[1]		Phenotype NWT[1]		Sensitivity (%)	Specificity (%)
		Genotype R	Genotype S	Genotype R	Genotype S		
Penicillins	78	78	0	0	0	-	-
Extended-spectrum cephalosporins[2]	78	0	78	0	0	-	100.0
Carbapenems	78	0	78	0	0	-	98.7
Fluoroquinolones	78	0	77	0	1	-	100.0
Tetracycline	78	0	77	1	0	100.0	100.0
Phenicols	78	0	69	9	0	100.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Yersinia enterocolitica* (v.13.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

RESULTS AND COMMENTS

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

In 2022 the NRL identified a total of four outbreak clusters of *Y. enterocolitica* O:3 (n=3) and *Y. enterocolitica* O:9 (n=1), including a total of 34 isolates. Antimicrobial resistance results from only a single isolate from each of these clusters are 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 was identified in 11.5% of the isolates which was attributed to the *catA1* gene.

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 2022, 80 human cases of shigellosis were notified to MSIS. Most cases were infected abroad (65%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 75 *Shigella* spp. isolates from primary diagnostic laboratories. All isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 72 *Shigella* isolates (Table 54). Isolates were susceptibility tested against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chloramphenicol. The results are presented in Tables 55-60, Figures 77-81, and in the text.

TABLE 54. Number of *Shigella* spp. isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2022, by species and place of acquisition.

Shigella spp.	No. of isolates tested in 2022		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. sonnei	41	43	10	12	27	27	4	4
S. flexneri	26	27	6	6	17	17	3	4
S. boydii	2	2	0	0	2	2	0	0
S. dysenteriae	3	3	0	0	3	3	0	0
Total	**72**	**75**	**16**	**18**	**49**	**49**	**7**	**8**

ANTIMICROBIAL RESISTANCE IN SHIGELLA SONNEI

TABLE 55. Percentage distributions of antimicrobial susceptibility categories in *Shigella sonnei* (n=41) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	43.9	-	56.1
Cefotaxime	≤ 1	> 2	46.3	0.0	53.7
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	29.3	-	70.7
Tetracycline[2]	≥ 17 mm	< 17 mm	17.1	-	82.9
Chloramphenicol	≤ 8	> 8	97.6	-	2.4

[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.13.0) [2]Breakpoints according to national zone distributions.

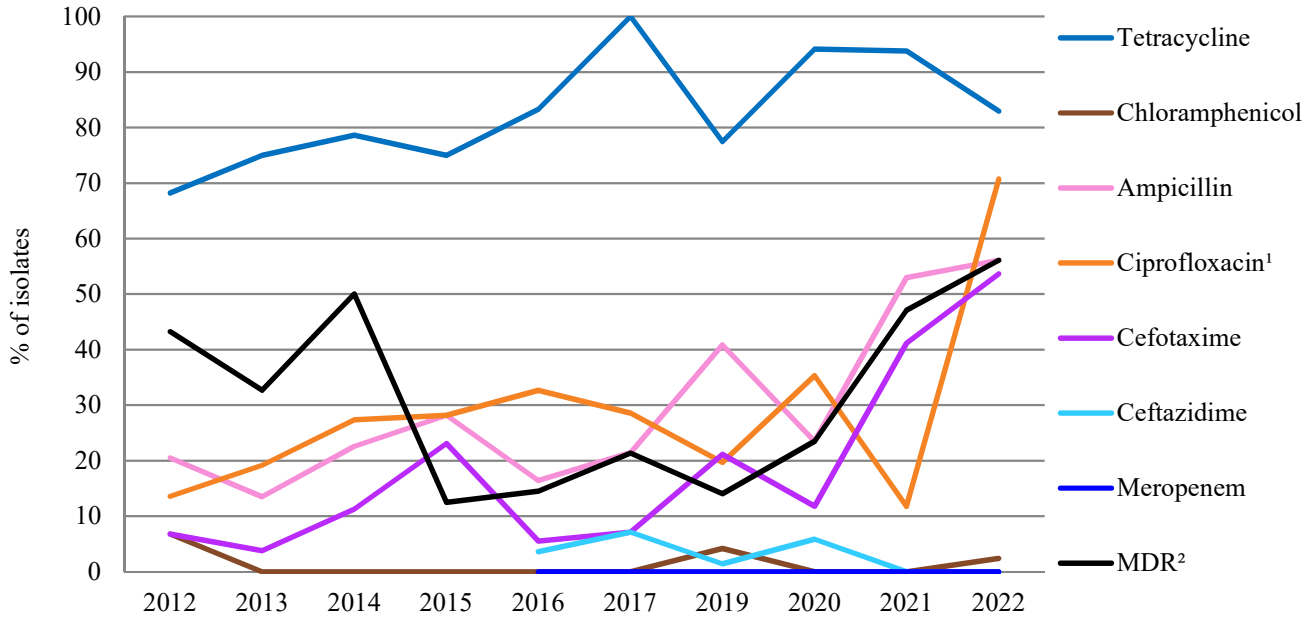

FIGURE 77. Trend 2012-2022. Percentage of *Shigella sonnei* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2022 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 56. Percentage distributions of genotypic resistant *Shigella sonnei* (n=43) compared to phenotypic wild type/non-wild type distribution (n=41) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	100.0	0.0
Streptomycin	-	-	4.7	95.3
Ampicillin	43.9	56.1	41.9	58.1
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	46.3	53.7	41.9	58.1
Ceftazidime[3]	100.0	0.0		
Colistin	-	-	100.0	0.0
Chloramphenicol	97.6	2.4	97.7	2.3
Ciprofloxacin	29.3	70.7	27.9	72.1
Sulfonamide	-	-	9.3	90.7
Tetracycline	17.1	82.9	23.3	76.7
Trimethoprim	-	-	0.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella sonnei* (v.13.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

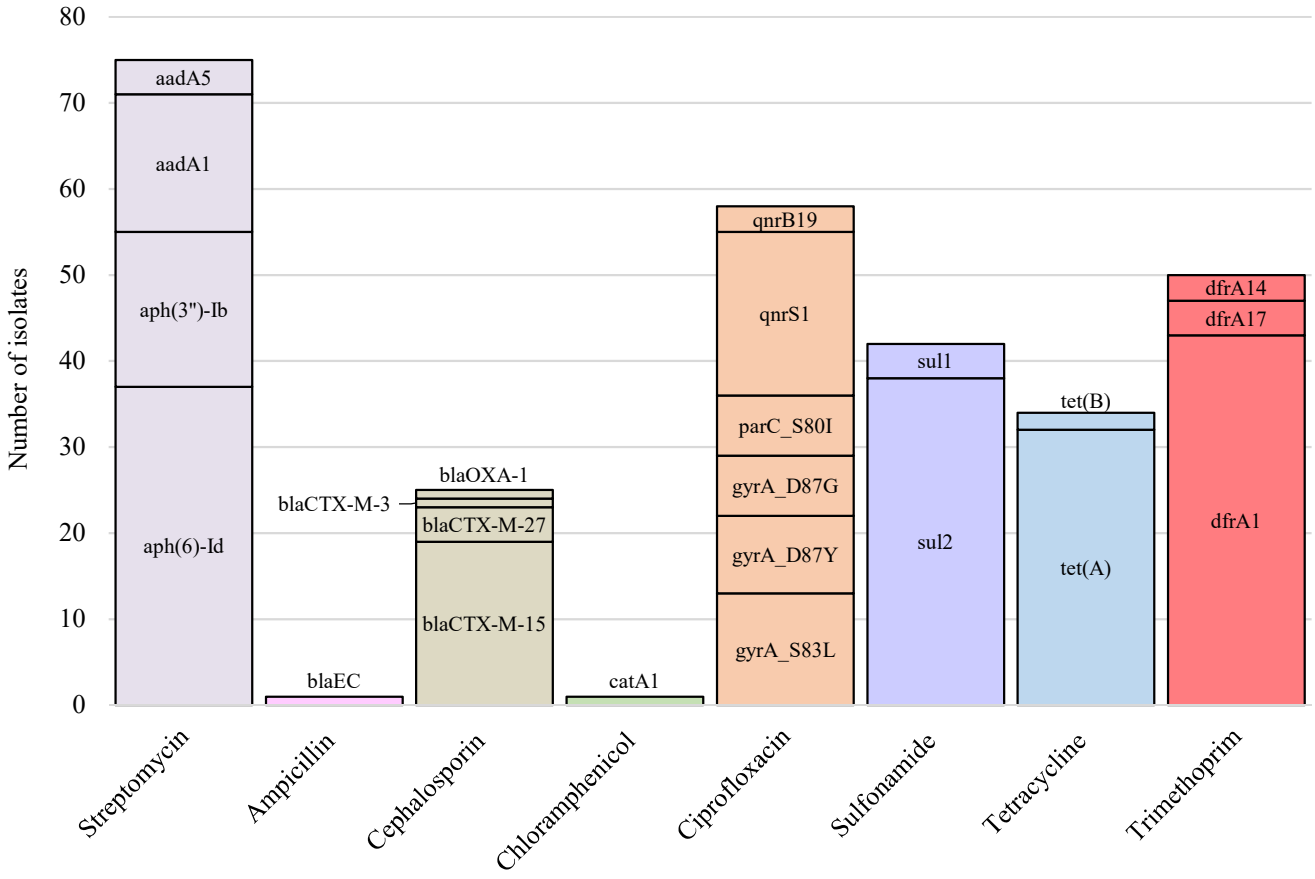

FIGURE 78. Identified resistance determinants in *Shigella sonnei* (n=43) to selected antimicrobial agents in Norway 2022.

ANTIMICROBIAL RESISTANCE IN SHIGELLA FLEXNERI

TABLE 57. Percentage distributions of antimicrobial susceptibility categories in *Shigella flexneri* (n=26) from human clinical specimens irrespective of place of acquisition in Norway 2022.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	23.1	-	76.9
Cefotaxime	≤ 1	> 2	76.9	0.0	23.1
Ceftazidime	≤ 1	> 4	92.3	7.7	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	53.8	-	46.2
Tetracycline[2]	≥ 17 mm	< 17 mm	26.9	-	73.1
Chloramphenicol	≤ 8	> 8	50.0	-	50.0

[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.13.0) [2]Breakpoints according to national zone distributions.

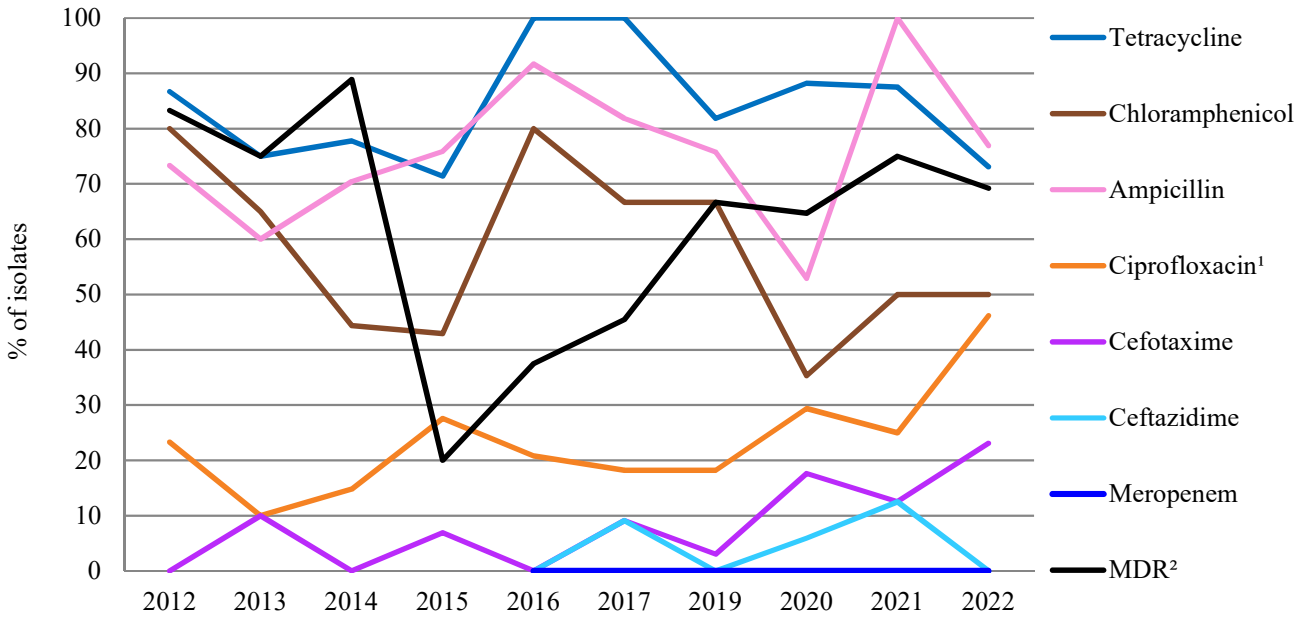

FIGURE 79. Percentage of *Shigella flexneri* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2012-2022. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2022 onwards. [2]MDR is defined as acquired non-susceptibility to antimicrobials from three or more categories.

TABLE 58. Percentage distributions of genotypic resistance in *Shigella flexneri* (n=27) compared to phenotypic wild type/non-wild type distribution (n=26) from human clinical specimens in Norway 2022.

	Phenotype[1] (%)		Predicted genotype[2] (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	-	-	96.3	3.7
Streptomycin	-	-	37.0	63.0
Ampicillin	23.1	76.9	22.2	77.8
Meropenem	100.0	0.0	100.0	0.0
Cefotaxime[3]	76.9	23.1	37.0	63.0
Ceftazidime[3]	92.3	7.7		
Colistin	-	-	100.0	0.0
Chloramphenicol	50.0	50.0	51.9	48.1
Ciprofloxacin	53.8	46.2	51.9	48.1
Sulfonamide	-	-	44.4	55.6
Tetracycline	26.9	73.1	25.9	74.1
Trimethoprim	-	-	14.8	85.2

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella flexneri* (v.13.0). [2]R and S categorisation based on presence or absence of resistance determinants. [3]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

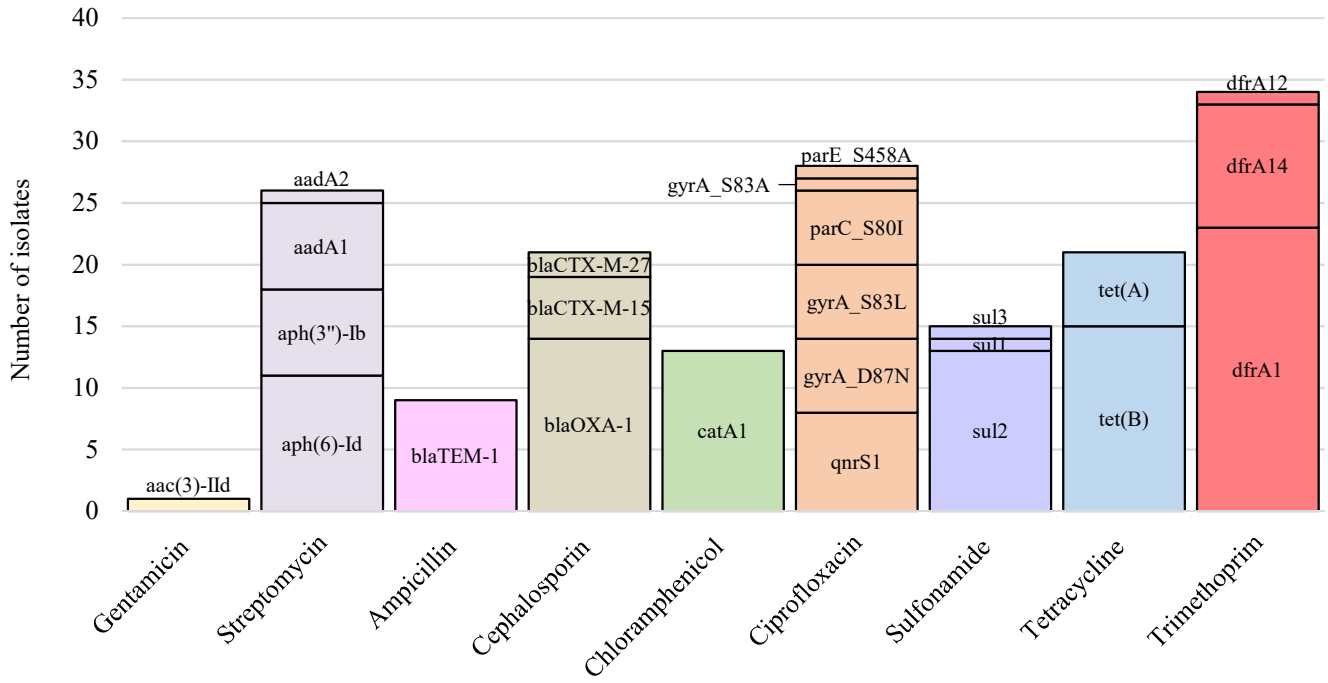

FIGURE 80. Identified resistance determinants in *Shigella flexneri* (n=27) to selected antimicrobial agents in Norway 2022.

MULTI-DRUG RESISTANCE IN SHIGELLA

TABLE 59. Number of predicted genotypic multi-drug resistance in (MDR) *Shigella* spp. isolates identified in Norway 2022, 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	39	39	25	25	1	30	38	33	39
Shigella flexneri	24	17	21	17	13	13	14	20	21
Shigella boydii	2	2	1	0	0	1	1	1	2
Shigella dysenteriae	3	2	3	1	0	3	2	1	3
Total no. of MDR isolates	**68**	**60**	**50**	**43**	**14**	**47**	**55**	**55**	**65**

[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.

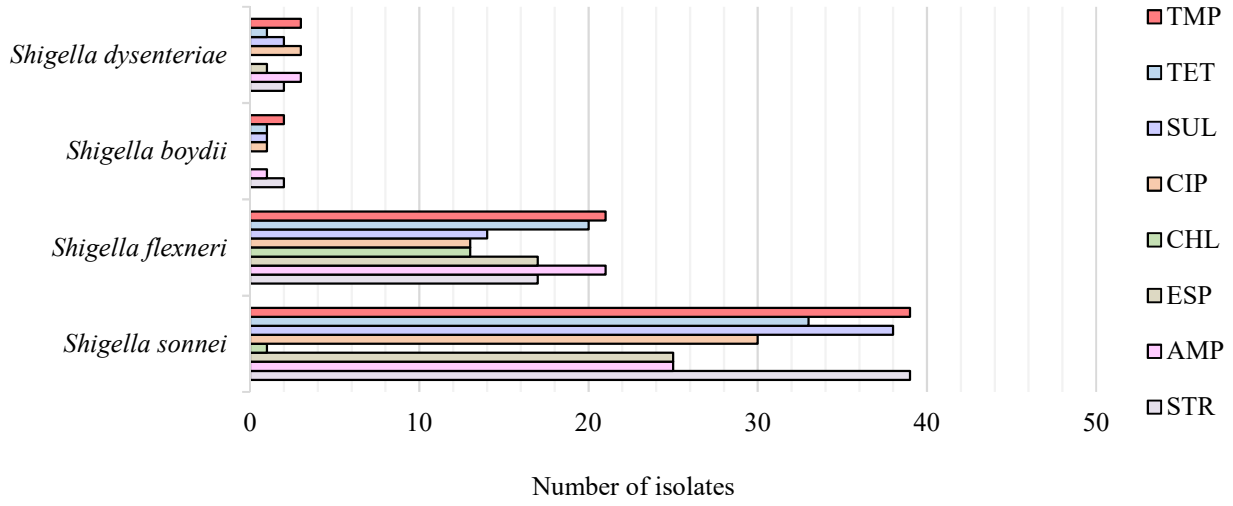

FIGURE 81. Number of predicted genotypically multi-drug resistant (MDR) *Shigella* spp. isolates (n=68) identified in Norway 2022, stratified according to species and resistance to different antibiotic categories; STR: Streptomycin, AMP; Ampicillin, ESP; Extended-Spectrum Cephalosporin, CHL; Chloramphenicol, CIP; Ciprofloxacin, SUL; Sulfonamide, TET; Tetracycline, TMP; Trimethoprim.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN SHIGELLA

TABLE 60. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Shigella spp*. (n=72) isolates identified in Norway 2022.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	72	0	25	47	0	100.0	100.0
Extended-spectrum cephalosporins[2]	72	11	32	29	0	72.5	100.0
Carbapenems	72	0	72	0	0	-	100.0
Fluoroquinolones	72	0	27	45	0	100.0	100.0
Tetracycline	72	0	17	53	2	100.0	89.5
Phenicols	72	0	58	14	0	100.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cut-off values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella spp.* (v.13.0). [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended-spectrum cephalosporins.

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 for ciprofloxacin disk diffusion, and to better align phenotypic resistance with predicted genotypic resistance. No outbreak clusters were identified in 2022.

A stable and large proportion of *S. sonnei* is recorded resistant to tetracycline (average 83%) over the last decade. In addition, since 2020 an increasing trend of resistance towards ampicillin and extended-spectrum cephalosporins is recorded. The observed increase in resistance to ciprofloxacin from around 30% in 2020 to 70% in 2022 is largely attributed to the change in the antibiotic used for screening. A total of 25 ESBL encoding strains (58%) were identified, of which 24 encoded variants of the $bla_{\text{CTX-M}}$-gene, and a single strain encoded $bla_{\text{OXA-1}}$. Phenotypically, the strain encoding $bla_{\text{OXA-1}}$ was not identified as an ESBL producer. When screening for genotypic resistance determinants for ciprofloxacin, the presence of mutations in the *gyrA*-gene as well as the presence of *qnr*-genes was confirmed. An MDR genotype was identified in 91% of the isolates, largely attributed to resistance against streptomycin, sulfonamide, and trimethoprim, but also a large proportion of strains were resistant to tetracycline, ciprofloxacin, and extended-spectrum cephalosporins.

For *S. flexneri* a stable and large proportion of isolates was recorded resistant to tetracycline (average 84%) and ampicillin (average 76%) over the last decade. In addition, an increasing trend of resistance towards extended-spectrum cephalosporins was observed. The observed increase in resistance to ciprofloxacin from around 30% in 2020 to 46% in 2022 is largely attributed to the change in the antibiotic used for screening. A total of 17 ESBL encoding strains (63%) were identified, of which three encoded the $bla_{\text{CTX-M-15}}$ gene, ten encoded $bla_{\text{OXA-1}}$, and four encoded both a variant of the $bla_{\text{CTX-M}}$ gene and $bla_{\text{OXA-1}}$. Phenotypically, strains only encoding $bla_{\text{OXA-1}}$ were not identified as ESBL producers. When screening for determinants for genotypic resistance to ciprofloxacin, mutations in the *gyrA*-gene as well as presence of *qnrS1*-genes were confirmed. An MDR genotype was identified in 89% of the isolates, largely attributed to resistance against trimethoprim, tetracycline, ampicillin, extended-spectrum cephalosporin and streptomycin.

In addition to the ESBL encoding strains identified from *S. sonnei* and S. *flexneri*, a single strain of S. *dysenteriae* (33%) also encoded the $bla_{\text{CTX-M-15}}$ gene. Overall correlation between phenotypic resistance and predicted genotypic resistance was high, although strains encoding $bla_{\text{OXA-1}}$ were not phenotypically identified as ESBL producers, as OXA-10 enzymes are weak hydrolysers of cefotaxime and ceftazidime.

HUMAN CLINICAL ISOLATES

Gunnar Skov Simonsen, Jan Egil Afset, Cecilie Torp Andersen, Dominique Caugant, Einar Heldal, Caroline V. Knudsen and Astrid L. Wester

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 61, 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 61. Number of blood culture isolates in 2022, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) 2018-2022. The table is based on data from the information systems of all laboratories in Norway (n=19).

Species	No. of isolates 2022	% of all isolates					% of all isolates excluding skin flora				
		2018	2019	2020	2021	2022	2018	2019	2020	2021	2022
Staphylococcus aureus	2,450	11.1	11.0	10.6	10.5	10.7	14.2	13.9	13.7	13.8	14.1
Coagulase negative staphylococci	4,895	19.5	18.7	20.4	21.1	21.3	-	-	-	-	-
Streptococcus pneumoniae	582	3.3	3.1	1.6	1.6	2.5	4.2	4.0	2.1	2.1	3.4
Streptococcus pyogenes	138	1.2	1.0	0.8	0.4	0.6	1.5	1.2	1.0	0.5	0.8
Streptococcus agalactiae	346	1.5	1.8	1.7	1.6	1.5	1.9	2.2	2.1	2.0	2.0
Beta-haemolytic streptococci group C and G	454	2.0	2.0	2.3	2.4	2.0	2.5	2.5	2.9	3.1	2.6
Viridans- and non-haemolytic streptococci	1,331	5.1	5.0	5.4	5.1	5.8	6.4	6.4	7.0	6.7	7.7
Enterococcus faecalis	813	3.4	3.4	3.5	3.7	3.5	4.4	4.3	4.5	4.9	4.7
Enterococcus faecium	312	1.2	1.3	1.1	1.4	1.4	1.5	1.7	1.4	1.8	1.8
Other Gram-positive aerobic and facultative anaerobic bacteria	997	3.1	3.7	3.5	4.2	4.3	2.0	2.3	2.4	2.7	2.5
Escherichia coli	4,950	25.5	25.4	24.7	23.2	21.7	32.6	32.2	32.0	30.7	28.4
Klebsiella spp.	1,789	6.8	7.4	7.5	7.7	7.8	8.7	9.4	9.6	10.1	10.3
Enterobacter spp.	399	1.9	1.7	1.7	1.9	1.7	2.4	2.1	2.2	2.4	2.3
Proteus spp.	301	1.6	1.6	1.6	1.4	1.3	2.0	2.0	2.1	1.8	1.7
Other *Enterobacterales*	553	3.4	2.2	2.3	1.9	2.4	4.3	2.7	3.0	2.5	3.2
Pseudomonas spp.	432	1.7	1.8	1.9	1.9	1.9	2.1	2.3	2.4	2.5	2.5
Other Gram-negative aerobic and facultative anaerobic bacteria	479	1.0	2.1	1.8	2.0	2.1	1.3	2.6	2.3	2.6	2.8
Bacteroides spp.	453	1.9	1.9	2.2	2.3	2.0	2.4	2.4	2.9	3.0	2.6
Other anaerobic bacteria	983	3.7	3.8	4.2	4.6	4.3	4.2	4.4	4.9	5.4	5.0
Yeasts	273	1.1	1.1	1.2	1.1	1.2	1.4	1.4	1.5	1.4	1.6
Total	**22,930**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 61 and Figure 82, aerobic and facultative Gram-positive and Gram-negative bacteria represented 53.6% and 38.9% 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 21.3%. This is practically unchanged from 21.1% in 2021. 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 39.6% 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 3.4%. The occurrence of *Streptococcus pyogenes* (n=138) has also increased from previous years, but their proportion of invasive isolates has not reached pre-panedmic levels so far. The rates for other aerobic Gram-positives have remained relatively stable over many years.

E. coli (28.4%) and other *Enterobacterales* (17.5%) accounted for the vast majority of aerobic Gram-negative isolates. The proportion of *E. coli* (28.4%) was lower than in previous years, but further surveillance is needed to confirm this trend. *Pseudomonas* spp. has remained stable at 2.5% in spite of a nosocomial outbreak in Norwegian intensive care units during late 2021 and early 2022, all figures excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 6.3% (7.6% excluding skin flora). Yeasts accounted for 1.2% (1.6% excluding skin flora). The major pathogens among anaerobes were members of *Bacteroides* spp. (2.0%/2.6%) and among yeasts *Candida albicans* (0.7%/0.9%). However, a multitude of other species were also represented.

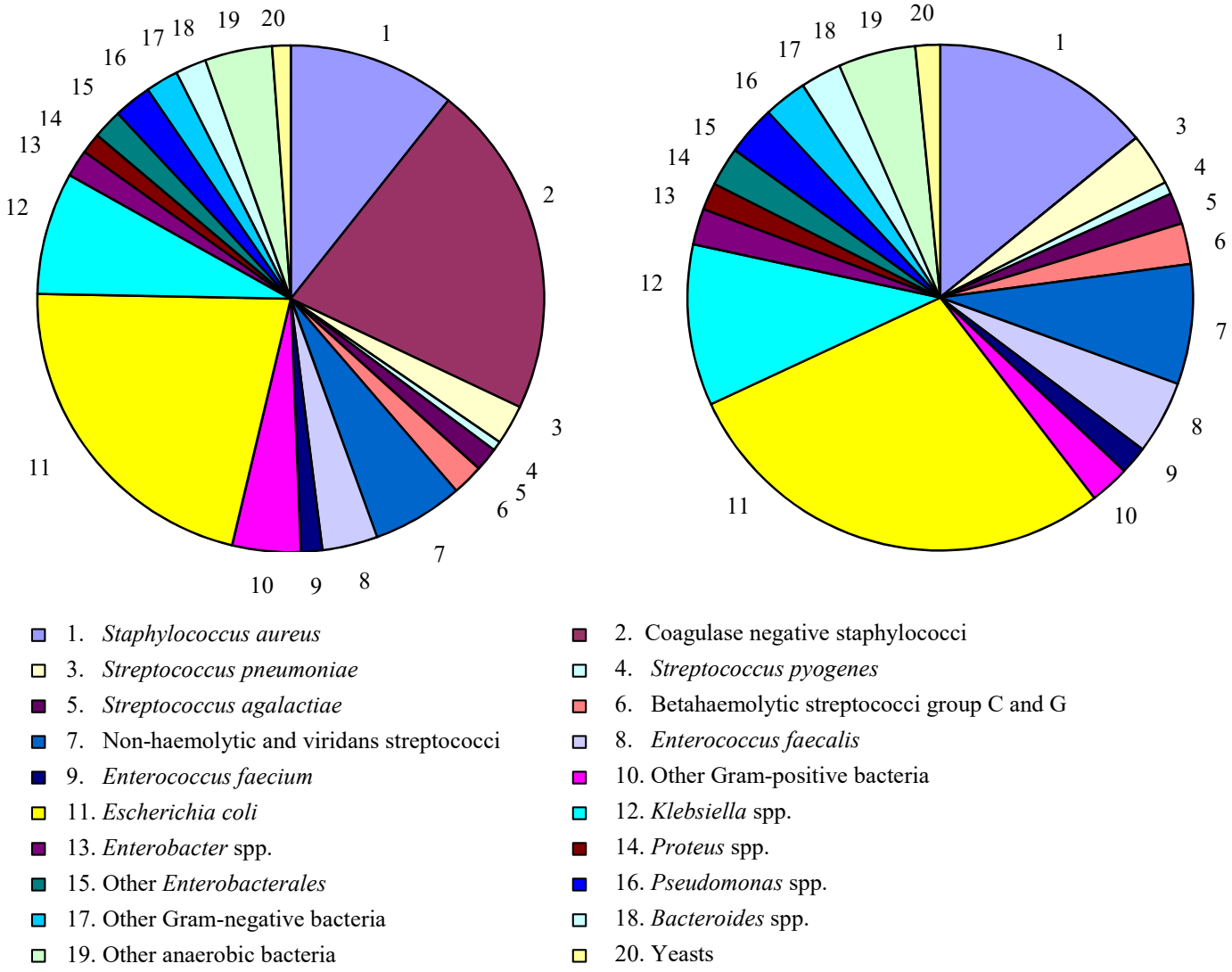

FIGURE 82. Distribution of all blood culture isolates (left, n=22,930) and blood culture isolates excluding common skin contaminants (right, n=17,354) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp. Data for 2022 were retrieved from the information systems of all Norwegian laboratories (n=19).

Escherichia coli in blood cultures

TABLE 62. *Escherichia coli* blood culture isolates in 2022 (n=2,229). 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	63.4	-	36.6
Amoxicillin-clavulanic acid*	≤ 8	> 8	74.9	-	25.1
Piperacillin-tazobactam	≤ 8	> 8	95.5	-	4.5
Cefuroxime*	≤ 0.001	> 8	0.0	90.0	10.0
Cefotaxime**	≤ 1	> 2	93.7	0.5	5.8
Ceftazidime	≤ 1	> 4	93.2	1.1	5.7
Cefepime	≤ 1	> 4	93.1	1.6	5.3
Meropenem**	≤ 2	> 8	99.9	0.1	0.0
Gentamicin***	≤ 2	> 2	94.9	-	5.1
Ciprofloxacin**	≤ 0.25	> 0.5	87.1	2.9	10.0
Tigecycline	≤ 0.5	> 0.5	99.8	-	0.2
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	79.3	0.5	20.2
ESBL	Negative	Positive	94.0	-	6.0

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 susceptible (S or I) to broad-spectrum agents such as cefotaxime (94.2%), ceftazidime (94.3%), gentamicin (94.9%), cefepime (94.7%), piperacillin-tazobactam (95.5%), tigecycline (99.8%) and meropenem (99.9%) (Table 62). There were no significant changes in resistance rates from 2021-2022.

The prevalence of resistance to gentamicin at 5.1% was a slight decline from 6.7% in 2020 and 5.6% in 2021 (Figure 83). The 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 (50/114, 43.9%) also produced ESBL enzymes. The prevalence at individual laboratories varied due to relatively small numbers. When aggregated by region there was some geographical variation (North 5.9%, West 5.6%, South-East 5.4% and Middle 3.0%).

The prevalence of resistance to ciprofloxacin was 10.0% in 2022 compared to 10.4% in 2021. 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 2006-2017 has now stabilised when using the present breakpoint. The temporal association between ciprofloxacin resistance and ciprofloxacin usage is depicted in Figure 84. 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 trimethoprim-sulfamethoxazole (21.7% in 2021, 20.2% in 2022) are slowly decreasing.

Detection of extended-spectrum beta-lactamases (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 133 isolates (6.0%) were reported as ESBL positive, which is at the same level as 5.8% in 2021 (Figure 86). 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; South-East (6.8%), Middle (5.2%), West (5.1%) and North (4.6%). Most of the ESBL isolates were phenotypically resistant to cefuroxime (n=131), cefotaxime (n=123), ceftazidime (n=109) and cefepime (n=107), whereas many were susceptible to piperacillin-tazobactam (n=108) and/or gentamicin (n=83). Seventy-nine isolates were susceptible to amoxicillin-clavulanic acid using breakpoints for non-urinary tract infections, whereas 54 were resistant. The ESBL isolates displayed high rates of co-resistance to ciprofloxacin (n=86) and trimethoprim-sulfamethoxazole (n=85). One isolate was clinically resistant to meropenem and contained both ESBL-A and NDM-5 enzymes. Another isolate was only susceptible to increased exposure to meropenem, but was negative for carbapenemase sequences. However, it demonstrated ESBL production and reduced membrane permeability. Finally, a third isolate was clinically susceptible, but had a zone diameter below the meropenem screening breakpoint. It harboured an OXA-48 like enzyme sequence.

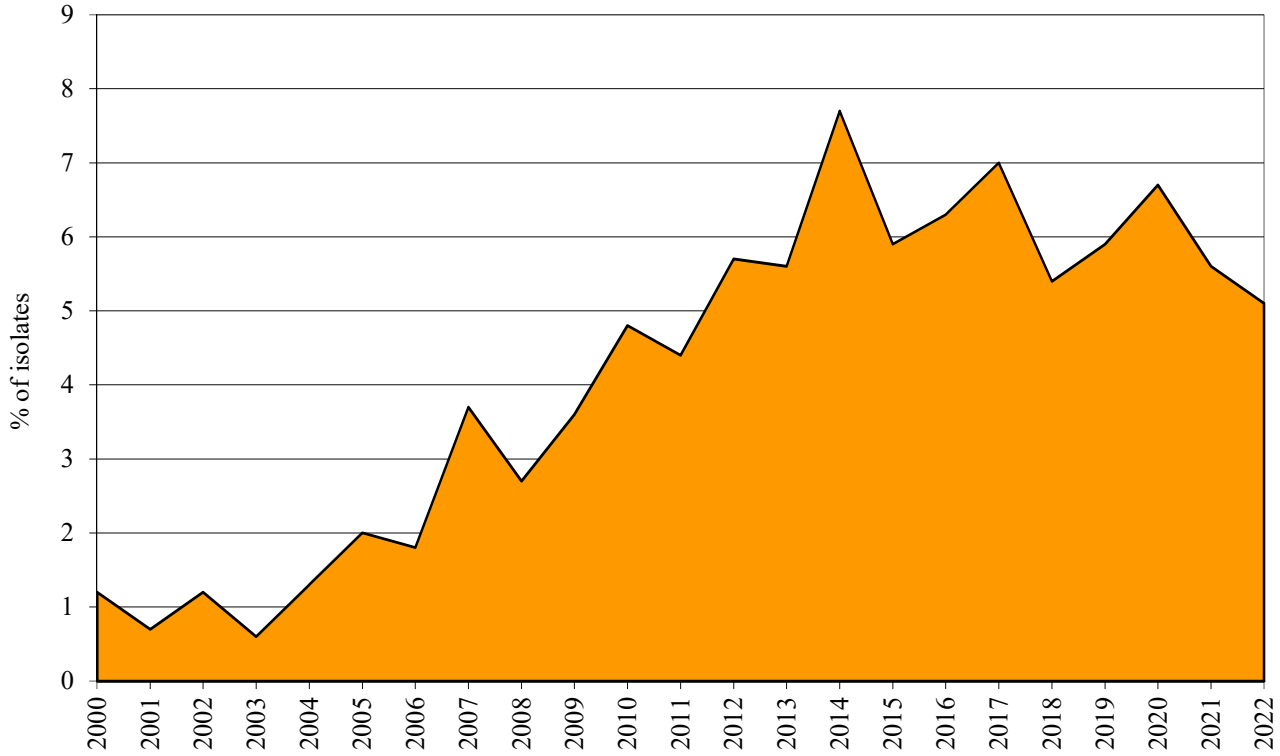

FIGURE 83. Prevalence of resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2022.

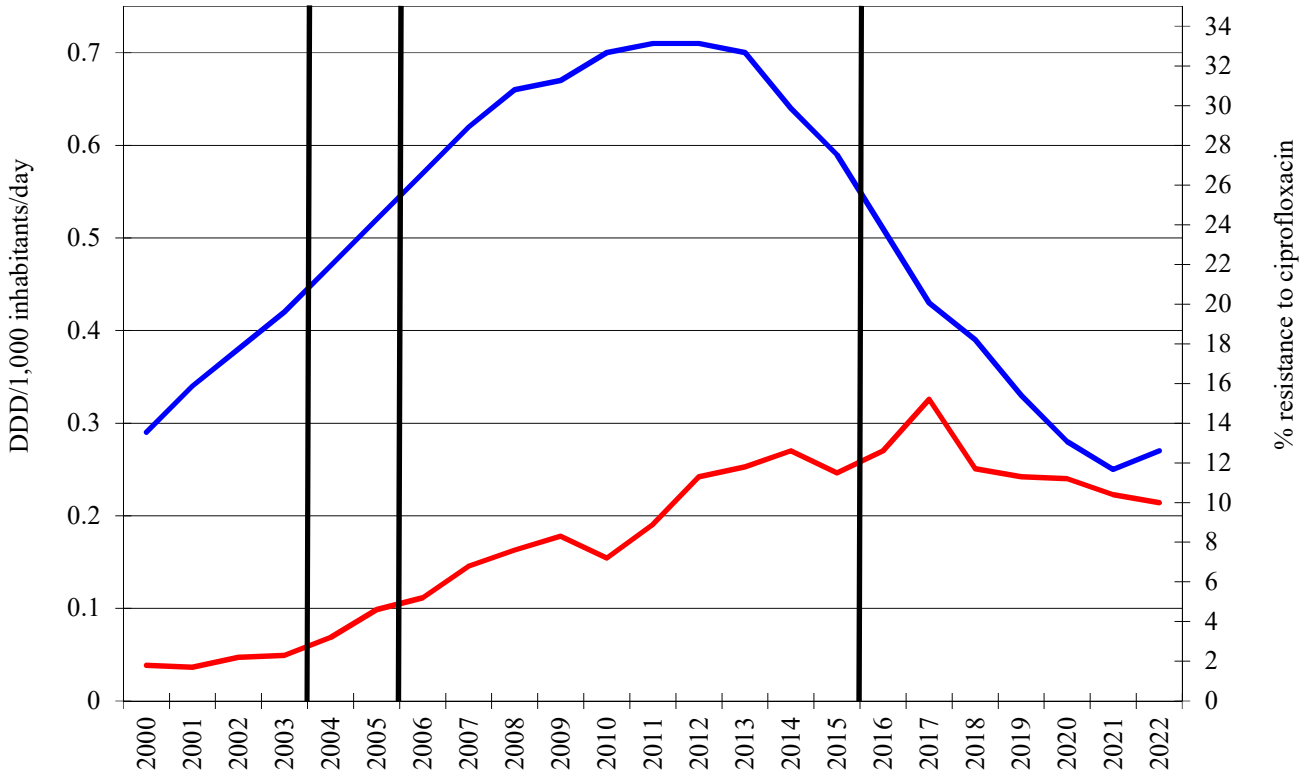

FIGURE 84. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates (red) as defined by MIC > 4 mg/L (2000-2003), MIC > 2 mg/L (2004-2005), MIC > 1 mg/L (2006-2015), and MIC > 0.5 mg/L (2016-2022). The breakpoints cannot be calibrated over the entire time period due to changes in susceptibility test methodology.

Escherichia coli in urine

TABLE 63. *Escherichia coli* urinary tract isolates in 2022 (n=1,308). 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	67.1	-	32.9
Mecillinam	≤ 8	> 8	95.6	-	4.4
Amoxicillin-clavulanic acid*	≤ 32	> 32	95.6	-	4.4
Piperacillin-tazobactam	≤ 8	> 8	97.3	-	2.7
Cefalexin	≤ 16	> 16	93.9	-	6.1
Cefotaxime**	≤ 1	> 2	96.2	0.1	3.7
Ceftazidime	≤ 1	> 4	96.6	0.5	2.9
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Gentamicin***	≤ 2	> 2	94.6	-	5.4
Ciprofloxacin**	≤ 0.25	> 0.5	90.8	1.2	8.0
Nitrofurantoin	≤ 64	> 64	99.5	-	0.5
Fosfomycin*	≤ 8	> 8	98.2	-	1.8
Trimethoprim	≤ 4	> 4	77.6	-	22.4
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	79.4	0.8	19.8
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 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 2022 is shown in Table 63 and the rates of resistance for 2000-2022 are shown in Figure 85. The footnotes denote where EUCAST/NordicASTR breakpoints specific for urinary tract infections have been applied.

The prevalence of resistance among urinary tract isolates has remained relatively stable over the last 15 years. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to around 35% (32.9% in 2022). Resistance to trimethoprim and trimethoprim-sulfamethoxazole has remained stable around 20-25% and was determined to be 22.4% and 19.8%, respectively, in 2022. The prevalence of resistance to mecillinam was 4.4% in 2022 compared to 6.2% in 2021. Susceptibility testing of mecillinam can be methodologically challenging. Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. When adjusting for changes in breakpoint (see legend Figure 84), the prevalence of resistance has remained remarkably stable around 8-9% over the last five years. In 2022, 8.0% of the isolates were resistant to ciprofloxacin in addition to 1.2% 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 2.9% 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 4.4% in 2022 compared to 8.0% in 2020 and 5.0% in 2021. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (99.5%) remained fully susceptible to nitrofurantoin. Fosfomycin has been included in NORM since 2017. The vast majority of isolates was categorised as susceptible (98.2%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Fifty isolates (3.8%) were reported as ESBL producers. This is at the same level as 3.4% in 2020 and 3.1% in 2021. As seen in Figure 86, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (6.0%). ESBL positive strains were isolated in all parts of the country. Twenty-eight isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=10) or patients in outpatient clinics (n=6), nursing homes (n=5) or other locations (n=1). The ESBL isolates were all resistant to ampicillin, and the majority were also resistant to cefalexin (48/50), cefotaxime (48/50) and ceftazidime (37/50). Almost all ESBL isolates were *in vitro* susceptible to mecillinam (47/50). Recent data suggest that this may be a viable treatment option in uncomplicated UTI provided a dosage of 400 mg x 3. Many ESBL isolates were resistant to trimethoprim (35/50), trimethoprim-sulfamethoxazole (34/50) and ciprofloxacin (27/50), but remained susceptible to nitrofurantoin (50/50), fosfomycin (48/50) and gentamicin (33/50). All isolates were clinically susceptible to meropenem, and no zone diameters below the screening breakpoint for carbapenemase producers were detected.

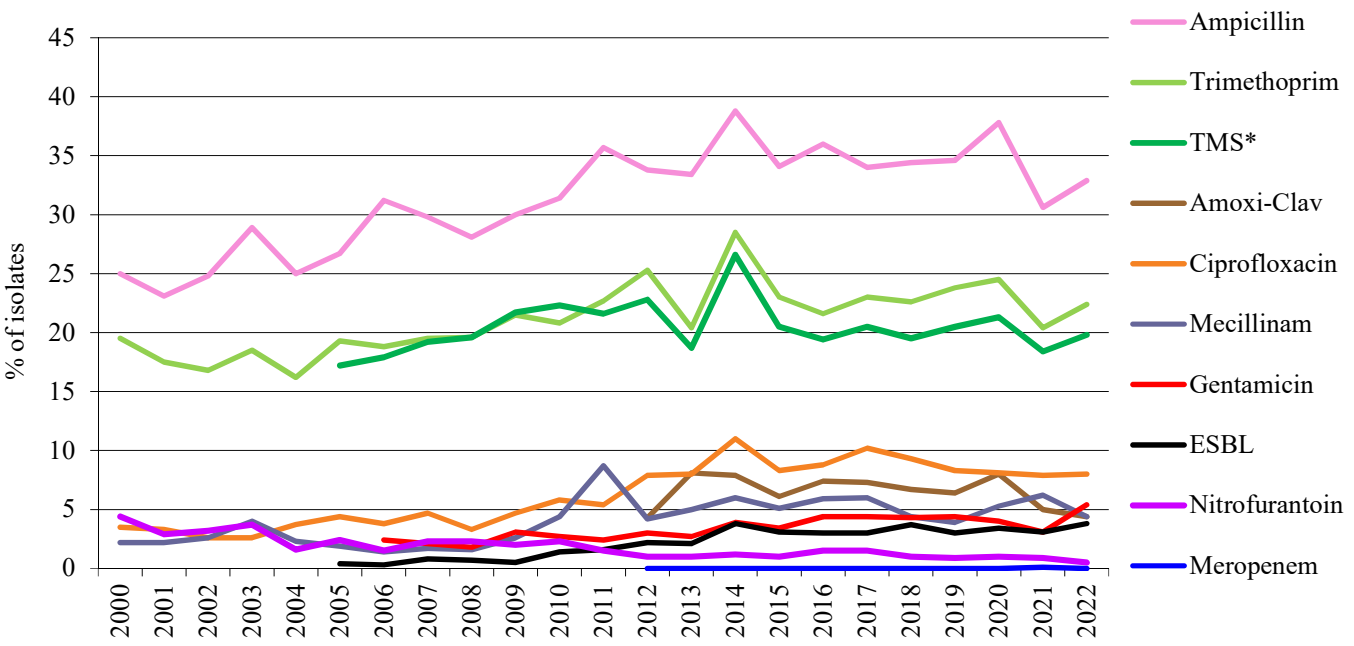

FIGURE 85. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2022. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

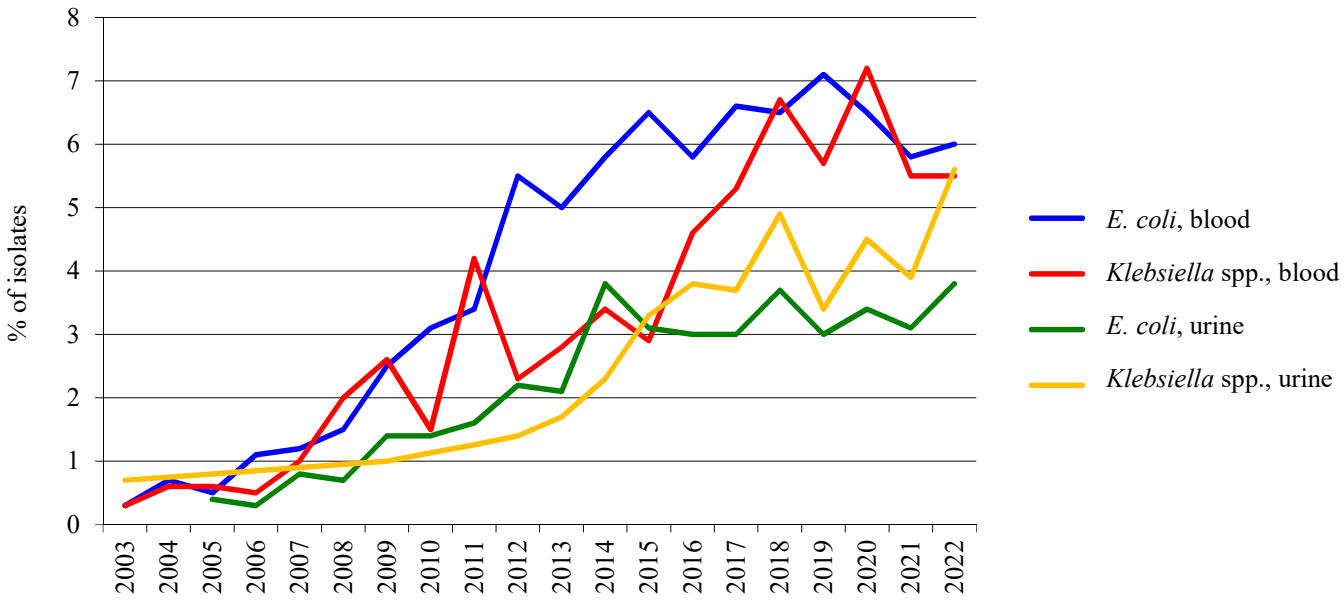

FIGURE 86. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2022.

Klebsiella spp. in blood cultures

TABLE 64. *Klebsiella* spp. blood culture isolates in 2022 (n=1,114 except for amoxicillin-clavulanic acid and cefuroxime (n=1,069) where 45 *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	86.7	-	13.3
Piperacillin-tazobactam	≤ 8	> 8	89.0	-	11.0
Cefuroxime*	≤ 0.001	> 8	0.0	88.1	11.9
Cefotaxime**	≤ 1	> 2	93.2	0.4	6.4
Ceftazidime	≤ 1	> 4	92.1	1.9	6.0
Cefepime	≤ 1	> 4	90.8	2.8	6.4
Meropenem**	≤ 2	> 8	99.6	0.2	0.2
Gentamicin***	≤ 2	> 2	95.5	-	4.5
Ciprofloxacin**	≤ 0.25	> 0.5	87.5	4.2	8.3
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	88.0	0.2	11.8
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 65. *Klebsiella pneumoniae* blood culture isolates in 2022 (n=798). 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	86.3	-	13.7
Piperacillin-tazobactam	≤ 8	> 8	89.3	-	10.7
Cefuroxime*	≤ 0.001	> 8	0.0	88.1	11.9
Cefotaxime**	≤ 1	> 2	93.3	0.3	6.4
Ceftazidime	≤ 1	> 4	91.9	1.6	6.5
Cefepime	≤ 1	> 4	90.3	2.9	6.8
Meropenem**	≤ 2	> 8	99.4	0.3	0.3
Gentamicin***	≤ 2	> 2	94.9	-	5.1
Ciprofloxacin**	≤ 0.25	> 0.5	85.3	4.8	9.9
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	85.5	0.3	14.2
ESBL	Negative	Positive	93.2	-	6.8

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 66. *Klebsiella oxytoca* blood culture isolates in 2022 (n=254). 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	87.8	-	12.2
Piperacillin-tazobactam	≤ 8	> 8	89.4	-	10.6
Cefuroxime*	≤ 0.001	> 8	0.0	87.8	12.2
Cefotaxime**	≤ 1	> 2	94.5	1.2	4.3
Ceftazidime	≤ 1	> 4	95.7	2.0	2.4
Cefepime	≤ 1	> 4	91.3	3.1	5.5
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Gentamicin***	≤ 2	> 2	96.9	-	3.1
Ciprofloxacin**	≤ 0.25	> 0.5	96.0	1.6	2.4
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	95.3	0.0	4.7
ESBL	Negative	Positive	97.6	-	2.4

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 aerogenes* blood culture isolates in 2022 (n=45). 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	80.0	-	20.0
Cefotaxime*	≤ 1	> 2	82.2	0.0	17.8
Ceftazidime	≤ 1	> 4	75.5	6.7	17.8
Cefepime	≤ 1	> 4	95.6	0.0	4.4
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.25	> 0.5	80.0	8.9	11.1
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	91.1	0.0	8.9
ESBL	Negative	Positive	100.0	-	0.0

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: 798 (71.7%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola* and *K. africana*); 254 (22.8%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis* and *K. spallanzanii*): 45 (4.0%) *K. aerogens*; and 17 unspecified *Klebsiella* isolates (1.5%), giving a total of 1,114 *Klebsiella* spp. isolates (Tables 64-67).

The majority of *Klebsiella* spp. isolates were susceptible to aminoglycosides, and the prevalence of gentamicin resistance remained stable at 4.5% in 2022 compared to 5.2% in 2020 and 4.2% in 2021. Gentamicin resistance was more common in *K. pneumoniae* (5.1%) than in *K. oxytoca* (3.1%), and was not seen at all in *K. aerogenes*. 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 8.9% in 2021 and 8.3% in 2022. The results should be interpreted with caution due to the repeated changes in breakpoints and test methodology over the last decade. Susceptibility testing for quinolones may be technically challenging, and further surveillance is needed to determine the long-term trend for ciprofloxacin resistance in *Klebsiella* spp. Resistance to ciprofloxacin is much more common in *K. pneumoniae* (9.9%) and *K. aerogenes* (11.1%) than in *K. oxytoca* (2.4%). Resistance to trimethoprim-sulfamethoxazole remained unchanged at 11.8% in 2022 compared to 11.9% in 2021. The prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (4.7%) and *K. aerogenes* (8.9%) than in *K. pneumoniae* (14.2%).

The comparison of resistance to beta-lactam antibiotics between *Klebsiella* species is complicated by the diagnostic challenges of the chromosomal K1 beta-lactamase in *K. oxytoca* and chromosomal AmpC in *K. aerogenes*. Most *Klebsiella* spp. isolates were susceptible (S+I) to cefotaxime (93.6%), ceftazidime (94.0%), cefepime (93.6%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (89.0%), see Figure 87. The prevalence of resistance to 3rd generation cephalosporins has remained essentially unchanged 2020-2022. The increased resistance rate to piperacillin-tazobactam over the last years (4.4% in 2019, 11.2% in 2020) was mainly due to a reduction of the breakpoint for resistance from R > 16 mg/L to R > 8 mg/L. The rate did not change significantly in the last year (11.9% in 2021 and 11.0% in 2022).

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 2021 (5.5% in *Klebsiella* spp.; 6.7% in *K. pneumoniae*) to 2022 (5.5% in *Klebsiella* spp.; 6.8% in *K. pneumoniae*), see Figure 86. The 61 ESBL isolates originated from 15 different laboratories and were identified as *K. pneumoniae* (n=54, 89%), *K. oxytoca* (n=6, 10%) and *Klebsiella* spp. (n=1). ESBL isolates were generally resistant to cefuroxime (59/61), cefotaxime (57/61), cefepime (54/61) and ceftazidime (51/61), and co-resistance was frequently seen for trimethoprim-sulfamethoxazole (56/61), ciprofloxacin (46/61) and gentamicin (38/61). Some isolates remained susceptible to piperacillin-tazobactam (24/61). Four *K. pneumoniae* isolates (0.4%) were verified as carbapenemase producers (CPE) (3 OXA48-like and 1 NDM). Two of them were clinically resistant to meropenem, whereas the remaining two were susceptible to increased (I) or standard (S) exposure, respectively. An additional isolate was only susceptible to increased exposure (I), but did not contain any known carbapenemase genes. The four CPE isolates originated from different hospitals.

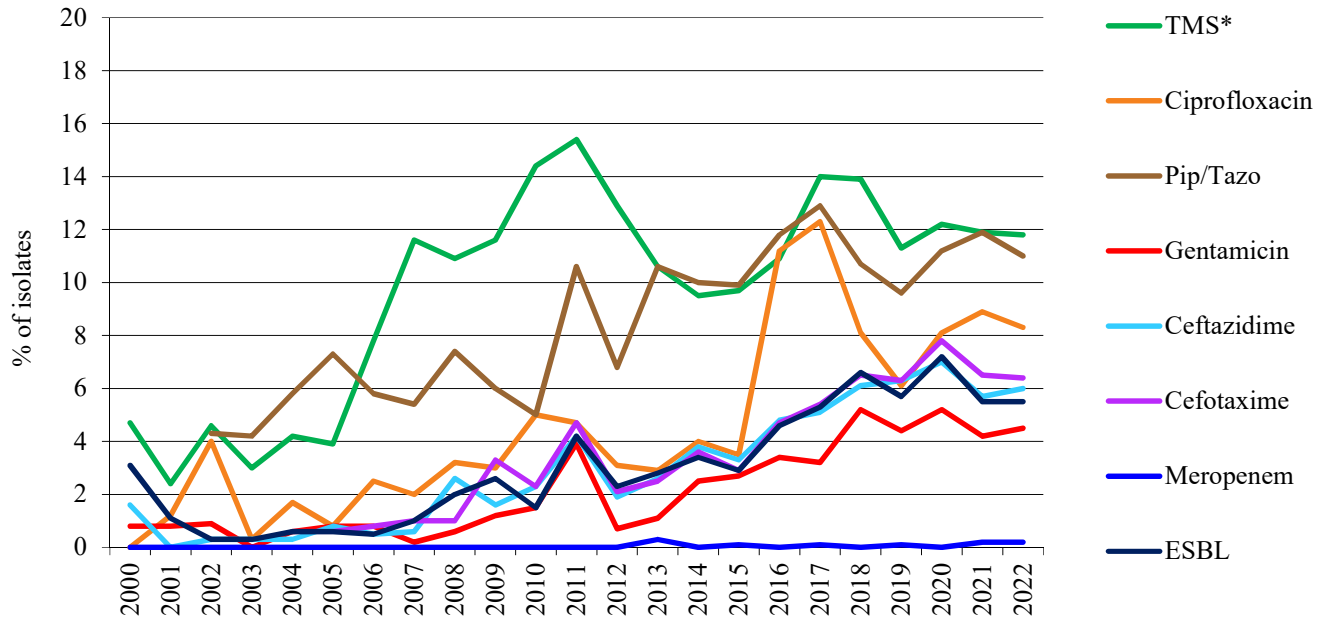

FIGURE 87. Prevalence of resistance to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2022. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 68. *Klebsiella* spp. urinary tract isolates in 2022 (n=1,069 except for amoxicillin-clavulanic acid and cefalexin (n=1,016) where 53 *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	91.1	-	8.9
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.3	-	6.7
Piperacillin-tazobactam	≤ 8	> 8	90.4	-	9.6
Cefalexin	≤ 16	> 16	92.2	-	7.8
Cefotaxime**	≤ 1	> 2	92.7	0.7	6.6
Ceftazidime	≤ 1	> 4	93.9	0.8	5.3
Cefepime	≤ 1	> 4	92.7	1.8	5.5
Meropenem**	≤ 2	> 8	99.9	0.0	0.1
Gentamicin***	≤ 2	> 2	95.7	-	4.3
Ciprofloxacin**	≤ 0.25	> 0.5	88.8	3.8	7.4
Trimethoprim	≤ 4	> 4	82.4	-	17.6
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	84.9	1.4	13.7
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 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 69. *Klebsiella pneumoniae* urinary tract isolates in 2022 (n=722). 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	92.5	-	7.5
Amoxicillin-clavulanic acid*	≤ 32	> 32	94.5	-	5.5
Piperacillin-tazobactam	≤ 8	> 8	91.1	-	8.9
Cefalexin	≤ 16	> 16	93.5	-	6.5
Cefotaxime**	≤ 1	> 2	93.5	0.7	5.8
Ceftazidime	≤ 1	> 4	94.2	1.0	4.8
Cefepime	≤ 1	> 4	92.8	1.8	5.4
Meropenem**	≤ 2	> 8	99.9	0.0	0.1
Gentamicin***	≤ 2	> 2	95.3	-	4.7
Ciprofloxacin**	≤ 0.25	> 0.5	86.6	4.3	9.1
Trimethoprim	≤ 4	> 4	79.1	-	20.9
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	82.4	1.8	15.8
ESBL	Negative	Positive	94.0	-	6.0

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 70. *Klebsiella oxytoca* urinary tract isolates in 2022 (n=211). 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	88.6	-	11.4
Amoxicillin-clavulanic acid*	≤ 32	> 32	90.0	-	10.0
Piperacillin-tazobactam	≤ 8	> 8	88.2	-	11.8
Cefalexin	≤ 16	> 16	89.6	-	10.4
Cefotaxime**	≤ 1	> 2	92.9	0.5	6.6
Ceftazidime	≤ 1	> 4	95.3	0.0	4.7
Cefepime	≤ 1	> 4	91.4	2.4	6.2
Meropenem**	≤ 2	> 8	100.0	0.0	0.0
Gentamicin***	≤ 2	> 2	95.3	-	4.7
Ciprofloxacin**	≤ 0.25	> 0.5	95.3	1.4	3.3
Trimethoprim	≤ 4	> 4	90.5	-	9.5
Trimethoprim-sulfamethoxazole****	≤ 2	> 4	91.0	0.0	9.0
ESBL	Negative	Positive	94.3	-	5.7

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 71. *Klebsiella aerogenes* urinary tract isolates in 2022 (n=53). 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	81.1	-	18.9
Piperacillin-tazobactam	≤ 8	> 8	86.8	-	13.2
Cefotaxime*	≤ 1	> 2	83.0	0.0	17.0
Ceftazidime	≤ 1	> 4	84.9	1.9	13.2
Cefepime	≤ 1	> 4	100.0	0.0	0.0
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.25	> 0.5	96.2	1.9	1.9
Trimethoprim	≤ 4	> 4	94.3	-	5.7
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	96.2	0.0	3.8
ESBL	Negative	Positive	100.0	-	0.0

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 2012-2021. 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 2022 were speciated as follows: 722 (67.5%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola* and *K. africana*); 211 (19.7%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis* and *K. spallanzanii*); 53 (5.0%) *K. aerogens*; and 83 isolates (7.8%) not identified to the species level, giving a total of 1,069 *Klebsiella* spp. isolates (Tables 68-71).

The prevalence of resistance to urinary tract antibiotics was slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Table 63). The majority of isolates remained susceptible to gentamicin at 95.7% compared to 96.2% in 2020 and 98.0% in 2021. Among urinary tract *E. coli*, 94.6% were gentamicin susceptible in 2022. The rates of resistance to ciprofloxacin in *Klebsiella* spp. increased from 4.4% in 2021 to 7.4% in 2022. The comparable rate for urinary tract *E. coli* in 2022 was 8.0%. Susceptibility to trimethoprim (85.5% in 2021; 82.4% in 2022) and trimethoprim-sulfamethoxazole (89.1% in 2021; 84.9% in 2022) was higher than in *E. coli* (77.6% and 79.4% in 2022, 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. Sixty isolates (5.6%) were reported as ESBL positive, of which 43 were *K. pneumoniae*, 12 were *K. oxytoca*, and five were unspeciated. They were retrieved from 17 different laboratories and originated from hospital inpatients (n=22), outpatient clinics (n=8), general practices (n=25), nursing homes (n=4) and an unspecified location (n=1). The 5.6% ESBL rate (6.0% in *K. pneumoniae*) was an increase from 2021 (3.9% for all *Klebsiella*, 4.5% in *K. pneumoniae*). The 60 ESBL isolates were often resistant to trimethoprim (n=55), trimethoprim-sulfamethoxazole (n=55), ciprofloxacin (n=37) and gentamicin (n=26), but many remained susceptible to mecillinam (n=53) and/or piperacillin-tazobactam (n=31). *K. aerogenes* isolates were generally susceptible to most non-beta-lactam agents. A single meropenem resistant *K. pneumoniae* isolate contained an OXA-48-like determinant, whereas additional isolates with zone diameters below the screening breakpoint of 28 mm did not display carbapenemase production.

Carbapenemase-producing Gram-negative bacteria in Norway 2022

Carbapenemases are epidemiologically the most important mechanism of carbapenem resistance in Gram-negative bacteria, and a major contributor to the global burden of antimicrobial resistance (1,2). A key factor in the spread of carbapenemase genes is their association with mobile genetic elements facilitating dissemination. Carbapenemase-producing Gram-negative bacteria are frequently multi-drug resistant, leading to difficult-to-treat infections. Infection and colonisation with carbapenemase-producing Gram-negative bacteria are 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 report a summary of the findings for 2022.

Enterobacterales

In 2022, 152 cases of carbapenemase-producing *Enterobacterales* (CPE) were identified (Figure 88), representing a >150% increase compared to 2021 (n=60). Sixty-one percent of the cases were linked to import, 8% likely associated with domestic acquisition, and for 31% the status related to import was unclear. Thirty-nine percent of the import cases were linked to import from Ukraine which constituted 24% of all cases in 2022. Each of the other countries represented ≤7% of the cases associated with import.

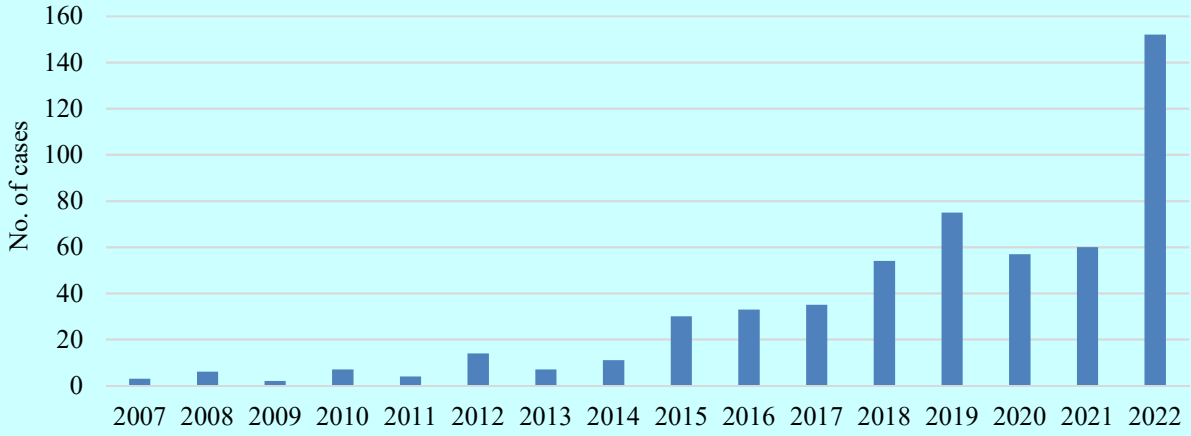

FIGURE 88. Number of cases with CPE in Norway 2007-2022

A total of 196 CPE isolates were identified from 152 patients, representing an increase of 216% compared to 2021 (n=62). In 26 patients, multiple CPE isolates (n=2-6) were identified belonging to different species, same species but with different carbapenemase genes, or same species and same carbapenemase gene but a different sequence type (ST). Most cases (60%) were identified through screening and only 3.1% in blood culture. As in previous years, the CPE-population was dominated by *E. coli* and *Klebsiella pneumoniae*, which increased by 176% and 230%, respectively, from 2021 (Figure 89). The number of non-*E. coli*/*K. pneumoniae* carbapenemase-producing isolates also increased in 2022 with 27 isolates compared to six in 2021.

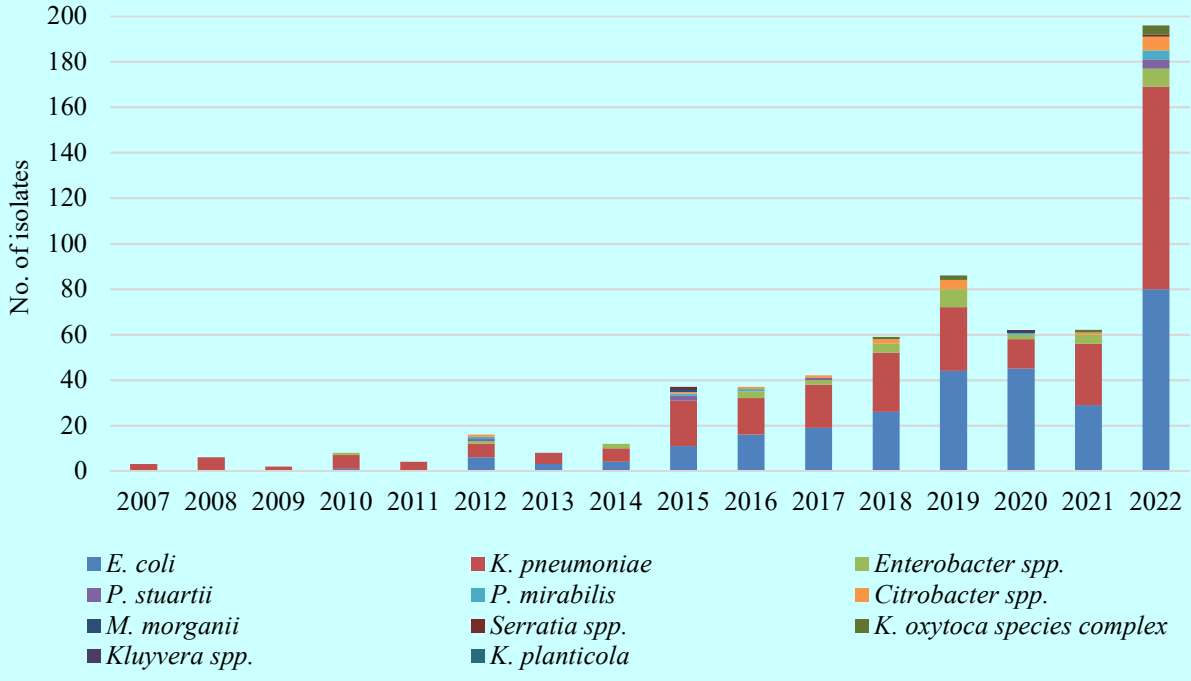

FIGURE 89. Number of CPE isolates according to species in Norway 2007-2022.

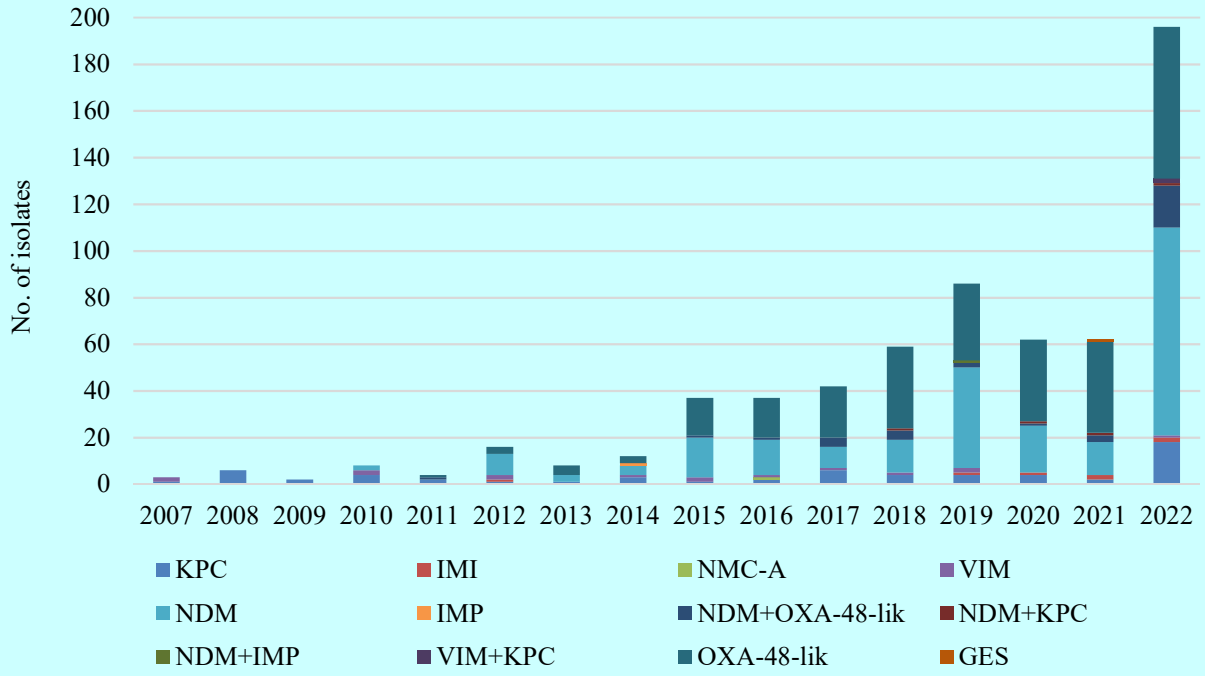

FIGURE 90. Distribution of carbapenemase variants among CPE isolates in Norway 2007-2022.

Whole genome sequencing showed a large diversity in terms of STs and carbapenemase variants. More than 25 different STs were identified among the 80 *E. coli* isolates (Figure 91). *E. coli* ST38-OXA-244 (n=9) was the most common combination followed by ST405-NDM-5 (n=8) and ST69-OXA-244 (n=5). The most common carbapenemase variants NDM-5 (n=36) and OXA-244 (n=23) were identified in 14 and eight different STs, respectively. Several of the most prevalent STs including ST38, ST405, ST167, ST69 are known globally disseminated multi-drug resistant high-risk clones (3).

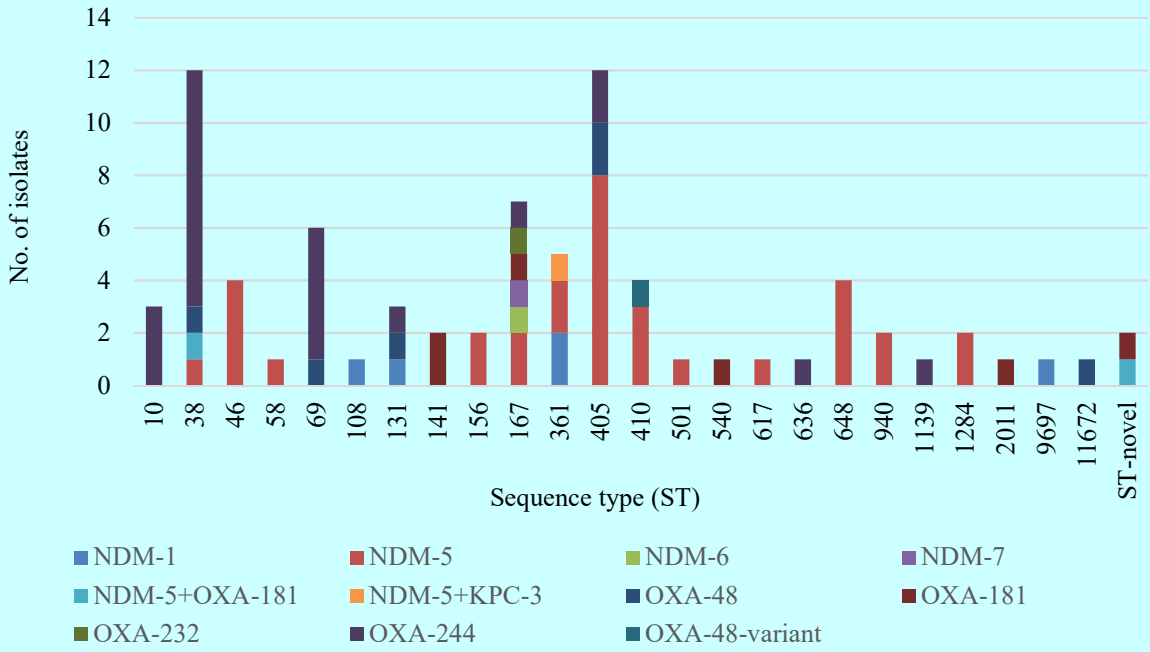

FIGURE 91. Carbapenemase variant according to ST among carbapenemase-producing *E. coli* identified in 2022.

Phylogenetic analysis based on core-genome multilocus sequence typing (cgMLST) identified eight clusters of closely related isolates (Figure 92). Seven clusters comprised two isolates, while the cluster with four isolates likely represents two separate clusters, as the isolates harboured different NDM variants (NDM-1 or NDM-5). Six of the clusters were linked to import including four clusters associated to import from Ukraine and identified at different laboratories in Norway. This indicates that transmission between patients had occurred before their transfer to Norway. One case of secondary transmission after import from Ukraine was suspected for one of the *E. coli* ST46-NDM-5 clusters. No connection to import was reported for the *E. coli* ST141-OXA-181 cluster and epidemiological investigations showed no clear link between the patients within this cluster. Although, none of the nine *E. coli* ST38-OXA-244 isolates identified in 2022 were closely related, the large proportion of isolates associated with no import or missing import information is worrying.

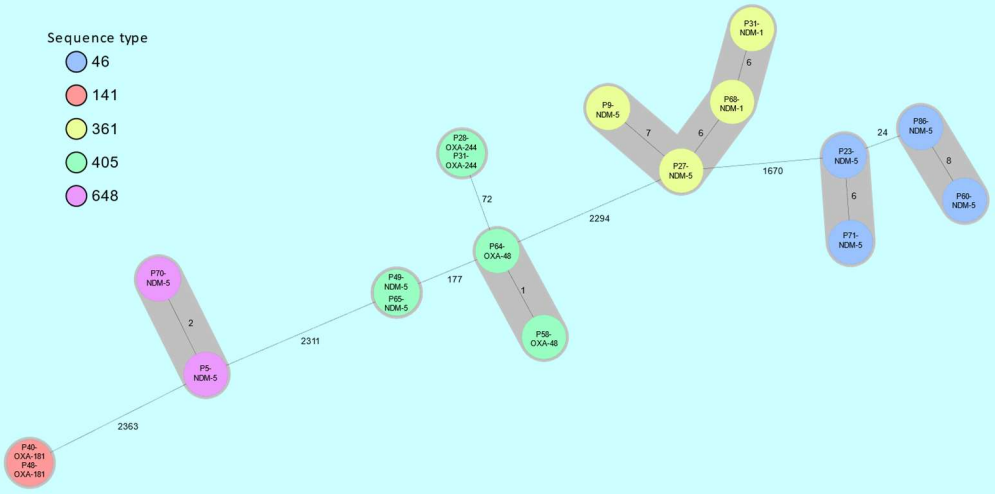

FIGURE 92. Minimum spanning tree based on the core genome allelic profile of closely related (≤10 allelic differences) carbapenemase-producing *E. coli* identified in 2022. The analysis is based on 2,513 core genome alleles using SeqSphere+ and *E. coli* K12 as a reference. The isolates are represented by circles and coloured according to the ST. Specific carbapenemase variant for each isolate and number of allelic differences between the isolates are indicated. Isolates within the same circle represent zero allelic differences.

The carbapenemase-producing *K. pneumoniae* isolates (n=89) represented 23 known STs (Figure 93). Two isolates belonged to undefined STs. Four globally disseminated high-risk clones (4,5), ST147 (n=28), ST395 (n=15), ST39 (n=9) and ST307 (n=9) dominated and represented 69% of *K. pneumoniae* isolates. NDM-1 or NDM-1+OXA-48 were dominant among ST147 isolates (24/28 isolates), while six of the nine ST39 isolates harboured KPC-2. The diversity of carbapenemase variants was largest among ST395 and ST307. Two isolates with NDM-1 or OXA-48 were genetically defined as hypervirulent and belonged to the known global hypervirulent ST23 clone (4).

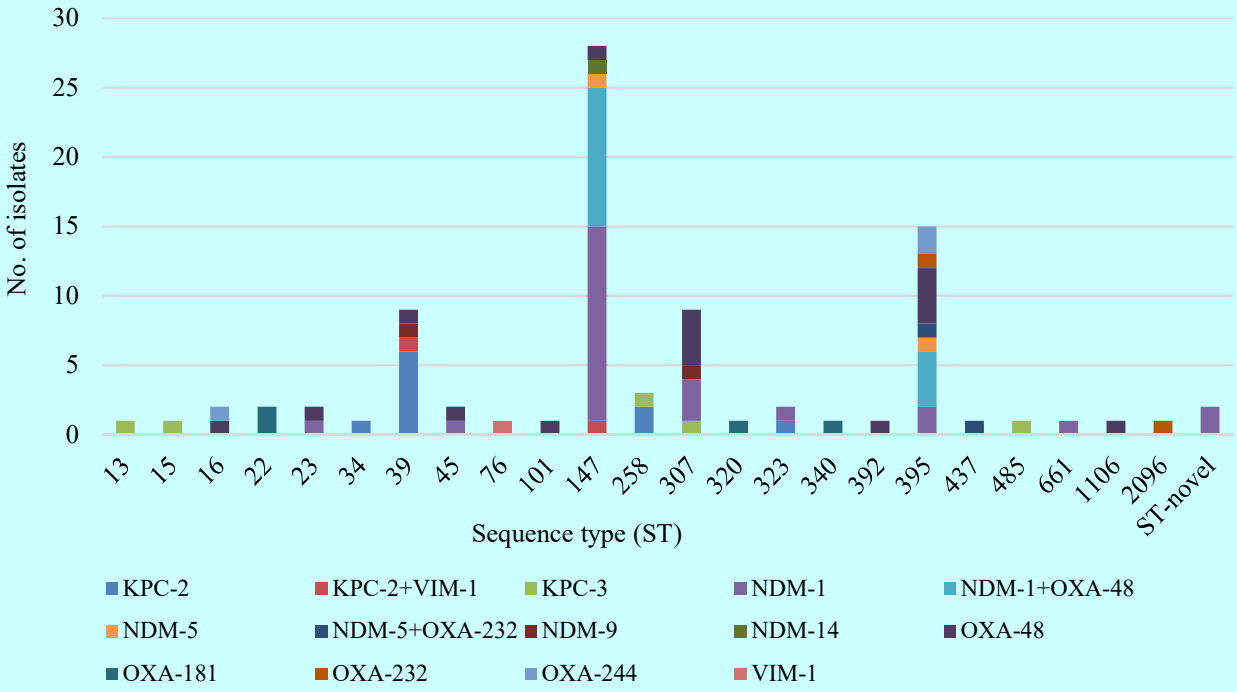

FIGURE 93. Carbapenemase variant according to ST among carbapenemase-producing *K. pneumoniae* identified in 2022.

Phylogenetic analysis of the carbapenemase-producing *K. pneumoniae* isolates revealed 16 clusters of two to 12 closely related isolates (Figure 94). Ten clusters comprised exclusively isolates with a link to import of which nine clusters included isolates which were connected to import from Ukraine. In several of these clusters the isolates were identified at different laboratories and over a long time-period, indicating transmission before import to Norway. All isolates in the largest ST147 cluster, harbouring NDM-1+OXA-48, NDM-1 or OXA-48, were associated with import from Ukraine and identified at eight laboratories in Norway. ST147 is a known global *K. pneumoniae* high-risk clone associated with multi-drug resistance (5).

Epidemiological investigations confirmed two cases of secondary transmission within Norway after import from Ukraine and Thailand. This included transmission of ST147-NDM-1 and a novel ST variant also with NDM-1. In both cases, only one secondary case was identified. Transmission was suspected after import of ST395-NDM-1+OXA-48, but not confirmed epidemiologically. In addition, two isolates of ST22-OXA-181 linked to an outbreak at a Norwegian hospital were identified.

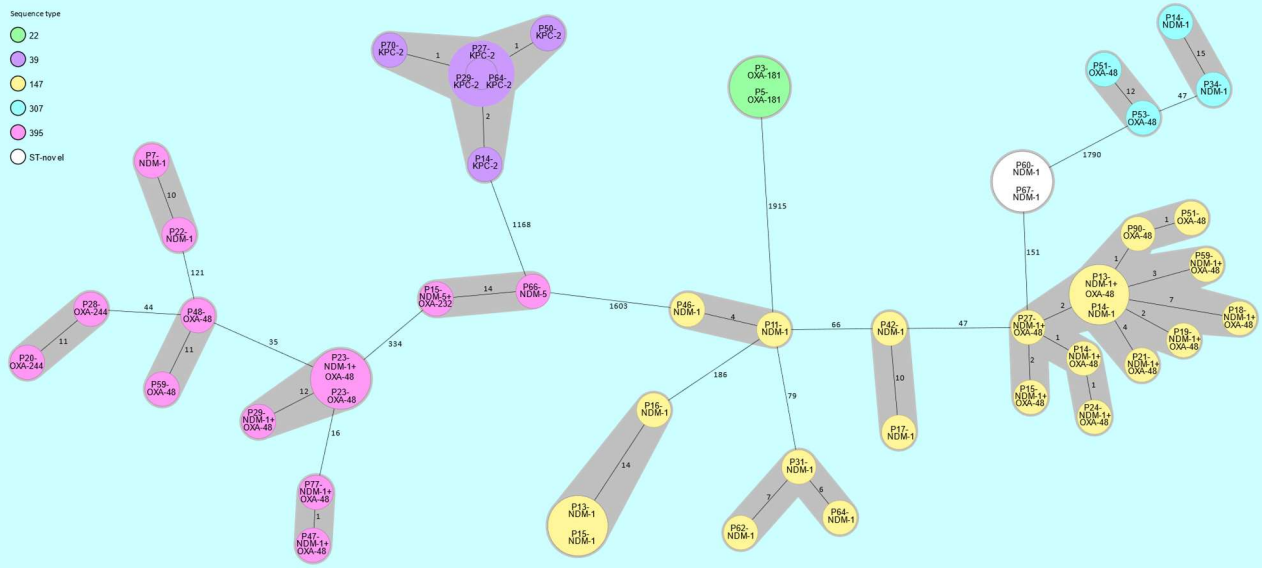

FIGURE 94. Minimum spanning tree based on the core genome allelic profile of closely related (≤15 allelic differences) carbapenemase-producing *K. pneumoniae* identified in 2022. The analysis is based on 2,358 core genome alleles using SeqSphere+ and *K. pneumoniae* NTUH-K2044 as a reference. The isolates are represented by circles and coloured according to the ST. Specific carbapenemase variant for each isolate and number of allelic differences between the isolates are indicated. Isolates within the same circle represent zero allelic differences.

Twenty-seven carbapenemase-producing non-*E. coli*/*K. pneumoniae* isolates were identified in 2022 compared to six in 2021 (Table 72).

TABLE 72. Sequence types (STs) and carbapenemase variants identified among *Enterobacter* spp., *Klebsiella oxytoca* species complex, *Citrobacter* spp., *Proteus mirabilis*, *Providencia stuartii* and *Serratia* spp. in 2022.

Species	ST-carbapenemase variant combination
E. hormaechei (*n*=4)	ST231-NDM-1 (*n*=2); ST114-NDM-1 (*n*=1); ST121-NDM-7 (*n*=1)
E. cloacae (*n*=2)	ST1-NDM-1 (*n*=1); ST-novel-IMI-novel
E. asburiae (*n*=1)	ST484-NDM-1 (*n*=1)
E. mori (*n*=1)	ST-novel-IMI-6 (*n*=1)
K. oxytoca (*n*=2)	ST2-NDM-1 (*n*=1); ST19-NDM-1 (*n*=1)
K. michiganensis (*n*=2)	ST83-KPC-2 (*n*=1); ST376-OXA-181 (*n*=1)
C. freundii (*n*=3)	ST18-KPC-2 (*n*=1); ST18-OXA-232 (*n*=1), ST114-NDM-1 (*n*=1)
C. amalonaticus (*n*=3)	ST565-KPC-3 (*n*=1); ST-novel-NDM-1 (*n*=2)
P. mirabilis (*n*=4)[1]	NDM-1 (*n*=4)
P. stuartii (*n*=4)[1]	NDM-1 (*n*=2); NDM-5 (*n*=2)
Serratia spp. (*n*=1)[1]	OXA-48

[1] MLST scheme not established.

Phylogenetic analysis of the *P. stuartii* isolates using cgMLST showed that the isolates with NDM-1 and NDM-5 belonged to two separate clusters. All four isolates were associated with import from Ukraine. No close phylogenetic relationship was found between the other isolates.

The antimicrobial susceptibility profile of all CPE isolates was investigated using broth microdilution, with the exception of cefiderocol where disk diffusion was used. The susceptibility data are shown in Figure 95. The increased proportion of resistant isolates compared to 2021 is mainly due to the increase in NDM-producing *Enterobacterales* since none of the new beta-lactamase inhibitors, such as avibactam, vaborbactam and relebactam, have inhibitory activity against metallo-beta-lactamases (MBLs) including NDM (6).

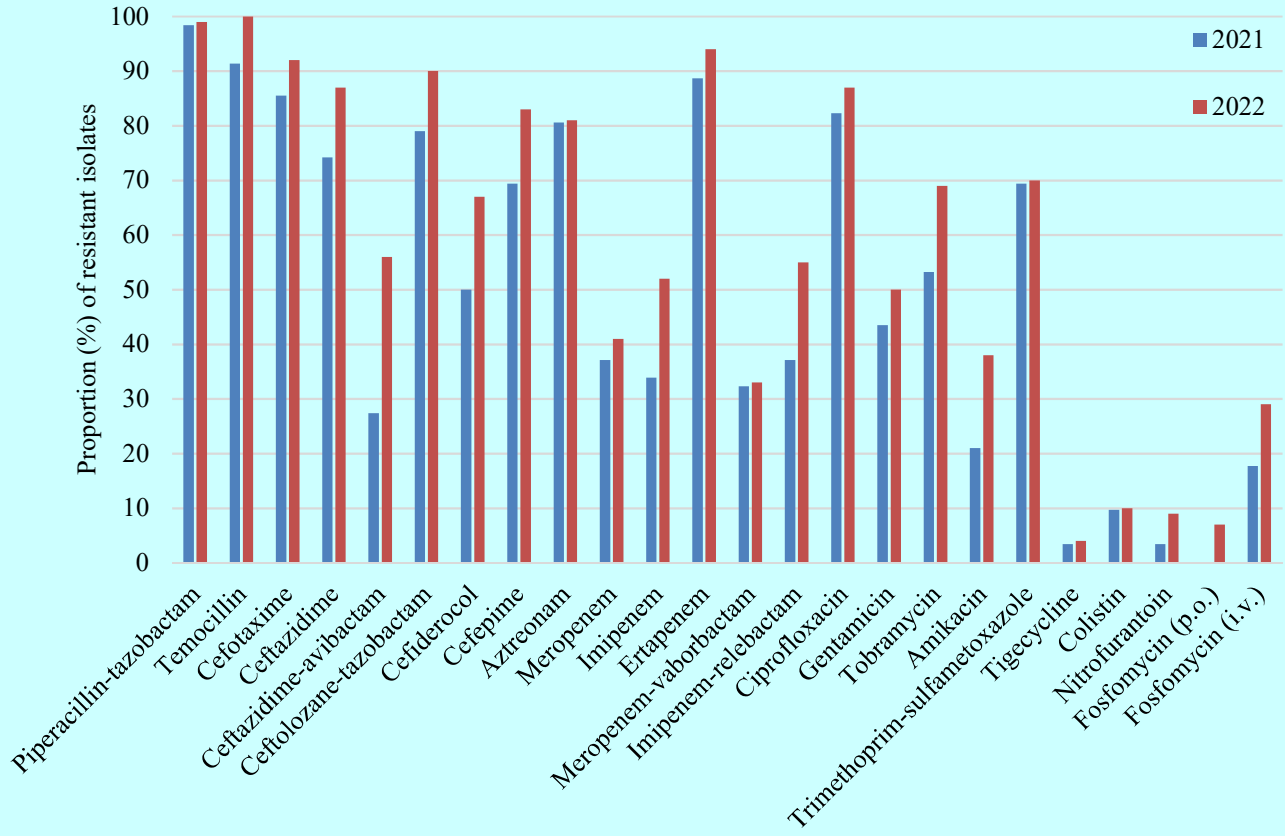

FIGURE 95. Proportion (%) of resistant isolates among CPE in 2021 and 2022. Categorisation was done according to the NordicAST breakpoint table v.13. Piperacillin-tazobactam MIC (16 mg/L) and ciprofloxacin MIC (0.5 mg/L) in area of technical uncertainty (ATU) was interpreted as resistant. Temocillin relates to *E. coli*, *Klebsiella* spp. (except *K. aerogenes*) and *P. mirabilis*. Cefiderocol data are based on disk diffusion and zone diameters in the ATU (18-22 mm) were interpreted as resistant. Tigecycline, nitrofurantoin and fosfomycin (p.o.) relate only to *E. coli.* Fosfomycin results must be interpreted with caution. The reference method for fosfomycin MIC determination is agar dilution and some studies have shown lack of correlation between broth microdilution and agar dilution, in particular for *K. pneumoniae* (7,8).

***Pseudomonas* spp.**

Carbapenemase-producing *Pseudomonas* spp. was identified in 18 patients in 2022 (Figure 96). Six were identified in screening samples and 12 in clinical samples. This is a marked increase compared to 2020 (n=4) and 2021 (n=1). Most cases were associated with import (n=17) and mainly from Ukraine (n=13). One isolate was identified as *Pseudomonas mendocina* while the others were *Pseudomonas aeruginosa*.

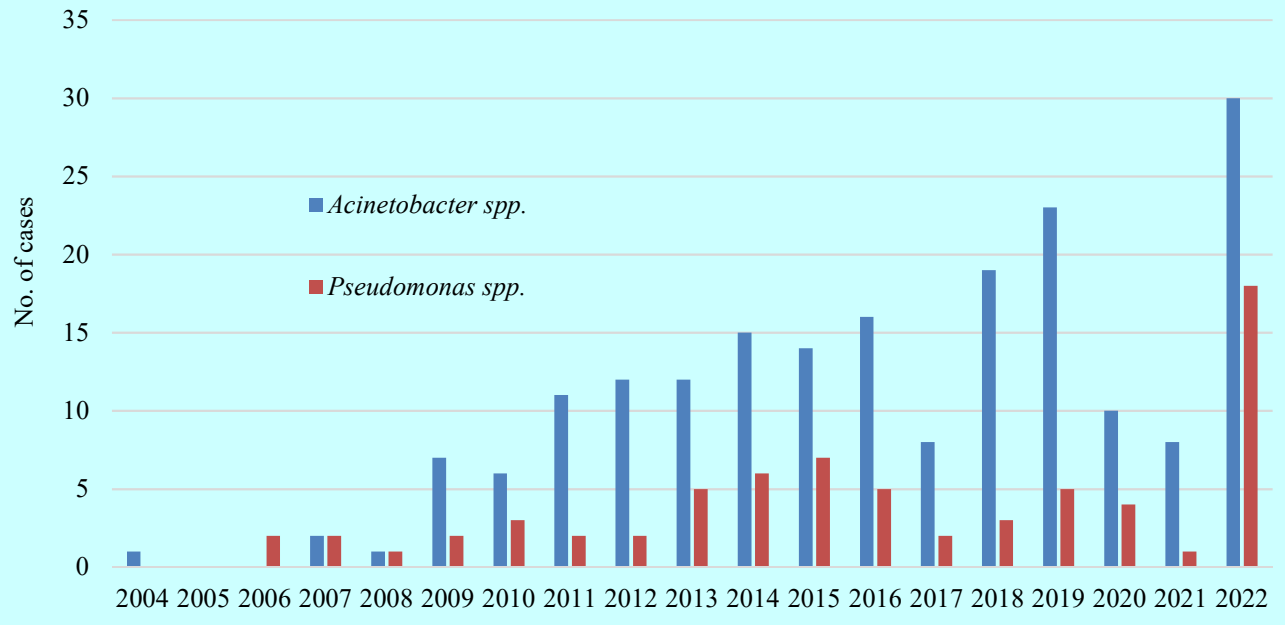

FIGURE 96. Number of carbapenemase-producing *Pseudomonas* spp. and *Acinetobacter* spp. in Norway 2004-2022**.**

Five different carbapenemase variants (VIM-1, VIM-2, IMP-1, IMP-18 and NDM-1) were identified among the *P. aeruginosa* isolates where the combination of ST773 with NDM-1 (n=6) and ST1047 with IMP (n=5) were dominant. Two isolates represented the globally disseminated high-risk clones ST111 and ST357 (9).

The ST773 and ST1047 isolates were identified at different hospitals in Norway. Phylogenetic analysis based on cgMLST (Figure 97) showed that all ST773 isolates were closely related (1-11 allelic differences). Two ST1047 isolates were also closely related (1 allelic difference). All isolates of ST773 and ST1047 as well as the *P. mendocina* isolate with VIM-1 were linked to import from Ukraine.

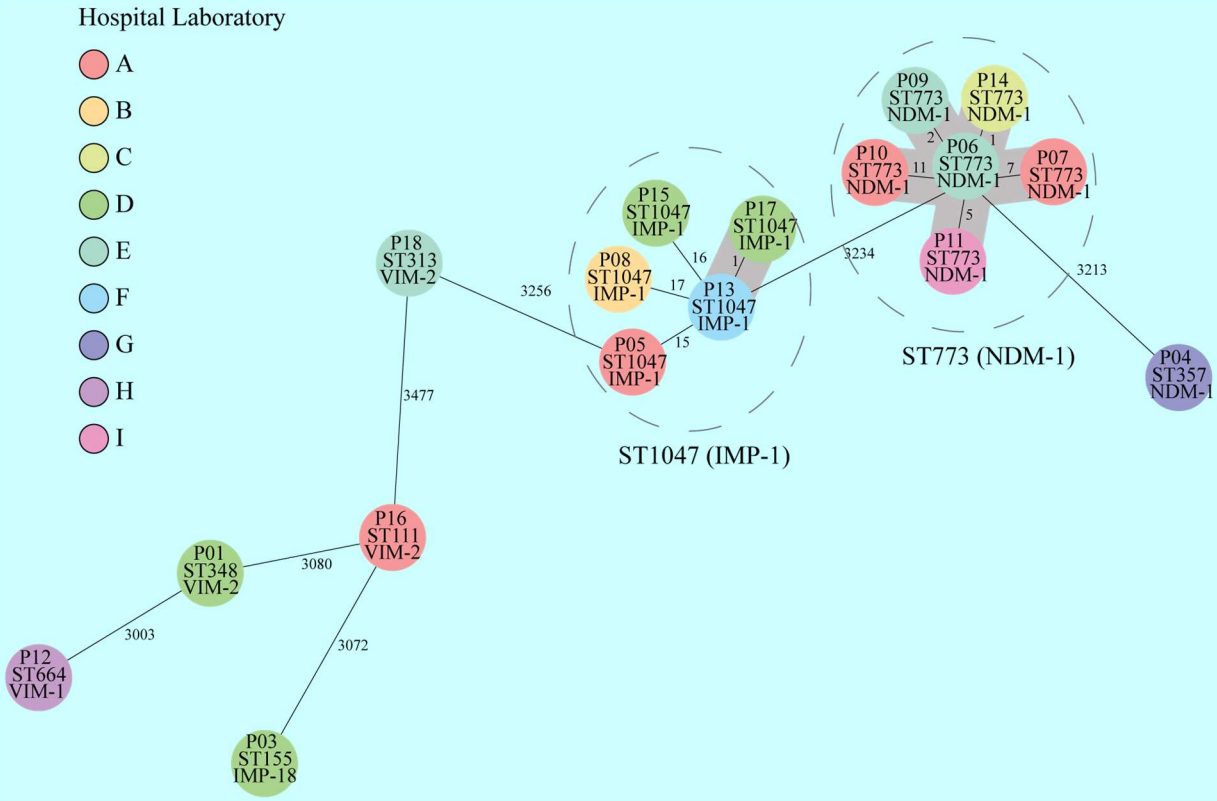

FIGURE 97. Minimum spanning tree of carbapenemase-producing *P. aeruginosa* isolates in 2022 based on 3,867 core genome alleles using SeqSphere+. Each circle represents one isolate (P01 to P18) and the colour codes the laboratory where the isolate was identified (A to I). The STs and carbapenemase variants are indicated. The number of allelic differences is shown along the lines. Closely related isolates (≤12 allelic differences) are highlighted with grey shading.

Acinetobacter spp.

Thirty cases of carbapenemase-producing *Acinetobacter* spp. were identified in 2022 compared to eight in 2021 (Figure 96). Twenty-six of the cases were associated with a possible link to import of which 15 from Ukraine. In total, 32 isolates were identified of which 31 were *Acinetobacter baumannii*. Three genetically unrelated *A. baumannii* ST2 with OXA-23 were identified in one patient. One *Acinetobacter pittii* with OXA-72 was identified.

Nineteen of the *A. baumannii* isolates belonged to the global high-risk clone ST2 (10) harbouring OXA-23 (n=18) or OXA-23+NDM-1 (n=1). Other ST-carbapenemase variant combinations included ST19-OXA-72 (n=3), ST417-OXA-420 (n=2), ST25-OXA-23 (n=1), ST78-OXA-72 (n=1), ST1077-OXA-72 (n=1) and four isolates belonging to undefined STs with OXA-23 (n=2) or OXA-72 (n=2).

Phylogenetic analysis showed three clusters of closely related isolates (≤9 allelic differences) (Figure 98). Two clusters of ST2-OXA-23 (n=4) and ST19-OXA-72 (n=3) consisted of isolates all linked to import from Ukraine. Epidemiological investigations indicate nosocomial transmission in the ST417-OXA-420 cluster.

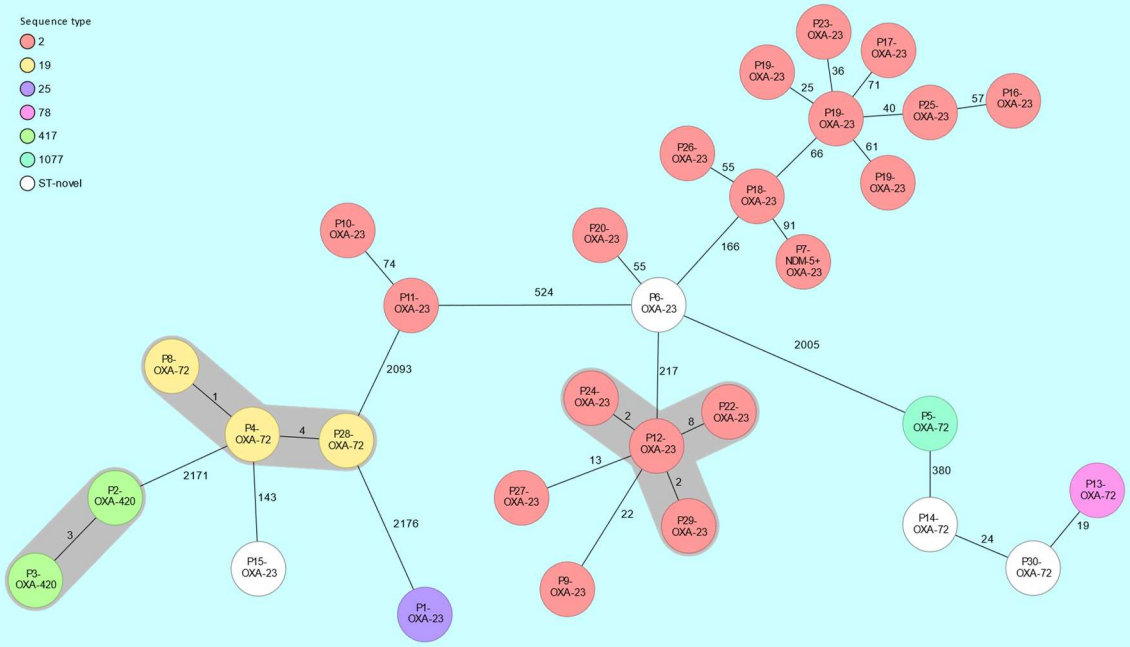

FIGURE 98. Minimum spanning tree of carbapenemase-producing *A. baumannii* in 2022 based on 2,390 core genome alleles using SeqSphere+ and *A. baumannii* ACICU as a reference strain. Each circle represents one isolate and is colour coded according to the ST. Carbapenemase variant is indicated in the circles and number of allelic differences along the lines. Clusters of isolates with ≤9 allelic differences are marked with grey shading.

Conclusion

The prevalence of carbapenemase-producing Gram-negative bacteria increased markedly in 2022 compared to 2021 and earlier years. The increase is due to a combination of cases linked to import after the reversal of the COVID-19 pandemic travel restrictions and the transfer of Ukrainian war victims to Norwegian hospitals.

Although whole genome sequencing showed a high level of genetic diversity, there is a predominance of known globally disseminated high-risk clones associated with specific carbapenemase genes. Clusters of closely related isolates were observed, mainly linked to import, and in particular from Ukraine. In several of these clusters the isolates were identified in different laboratories in Norway, indicating transmission before transfer to Norway. However, the identification of clusters with isolates lacking a clear connection to import or epidemiological link is a concern.

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Enterobacter spp. in blood cultures

TABLE 73. *Enterobacter* spp. blood culture isolates in 2022 (n=259). 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	81.1	-	18.9
Cefotaxime*	≤ 1	> 2	76.1	2.7	21.2
Ceftazidime	≤ 1	> 4	74.5	3.9	21.6
Cefepime	≤ 1	> 4	85.7	5.4	8.9
Meropenem*	≤ 2	> 8	99.6	0.4	0.0
Gentamicin**	≤ 2	> 2	96.1	-	3.9
Ciprofloxacin*	≤ 0.25	> 0.5	92.3	3.5	4.2
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	87.2	0.4	12.4

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

Enterobacter blood culture isolates have previously been included in the NORM surveillance programme in 2008, 2011 and 2016. Since the last survey in 2016, the breakpoint for resistance to piperacillin-tazobactam has been lowered from R > 16 mg/L to R > 8 mg/L, thus eliminating the I category. The present R category consequently corresponds to the previous results for I+R. Similarly, the breakpoint for resistance to gentamicin has been reduced from R > 4 mg/L to R > 2 mg/L, again with the effect that the updated R category should be compared to the previous results for I+R. The breakpoints applied for gentamicin are only valid for infections originating from the urinary tract. The remaining breakpoints have not been changed since 2016.

The present survey included 259 isolates identified as either *Enterobacter cloacae* complex or *Enterobacter* spp.. The *Enterobacter cloacae* complex (n=253) included *E. asburiae, E. bugandensis, E. cancerogenus, E. cloacae, E. hormaechei, E. kobei, E. ludwigii* and *E. xiangfangensis,* wheras all other species were registered as *Enterobacter* spp. (n=6). Please note that *Enterobacter aerogenes* has been reclassified as *Klebsiella aerogenes* since 2016. The taxon *Enterobacter* spp. in the present report is thus not exactly the same as in previous surveys.

In 2022, 3.9% of the isolates were resistant to gentamicin compared to 3.7% in 2016 (3.1% R + 0.6% I). In 2008, all isolates were fully susceptible to this agent. High-level aminoglycoside resistance has thus emerged in *Enterobacter* similarly to the development in other *Enterobacteriaceae*, but the prevalence has apparently stabilised at a relatively low level. Ciprofoxacin resistance (4.2% R; 3.5% I) was significantly less common than in *E. coli* (10.0% R; 2.9% I) and *Klebsiella* spp. (8.3% R; 4.2% I) blood culture isolates, but there was still an increase from 2.5% R and 1.9% I in 2016. The trimethoprim-sulfamethoxazole resistance rate increased from 9.3% in 2016 to 12.4% in 2022.

Enterobacter wild type strains contain a chromosomal AmpC beta-lactamase which is negatively regulated by the repressor AmpR. This mechanism is liable to escape mutants leading to high-level resistance to all penicillins and cephalosporins except cefpirome and cefepime. The spectrum of resistance may be expanded to include 4th generation cephalosporins as well as carbapenems when derepressed AmpC is combined with porin loss. Traditional beta-lactamase inhibitors are not active against AmpC enzymes. Cephalosporins can be used in the treatment of systemic infections with susceptible *Enterobacter* strains, but derepressed AmpC mutants may arise during therapy, and monotherapy is therefore not advisable. A primary objective of the *E. cloacae* surveillance protocol was to determine the prevalence of stable AmpC derepression in Norway. As seen in Table 73, 21.2% and 21.6% of the isolates were resistant to cefotaxime and ceftazidime, respectively. This is in accordance with international studies reporting 20-25% stably derepressed isolates in unselected materials, and it is also at the same level as in 2016 (cefotaxime 22.8% and ceftazidime 22.2%, respectively). As expected, the 4th-generation cephalosporin cefepime was more active with 85.7% being susceptible at standard dosage and a further 5.4% susceptible to increased exposure.

A single isolate was only susceptible to increased exposure (I) to meropenem, and three additional isolates had zone diameters below the *Enterobacter* screening breakpoints for carbapenemase production (meropenem 25-27 mm combined with piperacillin-tazobactam < 12 mm). None of the isolates were confirmed as carbapenemase producers by sequence analysis.

Enterobacter spp. in urine

TABLE 74. *Enterobacter* spp. urinary tract isolates in 2022 (n=119). 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	95.8	-	4.2
Piperacillin-tazobactam	≤ 8	> 8	94.1	-	5.9
Cefotaxime*	≤ 1	> 2	89.1	2.5	8.4
Ceftazidime	≤ 1	> 4	89.1	2.5	8.4
Cefepime	≤ 1	> 4	95.8	0.0	4.2
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	97.5	-	2.5
Ciprofloxacin*	≤ 0.25	> 0.5	95.8	1.7	2.5
Trimethoprim	≤ 4	> 4	88.2	-	11.8
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	89.1	2.5	8.4

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

Enterobacter urinary tract isolates were previously included in NORM in 2005 and 2016. As for blood culture isolates, the breakpoint for resistance to piperacillin-tazobactam has since 2016 been lowered from R > 16 mg/L to R > 8 mg/L, thus eliminating the I category. The present R category corresponds to the previous results for I+R. The breakpoint for resistance to gentamicin has also been reduced from R > 4 mg/L to R > 2 mg/L with the effect that the updated R category should be compared to the previous results for I+R. Gentamicin breakpoints are only valid for infections originating from the urinary tract. The remaining breakpoints have not been changed since 2016.

The present survey included 119 isolates identified as either *Enterobacter cloacae* complex (n=112) or *Enterobacter* sp. (n=7). The categorisation of species is described above. In 2016, a high proportion of *Enterobacter* isolates from urine were speciated as *E. aerogenes*. However, *E. aerogenes* has later been reclassified as *Klebsiella aerogenes*, and *Enterobacter* spp. in the present report is thus not exactly the same bacterial group as in previous surveys.

Resistance rates for gentamicin (2.5%), ciprofloxacin (2.5%) and trimethoprim-sulfamethoxazole (8.4%) were all lower than for blood culture isolates (3.9%, 4.2% and 12.4%, respectively), see Table 74. AmpC derepression was apparently less common among urinary tract *Enterobacter* spp. isolates (8-9%) than in systemic isolates (21-22%), and also than among urinary isolates in 2016 (12-13%). All isolates were clinically susceptible to standard doses of meropenem, and suspected carbapenemase production was not detected by the screening breakpoints for meropenem and piperacillin-tazobactam. Fosfomycin and nitrofurantoin are not suitable for treatment of *Enterobacter* urinary tract infections. Among the antibiotics traditionally used for this indication, resistance rates were lower for mecillinam (4.2%) and trimethoprim (11.8%) than for *E. coli* (4.4% and 22.4%, respectively) and *Klebsiella* spp. (8.9%, and 17.6%, respectively). The rates for *Enterobacter* spp. have not changed significantly since 2016.

Citrobacter spp. in blood cultures

TABLE 75. *Citrobacter* spp. blood culture isolates in 2022 (n=77). 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	77.9	-	22.1
Cefotaxime*	≤ 1	> 2	75.3	0.0	24.7
Ceftazidime	≤ 1	> 4	70.1	5.2	24.7
Cefepime	≤ 1	> 4	87.0	2.6	10.4
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	94.8	-	5.2
Ciprofloxacin*	≤ 0.25	> 0.5	88.3	2.6	9.1
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	88.3	0.0	11.7

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

Citrobacter blood culture isolates have never previously been included in the NORM surveillance programme, and internationally there is very limited surveillance data available for this genus. The protocol for 2022 defined the *Citrobacter freundii* complex isolates (n=45) to include *C. brakii, C. freundii, C. gillenii, C. murliniae, C. portucalensis, C. sedlakii, C. werkmanii* and *C. youngae.* All other isolates (n=32) were registered as *Citrobacter* spp., thus a total of 77 isolates were included. Relevant EUCAST/ NordicAST breakpoints were applied (Table 75).

Resistance rates for gentamicin (5.2%) and trimethoprim-sulfamethoxazole (11.7%) were comparable to the rates for *Enterobacter* spp. blood culture isolates (3.9% and 12.4%, respectively). Ciprofloxacin resistance was apparently more common in *Citrobacter* (9.1%) than in *Enterobacter* (4.2%). Practically all resistance to these three agents were found in the *C. freundii* complex group (gentamicin 8.9%, ciprofloxacin 15.6% and trimethoprim-sulfamethoxazole 17.8%), whereas the remaining *Citrobacter* spp. isolates had very low rates (0.0%, 0.0% and 3.1%, respectively).

Most clinical *Citrobacter* isolates harbour chromosomally encoded AmpC enzymes, and as for *Enterobacter* spp., these enzymes may be stably derepresed and mediate resistance to cephalosporins including cefotaxime and ceftazidime. In addition, several *Citrobacter* species contain various class A beta-lactamases that may also hydrolyse cefalosporins to varying degrees. At the genus level, the resistance rates for cefotaxime and ceftazidime were higher in *Citrobacter* (24.7% and 24.7%, respectively) than in *Enterobacter* (21.2% and 21.6%, respectively). Among *Citrobacter* isolates, beta-lactam resistance was more common within the *C. freundii* complex (piperacillin-tazobactam 31.1%; cefotaxime 37.8%, ceftazidime 37.8% and cefepime 15.6%) than in other species (9.4%; 6.2%; 6.2% and 3.1%, respectively). However, these differences should be interpreted with caution due to low numbers. All *Citrobacter* isolates were clinically susceptible to meropenem, and no carbapenemase production was detected by the screening procedure.

Citrobacter spp. in urine

TABLE 76. *Citrobacter* spp. urinary tract isolates in 2022 (n=148). 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	92.6	-	7.4
Piperacillin-tazobactam	≤ 8	> 8	91.9	-	8.1
Cefotaxime*	≤ 1	> 2	92.5	1.4	6.1
Ceftazidime	≤ 1	> 4	89.9	4.7	5.4
Cefepime	≤ 1	> 4	94.6	0.0	5.4
Meropenem*	≤ 2	> 8	99.3	0.7	0.0
Gentamicin**	≤ 2	> 2	93.2	-	6.8
Ciprofloxacin*	≤ 0.25	> 0.5	88.5	4.7	6.8
Trimethoprim	≤ 4	> 4	89.9	-	10.1
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	89.8	0.7	9.5

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

As for *Citrobacter* blood culture isolates, urinary tract isolates of this genus have never previously been included in the NORM surveillance programme. A total of 148 isolates were enrolled in the protocol, including 56 *Citrobacter freundii* complex isolates (see definition above) and 92 isolates which were either unspeciated or belonged to other species. Relevant EUCAST/NordicAST breakpoints were applied.

Resistance rates for gentamicin (6.8%) and trimethoprim-sulfamethoxazole (9.5%) were approximately at the same level as in blood culture isolates (5.2% and 11.7%, respectively), whereas ciprofloxacin resistance (6.8%) was less common (9.1% in blood culture isolates). Isolates in the *Citrobacter freundii* complex group had higher resistance rates for gentamicin (14.3%), trimethoprim-sulfamethoxazole (23.2%) and ciprofloxacin (16.1%) than the non-*freundii* group (2.2%, 1.1% and 1.1%, respectively).

Fosfomycin and nitrofurantoin are not suitable for treatment of *Citrobacter* urinary tract infections. The prevalence of resistance to mecillinam (7.4%) was comparable to *E. coli* (4.4%), *Klebsiella* spp. (8.9%) and *Enterobacter* spp. (4.2%) urinary tract isolates, but the rate for trimethoprim was generally lower (10.1%) compared to the other microorganisms (22.4%, 17.6% and 11.8%, respectively). Both mecillinam and trimethoprim resistance rates were higher in *Citrobacter freudii* complex isolates (10.7% and 25.0%) compared to non-*freundii* isolates (5.4% and 1.1%).

The prevalence of stably derepressed AmpC enzymes was apparently lower in urinary tract isolates than in blood culture isolates. Resistance rates to piperacillin-tazobactam (8.1%), cefotaxime (6.1%), ceftazidime (5.4%) and cefepime (5.4%) were all lower than the corresponding numbers for blood culture isolates (22.1%, 24.7%, 24.7%

and 10.4%, respectively). This may in part be due to a difference in species mix, as beta-lactam resistance was more common among *Citrobacter freundii* complex isolates (12.5%, 14.3%, 12.5% and 10.7%, respectively) than in non-*freundii* isolates (5.4%, 1.1%, 1.1% and 2.2%, respectively). However, this could also be a consequence of differences in antibiotic selection pressure prior to sampling and/or the dissemination of specific clones in different materials. The results should be interpreted with caution due to low numbers. A single *Citrobacter* spp. isolate was only susceptible to increased meropenem exposure (I) and contained a KPC-2 enzyme. All other isolates remained fully susceptible to meropenem.

Serratia spp. in blood cultures

TABLE 77. *Serratia* spp. blood culture isolates in 2022 (n=124). 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	92.7	-	7.3
Cefotaxime*	≤ 1	> 2	85.5	4.8	9.7
Ceftazidime	≤ 1	> 4	99.2	0.0	0.8
Cefepime	≤ 1	> 4	96.8	2.4	0.8
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.25	> 0.5	96.8	2.4	0.8
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	100.0	0.0	0.0

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

Serratia blood culture isolates have never previously been included in the NORM surveillance programme. A majority of the 124 included isolates were identified as *Serratia marcescence* (n=112), while the remaning 12 were either unspeciated or belonged to other *Serratia* species. The results were categorised according to EUCAST/Nordic-AST breakpoints (Table 77). It should be noted that a putative outbreak of *S. marcescence* was detected in Norway in October 2022. No common source has so far been identified, and possible transmission lines are not clear. It is assumed that the present results were not significantly affected by this event.

The resistance rates for gentamicin (0.0%), trimethoprim-sulfamethoxazole (0.0%) and ciprofloxacin (0.8%) were very low, and significantly lower than in other *Enterobacterales* genera in NORM 2022. In spite of the chromosomally encoded AmpC enzyme in *S. marcescence*, most isolates were fully susceptible to standard dosage of cefotaxime (85.5%), piperacillin-tazobactam (92.7%), cefepime (96.8%) and ceftazidime (99.2%). Furthermore, all isolates were fully susceptible to meropenem according to the clinical breakpoints for this agent. A single isolate had a zone diameter below the screening breakpoint for carbapenemase production, but no relevant determinants were identified by whole genome sequencing. It is assumed that the phenotype was caused by a combination of a class A beta-lactamase and porin alterations. The isolate originated from a Ukranian patient evacuated to a Norwegian hospital.

Serratia spp. in urine

TABLE 78. *Serratia* spp. urinary tract isolates in 2022 (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	94.4	-	5.6
Cefotaxime*	≤ 1	> 2	91.6	2.8	5.6
Ceftazidime	≤ 1	> 4	97.2	2.8	0.0
Cefepime	≤ 1	> 4	91.7	8.3	0.0
Meropenem*	≤ 2	> 8	100.0	0.0	0.0
Gentamicin**	≤ 2	> 2	97.2	-	2.8
Ciprofloxacin*	≤ 0.25	> 0.5	86.1	2.8	11.1
Trimethoprim	≤ 4	> 4	80.6	-	19.4
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	100.0	0.0	0.0

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

As for *Serratia* blood culture isolates, urinary tract isolates of this genus were surveyed in NORM for the first time in 2022. Only 36 isolates were included during the three-week sampling period, and most of these were identified as *Serratia marcescence* (n=31). The remaining five isolates were grouped as *Serratia* spp.. The low number of isolates precludes any firm conclusions about the resistance rates in this genus/specimen type combination. It is unlikely that the previously described putative outbreak should affect the results as urinary tract isolates were collected almost ten months prior to the detection of the outbreak.

The resistance rates for gentamicin (2.8%) and ciprofloxacin (11.1%) were higher than for blood culture isolates (0.0% and 0.8%, respectively) (Table 78). All isolates were fully susceptible to trimethoprim-sulfamethoxazole. Fosfomycin, nitrofurantoin and mecillinam are not suitable for treatment of *Serratia* urinary tract infections, and 19.4% of the isolates displayed resistance to trimethoprim.

Keeping the low number of isolates in mind, the rates of resistance to beta-lactam antibiotics were even lower among urinary tract isolates than for blood culture isolates. Only 5.6% were resistant to piperacillin-trazobactam and cefotaxime, and all isolates were susceptible to ceftazidime (2.8% with increased exposure) and cefepime (8.3% with increased exposure). All isolates were clinically susceptible to meropenem at standard dosage, and no carbapenemase production was detected by screening.

Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 79. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2022 (n=130). 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	85.4	-	14.6
Amoxicillin-clavulanic acid**	≤ 2	> 2	96.2	-	3.8
Cefuroxime**	≤ 1	> 2	72.3	17.7	10.0
Cefotaxime	≤ 0.125	> 0.125	99.2	-	0.8
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Meropenem*	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin*	≤ 0.06	> 0.06	100.0	-	0.0
Chloramphenicol	≤ 2	> 2	99.2	-	0.8
Tetracycline	≤ 2	> 2	100.0	-	0.0
Trimethoprim-sulfamethoxazole***	≤ 0.5	> 1	83.8	3.1	13.1
Beta-lactamase	Negative	Positive	89.2	-	10.8

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 2022 (n=130). 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*					3.1	8.5	25.4	41.5	6.9	7.7		0.8	1.5	2.3		2.3
Amoxi-clav**			0.8			7.7	6.9	41.5	35.4	3.8	1.5	0.8	0.8			0.8
Cefuroxime**						0.8	3.8	15.4	52.3	17.7	3.8	1.5		3.1	0.8	0.8
Cefotaxime	4.6	10.0	32.3	32.3	16.9	3.1	0.8									
Ceftriaxone			87.7	11.5	0.8											
Meropenem*	0.8	2.3	4.6	12.3	37.7	32.3	9.2	0.8								
Ciprofloxacin*	21.5	46.9	30.8		0.8											
Chloramp.							2.3	54.6	42.3			0.8				
Tetracycline						0.8	11.5	76.9	10.8							
TMS***	2.3	6.9	33.1	26.2	8.5	2.3	2.3	2.3	3.1	3.8	1.5	1.5	0.8	5.4		

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. *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 ongoing pandemic (n=63). In 2022, a total of 130 *H. influenzae* isolates were recovered from blood cultures (n=122) and cerebrospinal fluids (n=8). Both isolates were included from patients with combined bacteremia and meningitis (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 (18/19) and cefuroxime (12/13) resistant isolates. Twenty-four out of 116 (20.7%) beta-lactamase negative isolates were resistant to PCG1. Seven and twelve of these isolates were resistant to ampicillin and cefuroxime, respectively, and only six remained fully susceptible to both agents. The rate of ampicillin resistance decreased from 20.6% in 2021 to 14.6% in 2022. This is in line with the 16.3% rate of resistance in 2020. Beta-lactamase production was detected in 14/130 isolates (10.8%), which is at the same level as in 2021 (12.7%), but lower than in the pre-pandemic years 2016 (17.3%) and 2017 (17.8%), probably representing a decreasing trend during 2013-2022. 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 (10.0%) displayed this phenotype as compared to 11.6% in 2020 and 9.5% in 2021. Six of these isolates were also resistant to ampicillin and five were resistant to amoxicillin-clavulanic acid. All cefuroxime resistant isolates were beta-lactamase negative. A single blood culture isolate was resistant to cefotaxime (MIC 0.25 mg/L), but remained susceptible to ceftriaxone and meropenem.

As observed in previous surveys of systemic *H. influenzae* isolates, resistance rates to meropenem (0.0%), ciprofloxacin (0.0%), tetracycline (0.0%) and chloramphenicol (0.8%) were at very low levels. The 13.1% rate to trimethoprim-sulfamethoxazole was at approximately the same level as 15.9% in 2021.

Haemophilus influenzae in respiratory tract specimens

TABLE 81. *Haemophilus influenzae* in respiratory tract specimens in 2022 (n=243). 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	84.4	-	15.6
Amoxicillin-clavulanic acid**	≤ 2	> 2	96.3	-	3.7
Cefuroxime**	≤ 1	> 2	64.2	16.5	19.3
Cefotaxime	≤ 0.125	> 0.125	99.2	-	0.8
Ceftriaxone	≤ 0.125	> 0.125	99.2	-	0.8
Meropenem*	≤ 2	> 2	99.6	-	0.4
Ciprofloxacin*	≤ 0.06	> 0.06	98.8	-	1.2
Chloramphenicol	≤ 2	> 2	99.6	-	0.4
Tetracycline	≤ 2	> 2	99.6	-	0.4
Trimethoprim-sulfamethoxazole***	≤ 0.5	> 1	71.2	1.6	27.2
Beta-lactamase	Negative	Positive	89.3	-	10.7

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 82. *Haemophilus influenzae* in respiratory tract specimens in 2022 (n=243). 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	3.7	8.2	28.8	26.3	16.5	4.5	1.2	2.5	4.1	1.6	0.4	1.2
Amoxi-clav**			0.4	0.8	1.6	6.2	16.0	44.0	18.9	8.2	1.6	0.8	0.8			0.4
Cefuroxime**			0.4		0.4	1.6	7.4	20.2	34.2	16.6	11.5	2.9	2.1	0.8	0.8	1.2
Cefotaxime	3.7	11.1	36.2	22.6	19.3	6.2				0.8						
Ceftriaxone	53.1	19.3	22.2	4.1	0.4		0.4	0.4								
Meropenem*	1.2	1.2	4.9	14.0	30.4	28.4	13.6	4.5	0.8	0.4				0.4		
Ciprofloxacin*	15.2	53.9	28.4	1.2		0.4					0.4	0.4				
Chloramp.				0.8	0.4	0.8	8.2	26.7	51.4	11.1	0.4					
Tetracycline			0.4	0.4	2.9	19.8	56.0	18.1	2.1		0.4					
TMS***	0.4	2.1	8.2	29.6	18.5	8.2	2.5	1.6	1.6	2.9	1.6	2.9	1.2	18.5		

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. *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

H. influenzae has repeatedly been surveyed in NORM, most recently in 2014 and 2017. A total of 243 *H. influenzae* isolates were recovered from respiratory tract specimens including eye and middle ear samples during 2022 (Tables 81-82). Beta-lactamase production was detected in 10.7%, which is a decrease from 17.3% in 2014 and 15.2% in 2017 (Figure 99), which parallels the numbers in systemic isolates. The 15.6% ampicillin resistance rate was also lower than 19.7% in 2014 and 19.5% in 2017. Among these isolates, beta-lacta-mase production was present in 25/38 (65.8%). This is similar to the 64.5% rate detected in 2017. Five of the 25 isolates were concomitantly resistant to cefuroxime, thus indicating a combination of beta-lactamase production and chromosomal resistance mechanisms. Only a single isolate was reported as ampicillin susceptible in spite of being beta-lactamase positive, and all were resistant to the penicillin G 1 IU screening disk. This may indicate improved quality of interpretation of the beta-lactamase test. It should be noted that all beta-lactamase positive isolates should be reported as resistant to ampicillin and amoxicillin according to EUCAST/NordicAST guidelines.

About half of the beta-lactamase negative, ampicillin resistant strains (18/38) were resistant to cefuroxime, suggesting a chromosomal basis for beta-lactam resistance. Nine of them were also resistant to amoxicillin-clavulanic acid. A total of 47 isolates (19.3%) displayed resistance to cefuroxime (MIC > 2 mg/L) compared to 13.4% in 2014 and 13.5% in 2017. While the rate of beta-lactamase production is declining, it appears that PBP-mediated beta-lactam resistance is increasing. Many of the cefuroxime resistant isolates remained susceptible to ampicillin (29/47) and amoxicillin-clavulanic acid (38/47). Two isolates (0.8%) were reported as resistant to cefotaxime (MIC 2 mg/L). They were both beta-lactamase negative, but resistant to cefuroxime (MIC ≥ 256 mg/L) and ceftriaxone (MIC 0.25-0.5 mg/L). One of them was also resistant to meropenem (MIC 32 mg/L). The penicillin G 1U disk (PCG1) successfully identified all isolates resistant to ampicillin (38/38), amoxicillin-clavulanic acid (9/9) and cefuroxime (47/47). Conversely, 69/217 (31.8%) beta-lactamase negative isolates were resistant to PCG1. Thirteen of these were resistant to ampicillin and 42 were resistant to cefuroxime.

As seen in blood culture isolates and previous surveys of respiratory tract isolates, resistance rates to ciprofloxacin (1.2%), chloramphenicol (0.4%) and tetracycline (0.4%) were very low. The prevalence of resistance to trimethoprim-sulfamethoxazole was 27.2%. This is significantly higher than in blood cultures (13.1%) and a further increase from 2014 (19.0%) and 2017 (22.4%). There were no systematic differences in resistance rates to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

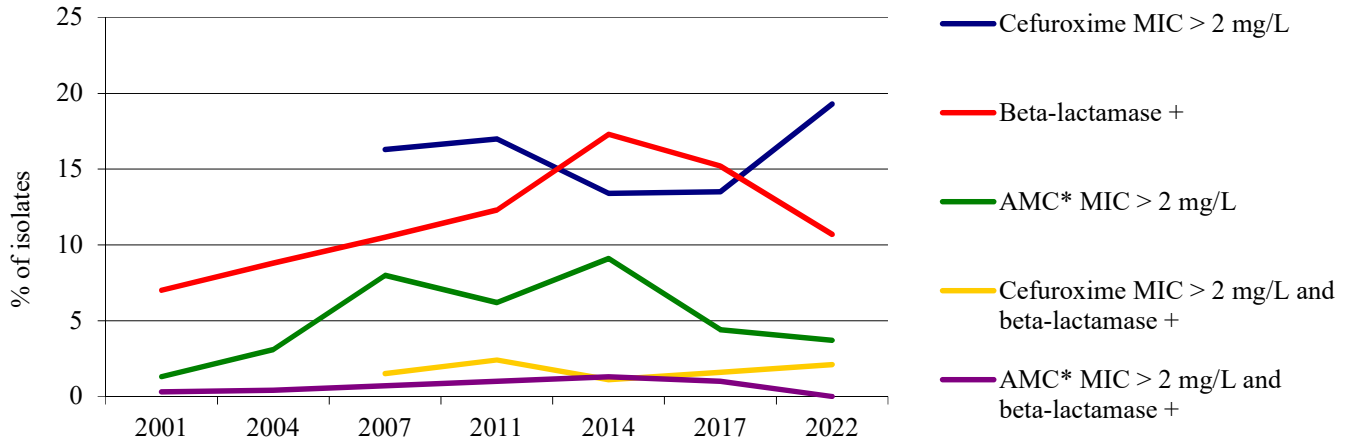

FIGURE 99. Prevalence of beta-lactamase production, chromosomally encoded beta-lactam resistance, and combination of both mechanisms in *Haemophilus influenzae* respiratory tract isolates 2001-2022. Please note that the time intervals on the x-axis are not identical. *AMC=Amoxicillin-clavulanic acid.

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 83. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2022 (n=9). 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	88.9	-	11.1
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 84. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2022 (n=9). 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*				2	4	2		1								
Ceftriaxone			9													
Ciprofloxacin	8	1														
Chloramph.								5	4							
Rifampicin	2	2	2		1	1	1									
Tetracycline						3	2	3	1							
Azithromycin						1		2	3	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. *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 for susceptibility to ciprofloxacin (all indications) was reduced from S ≤ 0.03 to S ≤ 0.016 mg/L and the corresponding breakpoint for resistance from R > 0.03 to R > 0.016 mg/l in 2023. The results are presented in Tables 83-84.

From the ten cases of systemic infections caused by *N. meningitidis* reported in 2022, nine isolates were received. This is slight increase from four and five isolates in the pandemic years 2020-2021, respectively. The nine isolates all originated from blood cultures and represented unique patients, with no known associations between the cases. The isolates belonged to serogroups B (n=4), Y (n=3), C (n=1) and A (n=1). A case caused by a serogroup A isolate was last seen in Norway in 2006. The four serogroup B isolates belonged to three different sequence types (STs) while the three serogroup Y isolates were ST-23. The serogroup A isolate was ST-75, a clone identified in Russia since the 1980ies. The serogroup C isolate belonged to the ST-269 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/ Nordic-AST has not established breakpoints for azithromycin, but the MIC distribution does not indicate the presence of acquired macrolide resistance (Table 84).

Neisseria gonorrhoeae

TABLE 85. *Neisseria gonorrhoeae* from all specimen types in 2022 (n=830). 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	4.0	78.2	17.8
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	99.8	-	0.2
Ciprofloxacin	≤ 0.03	> 0.06	39.6	0.5	59.9
Tetracycline	≤ 0.5	> 0.5	60.8	-	39.2
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	83.6	-	16.4

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

TABLE 86. *Neisseria gonorrhoeae* from all specimen types in 2022 (n=830). 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*		0.6	0.5	1.0	1.9	16.7	31.2	22.8	7.5	4.6	3.7	5.3	2.0	2.2		
Ceftriaxone	34.0	11.2	50.2	3.6	0.4	0.6										
Cefixime			78.1	10.2	10.1	1.3	0.2			0.1						
Ciprofloxacin	28.0	5.8	4.2	1.7	0.5	0.6	1,0	4.6	11.8	18.9	15.1	5.4	1.0	1.6		
Tetracycline				0.8	2.7	10.5	21.6	25.3	18.6	2.8	1.7	4.3	7.6	4.1	0.1	
Spectinomycin									0.1	0.4	1.9	33.9	54.0	9.5	0.2	
Azithromycin			0.1	2.0	6.4	14.3	18.9	17.5	19.5	15.7	2.3	1.0	1.1	0.2	0.4	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. *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. Epidemiological details for 2020-2022 are presented below.

In 2022, a total of 827 gonococcal isolates were available for further analyses. This is a dramatic increase from 2020 (n=442) and especially 2021 (n=220), when the low incidences of gonorrhoeae presumably were linked to changes in behaviour and travel during the pandemic. The ratio between positive cultures and total number of reported cases (including PCR-only positives) did not change significantly from 2021 (220/555; 39.6%) to 2022 (827/1857; 44.5%). This may suggest that the increased number of isolates reflects true epidemiological changes as opposed to improved microbiological methods.

The isolates in 2022 were reported to originate from urethra (n=324), anus (n=196), cervix uteri/vagina (n=164), throat (n=113), eye (n=5) or "others/unknown" (n=17). A total of 628 (75.9%) isolates were from men and 199 (24.1%) from 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. Over years there has been an ongoing outbreak among men who have sex with men, but the strains linked to this outbreak could not be identified in the NORM protocol.
The results from susceptibility testing are presented in Tables 85-86. A majority of isolates were either susceptible only to increased exposure (78.2%) or resistant (17.8%) to penicillin G. The corresponding figures for 2021 were 72.7% and 15.0%, respectively. One hundred thirty-six isolates (16.4%) produced beta-lactamase, which is at the same level as 2020 (18.8%) and 2021 (17.3%). Practically all beta-lactamase positive isolates (134/136, 98.5%) were also resistant to ciprofloxacin. Twenty-three isolates (3.3%) were resistant and 638 (91.9%) 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.

All isolates were categorised as susceptible to ceftriaxone (MIC ≤ 0.125 mg/L). Ceftriaxone resistant isolates from Norway have previously been linked to treatment failure. Two isolates were resistant to the oral cephalosporin cefixime, but this agent 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. Azithromycin was previously used in a combination with ceftriaxone, but 21.2% of the isolates displayed azithromycin MIC values above the EUCAST screening breakpoint for acquired resistance of 1 mg/L. The corresponding figure for 2021 was 11.4%. The prevalence of ciprofloxacin resistance persisted at a high level (59.9%) in 2022. Ciprofloxacin is consequently not a viable alternative except in cases where susceptibility has been documented. All strains were susceptible to spectinomycin.

Rebound of *Neisseria gonorrhoeae* infections after a low incidence during the Covid-19 pandemic and changes in the circulating strains

A total of 1,857 cases of gonococcal infections were reported to the Norwegian Surveillance System for Infectious Diseases (MSIS) in 2022. While in 2019 there were 1,703 such cases, this number decreased to 1,047 in 2020, as a result of the social restrictions put in place because of the Covid-19 pandemic, and further decreased to 555 in 2021.The resurgence in the number of gonococcal infections in 2022 occurred principally in the second part of the year, associated with the re-opening of society, and especially among young women. The total of number of cases was nearly 10% higher than in the pre-pandemic year.

The National Reference Laboratory (NRL) at the Norwegian Institute of Public Health received 827 gonococcal isolates from 785 infection episodes in 2022, that is for 42.3% of the cases reported to MSIS. The patients were between 15 and 74 years old, with 62.0% between 15 and 30 years old, with 188 (25.2%) female patients and 558 (74.5%) males. For two patients the gender was unknown. Of 33 patients with several gonococcal infections (2 to 4) in the course of 2022, 31 were male.

Whole genome sequencing was performed on all isolates received at the NRL and a total of 79 sequence types (STs) were identified. Thus, the diversity of the gonococcal population was similar to that found in 2019 (77 STs among 707 isolates). While 37 of the 79 STs (46.8%) were seen only once or twice, ten STs were represented by 25 or more isolates, with ST-1580 dominating with 133 isolates from 131 infections. Four of these ten STs (ST-1580, ST-7359, ST-7363 and ST-9363) were identified more frequently from females than on average, while ST-7822, ST-9362, and ST-11422 were recovered more frequently from males than in average. Remarkably, ST-7359 caused 32 infections, 21 of them (65.6%) in females. The site of infection for the cases caused by these ten predominant STs is shown in Table 87.

Comparing to the pre-pandemic situation, we observed a significant change in the frequency of the circulating STs in the Norwegian population. The dominant ST in 2022, ST-1580, increased in frequency from 3.1% in 2019 to 16.1%. ST-11422 mainly recovered from the homosexual male population has decreased from 15.1% in 2019 to 6.9% in 2022. Overall, we observed a trend of previously male-specific clones spreading to the female population. This is the case for ST-1599, ST-7822 and ST-10314 that were strictly male-associated in 2019 and that are now circulating among women.

The antimicrobial resistance pattern for the whole isolate collection is given in Table 85. We analysed in more details the resistance profiles for these ten dominant STs, individually (Table 88). All the 619 isolates in these ten STs were fully susceptible to ceftriaxone and spectinomycin, and one isolate (ST-9362) was resistant to cefixime. None of the isolates in ST-1580, ST-1599, ST-7822, ST-9363, ST-11422 and ST-11706 produced beta-lactamase, while only a single isolate of ST-7359 and ST-10314, respectively, did. In contrast, nearly all isolates of ST-7363 and ST-9362 were beta-lactamase positive. For all STs but ST-1599, the majority of the isolates had reduced susceptibility or were resistant to penicillin. The rates of ciprofloxacin and tetracycline resistance varied also largely between STs, from 3.5% to 100.0% for ciprofloxacin and 0.8% to 94.5% for tetracycline. For azithromycin, depending on the ST, from 1.1% to 35.1% of the isolates had MICs above the ECOFF.

Since the introduction of antimicrobial treatment, resistance in gonococci has emerged globally to sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones, and early-generation cephalosporins. Gonorrheae in Norway is currently treated with ceftriaxone as a single dose in injection form. While all isolates were susceptible to ceftriaxone and only two of the 827 isolates in 2022 were resistant to cefixime (one isolate each of ST-1579 and ST-9362), 11 isolates, among them five isolates from the emerging ST-11706, were borderline resistant (MIC = 0.125) to cefixime. Thus, while resistance to 3rd-generation cephalosporins has been only sporadically reported in Norway, it is essential to monitor closely the situation.

The number of reported gonorrhea cases in 2022 was higher than has been reported since the mid-80ies. In the second half of the year heterosexual young people (many students living in Bergen, Oslo, Trondheim and Stavanger) and especially women were affected, but no clusters were identified (https://www.fhi.no/nyheter/2023/bekymringsfull-okning-i-gonore/). The same trend has been seen in other European countries (https://www.ecdc.europa.eu/sites/default/files/documents/communicable-disease-threats-report-week-25-2023.pdf), emphasising the importance of surveillance and public health interventions.

TABLE 87. Frequency of isolation sites of isolates belonging to the 10 predominant sequence types.

ST	Number of isolates	Anus	Cervix/vagina	Urethra	Throat	Not known	Other
1580	133	20.3	28.6	36.1	11.3	2.3	1.5
1599	27	29.6	22.2	44.4	0.0	3.7	0.0
7359	34	5.9	55.9	32.4	2.9	0.0	2.9
7363	69	11.6	30.4	42.0	10.1	2.9	2.9
7822	55	41.8	7.3	20.0	29.1	1.8	0.0
9362	91	27.5	8.8	44.0	16.5	1.1	2.2
9363	75	12.0	32.0	41.3	13.3	1.3	0.0
10314	42	23.8	21.4	31.0	23.8	0.0	0.0
11422	57	45.6	8.8	26.3	17.5	1.8	0.0
11706	34	29.4	17.6	29.4	20.6	2.9	0.0

TABLE 88. Frequency of beta-lactamase production and antimicrobial resistance for penicillin, ciprofloxacin, tetracycline (SIR) and azithromycin (ECOFF) in isolates belonging to the 10 predominant sequence types.

	Beta-lactamase		Penicillin G			Ciprofloxacin		Tetracycline			Azithromycin	
ST	Neg	Pos	S	I	R	S	R	S	I	R	S	R
1580	100.0	0.0	3.0	84.2	12.8	50.4	49.6	98.2		0.8	69.9	30.1
1599	100.0	0.0	100.0			100.0		11.1		88.9	100.0	
7359	97.1	2.9	23.5	73.5	2.9	97.1	2.9	97.1		2.9	85.3	14.7
7363	5.6	94.4		7.0	93.0	1.4	98.6	4.2	2.8	93.0	98.6	1.4
7822	100.0	0.0		100.0		1.8	98.2	83.6	16.4		81.8	18.2
9362	3.3	96.7		5.5	94.5	1.1	98.9	3.3	2.2	94.5	98.9	1.1.
9363	100.0	0.0	1.3	98.7		84.0	16.0	60.0	32.0	8.0	68.0	32.0
10314	97.6	2.4		100.0			100.0	81.0	19.0		97.6	2.4
11422	100.0	0.0	1.8	98.2		96.5	3.5	70.2	26.3	3.5	64.9	35.1
11706	100.0	0.0	5.9	94.1		2.9	97.1	70.6	29.4		76.5	23.5

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Staphylococcus aureus in blood cultures

TABLE 89. *Staphylococcus aureus* blood culture isolates in 2022 (n=1,601). 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	94.5	-	5.5
Clindamycin	≤ 0.25	> 0.25	98.9	-	1.1
Fusidic acid	≤ 1	> 1	95.6	-	4.4
Ciprofloxacin	≤ 0.001	> 1	0.0	95.1	4.9
Gentamicin	≤ 2	> 2	99.4	-	0.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	98.8	-	1.2
Tetracycline	≤ 1	> 1	96.9	-	3.1
Tigecycline	≤ 0.5	> 0.5	99.1	-	0.9
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.8	0.1	0.1
Beta-lactamase	Negative	Positive	31.5	-	68.5
Cefoxitin screen	≥ 22	< 22	99.0	-	1.0
MRSA** (*mecA*)	Negative	Positive	99.0	-	1.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. MRSA=methicillin resistant *Staphylococcus aureus*. *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 2022 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.

Sixteen methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2022, corresponding to a prevalence of 1.0% (Table 89). This is at the same level as 1.4% in 2020 and 0.8% in 2021. The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from ten 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 erythromycin (4/16), ciprofloxacin (4/16), tetracycline (2/16), fusidic acid (2/16), gentamicin (1/16) and/or clindamycin (1/16). All MRSA isolates were susceptible to tigecycline, linezolid, rifampicin and trimethoprim-sulfamethoxazole. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 92 on page 138. The NORM findings are at the same level as reported from the databases of the participating laboratories where 23 out of 2,238 (1.0%) *S. aureus* blood culture isolates were MRSA. None of the eight *S. aureus* isolates recovered from cerebrospinal fluid were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 23/2,246 (1.0%). This is the same rate as in 2021.

Eighty-eight *S. aureus* isolates (5.5%) were resistant to erythromycin. This is at the same level as 5.9% in 2020 and 6.0% in 2021. 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, 61 (70%) were inducibly MLS_B resistant, and 24 (27%) displayed efflux mediated M-type resistance. These figures represent 0.2%, 3.8% and 1.5% of all *S. aureus* isolates from blood cultures, respectively. The proportion with M-type resistance was higher and the proportion with inducible MLS_B resistance was lower than in 2022.

The prevalence of resistance to fusidic acid (4.4%) was slightly increased from 3.7% in 2020 and 3.8% in 2022. The 4.9% prevalence of ciprofloxacin resistance is a decline from 8.8% in 2021, but at the same level as 4.6% in 2019 and 5.1% in 2020. 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 2022.

Figure 100 shows the prevalence of resistance to various antimicrobials. A total of 68.5% of the isolates were beta-lactamase positive, which is unchanged from 68.2% in 2021. There were no significant differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

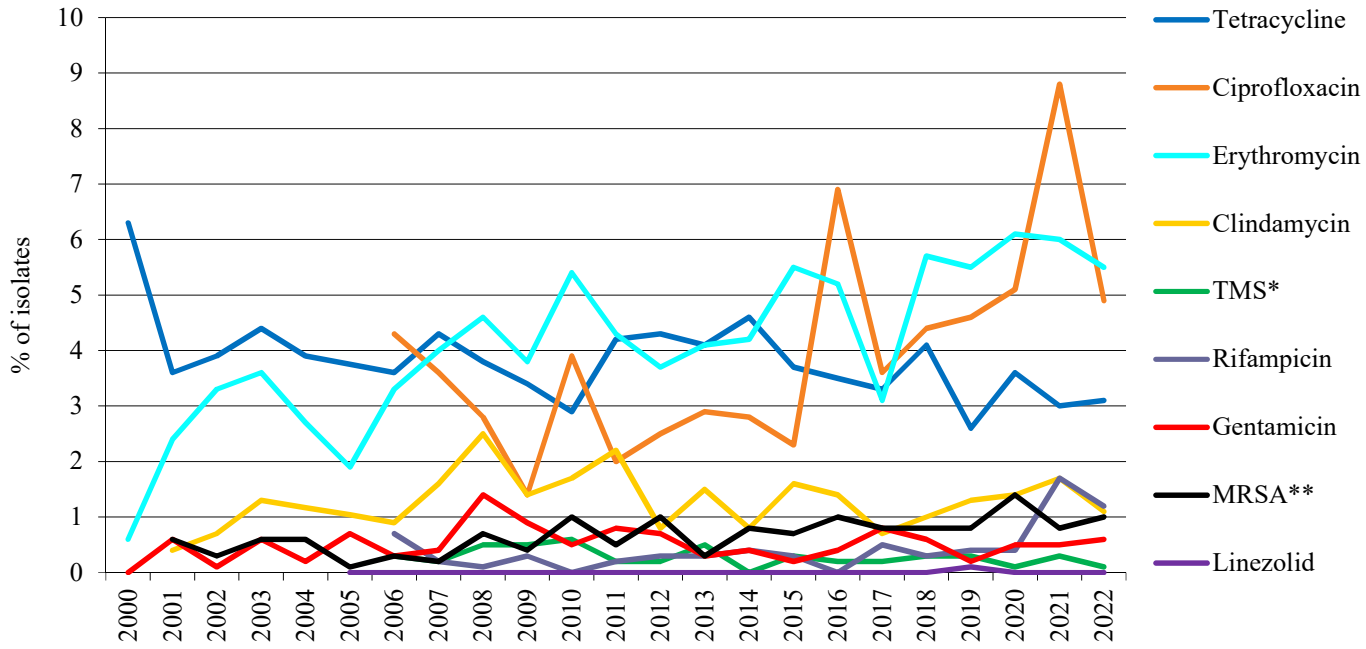

FIGURE 100. Prevalences of antimicrobial resistance among *Staphylococcus aureus* blood culture isolates 2000-2022. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Staphylococcus aureus in wound specimens

TABLE 90. *Staphylococcus aureus* isolates from wound specimens in 2022 (n=807). 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	94.2	-	5.8
Clindamycin	≤ 0.25	> 0.25	98.8	-	1.2
Fusidic acid	≤ 1	> 1	92.9	-	7.1
Ciprofloxacin	≤ 0.001	> 1	0.0	95.8	4.2
Gentamicin	≤ 2	> 2	99.8	-	0.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	98.3	-	1.7
Tetracycline	≤ 1	> 1	96.5	-	3.5
Tigecycline	≤ 0.5	> 0.5	99.1	-	0.9
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.8	0.1	0.1
Beta-lactamase	Negative	Positive	30.2	-	69.8
Cefoxitin screen	≥ 22	< 22	98.4	-	1.6
MRSA** (*mecA*)	Negative	Positive	98.4	-	1.6

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. MRSA=methicillin resistant *Staphylococcus aureus*. *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. Thirteen out of 807 (1.6%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at the same level as in 2020 (1.8%) and 2021 (1.5%). The MRSA isolates originated from patients visiting general practitioners (n=5), hospital wards (n=5) and outpatient clinics (n=3) in different parts of the country. Most MRSA isolates were co-resistant to erythromycin (6/13), ciprofloxacin (5/13), tetracycline (5/13), fusidic acid (3/13) and/or gentamicin (1/13) in different combinations. All MRSA isolates were susceptible to clindamycin, 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 138).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates increased to 7.1% in 2022 compared to 4.4% in 2020 and 4.2% in 2021 (Table 90 and Figure 101). Further surveillance is needed to determine whether this is the beginning of a new wave of fusidic acid resistance in *S. aureus* after the previous epidemic which peaked at 25.0% in 2004. The prevalence of resistance to fusidic acid is again significantly lower in blood culture isolates (4.4%) than in wound isolates (7.1%). For other antimicrobial agents such as gentamicin, rifampicin, trimethoprim-sulfamethoxazole and tetracycline there were only minor changes from 2021-2022, 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.

Forty-seven (5.8%) isolates were resistant to erythromycin. This is a decrease from 8.5% in 2021, but at the same level as 5.2% in 2020. The rates include the former I category due to a change of the breakpoint for resistance (see above). Most erythromycin resistant isolates were further examined to determine the macrolide resistance phenotype. The majority were either inducibly (40/46, 87% of erythromycin resistant isolates) or constitutively (2/46, 4% 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 (4/46, 9% 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 69.8% of the isolates were beta-lactamase positive compared to 69.8% in 2020 and 69.7% in 2021. The rate of tetracycline resistance was higher among beta-lactamase positive isolates (4.6%) than among beta-lactamase negative isolates (0.8%), but for other antibiotics there were no significant differences between these two groups.

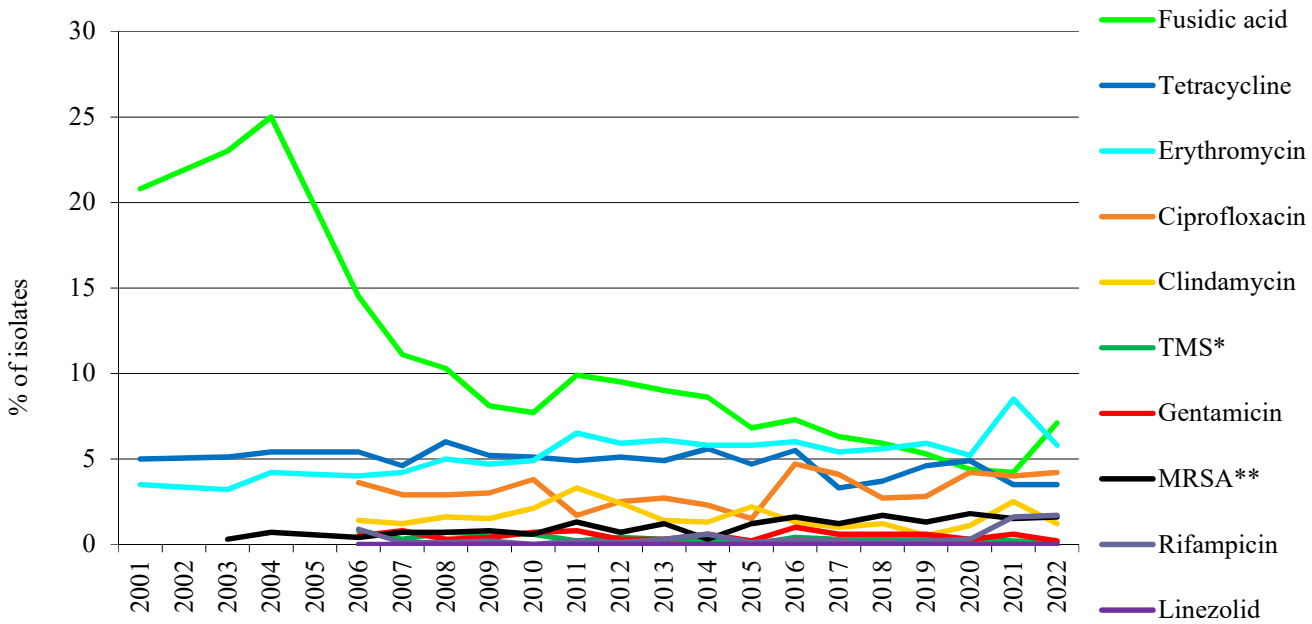

FIGURE 101. Prevalence of antimicrobial resistance among *Staphylococcus aureus* wound isolates 2001-2022. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis.
*TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2022

After a decrease in yearly number of notified cases of MRSA from 2018 to 2021, a small increase in cases was seen in 2022. A total of 1,934 persons were reported diagnosed with MRSA to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2022, including 843 infections and 1,091 colonisations. The incidence rate in the form of cases per 100,000 person-years was in total 38, and 16 and 22 for infections and colonisations respectively.

The incidence rate of persons reported with MRSA infections has not increased significantly over the last decade. The annual number of all notified cases reached a peak in 2017, decreased significantly until 2021, and increased slightly in 2022. Since the same pattern can be seen for MRSA colonisation, it is most likely the result of changes in the number of asymptomatic people being tested for MRSA by screening (Figure 102).

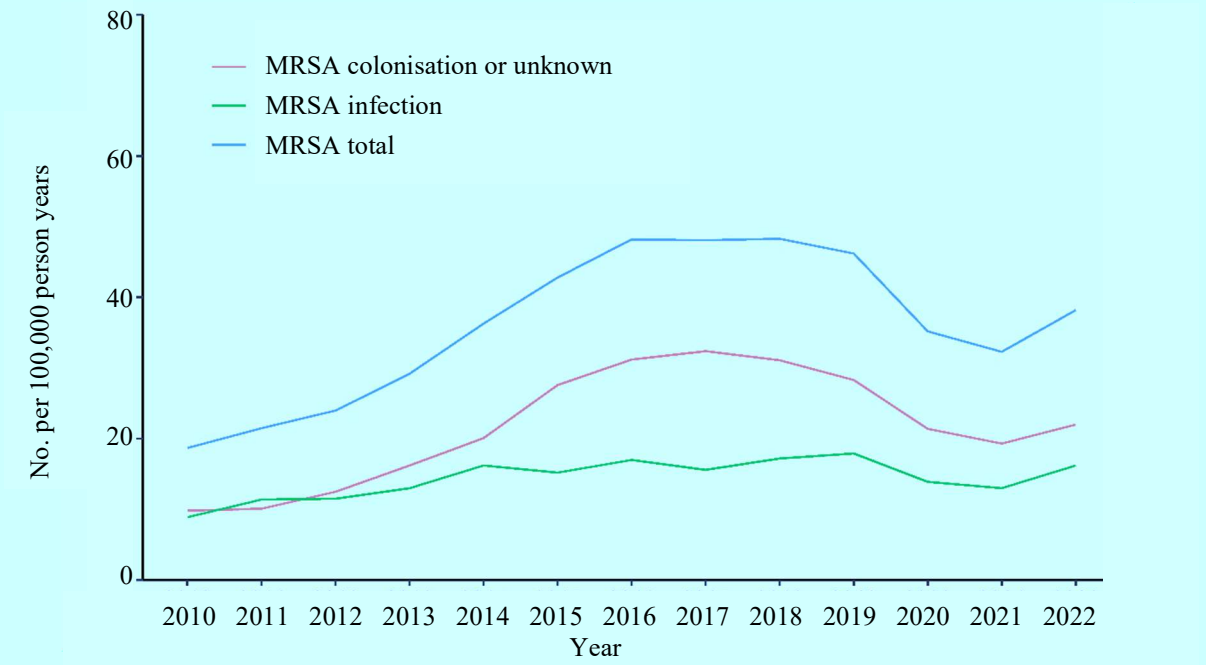

FIGURE 102. Number of persons notified with MRSA per 100,000 person-years in Norway in the last twelve years, by infection and colonisation.

The decrease in MRSA cases in 2020 and 2021 has most probably been influenced by prevention and control of Covid-19. In 2022, a total of 405 (21%) were reported to have acquired MRSA during travel abroad or prior to coming to Norway, while 535 (28%) were reported to have acquired MRSA in Norway. It is important to note that over 50% of all reported cases lack information about possible place of infection (Figure 103).

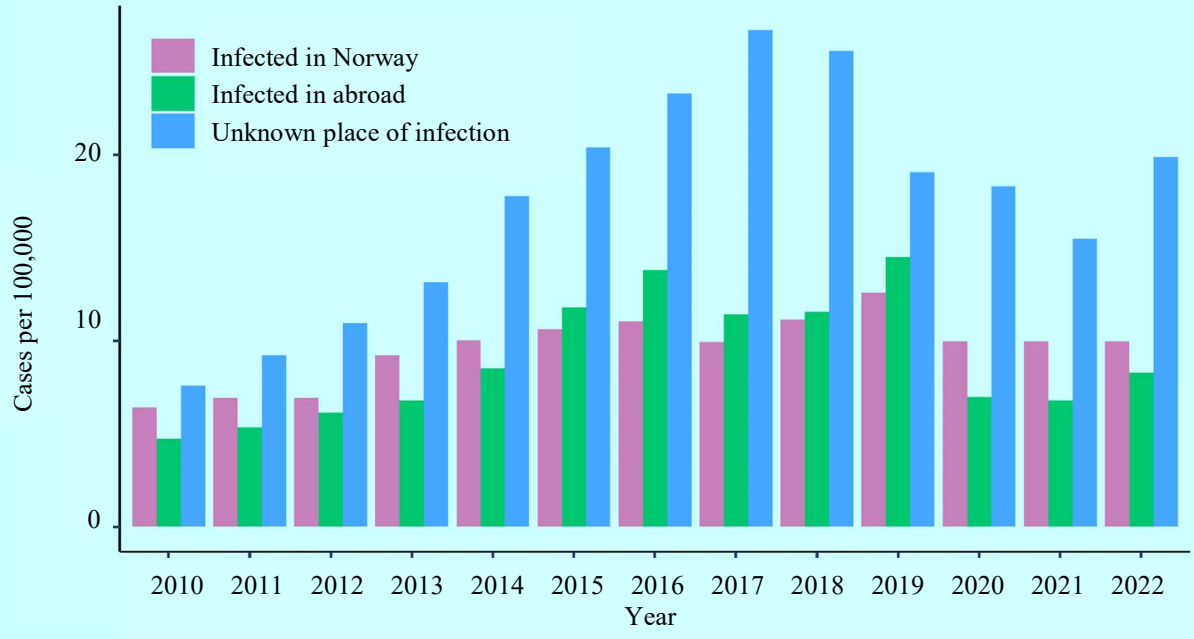

FIGURE 103. Number of persons notified with MRSA in Norway in the last twelve years, by assumed place of infection.

The Norwegian Reference Laboratory for methicillin resistant *Staphylococcus aureus* (MRSA) at St. Olavs Hospital, Trondheim University Hospital, received 2,232 MRSA isolates from 2,006 persons in 2022. Staphylococcal protein A (*spa*)-typing is the main genotyping method and was performed on all isolates. Three hundred thirty-two different *spa*-types were identified, of which 282 (84.9 %) were reported less than five times. Table 91 shows the ten most common *spa*-types in Norway in 2022. Eight out of the ten most frequent *spa*-types from 2022 were also on the top-ten list for 2021. MRSA t3841 and t1476 both show an increasing trend. These *spa*-types have previously been associated with multiresistance and need to be monitored closely.

TABLE 91. The ten most common *spa*-types among MRSA in Norway in 2022.

spa-type	CC	No. of isolates
t304	244	10.9 %
t127	152	6.8 %
t002	143	6.4 %
t008	129	5.8 %
t223	116	5.2 %
t3841	71	3.2 %
t021	66	3.0 %
t1476	66	3.0 %
t355	58	2.6 %
t005	51	2.3 %

The MRSA Reference Laboratory identified 17 livestock-associated MRSA (LA-MRSA) cases in humans, defined as PVL-negative MRSA belonging to CC398. The *spa*-types were t034 (n=11), and t011 (n=6). PVL-positive MRSA CC398 counted 23 human isolates, of *spa*-types t034 (n=16), t011 (n=4), t1255 (n=2) and t571 (n=1). Three human isolates were positive for *mecC* (all t843 and CC130). The laboratory received 21 *mecA*-positive *Staphylococcus argenteus* and 25 *mecA*-positive *Staphylococcus lugdunensis* isolates.

Antimicrobial susceptibility testing was performed by the referring laboratories according to the EUCAST disk diffusion method, and interpreted using the NordicAST 2022 breakpoints (Table 92). The MRSA Reference Laboratory received 2,138 complete antibiograms. Among these strains, 671 (31.4 %) were sensitive to all antibiotics tested except beta-lactams (cefoxitin). The highest proportion of resistance was found for erythromycin (38.8 %), followed by ciprofloxacin (31.7 %) and tetracycline (27.0 %). The rates of resistance for these three drugs have shown some variation the last years, potentially because of changing epidemiology of the most frequent *spa*-types. For ciprofloxacin there were many isolates with zone diameter close to the breakpoint, which may have contributed to different interpretation of the results by different laboratories. Low rates of resistance were found for rifampicin (1.8 %), trimethoprim-sulfamethoxazole (1.5 %) and mupirocin (1.2 %). Mupirocin antibiotic resistance has increased from 0.2 % in 2021 to 1.2 % in 2022 due to spread of a mupirocin resistant clone of MRSA t3841 CC 362. No isolates showed decreased susceptibility to linezolid or vancomycin.

TABLE 92. MRSA isolates with complete antibiograms from human cases in 2022. Distribution (% of isolates) of antimicrobial susceptibility by category (S, I, R).

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 1	61.2	-	38.8
Clindamycin*	≤ 0.25	> 0.25	84.2	-	15.8
Fusidic acid	≤ 1	> 1	84.0	-	16.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	97.6	0.9	1.5
Tetracycline	≤ 1	> 1	73.0	-	27.0
Gentamicin	≤ 2	> 2	85.1	-	14.9
Rifampicin	≤ 0.06	> 0.06	98.2	-	1.8
Mupirocin	≤ 1	> 256	95.6	3.2	1.2
Ciprofloxacin	≤ 0.001	> 1	0.0	68.3	31.7
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Proportion of isolates resistant to clindamycin are given in total. Of these, 13.5% were inducibly clindamycin resistant. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

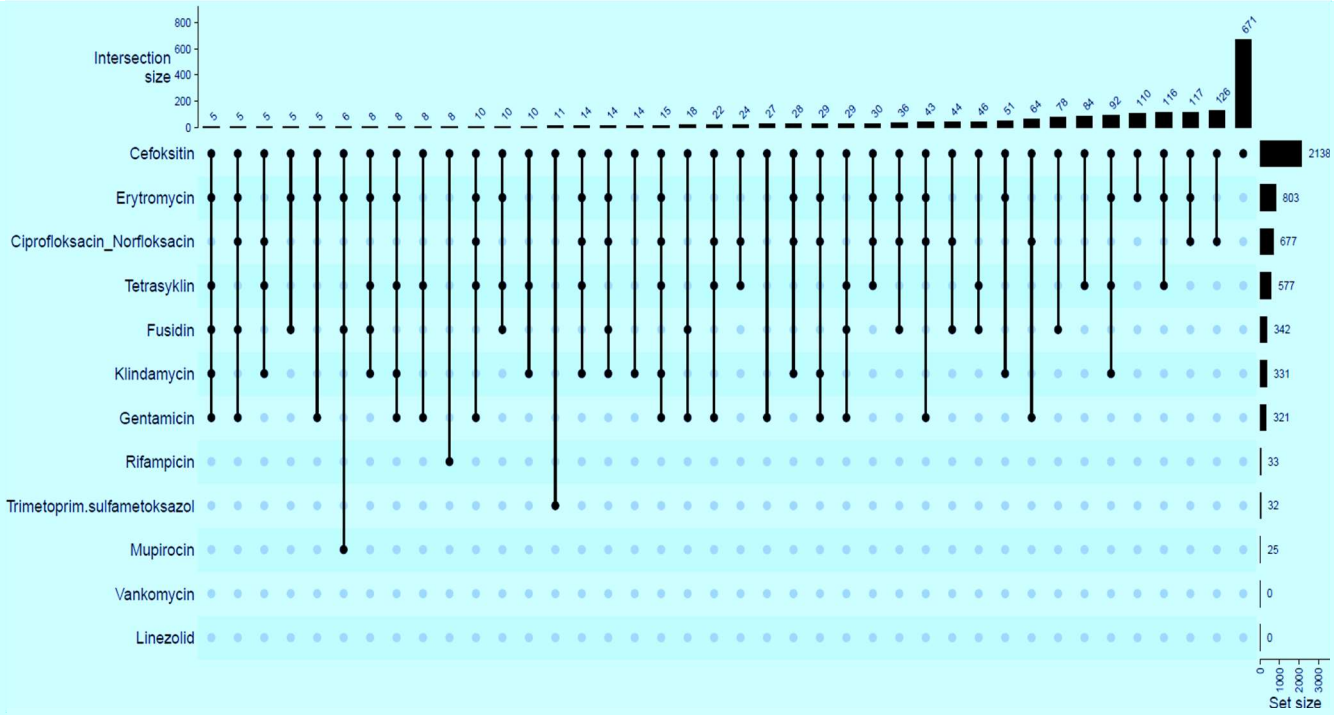

FIGURE 104. Common antibiotics with common combinations of resistance.

Figure 104 shows combinations of resistance to the most common antibiotics relevant for methicillin resistant *Staphylococcus aureus* in 2022. Cefoxitin resistance alone was the most common pattern for Norwegian MRSA isolates. The most frequent combination consisted of cefoxitin and ciprofloxacin resistance.

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Enterococcus spp. in blood cultures

TABLE 93. *Enterococcus* spp. blood culture isolates in 2022 (n=780). 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	77.8	0.3	21.9
Imipenem	≤ 0.001	> 4	0.0	75.9	24.1
Gentamicin HLR*	≤ 128	> 128	83.3	-	16.7
Linezolid	≤ 4	> 4	99.5	-	0.5
Tigecycline	≤ 0.25	> 0.25	97.9	-	2.1
Vancomycin (any genotype)	≤ 4	> 4	98.5	-	1.5
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.6	-	0.4

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *HLR=High Level Resistance.

TABLE 94. *Enterococcus faecalis* blood culture isolates in 2022 (n=551). 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	98.4	1.6
Gentamicin HLR*	≤ 128	> 128	93.1	-	6.9
Linezolid	≤ 4	> 4	99.6	-	0.4
Tigecycline	≤ 0.25	> 0.25	98.0	-	2.0
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 2022 (n=203). 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	16.3	0.5	83.3
Imipenem	≤ 0.001	> 4	0.0	12.8	87.2
Gentamicin HLR*	≤ 128	> 128	55.7	-	44.3
Linezolid	≤ 4	> 4	99.0	-	1.0
Tigecycline	≤ 0.25	> 0.25	97.5	-	2.5
Vancomycin (*vanA* or *vanB*)	Negative	Positive	98.5	-	1.5

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 2022 included 551 (70.6%) *E. faecalis* isolates (69.2% in 2021), 203 (26.0%) *E. faecium* isolates (25.5% in 2021), and 26 (3.3%) unspeciated or belonging to other species (5.3% in 2021). 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 remained relatively stable at 3.2 in 2019, 3.3 in 2020, 2.7 in 2021 and 2.7 in 2022. The panel of antimicrobial agents examined was unchanged from 2021-2022.

E. faecalis was universally susceptible to ampicillin (Table 94). The prevalence of resistance to ampicillin in *E. faecium* was 83.3% in 2022 compared to 71.5% in 2020 and 72.0% in 2021 (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 6.9%, which is a further decrease from 12.0% in 2020 and 8.5% in 2021 (Figure 105). The prevalence of HLGR in *E. faecium* was relatively stable at 44.3% compared to 46.2% in 2021. All HLGR *E. faecium* isolates (n=90) were also resistant to ampicillin and imipenem. Conversely, 90/169 (53.3%) 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. Twelve blood culture isolates (1.5%) were reported as vancomycin resistant in NORM 2022, but only three of these were confirmed by PCR to harbour transferrable vancomycin resistance (1 *vanA* and 2 *vanB E. faecium)*. The remaining phenotypically resistant isolates were either *E. casseliflavus* (n=7) or *E. gallinarum* (n=2), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. Four enterococcal isolates were phenotypically resistant to linezolid, and relevant genetic features were detected in three of them. Two *E. faecium* isolates had 23 rDNA mutations whereas one *E. faecalis* isolate harboured an *optrA* determinant.

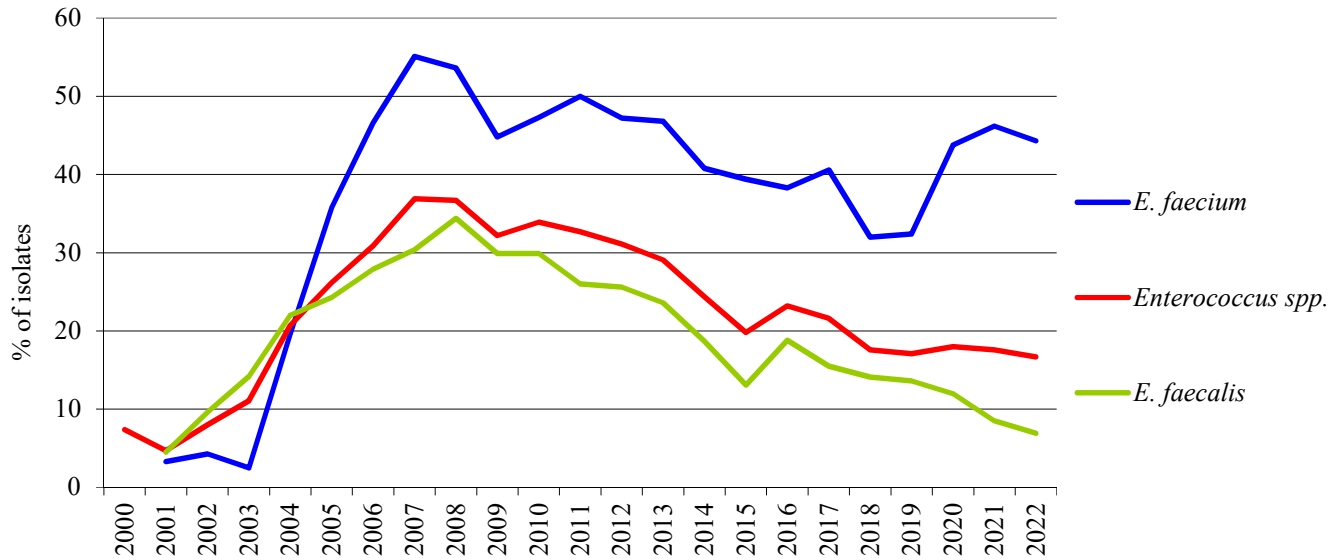

FIGURE 105. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2022. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Vancomycin and linezolid resistant enterococci in Norway 2022

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 side chain that prevents 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 *Enterococcus faecalis*, and are to varying degrees associated with successful mobile genetic elements such as plasmids and integrative conjugative elements. The most common acquired gene clusters are *vanA* and *vanB* (3).

In Norway, 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 Anti-microbial Resistance (K-res). K-res confirms the resistance phenotype when there is a discrepancy between pheno- and genotype with the reference microbroth dilution method 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 vancomycin resistant *E. faecium* has been reported from 2016 to 2020 (4), while in Norway the incidence of VRE infection/colonisation has varied during the last ten years. In 2022, 74 VRE were reported in Norway which is an increase of 40 isolates (118%) since 2021. Four of these were linezolid resistant (LVRE) (Figure 106). K-res has received isolates and/or WGS data on a subset (57/74; 77%) of VRE from 2022. Thus, this is not an overview of the molecular epidemiology of VRE in Norway in 2022. See Table 96 for an overview of the distribution by Health Regions of VRE in total and those analysed by WGS by K-res in 2022.

TABLE 96. Number of VRE isolates (n=57) in Norway for 2022 and those analysed by WGS at K-res, by Health Regions.

Health region	Number of VRE	Number of VRE with WGS data
South-Eastern	41	29
Western	25	20
Central	5	5
Northern	3	3

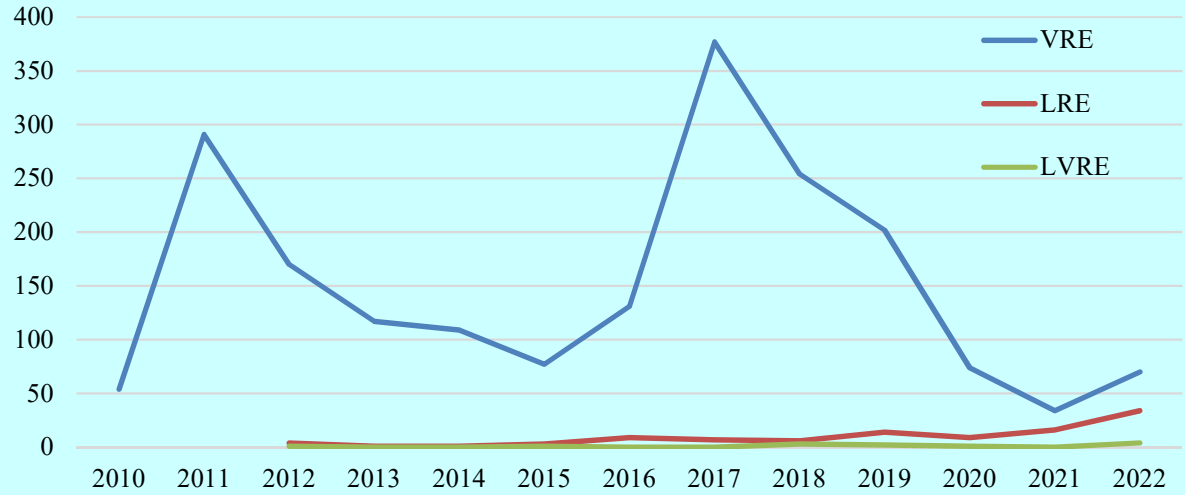

FIGURE 106. The number of vancomycin resistant (VRE), linezolid resistant (LRE) and both vancomycin and linezolid resistant (LVRE) enterococci in Norway 2010-2022. Combined data from MSIS.no and K-res.

Among the 57 VRE isolates from 2022, 35 were *vanA,* 11 *vanB*, and two *vanD E. faecium*, while one *E. faecium* isolate harboured both *vanA* and *vanB.* Four *vanA* and three *vanB E. faecalis* as well as one *E. gallinarum* isolate harbouring both *vanA* and *vanC* were also detected (Figure 107). VRE in Norway has previously been dominated by *vanB E. faecium* due to some larger outbreaks (5) while in 2022, most were *vanA E. faecium* (61% of the total), followed by *vanB E. faecium* (19%). Worldwide, vancomycin resistance is also much more prevalent in *E. faecium* than in *E. faecalis*, and *vanA* is more frequent than *vanB* (3).

We registered eight different sequence types (STs) of *E. faecium* in 2022 (Figure 108) which are known pandemic hospital adapted STs, as well as four different STs of *E. faecalis* (Figure 109) of which ST6 is often linked to clinical isolates and hospitals (6).

Nine smaller clusters were identified with two to seven isolates of ST17, ST18, ST80, ST117 and ST262 *E. faecium* (Figure 108) and one with two ST6 isolates of *E. faecalis* (Figure 109). Three of the smallest clusters contained two *E. faecium* with an epidemiological connection (*vanD* ST80 cluster 4, *vanA* ST17 cluster 9 and *vanB* ST80 cluster 8 in Figure 108) and were thus considered outbreaks. Cluster 4 represents the first outbreak of *vanD* registered in Norway. In the largest cluster of *E. faecium* (n=7, ST117; cluster 1 in Figure 108), all the isolates were associated with imports (e.g. from Ukraine) to six different hospitals in the South-Eastern and Western health regions. The six other clusters contained isolates that are not closely related in time and/or place. These were thus not considered to be outbreaks. Known hospital clones of *E. faecium* can typically survive for a long time and move with patients between hospitals, which makes it difficult to determine which isolates belong to an outbreak. Studies from the Public Health Laboratory in Melbourne, Australia (7), support the use of a three-month sliding window for genomic outbreak analyses of *E. faecium,* which we have implemented at K-res.

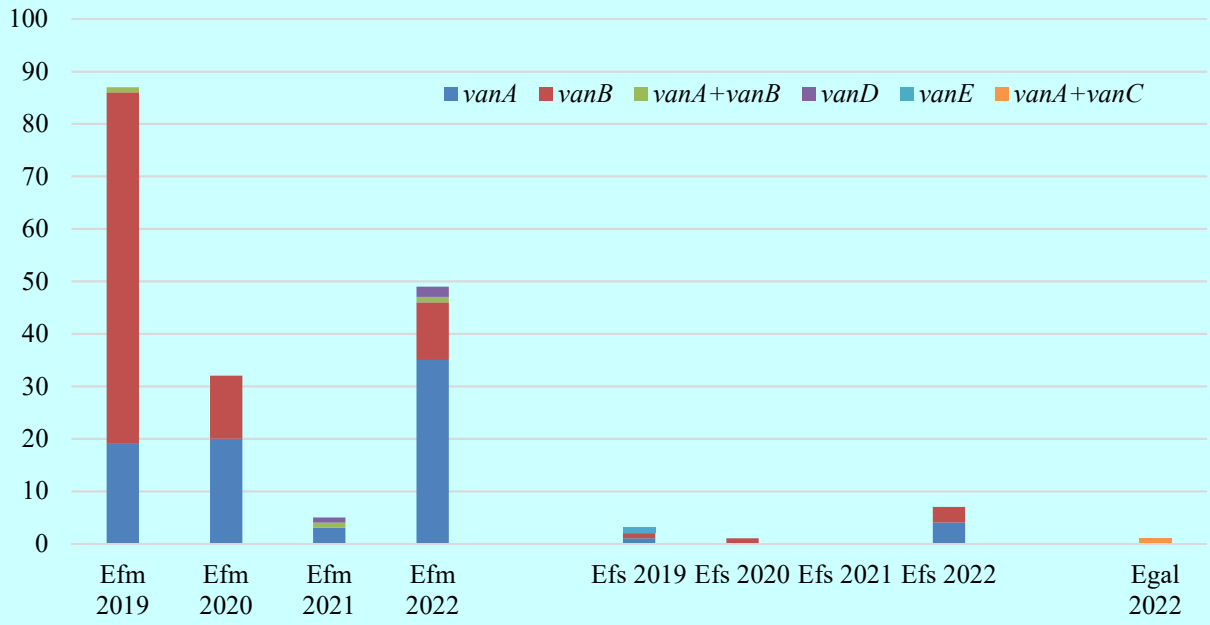

FIGURE 107. Species and genotype distribution of Norwegian VRE isolates that K-res has WGS data on for 2019, 2020, 2021 and 2022. This also includes linezolid resistant VRE. *Efm* = *E. faecium*, *Efs* = *E. faecalis*, *Egal* = *E. gallinarum.*

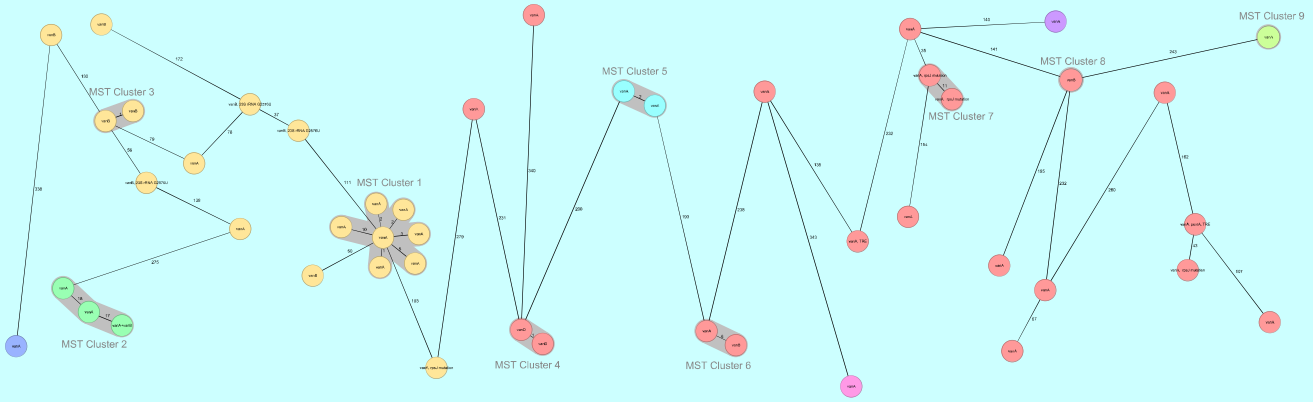

FIGURE 108. Minimum spanning network built from core genome allelic profiles of 49 Norwegian VRE *E. faecium* 2022 isolates using Ridom-SeqSphere+ software with integrated core genome (cg) MLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour-coded according to sequence type. VRE, LRE and tigecycline resistance is indicated in the circles. Isolates with zero allelic differences end up in the same circle. The number of allelic differences between isolates is indicated on lines between the circles. Nine different clusters (≤20 allelic differences) are highlighted with grey markings.

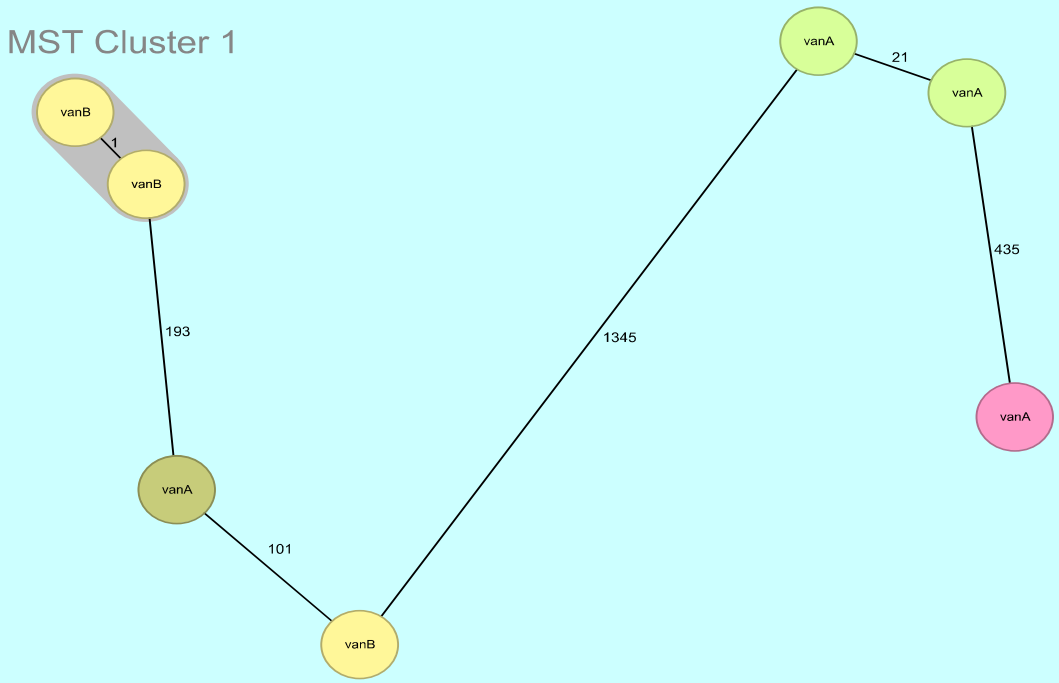

FIGURE 109. Minimum spanning network built from core genome allelic profiles of seven Norwegian VRE *E. faecalis* 2022 isolates using Ridom-SeqSphere+ software with integrated cgMLST scheme with *E. faecalis* OG1RF as reference strain. The isolates are colour-coded according to sequence type. VRE genotype is indicated in the circle, and number of allelic differences between isolates is indicated on lines between the circles. A cluster (≤7 allelic differences) is highlighted with grey marking.

Conclusion

In 2022, 74 cases of VRE were reported in Norway. This represents a significant increase (118%) from the previous year. In this report, we present genomic data for 57 isolates of which the majority were from screening samples (n=46). The VRE isolates are mainly sporadic isolates, but small clusters were identified in the South-Eastern and Western health regions. Most of the isolates were *E. faecium* (n=49) with *vanA* (n=35) or *vanB* (n=11). Three small outbreaks with *E. faecium* were registered (*vanD* ST80, *vanA* ST17 and *vanB* ST80). All VRE *E. faecium* belonged to widespread hospital adapted clones that has been reported worldwide.

Linezolid resistant enterococci

The oxazolidinone linezolid is considered an antibiotic of last resort in the treatment of infections caused by multi-drug resistant enterococci, and in particular VRE. The prevalence of linezolid resistance in enterococci is still low (<1%) worldwide (8) but is increasing in many countries (9).

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 (9). The *cfr*, *optrA* and *poxtA* genes can all be localised on mobile genetic elements (9-11). The *cfr* gene that confers resistance to 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 (9,12). Mutation based resistance often occurs after 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 (13).

In Norway, 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 microbroth dilution reference method and performs genetic characterisation with PCR and whole genome sequencing to find resistance mechanisms and monitor genetic relatedness between isolates. The Norwegian Working Group on Antibiotics and Methods for Antimicrobial Susceptibility Testing (AFA) recommends routine 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. All invasive *Enterococcus* isolates (n=1,392) were categorised as susceptible in the NORM report from 2021. Thus, there is no reason to believe that LRE is a large problem in Norway. However, the recommendations from AFA should be followed due to the global increase in LRE.

In 2022, 38 cases of LRE were detected in Norway. This is 22 more cases (138 % increase) compared to 2021 (Figure 110). The predominant species has changed from *E. faecium* towards *E. faecalis* the last years. The increase in *E. faecalis* LRE in Norway as of 2016 is mainly due to non-clonal spread of isolates with *optrA* (Figure 111; n=60).

Linezolid resistance in enterococci has traditionally mostly been mediated by point mutations in the chromosomal 23S rRNA regions, mainly the G2576U mutation. In 2022, 16 LRE were *E. faecium*, of which 15 had mutational based linezolid resistance and one *poxtA*. In the *E. faecalis* isolates (n=21), 19 had *optrA* and two mutational based linezolid resistance (Figure 111). The LRE cases in 2022 were mainly from infections (n=28), and 17 of these had *optrA*. Seven of the isolates were carrier isolates dominated by *E. faecium* (n=5) with mutational based resistance. Nine of the LRE isolates were associated with known import, but information about import is lacking for 20 isolates. All *E. faecium* isolates (*n*=16) belonged to well-known pandemic hospital associated sequence types (ST17, ST117 and ST80). The *E. faecalis* isolates (n=21) belonged to 12 different STs of which ST179, ST16 and ST895 were found in two or more isolates (Table 97).

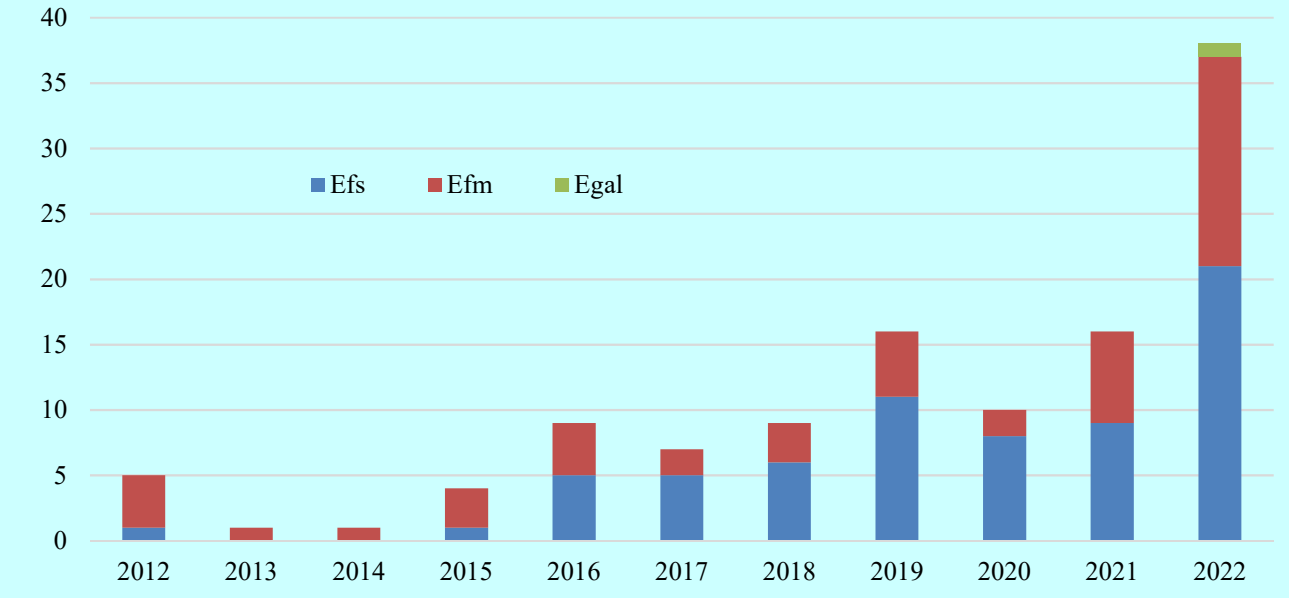

FIGURE 110. The number of linezolid resistant *E. faecium* (*Efm*), *E. faecalis* (*Efs*) and *E. gallinarum* (*Egal*) in Norway 2012-2022, including LRE that are vancomycin resistant.

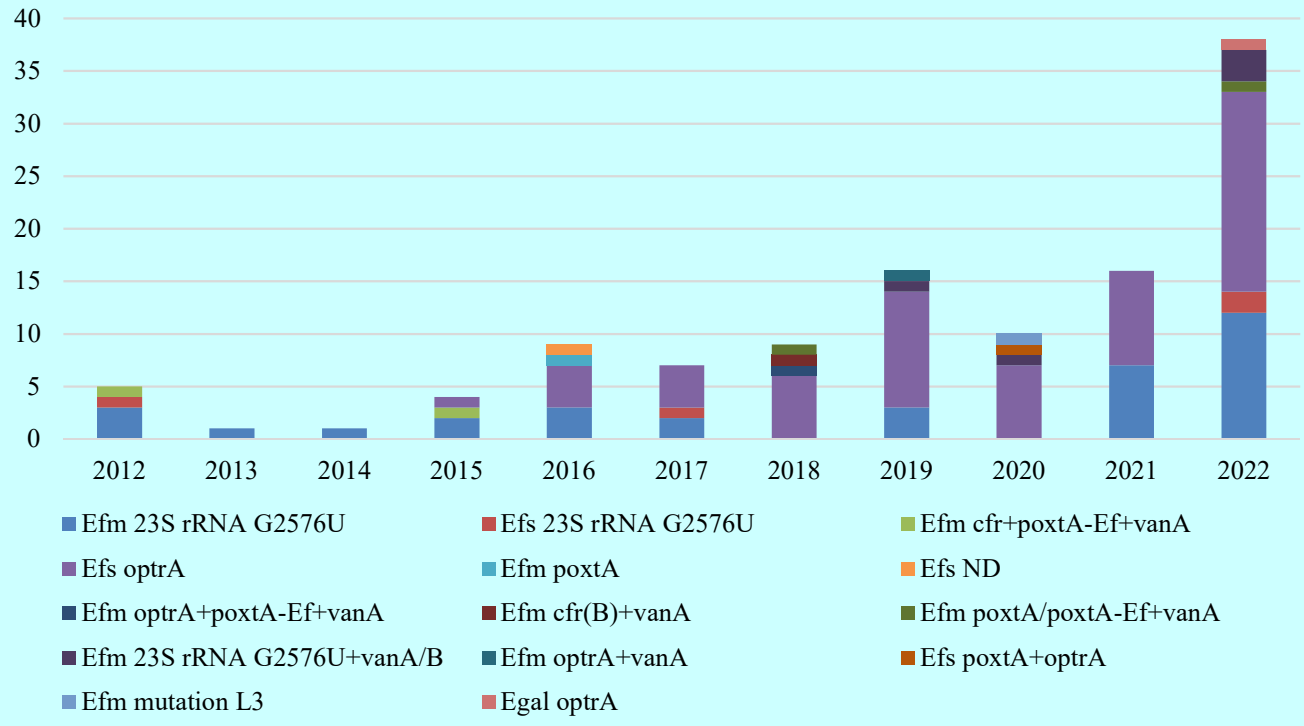

FIGURE 111. Number of LRE according to resistance mechanisms per year. *Efm = E. faecium. Efs = E. faecalis*. *Egal = E. gallinarum.* ND = not determined genotype. This isolate was not sent to K-res or archived at the primary laboratory.

TABLE 97. Species, resistance mechanism and sequence type among LRE in Norway 2022.

Species	Resistance mechanism	ST
E. faecalis (n=21)	*optrA* (n=19)	ST179 (n=6); ST16 (n=4); ST895 (n=2); ST310 (n=1); ST376 (n=1); ST1249 (n=1); ST1259 (n=1); ST1356 (n=1); ST1359 (n=1); ST1360 (n=1)
	23S rRNA G2576U mutation (n=2)	ST330 (n=1); ST333 (n=1)
E. faecium (n=16)	*23S rRNA G2576U mutation* (n=15)	ST17 (n=8); ST117 (n=4); ST80 (n=3)
	poxtA (n=1)	ST80 (n=1)
E. gallinarum (n=1)	*optrA* (n=1)	-

After the first hospital outbreak of LRE was registered in Norway in 2021, several cases of smaller clusters/outbreaks of LRE have been registered. Whole genome analyses showed that two ST16 and two ST895 *optrA E. faecalis* from 2022, respectively, belonged to the same clusters (Figure 112). Phylogenetic analyses showed two clusters of ST17 (n=4 and n=3), one with ST80 (n=3) and one with ST117 (n=2) of *E. faecium* with the G2576U mutation in the 23S rRNA V domain (Figure 113). ST895 *optrA E. faecalis* was considered to be an outbreak since both isolates came from the same hospital a few days apart and showed only one allelic difference in the core genome (Figure 113; cluster 1). This is the first outbreak registered in Norway with *optrA*. An epidemiological link was also demonstrated for one of the ST17 clusters from two different hospitals (Figure 113; cluster 3). This was therefore also considered an outbreak. For all the other clusters, the isolates were not closely connected in time and/or place and were thus not considered to be outbreaks.

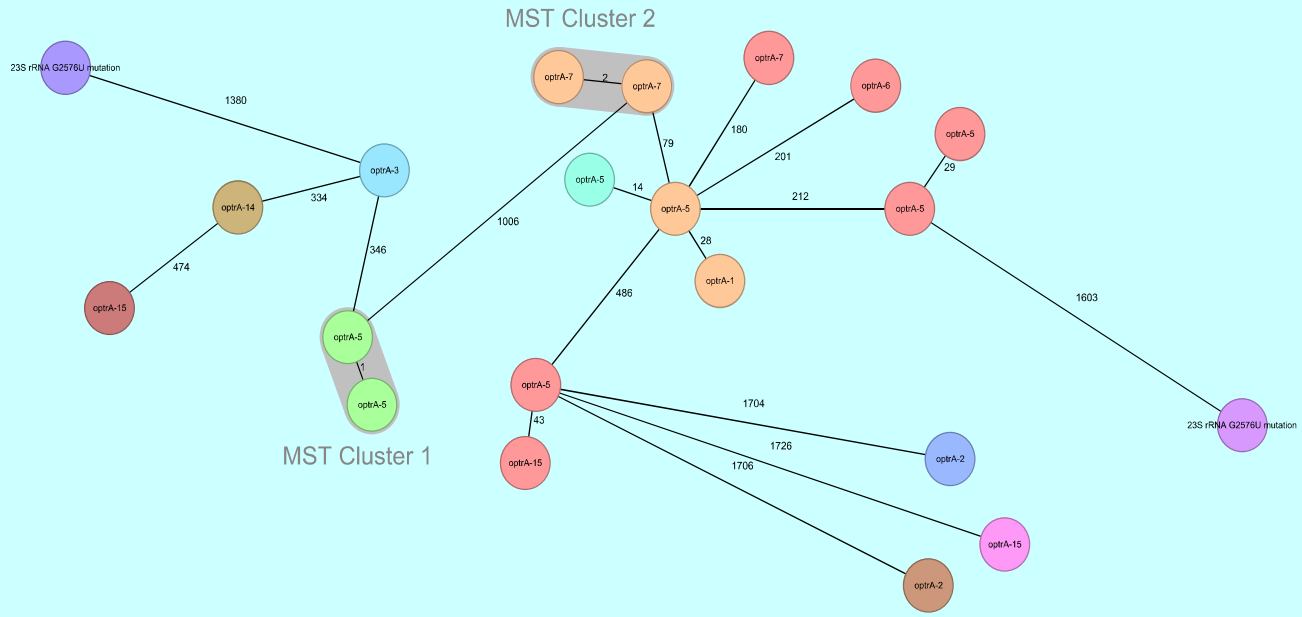

FIGURE 112. Minimum spanning network built from core genome allelic profiles of the 21 Norwegian LRE *E. faecalis* 2022 isolates using Ridom-SeqSphere+ with integrated cgMLST scheme with *E. faecalis* OG1RF as reference strain. The isolates are colour-coded according to ST. Two clusters (≤7 allelic distance) are indicated by grey marking.

Conclusion:
The number of reported LRE in Norway was still low in 2022 (n=38), although the number of isolates increased by 138% compared to 2021. The majority of the LRE are clinical isolates (n=28). *E. faecalis* with transferable resistance (*optrA* n=19) and *E. faecium* with 23S rRNA mutations (n=15) were the dominant LRE variants. Phylogenetic analyses confirmed two small outbreaks of *optrA E. faecalis* (n=2) and *E. faecium* (n=4) resistant to linezolid due to a mutation (G2576T) in the 23S rRNA gene. The increase in LRE is possibly due to more clinical isolates of enterococci being routinely tested for linezolid resistance following new national recommendations. However, lack of established routines and protocols for continuous analysis of combined data from the communicable disease registry and reference laboratory results in an incomplete overview of the proportion of linezolid resistant enterococci associated with import or possible internal spread within Norway.

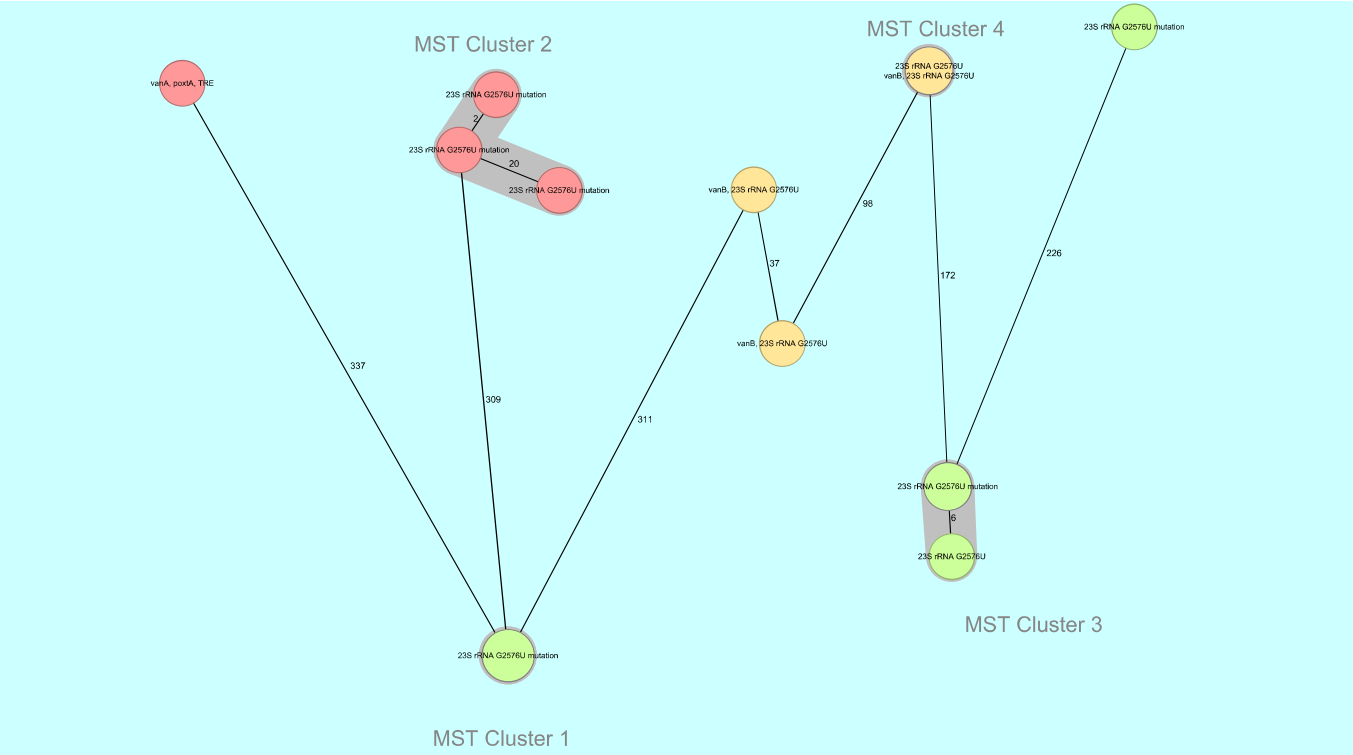

FIGURE 113. Minimum spanning network built from core genome allelic profiles of the 16 Norwegian LRE *E. faecium* 2022 isolates using Ridom-SeqSphere+ software with integrated cgMLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour-coded according to ST. Two isolates showed identical allelic profiles and are thus not showed as separate circles. VRE, LRE and tigecycline resistance is indicated in the circle. Number of allelic distances between the isolates are given at the lines between the circles. Four clusters with ≤20 allelic distances are highlighted with grey marking.

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Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 98. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2022 (n=546). 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	89.8	9.7	0.5
Cefotaxime*	≤ 0.5	> 2	98.9	1.1	0.0
Ceftriaxone*	≤ 0.5	> 2	98.7	1.3	0.0
Erythromycin	≤ 0.25	> 0.25	95.4	-	4.6
Clindamycin	≤ 0.5	> 0.5	96.0	-	4.0
Tetracycline	≤ 1	> 1	94.3	-	5.7
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	89.9	2.2	7.9

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 99. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2022 (n=546). 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*		4.9	37.7	44.3	2.7	2.2	3.8	2.7	0.5	0.4	0.4		0.2			
Cefotaxime*		4.4	41.9	42.7	4.4	3.3	1.8	0.4	0.7	0.4						
Ceftriaxone*			21.8	63.4	6.4	3.8	2.9	0.4	0.4	0.9						
Erythromycin	0.2			5.7	66.7	22.3	0.5				0.2	0.2		0.4		3.8
Clindamycin				3.8	56.8	34.8	0.4	0.2	0.2						0.2	3.7
Tetracycline						20.7	62.1	11.2	0.4	0.4	0.4	0.2	0.9	2.9	0.9	
TMS**					0.4	31.9	49.1	6.2	2.4	2.2	3.5	4.4				
Chloramph.							0.2		2.0	47.3	49.3		1.3			
Norfloxacin										1.8	24.4	58.4	14.5	0.9		

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 for resistance to erythromycin and tetracycline were reduced in 2023 from R > 0.5 mg/L to R > 0.25 mg/L, and from R > 2 mg/L to R > 1 mg/L, respectively. In both cases the effect was to eliminate the I category, and the present R categories thus correspond to the previous I+R categories. The text and figures have been updated accordingly for the period 2000-2022. Breakpoints for chloramphenicol are no longer valid. The oxacillin screening disk was not applied in the NORM 2022 protocol.

The results are summarised in Tables 98-99 and Figures 114-115. Seventeen strains were isolated from cerebrospinal fluids. Six of these were only isolated from this specimen type, whereas the remaining eleven 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 9.7% (53/546) of *S. pneumoniae* isolates were only susceptible to increased penicillin G exposure (MIC 0.125-2 mg/L), and three isolates (0.5%) 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 9.7% recorded in 2022 is higher than 6.3% in 2021, but lower than 11.1% in 2020. The three penicillin G resistant blood culture isolates (MIC 4 mg/L (n=2), MIC 16 mg/L (n=1)) were all susceptible only to increased cefotaxime and ceftriaxone exposure (MIC 1-2 mg/L). Four additional isolates susceptible to increased penicillin G exposure (MIC 0.125-2 mg/L) were also categorised as I to ceftriaxone (n=4) and cefotaxime (n=3). 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. Please note that the number of pneumococcal isolates was significantly reduced during the pandemic years 2020-2021, and the reported estimates for this period may therefore be biased by both random and systematic errors.

The prevalence of erythromycin resistance was reduced to 4.6% compared to 8.4% in 2020 and 6.0% in 2021 (Figure 114). Most of these isolates (21/25) were resistant to both erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining four 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 115).

The 7.9% resistance rate to trimethoprim-sulfamethoxazole was unchanged from 2021. The prevalence of tetracycline resistance decreased from 7.9% in 2021 to 5.7% in 2022 (Figure 114). The vast majority of isolates (98.7%) 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 99) may reflect the limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

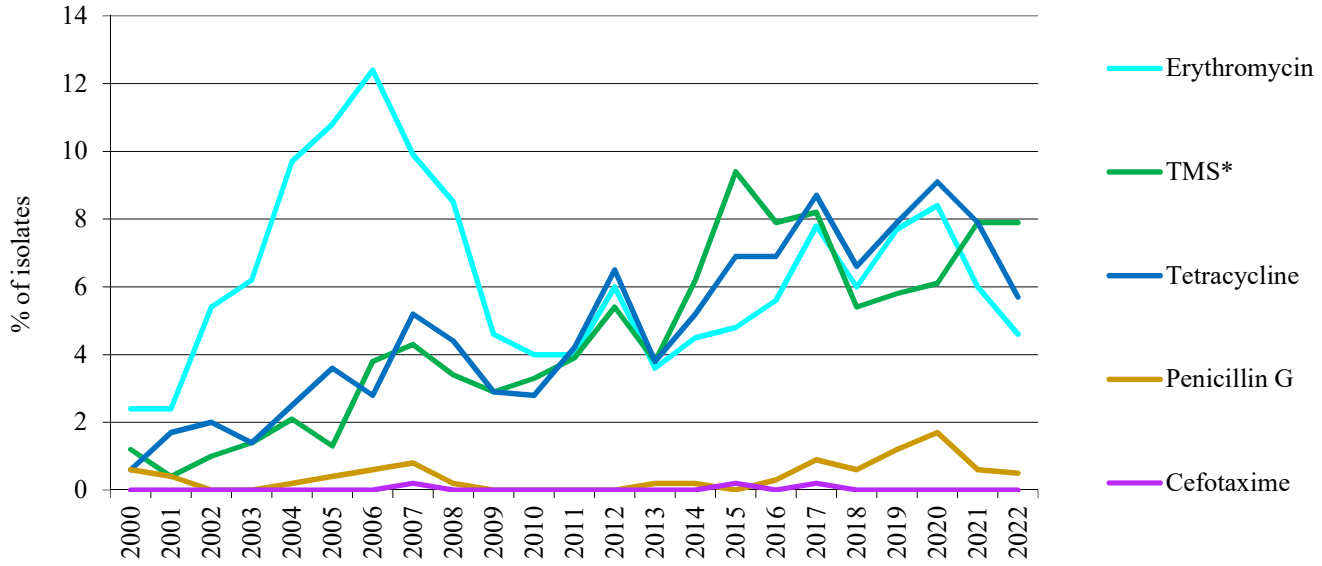

FIGURE 114. Prevalence (%) of resistance to antimicrobial agents in *Streptococcus pneumoniae* blood culture and cerebrospinal fluid isolates during 2000-2022. Doxycycline was substituted by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole.

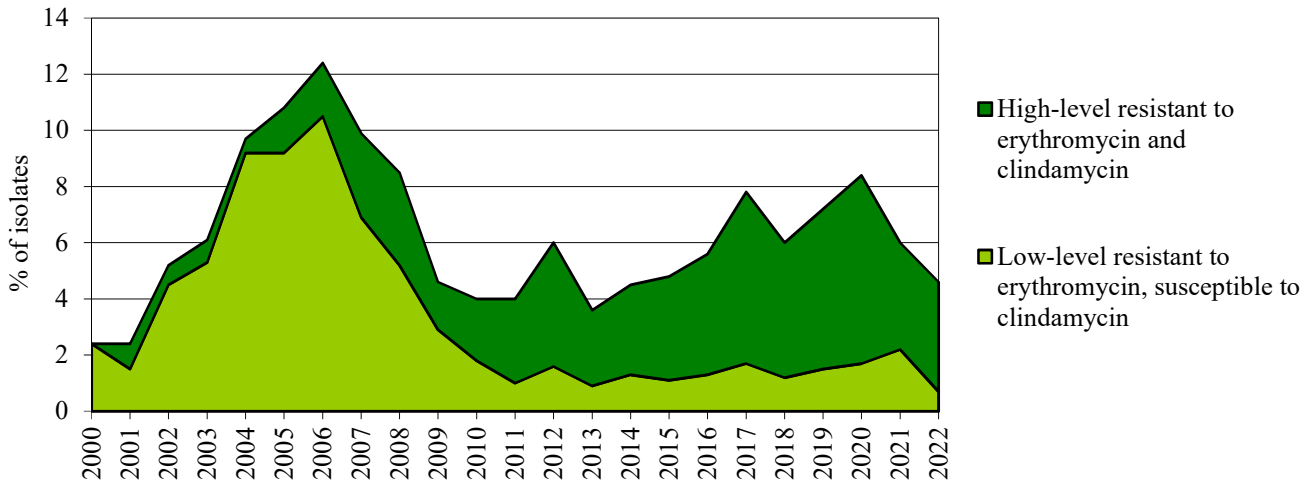

FIGURE 115. Prevalence of resistance (%) to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2022.

Streptococcus pyogenes in blood cultures

TABLE 100. *Streptococcus pyogenes* in blood cultures in 2022 (n=123). 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	95.9	-	4.1
Tetracycline	≤ 1	> 1	82.9	-	17.1
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	100.0	0.0	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.

TABLE 101. *Streptococcus pyogenes* in blood cultures in 2022 (n=123). 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	0.8	25.2	73.2	0.8												
Erythromycin					39.0	52.0	2.4		0.8		1.6					4.1
Clindamycin			0.8	26.0	61.8	5.7	1.6									4.1
Tetracycline						37.4	39.8	5.7			0.8	0.8	6.5	6.5	2.4	
TMS*			2.4	38.2	53.7	4.9			0.8							

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. *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 has been reduced during the pandemic 2020-2022 as compared to historical data, and the results should therefore be interpreted with caution. The results were categorised according to the most recent EUCAST/ NordicAST clinical breakpoint protocol. The breakpoints for resistance to erythromycin and tetracycline have been reduced from R > 0.5 mg/L to R > 0.25 mg/L, and from 2 mg/L to 1 mg/L, respectively. The I categories have thus been eliminated and the present R categories correspond to the I+R categories from previous years.

As expected, all isolates were fully susceptible to penicillin G (Tables 100-101). The rates of resistance to erythromycin reverted to 6.5%, which is lower than 19.2% in 2021 but similar to 6.7% in 2020. During the same time period, the prevalence of clindamycin resistance was 5.2% in 2020 and 11.5% in 2021 but decreased to 4.2% in 2022. High-level resistance to erythromycin was in all cases (5/5) linked to clindamycin resistance, presumably due to *erm*-encoded constitutive expression of MLS_B resistance. Three additional isolates displayed low-level erythromycin resistance combined with clindamycin susceptibility, thus suggesting a *mef*-encoded efflux mechanism (also consider Table 102, page 152). Phenotypic MLS testing was not performed.

The prevalence of tetracycline resistance decreased from 39.7% in 2021 to 17.1% in 2022. This figure corresponds well with the pre-pandemic rate of 15.7% in 2020. The prevalence of resistance to trimethoprim-sulfamethoxazole has remained stable at very low levels (0.7% in 2020; 1.3% in 2021), and this phenotype was not detected at all in 2022.

Streptococcus pyogenes – key results on *emm*-types and resistance genes

S. pyogenes, the most prevalent *Streptococcus* species among beta-hemolytic group A streptococci (GAS), is a strictly human pathogen with a global presence, and significant bacterial diversity (ref. Bessen 2009). The organism causes a range of infections in humans, from localised tonsilitis, otitis media, impetigo, and erysipelas, to more serious infections such as scarlatina (that can be complicated by rheumatic fever and glomerulonephritis), cellulitis, necrotising fasciitis, necrotising pneumonia, post-partum endometritis, septic arthritis, meningitis and sepsis. GAS is a major cause of death and disability, particularly in low- and middle-income countries (Sanyahumbi, 2016). No vaccine against GAS is available yet, but the World Health Organizaion (WHO) has outlined a strategic framework to expedite the development of GAS vaccines (WHO, 2018).

The M cell wall protein, encoded by the *emm*-gene, is regarded as a major virulence factor, contributing to bacterial adhesion to host tissue. It exhibits over 100 protein variants (Raynes 2009), and more than 220 gene variants. Additional virulence factors are streptococcal pyrogenic exotoxins (SpeA, SpeB), streptolysins (SLO, SLS) and others. A notable emerging lineage of M1, $M1_{UK,}$ was first reported from England in 2015/2016. It is characterised by 27 single nucleoptide polymorphisms (SNPs) in the core genome and increased production of SpeA (Lynskey, 2019).

In Norway, systemic *S. pyogenes* infection has been mandatorily notifiable since 1993. The annual incidence is typically 3-4 cases per 100,000 population, with around 200-250 cases reported annually. During the Covid-19 pandemic, the frequency decreased significantly, likely due to social distancing measures (Ledford, 2022). From 2017, Norwegian systemic GAS isolates were subjected to whole genome sequencing at the NIPH GAS reference laboratory, with a break during 2018 when the laboratory moved location within the NIPH. Their *emm*-types were determined by use of the CDC *Streptococcus* laboratory protocol, M1 lineages through core SNP analysis and resistance genes were identified.

During late autumn 2022, Norwegian clinicians reported informally to the NIPH on an apparent increase in extremely serious systemic GAS infections, in children often secondary to viral infections such as chickenpox and RS-virus. However, the crude number of systemic GAS reported to MSIS was still lower than the pre-Covid-19 level. At the same time, European countries reported an increase in systemic GAS and both the WHO and the European Centre for Disease Control (ECDC) were concerned. WHO evaluated the risk to public health in European countries to be low because the rise in cases was moderate, no new *emm* sequence types had been seen and neither was any increase in antibiotic resistance. In line with WHO recommendations, the NIPH increased its focus on systemic GAS epidemiology and undertook public health communication activities to ensure proper clinical assessment, diagnostic testing, and prompt treatment of GAS infections. Meanwhile, the question was raised if new bacterial traits had been introduced.

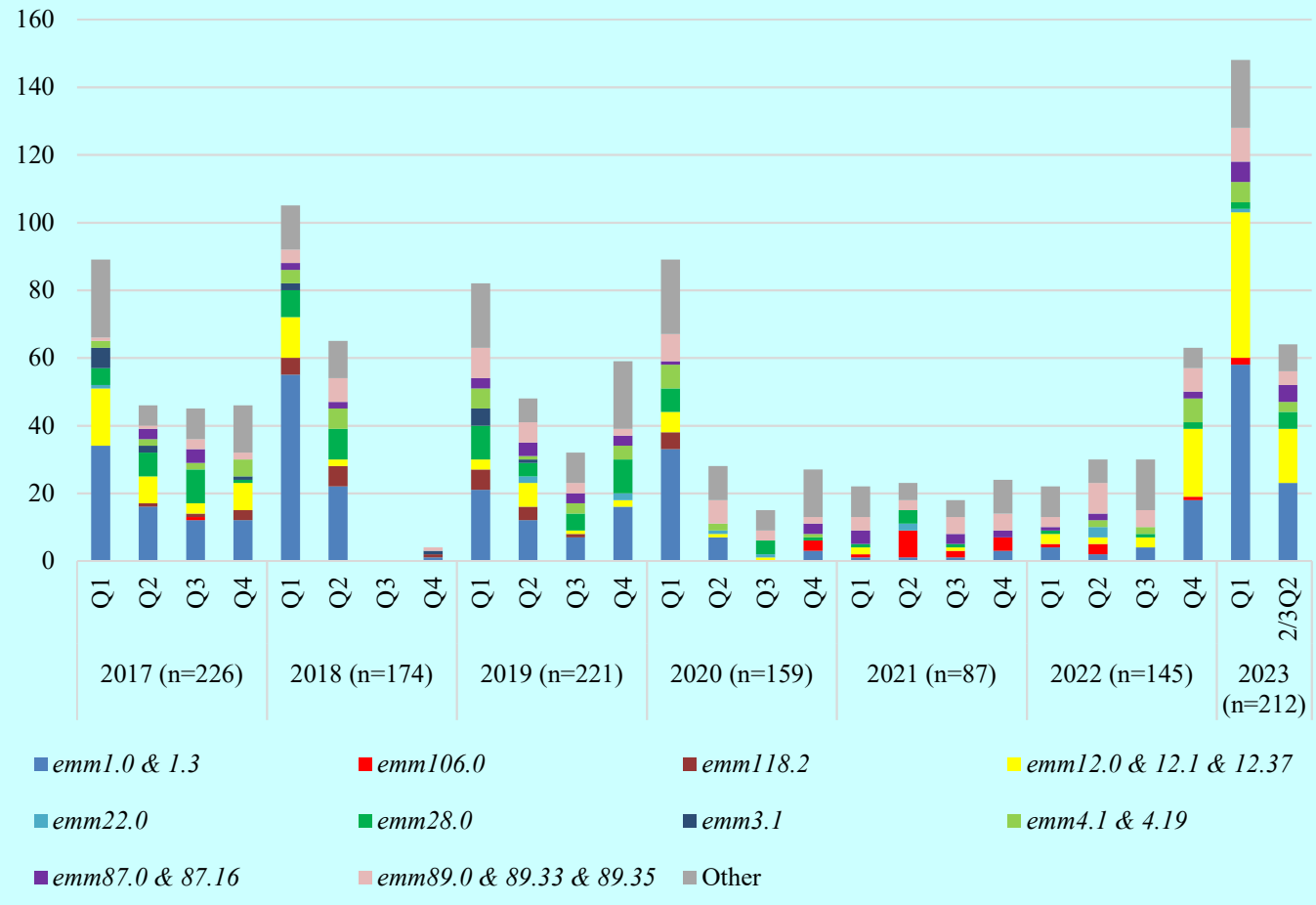

FIGURE 116. Number of systemic *S. pyogenes* isolates of most prevalent *emm* types, during 2017 to May 2023, by quartal and year of isolate arrival to the NIPH reference laboratory.

Of systemic GAS forwarded to the NIPH reference laboratory, whole genome sequencing concluded that a handful were other betahemolytic streptococci than *S. pyogenes*, resulting in 1,220 isolates eligible for inclusion in the study. Figure 116 shows that during late 2022 and early 2023, the number of isolates increased steeply, in line with what was reported from clinicians. Furthermore, *emm1* returned to pre-Covid-19 levels (31.7% vs. 34.7%, p-value 0.5), while *emm12* appears more frequently post Covid-19 (13.3% vs. 34.4%, p-value <0.001). *emm106* surged during the pandemic (0% - 9.3% - 0.8%), while *emm118.2* has disappeared (4.5% - 0% - 0%). Furthermore, among *emm1* isolates, the $M1_{UK}$ gained dominance (Figure 117), parallel to the development seen in England.

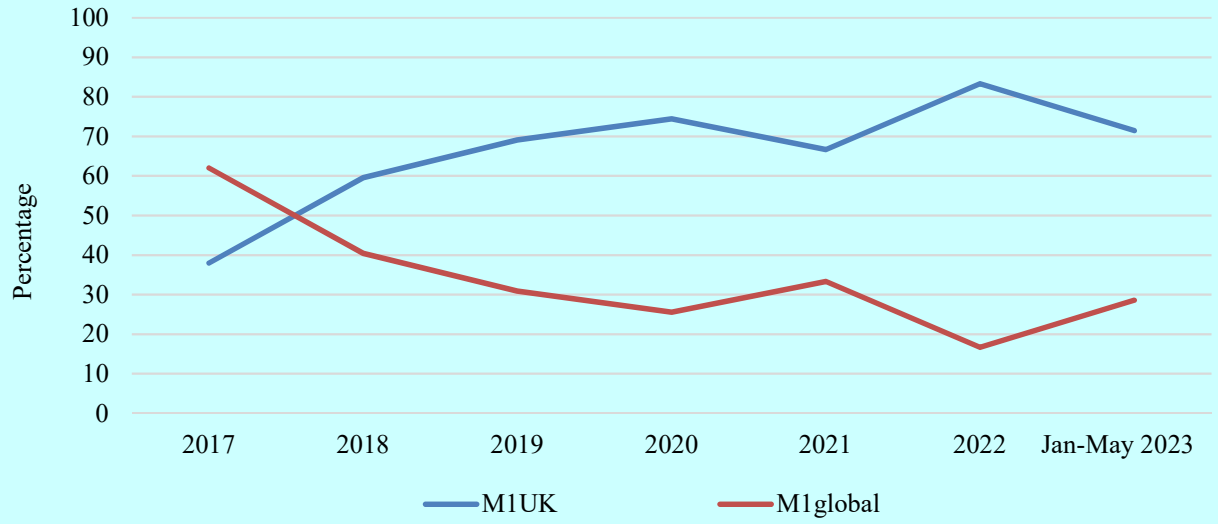

FIGURE 117. Proportion of $M1_{UK}$ among and $M1_{global}$ (i.e other lineages than $M1_{UK}$) among Norwegian *emm1 S. pyogenes* 2017 to May 2023.

15.7% of the 1,220 isolates carried one or more resistance genes (Table 102). Figure 118 shows the proportions of isolates carrying each group of resistance genes. Genotypic resistance corresponded very well with expected resistance phenotype (data not shown). Almost all isolates of *emm22, emm106*, and *emm118.2* carried resistance genes, while the opposite was the case with *emm1* and *emm87* and seen in a low frequency in *emm4* (7.7%), *emm12* (1.2%), *emm28* (3.1%) and *emm89* (5.3%) (data not shown).

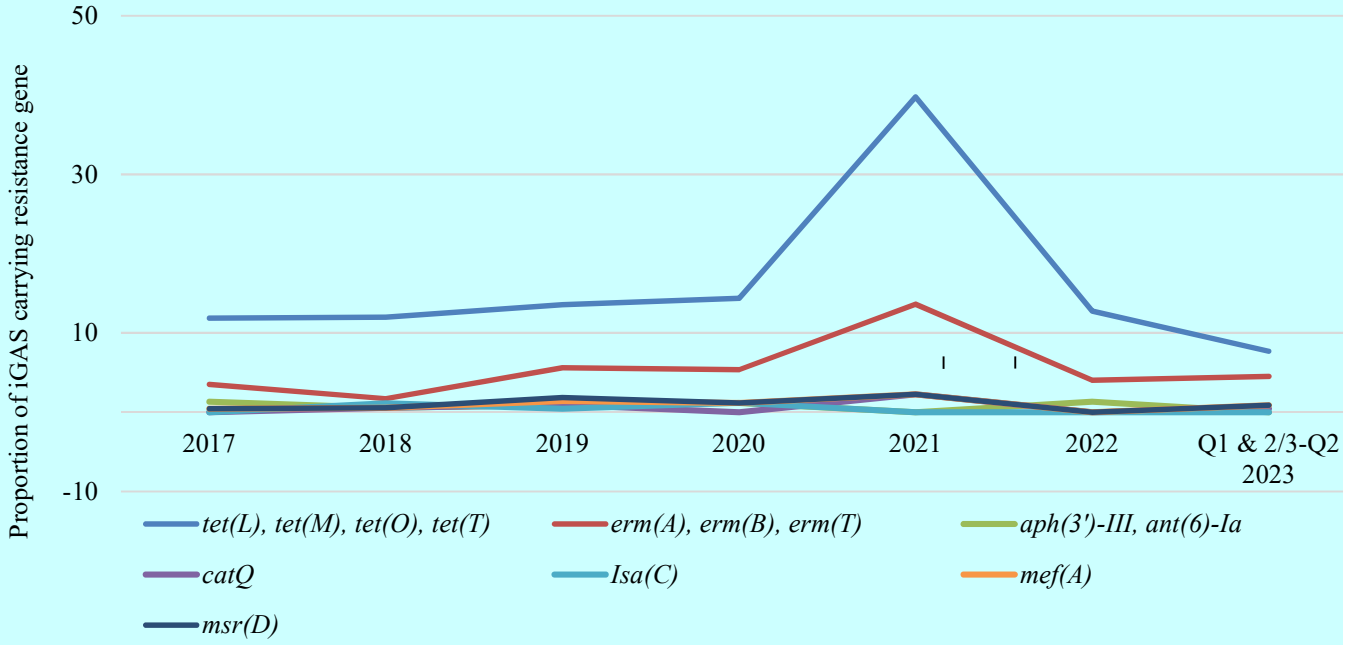

FIGURE 118. Proportion of Norwegian invasive *S. pyogenes* isolates analysed between 2017 and May 2023, with specified antibiotic resistance gene, by year.

TABLE 102. Resistance genes and which antibiotic group they confer resistance to (most prevalent within gene group in bold).

Resistance gene	Antibiotic class
tet(L), **tet(M)**, tet(O), tet(T)	Tetracyclines
erm(A), **erm(B)**, erm(T)	Lincosamides, macrolides, streptogramin b (MLS_B-phenotype)
mef(A) and msr(D)	Macrolides with 14 and 15 membered lactone ring (i.e erythromycin, azitrhromycin; M-phenotype)
Isa(C)	Lincosamides, streptogramin A, pleuromutilin (LS_AP-phenotype)
aph(3')-III, ant(6)-Ia	Aminoglycosides
catQ	Chloramphenicol

This study provides insights into the *emm*-types, M1 lineages, and resistance gene profiles of *S. pyogenes* in Norway. It confirms the persistence of known *emm* types and highlights the dominance of the $M1_{UK}$ lineage. The prevalence of resistance genes varies among *emm* types, with certain types exhibiting a higher frequency. The transient occurrence of both *emm22* and *emm106* systemic *S. pyogenes* during covid-19 probably explains the relatively high level of resistance in systemic *S. pyogenes* against tetracycline, macrolides and clindamycin seen in the 2021 NORM data. The findings contribute to our understanding of the epidemiology and bacterial traits of *S. pyogenes*, aiding in the development of strategies for its prevention and treatment.

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We would take the opportunity to thank all Norwegian clinical laboratories for their efforts in forwarding isolates to the GAS reference laboratory at NIPH.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 103. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2022 (n=311). 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	78.8	-	21.2
Clindamycin	≤ 0.5	> 0.5	86.5	-	13.5
Tetracycline	≤ 1	> 1	25.4	-	74.6
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 2022 (n=311). 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*		0.3	4.2	47.6	47.6	0.3										
Erythromycin					5.8	45.7	27.3		0.3	2.3	5.8	4.2	1.3	0.3		7.1
Clindamycin				0.3	7.7	74.3	1.9	2.3	2.3	0.3			0.3			10.6
Tetracycline			0.3	4.5	19.9	0.6				0.3	2.3	42.8	23.8	5.5		
Vancomycin					1.3	48.9	49.5	0.3								
Gentamicin												1.3	4.2	29.9	54.3	10.3

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 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*, the EUCAST/ NordicAST *S. agalactiae* erythromycin and tetracycline resistance breakpoints have been reduced from R > 0.5 mg/L to R > 0.25 mg/L, and from 2 mg/L to 1 mg/L, respectively. The I categories have thus been eliminated and the present R categories correspond to the I+R categories from previous years.

A total of 311 isolates were retrieved from invasive infections in 2022. Thirty-one isolates (10.0%) originated from neonates and small children < 1 year of age. Most isolates (99.4%) were recovered from blood cultures, but there were also two isolates from cerebrospinal fluids. All isolates represented individual infection episodes.

As seen in Tables 103-104 there were no isolates with reduced susceptibility to penicillin G or vancomycin. 21.2% (66 isolates) were resistant to erythromycin compared to 22.7% in 2021. All were analysed by double disk diffusion for MLS_B resistance phenotype. Constitutive MLS_B resistance was found in 47/66 isolates (71%), while inducible MLS_B resistance was detected in 9/66 isolates (14%). The remaining 10/66 isolates (15%) had results in accordance with the efflux-mediated M phenotype encoded by *mef* genes. Two isolates were recorded as clindamycin resistant (MIC 1 mg/L) in spite of being susceptible to erythromycin (MIC 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 10.3% of the isolates. The prevalence of resistance to tetracycline (74.6%) was at the same level as in 2020 (75.2%) and 2021 (80.0%) with the majority of isolates displaying MIC values of 8-16 mg/L (Table 104).

Resistance to empiric antibiotic combinations used to treat bloodstream infections – All quiet on the western front

Post Covid-pandemic, the occurrence of key bloodstream infection bacteria returned to prepandemic levels (see Table 61 in this report). Interestingly, resistance to empiric antibiotic combinations (Table 105), did not change significantly from 2021 (1). Gentamicin resistance rates, in particular in *E. coli* and *Klebsiella* spp., remained low. As shown by Samuelsen et.al. in this report, cases with carbapenemase-producing *Enterobacterales* (CPE) increased by >150% compared to 2021, but there was no significant ´spill-over´ to bloodstream infections.

New in this year's report is the inclusion of *Enterobacter* spp., *Citrobacter* spp. and *Serratia* spp. Despite accounting for just 3.9% of blood stream isolates, these *Enterobacterales* species are of particular interest due to their propensity for resistance to broad-spectrum cephalosporins and piperacillin-tazobactam via chromosomal AmpC beta-lactamases. Indeed, *Enterobacter* spp., *Citrobacter* spp., and, to a lesser extent, *Serratia* spp., exhibited substantial resistance to cefotaxime and piperacillin-tazobactam. Fortunately, resistance to gentamicin and meropenem was limited, comparable to *E. coli* and *Klebsiella* spp. Resistance rates in *Enterobacter* spp. have remained stable, compared to 2008 and 2016. *Citrobacter* spp. and *Serratia* spp. have not been monitored previously.

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=2,229)	*Klebsiella* spp. (n=1,114)	ESBL *Enterobacterales** (n=194)	*Enterobacter* spp. (n=259)	*Citrobacter* spp. (n=77)	*Serratia* spp. (n=124)	*H. influenzae* (n=130)	*Enterococcus* spp. (n=780)	*S. pneumoniae* (n=546)	*S. pyogenes* (n=123)	*S. agalactiae* (n=300)	*S. aureus* (n=1,601)	MRSA** (n=2,138)
PEN	GEN	5.1	4.5	45.4	3.9	5.2	0.0	28.5[2]	-	0.5	0.0	0.0	0.5	15.1
PEN	CIP	10.0	8.3	68.0	4.2	9.1	0.8	0.0	-	0.5	0.0	0.0	3.7	31.7
CLI	GEN	5.1	4.5	45.4	3.9	5.2	0.0	100.0	100.0	4.0	4.1	13.5	0.1	2.7
AMP	GEN	4.9	4.5	45.4	3.9	5.2	0.0	14.6	21.9[4]	X	0.0[5]	0.0[5]	0.5	15.1
PTZ	GEN	0.9	2.9	22.2	1.2	3.9	0.0	3.8[3]	21.9[4]	X	0.0[5]	0.0[5]	0.2[6]	15.1
CTX		5.8	6.4	92.8	21.2	24.7	9.7	0.8	100.0	0.0	0.0[5]	0.0[5]	1.9[7]	100.0
PTZ		4.5	11.0	32.0	18.9	22.1	7.3	3.8[3]	21.9[4]	X	0.0[5]	0.0[5]	1.0[7]	100.0
MER		0.0	0.2	1.5	0.0	0.0	0.0	0.0	100.0	X	0.0[5]	0.0[5]	1.0[7]	100.0

[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.

Overall, while "all is quiet on the western front" for the time being, the question of whether or not CPE will emerge significantly in bloodstream infections remains unanswered.

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Mycobacterium tuberculosis

In 2022 (2021 in parenthesis), 174 (155) persons were reported with tuberculosis disease (TB) to the Norwegian Surveillance System for Communicable Diseases (MSIS). Of these, 17 (26) were born in Norway. In addition to these 174 persons in 2022, five came to Norway under TB treatment.

139 (124) cases were confirmed with *M. tuberculosis*-complex (MTBC) by culture and 21 (9) cases were confirmed by genotypic test only (culture negative). Of the culture positive cases, 2 (1) were identified as *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 11 (12) rifampicin resistant (RR)-TB cases including 10 (11) multi-drug resistant (MDR)-TB cases (resistant to both rifampicin and isoniazid). None of the RR-TB cases in 2022 were culture negative, compared to two in 2021. In both 2022 and 2021, two 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 1 (2) MDR-TB cases who had received chemotherapy in the past, 0 (1) with unknown category and 1 (0) previously on preventive treatment.

In addition to the MDR-TB cases, 6 (5) TB cases had strains resistant to isoniazid (sensitive to rifampicin), three (two) of them only with low-level resistance.

TABLE 106. Antimicrobial resistance for MTBC reported to MSIS (not *M. bovis* BCG) in 2022 from isolates or direct samples. Figures from 2021 in parentheses.

Origin of birth	No. of cases	Resistance to antimicrobial agents				
		Isoniazid 139 (125)	Rifampicin 152 (131)	Ethambutol 130 (122)	Pyrazinamide 130 (123)	MDR-TB 139 (125)
Norway	17 (26)	1 (1)	1 (1)	0 (1)	1 (1)	1 (1)
Europe excl. Norway	44 (17)	8 (3)	6 (3)	4 (3)	3 (3)	6 (3)
Asia	68 (56)	4 (5)	2 (3)	1 (0)	2 (2)	1 (3)
Africa	45 (53)	3 (7)	2 (5)	1 (2)	1 (3)	2 (4)
America	0 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	174 (155)	16 (16)	11 (12)	6 (6)	7 (9)	10 (11)
Proportion resistant isolates (%)		11.5 (12.8)	7.2 (9.2)	4.6 (4.9)	5.4 (7.3)	7.2 (8.8)

MDR-TB: Multi-drug resistant tuberculosis, resistant to at least rifampicin and isoniazid. RR-TB: Rifampicin resistant tuberculosis, with or without resistance to other first line drugs (isoniazid, ethambutol, pyrazinamide).

References:

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Candida spp. in blood cultures

TABLE 107. Antimicrobial susceptibility of *Candida albicans* blood culture isolates in 2022 (n=139). 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	0.9
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 2022 (n=139). 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				0.7	2.2	24.5	63.3	9.4									
Fluconazole						4.3	54.7	41.0									
Voriconazole	11.6	61.9	25.9	0.7													
Anidulafungin	59.7	33.1	6.5	0.7													
Micafungin	1.6	36.7	59.0	2.2	0.7												
Caspofungin			2.9	10.8	46.0	33.1	7.2										

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 2022 (n=41). 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	83.0	17.0
Anidulafungin	≤ 0.06	> 0.06	95.1	-	4.9
Micafungin	≤ 0.03	> 0.03	95.1	-	4.9

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant.

TABLE 110. *Candida glabrata* blood culture isolates in 2022 (n=41). 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					2.4	12.2	39.3	46.3									
Fluconazole										7.3	29.3	22.0	24.4			2.4	14.6
Voriconazole				2.4	7.3	26.8	26.8	4.9	7.3	7.3	9.8	7.3					
Anidulafungin	2.4	12.2	75.6	2.4	2.4	4.9											
Micafungin	2.4	14.6	78.0		2.4	2.4											
Caspofungin					2.4	26.8	68.3	2.4									

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 2022 (n=12). 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 2022 (n=12). 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							50.0	25.0	25.0								
Fluconazole								41.7	33.3	25.0							
Voriconazole				41.7	25.0	33.3											
Anidulafungin			91.7	8.3													
Micafungin			41.7	58.3													
Caspofungin					25.0	16.7	58.3										

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 2022 (n=17). 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	≤ 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 2022 (n=17). 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					5.9	5.9	35.3	52.9									
Fluconazole						5.9	23.5	35.3	23.5	11.8							
Voriconazole	5.9	11.8	17.6	41.2	17.6	5.9											
Anidulafungin		5.9			5.9		11.8	17.6	35.3	11.8	11.8						
Micafungin				5.9			5.9	70.6	11.8	5.9							
Caspofungin					5.9		5.9	88.2									

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 2022 (n=19). 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 2022 (n=19). 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					15.8	57.9	21.1	5.3									
Fluconazole						63.2	26.3	10.5									
Voriconazole	15.8	57.9	21.1	5.3													
Anidulafungin	10.5	47.4	42.1														
Micafungin		5.3	73.7	21.1													
Caspofungin				5.3	42.1	42.1	10.5										

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.

The number of candidemias in Norway has been about 200 for years, with a significant increase last year when 246 unique candidemia isolates from 231 patients were included in the survey compared to 212 isolates from 193 patients in 2021. Six infections in five patients were reinfections with the same (n=4) or another species (n=2) more than four weeks apart. There were eight mixed infections with more than one *Candida* spp. in 2022. In two patients, acquired echinocandin resistance was observed within the same episode of *C. glabrata* candidemia. Isolates from one episode defined as cultures less than four weeks apart without such changes in susceptibility is not reported in this survey.

Candida albicans is still the most common species (n=139, 56.5%) but the proportion is declining from 60% in 2021 and 66% in 2020. The proportion of *C. glabrata* isolates remained unchanged at 16.7% (n=41). *C. dubliniensis* (n=19; 7.7%), *C. parapsilosis* species complex (n=17; 6.9%) and *C. tropicalis* (n=12; 4.9%) show small changes from year to year. The number of infrequent species was in total 18 (7.3%) compared to 10 (<5 %) last year. *Candida auris,* the only notifiable fungal pathogen, was not detected in blood cultures in Norway in 2022.

All isolates were susceptibility tested to amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin by E-test according to the manufacturer's instructions (AB bioMérieux) and interpreted according to EUCAST clinical breakpoints version 10.0 (2020). Unexpected susceptibility patterns were confirmed by EUCAST standardised broth microdilution method and *fks* sequencing at Statens Serum Institut in Copenhagen. The results are presented in Tables 107-116.

All isolates were susceptible to amphotericin B. With the exception of one echinocandin resistant *C. albicans* isolate from a patient with long-term ICU stay, all *C. albicans* isolates were susceptible to all antifungal agents. Three anidulafungin sensitive *C. albicans* with micafungin MIC 0.03 mg/L were regarded micafungin susceptible according to the evaluation of ATU.

Acquired fluconazole resistance were observed in seven *C. glabrata* isolates (MIC 64-256 mg/L), and two *C. glabrata* isolates were echinocandin resistant with mutations in the hot spot region of the *fks* gene. Both isolates were retrieved from haematological patients on echinocandin therapy.

All 15 *C. parapsilosis sensu stricto* and two siblings belonging to the *C. parapsilosis* complex were all susceptible to all antifungal agents, as was all *C. tropicalis* and *C. dubliniensis* isolates.

Of the18 isolates not shown in the tables, only the two *C. lusitaniae* isolates were regarded fluconazole susceptible. *C. krusei* (n=7) is inherently resistant to fluconazole. There are no breakpoints defined for *C. guillermondii,* but this species is often regarded multi-drug resistant, and all isolates (n=5) displayed fluconazole MIC values of 4-256 mg/L

All isolates with defined breakpoints were susceptible to voriconazole in 2022. There is still insufficient evidence that *Candida* spp. is a good target for therapy with isavuconazole, and breakpoints have not been set.

In conclusion, acquired resistance in *Candida* spp. is still rare in Norway. A species distribution with a proportion of *C. albicans* less than 50 % is seen in most other countries. Whether such a shift is ongoing in Norway cannot be confirmed presently, but a trend towards relatively fewer *C. albicans* isolates and an increase in fluconazole resistant species is suspected. Treatment guidelines recommend echinocandins as first-line treatment and are valid in Norwegian patients, with de-escalation to fluconazole in stable patients infected with susceptible *Candida* spp..

There is an ongoing debate on how to use the correct nomenclature of fungi and how to report to the clinicians. The new names listed in different libraries used for identification (MALDI-TOF) may not reflect the complexity of fungi, and naming has to combine the "interests" from clinical microbiologists, physicians, medical mycologists, and taxonomists. This issue also affects (previous) *Candida* spp.. New names are not implemented in the EUCAST breakpoint tables for fungi nor in current treatment guidelines. To avoid misinterpretations the reference laboratory still uses the old names. However, work is ongoing to implement reporting them *together* with the new ones on a regularly basis, and always to report if an isolate is related to a known species complex.

Azole resistant *Aspergillus fumigatus* in Norway

AMR policies have until now focused on bacterial resistance and the animal-environment-human interface, and payed little attention to AMR in fungi. However, the emerging threat of fungal resistance is now increasingly recognised by public health institutes. In October 2022, the World Health Organization (WHO) published the first fungal priority pathogens list, inspired by the bacterial priority pathogens list from 2017. *Aspergillus fumigatus* is ranked as number three on this watch list and considered "critical" (1). Azole resistance in *A. fumigatus* is a One Health resistance threat. Azole antifungals are widely used not only in treatment of human diseases, but also in cosmetics, in veterinary medicine, in material and wood preservation, agriculture and horticulture. There is a significant risk for azole resistance development in exposed fungi which do not harm the crops and the material to be protected, but may cause disease in humans like *A. fumigatus* (2). The broad use of the same antifungal class both as a pesticide and as treatment in medicine is unfortunate, as balancing food security against the preservation of medical treatment is extremely challenging.

Azoles is the main class for antifungal therapy for both chronic aspergillosis and acute invasive disease, and for prophylaxis. Azoles is the only antifungal class that may be administered both intravenously and orally. Moreover, alternative treatment options are limited as there are only three available antifungal classes for treatment of invasive disease. The mortality rates in invasive aspergillosis (IA) patients with azole resistant *A. fumigatus* are high (47–88%) and have been reported to be up to 100% in some studies (3). Environmental triazole resistance is characterised by genetic changes involving tandem repeats (TRs) in the promoter region of the *CYP51A* gene accompanied by point mutations that alter the drug target, mainly TR_{34}/L98H and TR_{46}/Y121F/T289A genotypes. High resistance rates in environmental *A. fumigatus* isolates have been reported in European countries (6–20%) with the Netherlands reporting the highest prevalence. Azole resistance may also develop during therapy in patients with chronic and allergic aspergillosis (15–20%), then often due to other genetic alterations of the *CYP51A* gene (5,6).

Presently we do not have any active surveillance of azole resistance in *A. fumigatus* in Norway. One environmental isolate of *A. fumigatus* sampled in Oslo in 2001 was retrospectively identified to harbour the resistance mutation TR_{34}/L98H (7). No resistant isolates were identified in Norway during the prospective multicentre international surveillance study of azole resistance in *A. fumigatus* from 2009 to 2011 (8). The National Reference Laboratory for Medical Mycology in Norway performs susceptibility testing of all clinical *A. fumigatus* isolates from Norwegian patients when considered relevant, and performs *cyp51A* sequencing of all resistant isolates. 1,000 isolates of *A. fumigatus* have been susceptibility tested between 2013 and 2023. Five patients with isolates harbouring the TR_{34}/L98H mutation and two patients with isolates harbouring the TR_{46}/Y121F/T289A mutations have been identified. Furthermore, five pan-azole resistant isolates (I242V, V436A/G448S or without known mutations in the *cyp51A* gene) have been detected, probably caused by long-term treatment of cystic fibrosis (CF) or chronic pulmonary aspergillosis (CPA) (Table 117). The reference laboratory participates in interdisciplinary networks and research collaborations addressing azole resistance, and The RezAzole network report "Azole resistance in a One Health perspective" in 2019 was one delivery (9). Funded by the Norwegian Research Council "Navigating the threat of azole resistance development in human, plant and animal pathogens in Norway (NavAzole 2021-26; NFR number 320821)", our network now addresses both mechanisms of fungal AMR and strategies for prevention in a multidisciplinary context. The project will collect and study azole resistant strains of *A. fumigatus* and plant pathogens and seek to establish methods, networks and routines for diagnostics and surveillance of azole resistance in Norway.

Following reports on environmental azole resistance in *A. fumigatus* from Danish patients, the Ministry of Health in Denmark requested a prospective national surveillance of azole resistant *A. fumigatus* and particularly that of environmental origin in 2018. The prevalence of azol resistant *A. fumigatus* was, based on this national surveillance programme, 6.1% between 2018 and 2020 (10). The prevalence of azole resistant *A. fumigatus* seems lower in preliminary data from Norway, but in the ongoing NavAzole-Project we aim to get more information, and the reference laboratory has implemented susceptibility testing of isolates not only from patients thought to have a resistant infection, in line with European guidelines (11). Given the high mortality rates in azole resistant IA, surveillance is warranted. The EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing Subcommittee on Antifungal Susceptibility Testing) has released a screening method (E.Def 10.1) for detection of azole resistant *A. fumigatus* isolates, but if and how to implement screening must be discussed (12, 13).

TABLE 117. Cyp 51A profiles in Norwegian *A. fumigatus* isolates 2013-23 (n=1,000).

No. of patients	Cyp51A profile	Azole resistance
5	TR_{34}/L98H	Pan-azole resistant
2	TR46/Y121F/T289A	Isavuconazole and voriconazole resistant
1	I242V	Itraconazole and voriconazole resistant
1	V436A/G448S	Pan-azole resistant
4	Wild type	Itraconazole resistant +/-Pan-azole resistant

Fungal infections remain in the shadow of public awareness, despite the fact that attributable annual deaths are similar to, or exceed, global mortalities due to malaria, tuberculosis or HIV (14). Antifungal resistance *is* more than azole resistance in *A. fumigatus.* Azole resistance and changes in the distribution of invasive *Candida* spp., emergence of "new" spp. like *C. auris* and the global dissemination of terbinafin resistant *Trichophyton indotineae* need urgent attention. We need to adopt an integrated One Health approach encompassing environmental, clinical, agricultural, and social perspectives. Surveillance and research are essential and must be in place to meet the public health challenges posed by antifungal resistance (15).

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Appendix 1: Collection and analysis of data on usage of antimicrobial agents in animals

Data sources

Sales data at wholsalers level

In Norway, all medicinal products for animals are prescription-only medicines – this includes both veterinary medicinal products (VMPs) and human medicinal products (HMPs). The latter can be prescribed to 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, HMP is allowed to be used. For food-producing species it requires that a maximum residue level (MRL) has been assigned for the active substance in question or that it is shown that MRL is not nessecary.

Both VMPs and HMP have to be dispensed through pharmacies that are supplied by wholesalers. Medicated feed (manufactured from premix VMPs) is supplied to the end user by feed mills and is currently only used for farmed fish; this is due to the small size of livestock herds in Norway and the low use of group/flock treatments. Group treatment of livestock (terrestrial animals) with antibacterial agents is administered through drinking water or as top-dressing on the feed.

Wholesalers and feed mills in Norway are mandated to provide sales statistics for all veterinary medicinal products, 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) of the included VMPs were obtained from the NIPH. One exeption is antibacterials for farmed fish for the years 2013-2022, which were obtained from Veterinary Prescription Register (VetReg). Veterinarians in Norway are not allowed to dispense VMPs, except for treatments until a pharmacy can provide the VMPs. In such cases the medicinal products have to be sold at cost price.

Prescription data

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 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 prescription of antibacterials has been shown to be complete for the years 2013-2018 (1) and this was the case also for the years 2019-2022. For the period 2013-2022 the VetReg data are used for reporting for farmed fish for these years.

For oral paste and intramammaries the VetReg data quality was unsatisfactory for the entire period 2012-2022, resulting in that the data were not valide (when compared to the sales data obtained from wholesalers of such products). Data for injectables, oral powders and oral solution from VetReg for 2015-2022 from VetReg were analysed and the outputs were compared to sales data for the corresponding forms obtained from NIPH for these years. The results show that the data on use reported to VetReg were lower than the sales data from wholesalers for VMP injectables and substantially lower for oral preparations for group treatment (oral powders and oral solution) in this sudy period. It could not be identified whether the data are represenative for the prescribing of VMPs by animal species, but as the prescribing patterns was relatively stable across this period the data is believed to give a rough picture of 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 according to targets set in the National Strategy against Antibiotic Resistance (2015-2020) (3).

Antibacterial 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 table below 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 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 (3). 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 1th of October, living sheep are as reported pr 1th 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) (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.

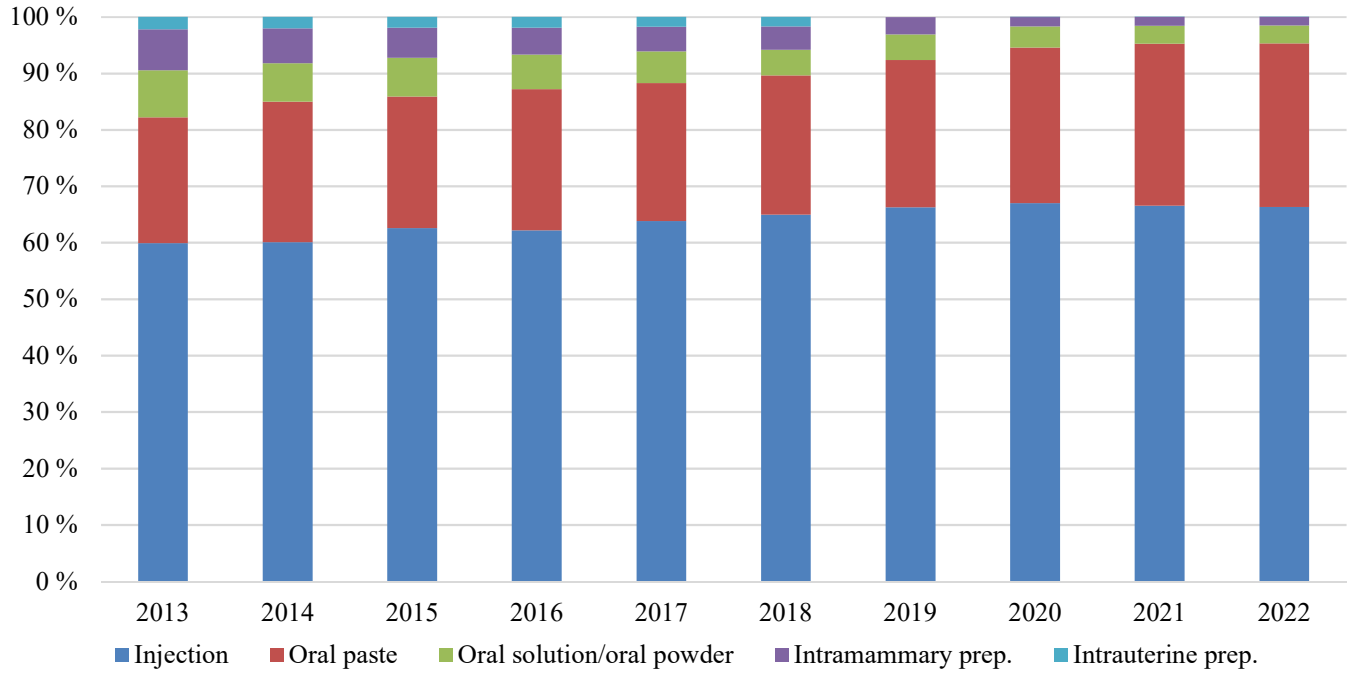
Analysis of the overall sales data
The sales data for each antibacterial VMP presentation were calculated to express weight of active substance. In order to comply with the ESVAC protocol (4), sales of derivatives (in previous report referred to as prodrugs) - e.g. procaine benzylpenicillin and penethamate hydriodide - has 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 (includs horses) and companion animals. Sales of antibacterial VMPs for companion animals refers 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 (includs horses). There is some use of injectable anti-bacterial 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 - bolus, oral paste injectables, intra-mammary preparations, intrauterine preparations and some tablets (dihydrostreptomycin pack size 20 and 100) and for group treatment (oral 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 2022 (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 in order to identify changes across time. Data on prescribtions per animal species obtained from the Veterinary Prescription Register (VetReg) has been used as supportive information to the sales data for this refinement. VetReg data shows that for the years 2016-2022, on average 96.2% (range 95.1% to 97.0%) of the number of pre-scriptions of antibacterial oral paste VMPs was for horses showing that off-lable 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 29% in 2022 (Figure). Oral paste (numerator) and PCU for horses (denominator) has therefore been excluded from the analysis of data for the estimation of usage of antibacterial VMPs for cattle, pigs, sheep, goats and poultry. Intramammaries have been excluded from the analysis of the VetReg data regarding prescribed amounts (kg) due to data quality issues (2).



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 2013-2022. Of note, there has been no sale 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 anti-bacterial 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 represent 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 anti-bacterial 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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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 prescription database (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 (*Nasjonalt senter 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 is collected from the Norwegian Patient Register at the Norwegian Directorate of Health. 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 requires hospitalisation for one or more days*" (2).

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 classify-cation system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2023 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 anti-bacterials 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, except for mupirocin, which is included in one table.

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Appendix 3:
Sampling, microbiological methods and data processing in NORM-VET

Sampling strategy
The clinical isolates included in NORM-VET 2022 were *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS) and *Pseudomonas aeruginosa*. All staphylococci isolates were retrieved through submissions to TINE Mastittlaboratoriet. The *S. aureus* (n=191) and CoNS (n=190) were from mastitis in cattle and sampled throughout 2021. The majority of the isolates originated from different farms, one isolate per submission.

The *P. aeruginosa* (n=118) were from dogs and retrieved through clinical submissions at the Norwegian Veterinary Institute (NVI) through the years 2018-2022.

Caecal samples of broiler and turkey flocks were collected at slaughter for isolation of the indicator bacteria *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus faecium*. From each poultry flock ten caecal samples were collected. A total of 363 pooled samples from broiler and 110 pooled samples from turkeys were included. In total, 303 broiler meat and 122 turkey meat samples were collected at retail in all regions of Norway. Sampling was conducted by the Norwegian Food Safety Authority (NFSA) following the specifications set by EFSA (EFSA Journal 2019;17(6):5709). Meat samples were to be taken without taking place of origin into consideration, though only one sample per lot.

All the caecal and meat samples were used for selective isolation of *E. coli* resistant to extended-spectrum cephalosporins (ESC) and carbapenem resistant *Enterobacterales* (CRE). In addition, selective isolation for vancomycin resistant *Enterococcus* spp. (VRE) and linezolid resistant *Enterococcus* spp. (LRE) was performed on the caecal samples.

Faecal and oral/perineal swabs from 250 cats were collected by veterinarians. The cats sampled were from all over the country, and were between a few months and 19 years old, about half were outdoor cats. The faecal samples were used for retrieving indicator *E. coli*, and for selective isolation of *E. coli* resistant to ESC and CRE. The oral/perineal swabs were used for retrieving *Staphylococcus felis* and/or *Staphylococcus aureus*, and selective isolation of methicillin resistant *S. aureus* (MRSA) and/or *Staphylococcus pseudintermedius* (MRSP).

Indicator isolates of *E. coli*
Sample material, i.e. faecal content from cat and caecal content from ten broilers or turkeys per flock were pooled and 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 ten broilers or turkeys per flock were pooled and 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.

Vancomycin resistant *Enterococcus* spp. (VRE)
Sample material, i.e. caecal content from ten broilers or turkeys per flock were pooled and plated directly onto Slanetz and Bartley agar containing 4 mg/L vancomycin (Oxoid) and incubated at 44±0.5°C for 24-48h. Typical colonies were subcultured on Slanetz and Bartley agar containing 4 mg/L vancomycin 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.

Linezolid resistant *Enterococcus* spp. (LRE)
Sample material, i.e. caecal content from ten broilers or turkeys per flock were pooled and 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 aureus* and *Staphylococcus felis*
Sample material, i.e. oral/perineal swabs from cats were enriched in 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 and incubated at 37±1°C for 20±2h. Colonies were identified as *S. aureus* or *S. felis* 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 cats were inoculated in 5 mL of BPW-ISO. A total of 25±0.5 g sample material of broiler and turkey meat were homogenised with 225 mL of BPW-ISO. Samples were incubated at 37±1°C for 20±2h according to the protocol from 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.

Carbapenem resistant *Enterobacterales* (CRE)
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 CRE 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)
Oral/perineal swabs from cats were analysed for methicillin resistant *Staphylococcus aureus* (MRSA) and/or *Staphylococcus pseudintermedius* (MRSP). Sample material was incubated in 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). Suspected colonies were subjected to species identification using MALDI-TOF MS before further phenotypical testing.

Genotyping
For genotyping of presumptive resistant isolates, whole genome sequencing (WGS) was performed at the NVI on an illumina® MiSeq or Illumina® NextSeq (Illumina, San Diego, California, USA). Paired end reads were subjected for analysis for both acquired genes and chromosomal point mutations using the ResPointFinder pipeline (commit 0cff411016d17acda1f76a88b5cdb5786e83973e) which the NVI has implemented on the IRIDA platform (www.irida.ca).

Susceptibility testing
Isolates were tested for antimicrobial susceptibility using a broth microdilution method at the NVI. Minimum inhibitory concentration (MIC) values were obtained using plates from Sensititre® (TREK Diagnostic LTD) 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 20.05.2023) 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.

Staphylococcus aureus and *S. felis* isolates from cat were also investigated for penicillinase (beta-lactamase) production using the clover leaf test and for methicillin resistance using oxacillin disk. Most of the *S. aureus* and some of the CoNS from mastitis were tested for penicillinase production using the clover leaf test at TINE Mastittlaboratoriet.

Overview of which Sensititre® TREK panel was used for which clinical isolate:

Clinical isolate tested	Sensititre® TREK panel
Pseudomonas aeruginosa	EUX2NF
Staphylococcus aureus	DNKDTUV1
Coagulase-negative *Staphylococcus* spp. (CoNS)	DNKDTUV1

Quality assurance systems
The following susceptible bacteria were included as quality control on a regular basis: *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *Staphylococcus aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853. 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 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 4.2.3 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
Caecal samples were collected by the Norwegian Food Safety Authority at slaughter. Ten caecal samples from broilers were collected from each flock identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks, and from flocks with unknown *Campylobacter* status. Caecal contents from ten broilers per flock were pooled and plated directly onto mCCDA agar (Oxoid) and incubated under microaerobic conditions at 41.5±1°C for 44±4h. Typical colonies were subcultured on blood agar and confirmed as *Campylobacter jejuni* 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 at the NVI. MIC values were obtained using plates 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 20.05.2023) were used, with some exceptions as further explained in Appendix 7.

Overview of Sensititre® TREK panels used:

Bacteria tested	Sensititre® TREK panel
Salmonella spp.	EUVSEC3
Camplylobacter 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, UK) 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 4.2.3 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 campylobacteriosis cases registered were submitted in the following way: Five regional laboratories submitted the first five independent 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.13.0 2023 were used if defined. In absence of clinical breakpoints, ECOFFs or national zone distributions were used (e.g. tetracycline). 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 (Velvet optimizer v.1.1.04 or SKESA 2.4.0) in Ridom SeqSphere+ (v.8.3.4 or v.8.4.0).

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 2000-2022 are presented in the table below, for enteric infections see Appendix 4. In 2022, 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 2022 were as follows: *E. coli* from blood cultures (6 months); *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Enterococcus* spp. and *Staphylococcus aureus* from blood cultures (9 months); *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* from wound specimens (1 week); *H. influenzae* from respiratory tract specimens (3 weeks); *E. coli* (3 days), *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp. and *Serratia* 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., *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Enterococcus* spp. and *S. aureus* 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* 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. 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* 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. 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 AMRFinderPlus 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
Respiratory tract	*S. pneumoniae*	50	50		50		50		3 w		3 u			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
	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	3w
	Enterococcus spp.	50	50									2 w					3 w			3 w				
	Enterobacter spp.						50											3 w						3w
	Citrobacter spp.																							3w
	Serratia spp.																							3w
	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
	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
	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
	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			
	Acinetobacter spp.								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
	N. menigitidis														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
	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
	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
	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
	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
	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
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
	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

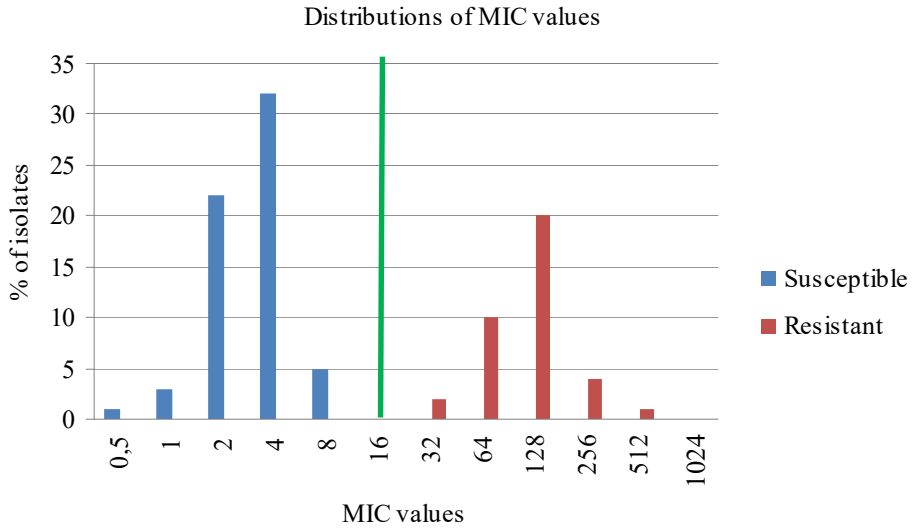
Surveillance at reference laboratories in red. d=days; w=weeks; m=months.

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. That is because the sampling and 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 typically 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. However, for some combinations of bacteria and antimicrobial agents these were not applicable to our data. In these cases, ECOFF values were defined based on the actual MIC distributions obtained in the NORM-VET programme. We applied the normalised resistance interpretation (NRI) method with permission from the patent holder, Bioscand AB, TÄBY, Sweden (European patent No 1383913, US Patent No. 7,465,559). The automatic and manual Excel programs were made available through courtesy of P. Smith, W. Finnegan, and G. Kronvall as further specified in Appendix 7.

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 European Union Summary Report 2020/2021, 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 20.05.2022) were used. For additional antimicrobial agents not defined in the EUCAST recommendations, EFSA-recommended cut-off values were applied or defined based on the actual MIC distributions obtained in the NORM-VET programme as described in Appendix 6. This was applied to *Staphylococcus aureus*, the coagulase negative staphylococci and *Pseudomonas aeruginosa*. For *Staphylococcus felis*, the cut-offs for *Staphylococcus aureus* were used.

In the NORM-VET figures, the penicillins are grouped together in the class "beta-lactams/penicillins"; trimethoprims and sulphonamides in the class "sulfonamides and trimethoprims"; macrolides, lincosamides and streptogramins in the class "macrolides/lincosamides/streptogramins" and the streptomycins are grouped with other aminoglycosides in the class "aminoglycosides".

Overview of the antimicrobial classes and agents tested for with corresponding epidemiological cut-off values (mg/L) used in NORM-VET 2022:

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella enterica*	*Campylobacter coli* / *C. jejuni*	*Enterococcus faecalis* / *E. faecium*	*Staphylococcus aureus* / *S. felis*	*Staphylococcus aureus* (clinical)	Coagulase negative *Staphylococcus* spp.*	*Pseudomonas aeruginosa*
Tetracyclines	Oxytetracycline						>0.5	>0.5	
	Tetracycline	>8	>8	>2 / >1	>4	>1			
	Tigecycline	>0.5	ND		>0.25				
Amphenicols	Chloramphenicol	>16	>16	>16	>32	>16			
Penicillins with	Ampicillin	>8	>4		>4 / >8				
extended-spectrum	Amoxicillin						>0.5	>0.5	
	Temocillin	(>16)							
Beta-lactamase sensitive penicillins	Benzylpenicillin					>0.125	>0.125	>0.06	
Beta-lactamase resistent penicillins	Cloxacillin						>1*	>2	
Combinations of penicillins, incl. beta-lactamase inhibitors	Piperacillin and enzyme inhibitor								>16
1st generation	Cephalexin						>8*	>8	
cephalosporins	Cephapirin						>0.25*	>0.5	
2nd generation cephalosporins	Cefoxitin	(>16)				>4			
3rd generation	Cefotaxime	>0.25	>0.5						
cephalosporins	Ceftazidime	>1	>2						>8
Combinations of 3rd generation	Cefotaxime-clavulanate	(>0.25)							
cephalosporins and clavulanic acid	Ceftazidime-clavulanate	(>1)							
4th generation cephalosporins	Cefepime	(>0.125)							>8
Monobactams	Aztreonam								>16
Carbapenems	Meropenem	>0.06	ND						>2
	Ertapenem	(>0.03)		>0.125					
	Doripenem								>2
	Imipenem	(ND)							>32*
Trimethoprim and derivatives	Trimethoprim	>2	>2			>2			
Sulfonamides	Sulfamethoxazole	>64#	ND			>128			

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella enterica*	*Campylobacter coli* / *C. jejuni*	*Enterococcus faecalis* / *E. faecium*	*Staphylococcus aureus* / *S. felis*	*Staphylococcus aureus* (clinical)	Coagulase negative *Staphylococcus* spp.*	*Pseudomonas aeruginosa*
Combinations of sulfonamides and trimethoprim, incl. derivates	Sulfamethoxazole and trimethoprim						>0.25	>0.125	
Macrolides	Erythromycin			>8 / >4	>4	>1			
	Azithromycin	>16	>16						
	Tylosin tartrate						>8*	>2	
Lincosamides	Lincomycin						>2	>2	
	Clindamycin					>0.25			
Streptogramins	Quinupristin and dalfopristin				>32 / >2	>1	>1		
Streptomycins	Streptomycin					>16	>16	>8	
Other aminoglycosides	Tobramycin								>2
	Gentamicin	>2	>2	>2	>64 / >32	>2			>8
	Amikacin	>8	>4						>16
	Kanamycin					>8			
Fluoroquinolones	Ciprofloxacin	>0.064	>0.125	>0.5	>4 / >8	>2			>0.5
	Levofloxacin								>2
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				ND / >4	>4			
	Mupirocin					>1			
	Daptomycin				>4 / >8				
	Narasin				>2				
	Rifampicin					>0.032			

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 values defined by the MIC distributions obtained in NORM-VET using "The Normalized Resistance interpretation (NRI) method with permission from the patent holder, Bioscand AB, TÄBY, Sweden (European patent No 1383913, US Patent No. 7,465,559)."

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).

Antimicrobials	MIC (mg/L)		*Escherichia coli*	*Klebsiella* spp.	*Enterobacter* spp.	*Citrobacter* spp.	*Serratia* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
	S	R																							
Amphotericin B	≤ 1	> 1																			■	■	■	■	■
Ampicillin	≤ 1	> 1						■																	
	≤ 4	> 4									■[1]														
	≤ 4	> 8															■								
	≤ 8	> 8	■								■	■	■												
Amoxi-Clav*	≤ 2	> 2						■																	
	≤ 8	> 8	■	■																					
	≤ 32	> 32	■	■																					
Anidulafungin	≤ 0.03	> 0.03																			■				
	≤ 0.06	> 0.06																				■	■		
	≤ 4	> 4																						■	
Cefalexin	≤ 16	> 16	■	■																					
Cefepime	≤ 1	> 4	■	■	■	■	■																		
Cefixime	≤ 0.125	> 0.125								■															
Cefoxitin	≥ 22 mm	< 22 mm														■									
Cefotaxime	≤ 0.125	> 0.125						■																	
	≤ 0.5	> 0.5									■[1]														
	≤ 0.5	> 2																■							
	≤ 1	> 2	■	■	■	■	■				■	■	■												
Ceftazidime	≤ 1	> 4	■	■							■	■	■												
	≤ 2	> 2									■[1]														
Ceftriaxone	≤ 0.125	> 0.125						■	■	■															
	≤ 0.5	> 2																■							
Cefuroxime	≤ 0.001	> 8	■	■																					
	≤ 1	> 2						■																	
Chloramphenicol	≤ 2	> 2						■	■																
	≤ 8	> 8									■	■	■												
	≤ 16	> 16									■[1]														
Ciprofloxacin	≤ 0.001	> 0.5												■	■										
	≤ 0.001	> 1														■									
	≤ 0.016	> 0.016							■																
	≤ 0.03	> 0.06								■															
	≤ 0.06	> 0.06						■			■[1]														
	≤ 0.25	> 0.5	■	■	■	■	■					■	■												

Antimicrobials	MIC (ml/L) S	MIC (ml/L) R	*Escherichia coli*	*Klebsiella* spp.	*Enterobacter* spp.	*Citrobacter* spp.	*Serratia* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Clindamycin	≤ 0.25	> 0.25														■									
	≤ 0.5	> 0.5																■	■	■					
	≤ 4	> 4																							
Colistin	≤ 2	> 2										■[1]	■[1]												
	≤ 16	> 16									■[1]														
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]	■[1]	■[1]	■[1]	■									
	≤ 128	> 128															■								
Imipenem	≤ 0.001	> 4															■								
Linezolid	≤ 4	> 4														■	■								
Mecillinam	≤ 8	> 8	■	■	■	■																			
Meropenem	≤ 0.06	> 0.06									■[1]														
	≤ 2	> 2						■																	
	≤ 2	> 8	■	■	■	■	■				■	■	■												
Micafungin	≤ 0.016	> 0.016																			■				
	≤ 0.03	> 0.03																				■			
	≤ 2	> 2																						■	
Mupirocin	≤ 1	> 256														■									
Nitrofurantoin	≤ 64	> 64	■																						
Oxacillin	≥ 20 mm	< 20 mm																■							
Penicillin G	≤ 0.06	> 1								■															
	≤ 0.06	> 2																■							
	≤ 0.25	> 0.25							■										■	■					
	≤ 0.25	> 0.5																							
Pefloxacin	≥ 24 mm	< 24 mm									■[2]														
Pip-Tazo**	≤ 8	> 8	■	■	■	■	■																		
Rifampicin	≤ 0.06	> 0.06														■									
	≤ 0.25	> 0.25							■																
Spectinomycin	≤ 64	> 64								■															
Streptomycin	≤ 16	> 16									■[1]														

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Enterobacter* spp.	*Citrobacter* spp.	*Serratia* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Salmonella* spp.	*Shigella* spp.	*Yersinia enterocolitica*	*Campylobacter jejuni*	*Campylobacter coli*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Tetracycline	≤ 0.5	> 1								■															
	≤ 1	> 1														■		■	■	■					
	≤ 2	> 2						■	■					■	■										
	≤ 4	> 4										■[1]	■[1]												
	≤ 8	> 8									■[1]														
	≥ 17 mm	< 17 mm									■[3]	■[3]	■[3]												
Tigecycline	≤ 0.25	> 0.25															■								
	≤ 0.5	> 0.5	■													■									
Trimethoprim	≤ 2	> 2									■[1]														
	≤ 4	> 4	■	■	■	■	■					■[1]	■[1]												
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. **Pip-Tazo=Piperacillin-Tazobactam. ***TMS Trimethoprim-sulfamethoxazole. Breakpoints for the combination are given for the trimethoprim component only. [1]Epidemiological cut-off value (ECOFF) based on the wild type distribution by EUCAST. [2] 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.12.0). [3] Epidemiological cut-off value (ECOFF) based on national distribution.

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