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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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CONTENTS

INTRODUCTION

Antimicrobial resistance is an emerging problem worldwide. It reduces the effectiveness of antimicrobial treatment of infectious diseases in humans and animals thereby leading to increased morbidity and mortality, as well as higher costs. It is well established that there is a strong association between the usage of antimicrobial agents and the occurrence of resistance. The selective pressure exerted following use of antimicrobial agents is a key issue in the epidemiology of resistance. In this report the term antimicrobial resistance is used synonymously with antibiotic resistance, although the term actually includes resistance in other microbes as well. Antimicrobial resistance can be disseminated through the spread of resistant pathogenic organisms themselves or by horizontal transfer of resistance genes from one type of organism 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 2022, 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-first annual joint report from NORM and NORM-VET, presents data on resistance and usage for 2021. 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 2022

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 2021. 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 2021 utgjorde salget av antibakterielle veterinærpreparater til landdyr totalt 4 875 kg, som er på samme nivå som i 2020.

Salget av antibakterielle veterinærpreparater til matproduserende landdyr, inkludert hest, var på 4 500 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-laktamase ømfintlige penicilliner (benzylpenicillinprokain) som ble benyttet. Fra 2013 til 2021 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 25 % målt i kg aktivt stoff. Når salget relateres til dyrepopulasjonen, var nedgangen i forbruket 21 %. Til hest ble det i hovedsak brukt trimetoprim-sulfa som oralpasta.

Salget av antibakterielle veterinærpreparater til flokkbehandling er fortsatt lavt; i 2021 representerte salg av slike preparater 2,6 % av totalsalget til matproduserende landdyr, inkludert hest.

Forbruket av veterinære antibakterielle midler til oppdrettsfisk (forbruk til rensefisk inkludert) var fortsatt svært lavt i 2021 og utgjorde 953 kg. Dette representerer en nedgang på over 99 % sammenlignet med 1987 da forbruket var på sitt høyeste. I 2021 ble det foretatt behandling med antibiotika i 2,2 % av sjølokalitetene for laks og regnbueørret.

Til kjæledyr (hund og katt) ble det i 2021 solgt 375 kg veterinære antibakterielle midler. Dette er en nedgang på 29 % sammenlignet med 2013. Data rapportert til VetReg for perioden 2015-2021 viser en reduksjon på totalt 11 % 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. generasjons 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 utgjør en svært liten andel (1,2 %) av totalsalget av veterinære antibakterielle midler til disse kategoriene, og 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 2021 ble det ikke foretatt noen behandling med antibiotika i slaktekylling-flokker.

Forbruk av antibiotika hos mennesker

I 2021 var det totale salget av antibakterielle midler til systemisk bruk hos mennesker (J01 ekskl. metamin) 11,2 definerte døgndoser (DDD)/1000 innbyggere/døgn. Siden 2012 har det vært en markant nedgang i total antibiotikabruk, i alt en reduksjon på 33 %. Under Covid-19 pandemien har det vært en signifikant reduksjon i bruken av systemiske antibiotika, hovedsakelig grunnet mindre forskrivning av antibiotika mot luftveisinfeksjoner i primærhelsetjenesten. Infeksjonskontrolltiltak kan ha redusert forekomsten av infeksjoner, i tillegg til at befolkningen kan ha hatt høyere terskel for å gå til lege med symptomer på luftveisinfeksjon.

Rundt 85 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. I 2021 var penicilliner (J01C) oftest forskrevet i primærhelsetjenesten; 38 % av all DDD og 54 % av reseptene i ATC-gruppe J01, ekskl. metenamin, etterfulgt av tetracykliner, J01A (19 %). De tre hyppigst foreskrevne antibiotika i 2021 var fenoksymetylpenicillin, pivmecillinam og dicloxacillin. Disse tre utgjorde 52 % av alle resepter og 47 % av all antibiotika målt i DDD. I Norge er smalspektret penicillin førstevalg ved luftveisinfeksjoner, og i 2021 utgjorde andelen smalspektrede penicilliner (J01CE) 25 % av det totale salget (J01, ekskl. metenamin). Metenamin benyttes forebyggende mot urinveisinfeksjoner og utgjorde 29 % av alle 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. i individualisering av doser eller varighet av kur og valg av antibiotika. Man kan derfor forvente at det er mulig å oppnå en ytterligere reduksjon i antibiotikaforbruket og en enda mer smalspektret terapiprofil.

Antibiotikasalg (i DDD) til sykehus utgjorde 8 % av totalt salg av antibakterielle midler til mennesker i 2021. Det har vært en nedgang på 14 % i DDD/1000 innbygger/døgn sammenlignet med 2012 og nedgang på 11 % sammenliknet med 2019 (dvs. før pandemien). Sykehusene omstrukturerte avdelingene sine og utsatte planlagt kirurgi som forberedelse til det forventede høye antallet inneliggende pasienter med alvorlig Covid-19 sykdom. Dette resulterte i færre innleggelser og færre liggedøgn, ettersom de fleste sykehus faktisk viste seg å ha overskuddskapasitet. I norske sykehus ble det gjennomsnittlig brukt 73 DDD/100 liggedøgn i 2021. Dette er en nedgang siden 2020, og en økning på 8 % siden 2012. Antall

DDD/sykehusinnleggelse (i 2021; 2,9 DDD/ innleggelse) ble redusert med 5 % i samme periode. Terapimønsteret for antibakterielle midler på sykehus endrer seg ikke mye fra det ene året til det andre, men det er en klar trend mot mer bruk av antibiotika som er anbefalt i retningslinjene. Bruken av bredspektrede antibiotika er redusert siden 2012. De utgjorde 21 % av bruken målt i DDD/100 liggedøgn i 2021 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 med 19 % av all DDD. Det er store variasjoner mellom sykehus, både målt i volum (DDD/100 liggedøgn) av antibiotika som brukes og i terapiprofil. Variasjonene kan ikke forklares med forskjeller i aktivitet eller sammensetningen av pasientgrunnlaget alene.

Resistens hos kliniske isolater fra dyr

I 2021 ble det undersøkt *Escherichia coli*, *Streptococcus dysgalactiae* og *Streptococcus uberis* fra mastitt-infeksjoner hos storfe. Totalt 83,9 % av 168 *E. coli* isolater var fullt følsomme overfor alle de antibiotika de ble testet for. Multiresistens (resistens mot tre eller flere antibakterielle klasser) ble påvist i 11,3 % av isolatene. Seks av disse var resistent mot hhv. fire og fem antibakterielle klasser. Resistens mot ekstendert-spektrum cefalosporiner (ESC) ble påvist i to av *E. coli* isolatene, hvorav det ble påvist $bla_{\text{OXA-1}}$ i ett av isolatene og mutasjon i *ampC* genet i det andre. Av de 153 *S. dysgalactiae* isolatene var 92,8 % fullt følsomme overfor alle de antibiotika de ble testet for, og kun 0,7 % var multiresistente. Totalt 79,9 % av 174 *S. uberis* isolater var fullt følsomme, og 2,8 % var multiresistente.

Resistens hos indikatorbakterier fra dyr og mat

Resultatene fra 2021 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 *Escherichia coli* resistente mot ekstendert-spektrum cefalosporiner (ESC), er fremdeles lav. Karbapenemase-produserende *Enterobacterales* (CPE) har ikke blitt påvist fra dyr eller mat i Norge. Dette gjelder også for 2021.

NORM-VET følger de krav til overvåking av antibiotika-resistens 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 fra nasjonale hensyn. *E. coli* og *Enterococcus* spp. benyttes som indikatorbakterier, dvs. at sensitivitetstesting av *E. coli og Enterococcus* spp. benyttes som indikator for forekomst av antibiotikaresistens. Selektive metoder brukes til over-våking av *E. coli* resistent mot ESC, CPE, kinolonresistente *E. coli* (QREC) og meticillinresistente *Staphylococcus aureus* (MRSA). 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 2021 ble det undersøkt blindtarmsprøver fra storfe under ett år og fra slaktegris, ett dyr per besetning. Fra disse ble det isolert og sensitivitetstestet *E. coli, Enterococcus faecalis* og *E. faecium*. Prøvene ble også undersøkt for forekomst av ESC-resistente *E. coli* og CPE. Svaberprøver fra hest var også inkludert for sensitivitetsundersøkelse av *E. coli*, samt for forekomst av ESC-resistente *E. coli*, QREC og CPE. Fra hest ble det også tatt nesesvabre som ble undersøkt for MRSA. Av matprøver ble det undersøkt for forekomst av ESC-resistente *E. coli* og CPE i storfekjøtt og svinekjøtt.

Majoriteten av de 289 *E. coli* isolatene fra storfe var fullt følsomme for de antibakterielle midlene de ble testet for (95,2 %), og kun 0,7 % av isolatene var multiresistente. Andelen fullt følsomme *E. coli* isolater har vært relativt stabilt de siste årene (2015-2021). Kun tre *E. faecalis* og 27 *E. faecium* ble påvist fra storfe. Av disse var alle tre *E. faecalis* og 21 av de 27 *E. faecium* fullt følsomme, og ingen var multiresistente. Resultatene er i samsvar med resultatene fra 2019.

Også i prøvene fra gris var majoriteten (85,9 %) av *E. coli* isolatene (n=320) fullt følsomme for de antibakterielle midlene de ble testet for. Totalt var 3,4 % av isolatene multiresistente. Andelen isolater som var fullt følsomme, har økt siden 2015, dog med en liten nedgang i 2021 sammenliknet med 2019. Disse endringene er forårsaket av endringer i følsomhet for sulfametoxazole, trimetoprim, ampicillin og tetrasyklin. Full følsomhet for de antibakterielle midlene de ble testet for, ble også påvist for seks av 20 *E. faecalis* isolater, samt for 63,1 % av *E. faecium* (n=103) fra gris. Multiresistens ble ikke påvist fra noen av disse enterokokkene. Resultatene er i samsvar med resultatene fra 2019.

I prøver fra hest, var majoriteten (84,1 %) av *E. coli* isolatene (n=189) fullt følsomme for de antibakterielle midlene de ble testet for. Multiresistens ble påvist hos 1,1 % av isolatene. Dette er i samsvar med resultater fra 2017.

ESC-resistente *E. coli* ble påvist i tre av prøvene fra storfe (1,0 %) og i 47 av prøvene fra gris (14,6 %). Alle de tre storfeisolatene og 44 av griseisolatene var ESC-resistente på grunn av mutasjoner i det kromosomale *ampC* genet. Blant de resterende griseisolatene, ble to genotypet som $bla_{\text{CTX-M-15}}$ og en som $bla_{\text{CTX-M-55}}$. ESC-resistente *E. coli* ble også funnet i en av de 312 prøvene av svinekjøtt (0,3 %), og genotypet som $bla_{\text{CMY-2}}$. Ingen av de 313 undersøkte prøvene fra storfekjøtt var positive for ESC-resistente *E. coli*. Fra hest ble det ikke påvist verken ESC-resistente *E. coli* eller MRSA, og kun 1,1 % av prøvene var positive for QREC.

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*. I 2021 ble prøvene samlet inn etter kravene satt i EU-regelverket (2020/1729/EU), dvs. 301 prøver fra storfe og 324 prøver fra slaktegris, undersøkt uten funn av *Salmonella*. Totalt ble 25 *Salmonella* spp. isolater fra dyr sensitivitetsundersøkt (ett isolat fra hhv. fjørfe, hest, gris og sau, to fra storfe, tre fra hund, fem fra katt og elleve fra villsvin). Disse isolatene kom fra det nasjonale *Salmonella* overvåkingsprogrammet, fra overvåkingsprogrammet på villsvin, og fra andre undersøkelser ved Veterinær-instituttet. Med unntak av ett isolat som var resistens mot kinoloner, var alle isolatene fullt følsomme for de antibakterielle midlene de ble testet for. I 2021 ble det også testet 15 *Salmonella* spp. isolater fra kjøtt som ikke var av norsk opprinnelse. Disse kom fra Nasjonalt referanse-

laboratorium for *Salmonella*. Majoriteten av disse isolatene var fullt følsomme, og kun ett *S.* Typhimurium isolat var multiresistent.

Campylobacter spp. isolert fra 307 storfe og 326 slaktegris var inkludert i 2021. Majoriteten av de 127 testede *C. jejuni* isolatene fra storfe (86,6 %) var fullt følsomme for de antibakterielle midlene de ble testet for, og ingen var multiresistente. Det ble ikke påvist *C. coli* fra storfe. Av de 17 påviste *C. jejuni* isolatene fra gris, var kun ett isolat resistent. Totalt 81,7 % av 290 *C. coli* isolater fra gris var fullt følsomme for de antibakterielle midlene de ble testet for, mens de resterende isolatene kun var resistente mot ciprofloksacin. Siden 2009 har det vært observert en økende trend i resistens mot ciprofloksacin hos *C. coli* fra gris.

Kliniske isolater av tarmpatogene bakterier fra mennesker

Referanselaboratorium for enteropatogene bakterier (NRL) utfører årlig antimikrobiell følsomhetstesting for *Salmonella, Campylobacter, Yersinia* og *Shigella* isolater. Fra og med 2020 har NRL screenet alle *Enterobacterales* isolater for antimikrobielle resistensdeterminanter etter helgenomsekvensering for å forutsi 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 innenlands ervervede stammer. Antibiotikaresistens var høyest blant *Salmonella* Typhi, med en økende trend for resistens mot utvidet spektrum cefalosporiner. Multiresistens (MDR) var også en karakteristisk egenskap for en betydelig andel av *S.* Typhi stammer (66,7 %). Tre *Salmonella* isolater var ESBL-produsenter, alle genotypet til $bla_{\text{CTX-M}}$.

For *Campylobacter jejuni* var det generelle resistensnivået for ciprofloksacin og tetracyklin høyere for stammer fra reiseassosierte infeksjoner sammenlignet med innenlands ervervede stammer. En økende trend av resistens mot ciprofloksacin og utvidet spektrum cefalosporiner ble observert hos *Shigella sonnei*. Åtte *Shigella* spp. ble bekreftet som $ESBL_A$-produsenter kodet av CTX-M. Antibiotikaresistens i *Yersinia enterocolitica* er fortsatt lav.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2021. Det ble påvist 12 tilfeller av meticillinresistente *Staphylococcus aureus* (MRSA) blant 1 455 blodkulturisolater (0,8 %) som ble inkludert i NORM 2021. Resultatene samsvarer med tall fra laboratorienes datasystemer som rapporterte 20 MRSA isolater blant 2 047 *S. aureus* (1,0 %) fra blodkultur og spinalvæske i 2021. Dette er en reduksjon fra 1,8 % i 2020. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 701 tilfeller av MRSA infeksjon i 2020 mot 945 i 2019 og 734 i 2020. 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 879; 1,5 %) slik de har gjort i tidligere år (1,3 % i 2019; 1,8 % i 2020). MSIS registrerte også 1 050 tilfeller av MRSA kolonisering i 2021 mot 1 499 i 2019 og 1 148 i 2020. I alt ble det meldt funn av MRSA hos 1 751 personer i 2021. Dette utgjør en insidensrate på 32/100 000 personår mot 46/100 000 i 2019 og 35/100 000 i 2020. 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 har blitt betydelig redusert de siste fire årene. En høy andel av tilfellene blir fortsatt smittet i utlandet, og den reduserte forekomsten i 2020 og 2021 kan delvis skyldes reduksjon av internasjonal reisevirksomhet. 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 2021. Andelen av gentamicinresistente isolater var 5,6% i 2021 sammenliknet med 5,9% i 2019 og 6,7 % i 2020, mens forekomsten av resistens mot ciprofloxacin var stabil med 10,4 % i 2021 mot 11,2 % i 2020. *Klebsiella* spp. har omtrent samme forekomst av resistens mot gentamicin (4,2 %) og ciprofloxacin (8,9 %) 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 128/2 212 (5,8 %) *E. coli* og 57/1 045 (5,5 %) *Klebsiella* spp. fra blodkultur ble rapportert som ESBL-positive i 2021. Forekomsten er svakt synkende for både *E. coli* (7,1 % i 2019; 6,5 % i 2020) og *Klebsiella* spp. (5,7 % i 2019; 7,2 % i 2020). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (5,8 %) enn fra urinprøver (3,1 %).

Kolonisering og/eller infeksjon med karbapenemaseproduserende *Enterobacterales* (CPE), *Pseudomonas aeruginosa* og *Acinetobacter* spp. har vært meldepliktige til MSIS siden juli 2012. Antallet pasienter meldt med CPE var uendret med 60 tilfeller i 2021 mot 57 i 2020. Antallet pasienter med karbapenemaseproduserende *P. aeruginosa* (n=1) var fortsatt lavt, mens antallet meldinger for *Acinetobacter* spp. gikk ned fra 10 i 2020 til 8 i 2021. En stor andel av påviste multiresistente Gram-negative bakterier kan knyttes til import fra land med høy forekomst av slike mikrober. Den mest sannsynlige forklaringen på den reduserte forekomsten i Norge er derfor reduksjonen av internasjonal reisevirksomhet som følge av koronaviruspandemien i 2020 og 2021.

Overvåkingen av resistens hos systemiske isolater av *Haemophilus influenzae* og *Neisseria meningitidis* ble tatt opp igjen ved referanselaboratoriet på Folkehelseinstituttet (FHI) i 2020, men som for andre luftveispatogener ble det diagnostisert svært få tilfeller (henholdsvis n=63 og n=5). *Neisseria gonorrhoeae* (n=220) viste utbredt resistens mot penicillin G (15,0 %), og bare 12,3 % var følsomme for standard dosering svarende til villtypepopulasjonen. Hele 53,2 % var resistente mot ciprofloxacin. Alle isolater var følsomme for ceftriaxon, mens i alt tre isolater (1,4 %) var resistente mot det perorale cefalosporinet cefixim. Alle isolater var fullt følsomme for spectinomycin.

Det ble kun påvist et enkelt enterokokkisolat fra blodkultur med klinisk signifikant vankomycinresistens i 2021 (*vanB E. faecium*). Forekomsten av resistens mot ampicillin i *E. faecium* ligger stabilt rundt 70-80 %. Høygradig gentamicinresistens ble redusert hos *E. faecalis* (8,5 % i 2021 mot 12,0 % i 2020), men økte til 46,2 % hos *E. faecium* (43,8 % i 2020). Den fallende tendensen for aminoglykosidresistens hos enterokokker gjennom det siste tiåret er dermed brutt. Nesten alle *E. faecium* med høygradig

gentamicinresistens var også resistente mot ampicillin. Det ble ikke funnet linezolidresistente enterokokker (LRE) i NORM-overvåkingen i 2021. Både VRE og LRE er meldepliktige til MSIS, og det ble bekreftet funn av 34 VRE (204 i 2019; 75 i 2020) og 16 LRE (16 i 2019; 10 i 2020) på referanselaboratoriet ved Nasjonal kompetansetjeneste for påvisning av antibiotikaresistens (K-res) på UNN i 2021. Forekomsten av VRE varierer med utbrudd fra år til år, men den nedadgående trenden i Norge skiller seg ut i europeisk sammenheng. Antallet påvisninger av LRE har vært langsomt økende, men ser nå ut til å ha stabilisert seg. Man kan spekulere på om den signifikante reduksjonen av antall VRE-tilfeller skyldes redusert reisevirksomhet og/ eller bedre smitteverntiltak i sykehusene under pandemien.

Overvåkingen av resistens hos systemiske isolater av *Streptococcus pneumoniae* (pneumokokker) og *Streptococcus pyogenes* (beta-hemolytiske streptokokker gruppe A) ble gjenopptatt ved referanselaboratoriet på FHI i 2020. Bare 0,6 % av pneumokokkisolatene fra blod og spinalvæske var resistente mot penicillin G, men i tillegg var 6,3 % kun følsomme for økt eksponering for dette middelet. Andelen kategorisert som I+R er blitt redusert fra 12,8 % i 2020 til 6,9 %, men dette kan delvis skyldes tekniske forhold knyttet til resistensbestemmelsen. Tre isolater (1,0 %) ble kategorisert som I for ett eller flere 3. generasjon cefalosporiner. Forekomsten av makrolidresistens var 6,0 % i 2021 sammenliknet med 8,4 % i 2020. Alle isolater av *S. pyogenes* fra blodkultur var følsomme for penicillin G. Forekomsten av erytromycinresistens (19,2 %) viser en dramatisk økning fra 6,7 % i 2020, men utviklingen må følges over tid før man kan trekke noen endelige konklusjoner om dette funnet. Systemiske isolater av *Streptococcus agalactiae* (beta-hemolytiske streptokokker gruppe B) var også følsomme for penicillin G, men hadde høy forekomst av resistens mot erytromycin (19,5 % i 2020; 22,7 % i 2021) og tetracyklin (75,2 % i 2020; 80,0 % i 2021).

I alt 154 pasienter med tuberkulose ble meldt til MSIS i 2021, og resistensresultater er tilgjengelige for 124 av dem. Ti isolater (8,0 %) ble definert som multiresistente (MDR) mot både rifampicin og isoniazid sammenliknet med 0,8 % i 2020. Pasientene hadde ervervet sine infeksjoner i Afrika (n=4), Europa utenom Norge (n=3), Asia (n=2) og Norge (n=1).

Det ble utført resistensbestemmelse av 212 *Candida* blodkulturisolater av 11 forskjellige species fra 193 ulike pasienter. De vanligste artene var *C. albicans* (n=126), *C. glabrata* (n=36), *C. parapsilosis* (n=14), *C. tropicalis* (n=13) og *C. dubliniensis* (n=11). Alle *C. albicans* var følsomme for de undersøkte midlene med unntak av et enkelt fluconazolresistent 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* (11,1 %). Nøyaktig species-bestemmelse 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 2021. 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 4,875 kg antibacterial ingredients in 2021, which is at the same level as in 2020.

Sales of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,500 kg in 2021. Penicillins continued to be the most-selling anti-bacterial 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 2013-2021, the estimated sales of antibacterial VMPs for cattle, pigs, sheep, goats and poultry declined by 25% when measured in kg and 21% 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 2021, such products accounted for only 2.6% of the total sales.

In 2021, the sales (kg) of antibacterial VMPs for farmed fish (cleaner fish included) were 953 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 2.2% of the on-grower locations were subjected to antibacterial treatment in 2021.

The sales (kg) of antibacterial VMPs marketed for companion animals were 375 kg in 2021. From 2013-2021 the sales of such VMPs for use in companion animals have been reduced by 29%. The prescriptions of human antibacterial medicinal products reported to the Veterinary Prescription Register declined gradually by 13% (kg) from 2015 to 2021. This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substitutet by prescribing of human products.

The European Medicines Agency (EMA) has suggested to restrict the use of some antibacterial classes in animals due to the potential risk to public health – i.e. 3rd and 4th generation cephalosporins, quinolones (fluoroquinolones and other quinolones) and polymyxins. In Norway, only quinolones are sold for use in food-producing terrestrial animals and farmed fish. The proportion sold of quinolones of the proportion sold of the total sales of antibacterial VMPs was very low (1.2%) and was mainly accounted for by sales for use in farmed fish.

In February 2015, the Norwegian poultry industry launched a project aiming at phasing out use of narasin as coccidiostat feed additive in broilers, a goal that was reached in June 2016. The usage of therapeutic antibiotics for broilers continues to be very low; in 2021, none of the broiler flocks were subjected to such treatment.

Usage of antimicrobial agents in humans

In 2021, the total sales of antibacterial agents for systemic use in humans (J01 excl. methenamine) were 11.2 Defined Daily Doses (DDD)/1,000 inhabitants/day. Since 2012 there has been a marked decline in total antibiotic use with a reduction of 33%. During the Covid-19 pandemic a significant reduction in the use of systemic antibiotics has been observed, mainly due to reduced use of antibiotics indicated for respiratory tract infections in primary care. Infection control measures may have decreased the incidence of infections, moreover, the threshold for seeing a general practitioner for symptoms of infections may have been raised.

Around 85% of the total human sales of antibacterials are used in primary care, i.e. outside healthcare institutions. For ambulatory care, the most important antibiotic group in 2021 was penicillins, J01C; 38% of DDDs and 54% of prescriptions in ATC group J01 (excl. methenamine), followed by tetracyclines, J01A (19%). The three most commonly prescribed antibiotics for outpatients in 2021 were phenoxymethylpenicillin, pivmecillinam and dicloxa-cillin. These three substances accounted for 52% of all prescriptions and 47% of all DDDs sold. In Norway, the main indication for narrow-spectrum penicillins in primary care is respiratory tract infections, and in 2021 the proportion of narrow-spectrum penicillins (J01CE) was reduced, accounting for 25% of total sales (J01, excl. methenamine). The urinary antiseptic methenamine accounted for 29% of all DDDs in the antibacterial J01 group. The steady decrease in primary care use over 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 of improvement, e.g. in individuali-sation of doses or duration of course length and choice of antibiotics, so one should expect that it is possible to achieve a further lowering of consumption rate and a better narrow-spectrum profile.

In 2021, the antibacterial sales (in DDDs) to hospitals represented 8% of total sales of antibacterials for human use in the country. There has been a decrease of 14% in DDD/1,000 inhibitants/day since 2012 and 11% compared to 2019 (before the 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 2021, a mean use of 73 DDD/100 bed days was observed, a decrease since 2020 but an increase by 8% since 2012. The DDD/admission in 2021 (2.9 DDD/admission) decreased by 5% in the same period.

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 national guidelines. The use of broad-spectrum antibiotics is reduced since 2012. They accounted for 21% of total DDDs for hospitals in 2021 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 hospitals in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile. These variations cannot be accounted for by differences in activity or patient population mix alone.

Resistance in animal clinical isolates

The clinical isolates included in 2021 were *Escherichia coli*, *Streptococcus dysgalactiae* and *Streptococcus uberis* from clinical mastitis in cattle. In total, 83.9% of 168 *E. coli* isolates were susceptible to all antimicrobial agents included in the susceptibility testing. Multi-drug resistance (MDR) (i.e. resistance to three or more antimicrobial classes) was detected in 11.3% of the isolates. Six of these MDR isolates were resistant to four and five antimicrobial classes, respectively. Resistance to extended spectrum cephalosporins (ESC) due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) and presence of the $bla_{\text{OXA-1}}$ gene, was detected in two isolates. Among the 153 *S. dysgalactiae* isolates, 92.8% were susceptible to all antimicrobial agents included in the susceptibility testing. Only 0.7% were MDR. A total of 79.9% of the 174 *S. uberis* isolates were fully susceptible, and 2.8% were MDR.

Resistance in indicator bacteria from animals and food

The 2021 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 *E. coli* resistant to ESC, is low. Carbapenemase-producing *Enterobacterales* (CPE) have never been isolated in samples from animals or food in Norway. This still applies for the 2021 results.

NORM-VET is following the requirements set in Commission Implementing Decision 2020/1729/EU on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria. In addition, antimicrobial susceptibility testing of bacteria from sources other than those covered by this legal act may be included. *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria, i.e. susceptibility testing of *E. coli* and *Enterococcus* spp. is used as an indicator for occurrence of antimicrobial resistance in the bacterial population. Selective methods are used to investigate the occurrences of *E. coli* resistant to ESC, CPE, quinolone resistant *E. coli* (QREC) and methicillin resistant *Staphylococcus aureus* (MRSA). 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 is summarised in the NORM/NORM-VET report as well.

In 2021, animal samples included caecal samples from cattle less than one year of age and fattening pigs for susceptibility testing of *E. coli* and *Enterococcus* spp., and detection of emerging resistant bacteria/resistance mechanisms such as ESC-resistant *E. coli* and CPE. Faecal swab samples from horses were also included for susceptibility testing of *E. coli*, and for detection of *E. coli* resistant to ESC, CPE and QREC. Nasal swabs were included for selective isolation of MRSA from horses. Food samples consisted of beef and pork, and were used for detection of *E. coli* resistant to ESC and CPE.

In samples from cattle less than one year, the majority (95.2%) of the *E. coli* (n=289) were fully susceptible to the antimicrobial classes in the test panel, and only 0.7% were MDR. The proportion of fully susceptible *E. coli* isolates has been relatively stable the last years (2015-2021). Full susceptibility to all antimicrobial classes included in the test panel was also present in the three *E. faecalis* isolates and in 21 of the 27 *E. faecium* isolates from cattle. None of the *E. faecium* isolates were MDR. This is in concordance with the results from 2019.

Also, from fattening pigs, the majority (85.9%) of the detected *E. coli* isolates (n=320) were fully susceptible to the antimicrobial agents in the test panel. Altogether, 3.4% of the isolates were MDR. The proportion of isolates being fully susceptible increased from 2015 to 2021, though with a small decrease in 2021 compared to 2019. These changes were due to corresponding changes in susceptibility for sulfamethoxazole, trimethoprim, ampicillin, and tetracycline. Full susceptibility to all antimicrobial classes included in the test panel was also present in six of the 20 *E. faecalis* isolates and in 63.1% of the *E. faecium* (n=103) isolates from fattening pigs. None of the *E. faecalis* or *E. faecium* isolates were MDR. The results are in concordance with the 2019 results.

In samples from horses, the majority (84.1%) of the *E. coli* isolates (n=189) were fully susceptible to the antimicrobial agents in the test panel. MDR was detected in 1.1% of the isolates. The results are in concordance with results from 2017.

ESC-resistant *E. coli* isolates (n=289) were detected from three of the cattle (1.0%) and 47 of the pig (14.6%) samples. In all three cattle isolates and in 44 of the pig isolates resistance was due to mutations in the chromosomally encoded *ampC* gene. Among the last three pig isolates, two were genotyped as $bla_{\text{CTX-M-15}}$ and one as $bla_{\text{CTX-M-55}}$. ESC-resistant *E. coli* was also detected in one of the 312 pork samples (0.3%), and resistance was due to presence of the $bla_{\text{CMY-2}}$ gene. ESC-resistant *E. coli* were not found in any of the 313 investigated beef samples. No ESC-resistant *E. coli*, no MRSA and only 1.1% QREC was detected from horse samples.

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 2021, detection of *Salmonella* spp. was performed on the samples collected with regard to Commission Implementing Decision 2020/1729/EU, i.e. on a total of 301 samples from cattle less than one year and 324 samples from fattening

pigs, without detecting any positive samples. In addition, 25 *Salmonella* spp. isolates from animals isolated through the Salmonella surveillance programme, the surveillance of wild boars, or from clinical submissions or necropsies were susceptibility tested (i.e. one each from poultry, horse, pig and sheep, two from cattle, three from dogs, five from cats and eleven from wild boars). With the exception of one isolate which was resistant to quinolones, the isolates were fully susceptible to all tested antimicrobial agents included in the panel. Also included in 2021 were 15 food isolates originating from non-domestic meat, retrieved through the Norwegian Reference Laboratory for Salmonella. The majority of the isolates were fully susceptible to all tested antimicrobial agents included in the panel, and only one *S.* Typhimurium isolate was MDR.

Campylobacter spp. isolated from caecal samples from 307 cattle less than one year and 326 fattening pigs were included in 2021. The majority of the 127 *C. jejuni* isolates from cattle (86.6%) were susceptible to all antimicrobial agents included in the test panel, and none were MDR. *C. coli* was not detected in samples from cattle. Of the 17 *C. jejuni* isolates from pigs, only one isolate was resistant to ciprofloxacin. A total of 81.7% of the 290 *C. coli* isolates from fattening pigs were susceptible to all antimicrobial agents included in the test panel. The remaining isolates were resistant only to ciprofloxacin. There has been an increasing trend in resistance to ciprofloxacin in *C. coli* from pig since 2009.

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, infection control measures including travel restrictions were enforced, which critically reduced the number of travel associated infections. Trends in antibiotic resistance must be interpreted accordingly.

For *Salmonella* Typhimurium and its monophasic variant, overall resistance levels were higher in strains with travel associated infections compared to domestically acquired. Antibiotic resistance was highest among *Salmonella* Typhi, with an increasing trend for resistance against extended spectrum cephalosporins. Multi-drug resistance (MDR) was also a characteristic trait for a considerable number of the *S.* Typhi isolates (66.7%). Three *Salmonella* isolates were characterised as ESBL producers and all were genotyped as $bla_{\text{CTX-M}}$.

For *Campylobacter jejuni*, overall resistance levels for ciprofloxacin and tetracycline were higher in travel associated infections compared to domestically acquired. An increasing trend of resistance towards ciprofloxacin and extended spectrum cephalosporins was observed in *Shigella sonnei.* Eight *Shigella* spp. were confirmed as ESBL_{A} producers encoding CTX-M. Antimicrobial resistance in *Yersinia enterocolitica* remains low.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2021. Only 12 methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,455 strains included in NORM 2021 (0.8%). During 2021, the total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 2,047 including 20 MRSA strains (1.0%). This is a reduction from 1.8% in 2020. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 701 cases of MRSA infections in 2021 compared to 945 in 2019 and 734 in 2020. 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 1.5% (13/879) and comparable to previous years (1.3% in 2019; 1,8% in 2020). Furthermore, MSIS registered 1,050 MRSA colonisations compared to 1,499 in 2019 and 1,148 in 2020. A total of 1,751 persons were reported with MRSA in 2021, corresponding to an incidence rate of 32/100,000 person years (46/100,000 in 2019; 35/100,000 in 2020). 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 has declined significantly in the last four years. A large proportion of cases are still infected abroad, and the reduced incidence in 2020 and 2021 may presumably be due to reduced international travel. Very few cases of livestock-associated MRSA are detected.

The rates of resistance to broad-spectrum antimicrobials in *E. coli* blood culture isolates remained essentially unchanged in 2021. The prevalence of gentamicin resistance was 5.6% in 2021 compared to 5.9% in 2019 and 6.7% in 2020, while the prevalence of ciprofloxacin resistance remained stable at 10.4% in 2021 compared to 11.2% in 2020. *Klebsiella* spp. isolates now demonstrate approximately the same rates of resistance to gentamicin (4.2%) and ciprofloxacin (8.9%) as *E. coli*. Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 128/2,212 (5.8%) *E. coli* and 57/1,045 (5.5%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2021. The prevalence has decreased slightly for both *E. coli* (7.1% in 2019; 6.5% in 2020) and *Klebsiella* spp. (5.7% in 2019; 7.2% in 2020). The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (5.8%) than in urinary tract isolates (3.1%).

Colonisation and/or infection with carbapenemase-producing *Enterobacterales* (CPE), *P. aeruginosa* and *Acinetobacter* spp. has been notifiable to MSIS since 2012. The number of CPE patients remained unchanged at 60 in 2021 compared to 57 in 2020. The number of patients with carbapenemase-producing *P. aeruginosa* (n=1) remained low, whereas *Acinetobacter* spp. notifications decreased from 10 in 2020 to eight in 2021. A large proportion of multi-resistant Gram-negative isolates can be linked to import from countries with high prevalence of these organisms. The most probable explanation for the reduced occurrence in Norway is therefore the reduction of international travel due to the coronavirus pandemic in 2020 and 2021.

Surveillance of resistance in systemic isolates of *Haemophilus influenzae* and *Neisseria meningitidis* resumed at the reference laboratory at the Norwegian Institute of Public Health (NIPH) in 2020, but as for other

respiratory tract pathogens, very few cases were diagnosed (n=63 and n=5, respectively). *Neisseria gonorrhoeae* isolates (n=220) displayed resistance to penicillin G (15.0%), and only 12.3% were susceptible to standard dosage corresponding to the wild type population. Ciprofloxacin resistance was detected in 53.2% of isolates. Three isolates (1.4%) were resistant to cefixime, but sensitive to ceftriaxone. All isolates remained susceptible to spectinomycin.

Only a single enterococcal blood culture isolate with clinically significant vancomycin resistance was detected in 2021 (*vanB E. faecium*). The prevalence of ampicillin resistance in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) was reduced in *E. faecalis* (12.0% in 2020; 8.5% in 2021) but increased to 46.2% in *E. faecium* (43.8% in 2020), thus the downward trend for aminoglycoside resistance in enterococci over the last decade was not continued. Almost all HLGR *E. faecium* isolates were also resistant to ampicillin. There were no linezolid resistant isolates (LRE) in the NORM surveillance programme in 2021. Both VRE and LRE should be reported to the national notification system (MSIS), and 34 VRE (204 in 2019; 75 in 2020) and 16 LRE (16 in 2019; 10 in 2020) were confirmed at the National Reference Laboratory at K-res/UNN in 2021. The prevalence of VRE varies over time due to outbreaks, but the decreasing trend seen in Norway over the last years differs from the development in other European countries. There has been a gradually increasing number of LRE cases from one year to another, but this has apparently now stabilised. One may speculate that the significant reduction of VRE cases in 2020 and 2021 was caused by reduced international travel and/or improved infection control practices in hospitals during the coronavirus pandemic.

Surveillance of resistance in systemic isolates of *Streptococcus pneumoniae* (pneumococci) and *Streptococcus pyogenes* (beta-haemolytic group A streptococci) resumed at the reference laboratory at the NIPH in 2021. Only 0.6% of *S. pneumoniae* isolates from blood cultures and cerebrospinal fluids were resistant to penicillin G, but another 6.3% would require increased exposure to be susceptible to this agent. The I+R categories thus decreased from 12.8% in 2020 to 6.9% in 2021, but this may in part be due to technical issues with the susceptibility testing. Three isolates (1.0%) were categorised as I for one or more 3rd generation cephalosporins. The prevalence of macrolide resistance was 6.0% in 2021 compared to 8.4% in 2020. All *Streptococcus pyogenes* blood culture isolates were susceptible to penicillin G. The prevalence of erythromycin resistance (19.2%) was dramatically increased from 6.7% in 2020, but this trend should be followed over time before drawing any firm conclusions. Systemic *Streptococcus agalactiae* isolates (beta-haemolytic group B streptococci) were similarly susceptible to penicillin G, but often resistant to erythromycin (19.5% in 2020; 22.7% in 2021) and tetracycline (75.2% in 2020; 80.0% in 2021).

A total of 154 patients with tuberculosis were reported to MSIS in 2021 and susceptibility test results were available from 124 of them. Ten isolates (8.0%) were defined as multi-drug resistant (MDR) to both rifampicin and isoniazid compared to 0.8% in 2020. The patients had acquired their infections in Africa (n=4), Europe outside Norway (n=3), Asia (n=2) and Norway (n=1).

Susceptibility testing was performed on 212 *Candida* spp. blood culture isolates of eleven different species from 193 unique patients. The most common species were *C. albicans* (n=126), *C. glabrata* (n=36), *C. parapsilosis* (n=14), *C. tropicals* (n=13) and *C. dubliniensis* (n=11). All *C. albicans* were susceptible to the substances examined with the exception of a single fluconazole 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* (11.1%). Precise species identification is essential to predict inherent resistance and select appropriate antifungal therapy. The results are in accordance with previous studies 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 01.01.2022. Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	280,040	143,787	136,253
5 to 14 years	635,947	326,556	309,391
15 to 24 years	653,657	336,450	317,207
25 to 44 years	1,465,101	751,545	713,556
45 to 64 years	1,401,051	715,174	685,877
65 years and older	989,474	463,820	525,654
All age groups	5,425,270	2,737,332	2,687,938

TABLE 2. Livestock population in Norway in 2021. Data provided by the Register of Production Subsidies as of 01.03.2021.

	Number* of	
Animal category	Herds	Animals
Cattle	12,900	883,000
Dairy cows only**	5,900	453,400
Suckling cow only**	4,900	249,900
Combined production (cow)**	1000	144,700
Goats	1,400	66,000
Dairy goats**	400	35,900
Sheep	13,800	1,902,000
Breeding sheep > 1 year**	13,800	944,000
Swine	1,900	749,000
Breeding animal > 6 months**	1,000	41,600
Fattening pigs for slaughter**	1,700	425,000
Laying hen flocks > 250 birds	563	4,142,500
Broilers	551[1]	74,290,000[2]
Turkey, ducks, geese for slaughter (flock > 250 birds)	39	315,800

*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 1992-2021. Data provided by the Norwegian Directorate of Fisheries updated by 25.05.2022.

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[3]	1,546,121	88,831	1,622	505	2,716	2,163	13	15

[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 2021 was eight buffalos, 89 sheep, one goat (not for livestock production), ten camelides and 17,997 day old chicks of chicken, guinea fowl, turkey and duck according to the yearly report from KOORIMP and KIF; https://www.animalia.no/no/Dyr/koorimp---import/arsmeldinger-koorimp-og-kif/

USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

Kari Grave, Kari Olli Helgesen and Petter Hopp

Sales data for 1993-2021 for antibacterial veterinary medicinal products (VMP) for terrestrial animal species obtained at wholesalers´ 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 analyses, including for supplementary information (see Appendix 1). Calculation of kg active substance per VMP presentation follows the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) protocol (see Appendix 1). This protocol has recently been updated in terms of standards for calculation. As a consequence, the annual amounts sold (kg) are slightly lower compared to the figures presented in previous NORM-VET reports but only for terrestrial food-producing animals (2013-2020; 2.1% to 3.9% lower).

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 2021 were 4,875 kg. A decline of the annual sales of such VMPs of 46% in the period 1993-2021 is observed (Figure 1).

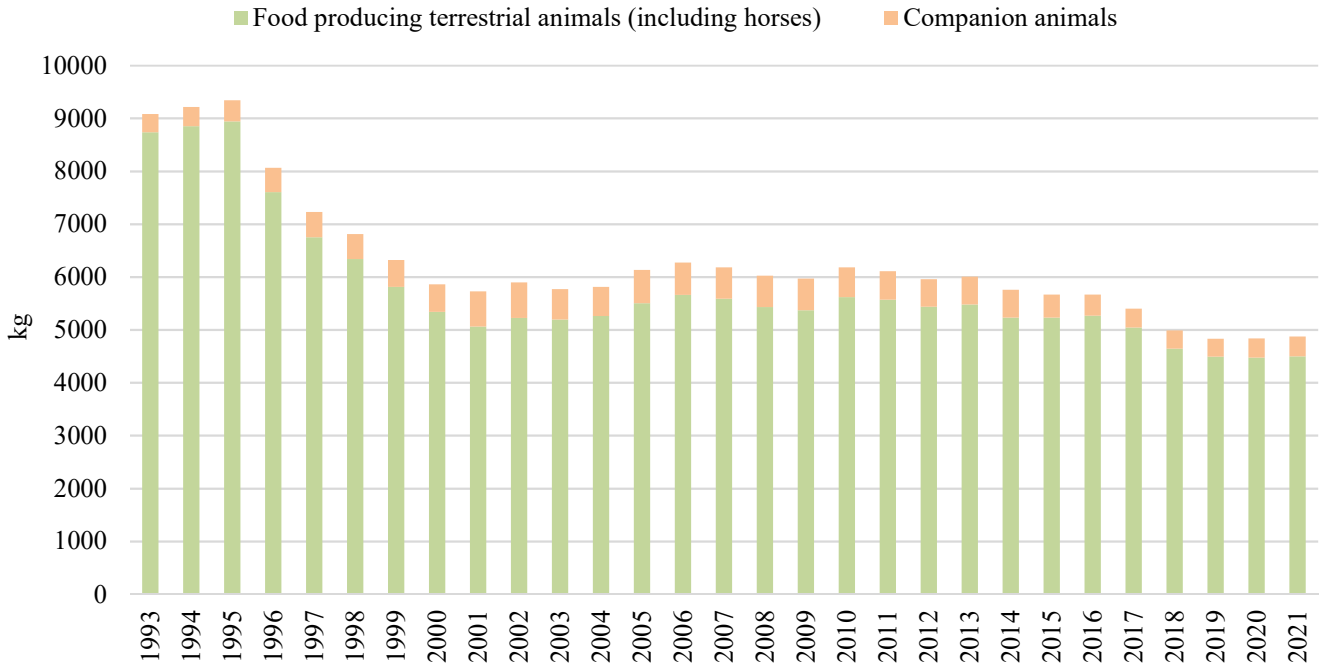

FIGURE 1. Total sales, in kg active substance, for food-producing terrestrial animals (including horses) and companion animals, of antibacterial veterinary medicinal products for therapeutic use in Norway in 1993-2021.

Food-producing terrestrial animals, including horses

In 2021 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,500 kg and compared to 1993 a decreased in the sales of such VMPs of 49% is observed (Figure 2). In total, 58% of the sales (kg) of antibacterial VMPs for this animal category in 2021 contained penicillins only, of which 95% was beta-lactamase sensitive penicillins. Of the total sales for use in terrestrial food-producing animals in 2021, 30% was sold as tri-methoprim-sulfa containing oral paste marketed for horses.

The proportion of sales of VMPs containing only penicillins for terrestrial food-producing animals increased from 18% to 62% during the period 1993-2021. This is mainly due to reduced sales of injectable and intra-mammary combination VMPs of penicillins and an aminoglycoside (dihydrostreptomycin) that has been gradually replaced by VMPs containing penicillins as the sole antibacterial agents.

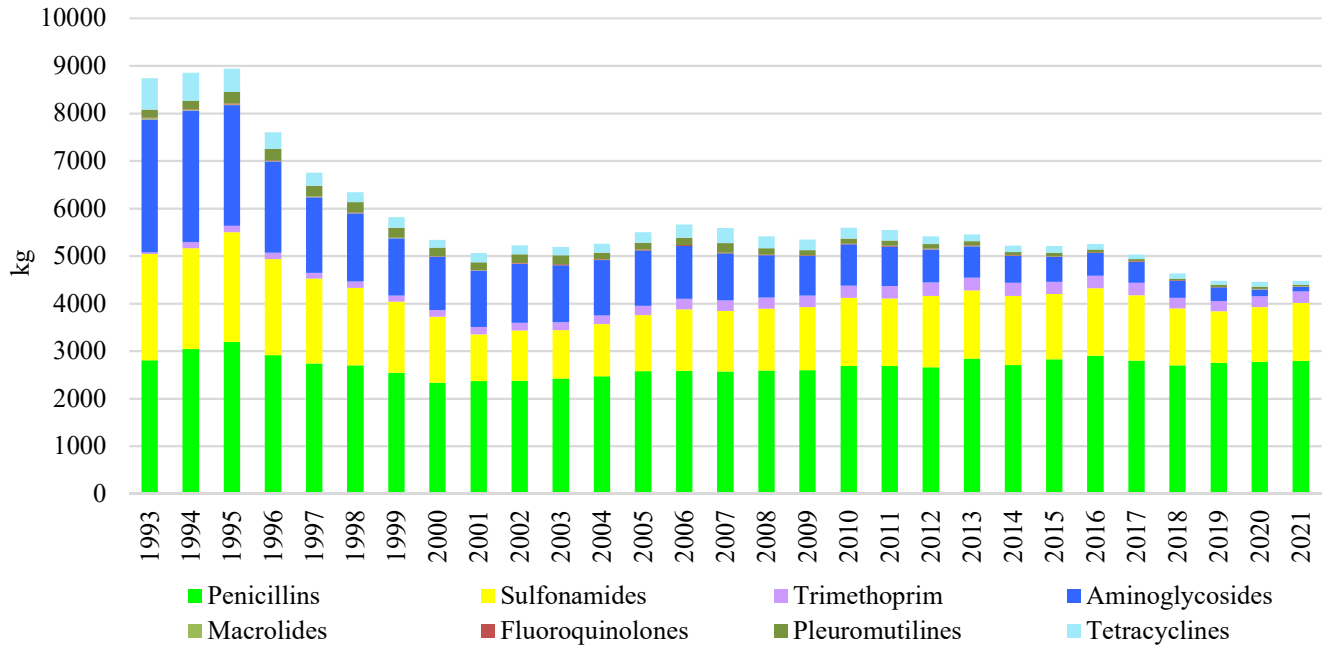

FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals (including horses) in Norway in 1993-2021. In addition, minor amounts of amphenicols VMPs were sold in 2008-2021 (range 16-27 kg) and of baquiloprim 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 2021, 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 1993-2021 no VMPs containing 3rd and higher generations of cephalosporins have been approved for food-producing animals in Norway via national procedures. Two 3rd generation products have been approved via community procedures, but these are not marketed in Norway. Applications for special permits to use such VMPs marketed in other EEA countries for food-producing animals are normally not approved – an approval would only be given for specific animals if sensitivity testing precludes all other options. This is the case also for polymyxins (Tonje Høy, Norwegian Medicines Authority, 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 2020, only 2.6% of the sales of antibiotic VMPs for food-producing terrestrial animals was for VMPs applicable for group treatment (oral treatment).

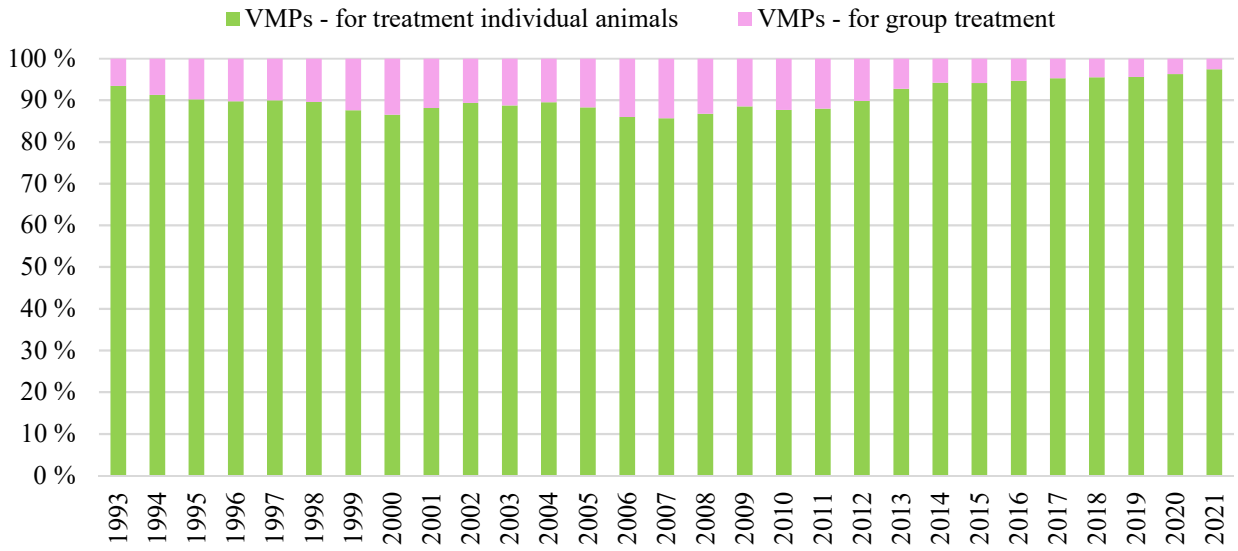

FIGURE 3. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals, including horses (bolus, injectables, intramammary preparations, intrauterine preparations, oral paste and some tablet VMP 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 2021. The data were extracted from the VetReg database 27 April 2022. 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 of antibacterial VMPs and human medicinal products reported to VetReg for which EMA advice restriction of the use due to potential public health risks, the proportions accounted for by cattle, pigs and sheep were 0.2%, 0.1% and 0.02%, respectively, and only fluoroquinolones were used (Figures 4-6).

Cattle

Of the prescriptions (VetReg data) of antibacterial veterinary and human medicinal products for cattle in 2021, 89.9% was for penicillins (kg active substance); 87.5% was beta-lactamse sensitive penicillins (intramammaries not included) (Figure 4) and this proportion 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 containing penicillins only were 85% in 2021 and for combinations of penicillins and aminoglycosides it was 15%.

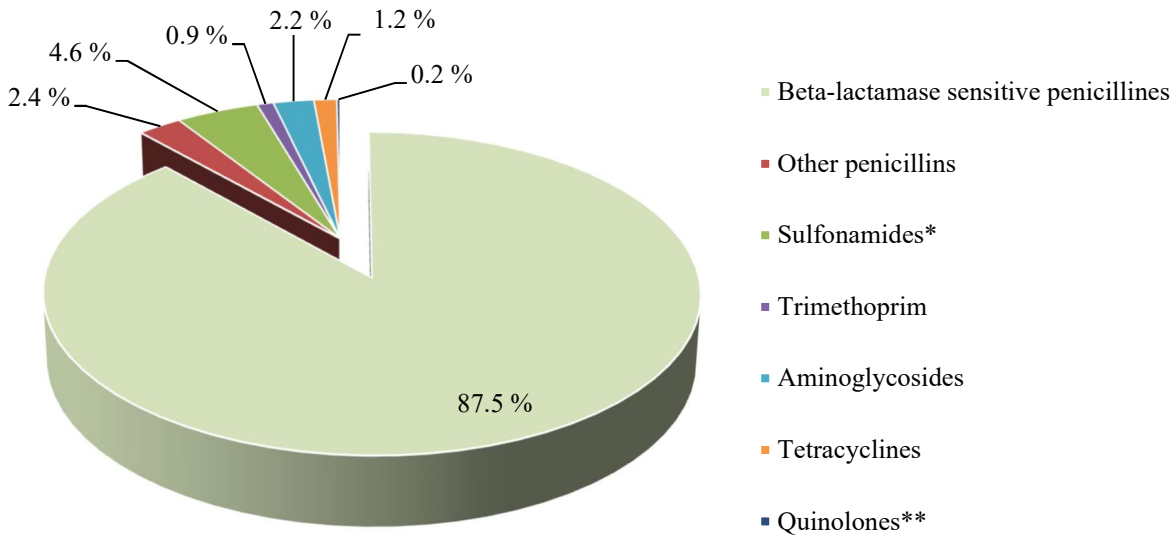

FIGURE 4. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for cattle in Norway in 2021. Data were obtained from the Veterinary Prescription Register (intramammaries not included in data in the figure). *In combination with trimethoprim only. **Fluoroquinolones only. In addition, 0.08% of the prescribed amounts was for macrolides and 0.9% for others (mainly amphenicols).

Pigs

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of pigs (Figure 5), 86.8% of the total amount reported to VetReg was penicillins; 76.9% was for beta-lactamse sensitive penicillins only and this proportion increased gradually from 65% in 2016.

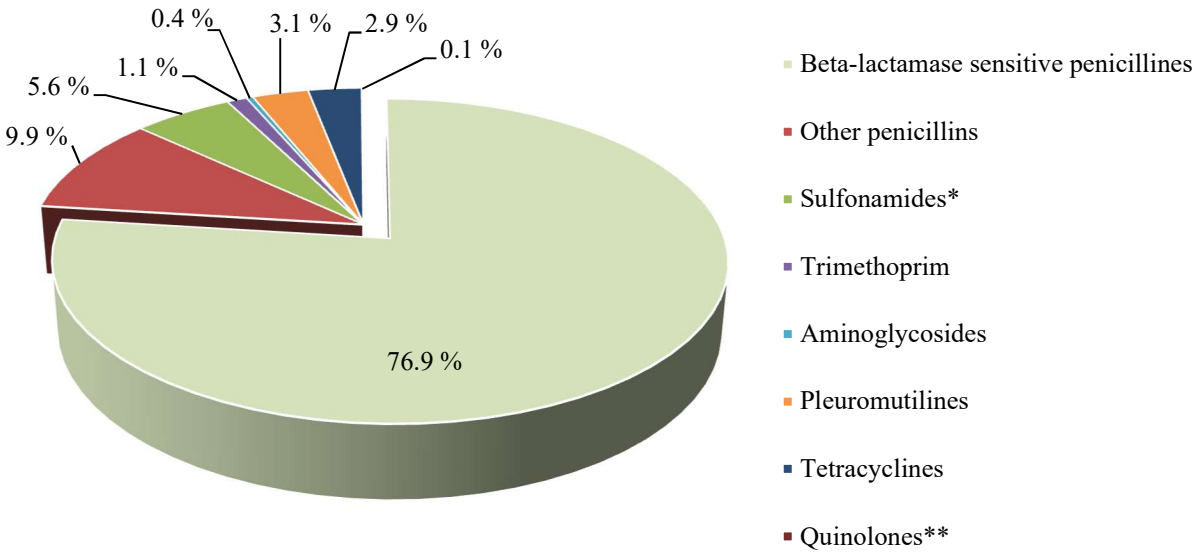

FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for pigs in Norway in 2021. Data are obtained from the Veterinary Prescription Register. *In combination with trimethoprim only. **Fluoroquinolones only. In addition, 0.1% of the prescribed amounts was for macrolides.

Sheep

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of sheep (Figure 6), 79.5% of the toal amount reported to VetReg was penicillins; 76.8% was for beta-lactamase sensitive penicillins only and this proportion increased gradually from 69% in 2016.

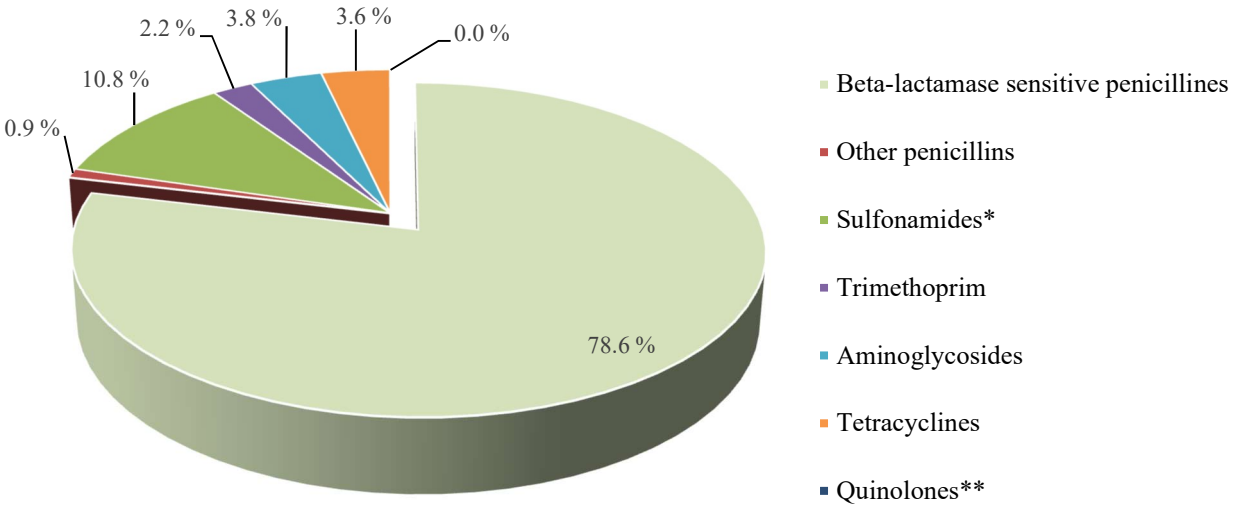

FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for sheep in Norway in 2021. Data are obtained from the Veterinary Prescription Register (intramammaries not included in data in the figure). *In combination with trimethoprim only. **Fluoroquinolones only. In addition, 0.05% of kg active substance prescribed was for amphenicols, macrolides and pleuromutilines.

Farmed fish

In 2021, the total amounts of antibacterials prescribed for use in aquaculture in Norway were 953 kg (Table 4); of this 949 kg were prescribed for farmed fish intended for human consumption (i.e. cleaner fish excluded). Of note is that in in 2017, 2018 and 2021 a few sea farms with Atlantic salmon with high weights were subjected to treatment with antibiotics (VetReg data); this was not the case for data from the other years in the period 2013-2021.

Of the antibacterials for which restriction of use in animals is adviced at EU/EEA level due to potential public health risk (1, 2), only other quinolones are used for farmed fish. From 2011 to 2021, the proportion of sales of quinolones has fluctuated; in 2021 this proportion was 6 % (57 kg) (Table 4).

TABLE 4. Usage, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2013-2021. 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	2021[1]
Tetracyclines									
Oxytetracycline	0	0	0	0	0	20	0	0.7	0
Amphenicols									
Florfenicol	236	399	188	136	269	858	156	115	896
Quinolones									
Flumequine	25	25	0	0	0	0	0	0	0
Oxolinic acid	599	99	84	66	343	54	66	107	57
Enrofloxacin			0.02	0.05	0.01		0.01	0.12	0.25
Total	**860**	**523**	**273**	**201**	**612**	**931**	**222**	**223**	**953**

[1]The total amount (kg) given is deviating due to rounding of the individual values.

For the years 2013-2021, the major proportion of prescriptions was for farmed fish in the pre-ongrower phase (Figure 7). The number of prescriptions of antibacterial VMPs for Atlantic salmon ongrowers were low during the period 2013-2021, 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.

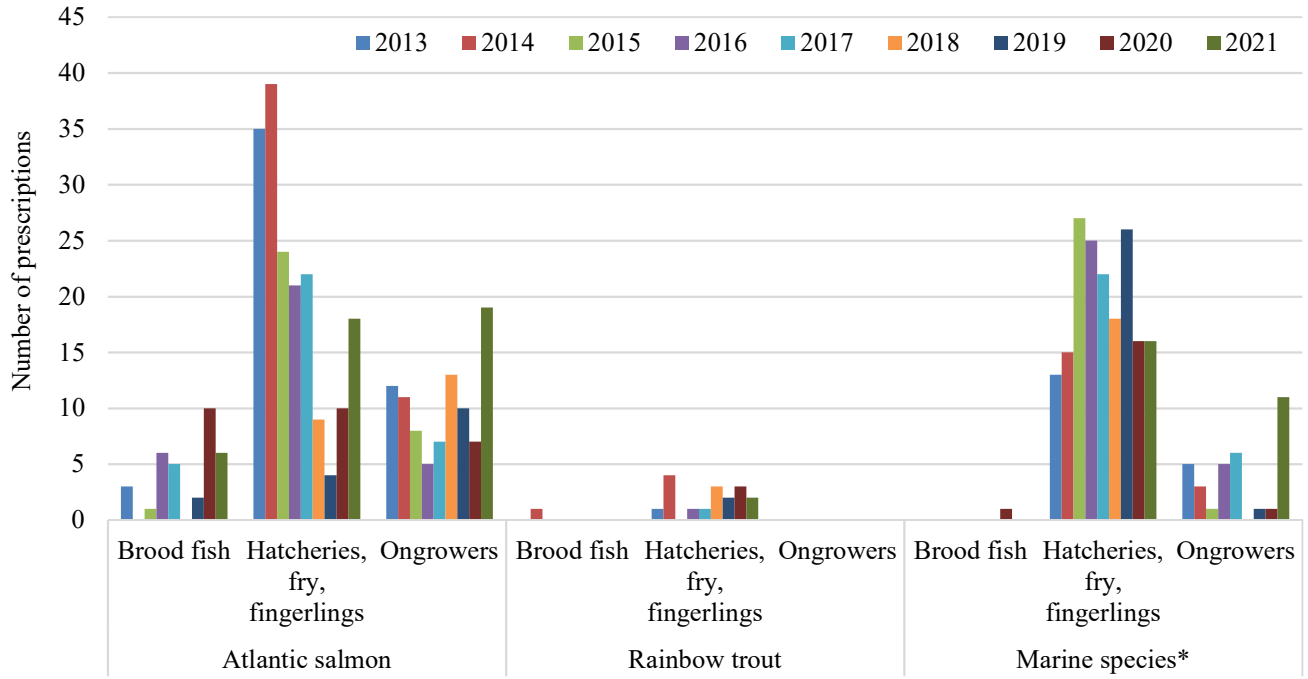

FIGURE 7. Number of prescriptions of antibiotics by fish species, split into production stages/types, in Norway in 2013-2021. Data were obtained from the Veterinary Prescription Register. *Cod, halibut, pollack, turbot and/or wolfish. Note that cleaner fish are not included.

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 2021 was 0.58 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.

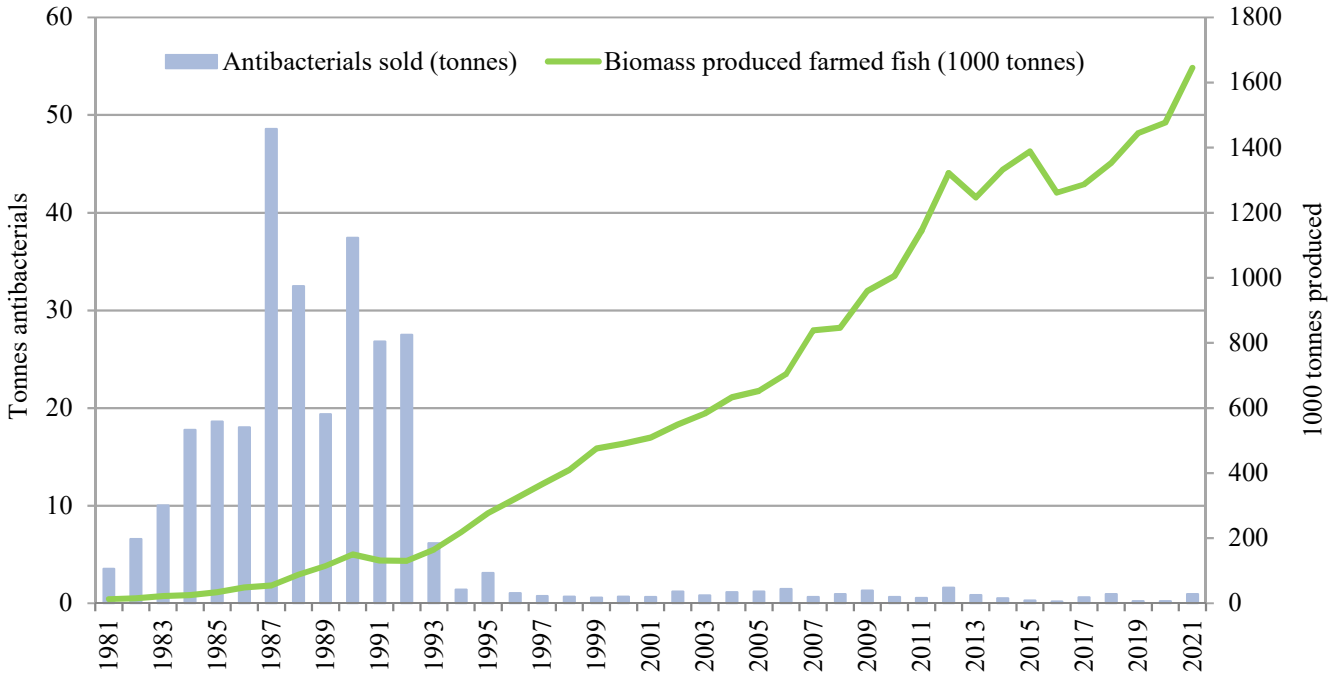

FIGURE 8. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish (including cleaner fish) in Norway in 1981-2021 versus tonnes produced (slaughtered) farmed fish. For the years 1981-2012 the data represent sales data provided by Norwegian Institute of Public Health; for 2013-2021 data represent prescription data obtained form the Veterinary Prescription Register. Data on slaughtered biomass farmed fish were obtained from the Norwegian Directorate of Fisheries (https://www.fiskeridir.no/Akvakultur/Tall-og-analyse/Akvakulturstatistikk-tidsserier).

In a report from 2019 (3) it was shown that only a low percentage of Atlantic salmon and rainbow trout in the ongrower phase were subjected to treatment with antibiotics (range 0.6%-1.4%). This was also the case for the years 2018-2021 when the figures were 1.6%, 1.2%, 0.8% and 2.2%, respectively.

Companion animals (dogs and cats)

The sales in 2021 of antibacterial VMPs approved solely for companion animals (include VMPs formulated as tablets, oral solution, injectable and oral paste) were 375 kg; in 2020 this figure was 360 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 2021 this figure had decreased to 38.

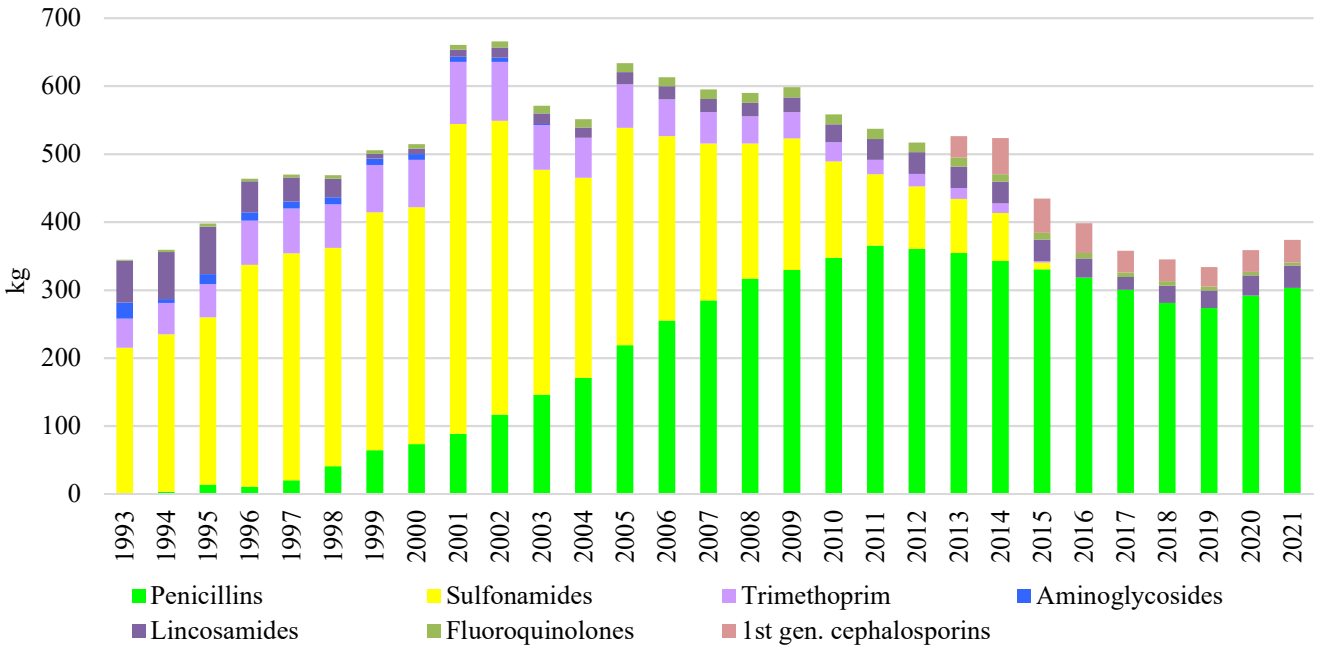

FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables, oral paste, oral solution and tablets; note the exceptions for tablets: see Appendix 1) in Norway for the period 1993-2021. Minor annual sales of a 3rd generation cephalosporin injectable VMP (range 0.4-1.1 kg) during 2008-2021 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 1993-2021 (Figure 9). The first penicillin VMP as tablets (the aminopenicillin amoxicillin) 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 since then the proportion of the combination amoxicillin and clavulanic acid increased steadily (Figure 10) peaking in the period 2009-2012 when it was 88% of the sales of aminopenicillins. Since then a decrease in this proportion is observed; in 2021 this figure was 78% (Figure 10).

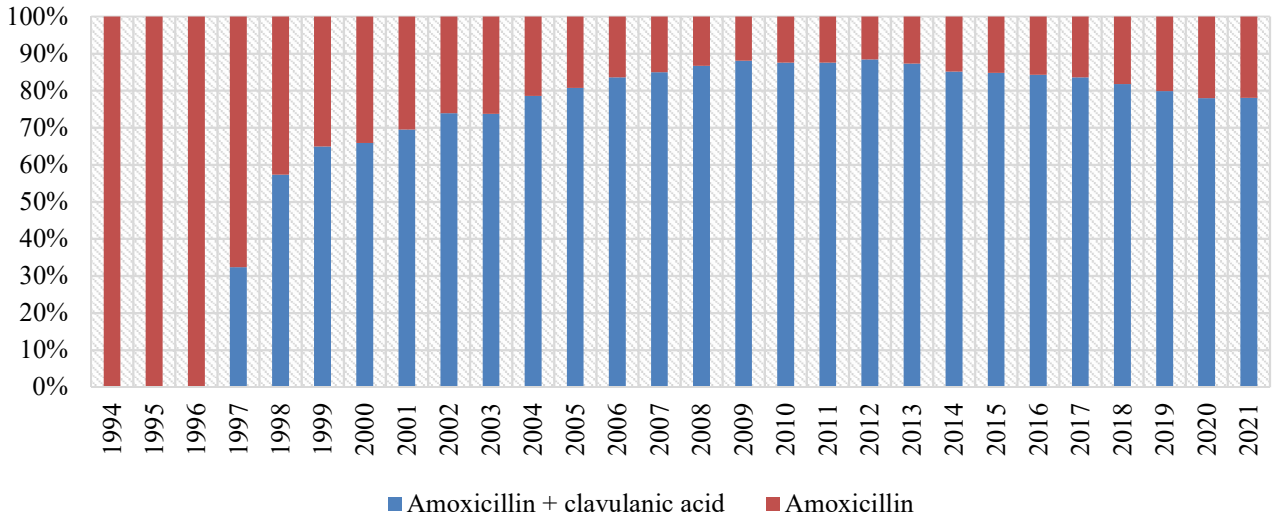

FIGURE 10. Proportions of sales (in kg active substance) of VMPs with amoxicillin combined with clavulanic acid versus amoxicillin for dogs and cats in Norway during 1994-2021.

From 1993 to 2021 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 gradually decreased to 1.2% in 2021 (Figure 9; Figure 11). The proportion of the total sales for dogs and cats of 3rd generation cephalosporins has been low since such VMPs were marketed in Norway; this figure was 0.2% in 2008 and declined to 0.1% in 2021 (Figure 11).

Antibacterials for which use in animals is adviced to be restricted

In 2019, the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency (EMA) published a categorisation (1, 2) of antibiotics for use in animals for prudent and responsible use at EU/EEA level. For certain classes – i.e. quinolones (fluoroquinolones and other quinolones), 3rd and 4th generation cephalosporins and polymyxins - it is advised that the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions. Figure 11 shows the amounts sold, in kg of the antibacterials belonging to the AMEG categories that EMA advice to restrict the use of, compared to the total sales of antibacterial VMPs, stratified by animal categories. In total, 1.2% of the total sales of antibacterial VMPs in 2021 belonged to the AMEG category that EMA has adviced to restrict the use of, and 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.

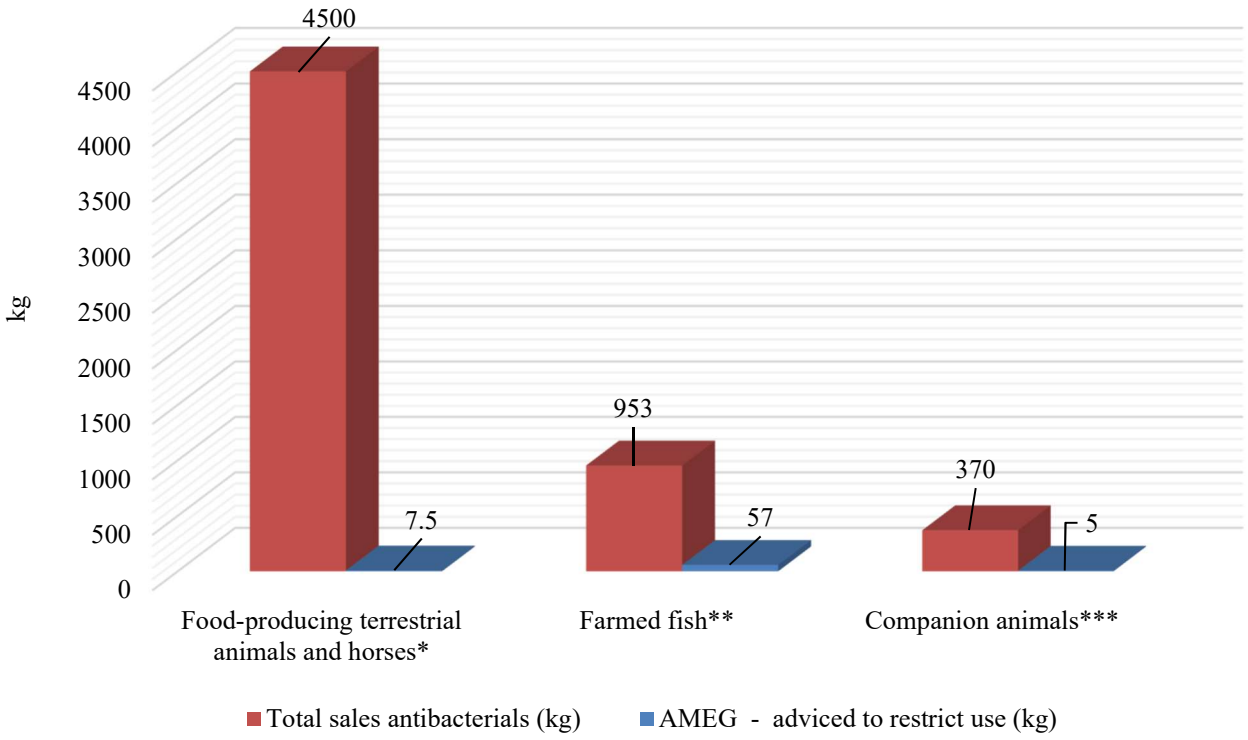

FIGURE 11. Total sales and sales of antibacterial veterinary medicinal products (VMPs) in 2021, for which the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency advises to restrict the use, stratified by animal category (1, 2). Of note, VMPs for topical treatment are not included. *Fluoroquinolones. **Other quinolones. ***3rd generation cephalosporins and fluoroquinolones.

References:

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National Strategy against Antibiotic Resistance (2015-2020)
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 since then the usage for this animal category has been on approximately the same level. On average the sales for the period 1999-2012 was 39% lower than in 1995 (Figure 2 and Figure 12).

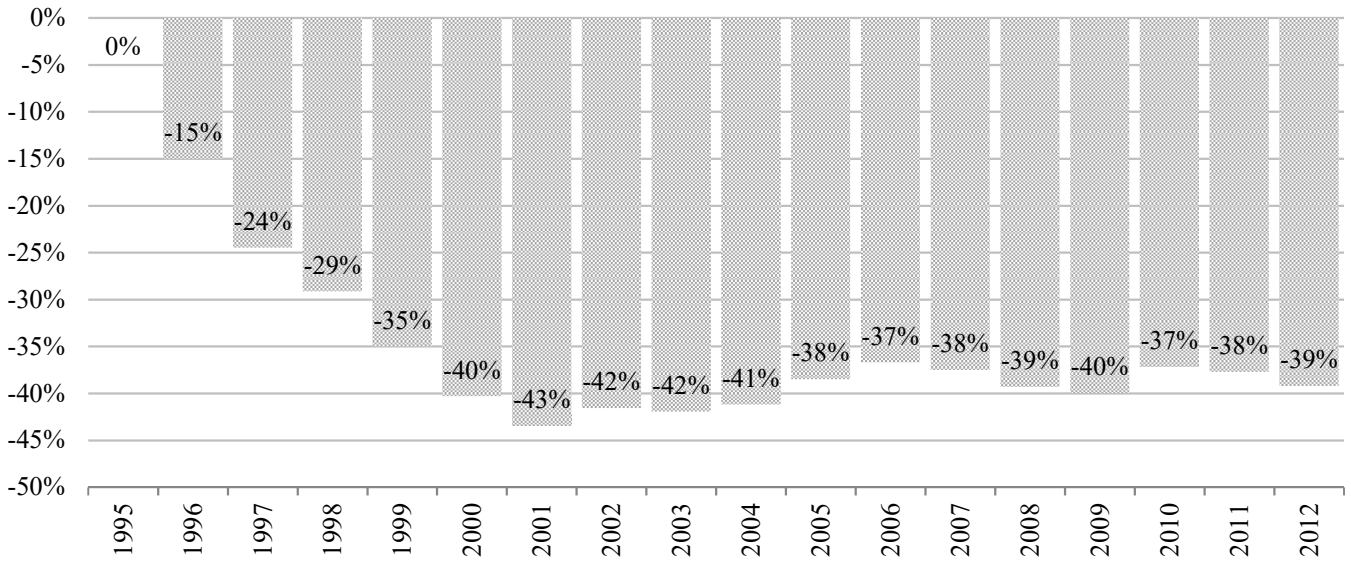

FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMP) approved for use in food-producing terrestrial animals, including horses, 1995 being the reference year.

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, in this report the further development in reference to the targets given in the National Strategy against Antibiotic Resistance (2015-2020) is presented.

Approach – assessment of changes

To evaluate progress in terms of reaching the goals set down in the national strategy, sales data for 2013-2021 have been further refined in order to obtain estimates of 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 2021 was 25% and 21%, when measured in kg and in mg/PCU respectively (Figure 13). The sales patterns (data from wholesalers) have been stable across the period 2013-2021, 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 proportions of prescribing of such products for horses and companion animals (VetReg data) were relatively stable (and very low) across 2015-2021. 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 (Directive 2001/82/EC, Article 10) – 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.

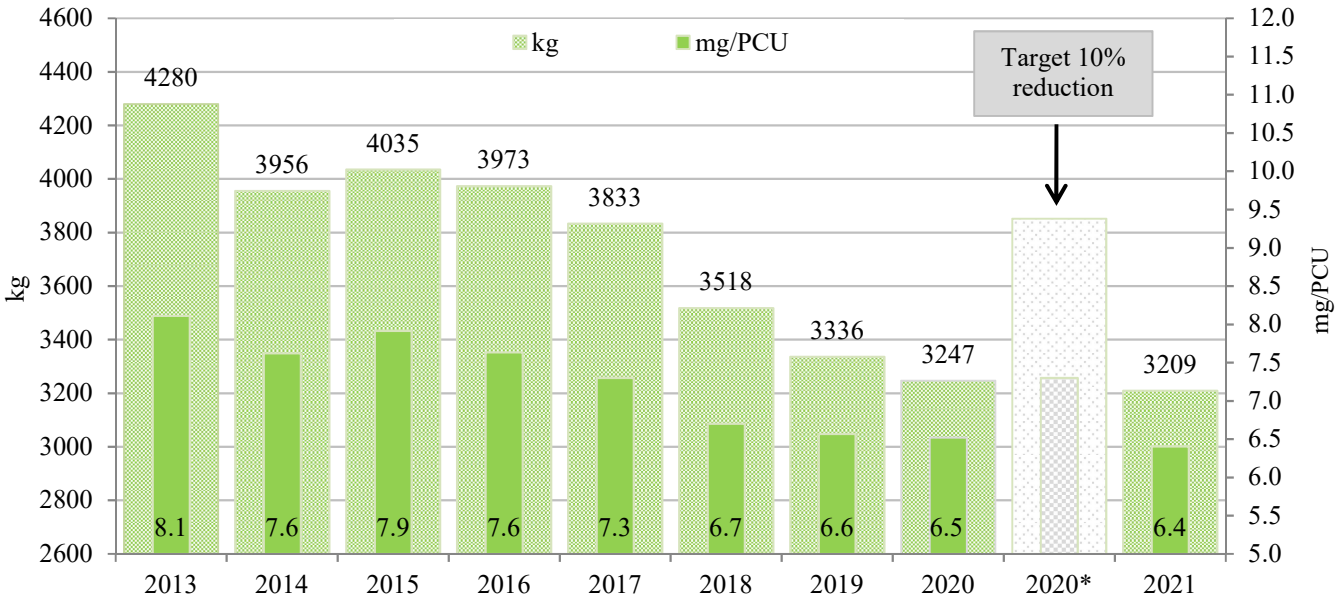

FIGURE 13. Estimated sales, in kg active substance and in mg/PCU, of antibacterial veterinary medicinal products for cattle, pigs, sheep, goats and poultry in Norway in 2013-2021 and the target (2020*) according to the National Strategy. Sales data were obtained from the Norwegian Institute of Public Health. Note that antibacterial human medicinal products are not included. 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 2004-2014 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 2015-2021.

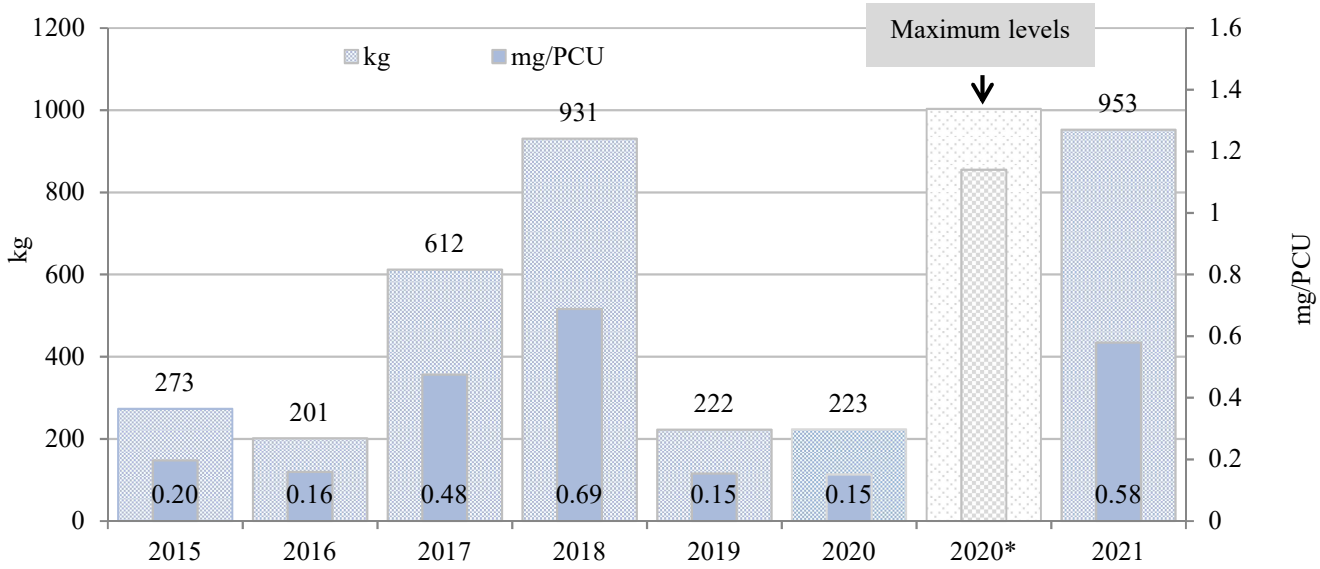

FIGURE 14. Prescription, in kg active substance and in mg/PCU, of antibacterial VMPs for farmed fish, in Norway in the period 2015-2021 and the maximum levels (2020*) according to the National Strategy. Maximum levels are based on the average for the period 2004-2014. Prescription data were obtained from the Veterinary Prescription Register and include prescriptions 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 2013-2021 a reduction in the sales of such antibacterial VMPs for companion animals of 29% is observed (Figure 15). As shown in Figure 15, the sales of antibacterial VMPs for companion animals declined gradually from 2013 to 2019 while for the following two 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 13% from 2015 to 2021. This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substituted by prescribing antibacterial HMPs.

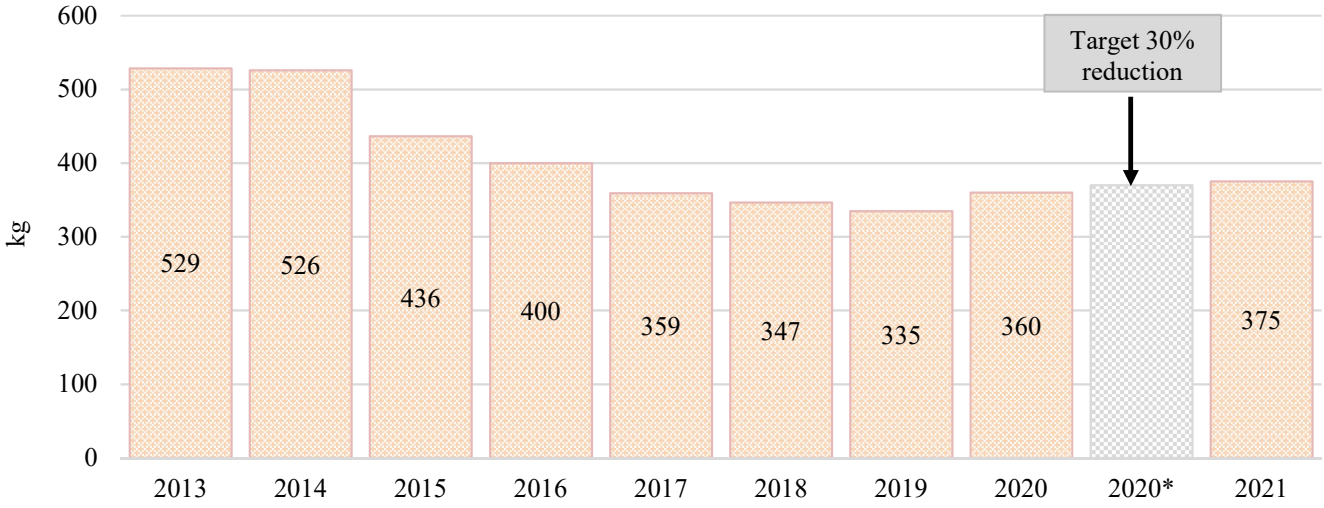

FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (oral paste, oral solution and tablets; exceptions for tablets - see Appendix 1) in the period 2013-2021 and the target (2020*) according to 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 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 2013-2020 and in 2021, none of the broiler flocks were subjected to antibiotic treatment. Concurrent with and in the years subsequent to the discontinuation of the use of the coccidiostat feed additive narasin in broilers, the Norwegian broiler industry has explored various measures in order to prevent increased occurrence of necrotic enteritis (NE). In cases where NE has been diagnosed or suspected, in particular a probiotic based on a *Bacillus subtilis* strain administered through drinking water has shown promising potential in preventing NE (see text box page 29).

TABLE 5. Number of broiler flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs)[1] in Norway in the period 2013-2021. Data were obtained from HelseFjørfe, Animalia.

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

[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 eneteritis annually). [5]Parents.

References:

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Non-antibiotic feed additives as alternatives to ionophorous coccidiostats

In addition to antiparasitic effects ionophorous coccidiostats (hereafter: ionophores) also exert antibacterial activities, mainly against Gram-positive bacteria. A negative public perception and consumer concerns regarding the use of feed additives with antibiotic properties in livestock production, in conjunction with concerns related to co-selection of antimicrobial resistance, have led to increased focus on broiler chickens raised without the use of ionophores (1–4).

In Norway, narasin was gradually phased out as coccidiostat feed additive by the broiler industry during the period February 2015 to June 2016. Concurrent with, and in the years subsequent to, the discontinuation of the use of the coccidiostat feed additive narasin in broilers, the Norwegian broiler industry has explored various measures in order to prevent increased occurrence of necrotic enteritis (NE).

In a study performed by the Norwegian Veterinary Institute in collaboration with Nortura, Felleskjøpet, Norgesfôr, Animalia and Fiskå Mølle, feed additives with active components categorised as probiotics, prebiotics, phytogenics and/or organic acids were assessed for their effect on intestinal health and production performance in broiler chickens (5). The study provides comparable results from testing of alternatives to ionophores in an experimental model highly relevant to commercial conditions. Each of twenty commercially available feed additives, four feed additive combinations and the ionophorous coccidiostat narasin were compared separately against a negative control diet without any feed additives. The study was performed on Ross 308 chicken housed on litter floor. Feed conversion ratio and body weight gain were registered from day 0 to 28. The chickens were challenged with *Eimeria* spp., and caecal *Clostridium perfringens* (CP) counts were investigated.

The results showed that narasin used prophylactically as a feed additive had a strong CP-reducing effect in combination with performance-promoting impact, while two of the alternatives to ionophores gave significantly beneficial effects on CP counts as well as feed conversion ratio during the rearing interval subsequent to *Eimeria* spp. challenge. One of these alternatives was a probiotic feed additive based on the *Bacillus subtilis* PB6 strain as the only active component (Clostat®). The other was a combination of two feed additives - one with components from the yeast *Saccharomyces cerevisiae* (Diamond V XPC®) and one with short- and medium-chain fatty acids together plus a phenolic compound (Presan FY®).

Overall, the study showed that different classes of feed additives had significantly beneficial impact during distinct rearing phases and on specific performance targets. Furthermore, results from the study suggest that optimised combinations of different feed additives with different active components could be useful disease-preventive measures in broiler reared without use of ionophores (5). Data from HelseFjørfe/Animalia show that the probiotic based on a *Bacillus subtilis* strain (Clostat®) occasionally is used in broiler and turkey flocks diagnosed with coccidiosis and/or necrotic enteritis (data not published). In 2021, Clostat® was administered in the drinking water of 2/5 broiler flocks diagnosed with coccidiosis, in 10/40 broiler flocks diagnosed with necrotic enteritis and in 3/10 broiler flocks diagnosed with both coccidiosis and NE. In comparison, narasin-supplemented feed was administered in 7/40 broiler flocks diagnosed with NE. A more comprehensive discussion of alternatives to ionophorous coccidiostats can be found in a PhD Thesis from 2021 (6).

References:

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6. Granstad, S. (2021). Impact of feed composition on rearing of broiler chickens without in-feed antimicrobials. Norwegian University of Life Sciences: Oslo, Norway; ISSN 1894-6402, ISBN 978-82-575-1811-0.

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USAGE IN HUMANS

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

Overall antibiotic sales

In 2021, the total sales of antibacterials for systemic use in humans (J01, excl. methenamine) decreased by 2% compared to 2020; from 11.5 to 11.2 Defined Daily Doses (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 33% since 2012, when a *Mycoplasma pneumoniae* epidemic caused a very high prescription rate of macrolides and tetracyclines. There has been a significant reduction in the use of systemic antibiotics during the Covid-19 pandemic, mainly due to reduced use of antibiotics indicated for respiratory tract infections (RTI-AB), Figure 16.

Although a lot has been achieved there are probably still areas for improvement, e.g. in individualisation of doses or duration of course length and choice of antibiotics, so one should expect that it is possible to achieve a further lowering of consumption rate and a better narrow-spectrum profile.

Antibiotics are prescription-only drugs in Norway. Overall antibiotic consumption includes all sales of antibiotics to humans in Norway i.e. in primary care, in hospitals and in long-term care institutions. Around 85% of the human use of antibacterials is used by patients outside healthcare institutions. In 2021, hospitals covered 8% of total DDDs of antibiotics and long-term care institutions around 6-7%. In the latest years, decreased sales are observed for all main antibiotic subgroups (Figure 17). Over 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 Norway, narrow-spectrum penicillins are 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 increased infection control have led to lower incidence of infections handled by health care. Especially respiratory tract infections have been sparsely reported during the Covid-19 pandemic. The reduced use of narrow-spectrum penicillins was observed for all age groups but was most pronounced in small children.

During 2021 there have been several shortage situations for antibiotics, but most often generics have been made available for the market and none of the shortage situations in 2021 were serious enough to impact the antibiotic consumption pattern.

TABLE 6. Human usage of antibacterial agents in Norway 2013, 2015, 2017, 2019 and 2021, by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2020-2021 and 2012-2021. 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	2013	2015	2017	2019	2021	2020-2021	2012-2021
J01A	Tetracyclines	3.54	3.39	3.01	2.96	2.68	+1	-31
J01B	Amphenicols	<0.001	<0.001	<0.001	<0.001	<0.001	-	-
J01CA	Penicillins with extended spectrum	2.82	2.73	2.47	2.53	2.19	-1.5	-21
J01CE	Beta-lactamase sensitive penicillins	4.09	3.88	3.61	3.56	2.70	-2	-37
J01CF	Beta-lactamase resistant penicillins	0.79	0.89	0.84	0.93	0.95	+1	+6
J01CR	Combination of penicillins, incl. beta-lactamase inhibitors	0.05	0.08	0.07	0.10	0.13	+17	+259
J01D	Cephalosporins, monobactams, carbapenems	0.50	0.43	0.38	0.37	0.34	-8	-37
J01E	Sulfonamides and trimethoprim	0.86	0.88	0.84	0.93	0.90	+1	+4
J01F	Macrolides, lincosamides and streptogramins	1.94	1.51	1.18	1.04	0.67	-16	-70
J01G	Aminoglycosides	0.07	0.08	0.09	0.10	0.07	-25	-6
J01M	Quinolones	0.71	0.60	0.45	0.36	0.27	-9	-63
J01X*	Other antibacterials	0.45	0.41	0.36	0.32	0.31	-8	-35
J01	**Total excluding methenamine**	**15.8**	**14.9**	**13.3**	**13.2**	**11.2**	**-2**	**-33**
J01XX05	Methenamine	3.70	3.99	4.11	3.39	3.94	+2	+10
J01	**Total all antimicrobial agents**	**19.5**	**18.9**	**17.4**	**16.6**	**15.2**	**-1**	**-26**

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

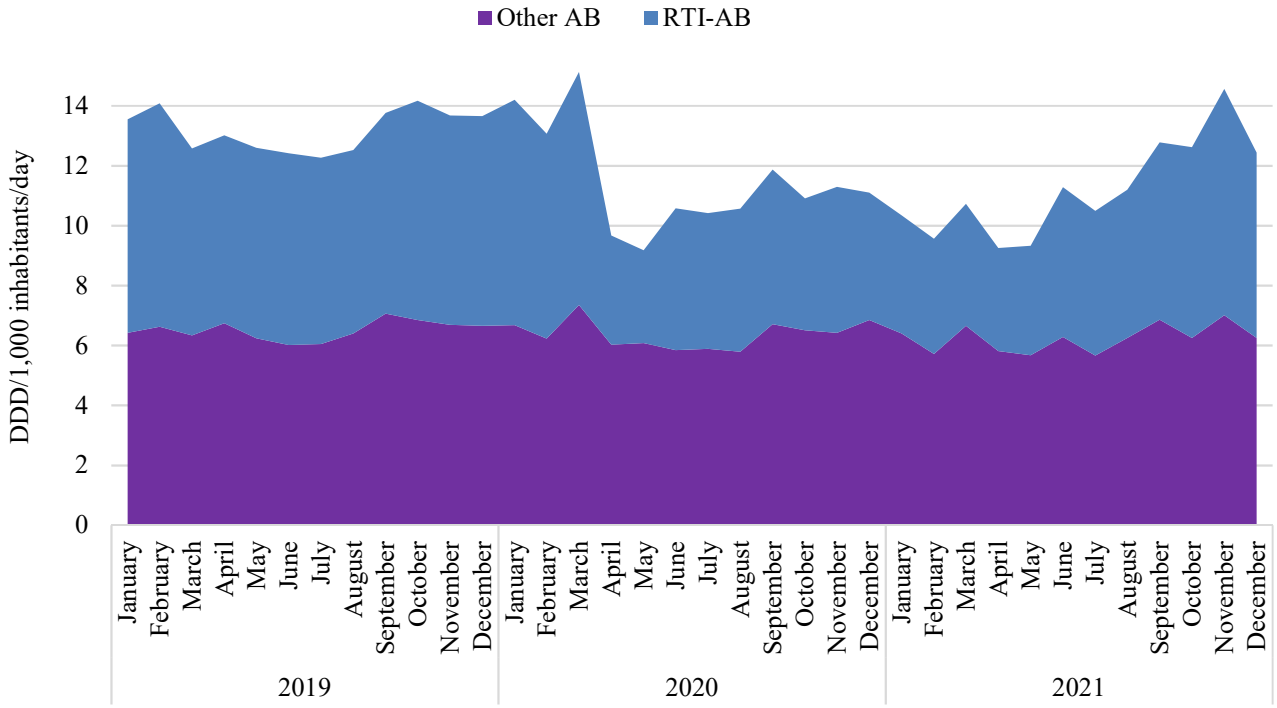

FIGURE 16. Monthly sales of antibiotics in 2019, 2020 and 2021 as measured in DDD/1,000 inhabitants/day. Sales of antibiotics for respiratory tract infections (RTI-AB) is defined as amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline. Other antibiotics (Other-AB) is defined as all other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

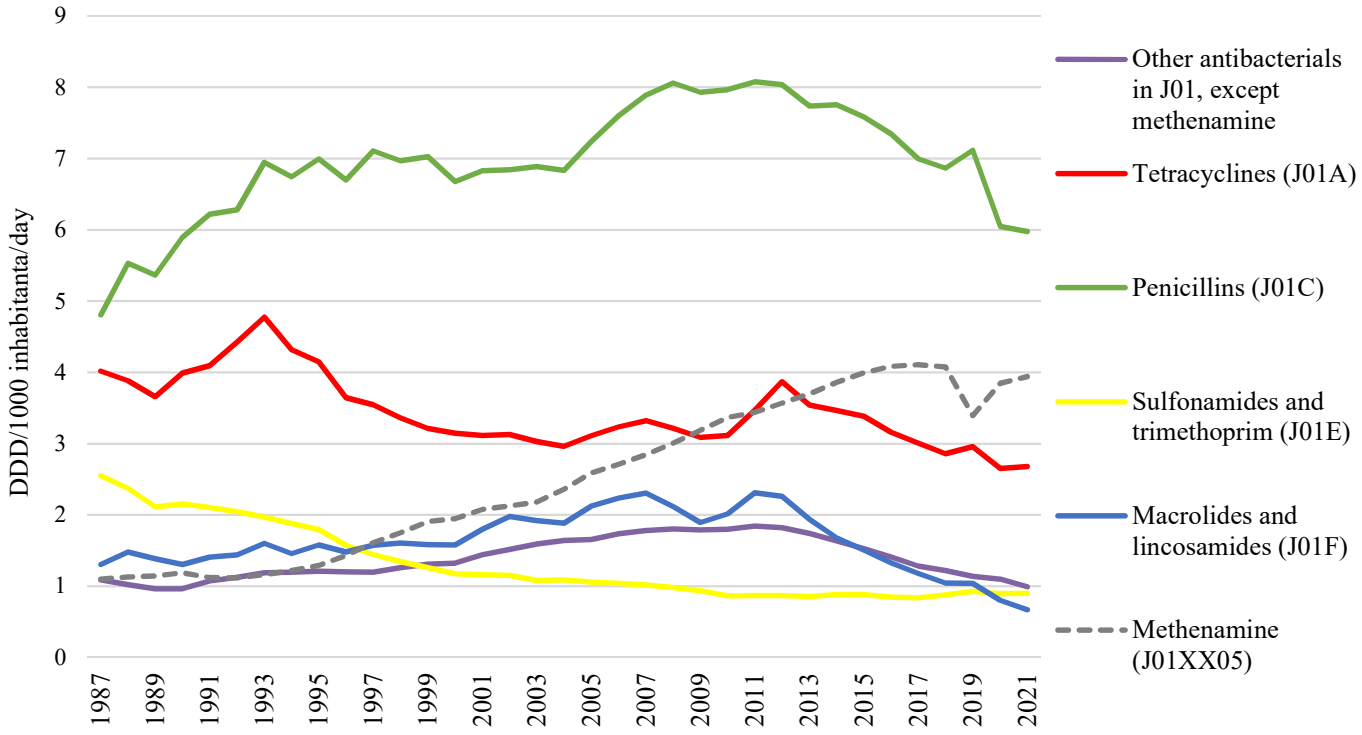

FIGURE 17. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine and other antibacterials in Norway 1987-2021. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05). Data from the Norwegian drug wholesales statistics database.

The beta-lactamase sensitive penicillin group (J01CE), the tetracyclines (J01A), and penicillins with extended spectrum (J01CA) were the three most commonly used antibacterial groups in Norway in 2021. 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 2021 the use was still lower than in 2017 (Table 6, Figure 17). Methenamine has the largest amounts of DDDs of all antibiotics used in Norway and accounted for 26% of total antibacterial use in 2021. Of the tetracyclines (J01A), doxycycline is most frequently used, followed by lymecycline, a drug indicated for acne (Table 7).

In 2021, the penicillins (ATC group J01C) accounted for 39% of the total antibacterial use in Norway (Figure 18). Over the years there has been a shift towards use of more broad-spectrum penicillins. In 2021, beta-lactamase sensitive penicillins accounted for almost half of the penicillin group (45% share) measured in DDDs. This is lower than in earlier years, but is probably caused by the effects of the Covid-19 as the earlier picture has been stable over many years. Penicillins with extended spectrum (J01CA) represent 37% 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 7). In May 2017, oral co-amoxiclav was approved in Norway, and since then a significant increase is observed. Pivmecillinam is the main antibiotic used for urinary tract infections, although pivmecillinam, trimethoprim and nitrofurantoin are all equal recommendations for acute cystitis.

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

Since 2012 the use of macrolides has dropped markedly, (Tables 6-7, Figures 17-18). Use of the group J01F macrolides, lincosamides and streptogramins has followed a wavy pattern over the years. The shifts in use could be explained to some degree by 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 infection in the primary care treatment guidelines, but since then doxycycline has been the only first line treatment. Reduction in the use of macrolides has been a focus in the primary care part of the National Action Plan. The use of macrolides is now at the same level as in the 1970s.

In the latest years, sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased, mainly due to decreased use of 1st and 2nd generation cephalosporins (Tables 6-7, Figure 18). Since 2019 there has been a slight reduction in the sales of cefotaxime, which may have at least two causes. Reduction in the use of cefotaxime and other 3rd generation cephalosporins were specifically targeted in the National Action Plan. Another factor is that since 2019, the European breakpoint committee EUCAST has recommended 1g x 3 as the standard dose for cefotaxime, whereas the most common dose in Norway has been 2g x 3. The new dosage has gradually been incorporated in guidelines and other recommendations in Norway.

The quinolones represent only a small fraction (2%) of total antibacterial sales (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 92% of the quinolone group in 2021.

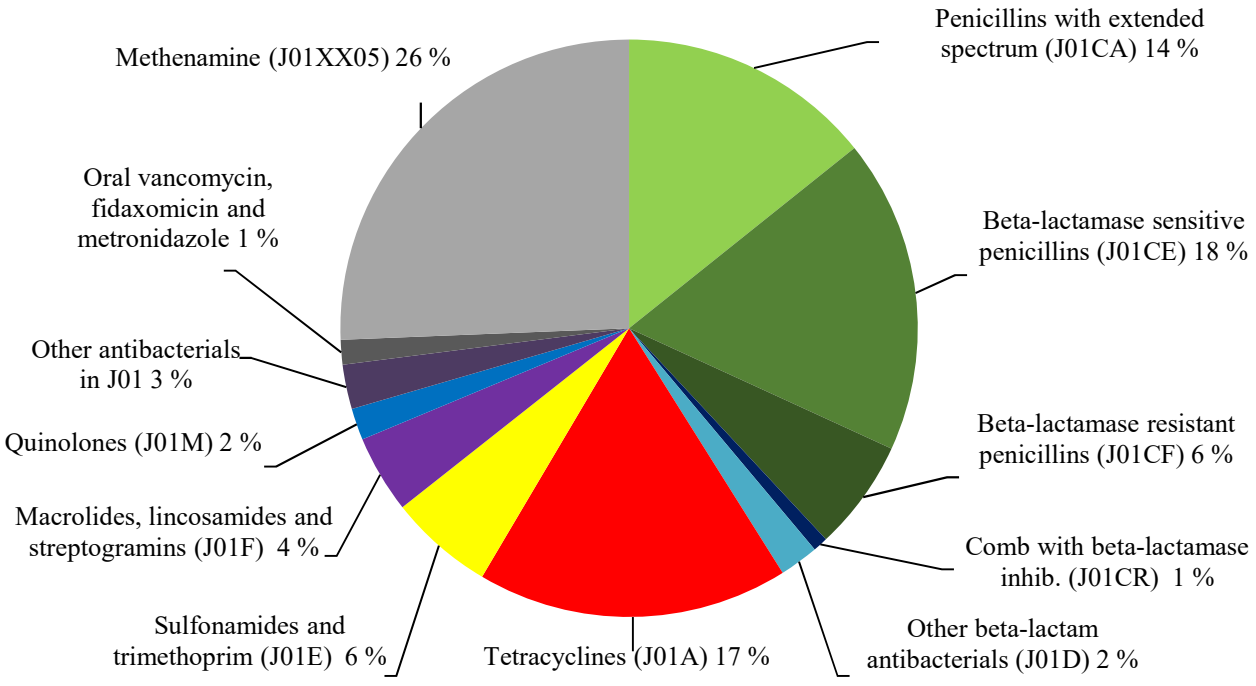

FIGURE 18. Relative amounts of antibacterial agents for systemic use in 2021 in Defined Daily Doses (DDD) (total sales in the country). Data from the Norwegian drug wholesales statistics database.

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	2021
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	1.99	1.82	1.60	1.38	1.30
	J01A A04	Lymecycline	0.90	0.96	0.94	0.93	1.08	1.10
	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	0.27
	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	0.03
	J01C A04	Amoxicillin	0.97	0.97	0.88	0.84	0.65	0.67
	J01C A08	Pivmecillinam	1.78	1.87	1.69	1.57	1.52	1.49
	J01C A11	Mecillinam	0.008	0.008	0.005	0.002	0.003	<0.001
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.24	0.24	0.23	0.24	0.23	0.14
	J01C E02	Phenoxymethyl-penicillin	4.07	3.64	3.50	3.18	2.53	2.56
	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	0.79
	J01C F02	Cloxacillin	0.14	0.19	0.17	0.16	0.16	0.16
	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	0.07
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.07	0.09	0.05	0.06	0.06
J01DB – first gen. 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 – second gen. cephalosporins	J01D C02	Cefuroxime	0.08	0.06	0.04	0.03	0.03	0.01
J01DD – third gen. cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	0.11	0.11
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.01	0.01	0.01
	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	0.02
	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	0.002
J01DI – Other cephalo-sporins and penems	J01D I02	Ceftaroline fosamil		<0.001	<0.001	<0.001	<0.001	<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	2021
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.46	0.38	0.34	0.33	0.31
	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	0.59
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.75	0.60	0.44	0.29	0.17
	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	0.10
	J01F A10	Azithromycin	0.48	0.35	0.30	0.24	0.19	0.18
	J01FS15	Telithromycin	<0.001	<0.001	<0.001			
	J01F G01*	Pristinamycin						<0.001
	J01F F01	Clindamycin	0.33	0.34	0.28	0.25	0.23	0.22
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	0.06
	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	0.01
	J01M A02	Ciprofloxacin	0.71	0.64	0.51	0.39	0.28	0.25
	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	0.009
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.02	0.02	0.02	0.02	0.01
	J01X A02	Teicoplanin	0.001	<0.001	<0.001	<0.001		
	J01X B01	Colistin	0.004	0.005	0.006	0.006	0.008	0.008
	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	0.03
	J01X E01	Nitrofurantoin	0.37	0.35	0.31	0.25	0.26	0.24
	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	3.94
	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	0.002
	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	0.003
	A07A A11	Rifaximin	0.004	0.012	0.043	0.076	0.10	0.11
	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	0.21
	D06A X09/ R01A X06*	Mupirocin (grams)[1]	145	174	186	247	288	228

*Drugs not licensed in Norway in 2021. [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 i.e. prescribed to persons in primary care, mainly those living at home. The basis for these data is captured from the Norwegian Prescription Database (NorPD) that includes all prescriptions of antibacterials dispensed to persons living in Norway including 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 2021, the use of antibacterials (J01) in primary care was 12.8 DDD/1,000 inhabitants, i.e. at the same level as in 2020. For primary care, the most important antibiotic group in 2021 was the penicillins, J01C (38% of DDDs and 54% of prescriptions in ATC group J01). Tetracyclines, J01A was the second most used group (19% of DDDs and 10% of prescriptions) followed by sulfonamides and trimethoprim, J01E (5% of DDDs and 12% of prescriptions). The five antibiotic substances most often prescribed for outpatients in 2021 were phenoxymethylpenicillin, pivmecillinam, methenamine, dicloxacillin and doxycycline. These five antibiotics represented 63% of all prescriptions and 71% of all DDDs of the antibacterial group J01. Phenoxymethylpenicillin was prescribed in 22% of the prescriptions representing 18% of DDDs while methenamine represented 29% of the DDDs and 10% of the J01 prescriptions.

The steady decrease in primary care the years before the Covid-19 pandemic may be due to an increased attention towards antimicrobial resistance, both among the public and healthcare personnel. A large proportion of general practitioners have completed quality improvement courses after the introduction of the Government's Action plan against AMR in 2016.

The decrease the last two years is probably due to the Covid-19 pandemic. Firstly, infection control measures may have decreased the prevalence of other RTIs. Secondly, the threshold for seeing a general practitioner for symptoms of infections has been raised, as GPs' offices to a large extent have been closed for these patients.

Geographical variation

The usage of antibacterials varies among the Norwegian regions as shown in Table 8. The county using the least is using around 85% in DDDs and 81% in prescriptions of the county using the most (Figures 19-20). Over the years, and measured in DDDs, some counties seem to be high-use counties and low-use counties, respectively. Antibiotic use has decreased in all counties the latest years, but with certain differences between the counties with Oslo being the county with the largest decrease in use of antibiotics (J01, excl. methenamine) - 37% reduction since 2012 (green dots in Figure 21).

Females use more antibiotics than males; 20% of the females purchased at least one antibiotic prescription (methenamine is excluded) in 2021 compared to 13% of the males. 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 in the country. Young children, young women and the elderly are high users of antibiotics (Figure 22). Among those who use antibacterials, the elderly population use more; for those above 75 years; 2.2 prescriptions/user for females and 2.1 prescriptions/user for males are dispensed every year compared to around 1.5 prescriptions/user for younger persons (men and women together, Figure 23). Compared to 2019 (i.e. a normal year), the number of DDDs/user has increased by 6% in children/adolescents; by 1% in middle ages; and decreased by 2% in 60-75 years old. For those older there was no change. This can be interpreted as those being treated were treated either by higher doses or longer time. The decrease in the elderly could probably be caused by shorter courses for urinary tract infections. Mean number of DDDs/prescription is 11.9 DDDs, which indicates a mean overall length of treatment of 11-12 days. However, for phenoxymethylpenicillin, the Guidelines recommend a higher therapeutic dose. The mean DDD/prescription was 12.2 and with the assumption that doses used were much higher than the given DDD-value of 2 g, the mean treatment length for phenoxymethylpenicillin can be estimated to be around 7-8 days, i.e. according to the Guidelines.

Antibiotics prescribed by dentists

Physicians are the main prescribers to humans, but in 2021 dentists prescribed around 5.9% (measured in DDDs) of antibiotics (J01) to humans in ambulatory care. Moreover, they prescribe 22% of all DDDs of metronidazole in oral forms. In 2020, dentists most often prescribed phenoxymethylpenicillin (77% of all antibiotic DDDs prescribed by dentists) followed by amoxicillin (9%), clindamycin and oral metronidazole, both 5%, Figure 24.

TABLE 8. Human usage of the 15 single antibacterial agents for systemic use most often prescribed by doctors in ambulatory care in the four health regions in Norway in 2021. Sales are given in DDD/1,000 inhabitants/day. Data from the Norwegian Prescription Database.

	Health region				Norway
	Mid	North	South-East	West	
Methenamine	4.21	4.10	3.56	3.48	3.68
Phenoxymethylpenicillin	1.62	1.21	1.78	1.75	1.71
Pivmecillinam	1.42	1.31	1.21	1.27	1.26
Doxycycline	1.17	1.05	1.12	1.16	1.13
Lymecycline	1.02	0.95	1.11	1.25	1.12
Dicloxacillin	0.68	0.71	0.71	0.63	0.70
Sulfamethoxazole and trimethoprim	0.47	0.49	0.41	0.46	0.43
Amoxicillin	0.41	0.38	0.45	0.43	0.43
Trimethoprim	0.34	0.33	0.25	0.23	0.26
Tetracycline	0.22	0.20	0.24	0.20	0.23
Nitrofurantoin	0.26	0.30	0.19	0.25	0.22
Ciprofloxacin	0.20	0.20	0.20	0.18	0.20
Azithromycin	0.10	0.13	0.16	0.19	0.16
Erythromycin	0.13	0.12	0.16	0.13	0.14
Clindamycin	0.11	0.12	0.13	0.12	0.13
All other antibiotics in ATC group J01	0.22	0.19	0.24	0.24	0.24

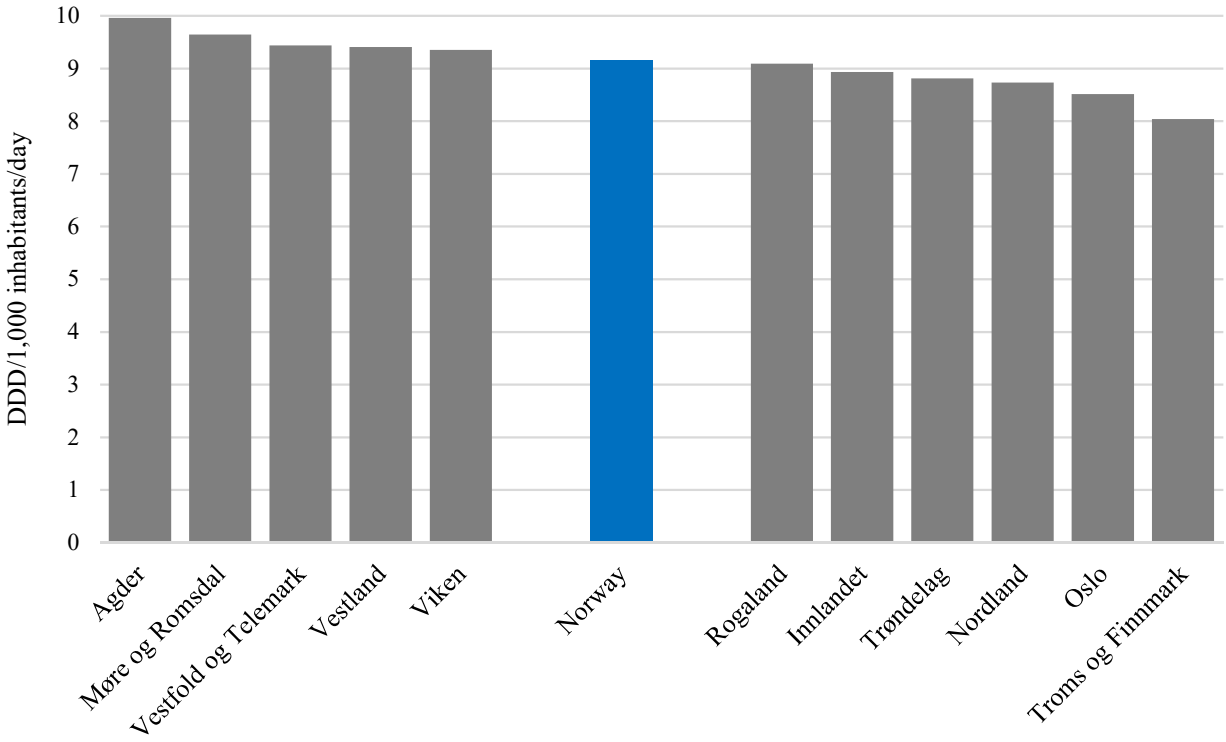

FIGURE 19. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2021. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

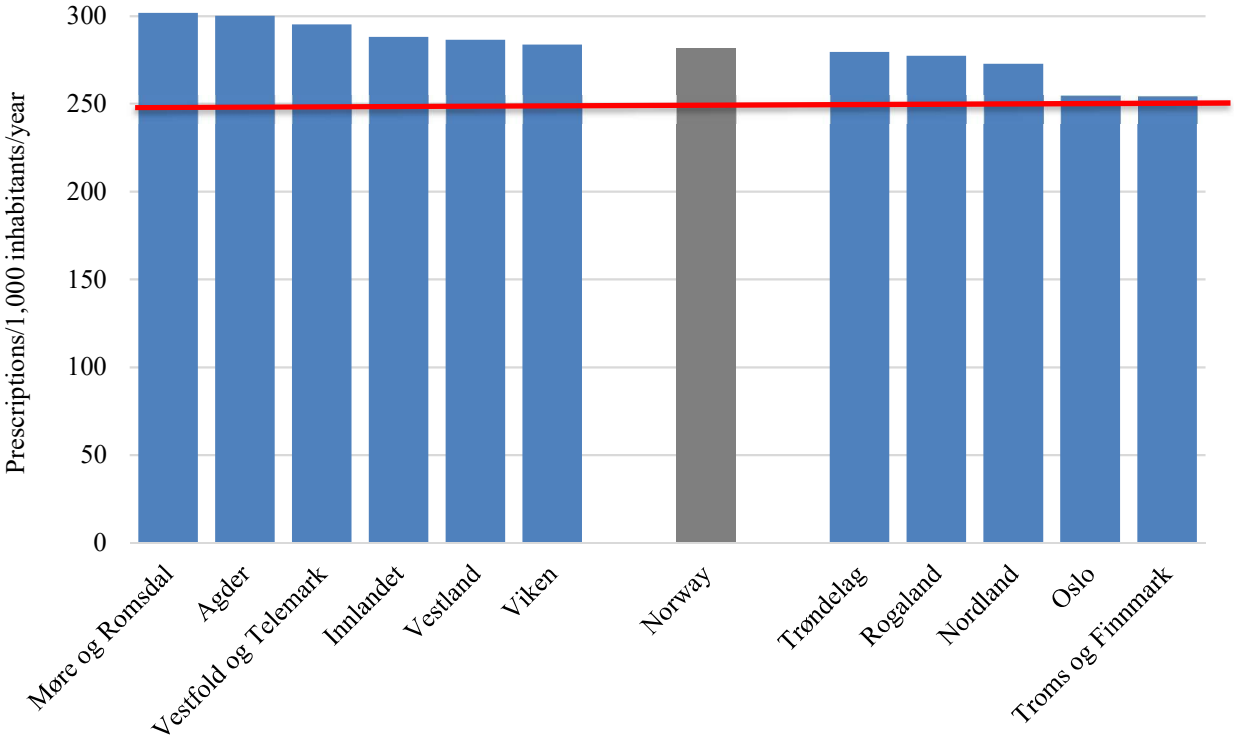

FIGURE 20. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2021. Measured as number of prescriptions/1,000 inhabitants. Data from NorPD (excl. health institutions). Red line: goal set by the National Strategy against Antibiotic Resistance 2015-2020.

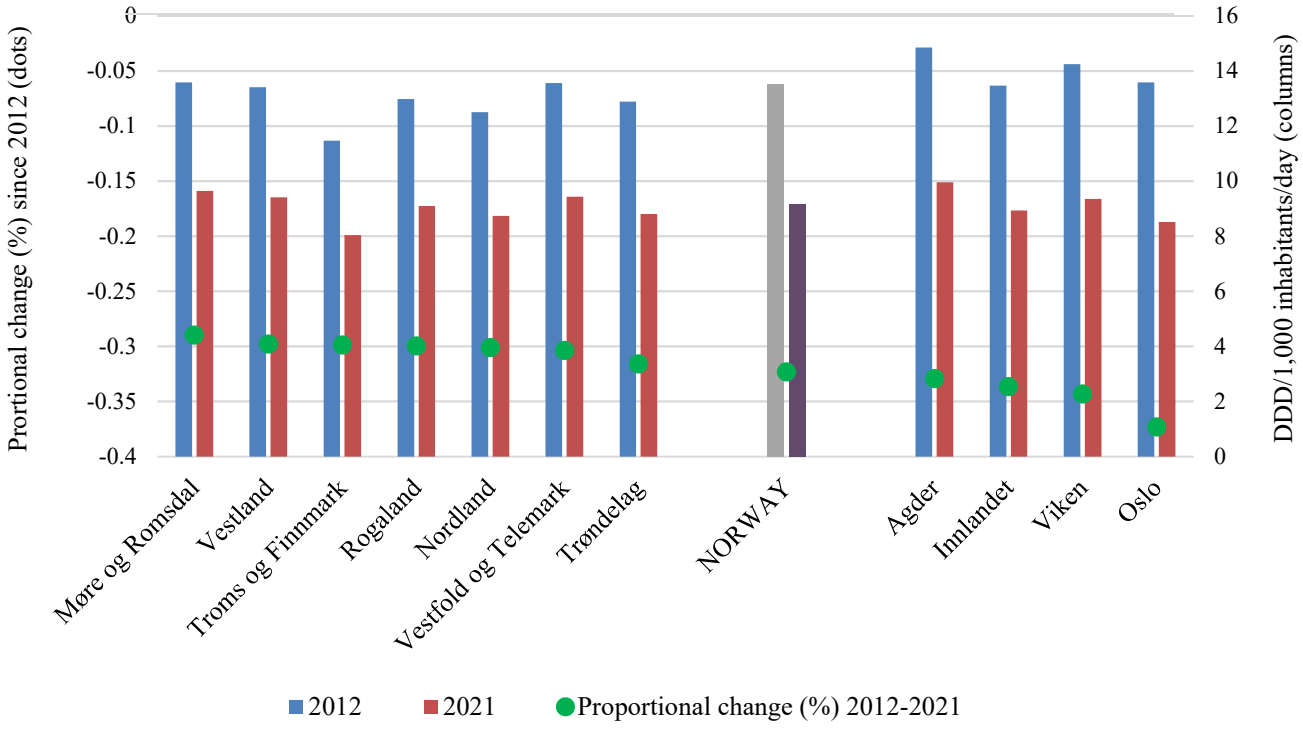

FIGURE 21. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2012 and 2021. Measured as number of DDD/1,000 inhabitants/day (columns) and proportional change (reduction in %, green dots). Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

FIGURE 22. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care by gender and age in Norway, 2021. 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.

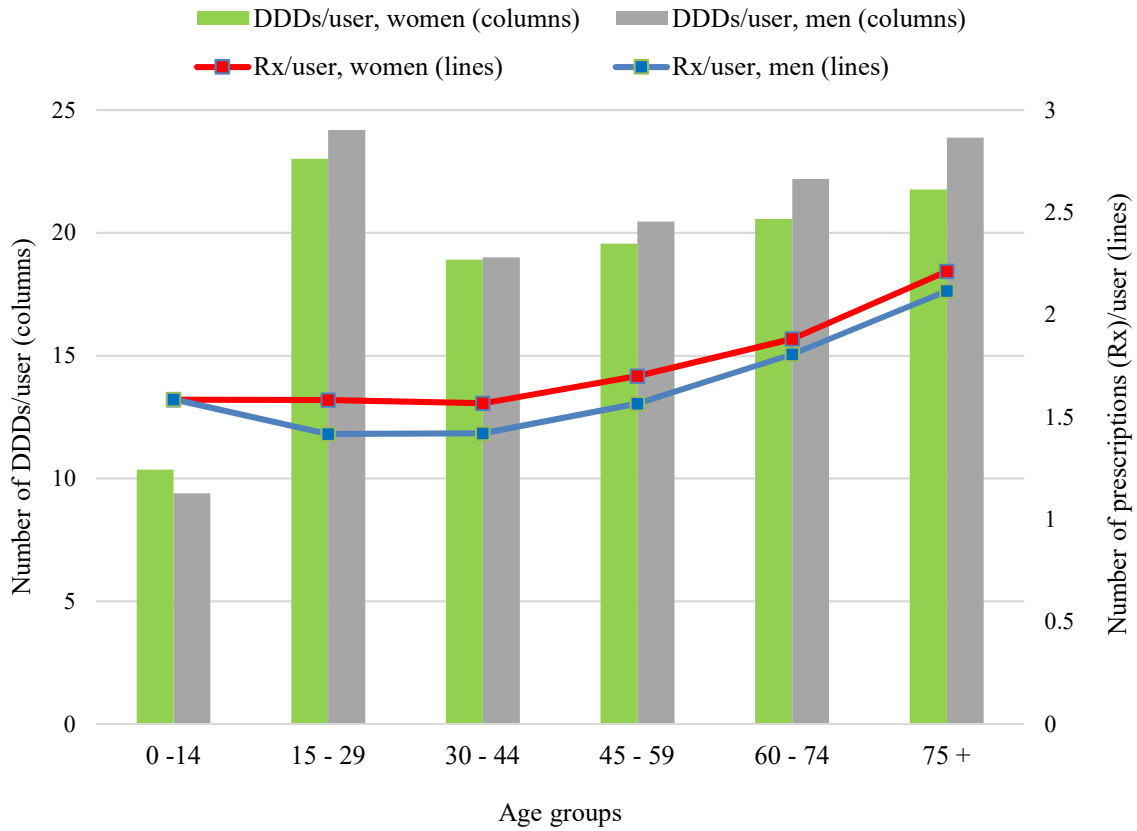

FIGURE 23. Mean number of prescriptions (Rx) per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway, 2021. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

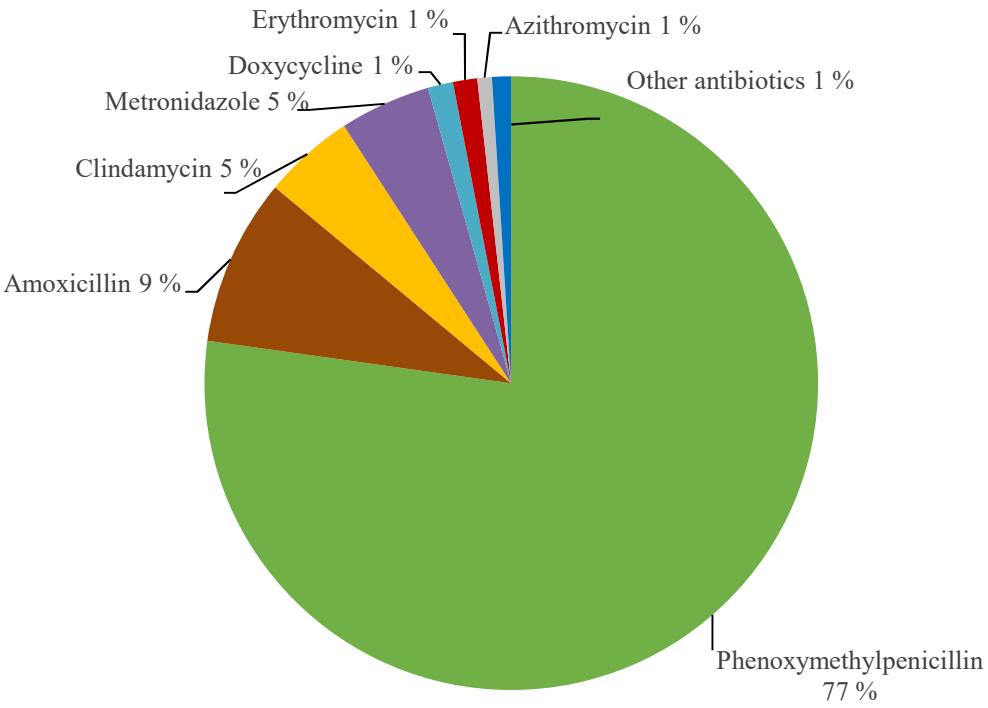

FIGURE 24. Relative amounts of antibacterial agents for systemic use prescribed by dentists in 2021 as measured in Defined Daily Doses (DDD).

Antibiotic consumption in hospital care

In 2021, the antibacterial sales (in DDDs) to hospitals represented around 8% of total sales of antibacterials for human use in the country. This is a decrease of 11% in DDD/1,000 inhibitants/day compared to 2019 and 1% since 2020 (Figure 25). This decrease is exceptional and 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 had been stable with regard to DDD/1,000 inhabitants/day but a change in pattern of use had occurred with increased use of narrow-spectrum antibiotics. The narrow-spectrum penicillins are highly utilised, and for this group the theoretical value of DDDs is lower than the therapeutic doses most commonly prescribed in Norway. Furthermore, combination regimens with a narrow-spectrum penicillin plus an aminoglycoside will account for more DDDs than if monotherapy with a cephalosporin or carbapenem is used. This implies that the total count of DDDs will show higher values for volume when combination therapy is used compared to broad-spectrum single agents.

The therapy pattern of antibacterials in hospitals does not change much from one year to another, however a decrease in use of selected broad-spectrum antibiotics has been observed since 2012. Broad-spectrum antibiotics (defined as J01_CR/DC/DD/DI/DF/DH/MA) accounted for 20% of total DDDs for hospitals in 2020 and 21% in 2021 compared to 26% in 2012. The share of beta-lactamase sensitive penicillins in 2021 was 15% of the total (Figure 25).

Penicillins (J01C) represent 46% of the use measured in DDDs in hospitals (J01CE 15%, J01CA 10% and J01CF 15%, J01CR 6%). The second largest group is the cephalosporins; 19% of all DDDs, the dominant subgroup being 3rd generation cephalosporins (J01DD). In 2021, six substances accounted for 52% of all DDDs used in hospitals. These were cloxacillin, benzylpenicillin, cefotaxime, cefazolin, gentamicin and doxycycline. Three single substances accounted for 34% of all antibacterial DDDs in hospitals; benzylpenicillin (13%), cloxacillin (13%) and cefotaxime (8%).

Figure 28 shows annual trends in national antibiotic use in hospitals by hospital activity data instead of population statistics. The two measurements (bed days and admissions) together show the interplay between shorter hospital stays and intensity of antibiotic treatment. The 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 correct for activity, because that makes comparisons between hospitals possible. The reduced number of bed days in Norway the latest years (apart from the effects of the Covid-19 pandemic) does probably not reflect reduced hospital activity in the country as a whole, but a shift from in-patient treatment to day-care and out-

patient treatment. Figur 29 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 30. The use of piperacillin/tazobactam has been increasing for many years but was markedly reduced in 2017 and 2018 due to a nationwide shortage. In 2019, there was no shortage, and in 2020 and 2021 an increase was observed. In 2021, there was increased use of penicillins with beta-lactamase inhibitors, 1st and 3rd generation cephalosporins and carbapenems compared to the use in 2020. Moreover, a small decrease in the use of aminoglycosides and beta-lactamase sensitive penicillins was observed in 2021. The reduced use of amino-glycosides and beta-lactamase sensitive penicillins in 2020 and 2021 may partly be explained by the type of patients admitted during the Covid-19 pandemic. The use of aminoglycosides has increased by 39% from 2016 to 2019, probably due to implementation of antibiotic stewardship programmes 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. 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 31 shows the distribution between "Preferred antibiotics" (which largely reflects standard treatment regimens in national guidelines) and resistance driving antibiotics for the different Norwegian hospitals. Proportions of preferred antibiotics vary between 78% and 53%.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between hospitals. Figure 32 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 population mix alone, but are probably related to different prescribing practices.

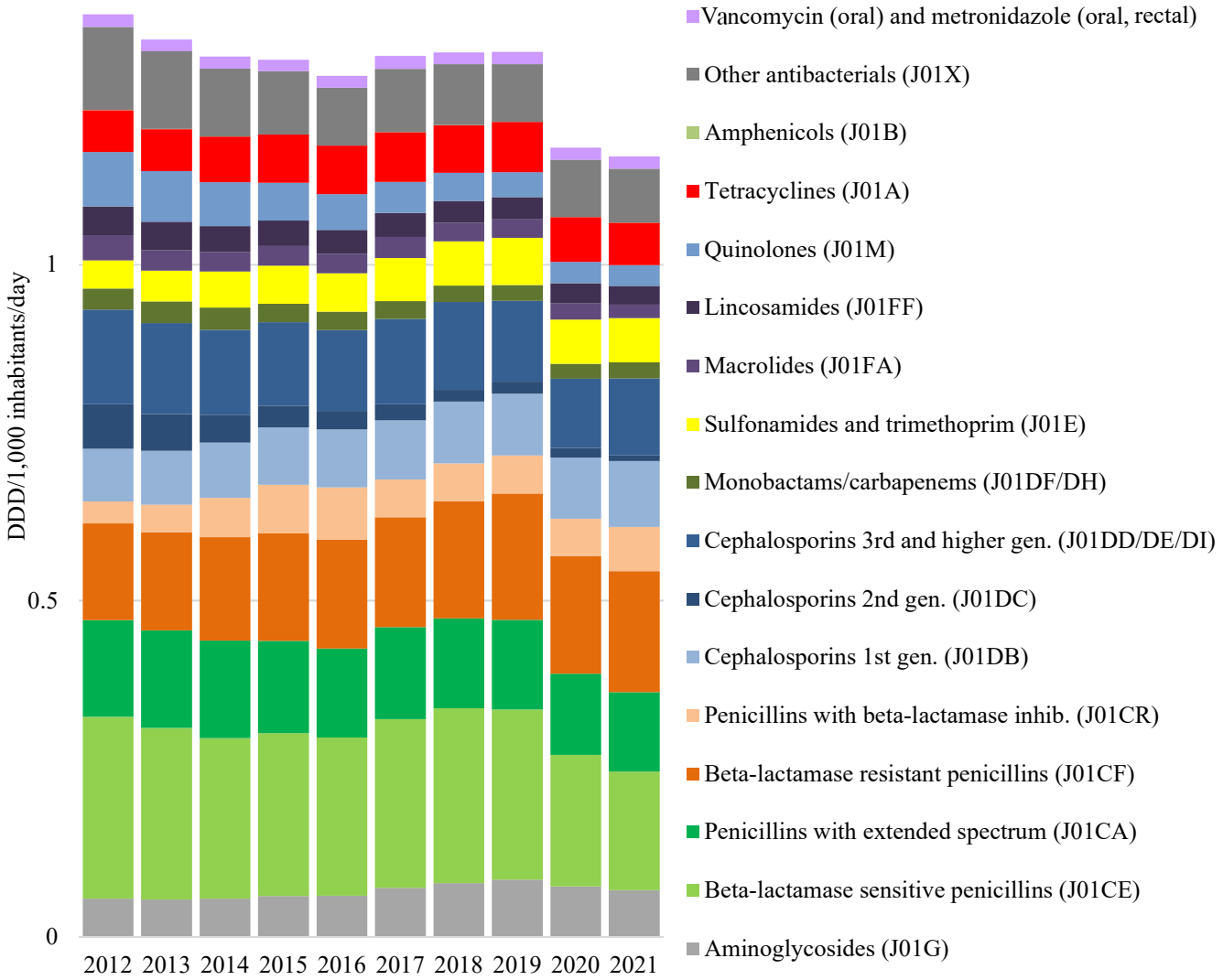

FIGURE 25. Proportions of antibacterial agents for systemic use (J01), vancomycin (A07AA09), and metronidazole (P01AB01) in Norwegian hospitals 2012-2021, measured in DDD/1,000 inhabitants/day.

Procalcitonin as a decision aid in antibiotic stewardship in Norwegian hospitals

Procalcitonin (PCT) is a calcitonin prohormone that increases as quickly as two hours after exposure to a bacterial stimulus and may reach levels as high as 1,000 mg/mL e.g. in sepsis and septic shock. Compared to the more unspecific and slower reacting inflammatory marker C-reactive protein (CRP), serum levels of PCT usually do not increase in non-bacterial infections.

The interest in this inflammatory marker is high. A recent PubMed search of "procalcitonin" over the last 20 years showed a significant increase, especially from 2016 and onwards (Figure 26). Initially, the PCT assay was evaluated mainly as a clinical diagnostic supplement to CRP in hospital patients. However, based on several well-conducted studies, PCT has increasingly been recommended as a decision aid in antibiotic stewardship programmes (ASPs) to terminate antibiotic use, particularly for patients with sepsis, lower respiratory tract infections and COPD exacerbations (1). Concise international consensus guidelines and algorithms for use have also been published (2). Still, the utility of PCT as an antibiotic-saving measure has been controversial since several quality studies have reported diverging results.

We conducted a national Web-based survey in August 2019 to investigate if and how PCT was used in Norwegian hospitals, emphasising its utilisation in ASPs. All nine university-affiliated and 19 non-university hospitals responded. One university hospital had never used the PCT assay, referring to a perceived lack of scientific documentation. Only twelve of the remaining 27 hospitals analysed PCT in their own laboratory. 77% of 22 respondents had used PCT for three years or more (7 university and 10 non-university hospitals). The annual number of assays per hospital ranged from 6 to 19 706 (median 1 046) and was equally distributed between university/non-university hospitals when related to total bed capacity.

In 60% of hospitals, the PCT marker had not been actively promoted as an aid to shorten antibiotics courses and only 20% had established PCT as part of an active ASP (Figure 27). Three of 19 hospitals restricted the use of PCT to certain medical departments and ICUs. Only 6 of 24 respondents had evaluated their hospital use of procalcitonin, and half of these only through informal questioning of clinicians regarding their opinion. The specific indications for PCT use were surveyed and respondents were asked to grade the use intensity (1-5) where an average was a low or low-moderate use (Table 9). The variability between hospitals could not be explained by the hospital affiliation, the number of beds or the years of experience with the assay.

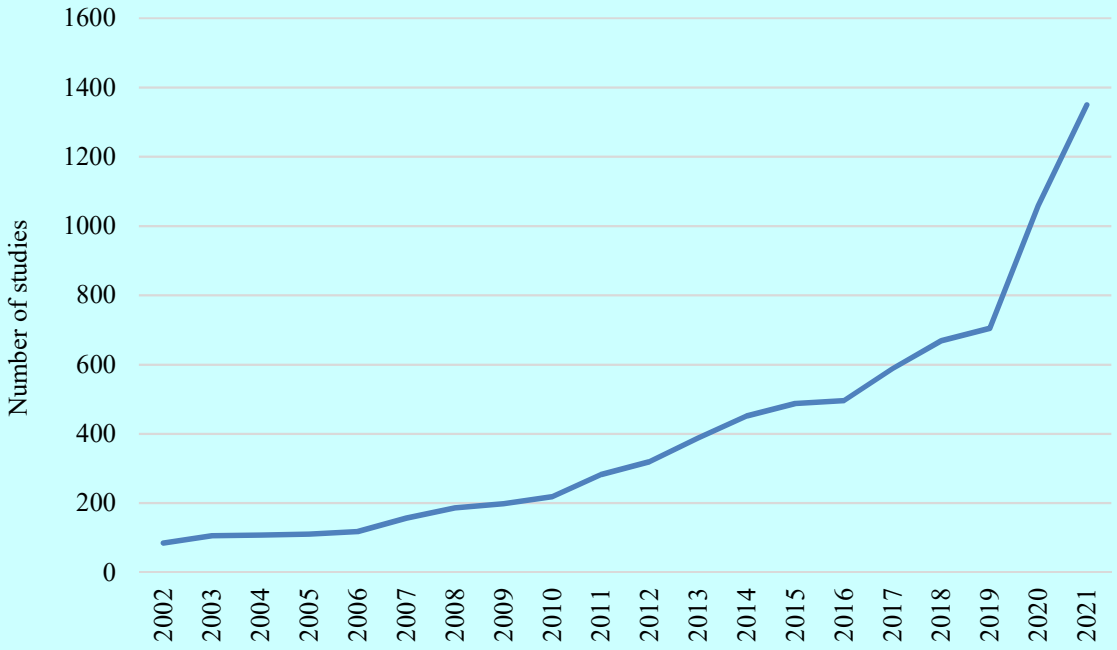

FIGURE 26. Increase over 20 years in number of human scientific studies, meta-analyses and reviews in English, using procalcitonin as search word in title of abstracts (PubMed, total: 8089).

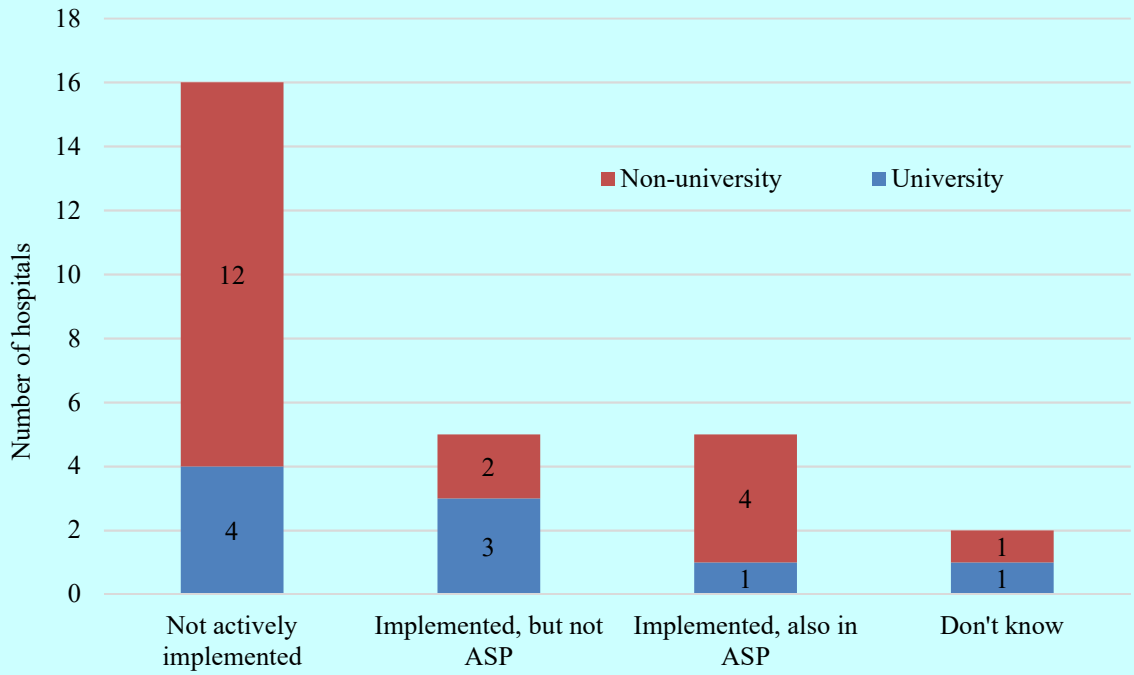

FIGURE 27. Implementation in Norwegian hospitals of the procalcitonin assay as a decision aid for antibiotic treatment duration, and if yes, whether also implemented in the antibiotic stewardship programme (ASP).

TABLE 9. 25 responders´ judgement of indications for procalcitonin use in their hospital, from score of 1=low degree or no use, to 5=very high use. DD=differential diagnosis, AB=antibiotics, ICU=intensive care unit, SD=standard deviation.

Use of procalcitonin (score 1-5)	Average	Median	Min	Max	SD
DD infection vs rheuma/autoimmune diseases	2.58	3	1	5	1.26
Terminate AB – sepsis/serious ICU infection	2.04	2	1	4	0.84
Terminate AB – lower RTI	1.83	2	1	3	0.75
DD bacterial versus viral infection (general)	1.83	2	1	4	0.94
Terminate AB for other indications	1,82	2	1	5	0.98
Initiate AB if infection suspected	1.71	1	1	4	0.93

We conclude that the use of PCT as an ASP decision aid is sparse in Norwegian hospitals, whether university or non-university affiliated. There is seemingly no widespread use of established algorithms meant for antibiotic restriction, and PCT seems to be used by most hospitals mainly for diagnostic purposes. In the multitude of publications from recent years, little focus has been on "real-world settings". One time-series analysis from a large Swiss tertiary centre found no increase in antibiotic use, mortality, or length of stay when a very high PCT use was drastically restricted (a 75% decrease) for cost reasons (3). However, the authors did not rule out PCT as useless but instead pointed out that although written procedures for use existed, the PCT results were never reviewed or handled by those responsible for the ASP. They introduced the term "diagnostic stewardship" which implies that PCT should be used more structured and in the context of ASPs to have an effect. A recent qualitative study from our hospital on physicians' experience with PCT supports this; two main findings were that clinicians were unsure when and how to use PCT and interpret the results (4). We propose that authoritative bodies must make efforts to establish sound guidelines for PCT use in Norway that promote a much tighter integration with ASPs.

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1. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:CD003543.
2. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med. 2019;57(9):1308-18.
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4. Christensen I, Haug JB, Berild D, Bjornholt JV, Jelsness-Jorgensen LP. Hospital physicians' experiences with procalcitonin - implications for antimicrobial stewardship; a qualitative study. BMC Infect Dis. 2020;20(1):515.

Jon Birger Haug and Ingrid Christensen, Department of Infection Control, Østfold Hospital Trust, Kalnes, Norway.

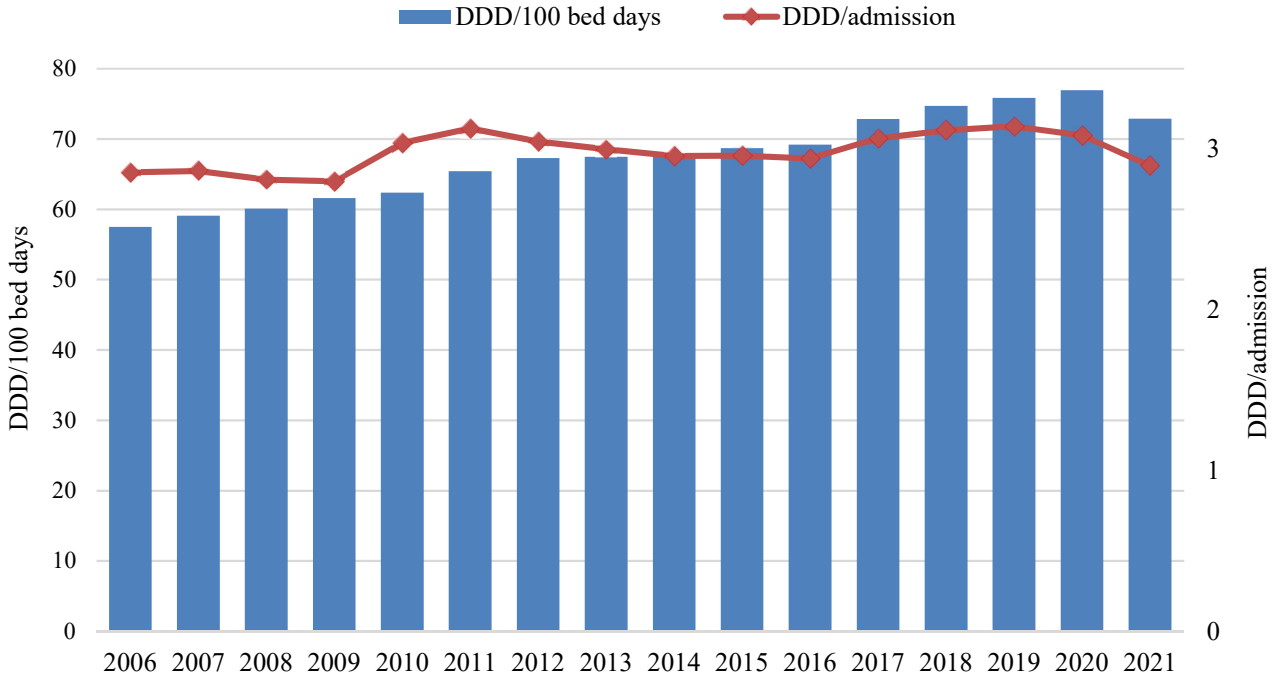

FIGURE 28. Total use of antibiotics in Norwegian hospital (somatic) 2006-2021, measured in DDD/100 bed days (blue bars) and DDD/admission (red line). Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

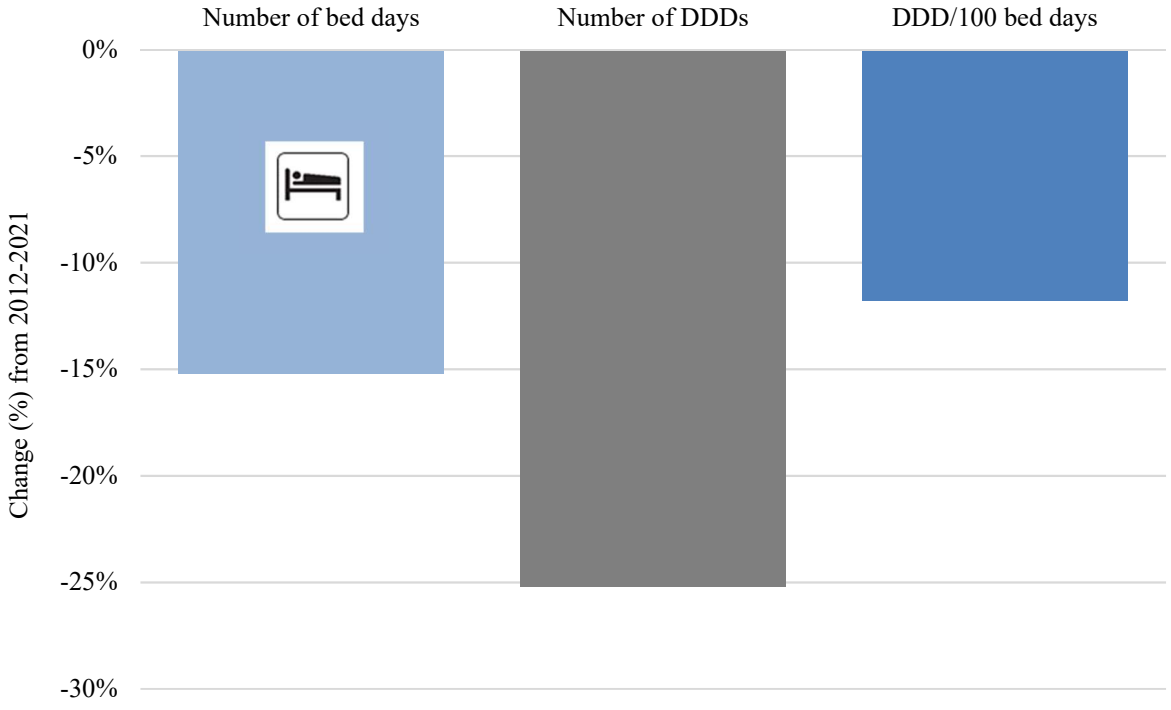

FIGURE 29. Proportional change will vary according to the measures used. Antibiotic usage in hospitals is often presented as DDD/100 bed days, but total number of DDDs may also be used as a measure. The number of bed days has been reduced by 15% since 2012. The figure visualises the impact of the reduction 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 2012-2021, measured as % change either as change of total DDDs (25% reduction - grey bar) or change of DDD/100 bed days (12% reduction - blue bar).

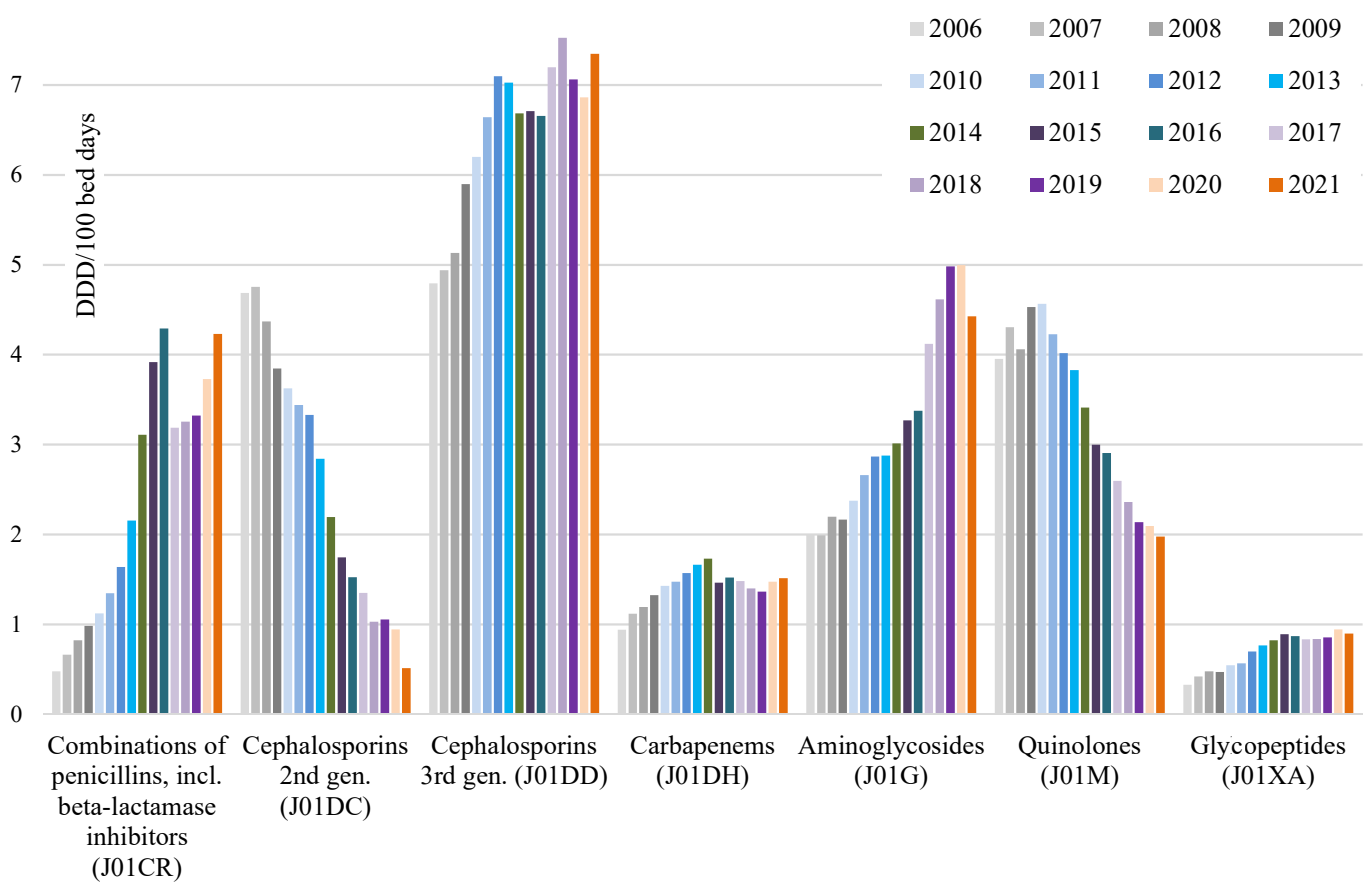

FIGURE 30. Consumption of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2021, measured in DDD/100 bed days.

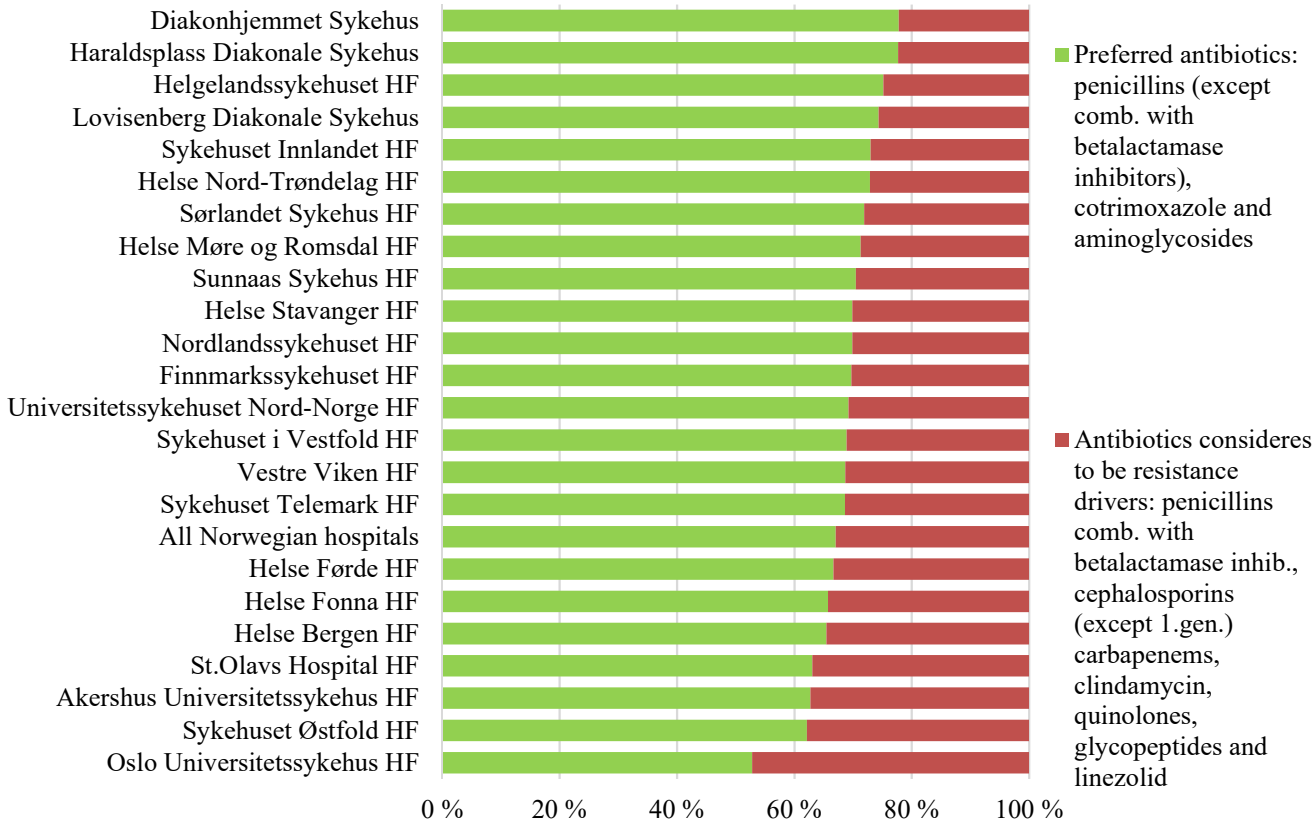

FIGURE 31. Proportions (% of DDDs) of preferred antibiotics (green part of the column) and antibiotics that are considered to be drivers of antibiotic resistance (red part i.e. belonging to ATC groups J01CR, J01DC, J01DD, J01DE, J01DI, J01DH, J01M, J01XA and J01XX08) in Norway, presented per hospital/health trust in 2021. 1st gen. 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 specifically targeting anaerobic bacteria.

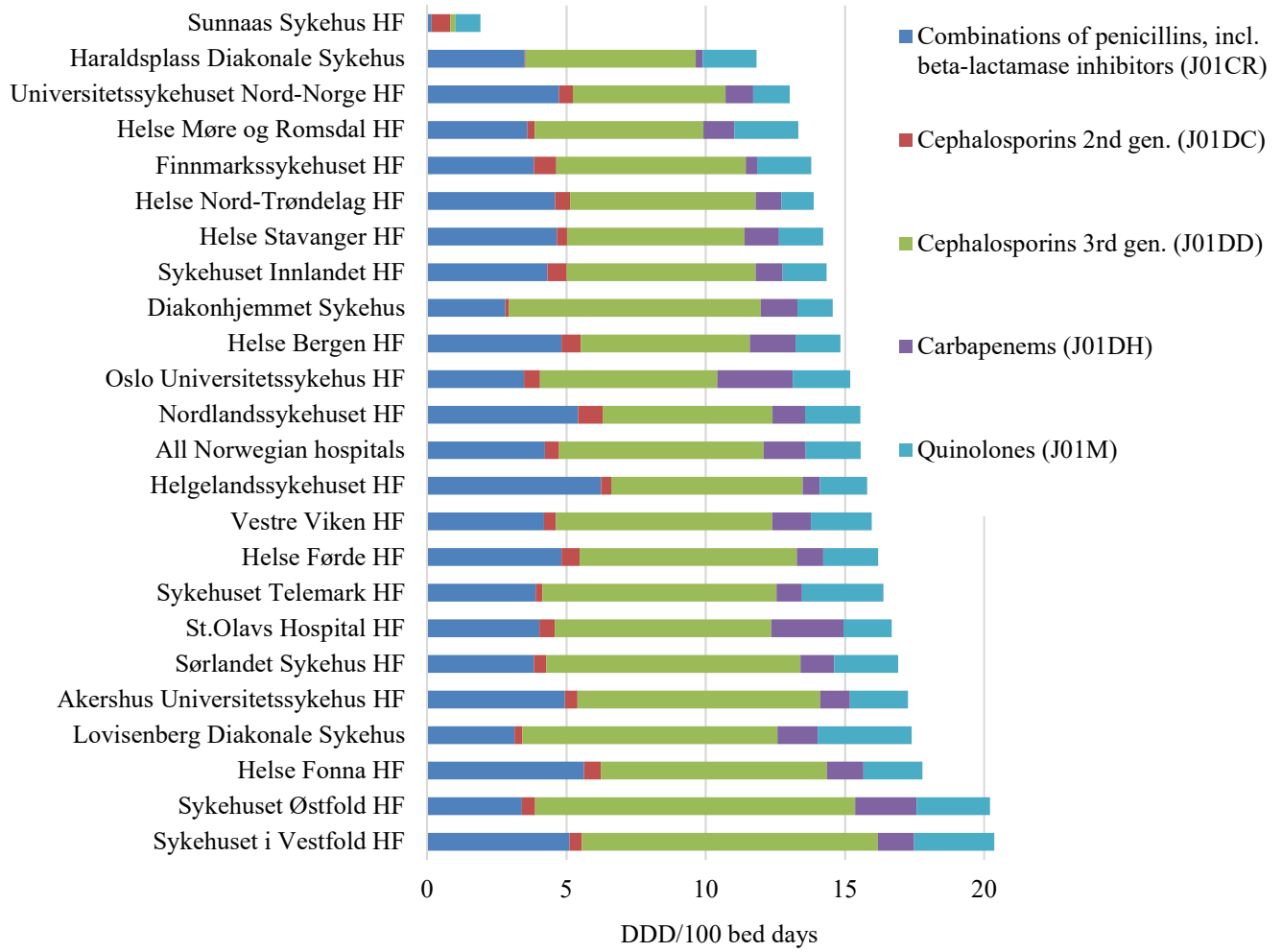

FIGURE 32. Consumption of selected antibacterial agents for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2021, measured in DDD/100 bed days. All hospitals, except one (Sunnaas Sykehus) are acute care hospitals.

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

In 2015, a National Strategy against Antibiotic Resistance was agreed upon, aiming to reduce the total volume of antibiotics by 30%, as compared to 2012, by the end of 2020. Due to the Covid-19 pandemic the strategy period has been extended. The Strategy was followed by a National Action Plan, issued January 2016, with suggested measures to reach the targets. The overall goal for total human consumption was reduction of DDDs by 30%. In addition, two sector specific goals in ambulatory care were introduced; reduction of 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 33 shows total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to National targets. DDD/1,000 inhabitants/day for J01 is reduced by 26% since 2012. When excluding methenamine the reduction in use is 33% (Table 6). There are significant county differences; some counties use more *Guidelines recommended antibiotics* (i.e. narrow-spectrum antibiotics), indicating a higher adherence rate to the national guidelines (Figure 34). There were smaller county differences in proportional use of *Guidelines recommended antibiotics* in 2021 compared to 2012. This may indicate that awareness of AMR as well as adherence to guidelines has increased in all counties in the period. Precriptions (Rx) per 1,000 inhabitants per year (J01, excl. methenamine) is reduced by 37% since 2012 from 444 Rx/1,000 inhabitants/year to 281 in 2021.

Between 2012 and 2019, there has been a reduced prevalence of use in all age groups, with the largest reduction in small children (0-9 years) and the lowest reduction for young adults (20-29 years) and elderly above 70 years. Moreover, the use in men is reduced more than in women. There was a dramatic reduction during the pandemic in 2020, which was mainly due to lower prescribing of antibiotics for respiratory tract infections (Figure 35). The largest reduction in prescriptions per 1,000 during the first year of the pandemic was observed in children 0-9 years old, but in the fall 2021 there was an increase, mainly in the smallest children. This could be due to over-prescribing or secondary infections connected to a respiratory syncytial virus (RS-virus) epidemic in fall 2021. Still compared to 2019 there were 30% less prescriptions per 1,000 children in 2021 compared to 2019.

For hospitals, the main target is 30% reduction in combined use of five selected groups of antibiotics. To reach this goal, the National Action Plan also made antibiotic stewardship programmes mandatory in Norwegian hospitals. Figure 36 shows the annual variation of total hospital use of these groups in the years 2006-2021 according to the national target. Figure 37 shows how the use of these five groups has changed in the different Norwegian hospitals/health trusts in relation to the national target of 30% reduction marked by a black dotted line in the figure. For all hospitals in Norway together there was 12% reduction in use of the five selected groups of broad-spectrum antibiotics from 2012 to 2021 when adjusted for activity (bed days). The number of bed days is going down every year and there is a large increase in outpatient consultation. Using only bed days as an indicator of clinical activity confounds the drug use data, and it is likely that the use of other activity indicators would produce different results. Unadjusted sales data measured in DDDs shows a reduction of 25% for the same period (see also Figure 29).

Norway has two national advisory units for antibiotic use, 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 (KAS). These advisory units have been strenghtened and appointed key roles in the National Action plan. 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.

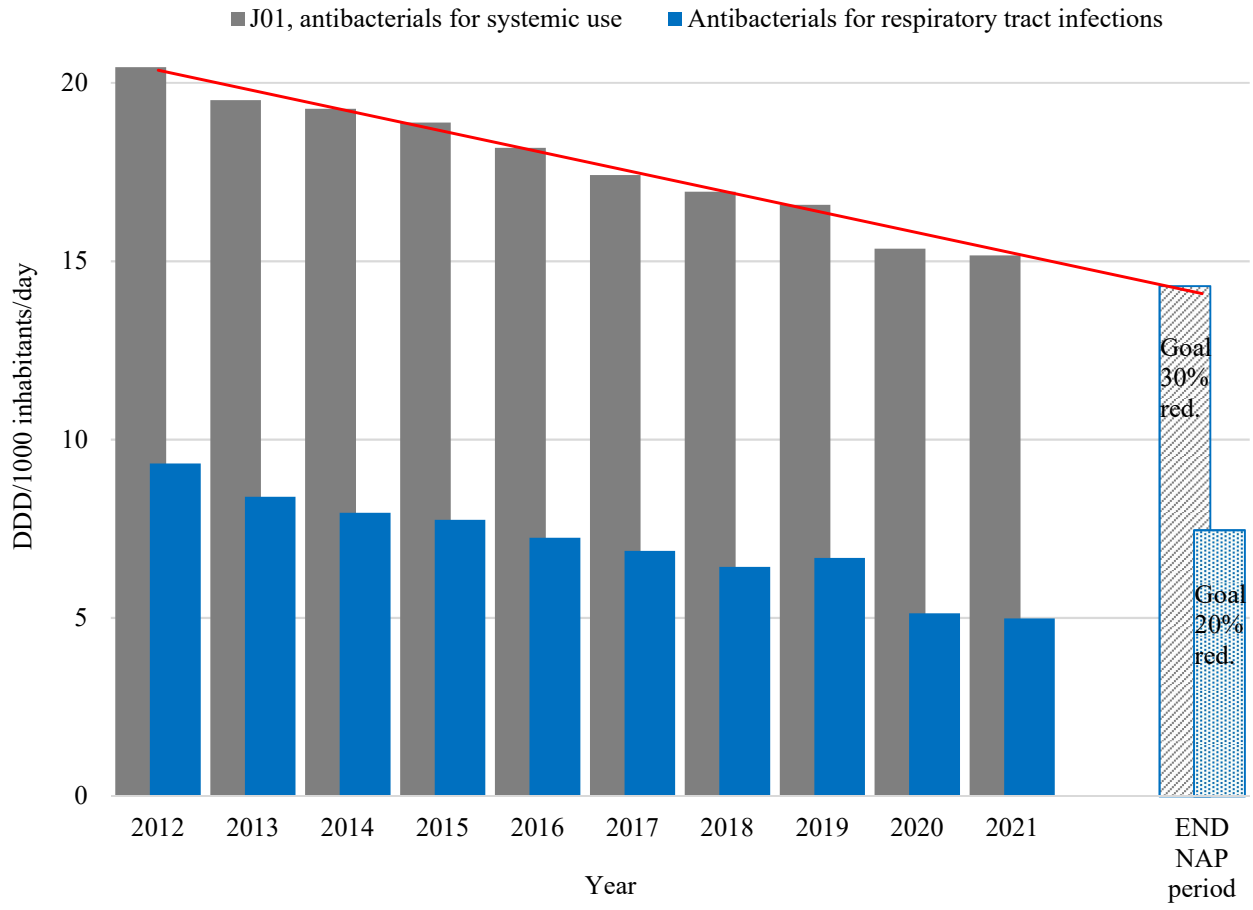

FIGURE 33. Total human sales of antibacterial agents for systemic use (ATC group J01) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2021 measured in DDD/1,000 inhabitants/day. According to the National Action Plan (NAP), the target for 2020 was 30% reduction of total use since 2012, measured in DDDs. Bars show measured use 2012-2021 (grey; J01, blue; antibiotics for respiratory tract infections), red line and hatched bars; targets set in the National Strategy against Antibiotic Resistance 2015-2021.

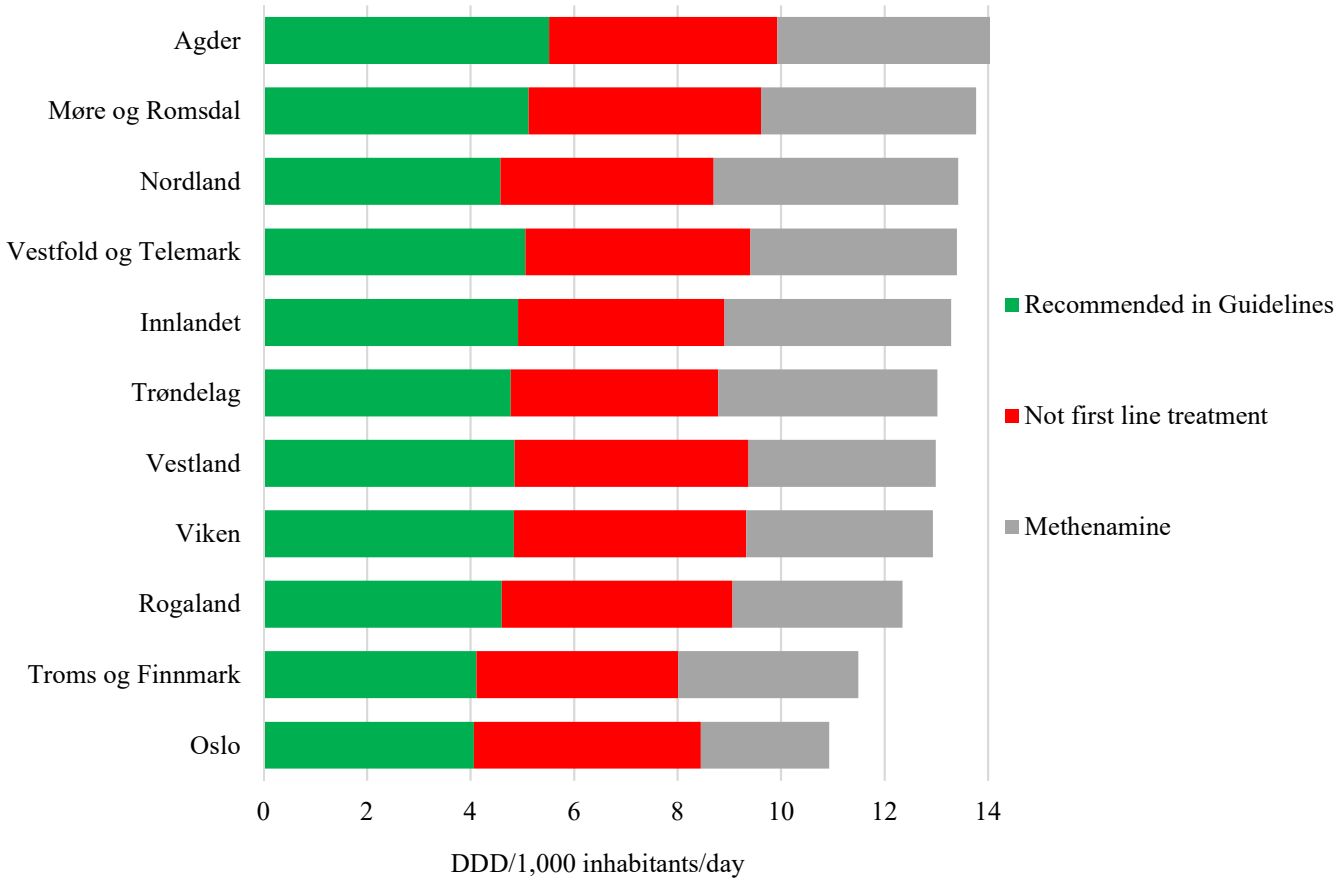

FIGURE 34. Consumption of antibacterial agents for systemic use (ATC group J01) in outpatients in the different counties of Norway in 2021. Aggregated in three groups; a) recommended as first line treatment in the guidelines for primary care (phenoxymethylpenicillin for respiratory tract infections, 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. healthcare institutions and sales to prescribers´ own practice not included).

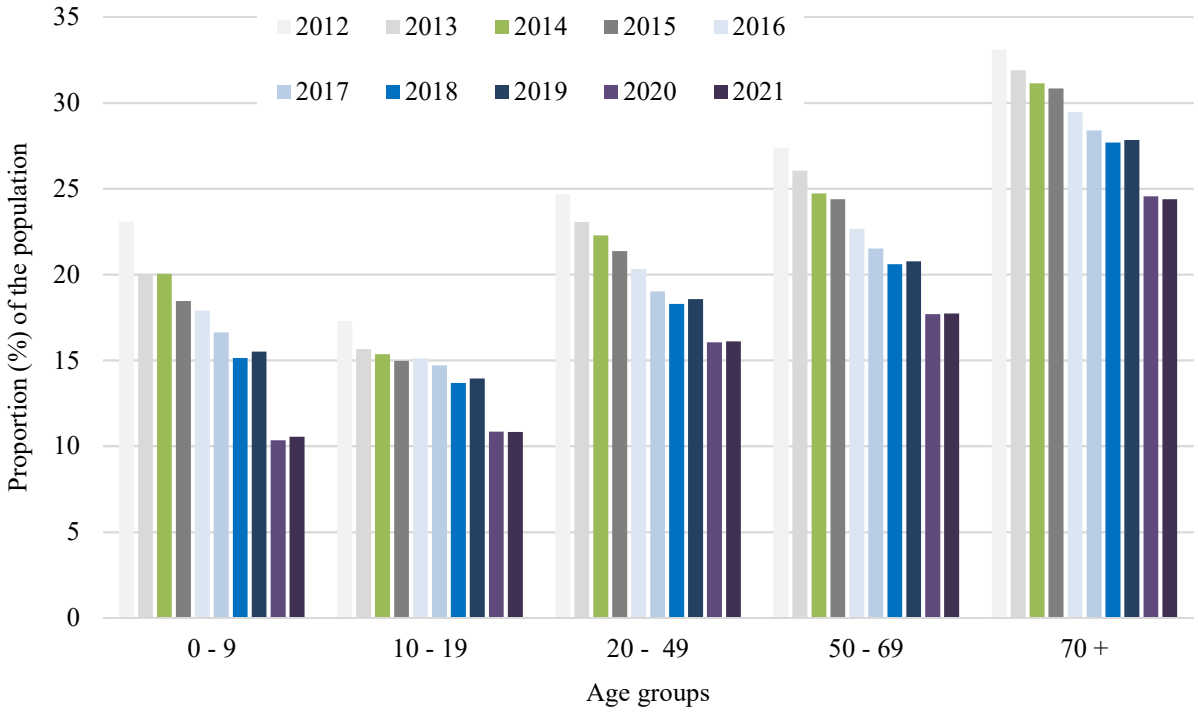

FIGURE 35. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care in Norway, 2012-2021. Antibiotics included are antibacterials for systemic use (ATC group J01, excl. methenamine).

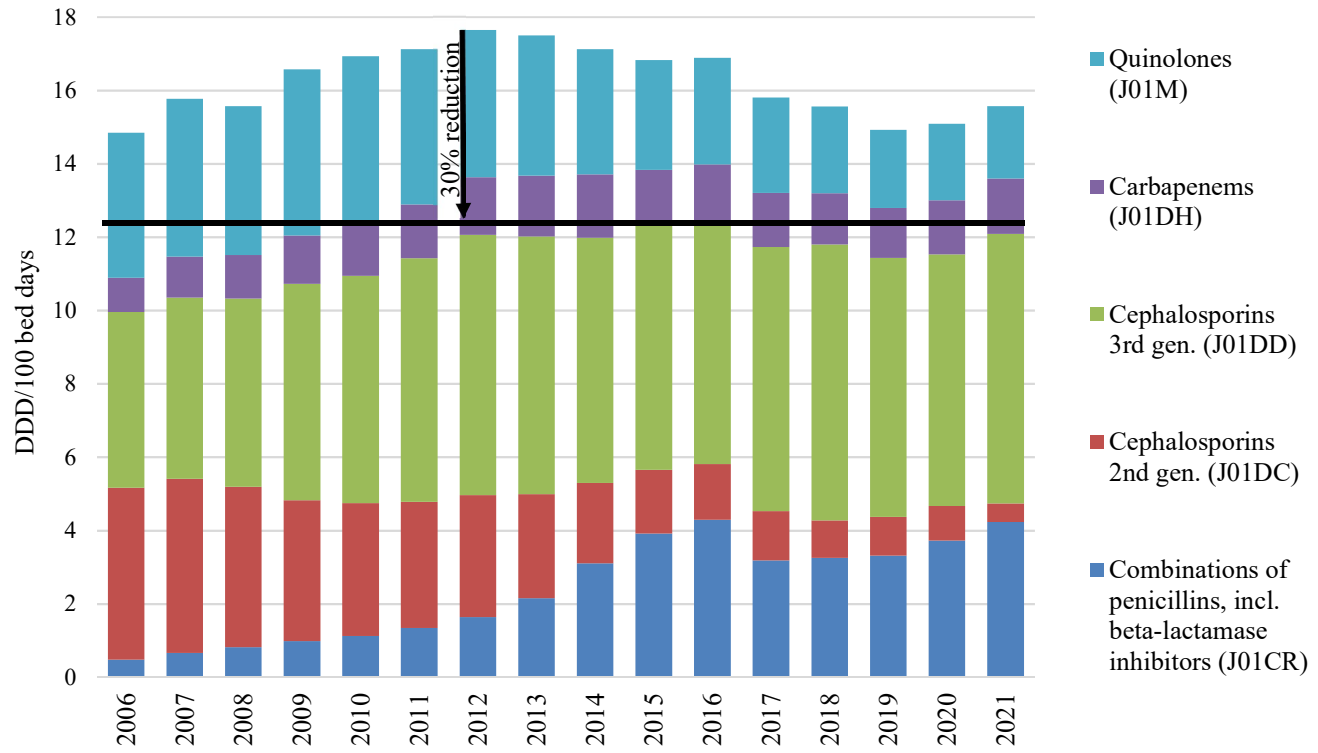

FIGURE 36. Consumption of selected antibacterial agents for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2021, measured in DDD/100 bed days.

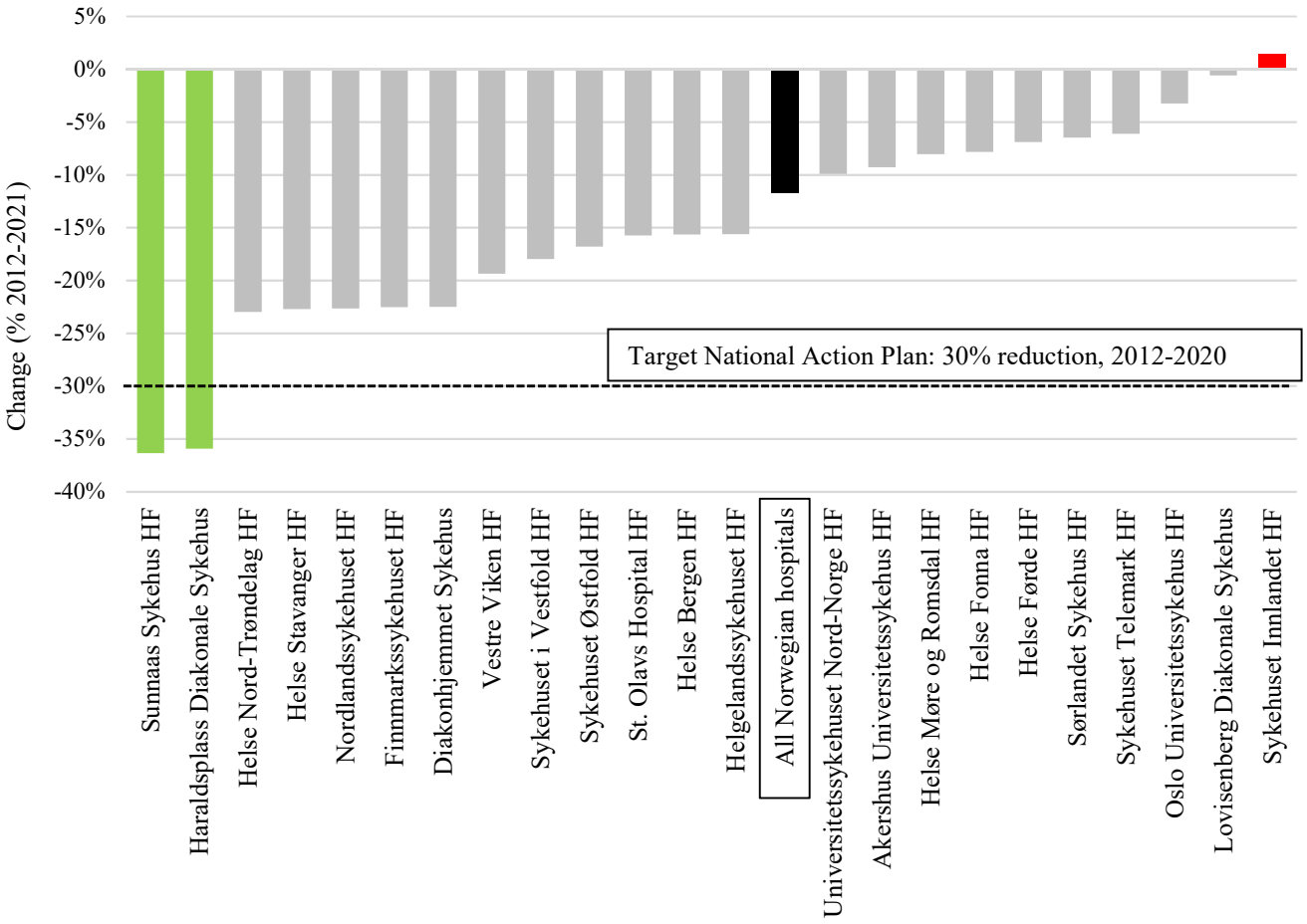

FIGURE 37. Change in consumption of selected antibacterials for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, 2012-2021. The data are presented per hospital/health trust as measured in DDD/100 bed days.

OCCURRENCE OF ANTIMICROBIAL RESISTANCE

ANIMAL CLINICAL ISOLATES

Madelaine Norström, Erik Paulshus, Jannice Schau Slettemeås, Marit Smistad, Marianne Sunde, Liv Synnøve Sølverød and Anne Margrete Urdahl

The clinical isolates included in NORM-VET 2021 were *Escherichia coli*, *Streptococcus dysgalactiae* and *Streptococcus uberis* from clinical mastitis in cattle. Sampling, laboratory methods and data processing are described in Appendix 3. One isolate per submission was susceptibility tested.

Escherichia coli from cattle

A total of 168 isolates of *Escherichia coli* from clinical mastitis in cattle were susceptibility tested. The isolates were collected in 2020. The results are presented in Table 10, Figures 38-40, and in the text.

TABLE 10. Antimicrobial resistance in clinical isolates of *Escherichia coli* from clinical mastitis in cattle (n=168) collected in 2020.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	4.8	[2.1 – 9.2]								89.9	5.4		0.6		4.2			
Tigecycline	0.0	[0.0 – 2.2]					97.0	3.0										
Chloramphenicol	2.4	[0.7 – 6.0]										92.9	4.8		0.6	1.8		
Ampicillin	14.3	[9.4 –20.5]							2.4	31.0	45.2	7.1		1.2	13.1			
Cefotaxime	1.2	[0.1 – 4.2]					98.8	0.6			0.6							
Ceftazidime	0.6	[0.0 – 3.3]					96.4	3.0				0.6						
Meropenem	0.0	[0.0 – 2.2]		97.6	2.4													
Trimethoprim	10.1	[6.0 – 15.7]					45.8	33.9	10.1					10.1				
Sulfamethoxazole	12.5	[7.9 – 18.5]										78.0	8.9	0.6				12.5
Azithromycin	0.0	[0.0 – 2.2]								4.8	30.4	61.3	3.6					
Gentamicin	0.0	[0.0 – 2.2]						88.1	10.1	1.8								
Amikacin	0.0	[0.0 – 2.2]									98.8	1.2						
Ciprofloxacin	1.2	[0.1 – 4.2]	87.5	11.3			0.6	0.6										
Nalidixic acid	0.6	[0.0 – 3.3]									97.6	1.8				0.6		
Colistin	0.0	[0.0 – 2.2]							100									

*Bold vertical lines denote epidemiological cut-off values for resistance. CI=confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC-values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. Clinical breakpoints are marked in blue dotted lines. In cases where clinical breakpoints are identical to ECOFFs, only ECOFFs are shown (i.e for ampicillin, tigecycline, gentamicin, amikacin and colistin, as well as for the CLSI clinical breakpoint for tetracycline). Clinical breakpoints are not defined by EUCAST for tetracycline, sulfamethoxazole, azithromycin and nalidixic acid, but clinical breakpoints are defined by CLSI for tetracycline, sulfonamides, nalidixic acid.

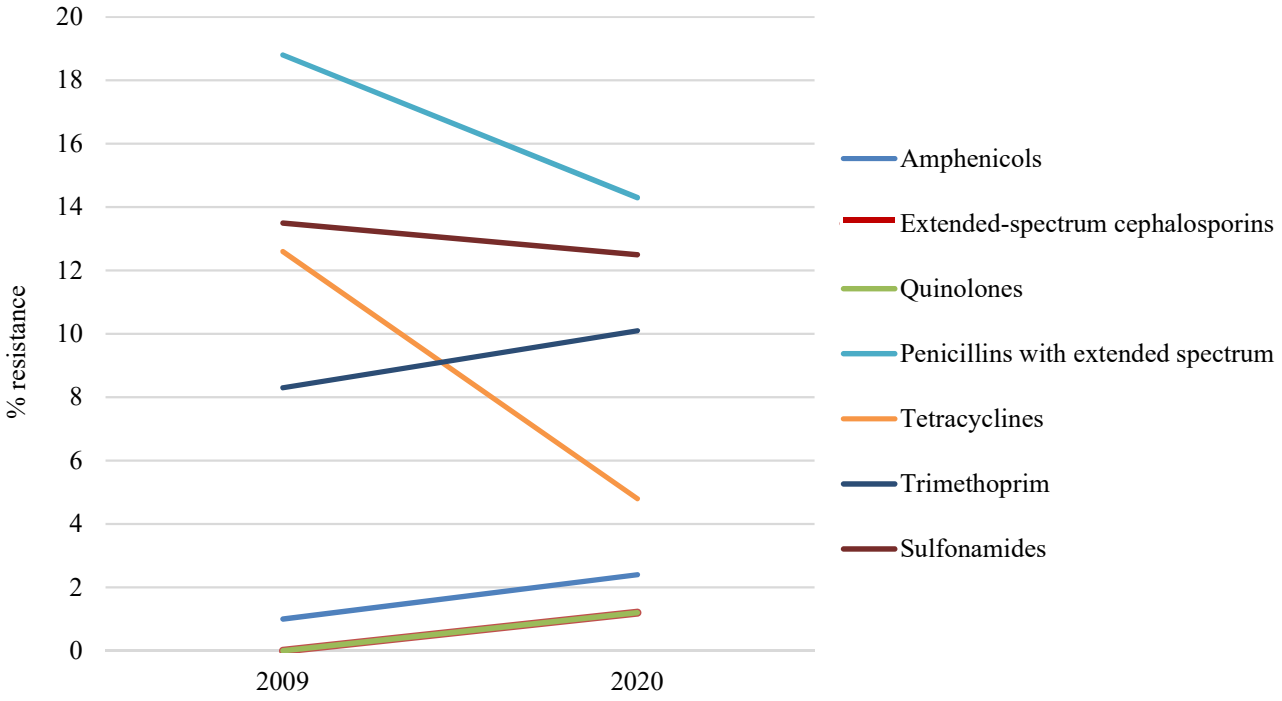

FIGURE 38. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from clinical samples (mastitis) from cattle sampled in 2009 and 2020, respectively. The ECOFFs used in NORM-VET 2021 were applied.

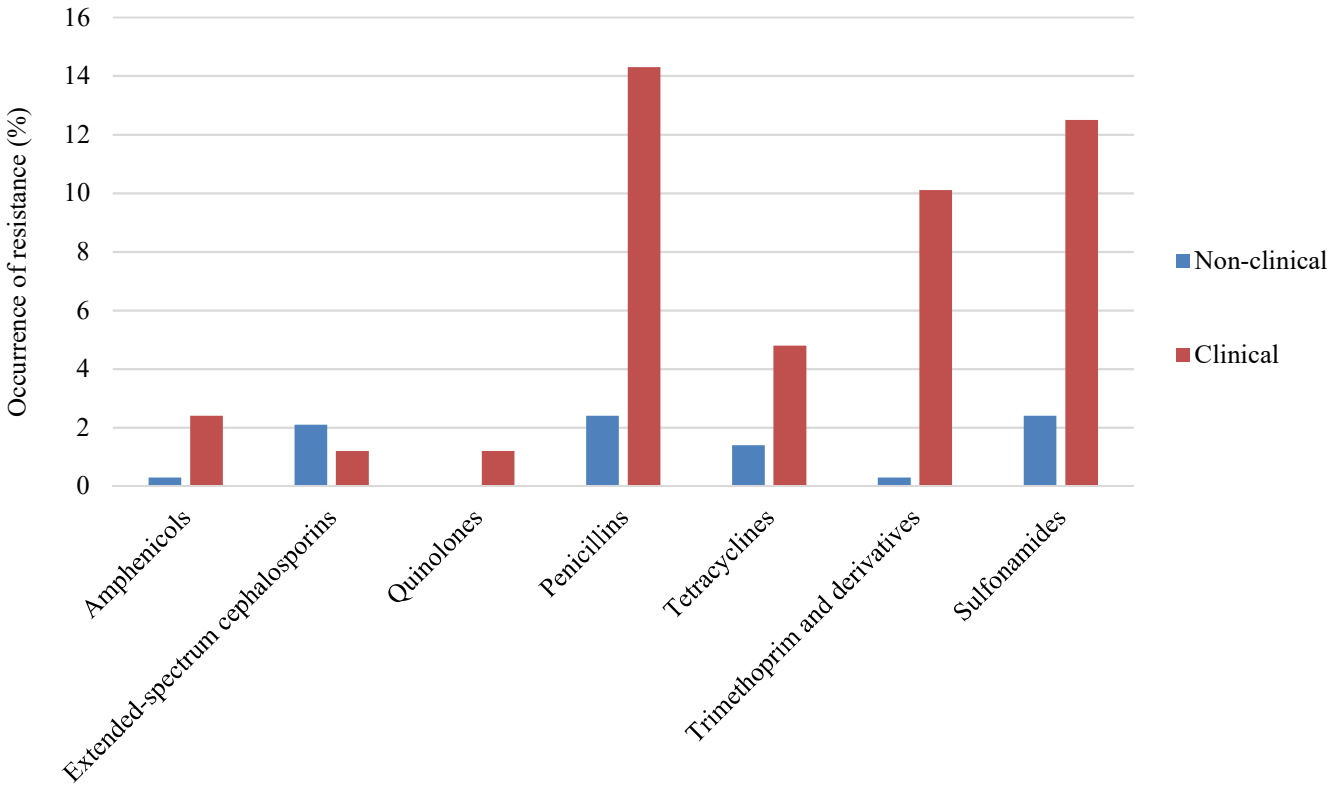

FIGURE 39. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from clinical mastitis and indicator *E. coli* from cattle sampled in 2020 and 2021, respectively. The ECOFFs used in NORM-VET 2021 were applied.

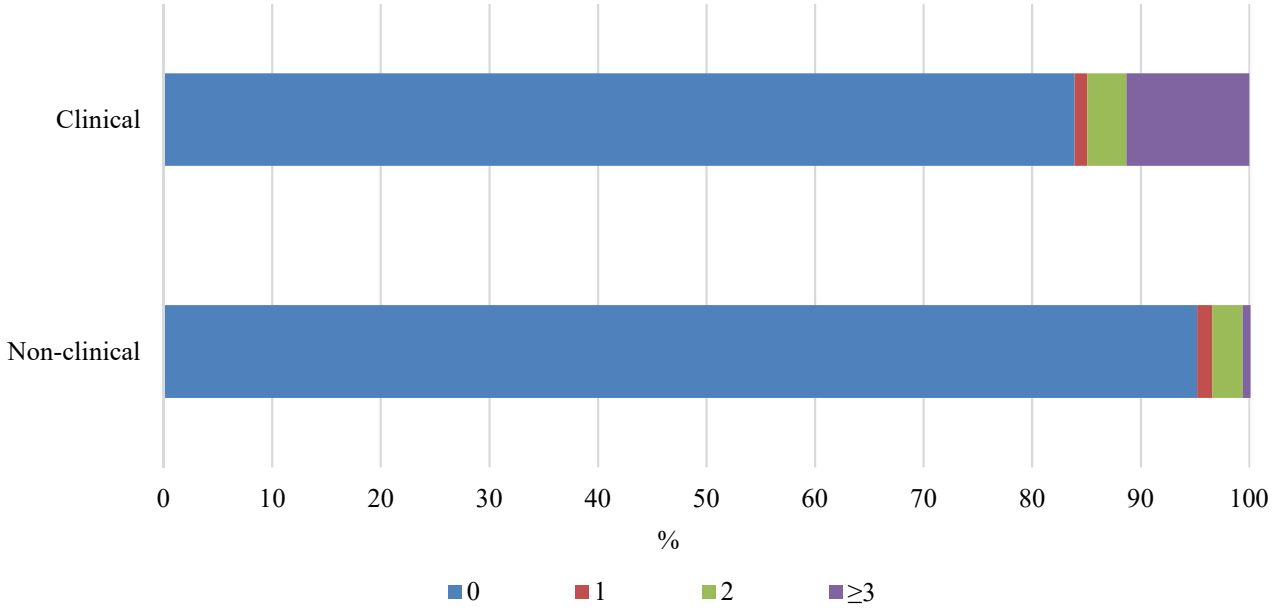

FIGURE 40. Antimicrobial resistance profile for *Escherichia coli* from clinical (n=168) and non-clinical (n=289) samples from cattle sampled in 2020 and 2021, respectively. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 83.9% [95% CI: 77.5 – 89.1] of the isolates were susceptible to all antimicrobials included in the test panel. Resistance to ampicillin was the most frequently identified resistance phenotype, followed by resistance to sulfamethoxazole and trimethoprim. The following proportions of isolates were resistant to one or more antimicrobial classes; 1.2% were resistant to one, 3.6% to two and 11.3% to three or more antimicrobial classes, respectively. One of the isolates was resistant to five antimicrobial classes and five isolates were resistant to four antimicrobial classes.

Two (1.2% [95% CI: 0.1 – 4.2]) of the isolates displayed resistance to the extended spectrum cephalosporins (ESC) cefotaxime and/or ceftazidime. One isolate displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. This isolate displayed additional resistance to ampicillin. The last isolate carried the $bla_{\text{OXA-1}}$ gene and displayed additional resistance to ampicillin, trimethoprim, sulfamethoxazole, chloramphenicol and cefepime (data not shown in Table 10).

E. coli from bovine mastitis was also examined in 2009. Comparisons, however, have to take into consideration changes made in the panel of antimicrobial agents tested. Resistance to streptomycin, which is no longer part of the panel, was the most frequently identified resistance in isolates in 2009 with 19.8% (NORM/NORM-VET 2009). Figure 38 indicates decrease in some resistances between 2009 and 2020, and for tetracycline resistance this decrease is significant (p=0.029). The general sales of intramammary preparations have been more than halved since 2009, and intramammary preparation containing tetracyclines have not been sold since 1997 (personal communication, Kari Grave). Reduced use of systemic treatment with tetracyclines for mastitis is a possible theory, but the data are insufficient to support or refute this. Reduced co-selective pressure from reduced use of all intrammary preparations since 2009 may be a contributing factor.

There is a higher proportion of overall antimicrobial resistance in these clinical *E. coli* isolates compared to antimicrobial resistance in indicator *E. coli* from cattle less than one year as presented in Figures 39-40 (see also page 57-60). Epidemiological cut-off values (ECOFFs) were used for classification of resistance in these clinical *E. coli* isolates, facilitating comparison to surveillance results for indicator *E. coli*. Clinical breakpoints (EUCAST for ampicillin, tigecycline, gentamicin, amikacin and colistin, CLSI for tetracycline) are shown in dotted blue lines in Table 10. 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.

Streptococcus dysgalactiae from cattle

A total of 153 isolates of *Streptococcus dysgalactiae* from clinical mastitis in cattle were susceptibility tested. The isolates were collected in 2020. The results are presented in Table 11, Figure 41, and in the text.

TABLE 11. Antimicrobial resistance in *Streptococcus dysgalactiae* from clinical mastitis in cattle (n=153) collected in 2020.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*																
Substance	[95% CI]		0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Oxytetracycline	0.0	[0.0-2.4]									6.5	11.1	52.3	26.8	3.3					
Amoxicillin	0.7	[0.0-3.6]				73.9	25.5				0.7									
Benzylpenicillin	0.7	[0.0-3.6]		9.8	88.2	1.3					0.7									
Cloxacillin	1.3	[0.2-4.6]						2.6	94.1	2.0	0.7			0.7						
Cefalexin	0.7	[0.0-3.6]								6.5	90.8	2.0	0.7							
Cefapirin	1.3	[0.2-4.6]					42.5	56.2				0.7				0.7				
Trimethoprim/ Sulfamethoxazole	0.7	[0.0-3.6]						28.1	68.6	2.6			0.7							
Tylosin	3.3	[1.1-7.5]							4.6	70.6	21.6	1.3			1.3	0.7				
Lincomycin	1.3	[0.2-4.6]						0.7	24.8	64.7	8.5	1.3								
Streptomycin	0.7	[0.0-3.6]												0.7	18.3	44.4	34.0	2.0	0.7	

*Bold vertical lines denote cut-off values for resistance. CI=confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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. Clinical breakpoints are not defined for oxytetracycline, cloxacillin, amoxicillin, cefalexin, cefapirin, tylosin, lincomycin and streptomycin.

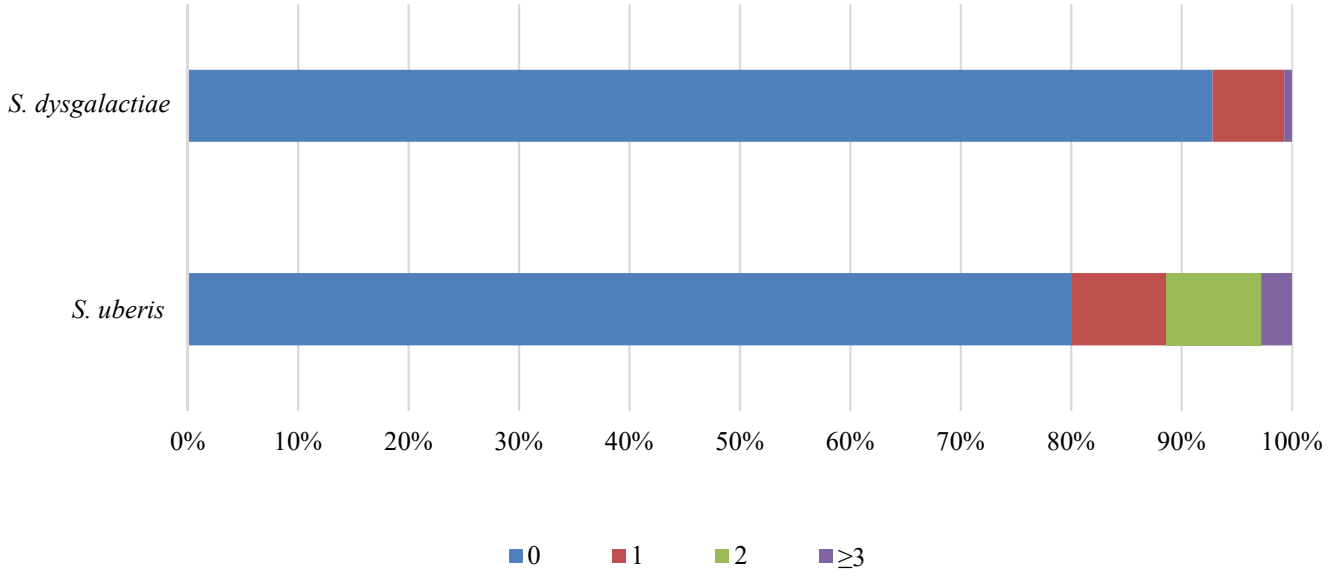

FIGURE 41. Antimicrobial resistance profile for *Streptococcus dysgalactiae* and *Streptococcus uberis* from clinical mastitis in cattle collected in 2020. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 92.8% of the isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to tylosin was the most frequently identified resistance phenotype, followed by resistance to lincomycin, cloxacillin and cefapirin. The following proportions of isolates were resistant to one or more antimicrobial classes: 6.5% were resistant to one and 0.7% to three antimicrobial classes, respectively (Figure 41). *S. dysgalactiae* has not been included in NORM-VET previously.

Clinical breakpoints are shown in dotted blue lines in Table 11. 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.

Streptococcus uberis from cattle

A total of 174 isolates of *Streptococcus uberis* from clinical mastitis in cattle were susceptibility tested. The isolates were collected in 2021. The results are presented in Table 12, Figure 41, and in the text.

TABLE 12. Antimicrobial resistance in *Streptococcus uberis* from clinical mastitis in cattle (n=174) 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	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Oxytetracycline	2.9	[0.9-6.6]							5.2	47.1	42.0	2.9	2.3			0.6				
Amoxicillin	9.8	[5.8-15.2]				1.7	12.6	69.0	6.9	4.6	5.2									
Benzylpenicillin	5.7	[2.8-10.3]	0.6	0.6	2.9	14.9	54.6	14.9	5.7	5.2				0.6						
Cloxacillin	9.8	[5.8-15.2]					0.6		1.7	10.3	74.7	2.9	5.2	4.6						
Cefalexin	1.1	[0.1-4.1]					0.6		1.7	11.5	77.0	8.0	0.6		0.6					
Cefapirin	10.3	[6.2-15.9]		0.6		0.6	13.2	72.4	2.9	6.9	3.4									
Trimethoprim/ Sulfamethoxazole	3.4	[1.3-7.4]					14.9	24.1	37.9	13.8	5.7	0.6	2.9							
Tylosin	1.7	[0.4-5.0]								0.6	15.5	46.6	33.3	2.3		1.7				
Lincomycin	5.2	[2.4-9.6]						2.9	54.6	32.2	5.2		1.1	1.7		2.3				
Streptomycin	ND	ND														1.7	7.5	34.5	56.3	

*Bold vertical lines denote cut-off values for resistance. ND=cut-offs not defined. CI=confidence interval. White fields denote 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 established for *Streptococcus uberis*.

RESULTS AND COMMENTS

In total, 79.9% of the isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to cefapirin was the most frequently identified resistance phenotype, followed by resistance to cloxacillin and amoxicillin. The following proportions of isolates were resistant to one or more antimicrobial classes: 8.6% were resistant to one, 8.6% to two and 2.8% to three or more antimicrobial classes, respectively (Figure 41). *S. uberis* has not been included in NORM-VET previously.

EARS-Vet - European Antimicrobial Resistance Surveillance network in Veterinary medicine

Antimicrobial resistance (AMR) cannot be tackled effectively without well-performing monitoring systems, covering both the animal and the human sectors. The European Centre for Disease Prevention and Control (ECDC) coordinates the European Antimicrobial Resistance Surveillance Network (EARS-Net), which monitors AMR in human clinical isolates of hospitalised patients (1), and the European Food- and Waterborne Diseases and Zoonoses Network (FWD-Net) monitors AMR in human *Salmonella* and *Campylobacter* infections (2). In the animal and food sector, the European Food Safety Authority (EFSA) coordinates a mandatory active monitoring of AMR in zoonotic bacteria (*Salmonella* and *Campylobacter*) and indicator bacteria (*Escherichia coli*) from healthy food-producing animals (cattle, poultry, pigs) and meat thereof, according to Directive 2003/99/EC (3) and Commission Implementing Decision (EU) 2020/1729 (4). There is, however, currently no European system monitoring AMR in clinical isolates from diseased animals.

In this context, the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), co-funded by the Third Health Programme of the EU, proposed to establish the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet), to strengthen a One Health AMR surveillance approach in Europe (5). The surveillance objective of EARS-Vet would be to describe the AMR situation, follow AMR trends and detect emerging AMR in bacterial pathogens of animals in Europe. The data generated could be used for (i) advising policy, (ii) monitoring interventions, (iii) evaluating marketing authorisations of antimicrobials, (iv) supporting antimicrobial stewardship initiatives, (v) generating epidemiological cut-off values, (vi) supporting risk assessment, and (vii) estimating antimicrobial resistance burden.

A pragmatic strategy was suggested to design EARS-Vet, where one of the first steps would be to define a surveillance framework, including a surveillance scope (i.e. the animal species, production types, age categories, bacterial species, sample types, and what antimicrobials to be included). To reach harmonisation, it was suggested that standards should be defined in an inclusive and bottom-up approach, i.e. according to what is considered relevant and feasible within the participating countries. In a follow up study, national monitoring systems for AMR in animal bacterial pathogens in Europe were reviewed, to be used as a basis for the development of EARS-Vet (6). In total, 15 national monitoring systems from 11 countries were described and analysed. The systems had different structures and operations, but most of them shared common weaknesses (e.g., data management and representativeness) and common threats (e.g., economic vulnerability and data access), which could be addressed collectively under EARS-Vet. The scope of EARS-Vet was then finally defined by consensus between European experts through a bottom up and One Health approach (7). In short, it is suggested that EARS-Vet monitors AMR in six animal species (i.e. cattle, swine, chickens (broilers and laying hens), turkeys, cats and dogs), for 11 bacterial species (*Escherichia coli, Klebsiella pneumoniae, Mannheimia haemolytica, Pasteurella multocida, Actinobacillus pleuro-pneumoniae, Staphylococcus aureus, Staphylococcus pseudintermedius, Staphylococcus hyicus, Streptococcus uberis, Streptococcus dysgalactiae* and *Streptococcus suis*). Relevant antimicrobials for their treatment were selected (e.g. tetracyclines) and complemented with antimicrobials of more specific public health interest (e.g. carbapenems). Molecular data detecting the presence of ESBLs, AmpC cephalosporinases and methicillin resistance should also be collected. Following these publications, the network has been established among the partners in the EU-JAMRAI project, and a first report is planned on data for the years 2016-2020.

References:

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5. Mader R, Damborg P, Amat J-P. et al. Building the European Antimicrobial Resistance Surveillance network in veterinary medicine (EARS-Vet). Euro Surveill 2021; 26: pii=2001359.
6. Mader R, Muñoz Madero C, Aasmäe B. et al. Review and analysis of national monitoring systems for antimicrobial resistance in animal bacterial pathogens in Europe: a basis for the development of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet). Front Microbiol. 2022 Apr 7;13:838490. doi: 10.3389/fmicb.2022.838490.
7. Mader R, Bourély C, Amat JP. et al. Defining the scope of the European Antimicrobial Resistance Surveillance network in Veterinary medicine (EARS-Vet): a bottom-up and One Health approach. J Antimicrob Chemother. 2022 Feb 23;77(3):816-826. doi: 10.1093/jac/dkab462.

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INTRODUCTION TO CHAPTER ON INDICATOR BACTERIA

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

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

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

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

INDICATOR BACTERIA FROM ANIMALS

Madelaine Norström, Jannice Schau Slettemeås, and Anne Margrete Urdahl

In 2021, samples from animals included caecal samples from cattle less than one year and fattening pigs, as well as faecal swabs from horses, for isolation of indicator bacteria and some emerging resistant bacteria. In addition, nasal swabs from horses were included for detection of MRSA. The results from the surveillance programme for MRSA in pigs are described as well (separate presentation page 68).

Some of the cut-off values defining resistance applied in NORM-VET have been changed over the years. To facilitate comparisons in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2021. For cattle less than one year and fattening pigs only data retrieved following the requirements set in decision 2013/652/EU and 2020/1729/EU are shown. For previous data, please see the respective annual reports. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from cattle and pigs

Caecal samples from a total of 295 cattle less than one year and 321 fattening pig were examined. *E. coli* isolates were obtained from 289 (98.0%) of the cattle and all the 321 (100%) pig samples. One isolate per positive sample was susceptibility tested (one pig isolate was not tested). The results are presented in Table 13 and Figures 42-44, and in the text.

TABLE 13. Antimicrobial resistance in *Escherichia coli* isolates from caecal samples of cattle less than one year (n=289) and fattening pigs (n=320) in 2021.

Substance	Animal	Resistance (%) [95% CI]	Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Cattle	1.4 [0.0 – 3.5]								95.8	2.4	0.3		0.3	1.0			
	Pig	5.9 [3.6 – 9.1]								88.8	5.3		0.3	0.6	5.0			
Tigecycline	Cattle	0.0 [0.0 – 1.3]					99.3	0.7										
	Pig	0.0 [0.0 – 1.1]					99.4	0.6										
Chloramphenicol	Cattle	0.3 [0.0 – 1.9]										96.9	2.8			0.3		
	Pig	0.3 [0.0 - 1.7]										96.9	2.8	0.3				
Ampicillin	Cattle	2.4 [1.0 – 4.9]							2.4	28.0	62.6	4.5			2.4			
	Pig	6.6 [4.1 – 9.9]							5.0	37.2	46.6	4.7			6.6			
Cefotaxime	Cattle	2.1 [0.8 – 4.5]					97.9		1.0	0.7	0.3							
	Pig	0.0 [0.0 - 1.1]					100											
Ceftazidime	Cattle	2.1 [0.8 – 4.5]					97.2	0.7		0.7	1.0	0.3						
	Pig	0.0 [0.0 – 1.1]					97.8	2.2										
Meropenem	Cattle	0.0 [0.0 – 1.3]		100														
	Pig	0.0 [0.0 – 1.1]		99.4	0.6													
Trimethoprim	Cattle	0.3 [0.0 – 1.9]					65.1	31.1	3.5					0.3				
	Pig	6.2 [3.9 – 9.5]					45.0	37.5	11.2					6.2				
Sulfamethoxazole	Cattle	2.4 [1.0 – 4.9]										67.8	26.6	2.4	0.7	0.7		1.7
	Pig	7.5 [4.9 – 11]										60.0	26.2	4.7	1.2	0.3		7.2
Azithromycin	Cattle	0.0 [0.0 – 1.3]								6.9	49.1	43.6	0.3					
	Pig	0.0 [0.0 – 1.1]								6.9	40.9	50.9	1.2					
Gentamicin	Cattle	0.0 [0.0 – 1.3]						93.1	6.6	0.3								
	Pig	0.0 [0.0 – 1.1]						84.4	15.0	0.6								
Amikacin	Cattle	0.0 [0.0 – 1.3]									98.3	1.7						
	Pig	0.0 [0.0 – 1.1]									96.6	3.4						
Ciprofloxacin	Cattle	0.0 [0.0 – 1.3]	92.7	7.3														
	Pig	0.9 [0.2 – 2.7]	87.8	11.2			0.6	0.3										
Nalidixic acid	Cattle	0.0 [0.0 – 1.3]									100							
	Pig	0.9 [0.2 – 2.7]									97.8	1.2			0.3	0.6		
Colistin	Cattle	0.0 [0.0 – 1.3]							99.3	0.7								
	Pig	0.0 [0.0 – 1.1]							99.7	0.3								

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

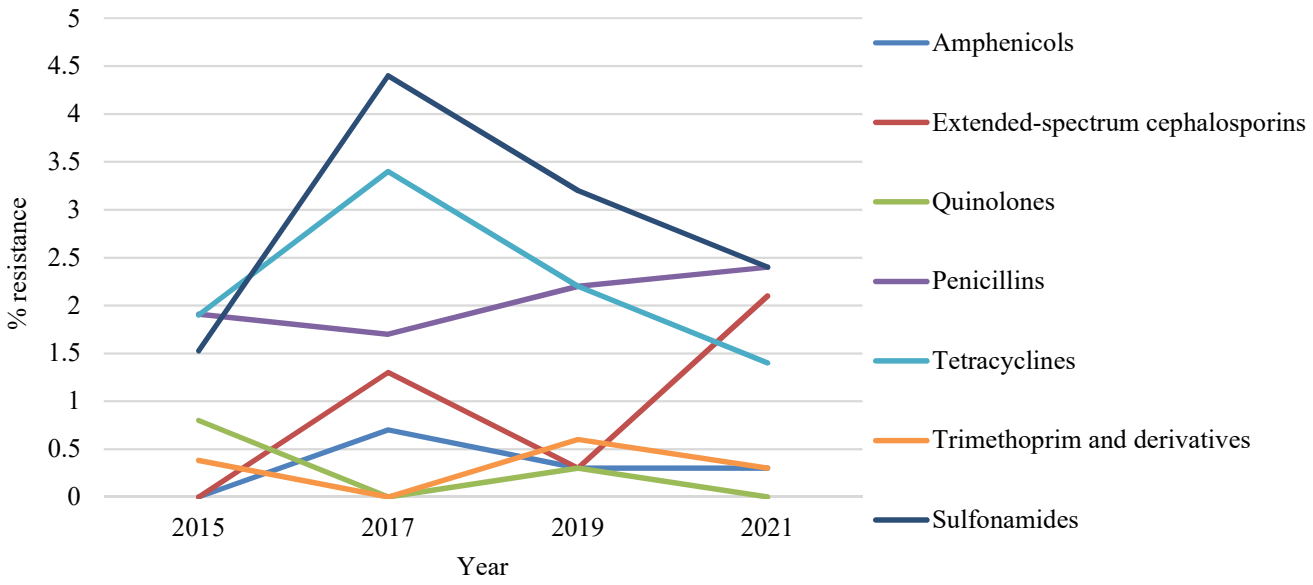

FIGURE 42. Prevalence of resistance to various antimicrobial agents in *Escherichia coli* from caecal samples from cattle less than one year of age collected in 2015-2021. The breakpoints used in NORM-VET 2021 were applied.

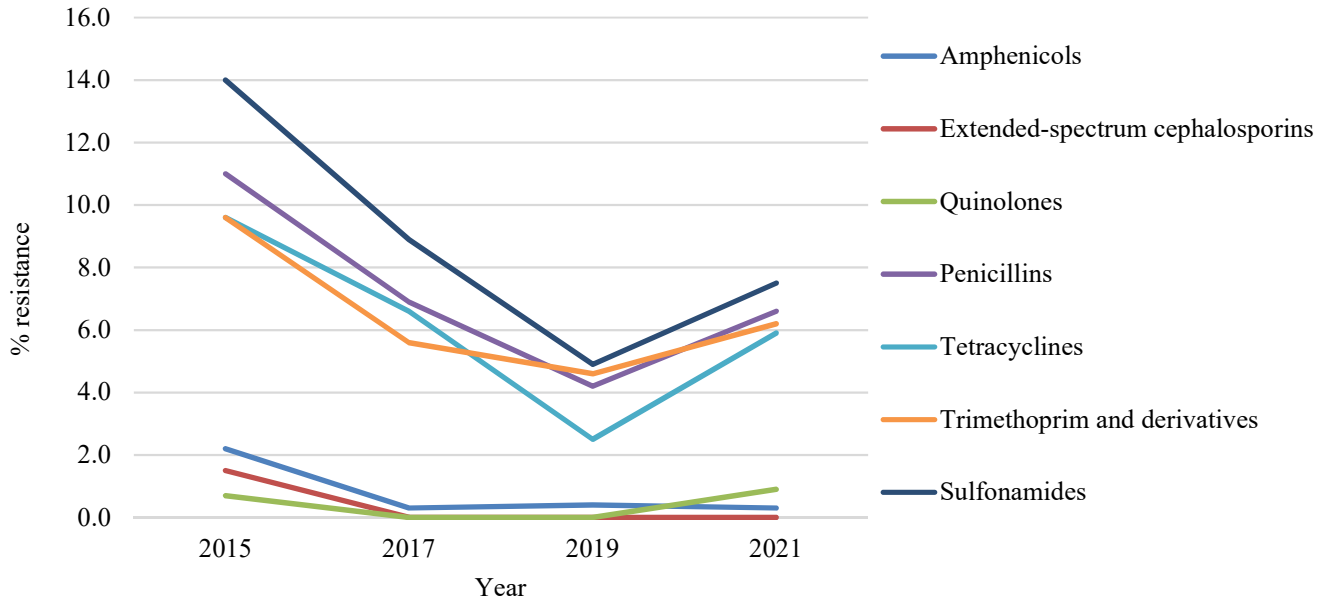

FIGURE 43. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from caecal samples from fattening pigs collected in 2015-2021. The breakpoints used in NORM-VET 2021 were applied.

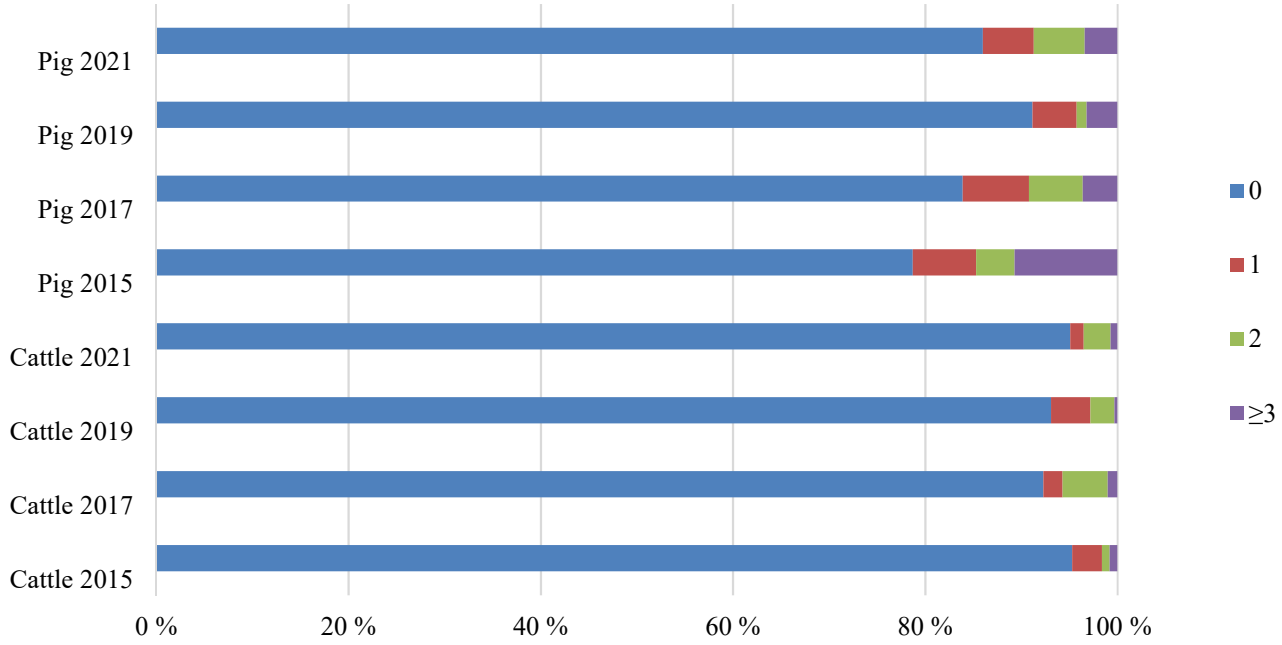

FIGURE 44. Antimicrobial resistance profile for *Escherichia coli* from caecal samples from fattening pigs and cattle less than one year collected in 2015-2021. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

CATTLE

A total of 95.2% of the *E. coli* isolates from cattle caecal samples were susceptible to all antimicrobial agents included in the test panel, indicating a low occurrence of resistance among *E. coli* from cattle caecal samples according to the EFSA classification described in Appendix 6. The low detected occurrence is in concordance with the results from 2015, 2017 and 2019. Resistance to ampicillin and sulfamethoxazole were the most frequently identified resistance phenotypes. Altogether, 1.4% of the isolates were resistant to one antimicrobial class, 2.8% to two, and 0.7% to three or more antimicrobial classes.

Six of the isolates displayed resistance to the extended spectrum cephalosporins (ESC) cefotaxime and ceftazidime (2.1% [95% CI: 0.8 – 4.5]). These isolates displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. In addition, selective methods were applied on the same sample material to

investigate the occurrence of *E. coli* resistant to ESC in cattle (see below). None of the isolates displayed any resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid). This is in concordance with results from the previous years.

In a European perspective, the occurrence of resistance among *E. coli* from cattle less than one year in Norway is among the lowest of the countries reporting to EFSA (EFSA and ECDC Summary Report 2019–2020). This situation corresponds to the limited use of antibiotics in the Norwegian cattle production.

PIG

A total of 85.9% of the *E. coli* isolates from pig caecal samples were susceptible to all antimicrobial agents tested, indicating a moderate occurrence of resistance among *E. coli* from caecal samples of fattening pigs according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole, ampicillin, trimethoprim, and tetracycline were the most frequently identified resistance phenotypes. Altogether, 5.3% of the isolates were resistant to one antimicrobial class, 5.3% to two, and 3.4% to three or more antimicrobial classes.

The proportion of isolates being fully susceptible increased from 78.7% [95% CI: 73.3 – 83.4] in 2015, 83.9% [95% CI: 79.3 – 87.8] in 2017, and 91.2% [95% CI: 87.3 – 94.2] in 2019, to 85.9% [95% CI: 81.6 – 89.6] in 2021 (Figure 44). These changes have all been due to corresponding changes in susceptibility to sulfamethoxazole, trimethoprim, ampicillin, and tetracycline, as indicated in Figure 43. Comparisons to data from years before 2015 have to take into consideration changes made in the panel of antimicrobial agents tested. Resistance to streptomycin, which is no longer part of the panel, has traditionally been most frequently identified in isolates from pig with 17.2% resistant isolates in 2011 (NORM/NORM-VET 2011). After the changes in the panel, the most frequently identified antimicrobial agent has been sulfamethoxazole, previously the second most frequently identified.

Three isolates displayed resistance to quinolones (i.e. ciprofloxacin and nalidixic acid). None of the isolates displayed reduced susceptibility to ESC (i.e. cefotaxime and/or ceftazidime). This is in concordance with results from previous years. Selective methods were applied on the same sample material to investigate the occurrence of *E. coli* resistant to ESC in fattening pigs (see below).

In a European perspective, the occurrence of resistance among *E. coli* from fattening pigs in Norway is among the lowest (EFSA and ECDC Summary Report 2019–2020). The occurrence varies markedly between countries reporting to EFSA, ranging from very few susceptible isolates and up to nearly 80% fully susceptible, with the levels of full susceptibility decreasing in a north to south gradient. This favourable Norwegian situation corresponds to the limited use of antibiotics in the Norwegian pig production.

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

A total of 295 cattle and 321 pig samples were examined for the presence of *E. coli* resistant to extended spectrum cephalosporins (ESC) by selective methods. One isolate per positive sample was susceptibility tested. Results are presented in Table 14, Figures 45-46, and in the text.

TABLE 14. Antimicrobial resistance in *Escherichia coli* isolates resistant to extended spectrum cephalosporins from caecal samples of cattle less than one year (n=3) and fattening pigs (n=47) in 2021.

		Distribution (n) of MIC values (mg/L)*															
Substance	n (resistance)	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	4								46					4			
Tigecycline	0					47	3										
Chloramphenicol	1										48	1			1		
Ampicillin	50													50			
Cefotaxime	50							2	40	5	3						
Ceftazidime	50									30	18	2					
Meropenem	0		50														
Trimethoprim	9					18	21	2	1				8				
Sulfamethoxazole	4										31	13	2			1	3
Azithromycin	0									5	45						
Gentamicin	0						46	3	1								
Amikacin	0									50							
Ciprofloxacin	3	27	20			2	1										
Nalidixic acid	2									48		1			1		
Colistin	0							50									

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

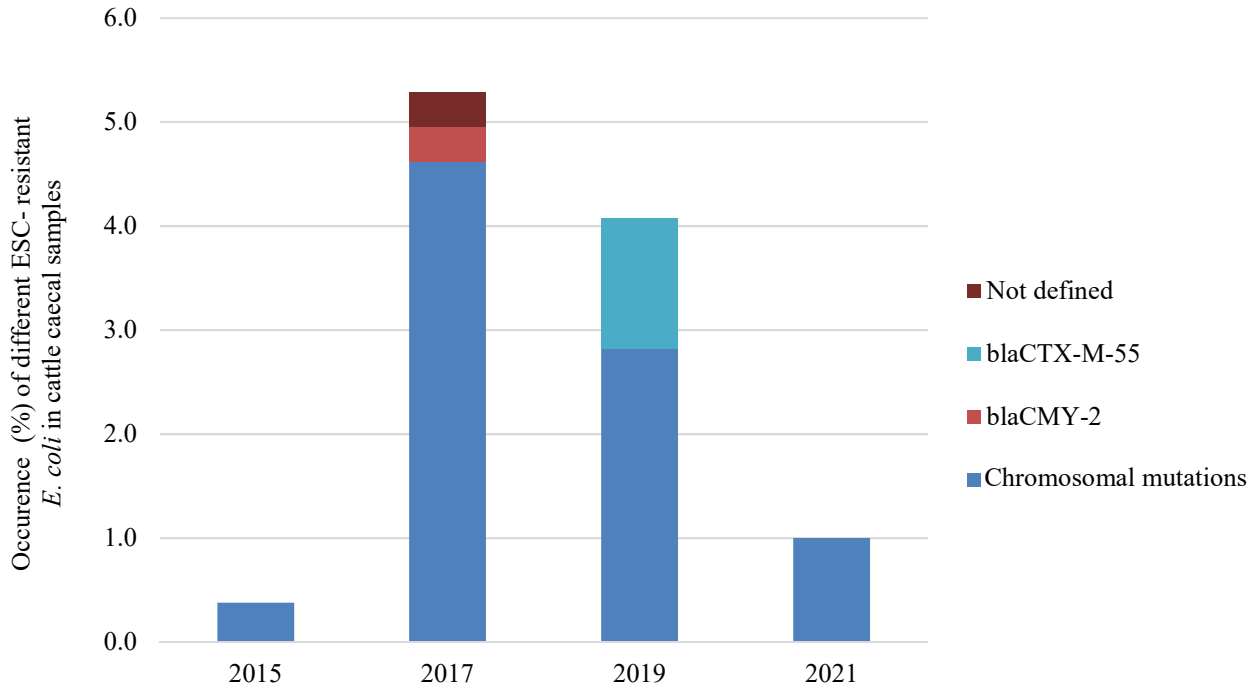

FIGURE 45. Occurrence (%) of different ESC-resistant *E. coli* from cattle less than one year 2015-2021.

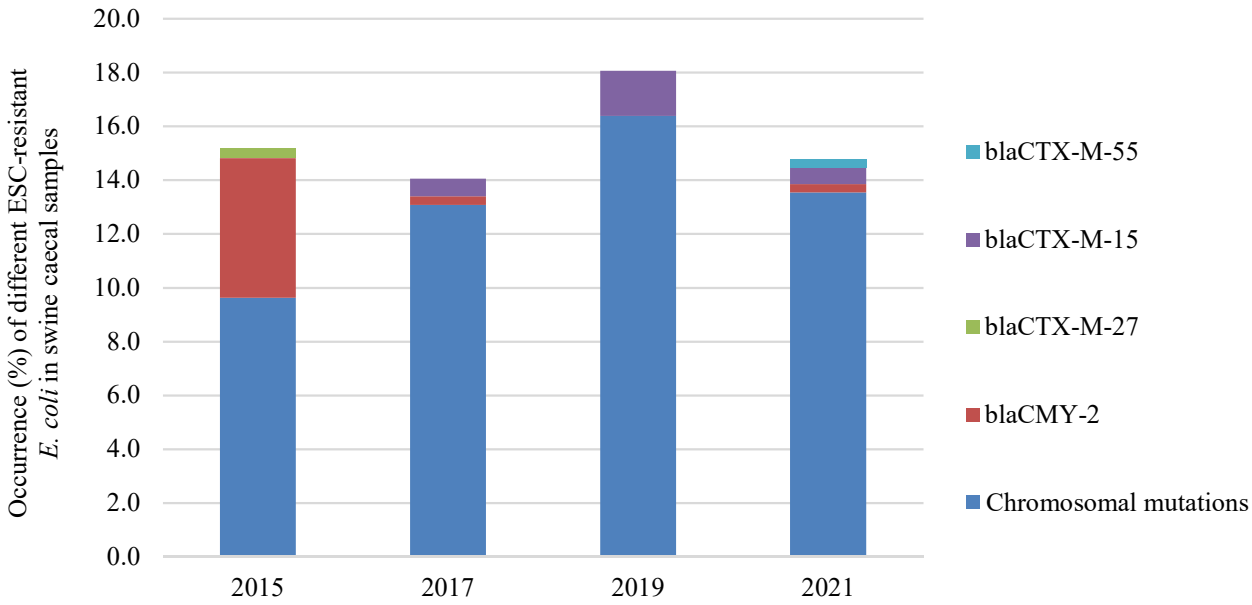

FIGURE 46. Occurrence (%) of different ESC-resistant *Escherichia coli* from fattening pigs 2015-2021.

RESULTS AND COMMENTS

ESC-resistant *E. coli* were detected from three of the cattle (1.0% [95% CI: 0.2 - 2.9]), and 47 of the pig (14.6% [95% CI: 11.0 - 19.0]) samples.

All three isolates from cattle caecal samples displayed an AmpC beta-lactamase phenotype. For these isolates the resistance was due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation.

Of the 47 isolates from pig caecal samples, 44 displayed an AmpC beta-lactamase phenotype due to mutations in the promoter and attenuator region of the chromosomally located *ampC* gene (p.C-42T) causing an upregulation. The last three isolates displayed an ESBL phenotype. Two were genotyped as $bla_{\text{CTX-M-15}}$, where one isolate in addition carried the *qnrS1* gene encoding quinolone resistance. The last isolate was genotyped as $bla_{\text{CTX-M-55}}$, and this isolate also carried the *qnrS1* gene.

Compared to the results from 2015, an increase was observed in overall occurrence of all genotypes of ESC-resistant *E. coli* in cattle in 2017 and 2019. In 2015, *E. coli* resistant to ESC were detected from 0.4% [95% CI: 0.0 -

2.1] of the samples, while the detection rate was 5.3% [95% CI: 3.0 - 8.4] in 2017 and 4.1% [95% CI: 2.2 - 6.9] in 2019 (NORM/NORM-VET 2015, NORM/NORM-VET 2017 and NORM/NORM-VET 2019). In 2021, the occurrence went down again to 1.0% [95% CI: 0.2 - 2.9]), and further monitoring is needed to assess whether there is a true change in occurrence. The overall occurrence of all genotypes of ESC-resistant *E. coli* in pigs is in concordance with previous years. The occurrence of *E. coli* resistant to ESC is in both cattle and pigs mainly due to isolates with mutations in the chromosomally located *ampC* gene. Additionally, there were some ESC-resistant *E. coli* isolated from pig in 2015 due to occurrence of $bla_{\text{CMY-2}}$. A few *E. coli* displaying an ESBL phenotype due to plasmid encoded genes have been detected as well through the years (Figures 45 and 46). The source of introduction of plasmid encoded resistance in *E. coli* to cattle and pigs in Norway, as well as their ability to disseminate further, is currently unknown. There is negligible numbers of import of live cattle and pigs to Norway, which is a preventive measure for importing *E. coli* resistant to ESC from areas/countries with higher prevalence.

In a European perspective, the occurrences of *E. coli* resistant to ESC in cattle less than one year and in fattening pigs in Norway are among the lowest, though the occurrences vary markedly between countries reporting to EFSA (EFSA and ECDC Summary Report 2019-2020). A continued awareness of animal bacterial reservoirs resistant to ESC is of importance to be able to implement control measures if needed.

Carbapenemase-producing *Enterobacterales* from cattle and pigs

Selective method for detection of carbapenemase-producing *Enterobacterales* (CPE) was performed on a total of 295 samples from cattle less than one year and 321 samples from pigs. No CPE were detected ([95% CI cattle: 0.0 – 1.2], [95% CI pigs: 0.0 – 1.1]). Carbapenems are not approved for use in food-producing animals in the EU and EEA countries. Nevertheless, resistance to these critically important antimicrobial agents has sporadically been reported from animals in some of the EU/EEA countries, and further monitoring is recommended to follow the situation in the years to come.

Persistence of and genetic diversity in extended spectrum cephalosporin-resistant *Escherichia coli* in Norwegian broiler production

Some years ago, the Norwegian broiler production was associated with high occurrence (>35% positive flocks in 2014) of extended spectrum cephalosporin (ESC)-resistant *Escherichia coli* [1-3]. Since then, the occurrence has decreased significantly and is currently very low (0.4%) [4, 5]. In a previous study, we found that the odds of a broiler flock being positive for ESC-resistant *E. coli* was significantly higher if the preceding flock in the same house was positive [2, 6]. However, there were knowledge gaps concerning the dynamics of ESC-resistant *E. coli* strains and their plasmids with regard to on-farm persistence. The aim of the current study was therefore to do in-depth characterisation of ESC-resistant *E. coli* and their resistance plasmids from broiler flocks in houses with multiple positive flocks during a six months period in 2016 using whole genome sequencing. In total, ESC-resistant *E. coli* from 43 unique broiler flocks originating from 14 broiler houses on 10 different farms were included.

In total, 11 different *E. coli* sequence types (STs) were identified among the 43 included isolates. The majority carried the $bla_{\text{CMY-2}}$ gene on IncK2 (n=29) or IncI1 (n=6) plasmids, and the remaining carried $bla_{\text{CTX-M-1}}$ on IncI1 plasmids (n=8) (Table 15). ESC-resistant *E. coli* of different STs and with different ESC resistance gene/plasmid combinations could be present on the same farm, while a single ST and ESC resistance gene/plasmid combination displaying zero or few SNP differences were present on other farms. A close genetic relationship was observed between three plasmids from Farm E and two plasmids from Farm I, respectively, which underlines that highly similar plasmids are present in different *E. coli* STs. Further, the results demonstrated that at least two IncK2/$bla_{\text{CMY-2}}$ plasmid variants circulated in the broiler production.

Our results indicate diversity on strain-, plasmid- and ESC resistance gene level. In conclusion, this study has increased our knowledge regarding the dynamics and diversity of ESC-resistant *E. coli* in Norwegian broiler production. Seemingly, local persistence and re-circulation of ESC-resistant strains happens. However, different *E. coli* STs and even different ESC resistance plasmids were observed in some houses/farms. We further describe the presence of highly similar plasmids in different *E. coli* STs, which could be due to persistence and horizontal transfer of ESC resistance plasmids.

TABLE 15. Multilocus sequence type (MLST), plasmid replicon and extended spectrum cephalosporin (ESC) resistance gene associated with ESC-resistant *Escherichia coli* isolated from different broiler flocks on 10 broiler farms sampled during May-October 2016.

Farm ID	House ID	Month sampled, *E. coli* ST and ESC resistance gene detected					
		May	**June**	**July**	**August**	**September**	**October**
Farm A	House 1		negative		**ST38** IncK2/*bla*$_{CMY-2}$		**ST38** IncK2/*bla*$_{CMY-2}$
	House 3		**ST38** IncK2/*bla*$_{CMY-2}$		**ST38** IncK2/*bla*$_{CMY-2}$		**ST38** IncK2/*bla*$_{CMY-2}$
	House 5		**ST38** IncK2/*bla*$_{CMY-2}$		**ST38** IncK2/*bla*$_{CMY-2}$		**ST38** IncK2/*bla*$_{CMY-2}$
Farm B	House 1		**ST1158** IncK2/*bla*$_{CMY-2}$		**ST1640** IncK2/*bla*$_{CMY-2}$		**ST2040** IncI1/*bla*$_{CMY-2}$
Farm C	House 1	**ST57** IncI1/*bla*$_{CTX-M-1}$		**ST1158** IncK2/*bla*$_{CMY-2}$	**ST57** IncI1/*bla*$_{CTX-M-1}$	**ST57** IncI1/*bla*$_{CTX-M-1}$	
Farm D	House 1		negative		**ST429** IncK2/*bla*$_{CMY-2}$	**ST429** IncK2/*bla*$_{CMY-2}$	**ST2040** IncI1/*bla*$_{CMY-2}$
Farm E	House 1	**ST6635** IncK2/*bla*$_{CMY-2}$		**ST162** IncK2/*bla*$_{CMY-2}$		**ST1158** IncK2/*bla*$_{CMY-2}$	**ST937** IncK2/*bla*$_{CMY-2}$
Farm F	House 1	**ST429** IncK2/*bla*$_{CMY-2}$	**ST429** IncK2/*bla*$_{CMY-2}$		negative	**ST429** IncK2/*bla*$_{CMY-2}$	negative
	House 1		**ST1158** IncK2/*bla*$_{CMY-2}$	**ST57** IncI1/*bla*$_{CTX-M-1}$		**ST1158** IncK2/*bla*$_{CMY-2}$	**ST2040** IncI1/*bla*$_{CMY-2}$
Farm G	House 2		**ST442** IncK2/*bla*$_{CMY-2}$	**ST937** IncK2/*bla*$_{CMY-2}$		negative	**ST2040** IncI1/*bla*$_{CMY-2}$
	House 3						**ST2040** IncI1/*bla*$_{CMY-2}$
Farm H	House 1	**ST57** IncI1/*bla*$_{CTX-M-1}$		**ST57** IncI1/*bla*$_{CTX-M-1}$	**ST57** IncI1/*bla*$_{CTX-M-1}$	**ST57** IncI1/*bla*$_{CTX-M-1}$	
Farm I	House 1	**ST1158** IncK2/*bla*$_{CMY-2}$		**ST429** IncK2/*bla*$_{CMY-2}$	**ST1163** IncK2/*bla*$_{CMY-2}$		negative
Farm J	House 1	negative		**ST429** IncK2/*bla*$_{CMY-2}$	**ST937** IncK2/*bla*$_{CMY-2}$		**ST2040** IncI1/*bla*$_{CMY-2}$

*ST=multilocus sequence type, ESC=Extended spectrum cephalosporin.

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The text is a summary of the main findings in the publication "Longitudinal Sampling Reveals Persistence of and Genetic Diversity in Extended Spectrum Cephalosporin-Resistant *Escherichia coli* From Norwegian Broiler Production" published in Frontiers in Microbiology 12:795127 (2021) DOI: 10.3389/fmicb.2021.795127.

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Enterococcus spp. from cattle and pigs

Caecal samples from a total of 293 cattle less than one year and 320 fattening pigs were examined. *E. faecalis* was obtained from three (1.0%) and *E. faecium* from 27 (9.2%) of the cattle caecal samples. From pigs, *E. faecalis* was obtained from 20 (6.3%) and *E. faecium* from 103 (32.2%) of the samples. One isolate of *E. faecalis* and/or *E. faecium* per positive sample was susceptibility tested. The results are presented in Tables 16-17, Figures 47-48, and in the text.

TABLE 16. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from cattle less than one year (n=3) and fattening pigs (n=20) in 2021.

Substance	n (resistance)	Distribution (n) of MIC values (mg/L)*															
		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	16						6	1				2	8	6			
Tigecycline	0		3	15	5												
Chloramphenicol	0									22	1						
Ampicillin	0						15	8									
Erythromycin	0						5	12	6								
Quinupristin – dalfopristin	ND								1	5	17						
Gentamicin	0									1	18	4					
Ciprofloxacin	0					3	19	1									
Vancomycin	0						17	6									
Teicoplanin	0					23											
Linezolid	ND							22	1								
Daptomycin	0					4	16	3									

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

TABLE 17. Antimicrobial resistance in *Enterococcus faecium* (n=103) from caecal samples from fattening pigs in 2021.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
			0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	33.0	[24.1 - 43]						67.0					32.0	1.0				
Tigecycline	0.0	[0.0 - 3.5]	1.0	55.3	43.7													
Chloramphenicol	0.0	[0.0 - 3.5]								2.9	68.0	29.1						
Ampicillin	0.0	[0.0 - 3.5]					10.7	12.6	27.2	19.4	30.1							
Erythromycin	2.9	[0.6 - 8.3]						14.6	43.7	38.8	2.9							
Quinupristin – dalfopristin		ND					28.2	13.6	1.0	57.3								
Gentamicin	0.0	[0.0 - 3.5]									78.6	20.4	1.0					
Ciprofloxacin	1.0	[0.0 - 5.3]				1.0	31.1	28.2	19.4	14.6	4.9	1.0						
Vancomycin	0.0	[0.0 - 3.5]						93.2	5.8	1.0								
Teicoplanin	0.0	[0.0 - 3.5]					97.1	2.9										
Linezolid	0.0	[0.0 - 3.5]							64.1	35.9								
Daptomycin	0.0	[0.0 - 3.5]					5.8	29.1	48.5	16.5								

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

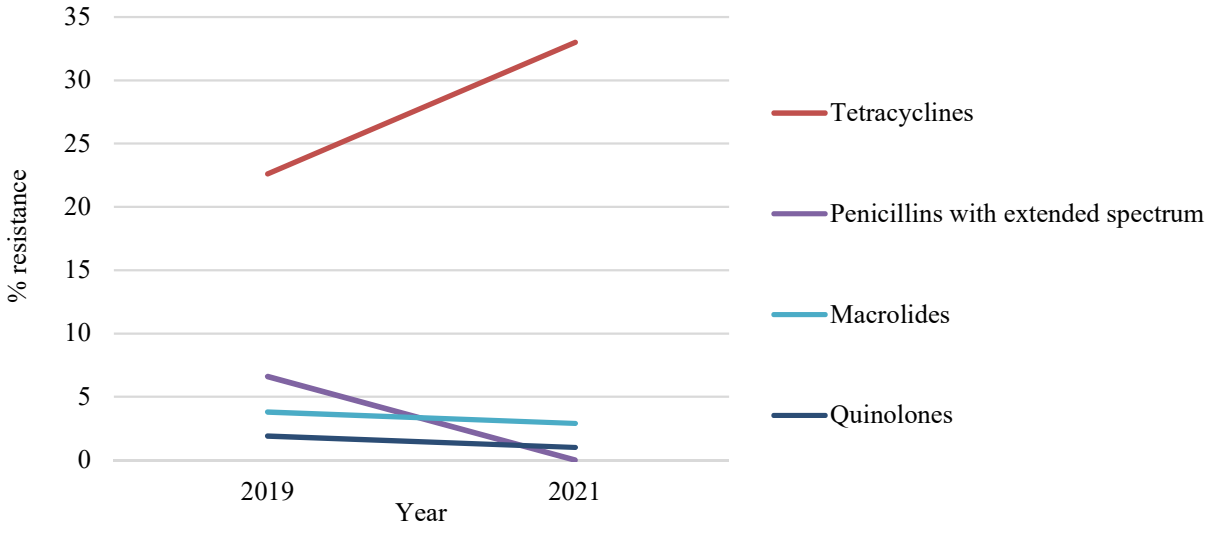

FIGURE 47. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* from caecal samples from fattening pigs collected in 2019 and 2021. The breakpoints used in NORM-VET 2021 were applied.

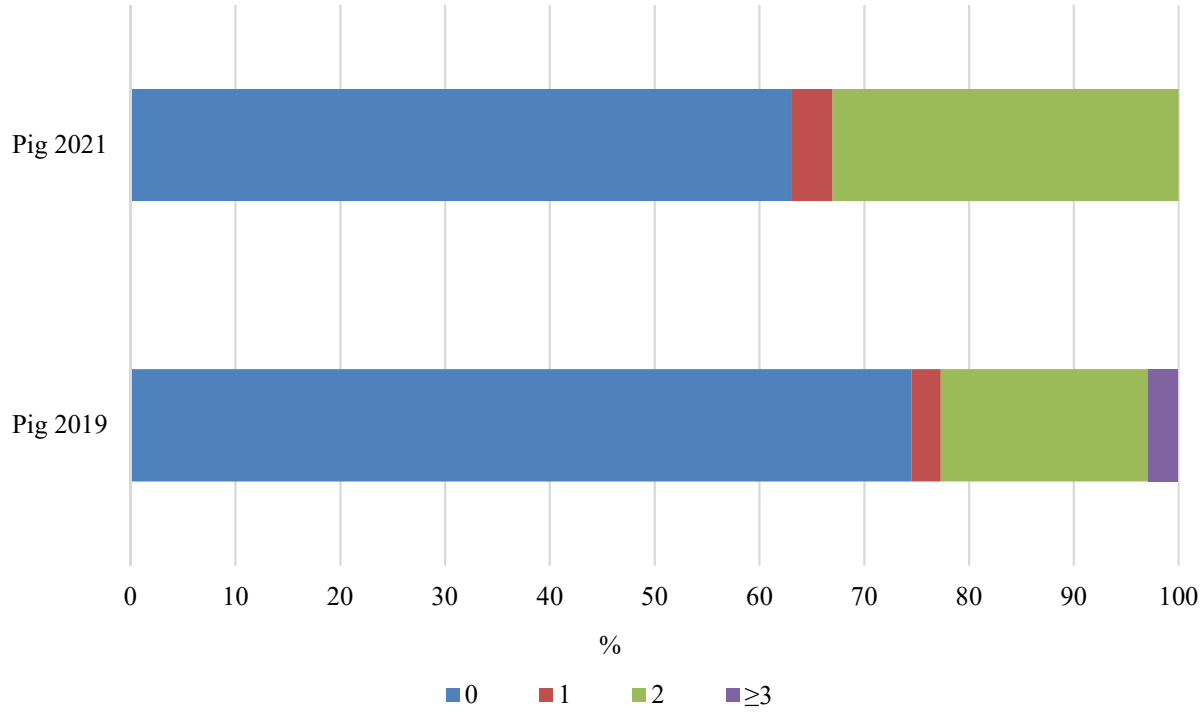

FIGURE 48. Antimicrobial resistance profile for *Enterococcus faecium* from caecal samples from fattening pigs collected in 2019-2021. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

CATTLE

The 2021 data showed that one of the three *E. faecalis* isolates and 21 of the 27 *E. faecium* isolates from cattle caecal samples were susceptible to all antimicrobial agents included in the test panel. The remaining *E. faecalis* isolates were resistant only to tetracycline and three *E. faecium* isolates were resistant to either tetracycline or erythromycin. This is in concordance with the results from 2019.

PIG

The 2021 data showed that six of the 20 *E. faecalis* and 63.1% of the 103 *E. faecium* isolates from pig caecal samples were susceptible to all antimicrobial agents included in the test panel. The remaining 14 *E. faecalis* isolates were only resistant to tetracycline. Among the *E. faecium* isolates, 18.4% were resistant to one antimicrobial class and 24.3% were resistant to two antimicrobial classes. Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to erythromycin and ciprofloxacin. In total, 42.7% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a high occurrence of resistance according to the EFSA classification described in Appendix 6.

The 2021 results are in concordance with the results from 2019. Figure 47 indicates an increase in occurrence of tetracycline resistance and a decrease in occurrence of resistance to penicillins with extended spectrum. These observed changes are; however, not statistically significant, and further monitoring is needed to follow the situation in the years to come.

SPORTS AND FAMILY ANIMALS

Escherichia coli from horses

Faecal swab samples from a total of 203 horses were examined. *E. coli* isolates were obtained from 189 (93.1%) of the samples. One isolate per positive sample was susceptibility tested. The results are presented in Table 18, Figures 49-50, and in the text.

TABLE 18. Antimicrobial resistance in *Escherichia coli* isolates (n=189) from faecal samples from horses in 2021.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	2.1	[0.6 - 5.3]								91.0	6.9				2.1			
Tigecycline	0.0	[0.0- 1.9]					98.9	1.1										
Chloramphenicol	0.0	[0.0- 1.9]										96.3	3.7					
Ampicillin	2.1	[0.6 - 5.3]								18.0	58.7	21.2			2.1			
Cefotaxime	0.0	[0.0- 1.9]					100											
Ceftazidime	0.0	[0.0- 1.9]					89.4	10.6										
Meropenem	0.0	[0.0- 1.9]		98.9	1.1													
Trimethoprim	13.8	[9.2 - 19.5]					56.1	20.1	8.5	1.6				13.8				
Sulfamethoxazole	14.3	[9.6- 20.1]										64.6	13.8	5.8	1.6			14.3
Azithromycin	0.0	[0.0- 1.9]								7.4	44.4	48.1						
Gentamicin	0.0	[0.0- 1.9]						79.9	18.5	1.6								
Amikacin	0.5	[0.0- 2.9]									97.4	2.1	0.5					
Ciprofloxacin	0.5	[0.0- 2.9]	81	18.5			0.5											
Nalidixic acid	0.5	[0.0- 2.9]									99.5					0.5		
Colistin	0.0	[0.0- 1.9]							100									

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

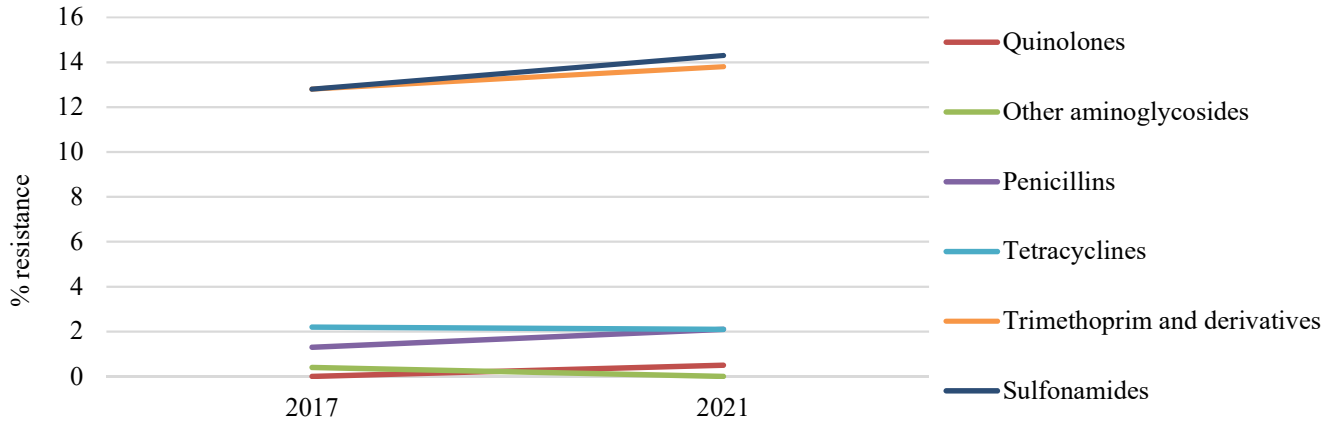

FIGURE 49. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* from faecal samples from horses collected in 2017 and 2021. The breakpoints used in NORM-VET 2021 were applied.

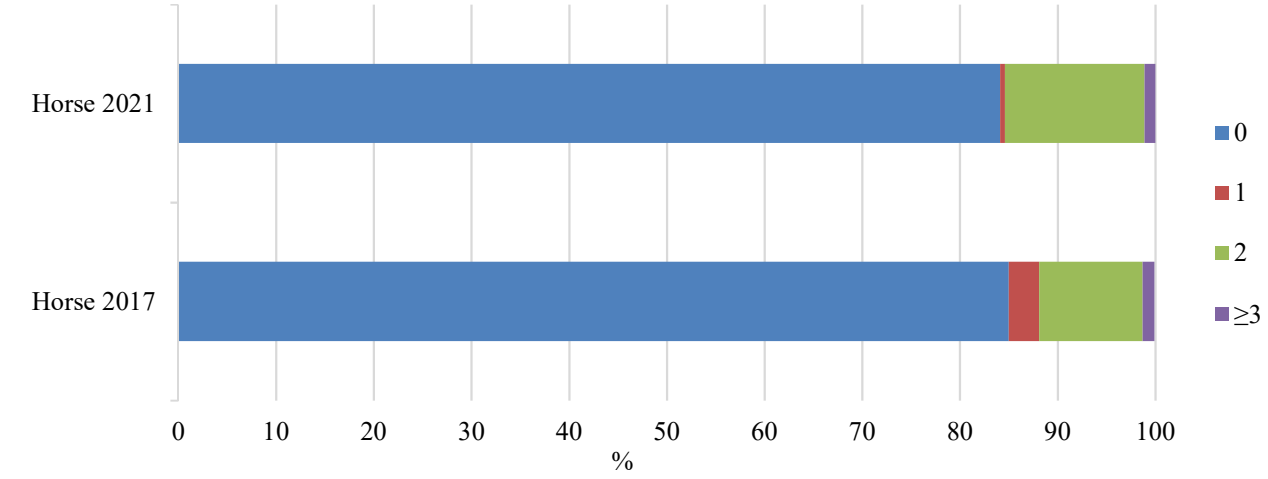

FIGURE 50. Antimicrobial resistance profile for *Escherichia coli* from faecal samples from horses collected in 2017 and 2021. Percentage of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥3) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

In total, 84.1% of the isolates were susceptible to all antimicrobial agents included. Altogether, 0.5% of the isolates were resistant to one antimicrobial class (predominantly ampicillin), 14.3% to two, and 1.1% to three or more antimicrobial classes. In total, 15.9% of the isolates were resistant to at least one of the tested antimicrobial agents, indicating a moderate occurrence of resistance among *E. coli* from faecal samples of horses according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole and trimethoprim were the most frequently identified resistance determinants.

None of the isolates displayed any resistance to the extended spectrum cephalosporins (ESC) cefotaxime or ceftazidime. One isolate displayed resistance to quinolones (i.e. ciprofloxacin and nalidixic acid). This is in concordance with previous results from 2009 and 2017 (NORM/NORM-VET 2009, NORM/NORM-VET 2017). Selective methods were also used on the same sample material to investigate the occurrence of these substances with more sensitive methods.

Samples from horses have been included in NORM-VET twice before, in 2009 and 2017. The 2021 results are in concordance with the results from 2017. Comparison to 2009 is difficult due to changes in the panel of antimicrobial agents tested. In 2009, 7.6% of the tested isolates displayed reduced sensitivity towards streptomycin. Streptomycin is no longer part of the test panel, and thereby comparison on the overall resistance is difficult. The data do, however, indicate an increase in resistance to sulfamethoxazole and trimethoprim from 7.6% and 8.8%, respectively, in 2009 to 12.8% each in 2017, and 14.3% and 13.8%, respectively, in 2021. These observed changes are not statistically significant and further monitoring is needed to follow the situation in the years to come.

Extended spectrum cephalosporin resistant *Escherichia coli* from horses

Selective screening for *E. coli* resistant to extended spectrum cephalosporins (ESC) was performed on 201 faecal swab samples from horses. *E. coli* resistant to ESC were not detected in any [95% CI: 0.0-1.8] of the samples. This is in concordance with the results from 2017 when *E. coli* resistant to ESC was detected in two of 246 samples (0.8% [95% CI: 0.1-2.9]). One of these isolates displayed an AmpC beta-lactamase phenotype due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene (p.C-42T), and the last isolate displayed an ESBL phenotype and was genotyped as $bla_{\text{CTX-M-1}}$.

Quinolone resistant *Enterobacteriaceae* from horses

Selective screening for *E. coli* resistant to quinolones was performed on faecal swab samples from 186 horses. *E. coli* resistant to quinolones were found in two (1.1% [95% CI: 0.1-3.8]) of the samples. This is in concordance with the results from 2017 when six (2.4% [95% CI: 0.9-5.2]) samples were positive for quinolone resistant *E. coli*. One of the isolates was additionally resistant to ampicillin and the other isolate to trimethoprim and sulfonamides. Whole genome sequencing of the two quinolone resistant isolates showed that the resistance mechanism in one of these isolates was due to a point mutation in the GyrA gene (p.S83L), and the last isolate carried a *qnrS13* gene.

Carbapenemase-producing *Enterobacterales* from horses

A total of 199 faecal swab samples from horses were screened for the presence of carbapenemase-producing *Enterobacterales*. No carbapenemase-producing *Enterobacterales* isolates were detected.

Methicillin resistant *Staphylococcus aureus* (MRSA) from horses

A total of 209 nasal swab samples from horses were screened for the presence of methicillin resistant *Staphylococcus aureus* (MRSA). MRSA was not detected from any of these horses [95% CI: 0.0-1.7%]. This result is in concordance with previous screening results in NORM-VET in 2009 where no MRSA were detected among the 186 sampled horses, and in 2017 when MRSA CC398 *spa*-type t011 was detected from one of the 246 investigated horses (NORM/NORM-VET 2009). MRSA CC398 spa-type t011 is associated with MRSA findings in horses as well as other animals, including pigs. It has previously been detected from clinical cases in horses in several countries, including Norway.

Methicillin resistant *Staphylococcus aureus* (MRSA) in pig in Norway in 2021

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 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. Further details can be found in the annual reports (2-8). In 2021, a total of 763 herds were included, of which 73 were genetic nucleus or multiplier herds, 11 herds were central units of the sow pool herds, 27 were of the largest farrow to grower or farrow to finish herds, and the remaining 652 were fattening herds. 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 2021" (9).

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 19 shows the number of herds identified by the MRSA surveillance programme and the total number of detected MRSA positive herds from 2014-2020, 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 (10).

TABLE 19. Pig herds positive for methicillin resistant *Staphylococcus aureus* 2014-2021. Table shows total number of MRSA positive herds detected by the MRSA surveillance programme, total number of MRSA positive herds, as well as results from the MRSA typing.

Year	No. MRSA positive herds detected by the MRSA surveillance programme (Total No. positive herds)	Herds investigated in the MRSA surveillance programme	MRSA typing* (No. isolates)
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	
Total	84 (9)		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.

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INDICATOR BACTERIA FROM FOOD

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

In 2021, food samples included beef and pork. 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 in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2021. Sampling, laboratory methods and data processing are described in Appendix 3.

MEAT

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

In total, 313 beef and 312 pork 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 Figure 51.

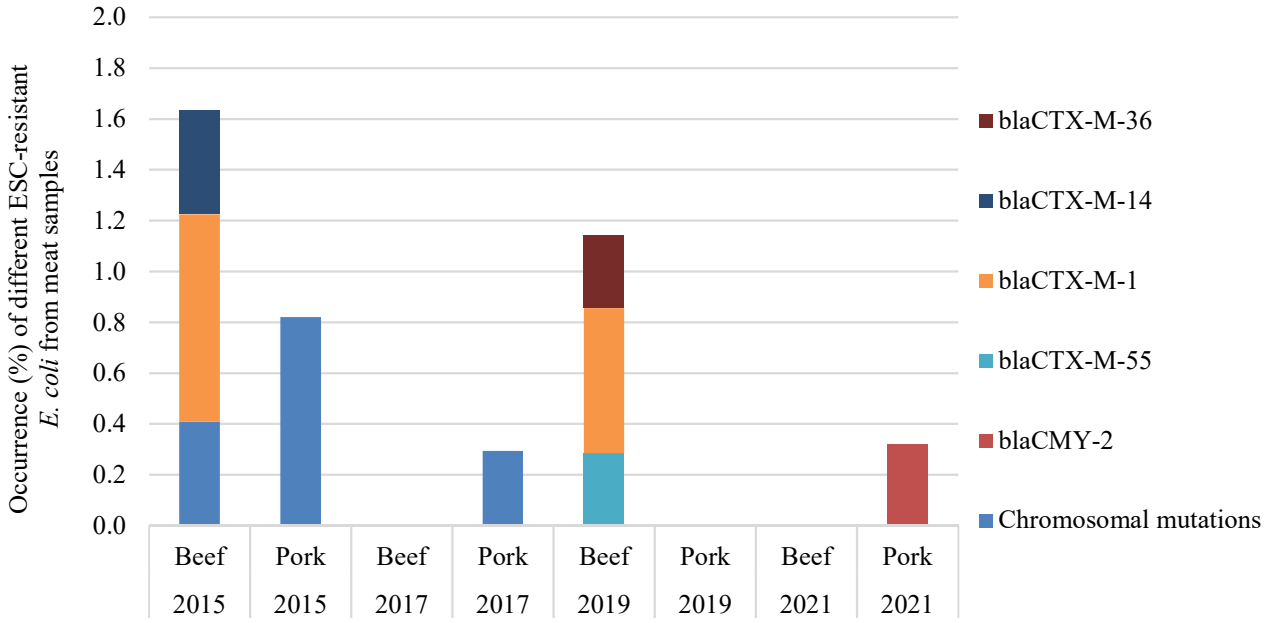

FIGURE 51. Occurrence of ESC-resistant *Escherichia coli* isolates from beef and pork from 2015-2021.

RESULTS AND COMMENTS

ESC-resistant *E. coli* was detected in one of the 312 pork samples (0.3% [95% CI: 0.0 – 1.8). The isolate displayed an AmpC phenotype and the resistance gene responsible was bla_{CMY-2}. ESC-resistant *E. coli* were not found in any of the beef samples (0% [95% CI: 0.0 – 1.2]). This is in concordance with previous NORM-VET results from 2019 where *E. coli* resistant to ESC were not detected in any of the pork samples, and in 0.9% of the beef samples (NORM/NORM-VET 2019).

In a European perspective, the occurrence of *E. coli* resistant to ESC in Norwegian beef and pork are among the lowest reported to EFSA (EFSA and ECDC Summary Report 2019–2020).

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

Carbapenemase-producing *Enterobacterales* from beef and pork

A total of 313 beef and 312 pork samples were examined for the presence of carbapenemase-producing *Enterobacterales* (CPE). No CPE were detected (beef: [95% CI: 0.0 – 1.2] and pork: [95% CI: 0.0 – 1.2]). This is in concordance with the results from 2019 where no CPE 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. One isolate of each serovar per incident was included for susceptibility testing.

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 2021 included those that were detected in these Salmonella surveillance programmes and the surveillance of wild boars, as well as isolates obtained from submissions to the National Reference Laboratory for Salmonella and from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). In addition, detection of *Salmonella* spp. was performed on the samples collected with regard to Commission Implementing Decision 2020/1729/EU, i.e. on a total of 301 caecal samples from cattle less than one year and 324 caecal samples from fattening pigs. The data are presented in Tables 20-21, and in the text.

TABLE 20. Antimicrobial resistance in *Salmonella* spp. (n=25) from animals (one poultry, one pig, two cattle, one horse, one sheep, three dogs, five cats and eleven wild boars); *S.* Typhimurium (n=10) and other *Salmonella* spp. (n=15) in 2021.

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	0								25								
Tigecycline	ND					19	6										
Chloramphenicol	0										25						
Ampicillin	0							8	17								
Cefotaxime	0					25											
Ceftazidime	0					16	9										
Meropenem	0		16	9													
Trimethoprim	0					21	4										
Sulfamethoxazole	ND										4	10	10	1			
Azithromycin	0									6	19						
Gentamicin	0						24	1									
Amikacin	0									25							
Ciprofloxacin	1	10	14				1										
Nalidixic acid	1									23	1	1					
Colistin	ND							18	5	2							

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

TABLE 21. Antimicrobial resistance in *Salmonella* spp. from non-domestic meat (n=15), *S.* Typhimurium (n=5), other *Salmonella* spp. (n=10) in 2021.

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	2								13			2					
Tigecycline	ND					5	7	1	2								
Chloramphenicol	2										11	2			2		
Ampicillin	3							3	9					3			
Cefotaxime	0					14	1										
Ceftazidime	0					8	7										
Meropenem	0		13	2													
Trimethoprim	2					12	1						2				
Sulfamethoxazole	ND										3	9					3
Azithromycin	0									1	12	2					
Gentamicin	0						14	1									
Amikacin	0									15							
Ciprofloxacin	0	3	12														
Nalidixic acid	0									14	1						
Colistin	ND							13	1	1							

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

RESULTS AND COMMENTS

In total, 25 *Salmonella* spp. isolates from animals isolated through the Salmonella surveillance programme, the surveillance of wild boars, or from clinical submissions or necropsies were susceptibility tested. None of the samples collected with regard to 2020/1729/EU were positive for *Salmonella* spp. ([95% CI cattle: 0.0 – 1.2], [95% CI pigs: 0.0 – 1.1]). Additionally, 15 *Salmonella* spp. isolates from non-domestic meat obtained from submissions to the National Reference Laboratory for Salmonella were susceptibility tested.

The animal isolates included one each from poultry, horse, pig and sheep, two from cattle, three from dogs, five from cats and eleven from wild boars. Ten isolates were of *S.* Typhimurium, nine were of *S. enterica* subsp. *diarizonae* three isolates were of *S.* Enteritidis, one of *S.* Derby, one of *S.* Newport, and one of *S.* Hessarek. With the exception of resistance to quinolones, the isolates were fully susceptible to all tested antimicrobial agents included in the panel.

The 15 food isolates included originated from non-domestic meat. Five isolates were of *S.* Typhimurium whereof two were monophasic (4,[5],12:i:-), while four isolates were of *S.* Enteritidis, two of *S.* Derby, one of *S.* Muenster, two of *S. enterica* subsp. *diarizonae* serovar 61:k:1,5,7 and one of *S. enterica* subsp. *salamae* serovar 55:k:z39. The majority of the isolates were fully susceptible to all tested antimicrobial agents included in the panel, and only one *S.* Typhimurium isolate was multiresistant.

Salmonella from human clinical specimens

In 2021, 390 human cases of nontyphoidal salmonellosis and 6 cases of typhoid fever were notified to the Norwegian Surveillance System for Communicable Disease (MSIS). The majority of these cases were domestically acquired (64%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 344 *Salmonella* isolates from primary diagnostic laboratories in Norway. 81 isolates were linked to 10 clusters/outbreaks. 273 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 235 isolates received before December 2021, including 91% of *Salmonella* Typhimurium, all *Salmonella* Typhi, one *Salmonella* Paratyphi A isolate, and based on information at the point of reception, 92% of other non-travel associated *Salmonella* isolates. In addition, antimicrobial susceptibility was performed on all *Salmonella* isolates recovered from blood cultures. Information on place of acquisition was completed and updated for all isolates by data provided to MSIS (Table 22). All isolates were susceptibility tested against six antibiotic classes: penicillins (ampicillin), extended spectrum cephalosporins (cefotaxime and ceftazidime), carbapenems (meropenem), fluoroquinolones (ciprofloxacin/pefloxacin), phenicols (chlorampenicol) and tetracyclines (tetracycline).

TABLE 22. Number of *Salmonella* isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2021, by serovar and place of acquisition.

Salmonella serovars	No. of isolates tested in 2021		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. Typhimurium	36	38	20	21	4	4	12	13
S. Typhimurium monophasic (4,[5],12:i-)	16	19	10	13	1	1	5	5
S. Enteritidis	46	61	30	32	9	21	7	8
S. Typhi	6	6	-	-	4	4	2	2
S. Paratyphi A	1	2	-	-	-	-	1	2
Other *Salmonella*	130	147	90	98	8	17	32	32
Total	**235**	**273**	**150**	**164**	**26**	**47**	**59**	**62**

A total of 27 isolates were recovered form blood cultures representing 8% of all *Salmonella* isolates tested to NRL including 6 *S.* Typhi, 1 *S.* Paratyphi A, 5 of the 46 *S.* Enteritidis (10.9%), 2 of the 36 *S.* Typhimurium (5.6%), and the rest from other *Salmonella* species (n=13, 10.0%).

The results from the antimicrobial susceptibility testing and genomic resistance screening for *Salmonella* isolates are presented in Tables 23-37, Figures 52-63 and in the related text.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHIMURIUM

TABLE 23. Percentage distributions of antimicrobial susceptibility categories of domestically acquired *Salmonella* Typhimurium (n=20) from human clinical specimens in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	80.0	-	20.0
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
Pefloxacin[1]	≥ 24 mm	< 24 mm	90.0	-	10.0
Tetracycline[2]	≥ 17 mm	< 17 mm	80.0	-	20.0
Chloramphenicol	≤ 8	> 8	90.0	-	10.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. [1]Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.12.0).[2]Breakpoints according to national zone distributions.

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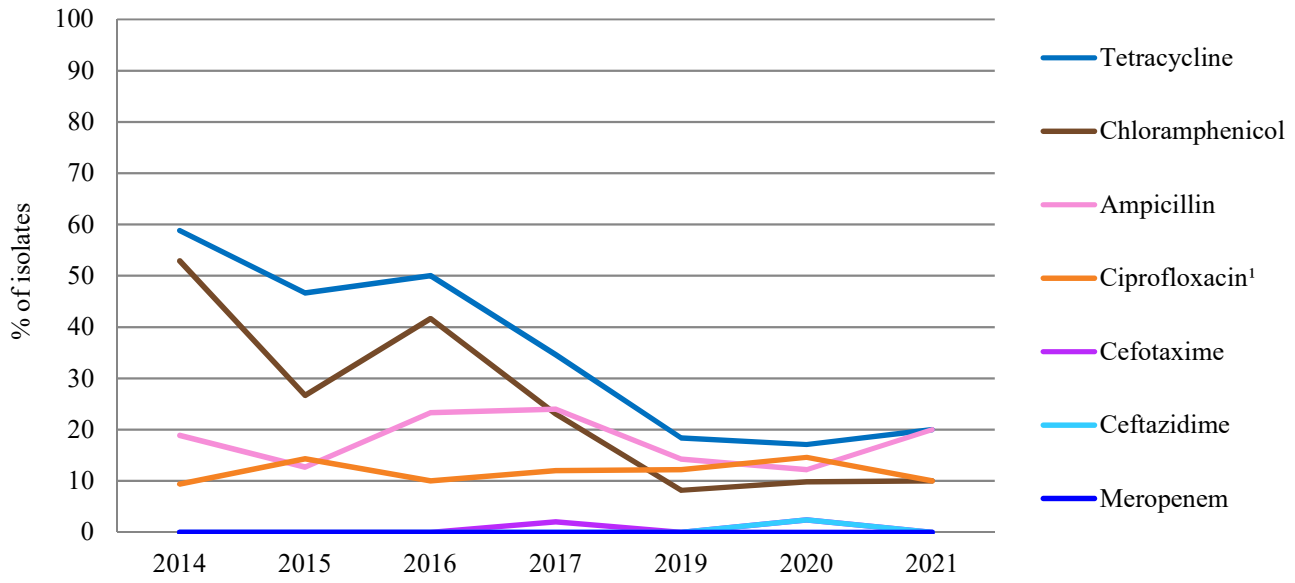

FIGURE 52. Trend 2014-2021. Percentage of domestically acquired *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway.[1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 24. Percentage distributions of predicted genotypic resistance in domestically acquired *Salmonella* Typhimurium (n=21) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	≤ 16	> 16	85.7	14.3
Ampicillin	≤ 4	> 4	81.0	19.0
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	90.5	9.5
Ciprofloxacin	≤ 0.064	> 0.064	95.2	4.8
Sulfonamide	-	-	90.5	9.5
Tetracycline	≤ 8	> 8	85.7	14.3
Trimethoprim	≤ 2	> 2	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

TABLE 25. Percentage distributions of antimicrobial susceptibility categories of travel associated *Salmonella* Typhimurium (n=4) from human clinical specimens in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	50.0	-	50.0
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
Pefloxacin[1]	≥ 24 mm	< 24 mm	100.0	-	0.0
Tetracycline[2]	≥ 17 mm	< 17 mm	75.0	-	25.0
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.12.0).[2]Breakpoints according to national zone distributions.

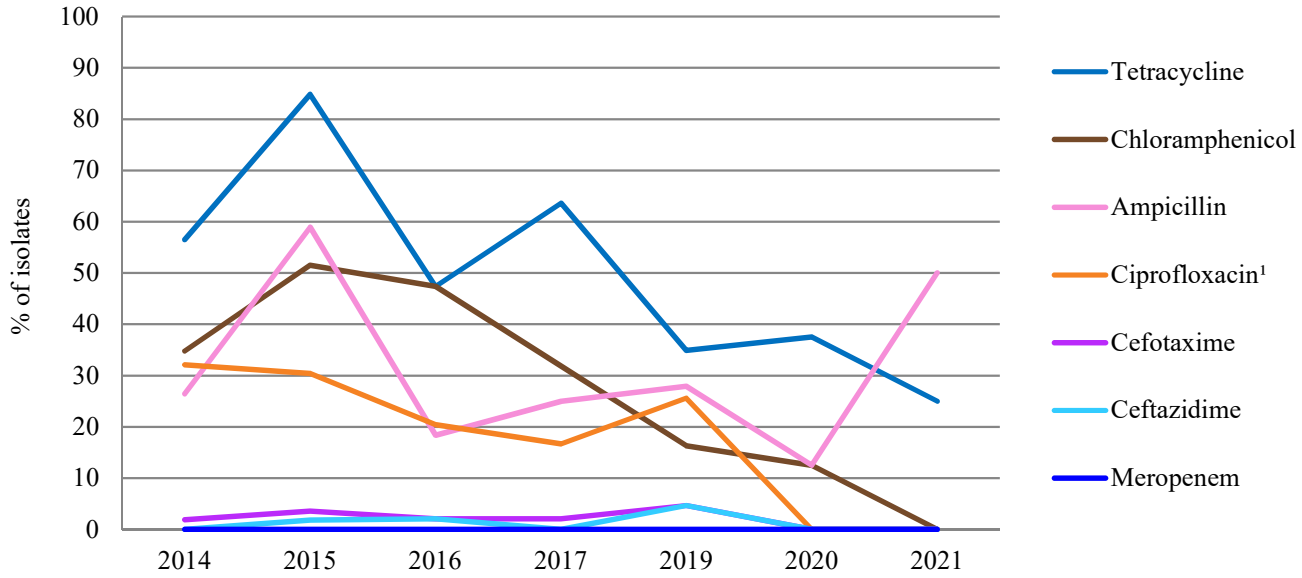

FIGURE 53. Trend 2014-2021. Percentage of travel associated *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 26. Percentage distributions of predicted genotypic resistance in domestically acquired *Salmonella* Typhimurium (n=4) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	≤ 16	> 16	75.0	25.0
Ampicillin	≤ 4	> 4	50.0	50.0
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	100.0	0.0
Ciprofloxacin	≤ 0.064	> 0.064	100.0	0.0
Sulfonamide	-	-	75.0	25.0
Tetracycline	≤ 8	> 8	75.0	25.0
Trimethoprim	≤ 2	> 2	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

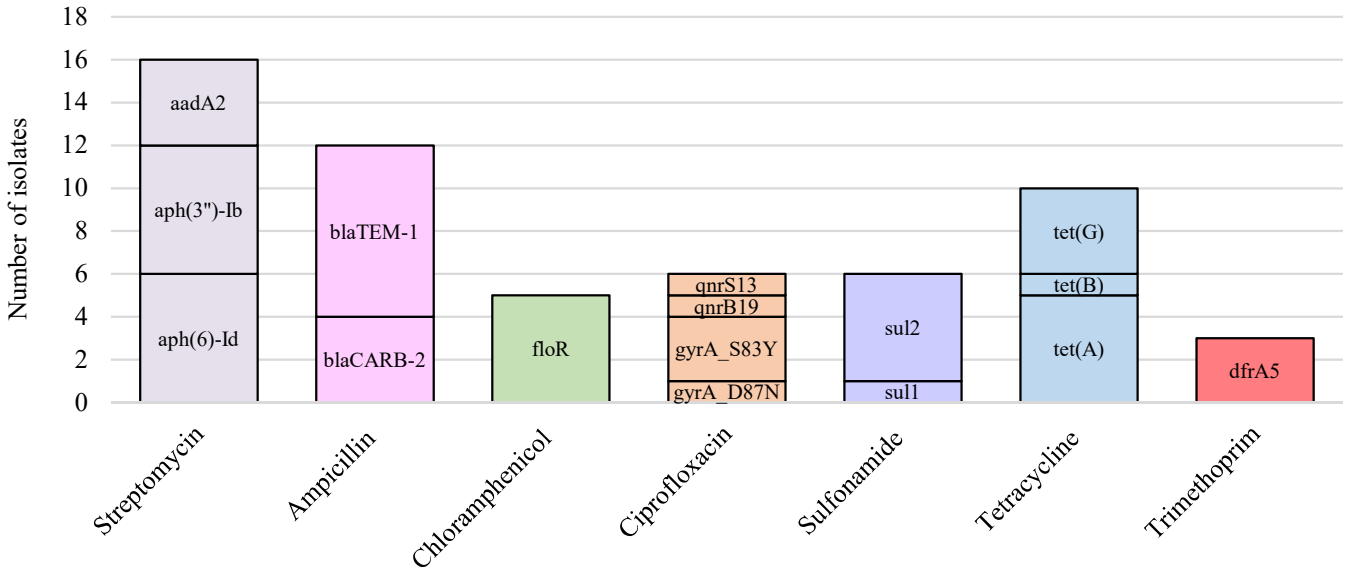

FIGURE 54. Identified resistance determinants in genotypic resistant *Salmonella* Typhimurium to selected antimicrobial agents in Norway 2021.

ANTIMICROBIAL RESISTANCE IN MONOPHASIC SALMONELLA TYPHIMURIUM

TABLE 27. Percentage distributions of antimicrobial susceptibility categories of domestically acquired monophasic *Salmonella* Typhimurium (n=10) from human clinical specimens in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	20.0	-	80.0
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
Pefloxacin[1]	≥ 24 mm	< 24 mm	100.0	-	0.0
Tetracycline[2]	≥ 17 mm	< 17 mm	20.0	-	80.0
Chloramphenicol	≤ 8	> 8	80.0	-	20.0

[1] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. Susceptibility to ciprofloxacin is inferred from pefloxacin disk diffusion according to EUCAST clinical breakpoints (v.12.0).[2]Breakpoints according to national zone distributions.

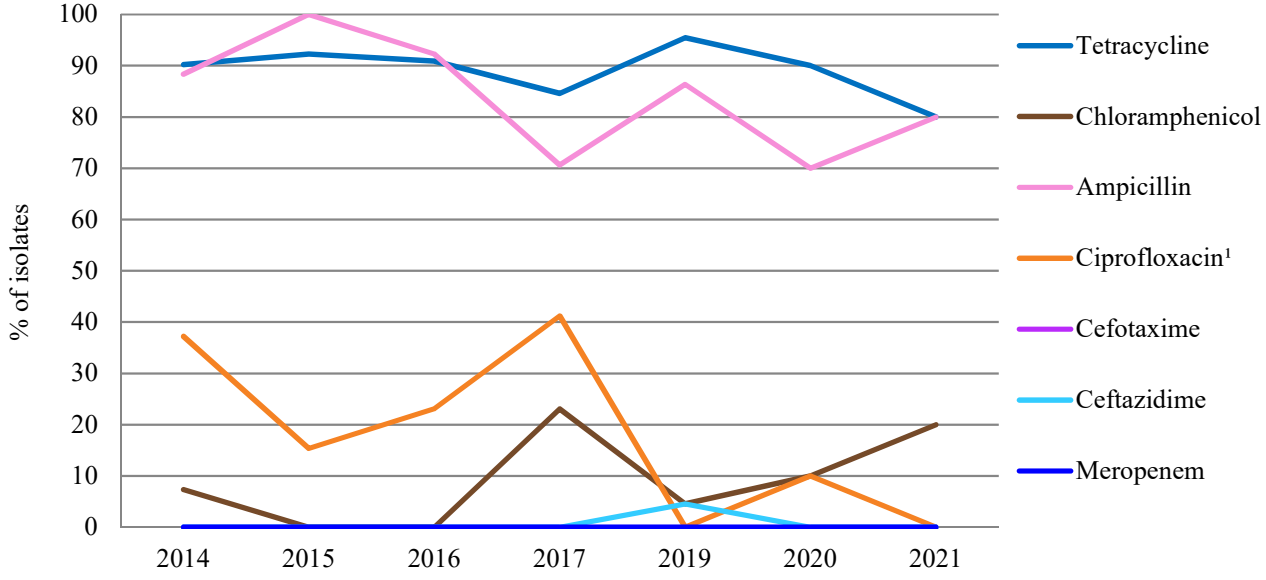

FIGURE 55. Trend 2014-2021. Percentage of domestically acquired monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway. [1] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 28. Percentage distributions of predicted genotypic resistance in domestically acquired monophasic *Salmonella* Typhimurium (n=13) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	92.3	7.7
Streptomycin	≤ 16	> 16	15.4	84.6
Ampicillin	≤ 4	> 4	15.4	84.6
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	84.6	15.4
Ciprofloxacin	≤ 0.064	> 0.064	100.0	0.0
Sulfonamide	-	-	30.8	69.2
Tetracycline	≤ 8	> 8	15.4	84.6
Trimethoprim	≤ 2	> 2	84.6	15.4

[1] Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

TABLE 29. Percentage distributions of antimicrobial susceptibility categories of travel associated monophasic *Salmonella* Typhimurium (n=1) from human clinical specimens in Norway 2021.

	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
Pefloxacin[1]	≥ 24 mm	< 24 mm	100.0	-	0.0
Tetracycline[2]	≥ 17 mm	< 17 mm	0.0	-	100.0
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.12.0). [2]Breakpoints according to national zone distributions.

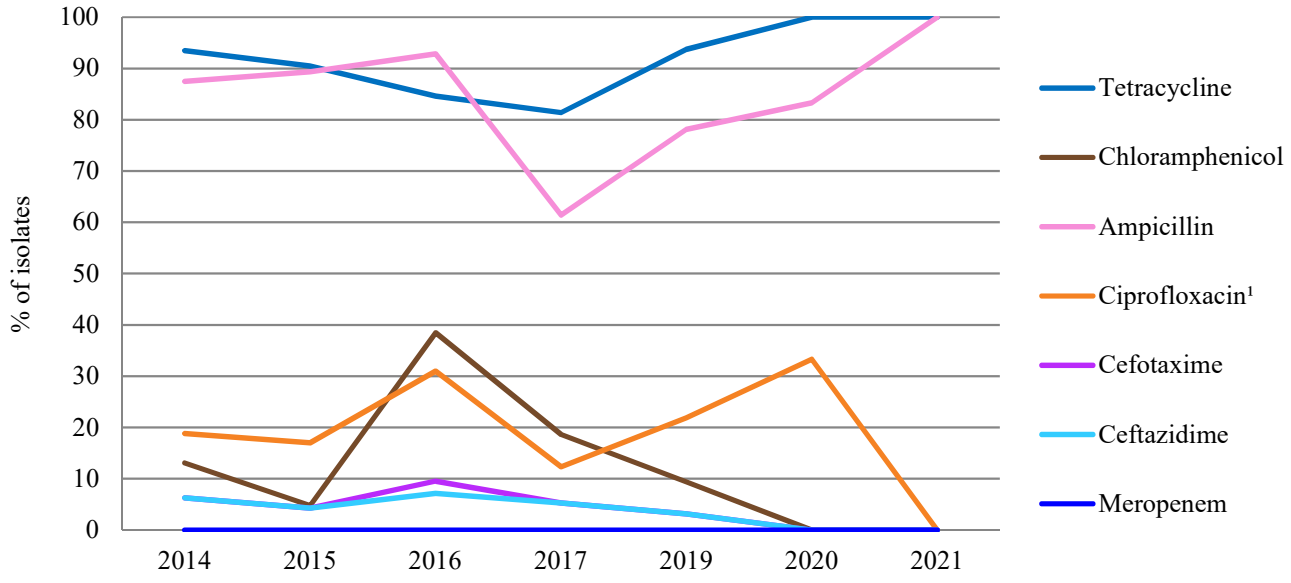

FIGURE 56. Trend 2014-2021. Percentage of travel associated monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 30. Percentage distributions of predicted genotypic resistance in travel associated monophasic *Salmonella* Typhimurium (n=1) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	≤ 16	> 16	0.0	100.0
Ampicillin	≤ 4	> 4	0.0	100.0
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	100.0	0.0
Ciprofloxacin	≤ 0.064	> 0.064	100.0	0.0
Sulfonamide	-	-	0.0	100.0
Tetracycline	≤ 8	> 8	0.0	100.0
Trimethoprim	≤ 2	> 2	100.0	0.0

[1] Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

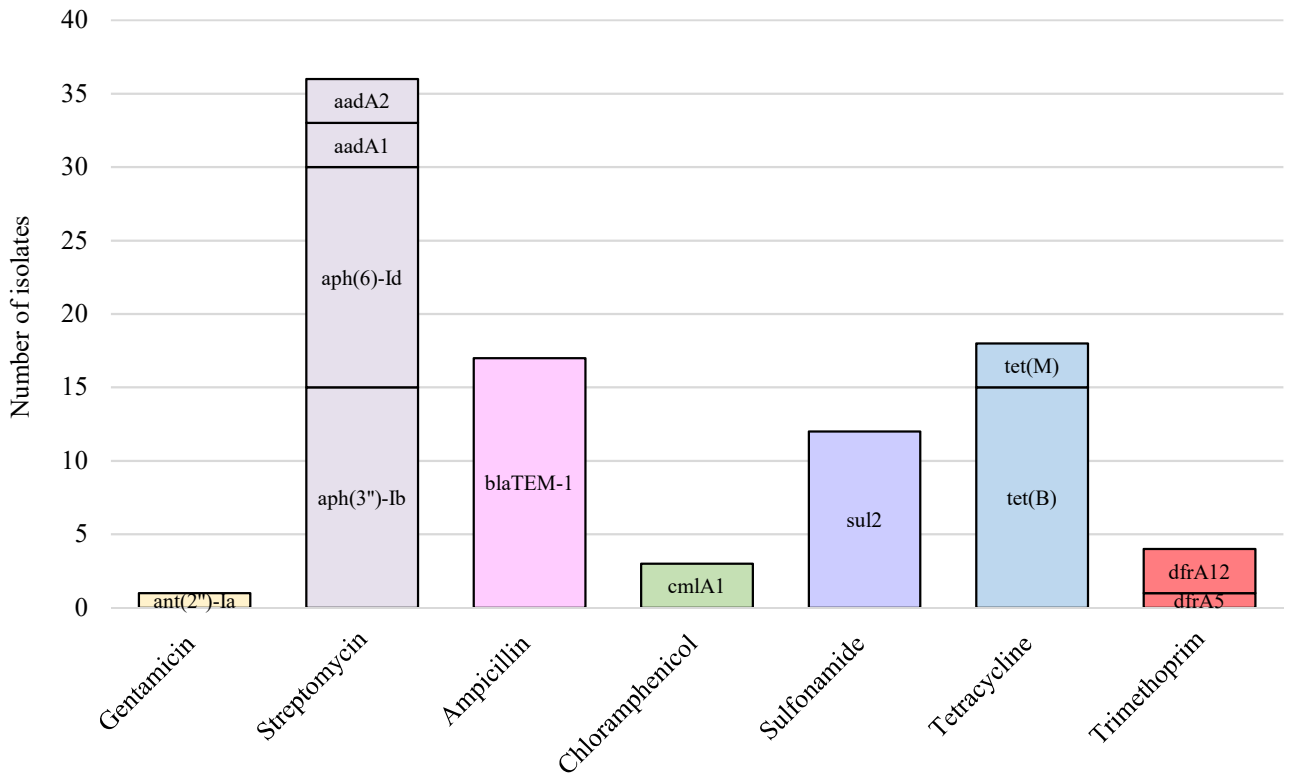

FIGURE 57. Identified resistance determinants in genotypic resistant monophasic *Salmonella* Typhimurium (n=19) to selected antimicrobial agents in Norway 2021.

ANTIMICROBIAL RESISTANCE IN SALMONELLA ENTERITIDIS

TABLE 31. Percentage distributions of antimicrobial susceptibility categories of *Salmonella* Enteritidis (n=46) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	97.8	-	2.2
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	78.3	-	21.7
Tetracycline[2]	≥ 17 mm	< 17 mm	97.8	-	2.2
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.12.0). [2]Breakpoints according to national zone distributions.

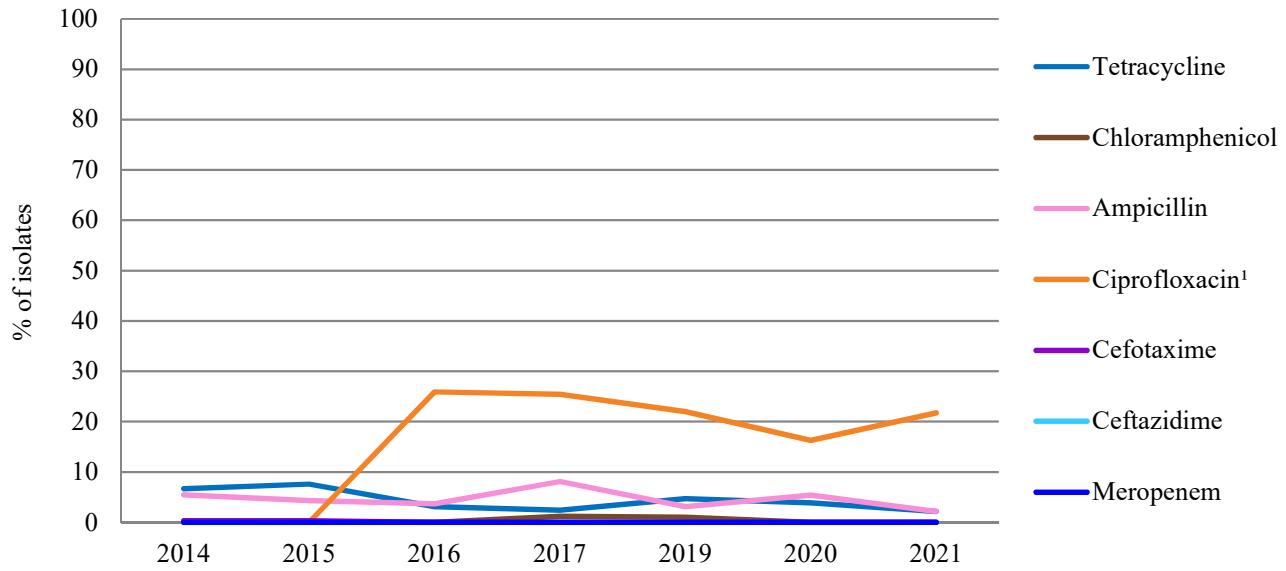

FIGURE 58. Trend 2014-2021. Percentage of *Salmonella* Enteritidis resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 32. Percentage distributions of predicted genotypic resistance in *Salmonella* Enteritidis (n=61) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	≤ 16	> 16	100.0	0.0
Ampicillin	≤ 4	> 4	98.4	1.6
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	100.0	0.0
Ciprofloxacin	≤ 0.064	> 0.064	78.7	21.3
Sulfonamide	-	-	100.0	0.0
Tetracycline	≤ 8	> 8	98.4	1.6
Trimethoprim	≤ 2	> 2	100.0	0.0

[1] Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

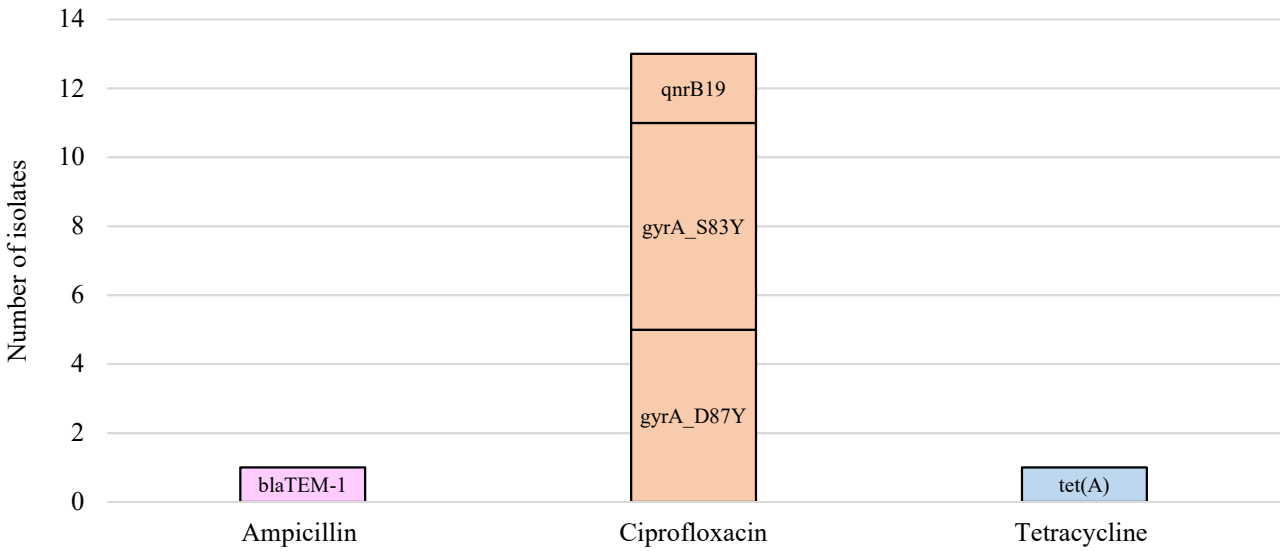

FIGURE 59. Identified resistance determinants in genotypic resistant *Salmonella* Enteritidis (n=61) to selected antimicrobial agents in Norway 2021.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHI

TABLE 33. Percentage distributions of antimicrobial susceptibility categories of *Salmonella* Typhi (n=6) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	33.3	-	66.7
Cefotaxime	≤ 1	> 2	66.7	0.0	33.3
Ceftazidime	≤ 1	> 4	66.7	0.0	33.3
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	100.0	-	0.0
Chloramphenicol	≤ 8	> 8	33.3	-	66.7

[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.12.0). [2] Breakpoints according to national zone distributions.

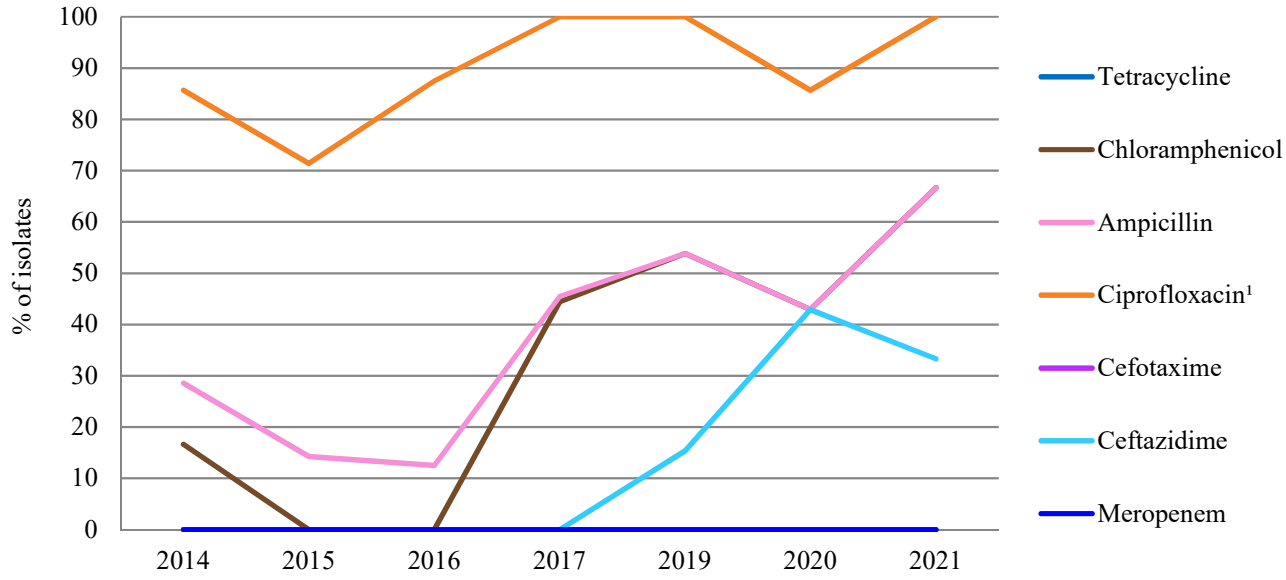

FIGURE 60. Trend 2014-2021. Percentage of *Salmonella* Typhi resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 34. Percentage distributions of predicted genotypic resistance in *Salmonella* Typhi (n=6) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	≤ 16	> 16	33.3	66.7
Ampicillin	≤ 4	> 4	33.3	66.7
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	66.7	33.3
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	33.3	66.7
Ciprofloxacin	≤ 0.064	> 0.064	0.0	100.0
Sulfonamide	-	-	33.3	66.7
Tetracycline	≤ 8	> 8	100.0	0.0
Trimethoprim	≤ 2	> 2	33.3	66.7

[1] Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin

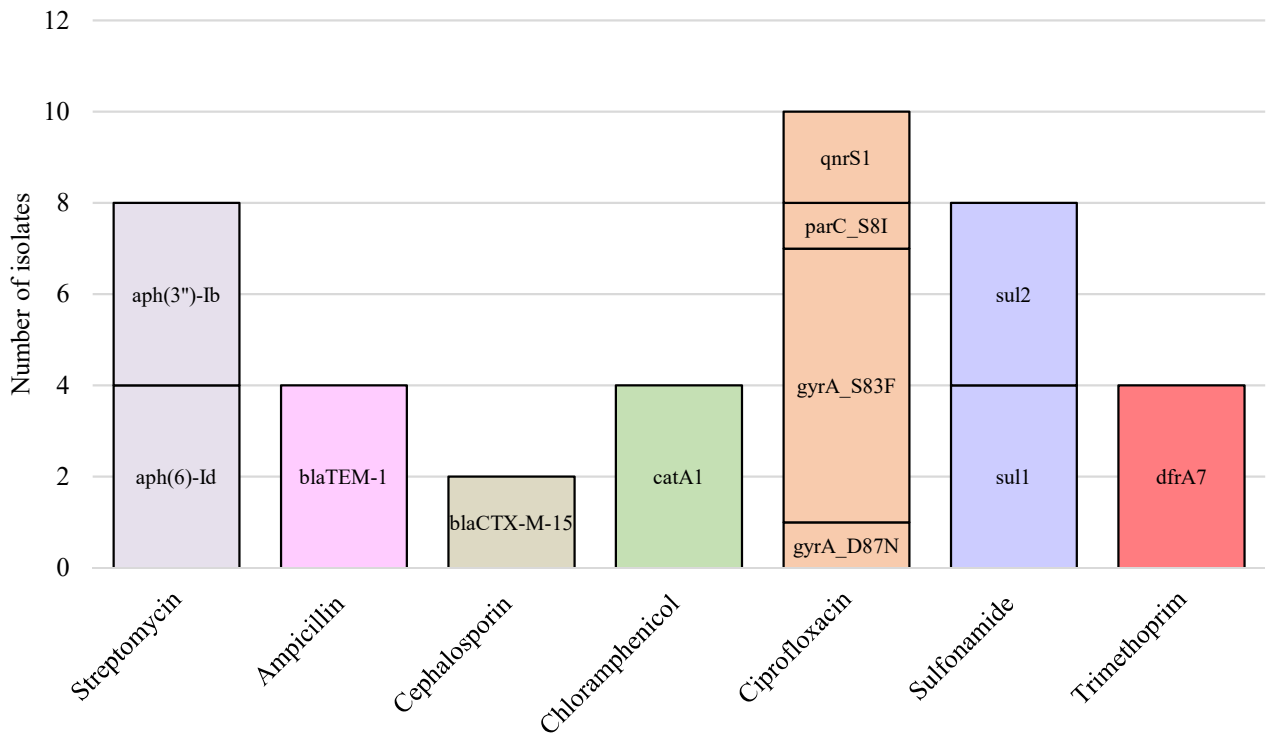

FIGURE 61. Identified resistance determinants in genotypic resistant *Salmonella* Typhi (n=6) to selected antimicrobial agents in Norway 2021.

ANITMICROBIAL RESISTANCE IN OTHER SALMONELLA SEROTYPES

TABLE 35. Percentage distributions of predicted genotypic resistance in other *Salmonella* serotypes (n=147) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	98.0	2.0
Streptomycin	≤ 16	> 16	94.6	5.4
Ampicillin	≤ 4	> 4	93.9	6.1
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Cefotaxime[2]	≤ 0.5	> 0.5	99.3	0.7
Ceftazidime[2]	≤ 2	> 2		
Colistin[3]	≤ 16	> 16	100.0	0.0
Chloramphenicol	≤ 16	> 16	98.0	2.0
Ciprofloxacin	≤ 0.064	> 0.064	91.2	8.8
Sulfonamide	-	-	95.9	4.1
Tetracycline	≤ 8	> 8	95.2	4.8
Trimethoprim	≤ 2	> 2	95.9	4.1

[1] Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins. [3]ECOFF for colistin given for *Salmonella* Dublin.

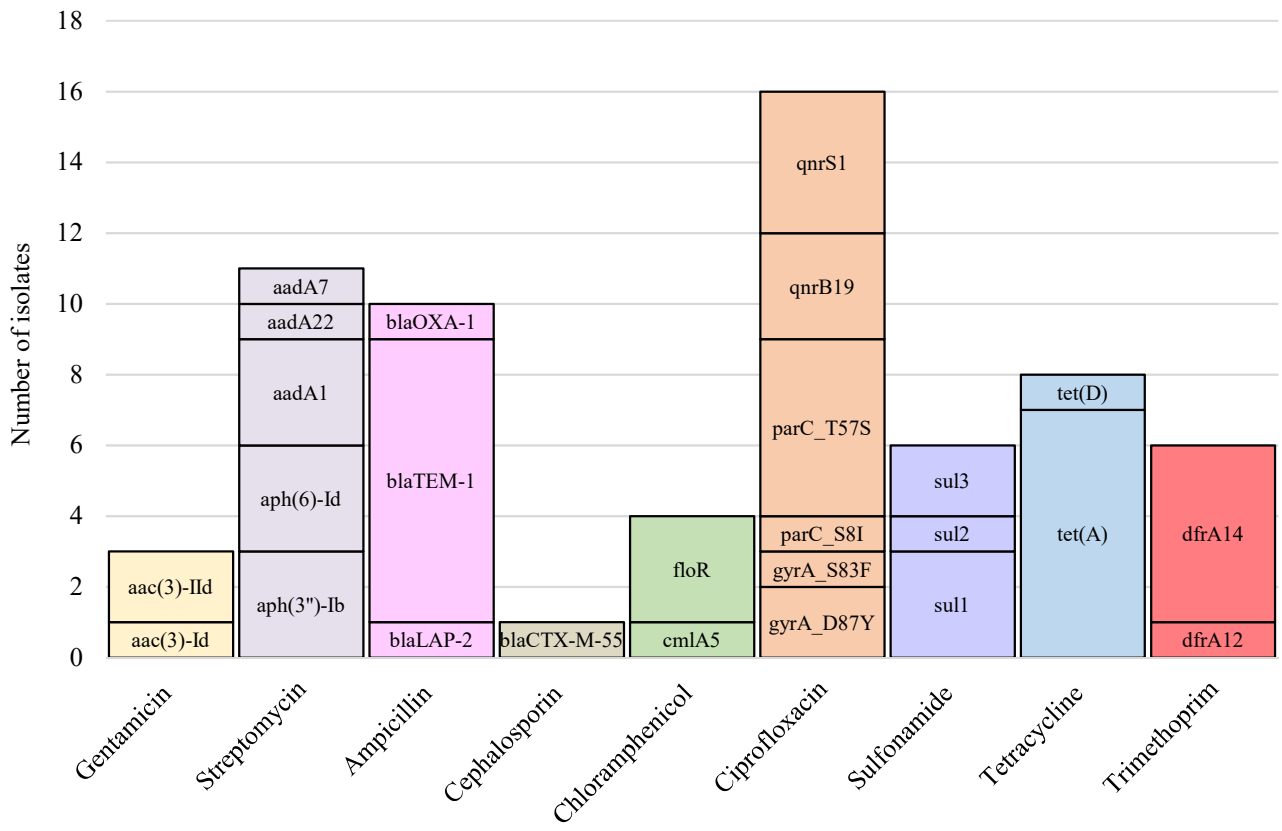

FIGURE 62. Identified resistance determinants in genotypic resistant in other *Salmonella* serotypes (n=147) to selected antimicrobial agents in Norway 2021.

MULTI-DRUG RESISTANCE IN SALMONELLA

TABLE 36. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates identified in Norway 2021, 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	15	15	15	-	3	-	12	14	3
Salmonella Typhimurium	10	10	9	-	4	4	4	-	4
Salmonella Typhi	4	4	4	2	4	4	4	-	4
Salmonella Enteritidis	1	-	1	-	-	1	-	1	-
Other *Salmonella*	7	7	5	1	3	5	6	6	6
Total no. of MDR isolates	**37**	**36**	**34**	**3**	**14**	**14**	**26**	**21**	**17**

[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.

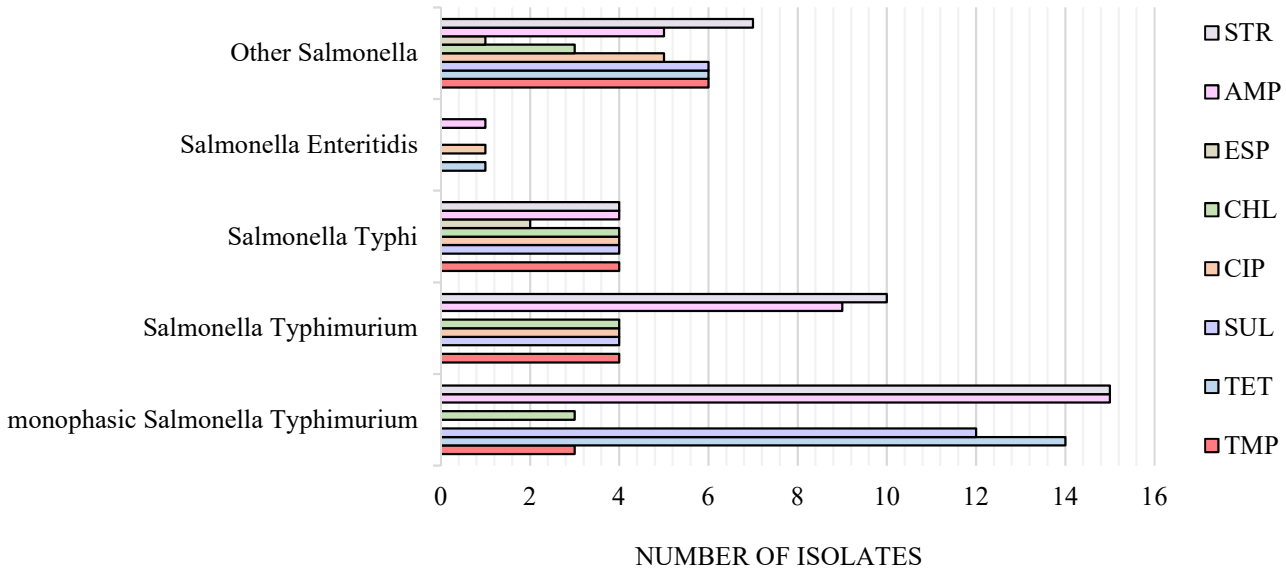

FIGURE 63. Number of predicted genotypic multi-drug resistant (MDR) *Salmonella* isolates (n=37) identified in Norway 2021, stratified according to serotype and resistance to different antibiotic categories; STR: Streptomycin, AMP; Ampicillin, ESP; Extended Spectrum Cephalosporin, CHL; Chloramphenicol, CIP; Ciprofloxacin, SUL; Sulfonamide, TET; Tetracycline, TMP; Trimethoprim.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN SALMONELLA

TABLE 37. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Salmonella* isolates identified in Norway 2021.

Antibiotic categories	Tested	Phenotype WT[1]		Phenotype NWT[1]		Sensitivity (%)	Spesificity (%)
		Genotype R	Genotype S	Genotype R	Genotype S		
Penicillins	235	-	196	39	-	100.0	100.0
Extended spectrum cephalosporins[2]	235	-	232	3	-	100.0	100.0
Carbapenems	235	-	233	-	2	-	99.1
Fluoroquinolones	235	2	191	32	10	94.1	95.0
Tetracycline	235	-	204	27	4	100.0	98.1
Phenicols	235	-	218	15	2	100.0	99.1

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Salmonella enterica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins.

RESULTS AND COMMENTS

The NRL annually performed antimicrobial susceptibility testing for a selection of the received *Salmonella* isolates. Selection criteria are set to ensure inclusion of the most important *Salmonella* serovars and important antibiotics for the monitoring of emergence and dissemination of antimicrobial resistance in Norway. Additionally, 2020 onwards the NRL has screened all *Salmonella* isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance. In 2020 and 2021, during the Covid-19 pandemic, infection control measures including travel restrictions were enforced, which critically reduced the number of travel associated *Salmonella* infections. Trends in antibiotic resistance must be interpreted accordingly.

A total of 10 outbreak clusters were identified in 2021: *S.* Blockley (n=12), *S.* Braenderup (n=5), *S.* Dublin (n=6), *S.* Mikawasima (n=5), *S.* Montevideo (n=4), *S.* Paratyphi B (n=3), and *S.* Typhimurium (n=2). Only a single isolate from each of these clusters are presented in the antimicrobial resistance results.

Overall resistance in *S.* Typhimurium was generally higher in strains associated with travel compared to domestically acquired infections. A stable trend in resistance to ampicillin, tetracycline, ciprofloxacin, chloramphenicol, and extended spectrum cephalosporins was seen in strains from domestically acquired infections. Only 4 out of 38 recovered *S.* Typhimurium isolates were associated with travel, and trend analysis was not possible due to the low number of isolates. The resistance determinants *qnr* and mutations in *gyrA* were identified as mediators for the observed ciprofloxacin resistance. No ESBL producing isolates were identified. An MDR genotype was identified for 26% (10/38) of the isolates, largely attributed to resistance against streptomycin, ampicillin, and tetracycline.

For the monophasic variant of *S.* Typhimurium, the overall resistance level was higher than for *S.* Typhimurium. We observed stable resistance levels over the last five years for all tested antibiotics. High resistance levels were seen for ampicillin and tetracycline in both domestically acquired, and travel associated strains. No ESBL producing isolates were identified. An MDR genotype was identified for 79% (15/19) of the isolates, largely attributed to resistance against streptomycin, ampicillin, and tetracycline.

Antibiotic resistance in *S.* Enteritidis is generally low and has been reported low over a long period. An apparent sudden emergence of ciprofloxacin resistance in 2016 was linked to the change in antibiotic used for screening fluoroquinolone resistance (from ciprofloxacin to pefloxacin). Screening for genotypic resistance confirms the presence of mutations in *gyrA* as well as presence of *qnr* mediated resistance to ciprofloxacin. No ESBL producing isolates were identified. An MDR genotype was identified in a single isolate (1/61), attributed to resistance against ampicillin, ciprofloxacin, and tetracycline.

The overall level 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 genotyped with $bla_{\text{CTX-M-15}}$. MDR was a characteristic feature of a considerable proportion of the *S.* Typhi isolates (4/6, 66.7%). 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=147), the most common serotypes identified were *S.* Newport (n=23), *S.* Mikawasima (n=6) and *S.* Montevideo (n=5). Overall predicted genotypic resistance was low for all antibiotics. One ESBL producing isolate was identified, serotyped *S.* Newport, and genotyped as $bla_{\text{CTX-M-55}}$. An MDR genotype in other *Salmonella* serotypes was identified in 4.8% (7/147) of the isolates, two isolates serotyped as *S.* Agona, and a single isolate of each of the following serotypes: *S.* Newport, *S.* Muenchen, *S.* Virchow, *S.* Kentucky, and *S.* Virginia. MDR genotype was largely attributed to resistance towards streptomycin, ampicillin, ciprofloxacin, sulfonamide, tetracycline and trimethoprim.

In total, three isolates were predicted as genotypically resistant to extended spectrum cephalosporins: *S.* Typhi (n=2) and *S.* Newport (n=1), mediated by $bla_{\text{CTX-M-15}}$ (n=2) and $bla_{\text{CTX-M-55}}$ genes, respectively. The overall correlation between phenotypic resistance and predicted genotypic resistance was good, both sensitivity and specificity were above 94% for all tested antibiotics.

CAMPYLOBACTER SPP.

Campylobacter spp. from cattle and pig

Caecal samples from a total of 307 cattle less than one year and 326 fattening pigs were examined. *C. coli* isolates were obtained from none of the cattle samples and from 293 (89.9%) of the pig samples. Of these, 290 isolates were susceptibility tested. *C. jejuni* isolates were obtained from 136 (44.3%) of the cattle samples and 17 (5.2 %) of the pig samples. Of the cattle isolates, 127 were susceptibility tested. The results are presented in Tables 38-39, Figure 64, and in the text.

TABLE 38. Antimicrobial resistance in *Campylobacter coli* isolates from caecal samples of fattening pigs (n=290) in 2021.

Substance	Resistance (%)	[95% CI]	Distribution (%) of MIC values (mg/L)*														
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	0.0	[0.0 – 1.3]				98.6	1.4										
Chloramphenicol	0.0	[0.0 – 1.3]						94.5	5.5								
Ertapenem	ND	ND		92.4	7.6												
Erythromycin	0.0	[0.0 – 1.3]					99.3	0.3	0.3								
Gentamicin	0.0	[0.0 – 1.3]			3.1	44.1	52.8										
Ciprofloxacin	18.3	[14.0 – 23.2]		81.4	0.3		0.3	0.7	6.9	10.3							

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

TABLE 39. Antimicrobial resistance in *Campylobacter jejuni* isolates from caecal samples of cattle less than one year (n=127) in 2021.

Substance	Resistance (%)	[95% CI]	Distribution (%) of MIC values (mg/L)*														
			0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	4.7	[1.8 – 10.0]				95.3							4.7				
Chloramphenicol	0.0	[0.0 – 2.9]						90.6	5.5	3.9							
Ertapenem	ND			88.2	4.7	4.7	2.4										
Erythromycin	0.0	[0.0 – 2.9]					100.0										
Gentamicin	0.0	[0.0 – 2.9]			17.3	76.4	6.3										
Ciprofloxacin	13.4	[8.0 – 20.6]		85.8	0.8		0.8			7.9	4.7						

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

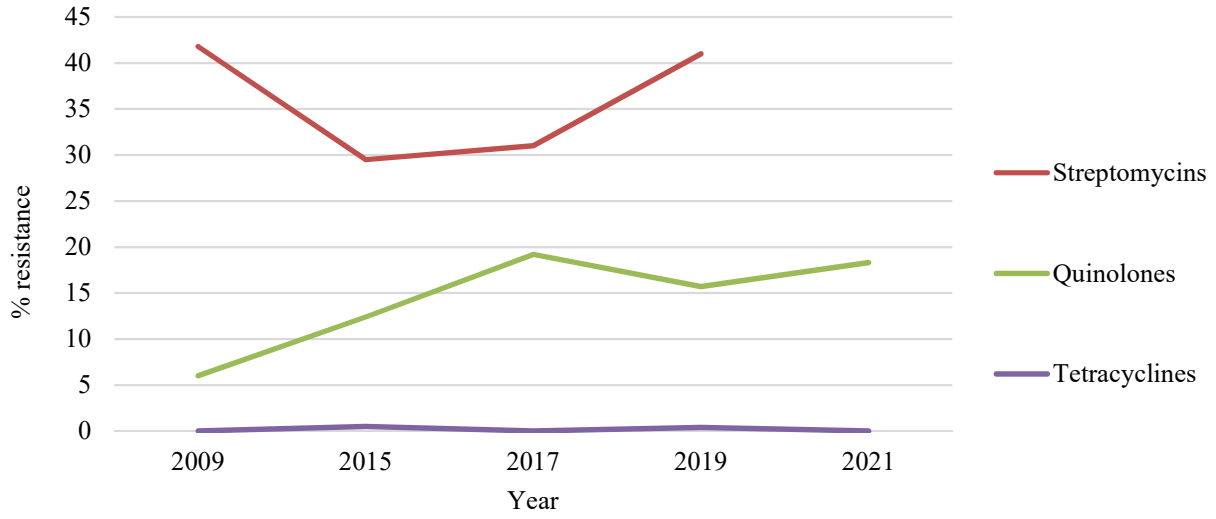

FIGURE 64. Prevalence of resistance to various antimicrobial classes in *Campylobacter coli* from pig faecal or caecal samples isolated between 2009-2021. The breakpoints used in NORM-VET 2021 were applied.

RESULTS AND COMMENTS

CATTLE

A total of 86.6% [95% CI: 79.4 – 92.0] of the *C. jejuni* isolates from cattle less than one year were fully susceptible to all antimicrobial agents included in the test panel. Altogether, 8.7% [95% CI: 4.4 – 15.0] were resistant to one antimicrobial class (quinolones) and 4.7% [95% CI: 1.8 – 10.0] to two of the antimicrobial classes (quinolones and tetracyclines). According to the EFSA classification described in Appendix 6, this corresponds to a moderate occurrence of resistance among *C. jejuni* from cattle.

C. jejuni from cattle has only been included once before; in 2010. However, due to differences in methodolgy as well as very low number of isolates in 2010, comparisons are difficult.

Resistance to the quinolone ciprofloxacin is the most common resistance observed in domestically acquired human clinical isolates from Norway, as well, with 14.4% of the 194 examined isolates (NORM/NORM-VET 2020). In the EFSA and ECDC Summary Report from 2019 and 2020, resistance to ciprofloxacin among *C. jejuni* from cattle was reported to be ~57%, though based on data from only four countries (EFSA and ECDC Summary Report 2019-2020). Among the human clinical isolates, ~61% were ciprofloxacin resistant. The results from Norway are lower than the results reported to EFSA and among the lowest reported to ECDC.

None of the cattle isolates showed reduced susceptibility to erythromycin. The occurrence of *Campylobacter* spp. isolates displaying combined resistance to ciprofloxacin and erythromycin is of great importance to public health, since both compounds are recognised as critically important antimicrobials for the treatment of *Campylobacter* infections in humans (WHO, 2019).

PIG

A total of 17 *C. jejuni* were isolated from fattening pigs, but only one of these isolates showed resistance to one of the antimicrobials included in the test panel, i.e. to ciprofloxacin.

A total of 81.7% of the *C. coli* isolates from fattening pigs were susceptible to all antimicrobial agents included in the test panel. Altogether, 18.3% were resistant to one of the antimicrobial classes tested, i.e. to ciprofloxacin. According to the EFSA classification described in Appendix 6, this corresponds to a moderate occurrence of resistance among *C. coli* from fattening pigs.

C. coli has previously been investigated in 2009, 2015, 2017, and 2019. There have, however, been changes to the antimicrobial test panel for *Campylobacter* spp., and thereby comparison to previous years has to be done with caution. Streptomycin is no longer part of the test panel, and streptomycin resistance has previously been common in *C. coli* isolates from pigs as shown in Figure 64. In 2019, 41% [95% CI: 34.8 – 47.4] of the isolates were streptomycin resistant. Streptomycin is rarely used in Norwegian pig production, and streptomycin resistance in *C. coli* is therefore difficult to explain.

The quinolone ciprofloxacin has been included in the test panel all these years, and as shown in Figure 64 there has been an increasing trend in resistance to quinolones, from 4.5% [95% CI: 1.2 – 13.4] in 2009 to 18.3% [95% CI: 14.0 – 23.2] being resistant to ciprofloxacin in 2021. Ciprofloxacin resistance has also been common in the examined human clinical isolates in Norway (NORM/ NORM-VET 2020). In the EFSA and ECDC Summary Report from 2019 and 2020, resistance to ciprofloxacin among *C. coli* is reported to be ~65% in human isolates and ~52% in isolates from pigs. The occurrence in fattening pigs varies, however, markedly between the reporting countries (EFSA and ECDC Summary Report 2019-2020).

The results from Norway are still among the lowest reported. This situation is most likely due to the rather limited use of antibiotics in the Norwegian pig production. None of the isolates showed reduced susceptibility to erythromycin. The occurrence of *Campylobacter* spp. isolates displaying combined resistance to ciprofloxacin and erythromycin is of great importance to public health, since both compounds are recognised as critically important antimicrobials for the treatment of *Campylobacter* infections in humans (WHO, 2019).

Campylobacter spp. from human clinical cases

In 2021, 2,055 human campylobacteriosis cases were notified to MSIS. The majority of cases 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.

Antimicrobial susceptibility testing was performed on a total of 296 *Campylobacter jejuni* and *Campylobacter coli* isolates received at NRL before December 2021 (Table 40) against four different antibiotic groups: macrolides (erythromycin), aminoglycosides (gentamicin), fluoro-quinolones (ciprofloxacin), and tetracycline. The results from the antimicrobial susceptibility testing are presented in Tables 41-43, Figures 65-67, and in the related text.

TABLE 40. Number of antimicrobial susceptibility tested *Campylobacter* spp. isolates recoved from human clinical specimens in Norway 2021, by species and place of acquisition.

Campylobacter spp.	No. of isolates tested in 2021	Place of acquistion		
		Norway	Abroad	Unknown
Campylobacter jejuni	291	166	25	100
Campylobacter coli	5	2	2	1
Total	**296**	**168**	**27**	**101**

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER JEJUNI

TABLE 41. Percentage distributions of antimicrobial susceptibility categories of domestically acquired *Campylobacter jejuni* (n=166) from human clinical specimens in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	91.6	-	8.4
Erythromycin	≤ 4	> 4	99.4	-	0.6
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.12.0, last accessed 02.07.22)

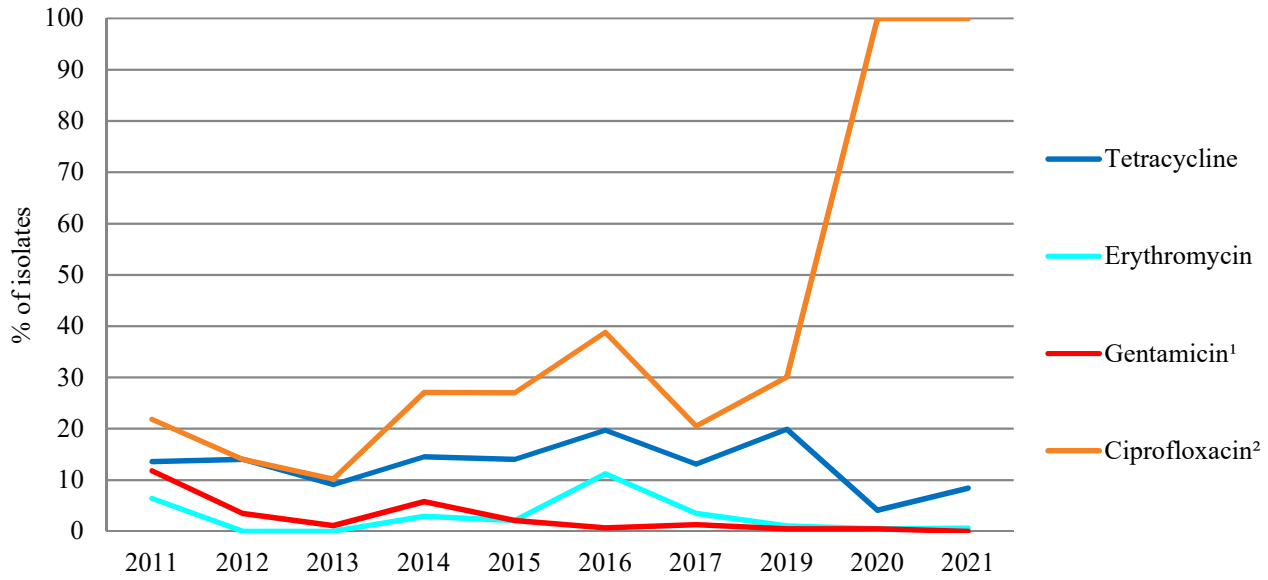

FIGURE 65. Trend 2011-2021. Percentage of domestically acquired *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.12.0, last accessed 02.07.22).

TABLE 42. Percentage distributions of antimicrobial susceptibility categories of travel associated *Campylobacter jejuni* (n=25) from human clinical specimens in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	44.0	-	56.0
Erythromycin	≤ 4	> 4	96.0	-	4.0
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.12.0, last accessed 02.07.22)

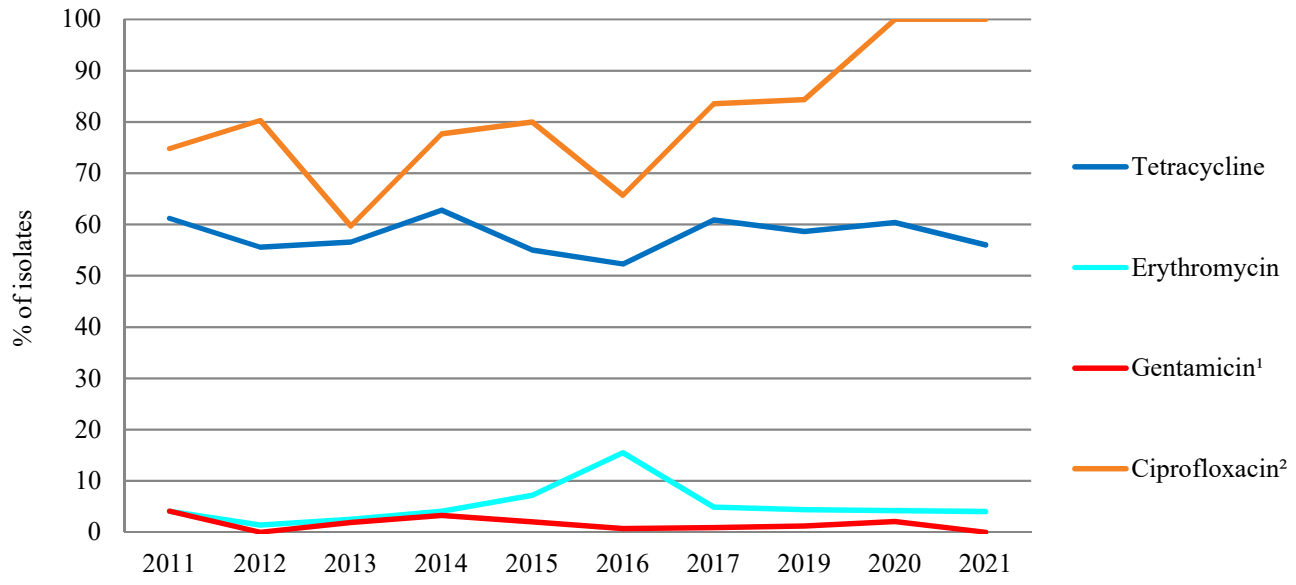

FIGURE 66. Trend 2011-2021. Percentage of travel associated *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted 2020 onwards according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.12.0, last accessed 02.07.22).

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER COLI

TABLE 43. Percentage distributions of antimicrobial susceptibility categories of *Campylobacter coli* (n=5) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	40.0	-	60.0
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.12.0, last accessed 02.07.22).

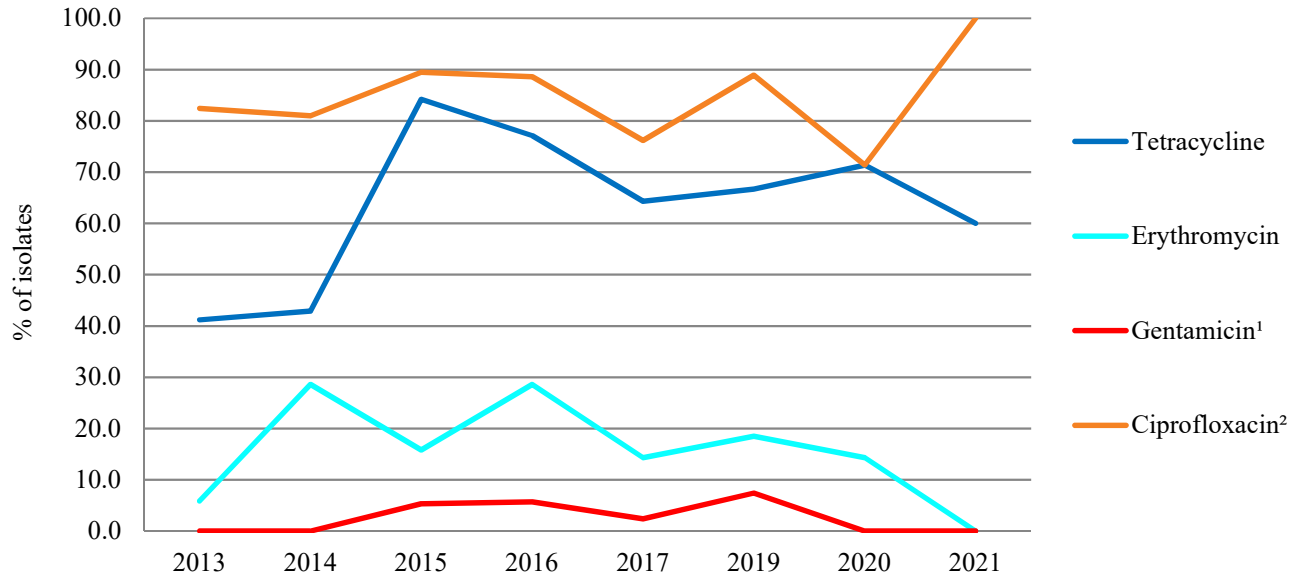

FIGURE 67. Trend 2013-2021. Percentage of *Campylobacter coli* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway. [1]Breakpoints according to ECOFF. [2]Breakpoints for ciprofloxacin adjusted according to EUCAST in keeping with the new I-definition and current dosing practice for infections (v.12.0, last accessed 02.07.22).

RESULTS AND COMMENTS

The NRL annually performs antimicrobial susceptibility testing for 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. Trends in antibiotic resistance must be interpreted accordingly.

For *C. jejuni* isolates, resistance levels against tetracycline were higher for travel associated strains when compared to domestically acquired strains. All strains were identified as ciprofloxacin resistant irrespective of place of acquisition.

Resistance in *C. coli* follows similar patterns as in *C. jejuni*, although *C. coli* isolates are usually reported as more resistant to erythromycin. For 2021, no *C. coli* isolates were identified as resistant to erythromycin.

An MDR phenotype was observed in two *C. jejuni* isolates, one isolate related to travel and one with an unknown travel history. Both isolates were resistant to ciprofloxacin, erythromycin and tetracycline.

YERSINIA ENTEROCOLITICA

Yersinia enterocolitica from human clinical specimens

In 2021, 87 human yersiniosis cases were notified to MSIS. The majority of cases were domestically acquired (80%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 87 isolates of pathogenic *Yersinia* from primary diagnostic laboratories in Norway. 31 isolates were linked to 5 clusters/outbreaks, and 61 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 55 isolates received before December 2021 (Table 44) against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chloramphenicol. The results are presented in Tables 45-47 and Figures 68-69, and in the related text.

TABLE 44. Number of *Yersinia enterocolitica* isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2021, by serotype and place of acquisition.

Yersinia enterocolitica	No. of isolates tested in 2021		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	45	49	35	38	-	-	10	11
Y. enterocolitica O:9	5	7	4	6	-	-	1	1
Y. entericolitica (other serotypes)	5	5	4	4	-	-	1	1
Total	**55**	**61**	**43**	**48**	-	-	**12**	**13**

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

TABLE 45. Percentage distributions of antimicrobial susceptibility categories of *Yersinia enterocolitica* O:3 and O:9 (n=50) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	0.0	-	100.0
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Tetracycline[1]	≥ 17 mm	< 17 mm	93.9	-	6.1
Chloramphenicol	≤ 8	> 8	83.7	-	16.3

[1]Breakpoints according to national zone distributions.

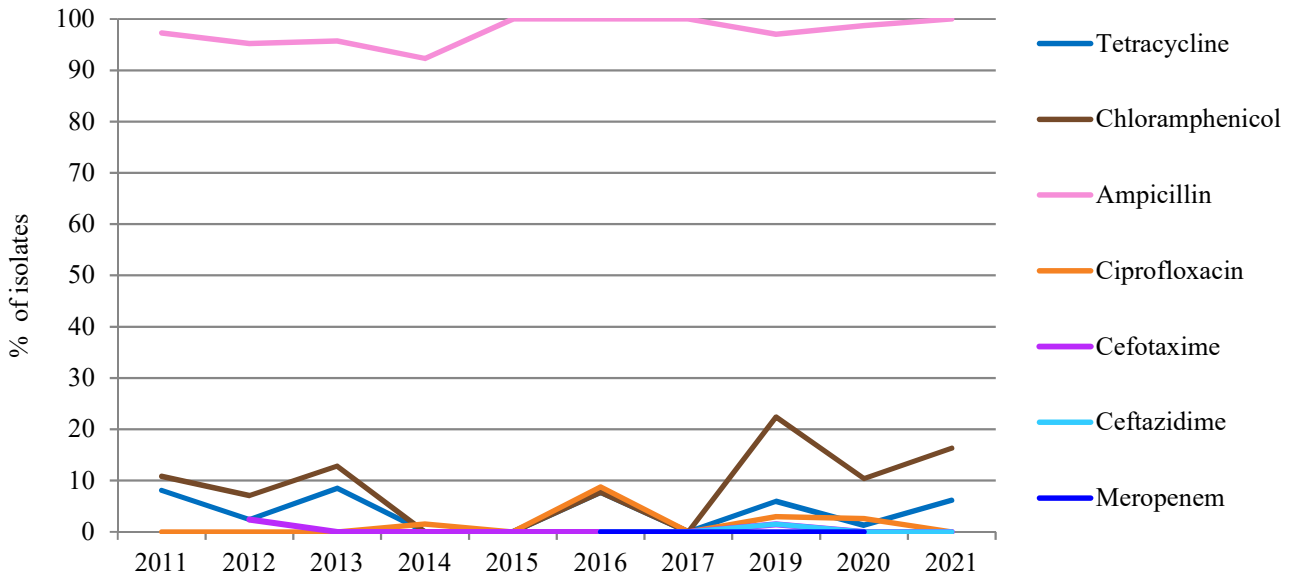

FIGURE 68. Trend 2011-2021. Percentage of *Yersinia enterocolitica* O:3 and O:9 resistant to selected antimicrobial agents irrespective of place of acquisition in Norway.

TABLE 46. Percentage distributions of genotypic resistance in *Yersinia enterocolitica* O:3 and O:9 (n=56) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	-	-	78.6	21.4
Ampicillin	≤ 8	> 8	0.0	100.0
Meropenem	≤ 2	> 8	100.0	0.0
Cefotaxime[2]	≤ 1	> 2	100.0	0.0
Ceftazidime[2]	≤ 1	> 4		
Colistin[3]	≤ 2	> 2	100.0	0.0
Chloramphenicol	≤ 8	> 8	83.9	16.1
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0
Sulfonamide	-	-	80.4	19.6
Tetracycline	≤ 4	> 4	100.0	0.0
Trimethoprim	≤ 4	> 4	100.0	0.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Yersinia enterocolitica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins.

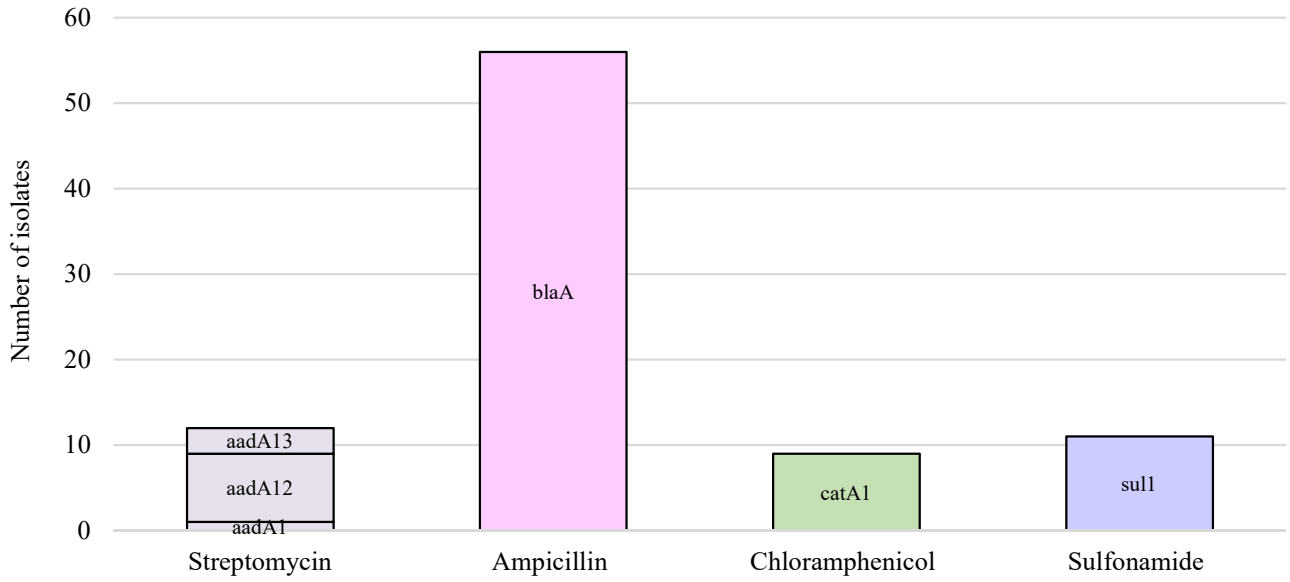

FIGURE 69. Identified resistance determinants in genotypically resistant *Yersinia enterocolitica* O:3 and O:9 to selected antimicrobial agents in Norway 2021.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN YERSINIA

TABLE 47. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Yersinia enterocolitica* O:3 and O:9 isolates identified in Norway 2021.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	55	51	4	-	-	-	100.0
Extended spectrum cephalosporins[2]	55	-	55	-	-	-	100.0
Carbapenems	55	-	55	-	-	-	100.0
Fluoroquinolones	55	-	50	-	5	-	100.0
Tetracycline	54	-	51	-	3	-	94.4
Phenicols	54	-	46	8	-	100.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Yersinia enterocolitica* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins.

RESULTS AND COMMENTS

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

A total of 5 outbreak clusters of *Y. enterocolitica* O:3 of 17, 5, 4, 3 and 2 isolates were identified in 2021. Only a single isolate from each of these clusters are presented in the antimicrobial resistance results.

Antimicrobial resistance for *Yersinia enterocolitica* serotypes O:3 and O:9 has been combined and presented without distinction of place of acquisition. All isolates expressed intrinsic resistance to ampicillin, attributed to the *blaA* gene. In addition, resistance to chloramphenicol was seen in 16.3% of the isolates which was attributed to *catA1*.

The overall correlation between phenotypic and predicted genotypic resistance was good, both sensitivity and specificity were above 94% for the tested antibiotics. Four isolates, serotyped O:5/27 were phenotypically resistant to ampicillin; however, no known resistance genes were identified.

Shigella spp. from human clinical specimens

In 2021, 33 human cases of shigellosis were notified to MSIS. The majority of cases were infected abroad (57.6%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 33 *Shigella* spp. isolates from primary diagnostic laboratories in Norway. Five where linked to an outbreak cluster, and 29 unique isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on 26 *Shigella* isolates (Table 48). 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 49-54, Figures 70-74, and in the text.

TABLE 48. Number of *Shigella* spp. isolates tested for phenotypic antimicrobial susceptibility (AST) and predicted genotypic resistance (GR) recovered from human clinical specimens in Norway 2021, by species and place of acquisition.

Shigella spp.	No. of isolates tested in 2021		Place of acquisition					
			Norway		Abroad		Unknown	
	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR	Phenotypic AST	Predicted GR
S. sonnei	17	17	3	3	12	12	2	2
S. flexneri	8	9	2	3	5	5	1	1
S. boydii	-	2	-	-	-	2	-	-
S. dysenteriae	1	1	-	-	1	1	-	-
Total	**26**	**29**	**5**	**6**	**18**	**20**	**3**	**3**

ANTIMICROBIAL RESISTANCE IN SHIGELLA SONNEI

TABLE 49. Percentage distributions of antimicrobial susceptibility categories of *Shigella sonnei* (n=17) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	47.1	-	52.9
Cefotaxime	≤ 1	> 2	58.8	0.0	41.2
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	70.6	17.6	11.8
Tetracycline[1]	≥ 17 mm	< 17 mm	6.3	-	93.8
Chloramphenicol	≤ 8	> 8	100.0	-	0.0

[1]Breakpoints according to national zone distributions.

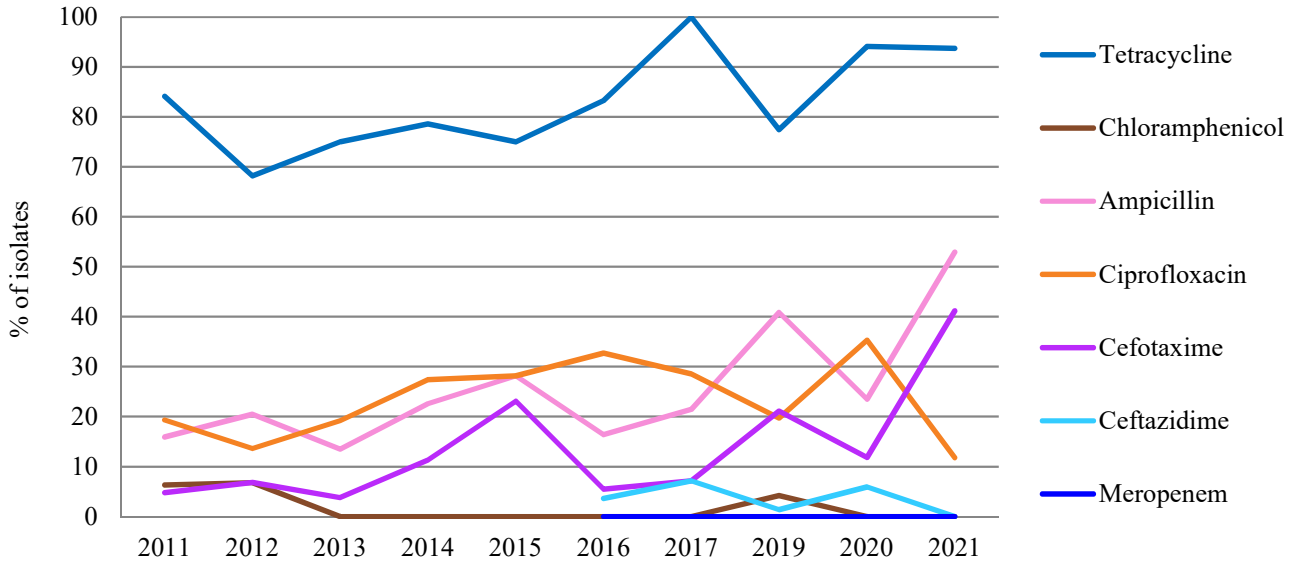

FIGURE 70. Trend 2011-2021. Percentage of *Shigella sonnei* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway.

TABLE 50. Percentage distributions of genotypic resistant *Shigella sonnei* (n=17) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	-	-	5.9	94.1
Ampicillin	≤ 8	> 8	47.1	52.9
Meropenem	≤ 2	> 8	100.0	0.0
Cefotaxime[2]	≤ 1	> 2	52.9	47.1
Ceftazidime[2]	≤ 1	> 4		
Colistin	≤ 2	> 2	100.0	0.0
Chloramphenicol	≤ 8	> 8	100.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	29.4	70.6
Sulfonamide	-	-	0.0	100.0
Tetracycline	≤ 4	> 4	23.5	76.5
Trimethoprim	≤ 4	> 4	5.9	94.1

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella sonnei* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins.

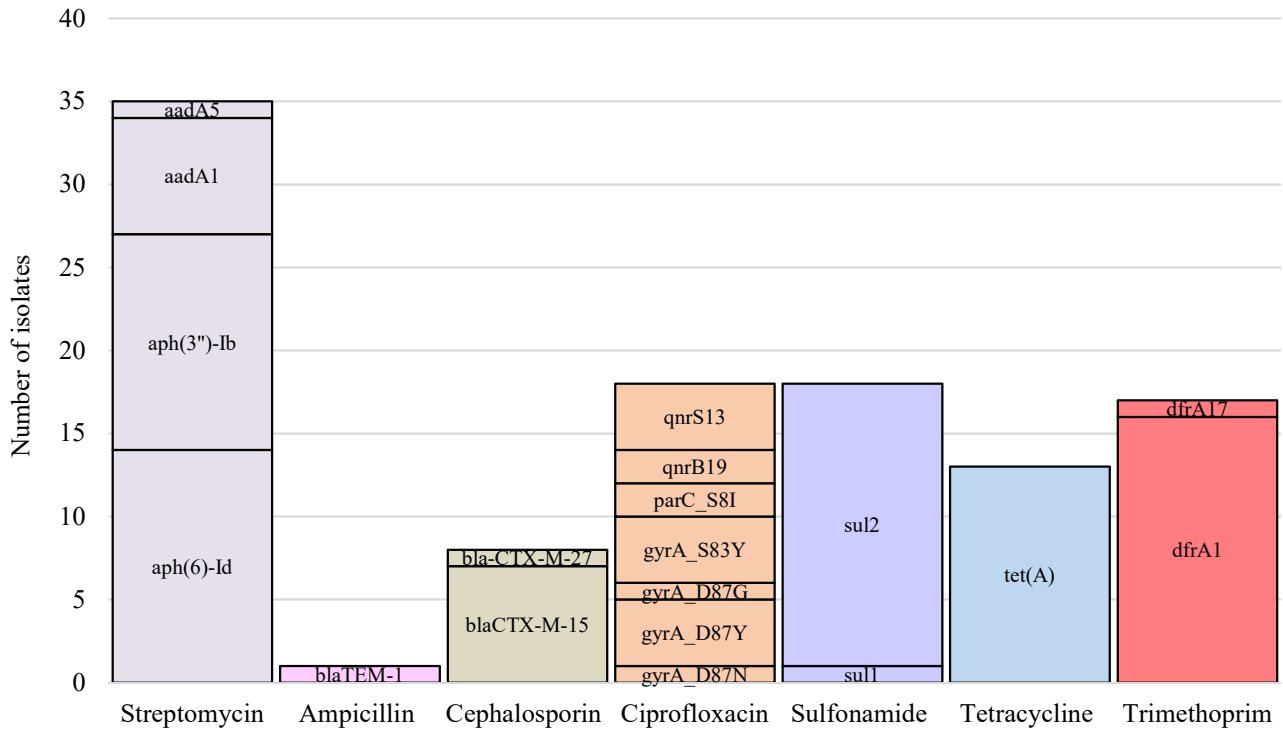

FIGURE 71. Identified resistance determinants in genotypically resistant *Shigella sonnei* (n=17) to selected antimicrobial agents in Norway 2021.

ANTIMICROBIAL RESISTANCE IN SHIGELLA FLEXNERI

TABLE 51. Percentage distributions of antimicrobial susceptibility categories of *Shigella flexneri* (n=8) from human clinical specimens irrespective of place of acquisition in Norway 2021.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	0.0	-	100.0
Cefotaxime	≤ 1	> 2	87.5	0.0	12.5
Ceftazidime	≤ 1	> 4	87.5	0.0	12.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	50.0	25.0	25.0
Tetracycline[1]	≥ 17 mm	< 17 mm	12.5	-	87.5
Chloramphenicol	≤ 8	> 8	50.0	-	50.0

[1] Breakpoints according to national zone distributions.

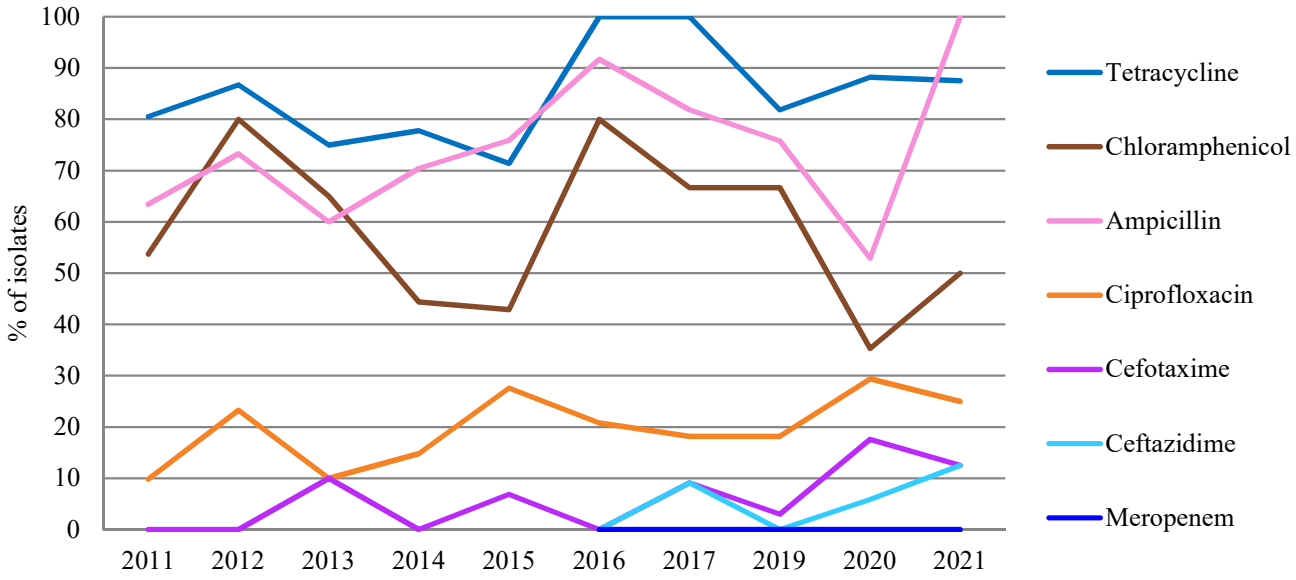

FIGURE 72. Percentage of *Shigella flexneri* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2011-2021.

TABLE 52. Percentage distributions of genotypic resistance in *Shigella flexneri* (n=8) from human clinical specimens in Norway 2021.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
Antibiotic	Wild type	Non-wild type	S	R
Gentamicin	≤ 2	> 2	100.0	0.0
Streptomycin	-	-	33.3	66.7
Ampicillin	≤ 8	> 8	0.0	100.0
Meropenem	≤ 2	> 8	100.0	0.0
Cefotaxime[2]	≤ 1	> 2	88.9	11.1
Ceftazidime[2]	≤ 1	> 4		
Colistin	≤ 2	> 2	100.0	0.0
Chloramphenicol	≤ 8	> 8	33.3	66.7
Ciprofloxacin	≤ 0.25	> 0.5	33.3	66.7
Sulfonamide	-	-	33.3	66.7
Tetracycline	≤ 4	> 4	22.2	77.8
Trimethoprim	≤ 4	> 4	11.1	88.9

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in absence of ECOFF for *Shigella flexneri* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [2]Predicted genotypic resistance to cefotaxime and ceftazidime is combined as predicted genotypic resistance against extended spectrum cephalosporins.

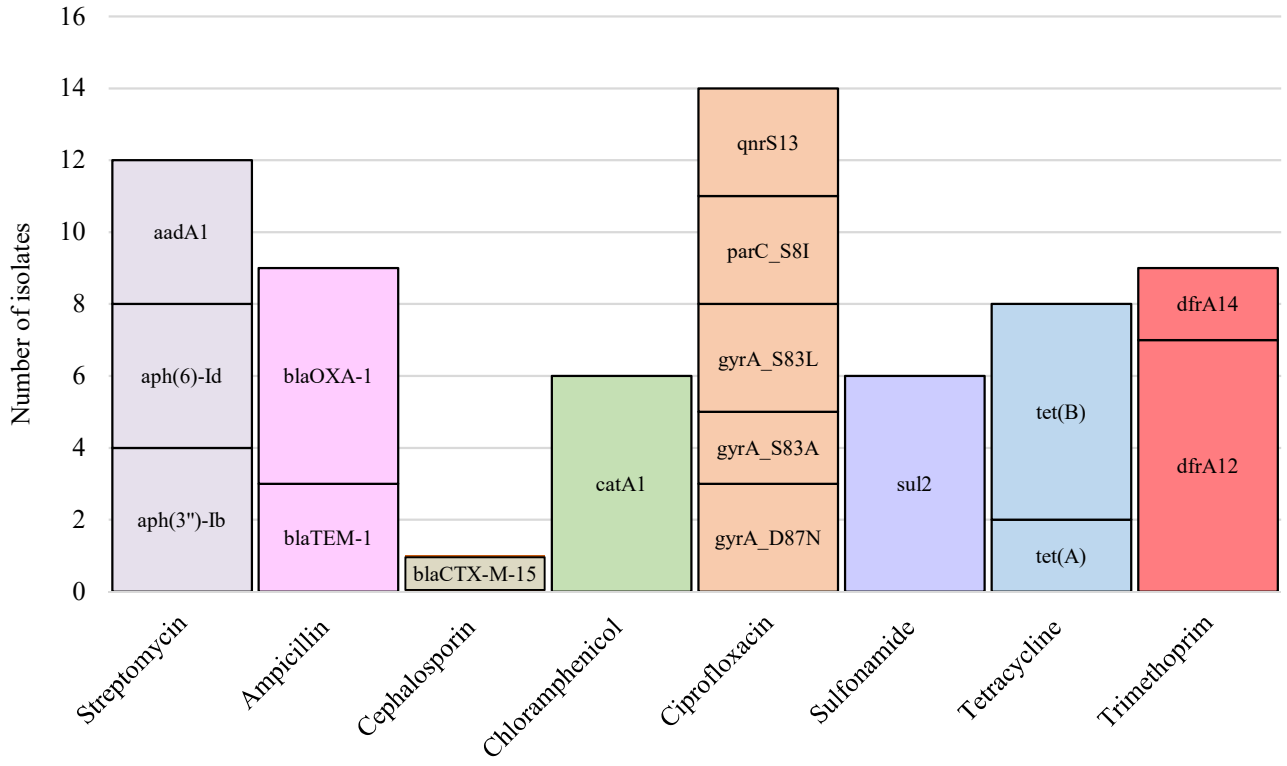

FIGURE 73. Identified resistance determinants in genotypically resistant *Shigella flexneri* (n=8) to selected antimicrobial agents in Norway 2021.

MULTI-DRUG RESISTANCE IN SHIGELLA

TABLE 53. Number of predicted genotypic multi-drug resistance in (MDR) *Shigella* spp. isolates identified in Norway 2021, 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	17	16	9	8	-	12	17	13	16
Shigella flexneri	9	6	9	1	6	6	6	7	8
Shigella boydii	1	1	1	-	-	-	1	1	1
Shigella dysenteriae	1	1	1	-	-	1	1	1	1
Total no. of MDR isolates	**28**	**24**	**20**	**9**	**6**	**19**	**25**	**22**	**26**

[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.

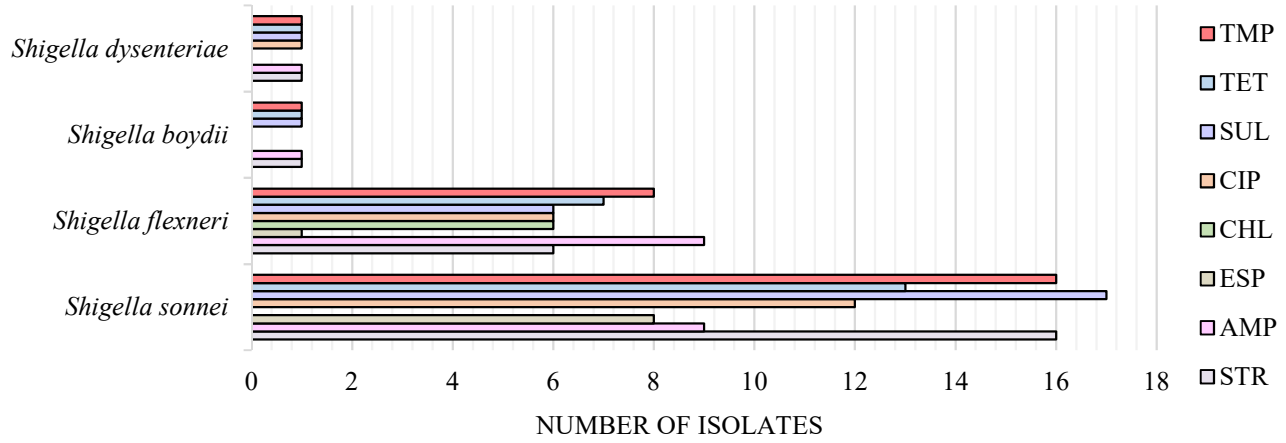

FIGURE 74. Number of predicted genotypically multi-drug resistant (MDR) *Shigella* spp. isolates (n=28) identified in Norway 2021, stratified according to species and resistance to different antibiotic categories; STR: Streptomycin, AMP; Ampicillin, ESP; Extended Spectrum Cephalosporin, CHL; Chloramphenicol, CIP; Ciprofloxacin, SUL; Sulfonamide, TET; Tetracycline, TMP; Trimethoprim.

CORRELATION BETWEEN PHENOTYPIC AND PREDICTED GENOTYPIC RESISTANCE IN SHIGELLA

TABLE 54. Concordance between phenotypic and predicted genotypic resistance to selected antibiotic categories in *Shigella spp*. (n=26) isolates identified in Norway 2021.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	26	-	8	18	-	100.0	100.0
Extended spectrum cephalosporins[2]	26	1	17	8	-	88.9	100.0
Carbapenems	26	-	25	-	1	-	96.2
Fluoroquinolones	26	1	8	17	-	94.4	100.0
Tetracycline	25	-	2	20	3	100.0	40.0
Phenicols	25	1	20	4	-	80.0	100.0

[1]Wild type (WT) and non-wild type (NWT) categorisation according to EUCAST epidemiological cutoff values (ECOFF), and clinical breakpoints in abscense of ECOFF for *Shigella spp.* (v.12.0, last accessed 02.07.22), used for comparing phenotypic resistance (when screened) with identified genotypic resistance determinants. [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 for all *Shigella* spp. isolates. From 2020 onwards, the NRL has screened all isolates for antimicrobial resistance determinants following whole genome sequencing to predict genotypic resistance.

One outbreak cluster was identified in 2021 of *S. sonnei* (n=5). The outbreak strain was resistant to ciprofloxacin, tetracycline and extended spectrum cephalosporins ($bla_{\text{CTX-M-15}}$). Antimicrobial resistance results only from a single isolate from this cluster are presented.

A stable and high proportion of *S. sonnei* (average 83%) have been seen resistant to tetracycline over the last decade. In addition, an increasing trend of resistance towards ampicillin and extended spectrum cephalosporins has been observed. In 2021, 93.2% of the isolates were resistant to ampicillin and 7 isolates (41.2%) were recorded with an ESBL phenotype. An ESBL genotype was confirmed in 8 isolates (47%), mediated by $bla_{\text{CTX-M-15}}$ (n=7) and $bla_{\text{CTX-M-27}}$ (n=1). An MDR genotype was identified in all isolates, largely attributed to resistance against streptomycin, sulfonamide and trimethoprim, but also high proportions of resistance to tetracycline, ciprofloxacin and extended spectrum cephalosporins.

Also, in *S. flexneri* a stable and high proportion of isolates (average 84.9%) has been observed resistant to tetracycline over the last decade. In addition, an increasing trend of resistance towards ampicillin and extended spectrum cephalosporins has been observed. In 2021, 100% of the isolates were resistant to ampicillin, and one isolate (12.5%) was recorded with an ESBL phenotype. An ESBL genotype was confirmed in this isolate and mediated by $bla_{\text{CTX-M-15}}$. An MDR genotype was identified in all isolates, largely attributed to resistance against ampicillin, trimethoprim, and tetracycline, but also high proportions of resistance to ciprofloxacin, sulfonamide, chloramphenicol and streptomycin.

In total, ten isolates were predicted as genotypically resistant to extended spectrum cephalosporins: *S. sonnei* (n=8), *S. flexneri* (n=1), and *S. boydii* (n=1), mediated by $bla_{\text{CTX-M-15}}$ (n=8), $bla_{\text{CTX-M-27}}$ (n=1) and $bla_{\text{CMY-4}}$ (n=1). The overall correlation between phenotypic resistance and predicted genotypic resistance was good, although specificity for tetracycline was low (40%).

HUMAN CLINICAL ISOLATES

Gunnar Skov Simonsen, Cecilie Torp Andersen, Dominique Caugant, Petter Elstrøm, Hege Enger, Frode Width Gran, Einar Heldal, Aleksandra Jakovljev and Didrik Frimann Vestrheim

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 55, 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 55. Number of blood culture isolates in 2021, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) 2017-2021. The table is based on data from the information systems of all laboratories in Norway (n=20).

Species	No. of isolates 2021	% of all isolates					% of all isolates excluding skin flora				
		2017	2018	2019	2020	2021	2017	2018	2019	2020	2021
Staphylococcus aureus	2,012	10.1	11.1	11.0	10.6	10.5	13.1	14.2	13.9	13.7	13.8
Coagulase negative staphylococci	4,071	20.9	19.5	18.7	20.4	21.1	-	-	-	-	-
Streptococcus pneumoniae	312	2.7	3.3	3.1	1.6	1.6	3.6	4.2	4.0	2.1	2.1
Streptococcus pyogenes	80	1.2	1.2	1.0	0.8	0.4	1.5	1.5	1.2	1.0	0.5
Streptococcus agalactiae	299	1.4	1.5	1.8	1.7	1.6	1.8	1.9	2.2	2.1	2.0
Beta-haemolytic streptococci group C and G	460	1.5	2.0	2.0	2.3	2.4	2.0	2.5	2.5	2.9	3.1
Viridans- and non-haemolytic streptococci	982	5.5	5.1	5.0	5.4	5.1	7.2	6.4	6.4	7.0	6.7
Enterococcus faecalis	719	3.6	3.4	3.4	3.5	3.7	4.7	4.4	4.3	4.5	4.9
Enterococcus faecium	268	1.4	1.2	1.3	1.1	1.4	1.9	1.5	1.7	1.4	1.8
Other Gram-positive aerobic and facultative anaerobic bacteria	810	3.5	3.1	3.7	3.5	4.2	2.2	2.0	2.3	2.4	2.7
Escherichia coli	4,479	24.9	25.5	25.4	24.7	23.2	32.2	32.6	32.2	32.0	30.7
Klebsiella spp.	1,473	7.0	6.8	7.4	7.5	7.7	9.1	8.7	9.4	9.6	10.1
Enterobacter spp.	358	1.9	1.9	1.7	1.7	1.9	2.4	2.4	2.1	2.2	2.4
Proteus spp.	265	1.5	1.6	1.6	1.6	1.4	2.0	2.0	2.0	2.1	1.8
Other *Enterobacteriaceae*	359	2.3	3.4	2.2	2.3	1.9	3.0	4.3	2.7	3.0	2.5
Pseudomonas spp.	364	1.4	1.7	1.8	1.9	1.9	1.8	2.1	2.3	2.4	2.5
Other Gram-negative aerobic and facultative anaerobic bacteria	377	2.0	1.0	2.1	1.8	2.0	2.6	1.3	2.6	2.3	2.6
Bacteroides spp.	442	2.3	1.9	1.9	2.2	2.3	2.9	2.4	2.4	2.9	3.0
Other anaerobic bacteria	876	3.7	3.7	3.8	4.2	4.6	4.4	4.2	4.4	4.9	5.4
Yeasts	209	1.2	1.1	1.1	1.2	1.1	1.6	1.4	1.4	1.5	1.4
Total	**19,215**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 55 and Figure 75, aerobic and facultative Gram-positive and Gram-negative bacteria represented 52.0% and 40.0% 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 21.1%. This is an increase from 20.4% in 2020, but minor fluctuations may result from inconsistent reporting from the laboratories. 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 37.6% aerobic Gram-positives and 52.6% 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. A further reduction to 2.1% (both 2020 and 2021) may be linked to the on-going coronavirus pandemic with reduced incidence of all respiratory tract pathogens. The occurrence of *Streptococcus pyogenes* (n=80) was similarly at an exceptionally low level. The proportions of other aerobic Gram-positives have remained relatively stable over many years.

E. coli (30.7%) and other *Enterobacteriaceae* (16.8%) accounted for the vast majority of aerobic Gram-negative isolates, but the proportions have remained relatively unchanged over the years. *Pseudomonas* spp. has been fairly stable in spite of a nosocomial outbreak in intensive care units during late 2021 (2.5%), all figures excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 6.9% (8.4% excluding skin flora). Yeasts accounted for 1.1% (1.4% excluding skin flora), which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (2.3%/3.0%) and among yeasts *Candida albicans* (0.7%/0.9%). However, a multitude of other species were also represented.

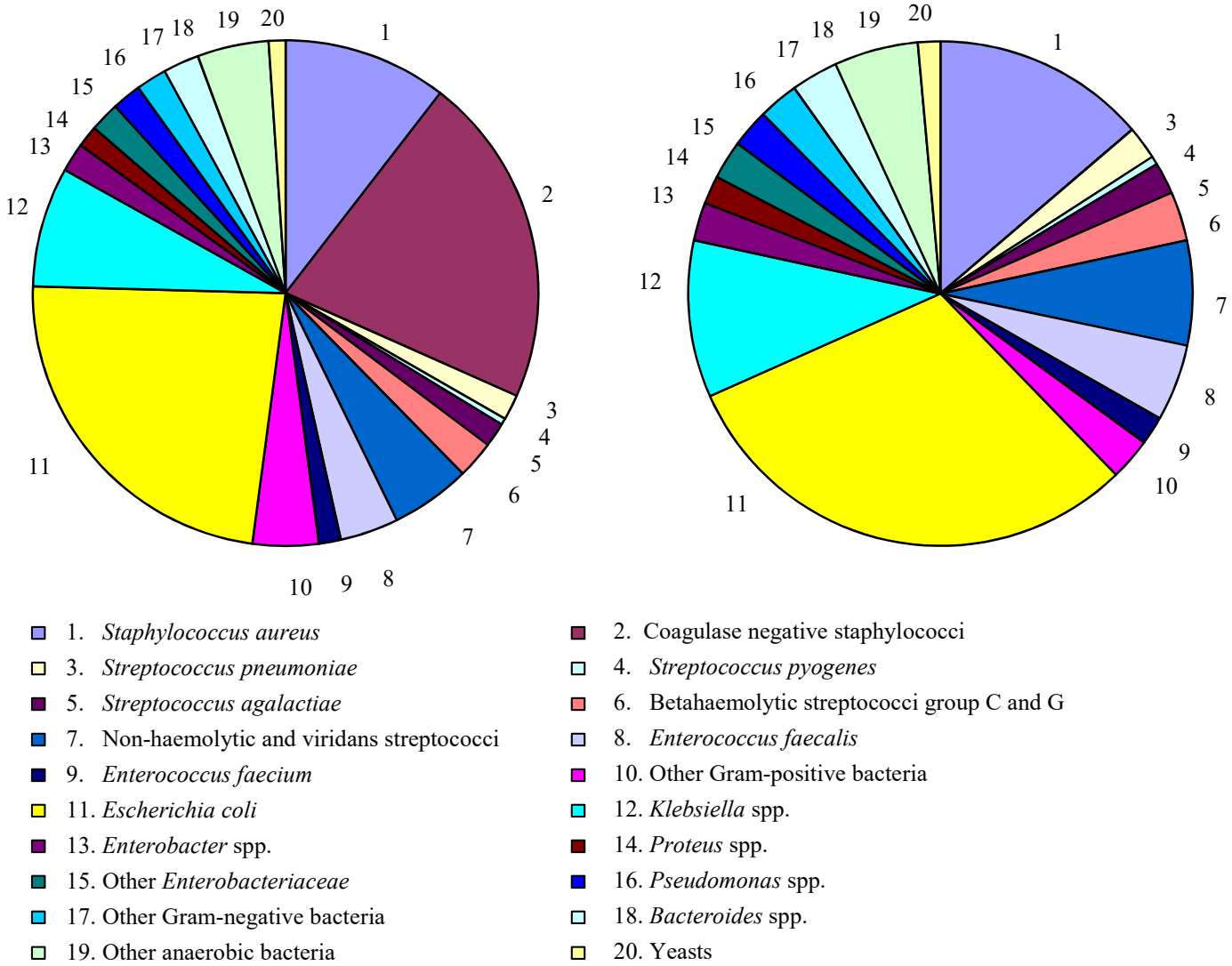

FIGURE 75. Distribution of all blood culture isolates (left, n=19,215) and blood culture isolates excluding common skin contaminants (right, n=14,642) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp. Data for 2021 were retrieved from the information systems of all Norwegian laboratories.

Escherichia coli in blood cultures

TABLE 56. *Escherichia coli* blood culture isolates in 2021 (n=2,212). 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	63.0	-	37.0
Amoxicillin-clavulanic acid*	≤ 8	> 8	75.3	-	24.7
Piperacillin-tazobactam	≤ 8	> 8	94.8	-	5.2
Cefuroxime	≤ 0.001	> 8	0.0	90.7	9.3
Cefotaxime	≤ 1	> 2	93.4	0.5	6.1
Ceftazidime	≤ 1	> 4	93.2	1.1	5.7
Cefepime	≤ 1	> 4	93.3	1.4	5.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	94.4	-	5.6
Tobramycin	≤ 2	> 2	94.3	-	5.7
Amikacin	≤ 8	> 8	97.2	-	2.8
Ciprofloxacin	≤ 0.25	> 0.5	87.0	2.6	10.4
Tigecycline	≤ 0.5	> 0.5	98.9	-	1.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	77.7	0.6	21.7
ESBL	Negative	Positive	94.2	-	5.8

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended spectrum beta-lactamase. *Breakpoints for infections other than uncomplicated urinary tract infections. **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 (93.9%), ceftazidime (94.3%), gentamicin (94.4%), cefepime (94.7%), piperacillin-tazobactam (94.8%), tigecycline (98.9%) and meropenem (100.0%) (Table 56). There were no significant changes in resistance rates from 2020-2021.

The prevalence of resistance to gentamicin at 5.6% was at the same level as 5.9% in 2019 and 6.7% in 2020 (Figure 76). 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 (51/124, 41.1%) also produced ESBL enzymes. The prevalence at individual laboratories varied due to relatively small numbers. When aggregated by region there were only minor geographical differences (South-East 6.0%, West 6.2%, North 4.6%, and Middle 3.9%). Tobramycin and amikacin were surveyed to broaden the perspective on aminoglycoside resistance. Susceptibility was seen in of 94.3% and 97.2% of isolates, respectively.

The prevalence of resistance to ciprofloxacin was 10.4% in 2021 compared to 11.2% in 2020. 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 77. A similar association between quinolone use and resistance in systemic *E. coli* isolates is also reported internationally. The resistance rates for ampicillin (41.6% in 2020, 37.0% in 2021) and trimethoprim-sulfamethoxazole (23.1% in 2020, 21.7% in 2021) 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 MIC gradient tests. A total of 128 isolates (5.8%) were reported as ESBL positive, which is a further reduction from 2019 (7.1%) and 2020 (6.5%) (Figure 79). 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 was some geographical variation in the prevalence of ESBL production; North (5.8%), West (5.7%), South-East (4.4%) and Middle (3.3%). Most of the ESBL isolates were phenotypically resistant to cefuroxime (n=127), cefotaxime (n=121), ceftazidime (n=111) and cefepime (n=107), whereas many were susceptible to piperacillin-tazobactam (n=105) and/or gentamicin (n=77). Thirty-nine isolates were susceptible to amoxicillin-clavulanic acid using breakpoints for non-urinary tract infections, whereas 89 were resistant. The ESBL isolates displayed high rates of co-resistance to ciprofloxacin (n=84), trimethoprim-sulfamethoxazole (n=82) and/or gentamicin (n=51), but many ESBL+/gentamicin R isolates remained susceptible to amikacin (n=45/51). All isolates were clinically susceptible to meropenem, but 17 isolates (0.8%) had zone diameters below the screening breakpoint of 28 mm. No carbapenemase-producing isolates were detected.

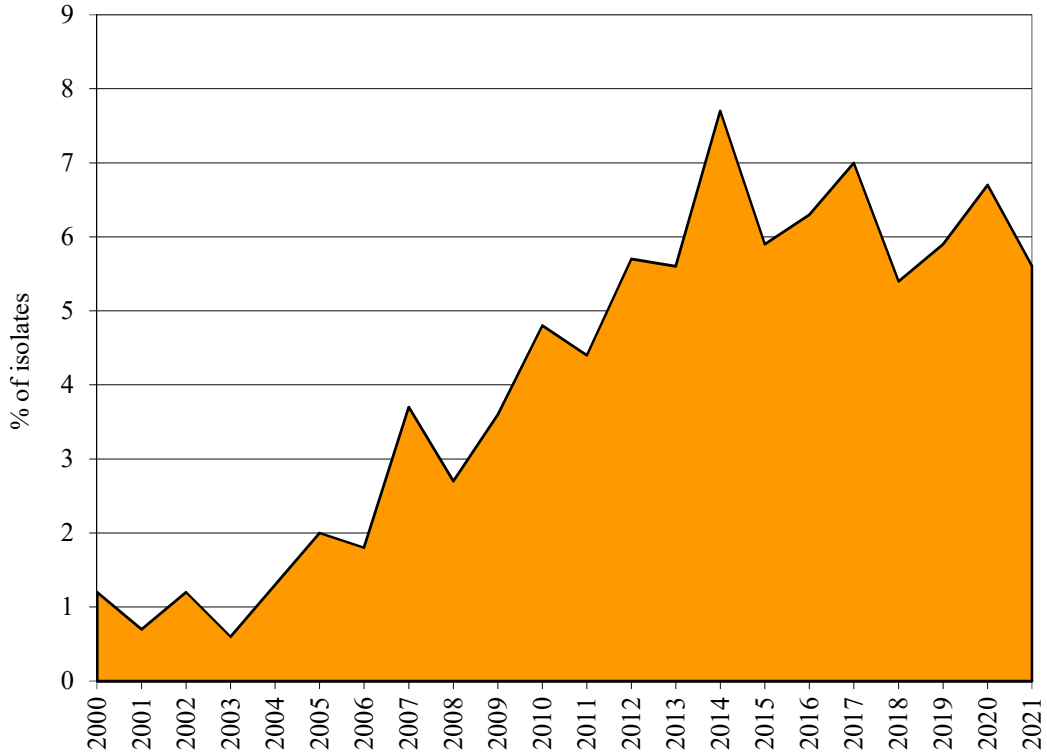

FIGURE 76. Prevalence of resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2021.

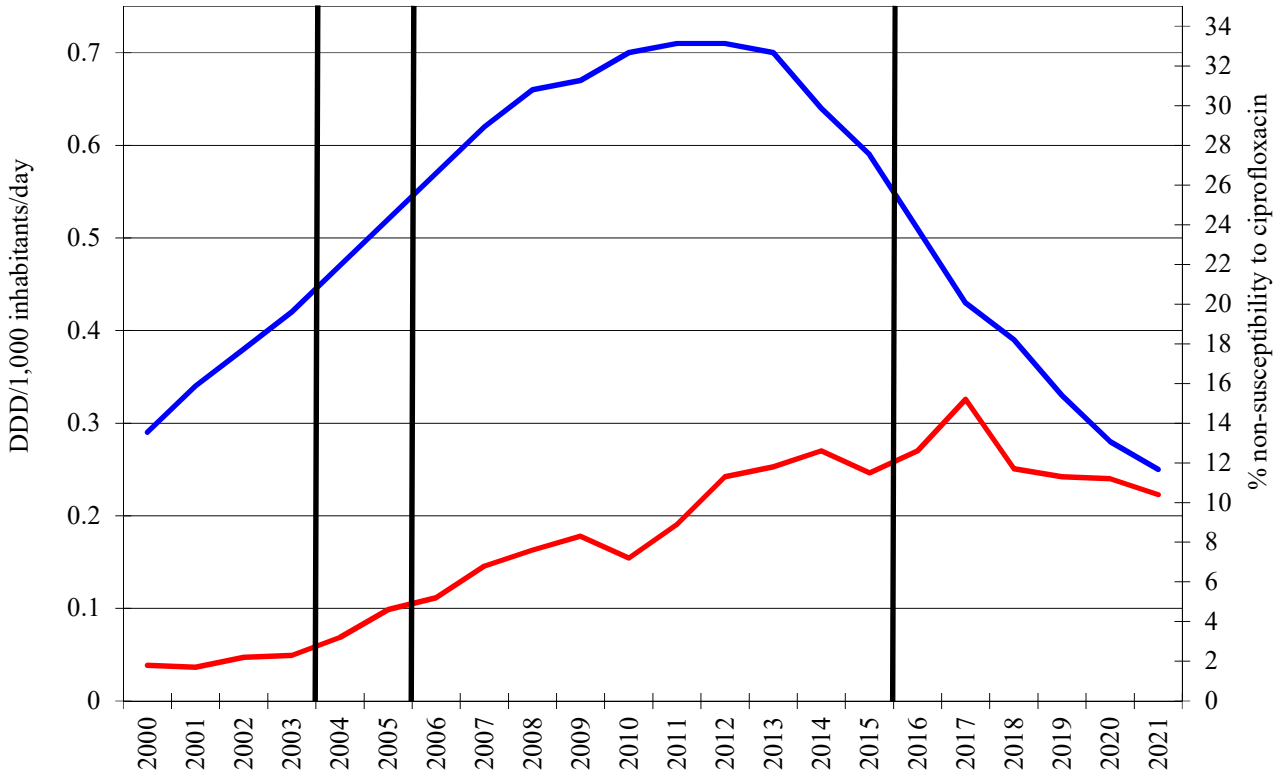

FIGURE 77. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates (red) as defined by MIC > 4 mg/L (2000-2003), MIC > 2 mg/L (2004-2005), MIC > 1 mg/L (2006-2015), and MIC > 0.5 mg/L (2016-2021). The breakpoints cannot be calibrated over the entire time period due to changes in susceptibility test methodology.

Escherichia coli in urine

TABLE 57. *Escherichia coli* urinary tract isolates in 2021 (n=1,335). 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	69.4	-	30.6
Mecillinam	≤ 8	> 8	93.8	-	6.2
Amoxicillin-clavulanic acid*	≤ 32	> 32	95.0	-	5.0
Cefalexin	≤ 16	> 16	92.1	-	7.9
Cefotaxime	≤ 1	> 2	96.5	0.3	3.2
Ceftazidime	≤ 1	> 4	96.6	1.0	2.4
Meropenem	≤ 2	> 8	99.1	0.0	0.1
Gentamicin	≤ 2	> 2	96.9	-	3.1
Tobramycin	≤ 2	> 2	96.8	-	3.2
Ciprofloxacin	≤ 0.25	> 0.5	90.7	1.4	7.9
Nitrofurantoin	≤ 64	> 64	99.1	-	0.9
Fosfomycin	≤ 8	> 8	97.7	-	2.3
Trimethoprim	≤ 4	> 4	79.6	-	20.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	81.3	0.4	18.4
ESBL	Negative	Positive	96.9	-	3.1

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended spectrum beta-lactamase. *Breakpoints for uncomplicated urinary tract infections. **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 2021 is shown in Table 57 and the rates of resistance for 2000-2021 are shown in Figure 78. The results for amoxicillin-clavulanic acid and fosfomycin are interpreted according to the EUCAST/NordicAST breakpoints specific for uncomplicated urinary tract infections.

The prevalence of resistance among urinary tract isolates has remained relatively stable over the last ten years, but a decline was observed in 2021 for several antibiotics. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to 38%, but decreased to 30.6% in 2021. Resistance to trimethoprim and trimethoprim-sulfamethoxazole has remained stable around 20-25%, but declined to 20.4% and 18.4%, respectively, in 2021. The prevalence of resistance to mecillinam was 6.2% in 2021 compared to 3.9% in 2019 and 5.3% in 2020. 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 77), the prevalence of resistance has remained stable around 8-9% over the last five years. In 2021, 7.9% of the isolates were resistant to ciprofloxacin in addition to 1.4% 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 10.4% resistance and 2.6% susceptibility to increased exposure. The persistent discrepancy between urinary tract isolates and isolates from bloodstream infections suggests that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and/or topoisomerase genes, whereas urinary tract isolates may be more representative of the wild type normal flora. The prevalence of resistance to amoxicillin-clavulanic acid was 5.0% in 2021 compared to 6.4% in 2019 and 8.0% in 2020. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (99.1%) remained susceptible to nitrofurantoin. Fosfomycin has been included in NORM since 2017. The vast majority of isolates were categorised as susceptible (97.7%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Fourty-two isolates (3.1%) were reported as ESBL producers. This is at the same level as 3.0% in 2019 and 3.4% in 2020. As seen in Figure 79, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (5.8%). ESBL positive strains were isolated in all parts of the country. Thirty isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=7) or patients in outpatient clinics (n=4) or nursing homes (n=1). The ESBL isolates were all resistant to ampicillin, and the majority were also resistant to cefalexin (41/42), cefotaxime (38/42) and ceftazidime (27/42). All ESBL isolates were *in vitro* susceptible to mecillinam. 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 (30/42), trimethoprim-sulfamethoxazole (29/42) and ciprofloxacin (26/42), but remained susceptible to nitrofurantoin (42/42), fosfomycin (42/42) and gentamicin (37/42). A single isolate was clinically resistant to meropenem and contained an NDM carbapenemase, whereas four additional isolates had zone diameters of 25-27 mm, but were susceptible to piperacillin-tazobactam and thus categorised as carbapenemase negative.

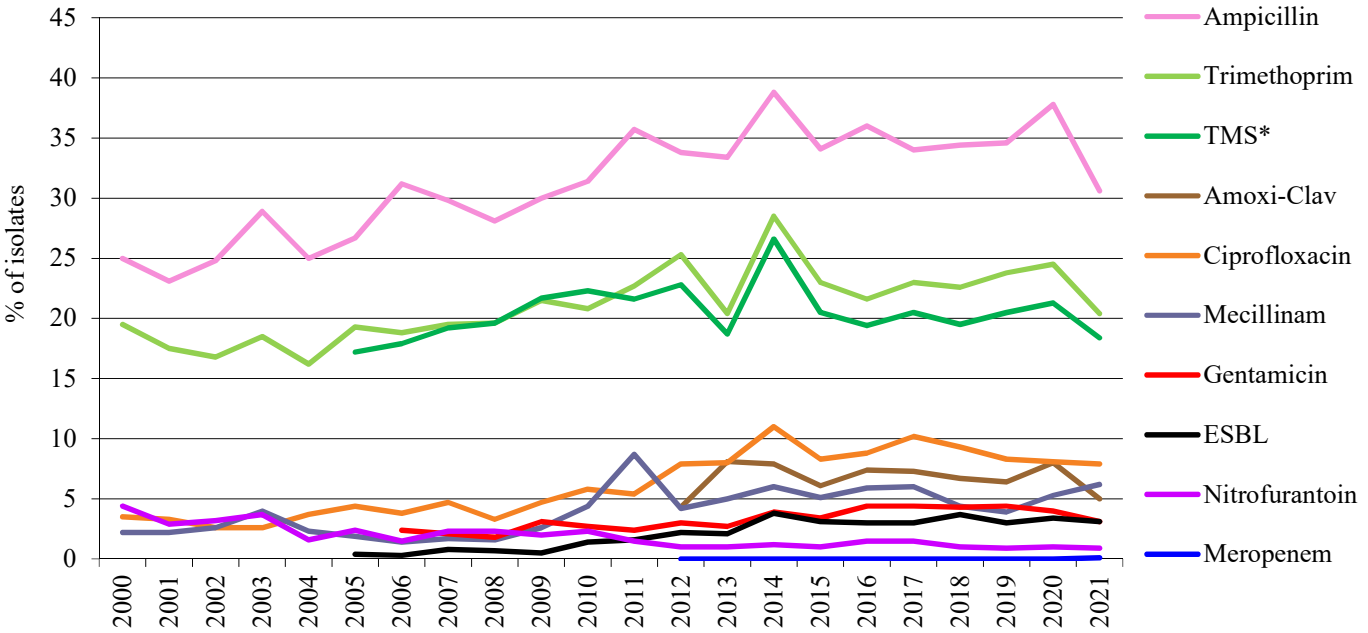

FIGURE 78. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2021. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

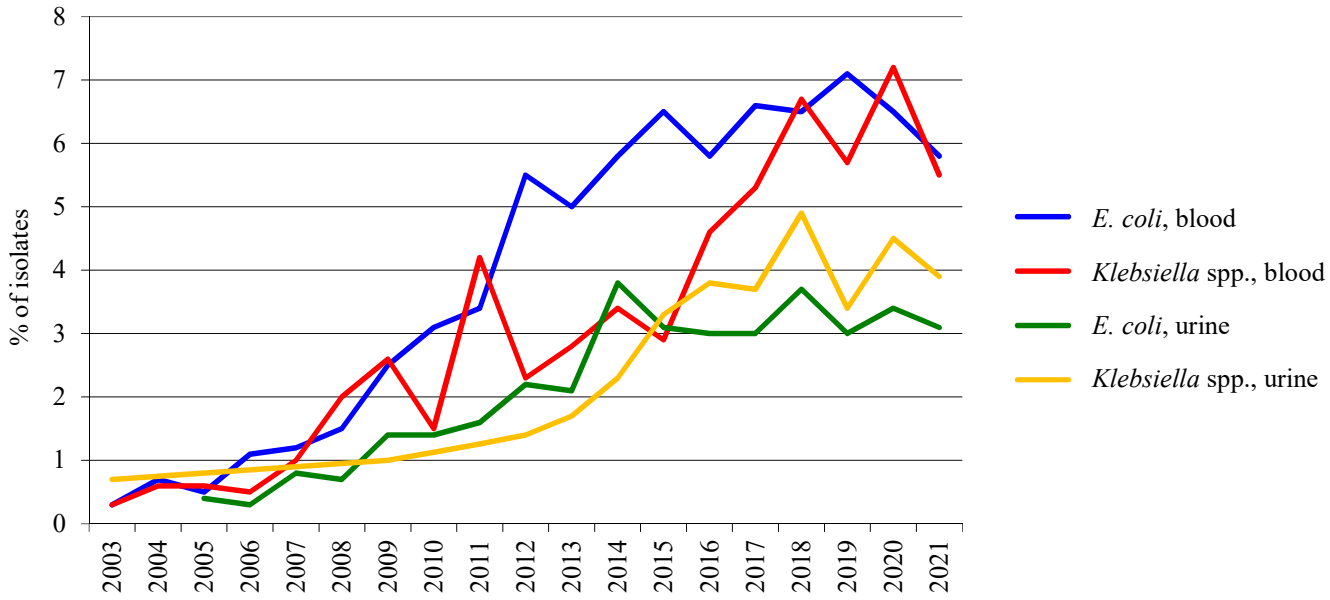

FIGURE 79. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2021.

Antibiotic use and resistance data from children in Norway

Over the last decade there has been a push to decrease the use of antibiotics in all age groups, also in children (1). The overall aim is clearly to reduce antibiotic resistance development, but also to reduce other side effects of antibiotic use. In particular newborn infants are a vulnerable group. Prolonged antibiotic exposure in early life may have lasting effects (2). Overuse and misuse of broad-spectrum antibiotics is associated with increased risk of necrotising enterocolitis, invasive fungal infections and death in preterm infants (3). A healthy gut microbiota with a normal diversity stimulates the developing normal immune system, and early life antibiotic exposure is associated with increased risk of developing immune-mediated diseases like asthma, allergy, obesity and inflammatory bowel disease later in life (4).

To optimise antibiotic use in children we need to know local epidemiology. Moreover, surveillance of antibiotic resistance data for bacteria causing serious infections is of high importance, but data specific for children are often lacking. Here we summarise some recent scientific studies from Norway focusing on antibiotic use and resistance data in newborns and older children.

In a Norwegian population-based study (2015-2019), more than 282,000 term and near-term newborns were included (5). During the study period, a substantial decrease in the proportion of newborns treated with antibiotics was observed, from 3.1% in 2015 to 2.2% in 2019 (30% decrease, $p<0.001$). The overall number of days with antibiotic treatments was reduced by 37% from 2015 to 2019 (119/1,000 versus 76/1,000, $p<0.001$). The decline in rates of infants treated with antibiotics and treatment duration was not associated with an increase in later diagnosed sepsis or "breakthrough" infections (5). In newborns diagnosed with a culture-proven sepsis Group B streptococcus (GBS) was the most prevalent pathogen (34%), followed by *Escherichia coli* and *Staphylococcus aureus.*

It is challenging to diagnose infections in newborn infants due to vague symptoms that may overlap with normal infant behavior. In the neonatal unit in Stavanger a specific quality improvement (QI) programme was developed to reduce early antibiotic exposure in term infants. The QI programme included serial physical examination (SPE) of infants with possible symptoms of sepsis, and antibiotic treatment was only instituted if symptoms persisted or deteriorated. Rates of infants treated for suspected sepsis was more than halved from 2.9% to 1.3% after implementing SPE. Concomitantly, the use of laboratory tests (e.g. C-reactive protein) was reduced, most likely by focusing more on the clinical presentation and less on suboptimal tests, which also may inflict pain in the infants (6).

Two publications with prospectively collected data from the Norwegian Surveillance System for Antimicrobial Resistance (NORM) have elucidated on epidemiology of systemic infections in children, and differences in antibiotic resistance profiles in bacteria causing infections in children compared with adults (7, 8).

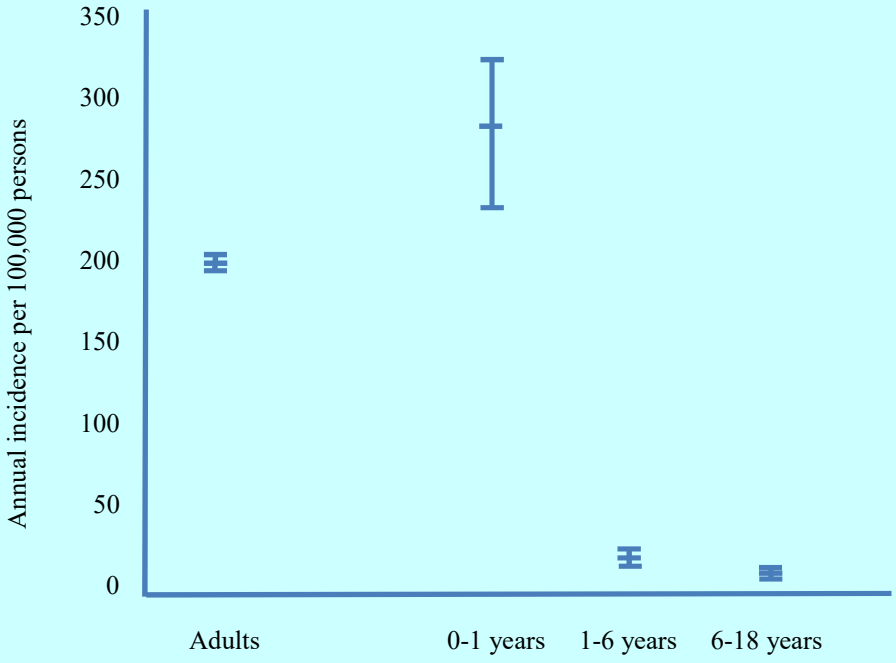

FIGURE 80. Estimated incindence rates for different age groups of invasive bacterial infections confirmed by isolates from blood/CSF in Norway. Vertical line represents the 95% CI around the point estimate for each category. The number of isolates is estimated based on sampling from the Norwegian Surveillance System for Antimicrobial Resistance (NORM) 2013-2017. Bacteria included as follows: *S. aureus, S. pneumoniae, S. pyogenes, S. agalactiae, Enterococcus* spp., *E. coli, Klebsiella* spp., *H. influenzae* and *N. meningitidis.* CI indicates confidence intervals; CSF, cerebrospinal fluid.

The estimated annual incidence of invasive bacterial infections was highest in infants under 1 year of age (Figure 80), but for older children incidence rates were lower than in adults (7). The most prevalent pathogens in children varied by age. *E. coli* and GBS dominated among infants (58%), *S. aureus* and *Streptococcus pneumoniae* dominated among preschool children (41%) and *S. aureus* dominated among schoolchildren (46%). Compared with *S. pneumoniae* isolates from adults, higher non-susceptibility rates in isolates from children were found to penicillin (11.9% versus 5.8%), erythromycin (11.3% vs. 4.9%), clindamycin (9.3% vs. 3.6%), and trimethoprim/sulfamethoxazole (17.9% vs. 6.4%). In contrast, higher rates of ESBL production was observed in *E. coli* isolates from adults (6.1%) versus in children (2.4%).

In a study focusing on urinary tract infections (8), *E. coli* accounted for 85% of the isolates from children. For *E. coli*, there was a higher proportion of trimethoprim resistance in urine samples from children (27.0%) compared to adults (22.9%). In contrast, for ciprofloxacin, there was a lower resistance rate in *E. coli* in urine samples from children (5.7%) compared to adults (8.7%). For other selected antibiotics, the following resistance rates in *E. coli* in children were observed: nitrofurantoin (0.5%), mecillinam (4.0%), cephalexin (4.3%), amoxicillin-clavulanic acid (7.2%) and trimethoprim-sulfamethoxazole (24.1%).

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Klebsiella spp. in blood cultures

TABLE 58. *Klebsiella* spp. blood culture isolates in 2021 (n=1,045). 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	83.9	-	16.1
Piperacillin-tazobactam	≤ 8	> 8	88.1	-	11.9
Cefuroxime	≤ 0.001	> 8	0.0	87.3	12.7
Cefotaxime	≤ 1	> 2	92.6	0.9	6.5
Ceftazidime	≤ 1	> 4	92.6	1.7	5.7
Cefepime	≤ 1	> 4	89.7	3.4	6.9
Meropenem	≤ 2	> 8	99.8	0.0	0.2
Gentamicin	≤ 2	> 2	95.8	-	4.2
Tobramycin	≤ 2	> 2	95.4	-	4.6
Amikacin	≤ 8	> 8	97.8	-	2.2
Ciprofloxacin	≤ 0.25	> 0.5	87.1	4.0	8.9
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	87.9	0.2	11.9
ESBL	Negative	Positive	94.5	-	5.5

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

TABLE 59. *Klebsiella pneumoniae* blood culture isolates in 2021 (n=759). 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	88.4	-	11.6
Cefuroxime	≤ 0.001	> 8	0.0	87.9	12.1
Cefotaxime	≤ 1	> 2	92.9	0.1	7.0
Ceftazidime	≤ 1	> 4	91.6	2.1	6.3
Cefepime	≤ 1	> 4	89.2	3.2	7.6
Meropenem	≤ 2	> 8	99.7	0.0	0.3
Gentamicin	≤ 2	> 2	95.3	-	4.7
Tobramycin	≤ 2	> 2	94.7	-	5.3
Amikacin	≤ 8	> 8	98.0	-	2.0
Ciprofloxacin	≤ 0.25	> 0.5	83.7	5.1	11.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.5	0.3	14.2
ESBL	Negative	Positive	93.3	-	6.7

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

TABLE 60. *Klebsiella oxytoca* blood culture isolates in 2021 (n=258). 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	85.7	-	14.3
Piperacillin-tazobactam	≤ 8	> 8	87.6	-	12.4
Cefuroxime	≤ 0.001	> 8	0.0	86.0	14.0
Cefotaxime	≤ 1	> 2	93.0	3.1	3.9
Ceftazidime	≤ 1	> 4	96.1	0.8	3.1
Cefepime	≤ 1	> 4	90.3	4.7	5.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	96.9	-	3.1
Tobramycin	≤ 2	> 2	96.9	-	3.1
Amikacin	≤ 8	> 8	97.7	-	2.3
Ciprofloxacin	≤ 0.25	> 0.5	96.1	0.8	3.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	93.8	0.0	6.2
ESBL	Negative	Positive	97.7	-	2.3

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

TABLE 61. *Klebsiella aerogenes* blood culture isolates in 2021 (n=28). 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	3.6	-	96.4
Piperacillin-tazobactam	≤ 8	> 8	85.7	-	14.3
Cefuroxime	≤ 0.001	> 8	0.0	82.1	17.9
Cefotaxime	≤ 1	> 2	82.1	0.0	17.9
Ceftazidime	≤ 1	> 4	85.7	0.0	14.3
Cefepime	≤ 1	> 4	96.4	0.0	3.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	100.0	-	0.0
Tobramycin	≤ 2	> 2	100.0	-	0.0
Amikacin	≤ 8	> 8	92.9	-	7.1
Ciprofloxacin	≤ 0.25	> 0.5	96.4	3.6	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	100.0	0.0	0.0
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 infections other than uncomplicated urinary tract infections. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Klebsiella spp. isolates in blood cultures were categorised as follows: 759 (72.6%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola,* and *K. africana*); 258 (24.7%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis,* and *K. spallanzanii*): and 28 (2.7%) *K. aerogens*, giving a total of 1,045 *Klebsiella* spp. isolates (Tables 58-61).

The majority of *Klebsiella* spp. isolates were susceptible to aminoglycosides, and the prevalence of gentamicin resistance remained stable at 4.2% in 2021 compared to 4.4% in 2019 and 5.2% in 2020. The prevalence of resistance to tobramycin was 4.6%, whereas almost all isolates (97.8%) were susceptible to amikacin. Gentamicin resistance was equally common in *K. pneumoniae* (4.7%) and *K. oxytoca* (3.1%), but was not seen 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 8.1% in 2020 and 8.9% in 2021. 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* (11.2%) than in *K. oxytoca* (3.1%) and *K. aerogenes* (0.0%). Resistance to trimethoprim-sulfamethoxazole remained unchanged at 11.9% in 2021 compared to 12.2% in 2020. As for ciprofloxacin, the prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (6.2%) and *K. aerogenes* (0.0%) 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 (defined as S+I) to cefotaxime (92.6%), ceftazidime (92.6%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (88.1%), see Figure 81. The prevalence of resistance to 3rd generation cephalosporins remained essentially unchanged 2020-2021. The increased resistance to piperacillin-tazobactam (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 and did not change significantly in the last year (11.9% in 2021).

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 MIC gradient tests. The prevalence of phenotypically confirmed ESBL isolates decreased from 7.2% in 2020 (9.7% in *K. pneumonia*) to 5.5% in 2021 (6.7% in *K. pneumoniae*) (Figure 79). The 57 ESBL isolates originated from 15 different laboratories and were identified as *K. pneumoniae* (n=51, 89%) or *K. oxytoca* (n=6, 11%). ESBL isolates were generally resistant to cefuroxime (56/57), cefotaxime (56/57), cefepime (53/57) and ceftazidime (49/57), and co-resistance was frequently seen for trimethoprim-sulfamethoxazole (50/57), ciprofloxacin (42/57) and gentamicin (26/57). Many isolates remained susceptible to piperacillin-tazobactam (26/57) and/or amikacin (54/57). Two *K. pneumoniae* isolates were resistant to meropenem according to the clinical breakpoint. One contained an OXA-181 enzyme whereas the other was ESBL positive, but without specific carbapenemase activity. Sixty-six additional isolates (6.3%) displayed a zone diameter below the meropenem screening breakpoint of 28 mm, but carbapenemase production was not confirmed in any of them.

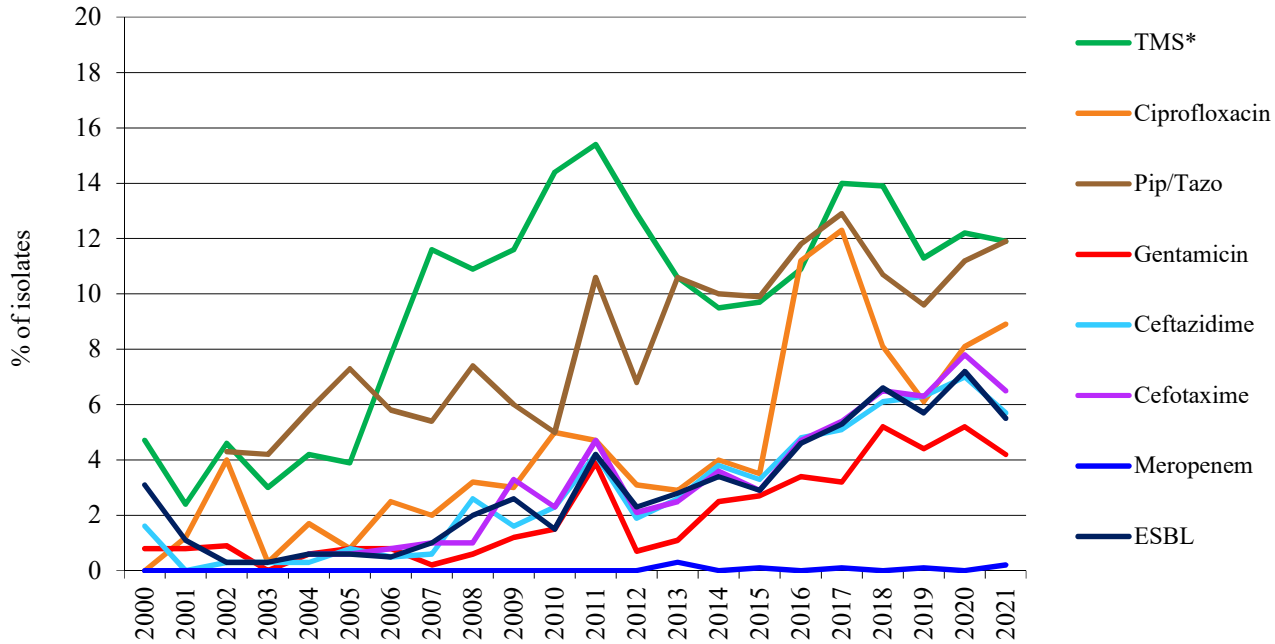

FIGURE 81. Prevalence of resistance to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2021. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 62. *Klebsiella* spp. urinary tract isolates in 2021 (n=986). 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	90.4	-	9.6
Piperacillin-tazobactam	≤ 8	> 8	92.1	-	7.9
Cefalexin	≤ 16	> 16	90.0	-	10.0
Cefotaxime	≤ 1	> 2	94.9	0.7	4.4
Ceftazidime	≤ 1	> 4	94.8	1.3	3.9
Cefepime	≤ 1	> 4	93.1	2.1	4.8
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 2	98.0	-	2.0
Tobramycin	≤ 2	> 2	97.6	-	2.4
Ciprofloxacin	≤ 0.25	> 0.5	92.4	3.2	4.4
Trimethoprim	≤ 4	> 4	85.5	-	14.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	89.1	0.5	10.4
ESBL	Negative	Positive	96.1	-	3.9

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

TABLE 63. *Klebsiella pneumoniae* urinary tract isolates in 2021 (n=734). 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	92.2	-	7.8
Amoxicillin-clavulanic acid*	≤ 32	> 32	95.5	-	4.5
Piperacillin-tazobactam	≤ 8	> 8	92.4	-	7.6
Cefalexin	≤ 16	> 16	93.6	-	6.4
Cefotaxime	≤ 1	> 2	95.2	0.3	4.5
Ceftazidime	≤ 1	> 4	94.5	1.5	4.0
Cefepime	≤ 1	> 4	92.7	2.0	5.3
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 2	97.5	-	2.5
Tobramycin	≤ 2	> 2	97.1	-	2.9
Ciprofloxacin	≤ 0.25	> 0.5	90.7	4.1	5.2
Trimethoprim	≤ 4	> 4	82.7	-	17.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	87.4	0.5	12.1
ESBL	Negative	Positive	95.5	-	4.5

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

TABLE 64. *Klebsiella oxytoca* urinary tract isolates in 2021 (n=205). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	93.7	-	6.3
Amoxicillin-clavulanic acid*	≤ 32	> 32	91.2	-	8.8
Piperacillin-tazobactam	≤ 8	> 8	91.7	-	8.3
Cefalexin	≤ 16	> 16	94.1	-	5.9
Cefotaxime	≤ 1	> 2	95.6	2.0	2.4
Ceftazidime	≤ 1	> 4	98.0	0.5	1.5
Cefepime	≤ 1	> 4	94.2	2.9	2.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	99.0	-	1.0
Tobramycin	≤ 2	> 2	98.5	-	1.5
Ciprofloxacin	≤ 0.25	> 0.5	96.6	1.0	2.4
Trimethoprim	≤ 4	> 4	93.2	-	6.8
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	93.6	0.5	5.9
ESBL	Negative	Positive	98.5	-	1.5

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

TABLE 65. *Klebsiella aerogenes* urinary tract isolates in 2021 (n=47). 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	91.5	-	8.5
Amoxicillin-clavulanic acid*	≤ 32	> 32	6.4	-	93.6
Piperacillin-tazobactam	≤ 8	> 8	89.4	-	10.6
Cefalexin	≤ 16	> 16	14.9	-	85.1
Cefotaxime	≤ 1	> 2	87.3	2.1	10.6
Ceftazidime	≤ 1	> 4	85.1	2.1	12.8
Cefepime	≤ 1	> 4	95.7	0.0	4.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	100.0	-	0.0
Tobramycin	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Trimethoprim	≤ 4	> 4	95.7	-	4.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.7	0.0	4.3
ESBL	Negative	Positive	95.7	-	4.3

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. ESBL=Extended spectrum beta-lactamase. *Breakpoints for uncomplicated urinary tract infections. **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 2012-2020. 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. The urinary tract isolates in NORM 2021 were categorised as follows: 734 (74.4%) *K. pneumoniae* (including *K. pneumoniae, K. quasipneumoniae, K. variicola, K. quasivariicola* and *K. africana*); 205 (20.8%) *K. oxytoca* (including *K. oxytoca, K. michiganensis, K. grimontii, K. pasteurii, K. huaxiensis* and *K. spallanzanii*): and 47 (4.8%) *K. aerogens*, giving a total of 1,045 *Klebsiella* spp. isolates (Tables 62-65).

The prevalence of resistance to urinary tract antibiotics was slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Table 57). The majority of isolates remained susceptible to gentamicin at 98.0% compared to 96.2% in 2020. Among urinary tract *E. coli*, 96.9% were susceptible to gentamicin in 2021. The rates of resistance to ciprofloxacin in *Klebsiella* spp. decreased from 6.1% in 2020 to 4.4% in 2021. The comparable rate for urinary tract *E. coli* in 2021 was 7.9%. Susceptibility to trimethoprim (84.3% in 2020; 85.5% in 2021) and trimethoprim-sulfamethoxazole (88.0% in 2020; 89.1% in 2021) was higher than in *E. coli* (79.6% and 81.3% in 2021, respectively). Our results indicate that the *E. coli* breakpoints for fosfomycin are not suitable for *Klebsiella* (data not shown).

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 MIC gradient tests. Thirty-eight isolates (3.9%) were reported as ESBL positive, of which 33 were *K. pneumoniae*, three were *K. oxytoca*, and two were identified as *K. aerogenes*. They were retrieved from 11 different laboratories and originated from hospital inpatients (n=20), outpatient clinics (n=4), general practices (n=11) or nursing homes (n=3). The 3.9% ESBL rate (4.5% in *K. pneumoniae*) was a decrease from 2020 (4.5% for all *Klebsiella*, 5.7% in *K. pneumoniae*). The 38 ESBL isolates were often resistant to trimethoprim (n=29), trimethoprim-sulfamethoxazole (n=28), ciprofloxacin (n=14) and gentamicin (n=13), but many remained susceptible to mecillinam (n=31) and piperacillin-tazobactam (n=25). *K. aerogenes* isolates demonstrated high rates of resistance to amoxicillin-clavulanic acid (93.6%) and cefalexin (85.1%), presumably due to chromosomal AmpC production. A single meropenem resistant *K. pneumoniae* isolate contained an NDM determinant, whereas 26 additional isolates with zone diameters below the screening breakpoint of 28 mm did not display carbapenemase production.

Carbapenemase-producing Gram-negative bacteria in Norway 2021

Carbapenem resistance in Gram-negative bacteria is increasing and is a major contributor to the burden of antimicrobial resistance (1,2). The epidemiologically most important resistance mechanism is carbapenemases encoded by genes located on mobile genetic elements. In Norway, colonisation or infections with carbapenemase-producing Gram-negative bacteria (*Enterobacterales*, *Pseudomonas* sp. and *Acinetobacter* sp.) are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS). Confirmation and characterisation of isolates is performed at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance. Here we summarise the findings for 2021.

Enterobacterales

Sixty cases of carbapenemase-producing *Enterobacterales* (CPE) were identified in 2021 (Figure 82). This is at a similar level as in 2020. Thirty-four percent of the cases were associated with import and 20% likely associated with domestic acquisition or spread. For the remaining 46%, status related to import was not reported.

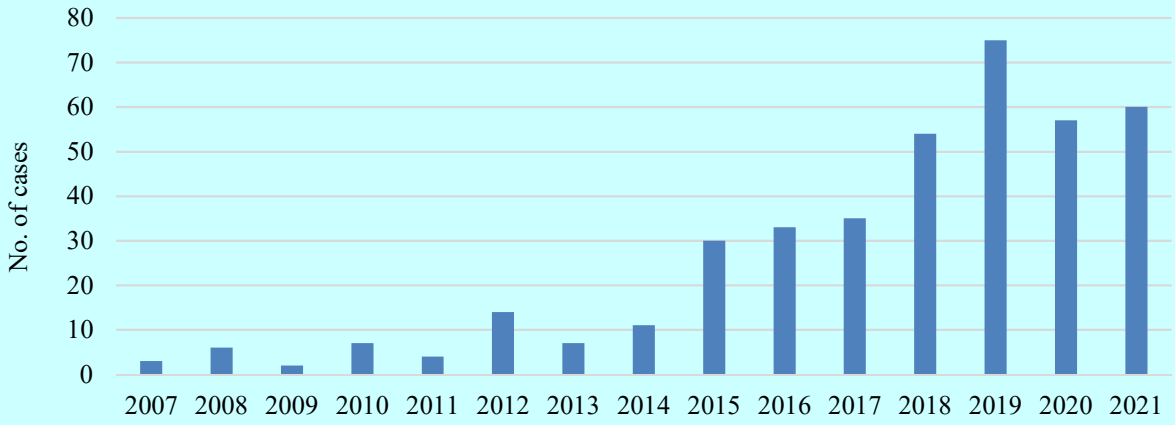

FIGURE 82. Number of cases with carbapenemase-producing *Enterobacterales* in Norway 2007-2021.

Sixty-two CPE isolates were identified and 46% reported as associated to clinical infection. *Escherichia coli* isolates decreased from 45 in 2020 to 29 in 2021 while the number of *Klebsiella pneumoniae* isolates increased from 13 in 2020 to 27 in 2021 **(**Figure 83). Four carbapenemase-producing *Enterobacter* sp. and one each of *Citrobacter* sp. and *Klebsiella oxytoca* were identified.

As in previous years OXA-48-like (n=42) and NDM variants (n=18) were dominating (Figure 84). This includes four isolates where more than one carbapenemase gene (NDM-1 + OXA-181, NDM-5 + OXA-181, NDM-5 + OXA-232 and NDM-1 + KPC-2) were identified. The GES carbapenemase variant GES-9, was for the first time identified among CPE isolates in Norway in a *Citrobacter* sp. isolate. IMI (IMI-1 and IMI-4) was identified in two *Enterobacter* sp. isolates. The *K. oxytoca* isolate harboured KPC-2.

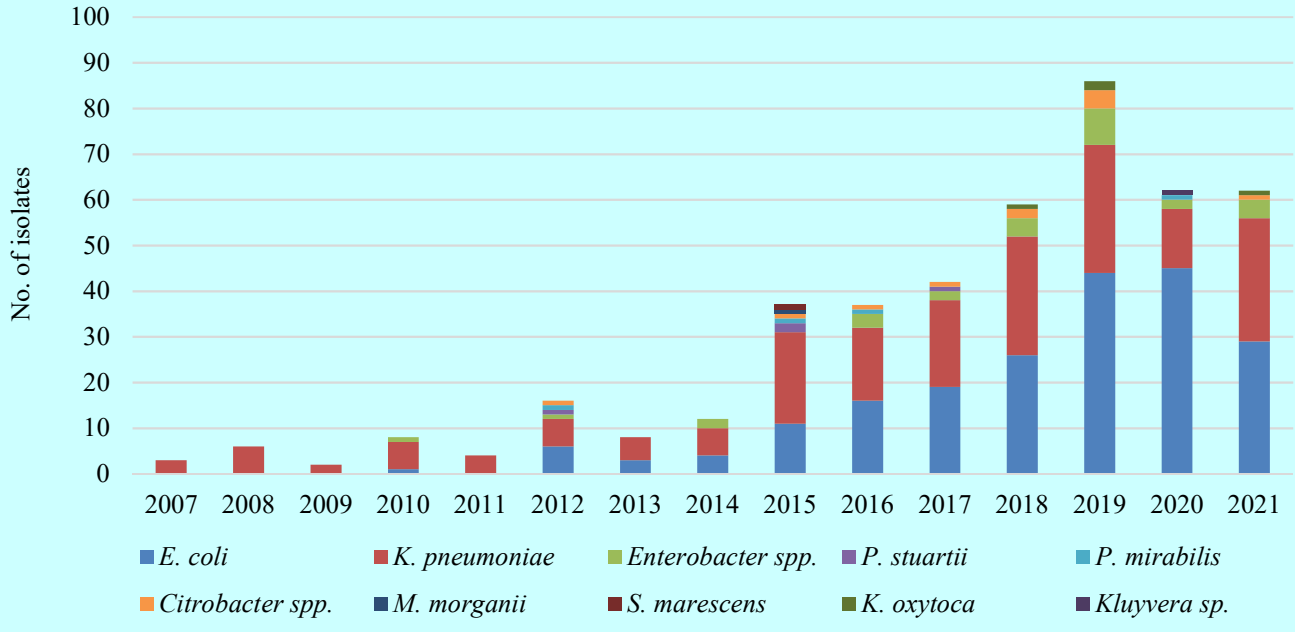

FIGURE 83. Number of carbapenemase-producing *Enterobacterales* isolates according to species.

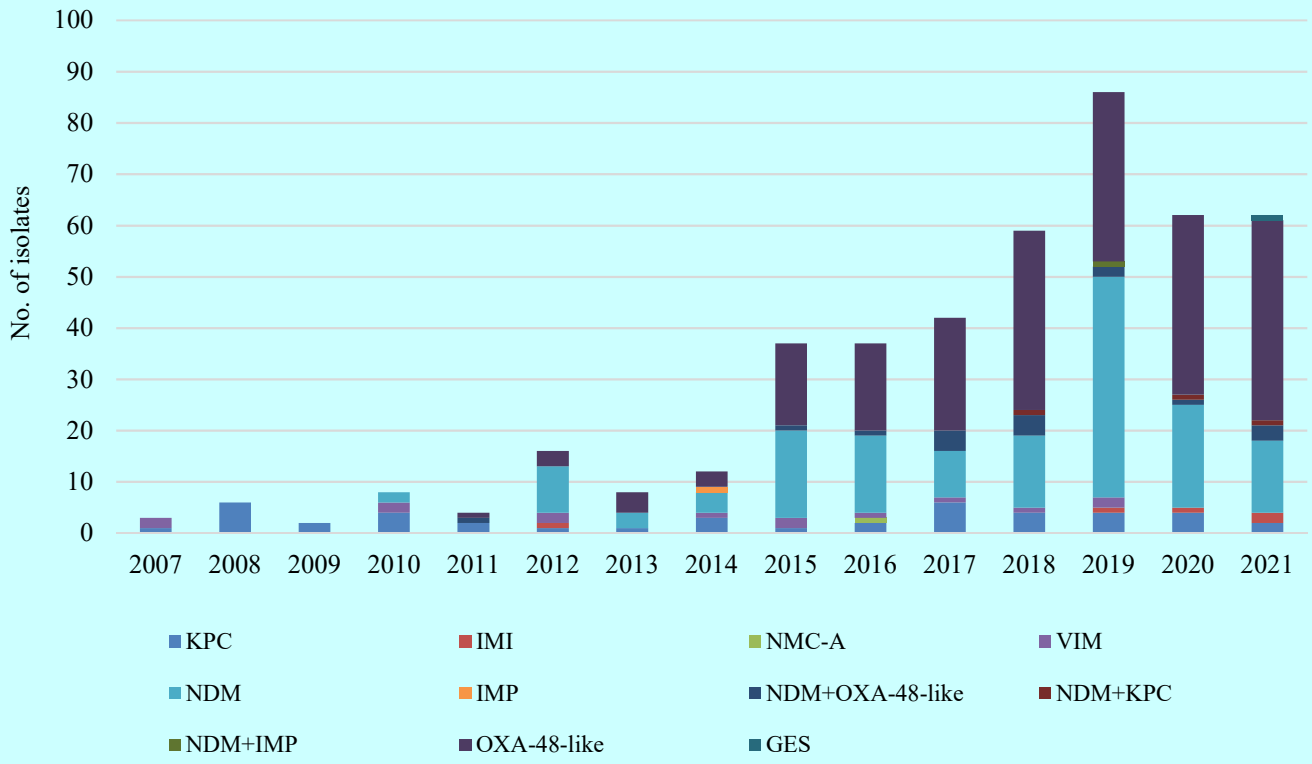

FIGURE 84. Number of carbapenemase variants among *Enterobacterales* isolates in Norway 2007-2021.

Whole genome sequencing of the isolates revealed a large diversity in terms of sequence types (ST) and carbapenemase variants. Twenty-two different STs were identified among the 29 *E. coli* isolates (Figure 85). Several identified STs including ST131, ST167, ST410 and ST1193 are known globally disseminated multi-drug resistant high-risk clones (3). In only three isolates the same carbapenemase variant was identified in an isolate of the same ST. No closely related isolates were revealed by phylogenetic analysis based on core genome multilocus sequence typing (cgMLST) (Figure 86).

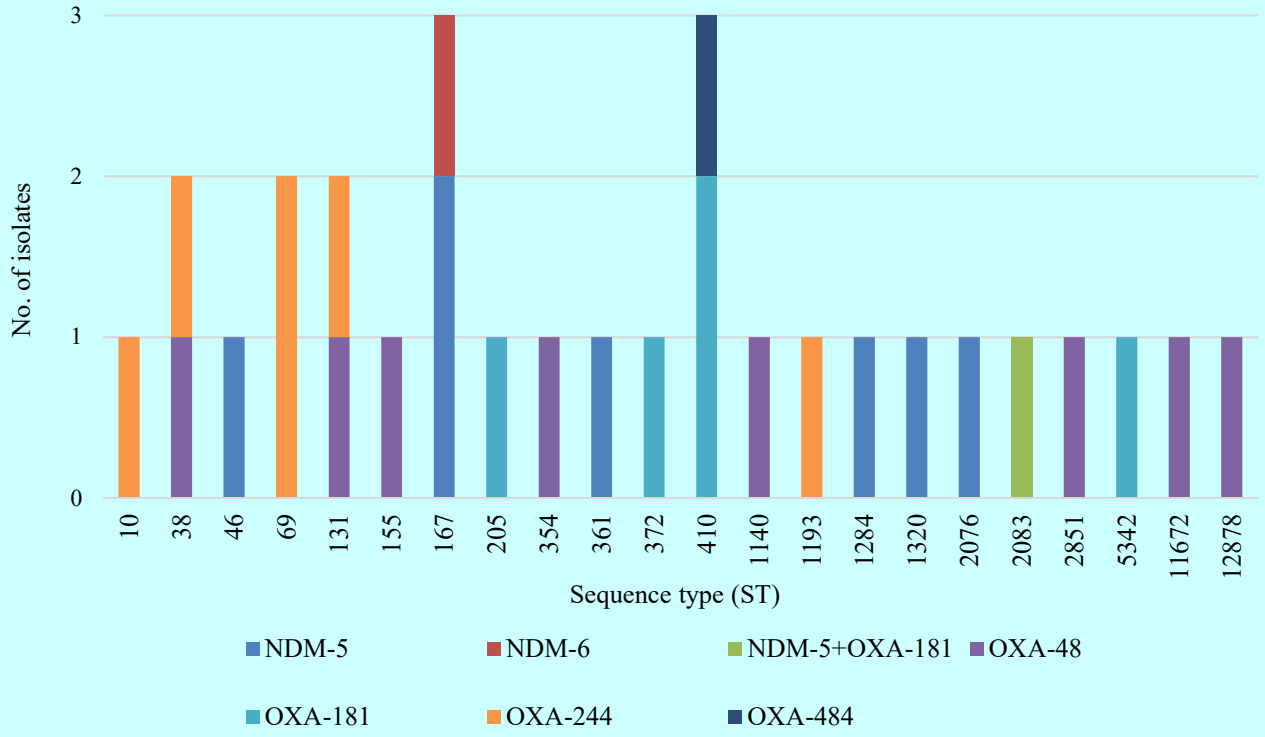

FIGURE 85. Carbapenemase variant according to ST among carbapenemase-producing *E. coli* identified in 2021.

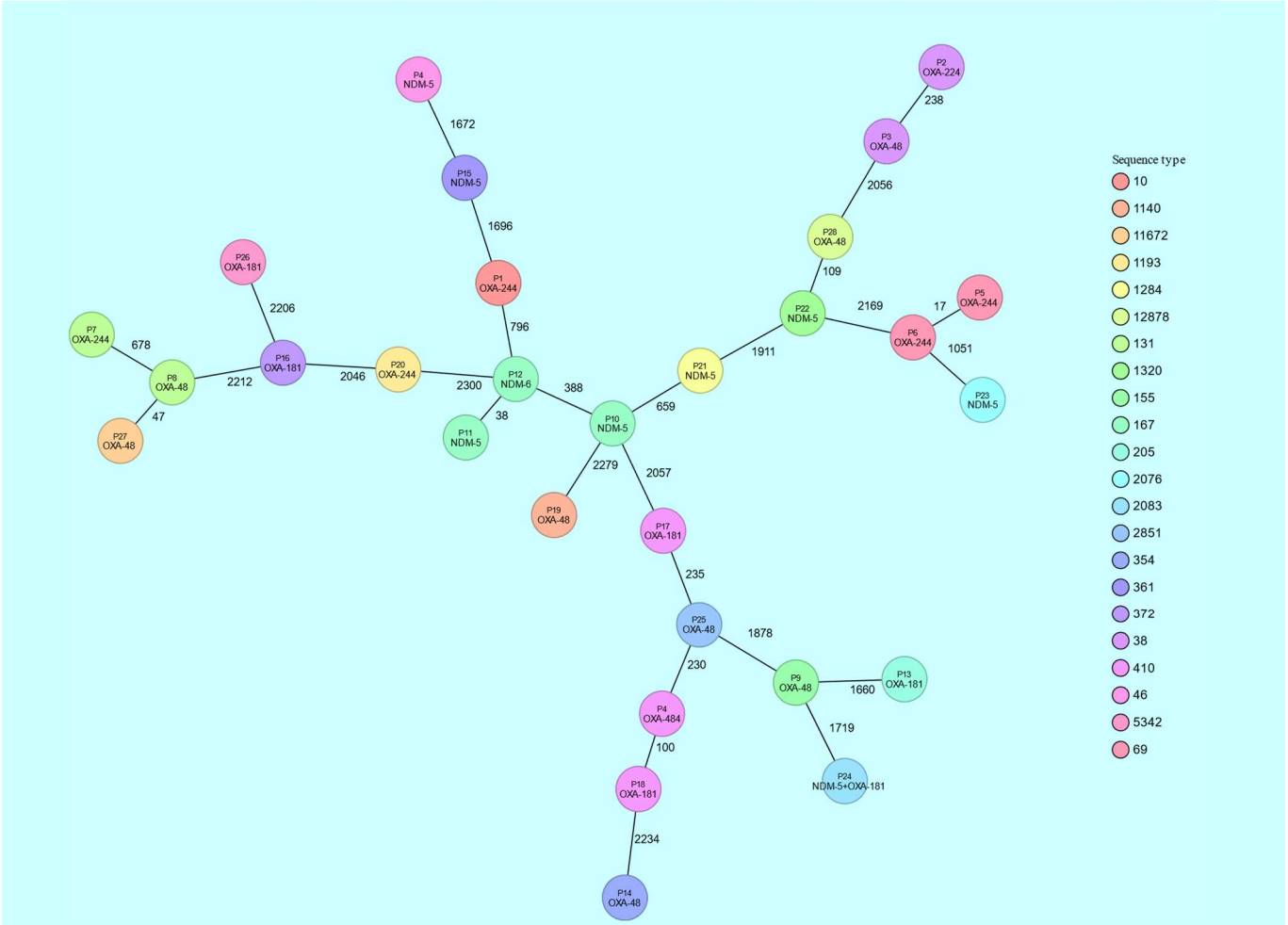

FIGURE 86. Minimum spanning tree based on the core genome allelic profile of carbapenemase-producing *E. coli* identified in Norway 2021, using Ridom-SeqSphere+ with integrated cgMLST scheme and *E. coli* K12 as reference. Each isolate is represented by a circle coloured according to ST. Specific carbapenemase variant(s) is indicated for each isolate and number of allelic differences between isolates.

The 27 carbapenemase-producing *K. pneumoniae* belonged to 14 STs and nine ST/carbapenemase variant combinations (Figure 87).

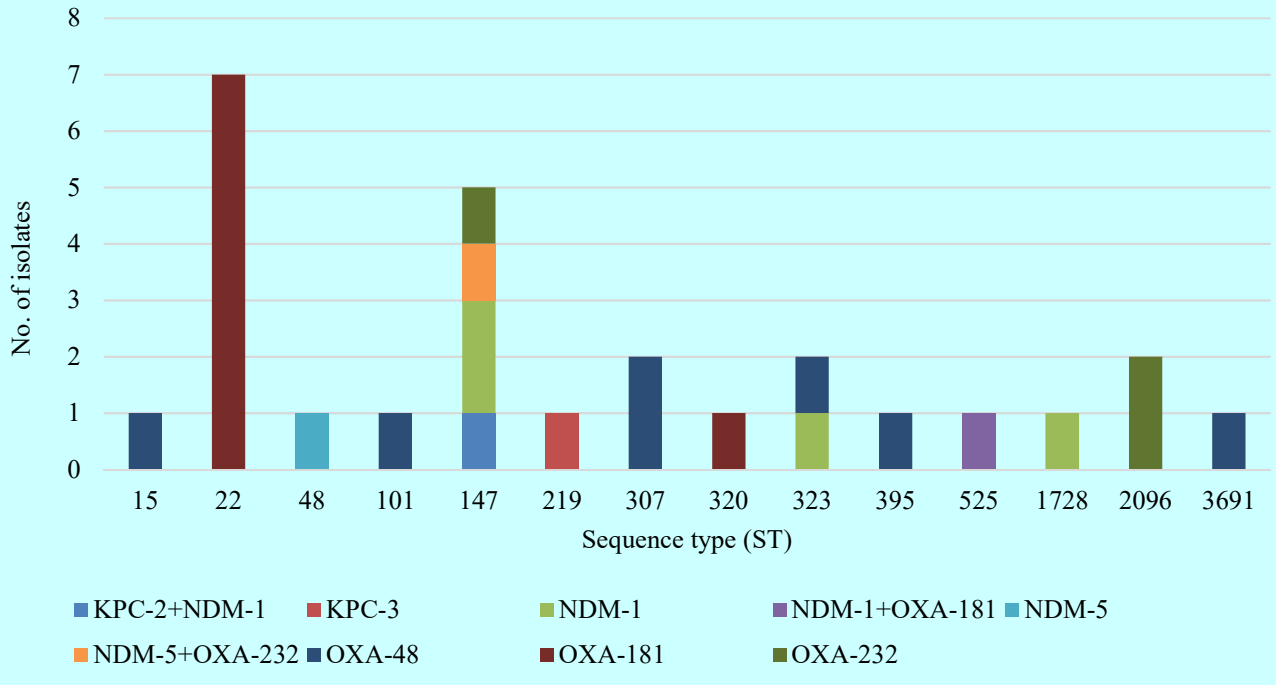

FIGURE 87. Carbapenemase variant according to ST among carbapenemase-producing *K. pneumoniae* identified in 2021.

Seven *K. pneumoniae* ST22 isolates harbouring OXA-181 were identified at the same hospital in a time-period of 10 months. Phylogenetic analysis based on cgMLST revealed close relationship between the isolates (0-7 allelic differences) (Figure 88). Epidemiological investigation confirmed an outbreak. Two other clusters of related isolates were also identified (Figure 88). Two ST147 harbouring NDM-1 and one ST147 harbouring NDM-1+KPC-2 showed 0-2 cgMLST allelic differences. The isolates were identified over a time-period of nine months and from three different laboratories. None of the isolates were associated with import. In addition, two ST307 isolates harbouring OXA-48 from two different laboratories within a three-week time-period showed two cgMLST allelic differences. Both ST307 cases were associated with import from Spain and Gran Canaria. For both the ST147 and ST307 clusters no epidemiological link between the cases could be identified. Domestic spread within Norway cannot be ruled out, but it is likely that this reflects limited within-clone evolution. Several of the STs represent known globally disseminated multi-drug resistant high-risk clones (e.g. ST15, ST101, ST147, and ST307) associated with the spread of carbapenemase genes (4,5).

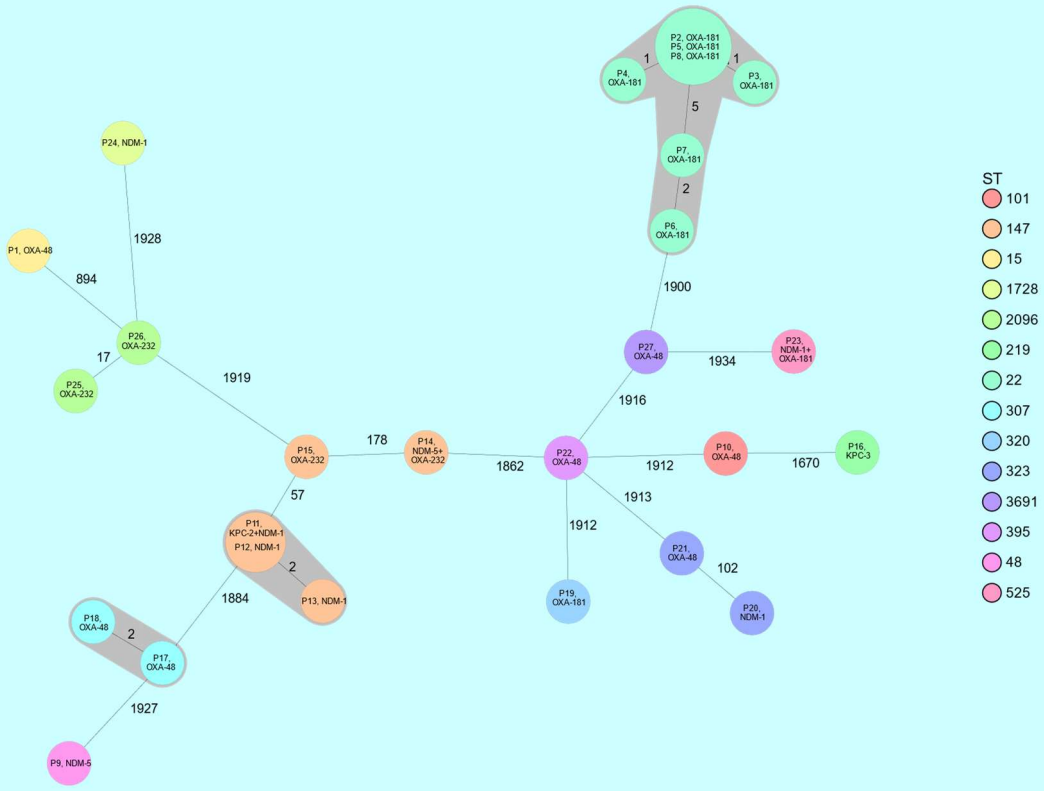

FIGURE 88. Minimum spanning tree based on the core genome allelic profile of carbapenemase-producing *K. pneumoniae* identified in Norway 2021, using Ridom-SeqSphere+ with integrated cgMLST scheme and *K. pneumoniae* NTUH-K2044 as reference. Each isolate is represented by a circle coloured according to ST. Specific carbapenemase variant is indicated for each isolate and number of allelic differences between isolates. Closely related isolates (≤15 allelic differences) are highlighted with grey shading.

Six other isolates of carbapenemase-producing non-*E. coli*/*K. pneumoniae* were identified in 2021 (Table 66) compared to four in 2020. One *Enterobacter* sp. isolate with OXA-181 was identified in a patient with an *E. coli* with OXA-181 which could indicate within-patient plasmid transfer.

TABLE 66. Sequence type (ST) and carbapenemase variant identified among *Enterobacter* sp., *K. oxytoca* and *Citrobacter* sp. in 2021.

Species	ST-carbapenemase variant
Enterobacter sp. (n=4)	ST901-IMI-1 (n=1); ST-novel-NDM-1 (n=1); ST-novel-IMI-4 (n=1); ST-novel-OXA-181 (n=1)
K. oxytoca (n=1)	ST199-KPC-2
Citrobacter sp. (n=1)	ST116-GES-9

The antimicrobial susceptibility categorisation of the CPE isolates is shown in Table 67. Thirty-seven percent and 34% of the isolates were resistant to meropenem and imipenem, respectively. Eighty-nine percent were resistant to ertapenem. Six *E. coli* isolates with an OXA-48-like variant, including four isolates with OXA-244, had an MIC below the NordicAST meropenem MIC screening breakpoint (<0.25 mg/L). It is known that OXA-48-like variants and in particular OXA-244 have a relatively low activity against carbapenems (6). All isolates with a meropenem MIC below the screening breakpoint were resistant to piperacillin-tazobactam. Regarding the new beta-lactam/beta-lactamase inhibitor combinations, 73% were susceptible to ceftazidime-avibactam. Avibactam has inhibitory activity against OXA-48 and KPC, but no effect against metallo-beta-lactamases (7) and all isolates resistant to ceftazidime-avibactam harboured an NDM variant. The effect of vaborbactam and relebactam in combination with meropenem and imipenem, respectively, was limited. This is due to the lack of activity of vaborbactam and relebactam against OXA-48-like and NDM variants (7) which dominates in Norway. Fifty percent of the CPE isolates were resistant to the novel siderophore cephalosporin cefiderocol (8). This includes isolates with a disc diffusion zone diameter within the EUCAST ATU (area of technical uncertainty). Forty percent of the isolates had a disc diffusion zone diameter within the ATU. Cefiderocol resistant isolates either harboured OXA-48-like (n=21), NDM (n=8) or both NDM and OXA-48-like (n=2). A high degree of co-resistance to other antimicrobial agents was observed with 82%, 44% and 69% of the CPE isolates resistant to ciprofloxacin, gentamicin and trimethoprim-sulfamethoxazole, respectively. A lower degree of resistance (21%) against amikacin was observed. A high degree of susceptibility of carbapenemase-producing *E. coli* to tigecycline (97%), nitrofurantoin (97%) and fosfomycin p.o. (100%) was observed. Ninety percent of the isolates were susceptible to colistin and 82% to fosfomycin i.v.

TABLE 67. Susceptibility profile of carbapenemase-producing *Enterobacterales* identified in Norway in 2021[1].

Antimicrobial agent	S (%)	I (%)	R (%)
Piperacillin-tazobactam	1.6		98.4
Temocillin		8.6	91.4
Cefotaxime	9.7	4.8	85.5
Ceftazidime	11.3	14.5	74.2
Ceftazidime-avibactam	72.6		27.4
Ceftolozane-tazobactam	21.0		79.0
Cefiderocol[2,3]	50.0		50.0
Cefepime	14.5	16.1	69.4
Aztreonam	17.7	1.6	80.6
Meropenem	51.6	11.3	37.1
Imipenem	51.6	14.5	33.9
Ertapenem	11.3		88.7
Meropenem-vaborbactam	67.7		32.3
Imipenem-relebactam	62.9		37.1
Ciprofloxacin	12.9	4.8	82.3
Gentamicin	56.5		43.5
Tobramycin	46.8		53.2
Amikacin	79.0		21.0
Trimethoprim-sulfamethoxazole	29.0	1.6	69.4
Tigecycline[4]	96.6		3.4
Colistin	90.3		9.7
Nitrofurantoin[4]	96.6		3.4
Fosfomycin (p.o.)[4.5]	100.0		0.0
Fosfomycin (i.v.)[5]	82.3		17.7

[1]Categorisation according to NordicAST breakpoint table v.12. [2]Based on disc diffusion, other agents based on MIC using broth microdilution. [3]Zone diameters within the ATU (18-22 mm) interpreted as resistant. [4]*E. coli* only.[5]Fosfomycin results must be interpreted with caution. The reference method for fosfomycin MIC determination is agar dilution. Some studies have shown lack of correlation between broth microdilution and agar dilution in particular for *K. pneumoniae* (9,10).

***Pseudomonas* sp.**

A single case of carbapenemase-producing *P. aeruginosa* was identified in 2021 compared to four in 2020 (Figure 89). The case was associated with import and identified in a clinical sample material. The isolate belonged to the known global high-risk clone ST235 and harboured VIM-4.

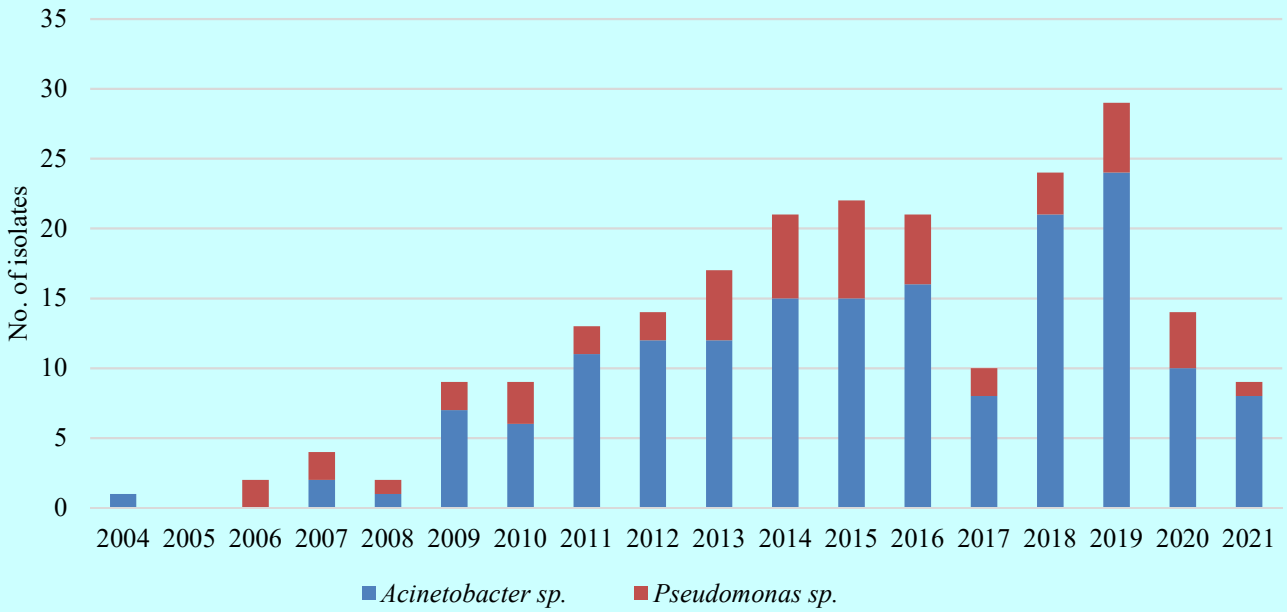

FIGURE 89. Number of carbapenemase-producing *Pseudomonas* sp. and *Acinetobacter* sp. in Norway 2004-2021.

***Acinetobacter* sp.**

Eight cases of carbapenemase-producing *A. baumannii* were identified in 2021 compared to 10 in 2020 (Figure 89). All cases were associated with import. Seven isolates were *A. baumannii* of which six of the isolates belonged to the global clone ST2 (11) harbouring either OXA-23 (n=5) or OXA-72 (n=1). One *A. baumannii* ST215 harbouring OXA-23 was identified. In addition, one NDM-1 harbouring *Acinetobacter* sp. (probably *Acinetobacter indicus*) was identified. Phylogenetic analysis based on cgMLST showed that none of the *A. baumannii* isolates were closely related (Figure 90). Thus, there is no indication of within-country spread of carbapenemase-producing *Acinetobacter* sp.

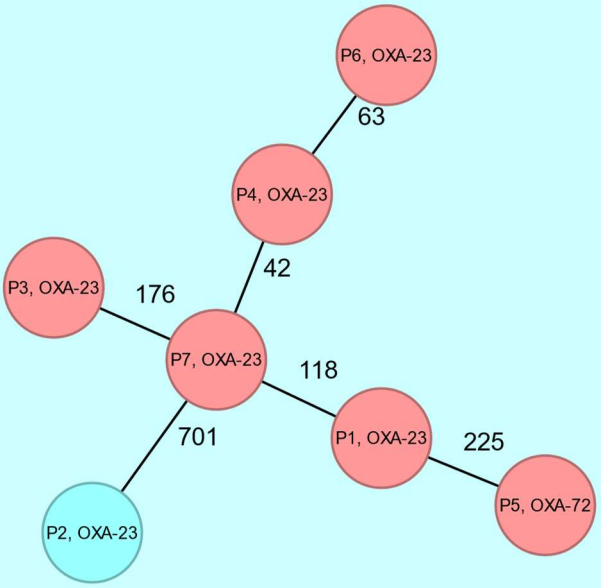

FIGURE 90. Minimum spanning tree based on the core genome allelic profile of carbapenemase-producing *A. baumannii* identified in Norway 2021, using Ridom-SeqSphere+ with integrated cgMLST scheme and *A. baumannii* ACICU as reference. Each isolate is represented by a circle coloured according to ST (red: ST2; blue: ST215). Specific carbapenemase variant is indicated for each isolate and number of allelic differences between isolates.

Conclusion

No significant changes in the prevalence of carbapenemase-producing Gram-negative bacteria have occurred between 2020 and 2021. This might be due to travel restrictions and infection control measures implemented in connection with the Covid-19 pandemic. Whole genome sequencing shows a large diversity of clones and carbapenemase genes, including known multi-drug resistant high-risk clones. The outbreak of *K. pneumoniae* ST22 harbouring OXA-181 (n=7) shows that carbapenemase-producing isolates can get a foothold in Norwegian hospitals.

Detection of known carbapenemase-producing high-risk clones like *P. aeruginosa* ST235 and *A. baumannii* ST2 associated with import shows that Norway takes part in the global spread of antimicrobial resistance. There is no indication of within-country spread of carbapenemase-producing *P. aeruginosa* or *A. baumannii* based on the genetic analyses or epidemiological data.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 68. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2021 (n=63). 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	79.4	-	20.6
Amoxicillin-clavulanic acid	≤ 2	> 2	100.0	-	0.0
Cefuroxime	≤ 1	> 2	77.8	12.7	9.5
Cefotaxime	≤ 0.125	> 0.125	100.0	-	0.0
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	95.2	-	4.8
Tetracycline	≤ 2	> 2	95.2	-	4.8
Trimethoprim-sulfamethoxazole**	≤ 0.5	> 1	80.9	3.2	15.9
Beta-lactamase	Negative	Positive	87.3	-	12.7

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 69. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2021 (n=63). 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*					1.6	3.2	11.1	47.6	15.9	7.9	1.6	1.6	3.2	1.6		4.8
Amoxi-clav**					1.6	1.6	12.7	42.9	30.2	11.1						
Cefuroxime							3.2	9.5	65.1	12.7		1.6	1.6	4.8	1.6	
Cefotaxime	3.2	15.9	39.7	28.6	7.9	4.8										
Ceftriaxone			87.3	9.5	3.2											
Meropenem*		1.6	4.8	14.3	36.5	34.9	7.9									
Ciprofloxacin	19.0	57.1	23.8													
Chloramph.							1.6	55.6	38.1			4.8				
Tetracycline							3.2	77.8	14.3		4.8					
TMS***		7.9	33.3	22.2	7.9	3.2	1.6	4.8	3.2		3.2			12.7		

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. *The breakpoints used are for indications other than meningitis. **Amoxi-clav=Amoxicillin-clavulanic acid. ***TMS=Trimethoprim-sulfamethoxazole. 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 by the Reference Laboratory at the Norwegian Institute of Public Health on a yearly basis, but the number of isolates was limited in 2021 due to the ongoing pandemic. A total of 63 *H. influenzae* isolates were recovered from blood cultures (n=58) and cerebrospinal fluids (n=5). Both isolates were included from patients with combined bacteremia and meningitis (Tables 68-69). The results should be interpreted with caution due to a low number of isolates.

The rate of ampicillin resistance increased from 16.3% in 2020 to 20.6% in 2021, but the number of isolates is too low to draw any firm conclusions. Beta-lactamase production was detected in 8/63 isolates (12.7%), which is a decrease compared to the pre-pandemic years 2016 (17.3%) and 2017 (17.8%). Cefuroxime MIC > 2 mg/L has been suggested as the most precise indicator for chromosomal beta-lactam resistance encoded by alterations in the wild type PBP3 sequence. Six isolates (9.5%) displayed this phenotype compared to 11.6% in 2020. Five of these isolates were also resistant to ampicillin, but all remained susceptible to amoxicillin-clavulanic acid. All cefuroxime resistant isolates were beta-lactamase negative. Reduced susceptibility to cefotaxime, ceftriaxone and/or meropenem was not found, but such isolates have previously been detected in Norway.

Different substrates have been suggested for screening of beta-lactam resistance in *H. influenzae*. The penicillin G 1U disk (PCG1) successfully identified all ampicillin (n=13) and cefuroxime (n=6) resistant isolates. Eleven out of 55 (20.0%) beta-lactamase negative isolates were resistant to PCG1. Most of these isolates were resistant to both ampicillin (n=5) and cefuroxime (n=6), and only five isolates remained fully susceptible to both agents.

As seen in previous surveys of systemic *H. influenzae* isolates, resistance to ciprofloxacin (0.0%), tetracycline (4.8%) and chloramphenicol (4.8%) was at very low levels. The 15.9% resistance rate to trimethoprim-sulfamethoxazole was a decrease compared to 30.2% in 2020, but at the same level as 15.3% in 2017.

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 70. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2021 (n=5). 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	100.0	-	0.0
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Ciprofloxacin	≤ 0.03	> 0.03	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 71. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2021 (n=5). 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		3											
Ceftriaxone			5													
Ciprofloxacin	5															
Chloramph.							1	3	1							
Rifampicin	5															
Tetracycline						3	1	1								
Azithromycin				1		1	2	1								

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 a yearly basis. The EUCAST/NordicAST breakpoint for susceptibility to penicillin G was increased to S ≤ 0.25 in 2020, thus eliminating the I category. The results are presented in Tables 70-71.

Only five cases of systemic infections caused by *N. meningitidis* were reported in 2021. This is at the same level as in 2020 and the lowest number of reported cases in Norway since surveillance was initiated in 1977, and it must be seen in context with the ongoing coronavirus pandemic. All five isolates were available for further analysis and originated from blood cultures (n=3) and cerebrospinal fluids (n=2). All five isolates represented unique patients and there were no known associations between the cases. The isolates belonged to serogroups B (n=2) and Y (n=3). The three serogroup Y isolates belonged to the ST-23 clonal complex while the two serogroup B isolates belonged to two different clonal complexes, the ST-41/44 and the ST-269 clonal complexes.

All five isolates were fully susceptible to the tested antimicrobials. No clinical breakpoints have been established for azithromycin, but the MIC distribution does not indicate the presence of acquired macrolide resistance (Table 71).

Neisseria gonorrhoeae

TABLE 72. *Neisseria gonorrhoeae* from all specimen types in 2021 (n=220). 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	12.3	72.7	15.0
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	98.6	-	1.4
Ciprofloxacin	≤ 0.03	> 0.06	46.8	0.0	53.2
Tetracycline	≤ 0.5	> 1	60.9	23.6	15.5
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	82.7	-	17.3

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

TABLE 73. *Neisseria gonorrhoeae* from all specimen types in 2021 (n=220). 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*	0.9		1.4	2.3	7.7	22.3	28.6	11.4	10.5	2.7	1.8	3.2	0.9	6.4		
Ceftriaxone	46.4	5.9	42.3	3.2	2.3											
Cefixime			89.1	5.5	3.2	0.9	1.4									
Ciprofloxacin	36.8	7.3	2.3	0.5		0.5		0.9	8.2	18.2	15.0	4.5	1.4	4.5		
Tetracycline			1.4	0.5	7.7	12.7	26.4	12.3	23.6	2.7		2.7	5.5	4.1	0.5	
Spectinomycin									0.5	1.8	10.5	35.9	50.5	0.9		
Azithromycin			1.4	1.4	9.5	11.4	27.7	26.8	10.5	9.5		0.5				1.4

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. *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. The microbiological data could not be linked to information in the Norwegian Surveillance System for Communicable Diseases (MSIS).

In 2021, a total of 220 isolates were available from 207 disease episodes; 11 episodes were represented by more than one isolate. The total number is a decline from 2020 (n=442) which is presumably linked to changes in behaviour and travel during the pandemic. The isolates were reported to originate from urethra (n=92), cervix uteri (n=23), anus (n=60), throat (n=30) or "others/unknown" (n=15). A total of 182 (82.7%) isolates originated from men, 37 (16.8%) from women and one (0.5%) from unknown gender. The geographical location where the infections were acquired was in most cases unknown to the laboratory. From MSIS it is reported that gonococcal infections frequently are acquired abroad with secondary transmission in sexual networks within Norway. There is 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 72-73. A majority of isolates were either susceptible only to increased exposure (72.7%) or resistant to (15.0%) penicillin G. The corresponding figures for 2020 were 72.9% and 21.9%, respectively. Thirty-eight isolates (17.3%) produced beta-lactamase, which is a slight decrease from 2020 (18.8%). Practically all beta-lactamase positive isolates (37/38, 97.4%) were also resistant to ciprofloxacin. Three isolates (1.6%) were resistant, and 152 (83.5%) were only susceptible to increased exposure to penicillin G in spite of being beta-lactamase negative. This illustrates the alternative mechanisms for penicillin resistance, such as alterations in penicillin binding proteins (PBPs) and/or reduced permeability through the outer cell membrane.

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. Three isolates were susceptible to ceftriaxone, but resistant to cefixime. Cefixime is no longer recommended for empirical treatment in Norway. The results confirm the emergence of cephalosporin resistant gonococci in Norway, which is extremely alarming from both a clinical and a public health perspective.

The standard treatment for gonorrhoeae in Norway is now ceftriaxone 1 gram i.m. Azithromycin was previously used in a combination regimen with ceftriaxone, but it should be noted that 11.4% of the isolates displayed azithromycin MIC values above the EUCAST screening breakpoint for acquired resistance of 1 mg/L. The corresponding figure for 2020 was 7.7%. Ciprofloxacin was previously used for empirical treatment of gonorrhoeae acquired outside South-East Asia. The prevalence of ciprofloxacin resistance persisted at a high level (53.2%) in 2021. Ciprofloxacin is consequently not a viable alternative except in cases where susceptibility has been documented. All strains were susceptible to the aminocyclitol spectinomycin.

Staphylococcus aureus in blood cultures

TABLE 74. *Staphylococcus aureus* blood culture isolates in 2021 (n=1,455). 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	> 2	94.0	0.0	6.0
Clindamycin	≤ 0.25	> 0.25	98.4	-	1.6
Fusidic acid	≤ 1	> 1	96.2	-	3.8
Ciprofloxacin	≤ 0.001	> 1	0.0	91.2	8.8
Gentamicin	≤ 1	> 1	99.5	-	0.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	98.3	-	1.7
Tetracycline	≤ 1	> 2	97.0	0.4	2.6
Tigecycline	≤ 0.5	> 0.5	99.0	-	1.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.7	0.0	0.3
Beta-lactamase	Negative	Positive	31.8	-	68.2
Cefoxitin screen	≥ 22	< 22	99.2	-	0.8
MRSA** (*mecA*)	Negative	Positive	99.2	-	0.8

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

EUCAST/NordicAST has recently eliminated the I categories for clindamycin and rifampicin, thus merging them with the R categories. This will have minimal impact on AMR surveillance data as very few isolates fall within this range.

Twelve methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2021, corresponding to a prevalence of 0.8% (Table 74). This is a decline from 1.4% in 2020, but at the same level as in 2018 and 2019 (both 0.8%). The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from nine different hospitals, and there was no 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 (5/12), ciprofloxacin (5/12), gentamicin (3/12), clindamycin (2/12), trimethoprim/sulfamethoxazole (2/12), tetracycline (2/12), fusidic acid (1/12) and/or tigecycline (1/12). All MRSA isolates were susceptible to rifampicin and linezolid. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 77 on page 125. The NORM findings are at the same level as reported from the databases of the participating laboratories where 20 out of 2,028 (1.0%) *S. aureus* blood culture isolates were MRSA. None of the 19 *S. aureus* isolates recovered from cerebrospinal fluid were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 20/2,047 (1.0%). This is a slight decrease since 2020 (1.8%).

Eighty-seven *S. aureus* isolates (6.0%) were resistant to erythromycin. This is at the same level as 5.4% in 2019 and 5.9% in 2020. The macrolide resistance phenotypes of erythromycin resistant isolates were determined by the double disk diffusion (DDD) test. Five isolates (6%) were constitutively MLS_B resistant, 73 (84%) were inducibly MLS_B resistant, and 9 (10%) displayed efflux mediated M-type resistance. These figures represent 0.3%, 5.0% and 0.6% of all *S. aureus* isolates from blood cultures, respectively. The distribution of MLS phenotypes was essentially unchanged from 2020-2021.

The prevalence of resistance to fusidic acid at 3.8% was at the same level as 3.6% in 2019 and 3.7% in 2020. The 8.8% prevalence of ciprofloxacin resistance is an increase from 4.6% in 2019 and 5.1% in 2020. The breakpoint for susceptibility to ciprofloxacin was reduced from S ≤ 1 mg/L to S ≤ 0.001 mg/L in 2020, thus the wild type population of *S. aureus* is now 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 2021.

Figure 91 shows the prevalence of resistance to various antimicrobials. A total of 68.2% of the isolates were beta-lactamase positive, which is a modest decrease from 70.6% in 2019 and 68.6% in 2020. There were only minor differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

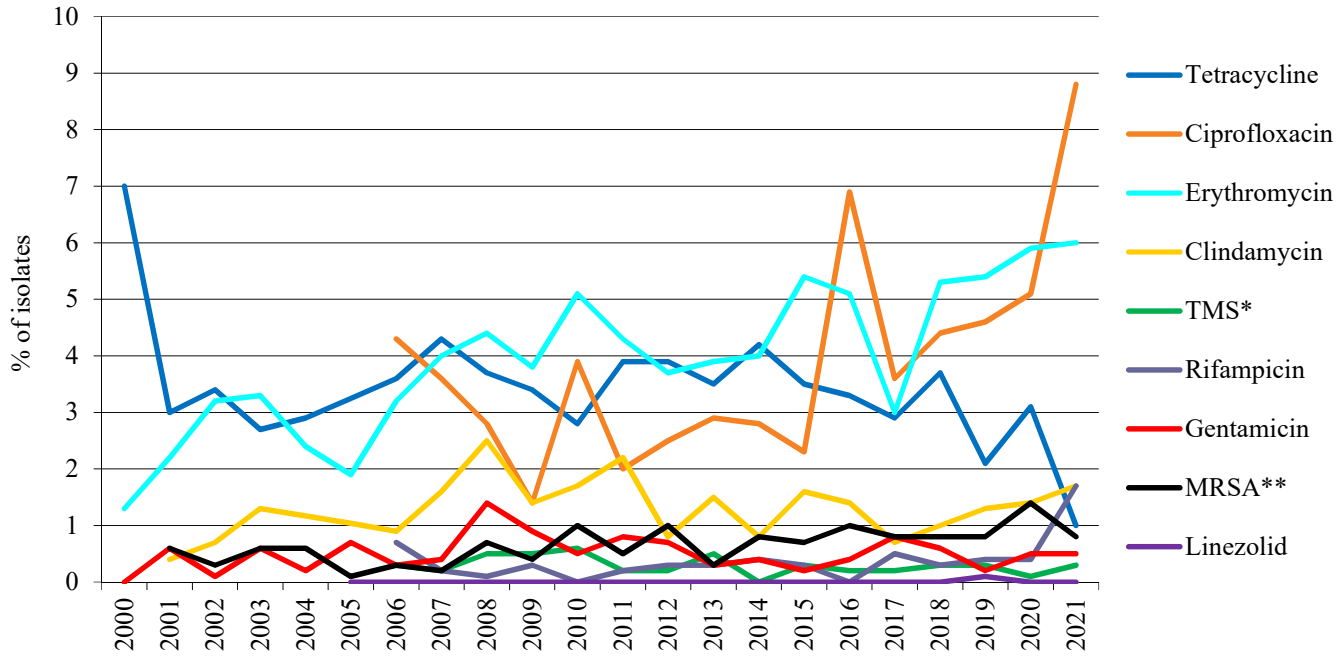

FIGURE 91. Prevalences of antimicrobial resistance among *Staphylococcus aureus* blood culture isolates 2000-2021. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Staphylococcus aureus in wound specimens

TABLE 75. *Staphylococcus aureus* isolates from wound specimens in 2021 (n=879). 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	> 2	91.5	0.5	8.0
Clindamycin	≤ 0.25	> 0.25	97.5	-	2.5
Fusidic acid	≤ 1	> 1	95.8	-	4.2
Ciprofloxacin	≤ 0.001	> 1	0.0	96.0	4.0
Gentamicin	≤ 1	> 1	99.4	-	0.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.06	98.4	-	1.6
Tetracycline	≤ 1	> 2	96.5	0.8	2.7
Tigecycline	≤ 0.5	> 0.5	99.3	-	0.7
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.7	0.1	0.2
Beta-lactamase	Negative	Positive	30.3	-	69.7
Cefoxitin screen	≥ 22	< 22	98.5	-	1.5
MRSA** (*mecA*)	Negative	Positive	98.5	-	1.5

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. **MRSA=Methicillin resistant *Staphylococcus aureus*.

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Thirteen out of 879 (1.5%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at approximately the same level as in 2019 (1.3%) and 2020 (1.8%). The MRSA isolates originated from patients visiting general practitioners (n=7, hospital wards (n=3) and nursing homes (n=3) in different parts of the country. Most MRSA isolates were co-resistant to erythromycin (6/13), tetracycline (3/13), fusidic acid (2/13), gentamicin (2/13), clindamycin (1/13), and/or ciprofloxacin (1/13) in different combinations. All MRSA isolates were susceptible to tigecycline, rifampicin, trimethoprim-sulfamethoxazole and linezolid. No isolates were reported with zone diameters below the cefoxitin screening breakpoint without being confirmed as MRSA by *mecA* PCR. This indicates high specificity of the cefoxitin screen as well as a low prevalence of *mecC* MRSA (see page 125).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates remained stable at 4.2% compared to 4.4% in 2020 (Table 75 and Figure 92). This confirms that the gradually declining prevalence of fusidic acid resistance has now levelled off after the epidemic which peaked at 25.0% in 2004. The prevalence of resistance to fusidic acid is still slightly lower in blood culture isolates (3.8 %). For other antimicrobial agents such as gentamicin, rifampicin, trimethoprim-sulfamethoxazole and tetracycline there were only minor changes from 2020-2021, and the prevalence of resistance was in general similar for blood culture isolates and isolates from wound specimens. All isolates remained phenotypically susceptible to linezolid. Seventy (8.0%) isolates were resistant to erythromycin, which is an increase from 5.9% in 2019 and 5.2% in 2020. The isolates were further examined for determination of resistance phenotype and the majority were either inducibly (53/70, 75% of erythromycin resistant isolates) or constitutively (6/70, 9% 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 (11/70, 16% of erythromycin resistant isolates) compatible with efflux mediated M-type resistance. The findings are overall in accordance with the results from previous years.

A total of 69.7% of the isolates were beta-lactamase positive compared to 75.0% in 2019 and 69.8% in 2020. There were no significant differences in resistance rates to non beta-lactam antibiotics between beta-lactamase positive isolates and beta-lactamase negative isolates.

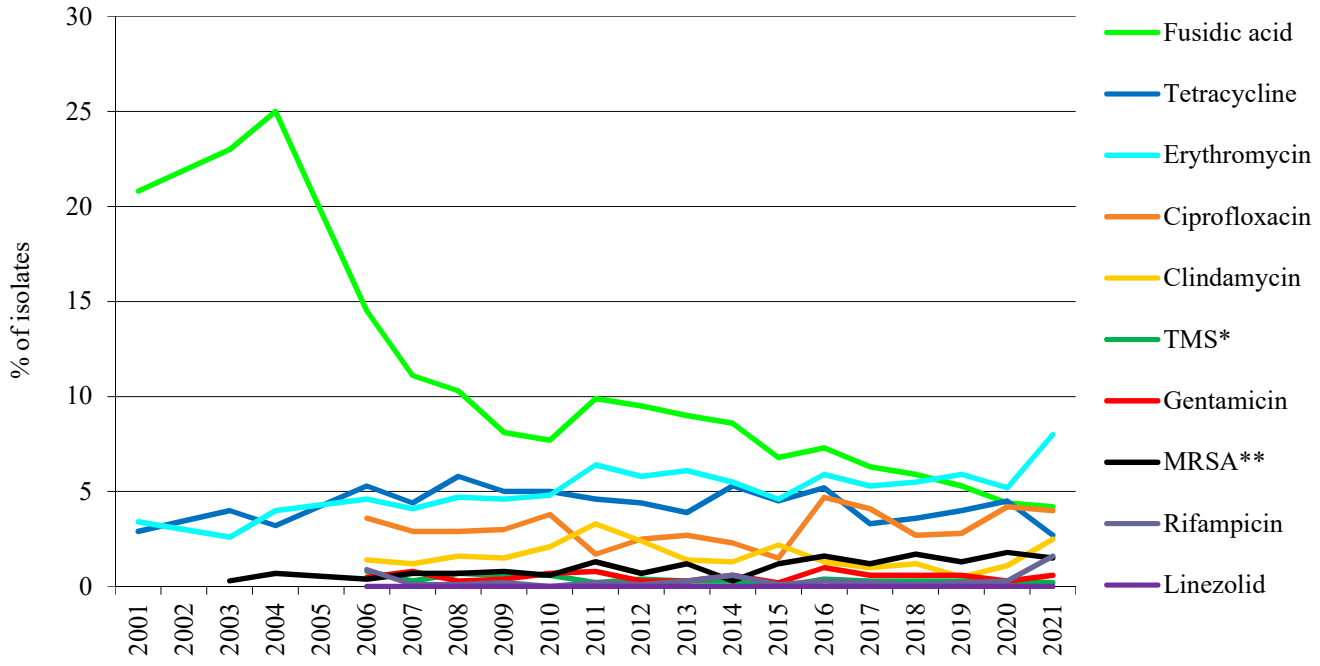

FIGURE 92. Prevalence of antimicrobial resistance among *Staphylococcus aureus* wound isolates 2001-2021. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2021

The decrease in yearly number of notified cases of MRSA continued in 2021. A total of 1,751 persons were reported diagnosed with MRSA to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2021, including 701 infections and 1,050 colonisations. The incidence rate in the form of cases per 100,000 person-years was in total 32, and 13 and 19 for infections and colonisations respectively.

The monthly number of infections has not changed significantly over the last eight years (IRR 1.01; 95% CI 1.00 – 1.02). The annual number of notified colonisations reached a peak in 2017 and has decreased significantly in the last four years (IRR 0.88; 95% CI 0.87 – 0.90) (Figure 93).

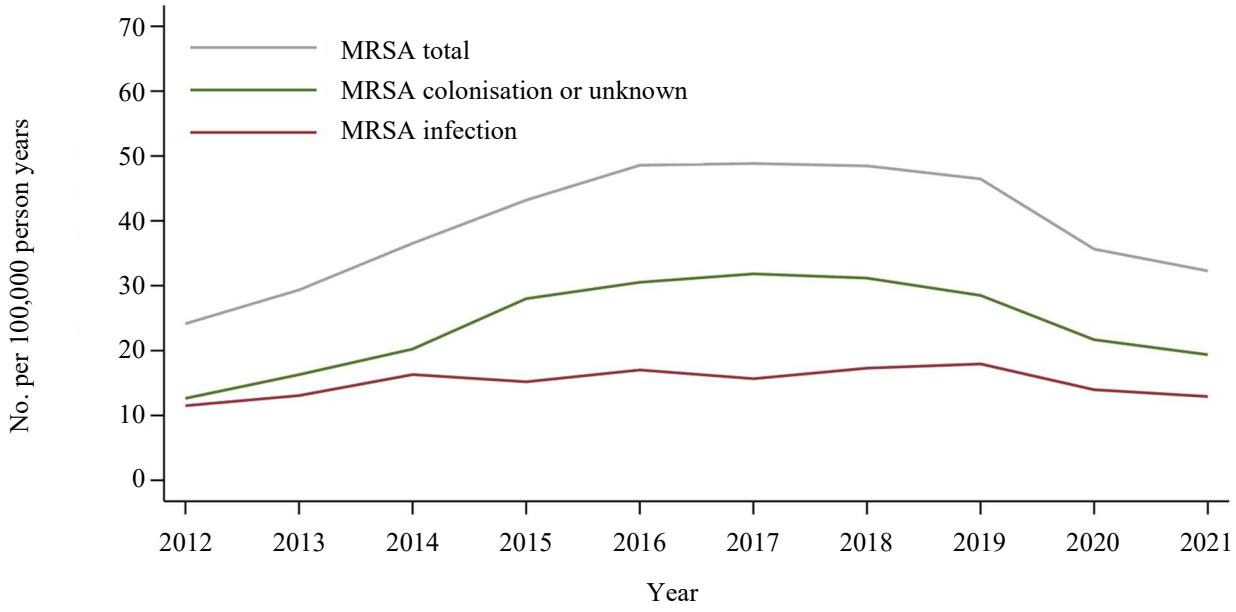

FIGURE 93. Number of persons notified with MRSA per 100,000 person-years in Norway in the last ten years, by infection and colonisation.

The spread of MRSA in the last two years has most probably been influenced by prevention and control of Covid-19, both when it comes to importation and domestic transmission of MRSA. In 2021, a total of 474 (27%) were reported to have acquired MRSA during travel abroad or prior to coming to Norway, while 560 (32%) were reported acquired MRSA in Norway. It is important to note that over 40% of all reported cases lack information about possible place of infection (Figure 94).

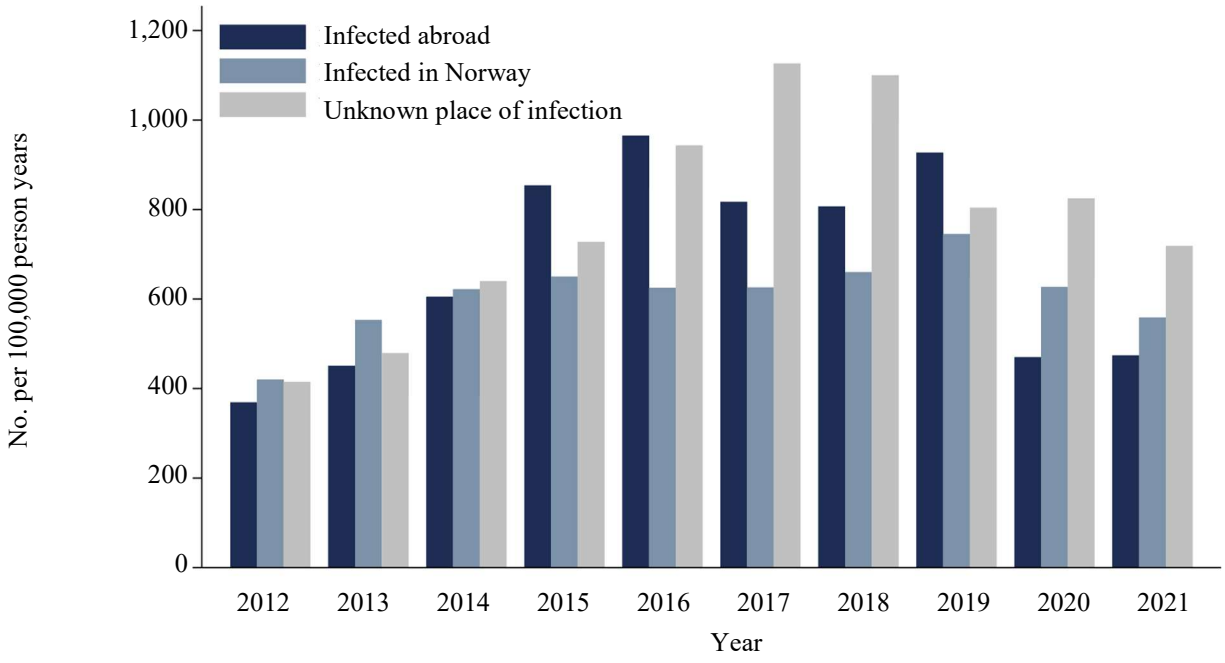

FIGURE 94. Number of persons per 100,000 person-years notified with MRSA in Norway in the last ten years, by assumed place of infection.

The Norwegian Reference Laboratory for Methicillin-resistant *Staphylococcus aureus* (MRSA) at St. Olavs Hospital, Trondheim University Hospital, received 1,899 MRSA isolates from 1,697 unique patients in 2021. Staphylococcal protein A (*spa*) typing is the main genotyping method, and 921 of 1,899 (56.6%) isolates were prioritised for *spa*-typing. Additionally, 344 isolates (18.1%) were randomly selected for s*pa*-typing, and 60 isolates (3.2%) underwent *spa*-typing by request from referring microbiology laboratories.

240 different *spa*-types were identified, of which 205 were reported less than five times.

Seven out of the ten most frequent human *spa*-types detected in 2021 were also on the top ten list for 2020 (Table 76).

TABLE 76. The ten most common *spa*-types in Norway in 2021.

spa-type	CC	No. of isolates	% of isolates genotyped
t304	6	117	8.8
t223	22	103	7.8
t127	1	88	6.6
t002	5	86	6.5
t008	8	51	3.8
t019	30	37	2.8
t021	30	36	2.7
t005	22	30	2.3
t355	152	28	2.1
t359	97	26	2.0

The MRSA Reference Laboratory identified 11 livestock-associated MRSA (LA-MRSA) in humans, defined as PVL-negative MRSA CC398. The *spa*-types were t034 (n=5), t571 (n=3), t2582 (n=2) and t011 (n=1). PVL-positive MRSA CC398 counted 21 human isolates, of *spa*-types t034 (n=17), t011 (n=2), t3275 (n=1) and t8616 (n=1). Two human isolates were positive for *mecC* (*spa*-types t6292, CC425 and t6220, CC130).

The laboratory received 27 *mecA*-positive *Staphylococcus argenteus* and 19 *mecA*-positive *Staphylococcus lugdunensis* isolates.

Antimicrobial susceptibility testing was performed by the referring laboratories according to the EUCAST disc diffusion method and interpreted using the NordicAST 2021 breakpoints (Table 77). The MRSA Reference Laboratory received 1,885 complete antibiograms. Among these strains, 684 (36.3%) were sensitive to all antibiotics tested except beta-lactams (cefoxitin). The highest proportion of resistance was found for erythromycin (35.7%), followed by tetracycline (25.3%) and ciprofloxacin (25%) The lowest rates of resistance were found for mupirocin (0.2%), rifampicin (0.9%) and trimethoprim-sulfamethoxazole (2.1%). No isolates showed decreased susceptibility to linezolid or vancomycin.

TABLE 77. MRSA isolates from human cases in 2021 (n=1,895). Distribution (% of isolates) of antimicrobial susceptibility by category.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 2	64.0	0.3	35.7
Clindamycin*	≤ 0.25	> 0.5	81.1	1.9	17.0
Fusidic acid	≤ 1	> 1	85.3	-	14.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	96.2	1.7	2.1
Tetracycline	≤ 1	> 2	74.3	0.4	25.3
Gentamicin	≤ 1	> 1	87.5	-	12.5
Rifampicin	≤ 0.06	> 0.5	98.5	0.6	0.9
Mupirocin	≤ 1	> 256	95.2	4.6	0.2
Ciprofloxacin	≤ 0.001	> 1	0.0	75.0	25.0
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, 11.5% were inducibly clindamycin resistant. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

Enterococcus spp. in blood cultures

TABLE 78. *Enterococcus* spp. blood culture isolates in 2021 (n=715). 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	86.0	0.0	14.0
Imipenem	≤ 0.001	> 4	0.0	77.5	22.5
Gentamicin HLR*	≤ 128	> 128	82.4	-	17.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	99.0	-	1.0
Vancomycin (any genotype)	≤ 4	> 4	98.9	-	1.1
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.9	-	0.1

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

TABLE 79. *Enterococcus faecalis* blood culture isolates in 2021 (n=495). 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	97.6	2.4
Gentamicin HLR*	≤ 128	> 128	91.5	-	8.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	99.4	-	0.6
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 80. *Enterococcus faecium* blood culture isolates in 2021 (n=182). 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	26.9	1.1	72.0
Imipenem	≤ 0.001	> 4	0.0	19.8	80.2
Gentamicin HLR*	≤ 128	> 128	53.8	-	46.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	97.8	-	2.2
Vancomycin (1 stk *vanA* or *vanB*)	Negative	Positive	99.5	-	0.5

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 78. The surveillance in NORM 2021 included 495 (69.2%) *E. faecalis* isolates (71.2% in 2020), 182 (25.5%) *E. faecium* isolates (21.2% in 2020), and 38 (5.3%) unspeciated or belonging to other species (7.5% in 2020). 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 and 2.7 in 2021. The panel of antimicrobial agents examined was unchanged from 2020-2021.

E. faecalis was universally susceptible to ampicillin (Table 79). The prevalence of resistance to ampicillin in *E. faecium* was 72.0% in 2021 compared to 75.9% in 2019 and 71.5% in 2020 (Table 80). As expected, the results for imipenem closely mirrored those of ampicillin. The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 8.5%, which is a further decrease from 13.6% in 2019 and 12.0% in 2020 (Figure 95). The prevalence of HLGR in *E. faecium* increased from 43.8% in 2020 to 46.2% in 2021. Almost all (81/84) HLGR *E. faecium* isolates were concomitantly resistant to ampicillin and imipenem. Conversely, 81/131 (61.8%) ampicillin resistant *E. faecium*

also displayed HLGR. High-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between amino-glycosides 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. Eight blood culture isolates were reported as vancomycin resistant in NORM 2021 (1.1%), but only one of them was confirmed by PCR to harbour transferrable vancomycin resistance (*vanA E. faecium)*. The remaining phenotypically resistant isolates were either *E. gallinarum* (n=4) or *E. casseliflavus* (n=3), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All enterococcal isolates were susceptible to linezolid.

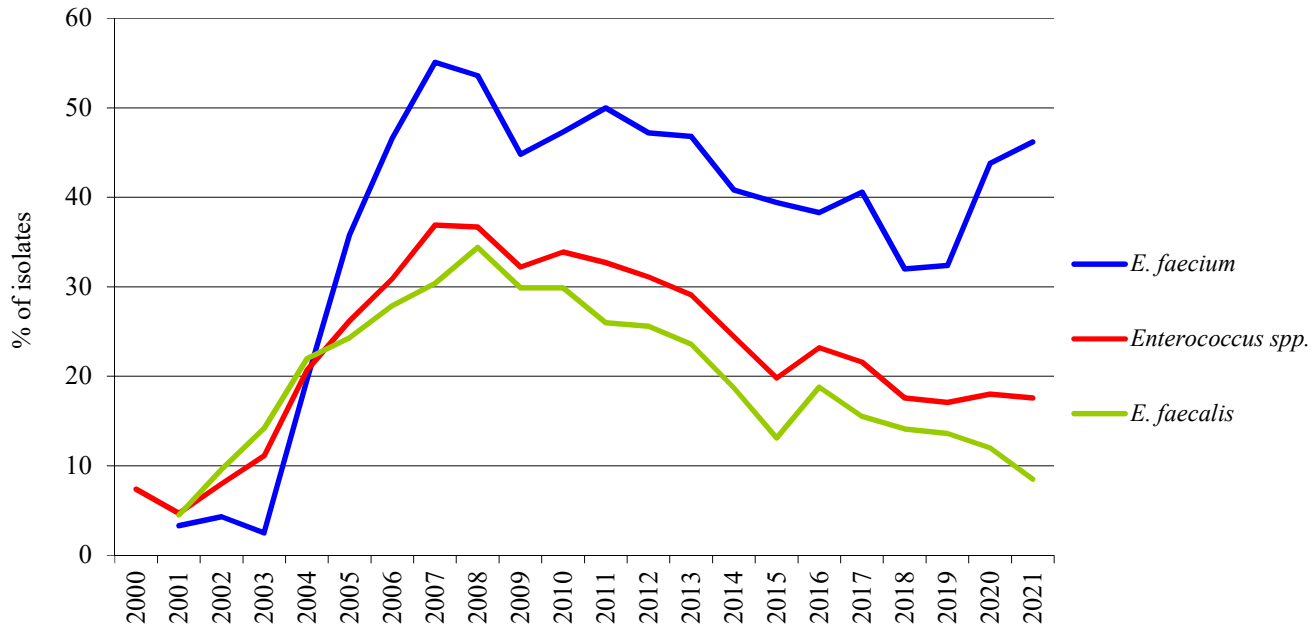

FIGURE 95. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2021. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Vancomycin and linezolid resistant enterococci in Norway 2021

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 (2). They are intrinsically resistant to many antimicrobial agents and readily acquire resistance towards clinically important antimicrobials including vancomycin (3).

Vancomycin resistance in enterococci is due to changes in the peptide side chain that prevent vancomycin from inhibiting crosslinking in the peptidoglycan cell wall (4). 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 and occur mostly in *Enterococcus faecalis* and/or *Enterococcus faecium*. The most common acquired gene clusters are *vanA* then *vanB* (5,6).

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 Antimicrobial Resistance (K-res). K-res confirms the resistance phenotype when there is a discrepancy between pheno- and genotype with the reference method (microbroth dilution) and performs genetic characterisation with PCR and whole genome sequencing (WGS) on selected isolates to clarify resistance mechanisms and potential genetic relatedness indicating regional/national spread.

In Europe, a worrying increase in vancomycin resistant *E. faecium* has been reported from 2016-2020 (7), while in Norway the incidence of VRE-infection/colonisation has fluctuated during the last 10 years. In 2021 34 VRE were reported in Norway. None of these were linezolid resistant (LVRE) (Figure 96). In contrast to many other countries in Europe (7) there has been a significant decrease in VRE from 2019 to 2020 (63%) in Norway. The trend has continued with an additional decrease (55%) from 2020 to 2021. K-res has received isolates and/or WGS data on only 5/34 (15%) VRE from 2021. Thus, this is not an overview of the molecular epidemiology of VRE in Norway in 2021. Consequently, we have asked the laboratories to submit all VRE to K-res from 2022. See Table 81 for an overview of the distribution by Health Regions of VRE in total and those analysed by WGS by K-res in 2021.

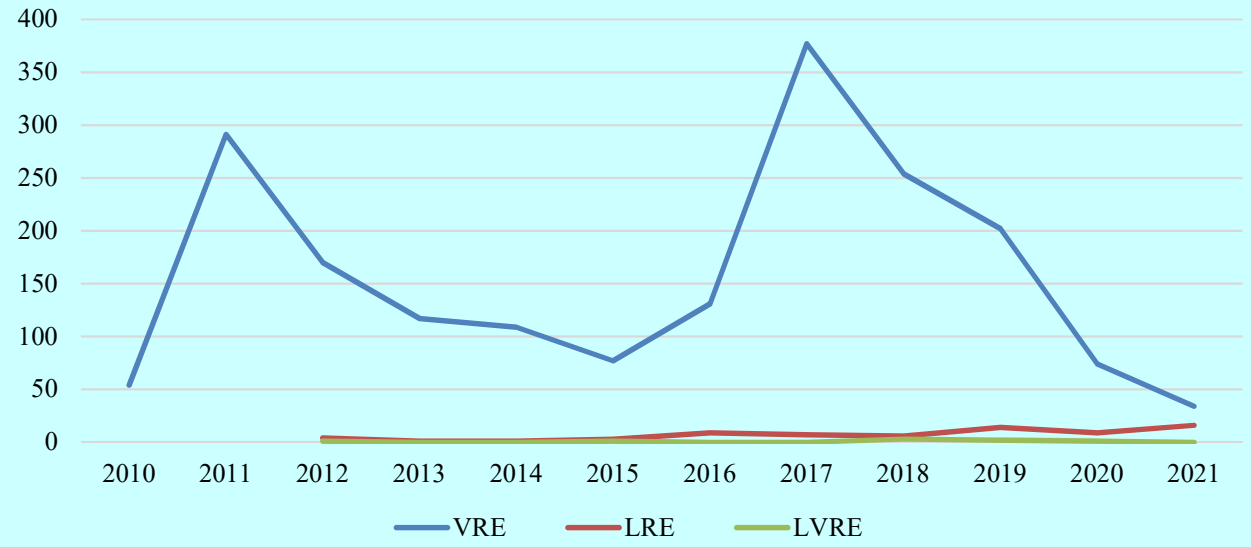

FIGURE 96. The number of vancomycin resistant (VRE), linezolid resistant (LRE) and both vancomycin and linezolid resistant (LVRE) enterococci in Norway 2010-2021. Combined data from MSIS.no and K-res.

TABLE 81. Total number of VRE isolates (n=34) in Norway for 2021 as well as those analysed by WGS at K-res, distributed by Health Regions.

Health region	Number of VRE	Number of VRE with WGS data
South-Eastern	21	4
Western	11	1
Central	2	0
Northern	0	0

Of the five 2021 VRE isolates, three were *vanA* and one *vanD E. faecium*, while one *E. faecium* isolate harboured both *vanA* and *vanB* (Figure 97). VRE in Norway has previously been dominated by *vanB E. faecium* (8). Worldwide vancomycin resistance is also much more prevalent in *E. faecium* than *E. faecalis* (9,10), and *vanA* is more frequent than *vanB* (5). Four of the analysed VRE belonged to sequence type (ST) 80 which is a known pandemic hospital adapted ST. The remaining, which was an import isolate, belonged to a new sequence type (ST2137). All were sporadic isolates (Figure 98).

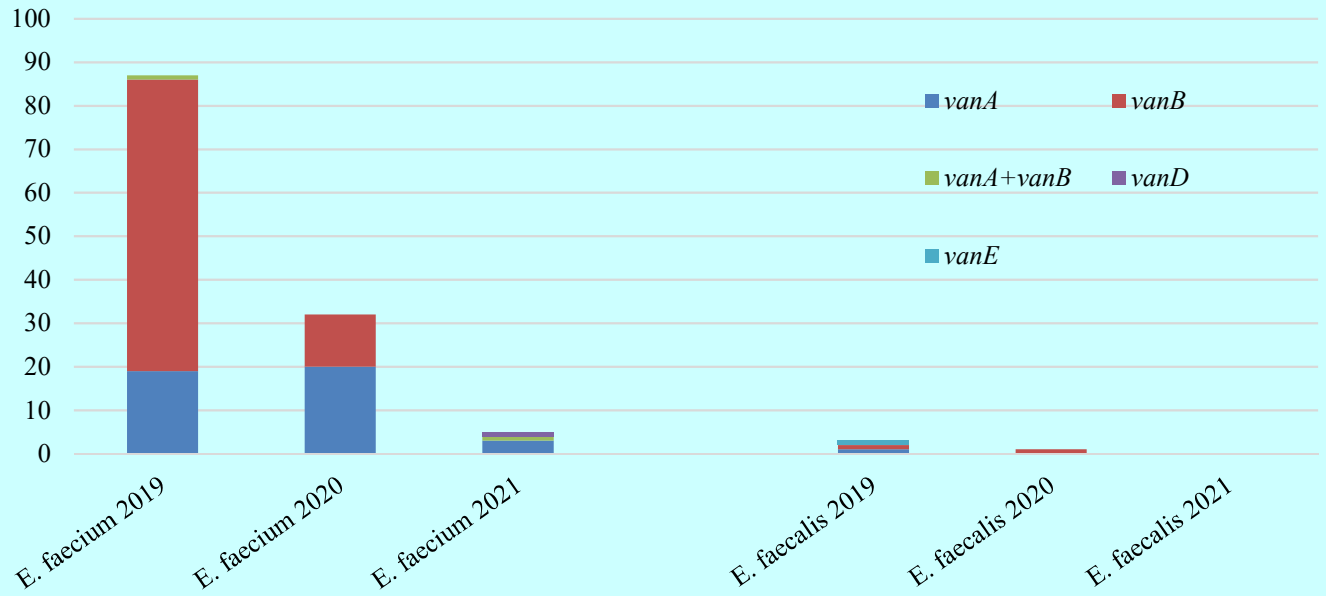

FIGURE 97. Species and genotype distribution of Norwegian VRE isolates that K-res has WGS data on for 2019, 2020 and 2021. This also includes linezolid resistant VRE.

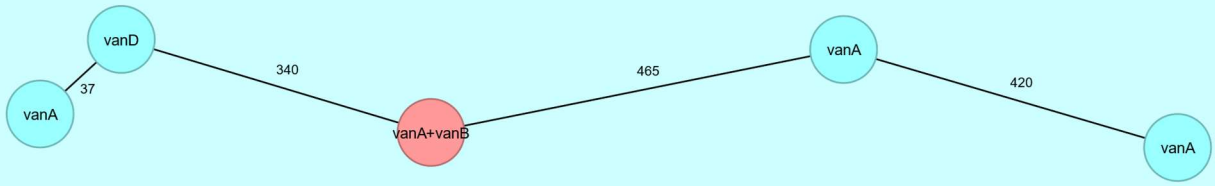

FIGURE 98. Minimum spanning network built from core genome allelic profiles of the five Norwegian VRE *E. faecium* 2021 isolates using Ridom-SeqSphere+ software with integrated core genome (cg) MLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour coded according to sequence type. The isolates are not closely genetically related (>20 allelic distances).

Conclusion
The number of cases with vancomycin resistant enterococci (VRE) (n=34) registered in MSIS in Norway in 2021 represents a further significant decrease (55%) from 2020. In this report, we present genomic data for only five *E. faecium* isolates. Four of these belong to a globally dispersed hospital adapted clone (ST80), but the isolates are not closely related. We have asked the laboratories to send all VRE-isolates to K-res from 2022 to gain a better molecular overview of the VRE-situation in Norway.

Linezolid resistant enterococci

The oxazolidinone linezolid is considered an antibiotic of last resort in the treatment of infections caused by multi-resistant enterococci, and in particular VRE. The prevalence of linezolid resistance in enterococci is still low (<1%) worldwide (11) but is increasing in many countries (12,13).

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 (14). The *cfr*, *optrA* and *poxtA* genes can all be localised on mobile genetic elements (12,15,16). The *cfr* gene that confers resistance against oxazolidinones, phenicols, lincosamides, pleuromutilins and streptogramin A in *E. coli* and staphylococci does not seem to mediate linezolid resistance in enterococci although expressed. This is probably due to specific ribosomal structures in enterococci (12,17). Mutation-based resistance often occurs after treatment with oxazolidinones (18). 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 (19,20).

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 reference method (microbroth dilution) and performs genetic characterisation with PCR and whole genome sequencing to find resistance mechanisms and monitor genetic relatedness between the isolates. The Norwegian Working Group on Antibiotics and Methods for Anti-microbial Susceptibility Testing (AFA) recommends routine susceptibility testing for linezolid of clinical isolates of *Enterococcus* in Norway. All invasive *Enterococcus* isolates (n=1203) were categorised as susceptible in the NORM report from 2020. 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 2021 sixteen cases of LRE were detected in Norway, compared to ten in 2020 (Figure 99). 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 100; n=41).

Linezolid resistance in enterococci has traditionally mostly been mediated by point mutations in the chromosomal 23S rRNA regions, mainly the G2576U mutation. In 2021 seven LRE were *E. faecium*, of which all had mutational based linezolid resistance. All nine linezolid resistant *E. faecalis* had *optrA* (Figure 100). Fifteen of the 2021 LRE-isolates were from infections and eight of these had *optrA*. The remaining isolate was a carrier isolate. None of the LRE-isolates were associated with import, but information about import is lacking for thirteen isolates. Of the *E. faecium* isolates six belonged to ST80 and one to ST17, both well-known pandemic hospital associated sequence types. The *E. faecalis* isolates (n=9) belonged to eight different STs of which ST179 was found in two isolates (Table 83).

Table 83. Species, resistance mechanism and sequence type among LRE in Norway 2021.

Species	Resistance mechanism	ST
E. faecalis (*n*=9)	*optrA* (*n*=9)	ST179 (*n*=2); ST16 (*n*=1); ST21 (*n*=1); ST506 (*n*=1); ST1022 (*n*=1); ST1115 (*n*=1); ST1116 (*n*=1); ST1238 (*n*=1)
E. faecium (*n*=7)	*23S rRNA G2576U mutation* (*n*=7)	ST80 (*n*=6); 17 (*n*=1)

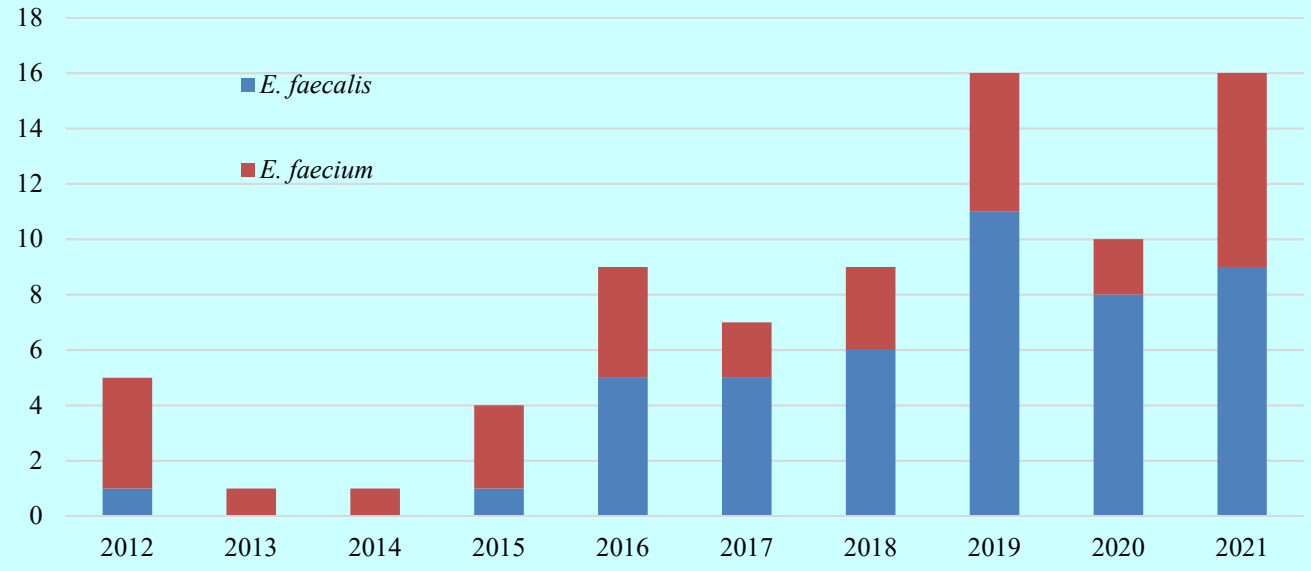

FIGURE 99. The number of linezolid resistant *E. faecium* and *E. faecalis* in Norway 2012-2021, including LRE that are vancomycin resistant.

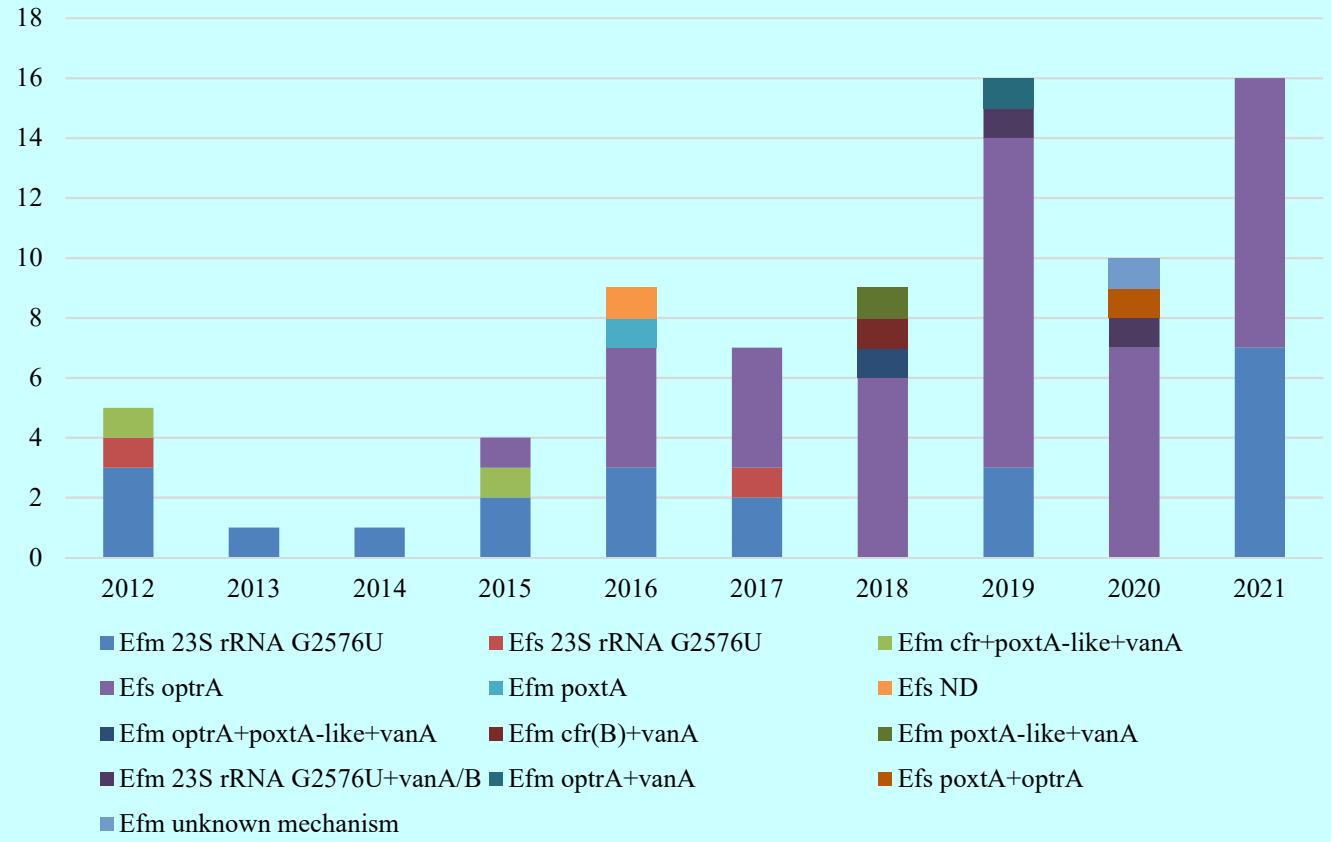

FIGURE 100. Number of LRE according to resistance mechanisms per year. *Efm=E. faecium. Efs=E. faecalis*. ND=not determined genotype. This isolate was not sent to K-res or archived at the primary laboratory.

Whole genome sequence analyses showed that none of the *E. faecalis* isolates belonged to the same cluster (Figure 101). However, phylogenetic analyses showed a cluster of ST80 *E. faecium* (n=6) with G2576U mutation in the 23S rRNA V domain (Figure 102). Epidemiological data as well as alternative phylogenetic analyses supported that five of these isolates belonged to an outbreak linked to two hospitals at Oslo University Hospital. Domestic spread of LRE has not been documented except for a cluster of three isolates with linezolid resistant *E. faecium* in 2012-13 (21). Thus, this is the first registered hospital outbreak of LRE in Norway.

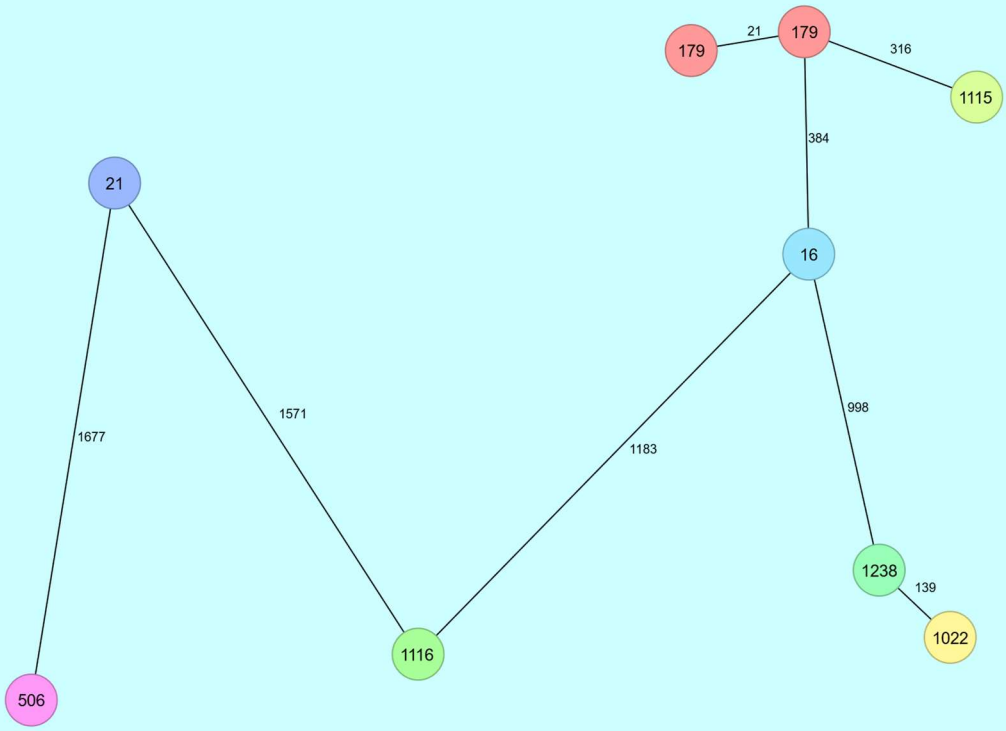

FIGURE 101. Minimum spanning network built from core genome allelic profile of the 9 Norwegian LRE *E. faecalis* 2021 isolates using Ridom-SeqSphere+ with integrated core genome (cg) MLST scheme with *E. faecalis* OG1RF as reference strain. The isolates are colour coded according to primary laboratory. The isolates are not closely related (> 7 allelic distance). The two ST179 isolates showed 21 allelic differences.

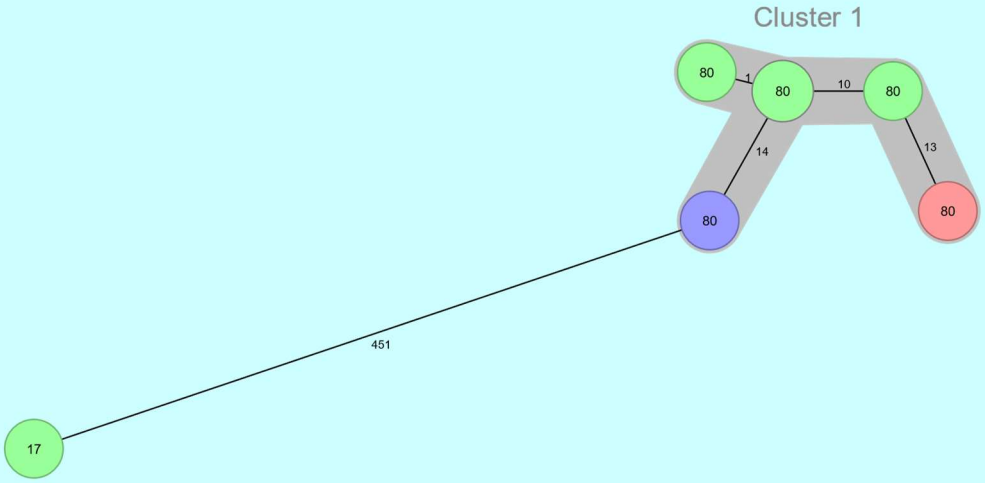

FIGURE 102. Minimum spanning network built from core genome allelic profiles of the 7 Norwegian LRE *E. faecium* 2021 isolates using Ridom-SeqSphere+ software with integrated core genome (cg) MLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour coded according to laboratory. Two isolates showed identical allelic profile and are thus not showed as separate circles. The six ST80 isolates cluster (≤20 SNP allelic distances).

Conclusion:

The prevalence of linezolid resistant enterococci (LRE) in Norway is still low in 2021 (n=16). The majority of the LRE isolates are from infections (n=14). *Enterococcus faecalis* with transferable resistance (*optrA*) was the dominant LRE-variant (n=9). Phylogenetic analyses and epidemiological data confirmed a single hospital outbreak of *E. faecium* (n=5*)* resistant to linezolid due to a mutation (G2576T) in the 23S rRNA gene.

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Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 84. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2021 (n=315). 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	93.1	6.3	0.6
Cefotaxime*	≤ 0.5	> 2	99.7	0.3	0.0
Ceftriaxone*	≤ 0.5	> 2	99.0	1.0	0.0
Erythromycin	≤ 0.25	> 0.5	94.0	0.0	6.0
Clindamycin	≤ 0.5	> 0.5	96.2	-	3.8
Tetracycline	≤ 1	> 2	92.1	1.6	6.3
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	90.5	1.6	7.9
Chloramphenicol	≤ 8	> 8	99.7	-	0.3
Oxacillin screen (mm)	≥ 20	< 20	89.2	-	10.8

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

TABLE 85. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2021 (n=315). 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*		9.2	53.3	25.7	4.8	1.3	3.8	1.3			0.3	0.3				
Cefotaxime*	0.3	24.1	60.9	5.7	4.1	2.2	1.0	1.3	0.3							
Ceftriaxone*			81.9	10.2	3.2	2.2	0.6	1.0	1.0							
Erythromycin				0.6	16.8	74.6	1.9			1.0	0.6	0.6		0.3		3.5
Clindamycin				0.6	25.4	63.2	6.7	0.3			0.3					3.5
Tetracycline					3.5	69.8	18.4	0.3		1.6	0.3	1.0	1.9	2.2	1.0	
TMS**						24.8	60.0	4.1	1.6	1.6	4.4	1.6	0.6	1.3		
Chloramph.									8.3	88.9	2.2	0.3	0.3			
Norfloxacin										7.6	56.5	33.7	1.9	0.3		
	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	10.8	0.6	1.9	8.2	12.7	16.5	11.1	11.1	7.0	9.5	5.1	2.2	3.2			

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. *The breakpoints used are 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. Due to reorganisation of the laboratory, no data were available for the last nine months of 2018 and all of 2019. The Reference Laboratory has resumed normal services from 2020 onwards.

The results are summarised in Tables 84-85 and Figures 103-104. Seventeen strains were isolated from cerebrospinal fluids. Eight of these were only isolated from this specimen type, whereas the remaining nine were concomitantly retrieved from blood cultures. Both blood culture isolates and isolates from other sterile sites were included from patients with positive cultures from more than one specimen type. Norwegian breakpoints for pneumococci are in accordance with EUCAST, and these remained unchanged in 2021. The results for penicillin G were interpreted according to the general breakpoints for pneumococci (S ≤ 0.06, R > 2 mg/L). The isolates from cerebrospinal fluids were in addition categorised according to penicillin G breakpoints for meningitis (R > 0.064).

A total of 6.3% (20/315) of *S. pneumoniae* isolates were only susceptible to penicillin G with increased exposure (MIC 0.125-2 mg/L), and two isolates (0.6%) were classified as resistant (MIC > 2 mg/L). These rates have fluctuated over the last years and are presently at a relatively low level (I+R combined were 8.9% in 2018, 12.8% in 2020 and 6.9% in 2021, respectively). The two penicillin G resistant isolates (MIC 4-8 mg/L) were categorised as S (MIC 0.5 mg/L) or I (MIC 1 mg/L) for cefotaxime, and both were I for ceftriaxone (MIC 1 mg/L). One additional isolate was categorised as I for penicillin G (MIC 0.5 mg/L) and ceftriaxone (1 mg/L), but was susceptible to cefotaxime. All isolates recovered from cerebrospinal fluids were fully susceptible to penicillin G (MIC ≤ 0.06 mg/L) and 3rd generation cephalosporins (S ≤ 0.03).

The oxacillin screening disk is often used to differentiate isolates susceptible to standard penicillin G doses from isolates that are resistant or require increased exposure. All the 22 penicillin G I+R isolates were resistant to oxacillin. Conversely, 12/293 penicillin G S isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 100% and 95.9%, respectively. Many of the *S. pneumoniae* isolates categorised as I+R to penicillin G were also resistant to tetracycline (13/22), trimethoprim-sulfamethoxazole (12/22), erythromycin (11/22), and/or clindamycin (7/22).

The prevalence of erythromycin resistance was relatively stable at 6.0% in 2021 compared to 6.0% in 2018 and 8.4% in 2020 (Figure 103). Most of these isolates (12/19) were resistant to both erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining seven 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 2020. The results may suggest a continuing predominance of *erm*-encoded macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 104).

The 7.9% resistance rate to trimethoprim-sulfamethoxazole was an increase from 5.4% in 2018 and 6.1% in 2020. The prevalence of tetracycline resistance decreased slightly from 8.1% in 2020 to 6.3% in 2021 (Figure 103). Almost all isolates (99.7%) were susceptible to chloramphenicol, which was earlier used for empirical treatment of meningitis in Norway. The low prevalence of high-level norfloxacin resistance (Table 85) may reflect the very limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

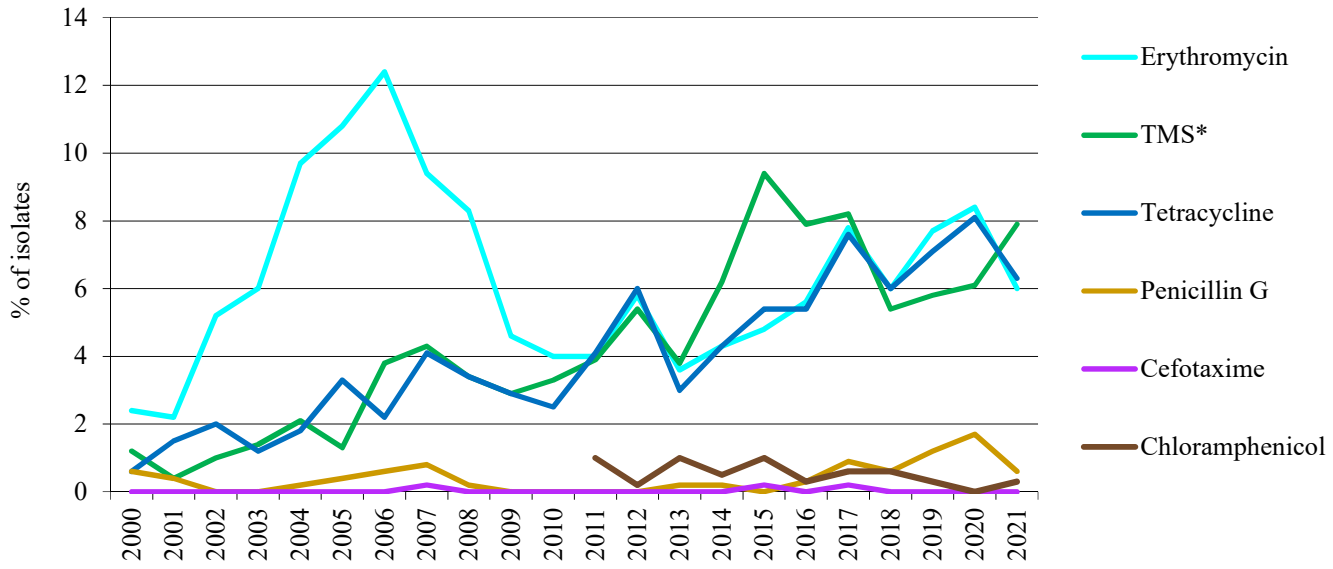

FIGURE 103. Prevalence (%) of resistance to antimicrobial agents in *Streptococcus pneumoniae* blood culture and cerebrospinal fluid isolates during 2000-2021. Doxycycline was substituted by tetracycline in 2005. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

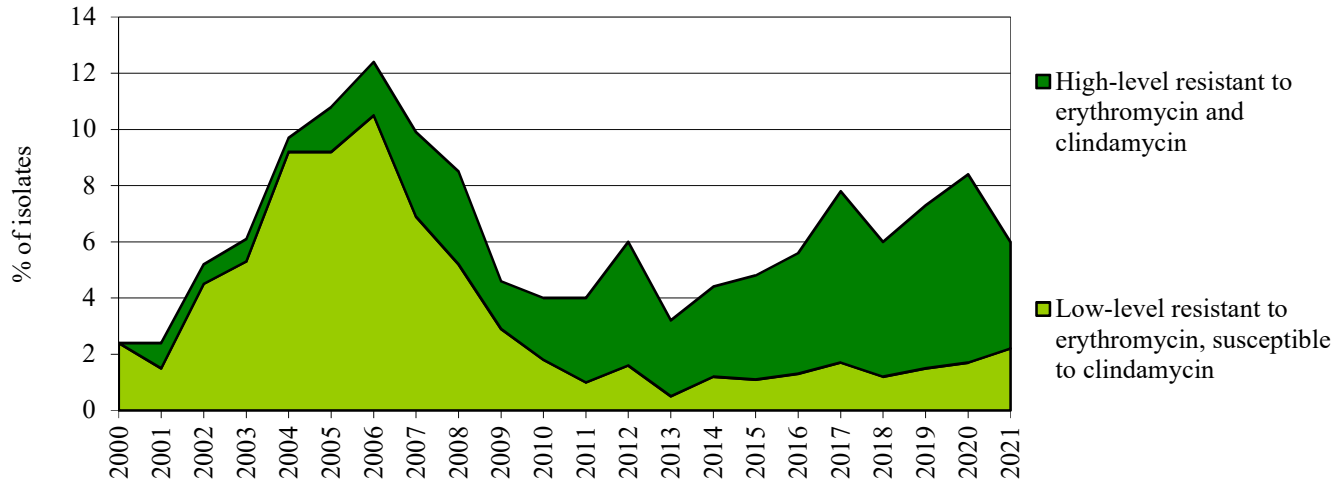

FIGURE 104. Prevalence of resistance (%) to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2021.

Streptococcus pyogenes in blood cultures

TABLE 86. *Streptococcus pyogenes* in blood cultures in 2021 (n=78). 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	> 0.5	80.8	0.0	19.2
Clindamycin	≤ 0.5	> 0.5	88.5	-	11.5
Tetracycline	≤ 1	> 2	59.0	1.3	39.7
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	98.7	0.0	1.3

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

TABLE 87. *Streptococcus pyogenes* in blood cultures in 2021 (n=78). 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		17.9	64.1	17.9												
Erythromycin				3.8	39.7	35.9	1.3			1.3	2.6	3.8				11.5
Clindamycin				15.4	60.3	11.5	1.3									11.5
Tetracycline					5.1	50.0	3.8			1.3		3.8	2.6	24.4	7.7	1.3
TMS*			3.8	16.7	26.9	32.1	14.1	3.8	1.3					1.3		

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

RESULTS AND COMMENTS

The Reference Laboratory at the Norwegian Institute of Public Health provides resistance data for systemic *S. pyogenes* isolates on a yearly basis, but very limited data were available from 2018-2019 as the laboratory was reorganised during that period. The number of isolates has also been reduced during the pandemic 2020-2021 compared to historical data, and the results should therefore be interpreted with caution.

As expected, all isolates were fully susceptible to penicillin G (Tables 86-87). The rates of resistance to erythromycin increased from 4.2% in 2017 to 6.7% in 2020 and now 19.2% in 2021. During the same time period, the prevalence of clindamycin resistance increased from 2.5% in 2017 to 5.2% in 2020 and 11.5% in 2021. High-level resistance to erythromycin was in most cases (8/9) linked to clindamycin resistance, presumably due to *erm*-encoded constitutive expression of MLS_B resistance. Five isolates displayed low-level erythromycin resistance combined with clindamycin susceptibility, thus indicating a *mef*-encoded efflux mechanism. The remaining two isolates had discrepant results (high-level erythromycin resistance combined with low-level clindamycin resistance and vice versa), which may suggest the presence of inducible resistance determinants or ribosomal mutations. Formal MLS testing was not performed.

The prevalence of tetracycline resistance increased from 15.7% in 2020 to 39.7% in 2021, whereas the prevalence of resistance to trimethoprim-sulfamethoxazole remained relatively stable at 1.3% in 2021 compared to 0.7% in 2020.

Antimicrobial resistance in *Streptococcus dysgalactiae* – a One Health perspective

Streptococcus dysgalactiae has emerged as an important human pathogen, and increasing rates of invasive *S. dysgalactiae* infections are being reported worldwide. In a recent epidemiological report, this species was found to be the fifth most common cause of blood stream infections in Western Norway (1). Although *S. dysgalactiae* remains uniformly susceptible to penicillin, increasing resistance rates to the important second line alternatives, macrolides and clindamycin (MLS-resistance), have raised concerns in many geographic regions. In the United Kingdom, resistance to clindamycin has gradually increased from 6 % in 2004 to 43 % in 2020, and a similar development is observed for erythromycin (2). A rising temporal trend has also been detected in Norway in the same time period, albeit only from 0 % to 12 % resistance to these two agents (12).

In 2018, *S. dysgalactiae* was included in the NORM surveillance programme for the first time. Of 274 isolates tested, phenotypic erythromycin resistance was detected in 28 isolates (10 %), whereof 8 isolates displayed constitutive MLS-resistance, and the remaining were inducibly resistant to clindamycin. One isolate displayed L-phenotype resistance, but no isolates were categorised as M-type resistant.

The 274 *S. dysgalactiae* isolates were whole genome sequenced to explore resistance determinants and phylogenetic relationships, and potentially reveal modes of dissemination and transmission of antimicrobial resistance in this pathogen. A total of 20 different genotypes were detected among the 29 MLS-resistant *S. dysgalactiae* isolates, indicating a highly polyclonal population. The vast majority harboured the *erm*(A) gene (24 isolates), whereas the remaining carried *erm*(B) (n=2), *erm*(T) (n=1) and *lsa*(C) (n=1). In one phenotypically resistant isolate, resistance genes were not detected.

All the *erm*(A) resistance genes resided in the integrative conjugative mobile element, ICEsp2905. Notably, almost identical ICEsp2905 elements could be identified in isolates belonging to very different genetic lineages, indicating dissemination of antimicrobial resistance genes by conjugation rather than clonal expansion in *S. dysgalactiae*. Moreover, highly similar elements were detected in *Streptococcus agalactiae* and *Streptococcus pyogenes* using BLAST search, suggesting that horizontal genetic exchange with other streptococcal species is a potential source for acquisition of novel resistance determinants (Figure 105).

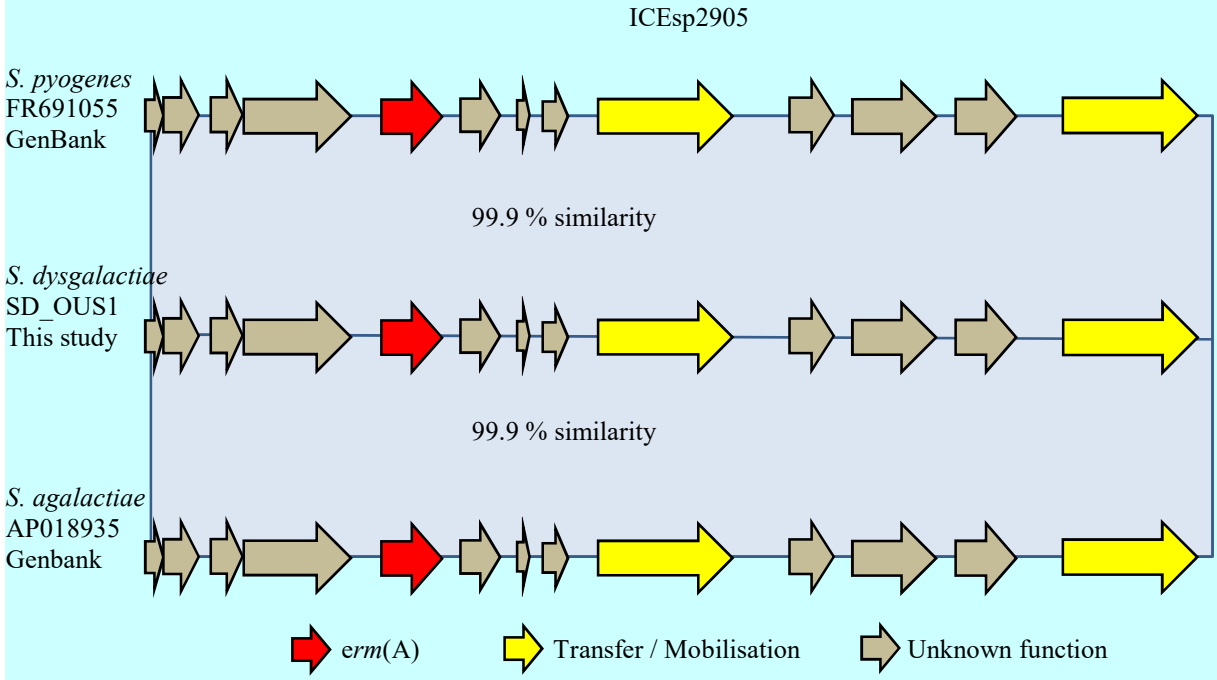

FIGURE 105. Comparison of the ICEsp2905 element detected in strains from three different beta-haemolytic streptococcal species. Comparison of the central part of the ICEsp2905 element harbouring the *erm*(A) gene, often referred to as IMEsp2907. Similarity is based on pairwise identity.

Streptococcus dysgalactiae is a common pathogen also in livestock and companion animals. Clindamycin resistance rates exceeding 80 % have been reported in livestock associated *S. dysgalactiae* isolates from other continents (4,5), but *S. dysgalactiae* isolates from Norwegian animals have not been systematically tested for antimicrobial susceptibility. In a One Health perspective, we sought to explore antimicrobial resistance in this species in Norwegian animal populations, and to examine the possibility of zoonotic transmission of resistance determinants or resistant strains to humans.

The Norwegian Veterinary Institute collected 137 *S. dysgalactiae* strains during 2018 and 2019, comprising isolates obtained from infected cows (n=74), sheep (n=13), dogs (n=20), horses (n=16), swine (n=12), a cat (n=1) and a lizard (n=1). Both isolates belonging to subspecies *dysgalactiae* and subspecies *equisimilis* were included.

Very low rates of phenotypic resistance to erythromycin (1.5 %) and clindamycin (2.2 %) were detected, and were exclusively found in *S. dysgalactiae* isolates from dogs. All 137 isolates were whole genome sequenced. The *erm*(B) gene was detected in two constitutively MLS-resistant dog isolates, whereas *lsa(C)* was identified in two dog isolates and one obtained from a horse. Two of the *lsa*(C)-positive isolates did not display reduced phenotypic susceptibility to clindamycin.

A phylogenetic tree was constructed from the 411 *S. dysgalactiae* genomes from various host species (Figure 106). Notably, the isolates could be delineated in almost perfect concordance with their host of origin, suggesting the existence of different host adapted lineages. Moreover, it highlights that the phylogenetic complexity of this pathogen extends beyond the current division into subspecies *dysgalactiae* and subspecies *equisimilis*. Among the human derived isolates, only one clustered phylogenetically with animal associated strains, indicating that zoonotic transmission of this pathogen is likely a rare event.

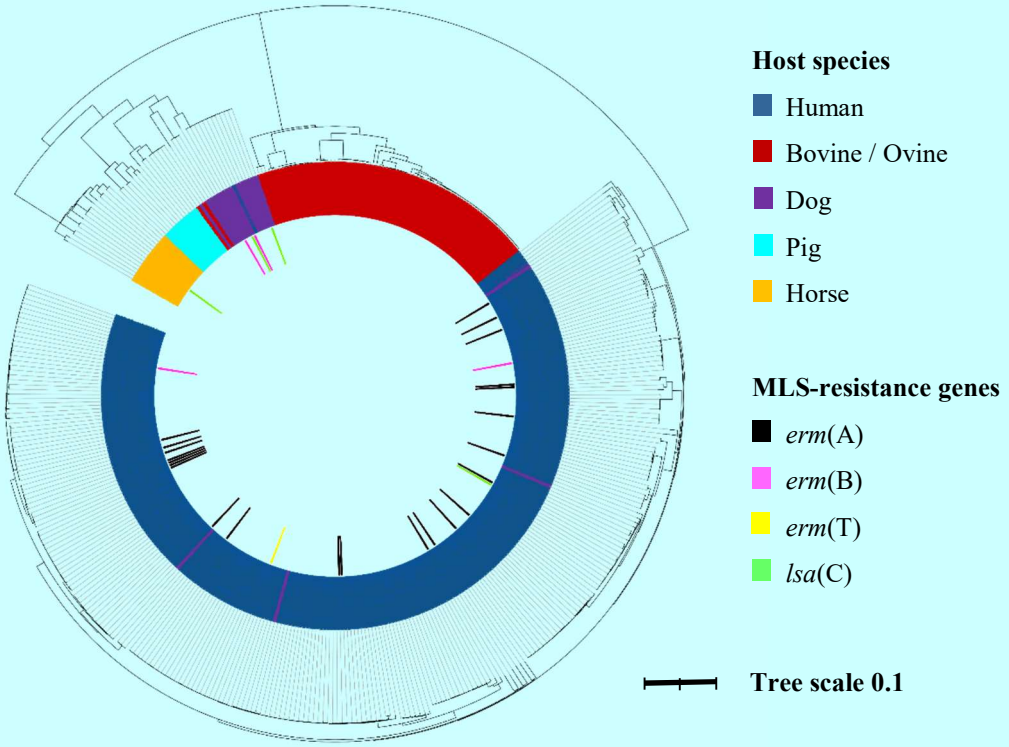

FIGURE 106. Phylogenetic tree of *Streptococcus dysgalactiae* isolates from various host species. The core genome comparison of 411 *S. dysgalactiae* isolates was performed using CSI phylogeny (cge.food.dtu.dk/services/CSIPhylogeny) and the phylogenetic tree was constructed in the Interactive Tree of Life website (itol.embl.de). Scale indicates substitutions per site.

Nevertheless, the integrative conjugative Tn5252 element carrying the *erm*(B) gene in a dog associated strain, showed 95 % homology to elements previously detected in human associated *S. dysgalactiae* and *S. agalactiae* strains. Exchange of mobile genetic elements carrying resistance determinants between different host adapted lineages is thus plausible. However, the differences in MLS-resistance rates suggest that animal associated *S. dysgalactiae* isolates could well be at the receiving end of such transmission.

Conclusions

Erythromycin and clindamycin resistance is slowly increasing in human associated *S. dysgalactiae* lineages in Norway. Resistance is predominantly mediated by the dissemination of the integrative conjugative element ICEsp2905, harbouring the *erm*(A) gene. Conversely, MLS-resistance remains low in *S. dysgalactiae* isolates from Norwegian livestock and companion animals. Although there is some evidence to suggest potential zoonotic transmission of resistance determinants, it is unlikely to contribute to the increasing incidence rates observed in human *S. dysgalactiae* disease. Horizontal genetic exchange between human associated streptococcal species is a more likely mode of acquisition.

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Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 88. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2021 (n=300). 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	> 0.5	77.3	0.0	22.7
Clindamycin	≤ 0.5	> 0.5	84.3	-	15.7
Tetracycline	≤ 1	> 2	20.0	0.0	80.0
Vancomycin	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *The breakpoints used are for indications other than meningitis, see text.

TABLE 89. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2021 (n=300). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*			3.3	60.7	36.0											
Erythromycin				0.3	1.3	37.7	38.0			2.0	2.6	5.0	2.3	0.3		10.3
Clindamycin				0.3	5.3	68.7	9.7	0.3	2.3	0.6			0.6			12.0
Tetracycline				0.6	17.3	1.7			0.3		0.6	8.7	43.0	26.7	1.0	
Vancomycin					1.0	29.0	68.7	1.3								
Gentamicin												0.6	3.3	31.7	53.7	10.7

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. *The breakpoints used are 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. Relevant breakpoints have remained unchanged since 2009.

A total of 300 isolates were retrieved from invasive infections (bacteremia and cerebrospinal infections) in 2021. Twenty-eight isolates originated from neonates and small children < 1 year of age. Most isolates (98.3%) were recovered from blood cultures, but there were also five isolates from cerebrospinal fluids. All isolates represented individual patients.

As seen in Tables 88-89 there were no isolates with reduced susceptibility to penicillin G or vancomycin. Sixty-eight isolates (22.7%) were resistant to erythromycin compared to 25.5% in 2019 and 19.5% in 2020. Almost all were analysed by double disk diffusion for MLS_B resistance phenotype. Constitutive MLS_B resistance was found in 45/67 isolates (67%), while inducible MLS_B resistance was detected in 13/67 isolates (19%). The remaining 9/67 isolates (13%) had results in accordance with the efflux-mediated M phenotype encoded by *mef* genes. Three isolates were recorded as clindamycin resistant (MIC 1-2 mg/L) in spite of being susceptible to erythromycin (MIC 0.125-0.25 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 10.7% of the isolates. The prevalence of resistance to tetracycline (80.0%) was at the same level as in 2019 (77.7%) and 2020 (75.2%) with the majority of isolates displaying MIC values of 8-32 mg/L (Table 89).

Resistance against empiric antibiotic combinations in the treatment of bloodstream infections – 2021 update

The recent Covid-19 pandemic resulted in major changes in both individual behaviours and infection control practices, which may have influenced the occurrence of invasive bacterial species and the rates of antibacterial resistance.

The relative abundance of most important invasive bacterial species remained stable, as shown in Table 55 in this report. While there were lower levels of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Streptococcus pyogenes* compared to previous years, current MSIS data (2) suggests a return to pre-pandemic levels in 2022.

The resistance rates against broad-spectrum antibiotics and antibiotic combinations in key bloodstream infection pathogens are shown in Table 90. In light of last year's report (1), the ESBL rates in *Escherichia coli* and *Klebsiella spp*. stopped increasing. The gentamicin resistance rate in *E. coli* continued its zig-zag decline from the top year of 2014, while in *Klebsiella spp*. it decreased by 3 percentage points compared to 2020. It remains to be seen if these rates will return to pre-pandemic levels in 2022.

TABLE 90. Resistance (%) to broad-spectrum antibiotics and antibiotic combinations in key bloodstream infection pathogens.

Antibiotic drug combiantions		Proportion of invasive isolates resistant (%)									
		E. coli (n=2,212)	*Klebsiella* spp. (n=1,045)	ESBL *Enterobacterales** (n=185)	*H. influenzae* (n=63)	*Enterococcus* spp. (n=715)	*S. pneumoniae* (n=315)	*S. pyogenes* (n=78)	*S. agalactiae* (n=300)	*S. aureus* (n=1,455)	MRSA* (n=1,895)
Benzylpenicillin	Gentamicin	5.6	4.2	41.6	30.2[1]	-	0.6	0.0	0.0	0.5	12.5
Benzylpenicillin	Ciprofloxacin	10.4	8.9	68.1	0.0	-	0.0	0.0	0.0	8.8	25.0
Clindamycin	Gentamicin	5.6	4.2	41.6	100.0	100.0	3.8	11.5	15.7	0.1	1.1
Ampicillin	Gentamicin	4.9	4.2	41.6	20.6	11.3[3]	X	0.0[4]	0.0[4]	0.5	12.5
Piperacillin/tazobactam	Gentamicin	0.8	2.5	16.8	0.0[2]	11.3[3]	X	0.0[4]	0.0[4]	0.2[5]	12.5
Cefotaxime		6.1	6.5	95.7	0.0	100.0	0.0	0.0[4]	0.0[4]	0.8[6]	100.0
Piperacillin/tazobactam		5.2	11.9	29.2	0.0[2]	19.0[3]	X	0.0[4]	0.0[4]	0.8[6]	100.0
Meropenem		0.0	0.2	1.1	0.0	100.0	X	0.0[4]	0.0[4]	0.8[6]	100.0

[1]Inferred from benzylpenicillin 1 unit (PCG1). [2]Inferred from amoxicillin-clavulanate. [3]Inferred from ampicillin only. [4]Inferred from penicillin only. [5]Piperacillin/tazobactam inferred from cefoxitin. [6]Inferred from cefoxitin. X: No data available. -: No breakpoint/Susceptibility testing not recommended. **Escherichia coli* and *Klebsiella* spp. **Includes MRSA from all sources.

References:

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Mycobacterium tuberculosis

In 2021 (2020 in parenthesis), 154 (159) persons were reported with tuberculosis disease (TB) to the Norwegian Surveillance System for Communicable Diseases (MSIS). Of these, 26 (29) were born in Norway. 124 (131) had TB for the first time, of which 4 (1) had received preventive treatment. 17 (16) had had previous TB, of which 13 (15) had been treated with anti-TB drugs previously. The rest, 13 (12) cases, were categorised as uncertain if they had received TB treatment previously.

124 (134) cases were confirmed with *M. tuberculosis*-complex (MTBC) by culture. Of these 1 (1) was identified as *M. africanum,* the rest were *M. tuberculosis*. Another 8 patients were confirmed by molecular genotypic tests as *M. tuberculosis complex* but without positive culture. Resistance results reported to MSIS are shown in table 91. Results from testing of both isolates and direct samples are included. There were 12 (2) rifampicin resistant (RR)-TB cases including 10 (1) multi-drug resistant (MDR)-TB cases (resistant to both rifampicin and isoniazid). Two of the RR-TB cases were culture negative but confirmed by genotype (*rpo*B mutation), one with isoniazid resistance (MDR-TB), the other without isoniazid resistance result. The RR-TB cases were susceptible to the second-line drugs tested (including bedaquiline and linezolid), except two of the MDR cases with resistance also to fluoroquinolones, so-called pre-XDR (extensively drug-resistant) TB. All RR-TB cases had TB for the first time, except two MDR-TB cases who had received chemotherapy in the past. In addition to the MDR-TB cases, 5 TB cases had strains resistant to isoniazid (sensitive to rifampicin), 3 of them only with low-level resistance.

TABLE 91. Antimicrobial resistance for MTBC reported to MSIS (not *M. bovis* BCG) in 2021 from isolates or direct samples. Figures from 2020 in parentheses.

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents				
			Isoniazid 125 (133)	Rifampicin 131 (138)	Ethambutol 122 (133)	Pyrazinamide 123 (133)	MDR-TB 125 (133)
Norway	26 (29)	21 (25)	1 (2)	1(0)	1 (1)	1 (0)	1 (0)
Europe excl. Norway	17 (10)	16 (9)	3 (0)	3 (0)	3 (0)	3 (0)	3 (0)
Asia	56 (57)	41 (47)	4 (7)	3 (2)	0 (1)	2 (2)	2 (1)
Africa	52 (62)	43 (52)	7 (6)	5 (0)	2 (0)	3 (0)	4 (0)
America	3 (1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	154 (159)	124 (134)	15 (15)	12 (2)	6 (2)	9 (2)	10 (1)
Proportion resistant isolates (%)			12.0 (11.3)	9.2 (1.4)	4.9 (1.5)	7.3 (1.5)	8.0 (0.8)

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)

Candida spp. in blood cultures

TABLE 92. Antimicrobial susceptibility of *Candida albicans* blood culture isolates in 2021 (n=128). 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	99.1	0.0	0.9
Voriconazole	≤ 0.06	> 0.25	100.0	0.0	0.0
Anidulafungin	≤ 0.03	> 0.03	100.0	-	0.0
Micafungin*	≤ 0.016	> 0.016	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020 v.10.0. There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin. *With EUCAST revised breakpoints 2020-02-04, micafungin MIC 0.03 mg/L is defined as an area of technical uncertainty (ATU). If the isolate is anidulafungin susceptible it is regarded suseptible to micafungin.

TABLE 93. *Candida albicans* blood culture isolates in 2021 (n=128). 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			0.8		3.1	21.9	59.4	14.8									
Fluconazole				0.8	1.6	7.8	50.8	36.7	1.6			0.8					
Voriconazole	12.4	62.0	22.5	3.1													
Anidulafungin	73.4	21.9	4.7														
Micafungin*	1.6	41.5	53.9	3.1													
Caspofungin**			0.8	12.5	45.3	33.6	7.8										

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. *With EUCAST revised breakpoints 2020-02-04, micafungin MIC 0.03 mg/L is an area of technical uncertainty (ATU). Four ATU isolates were anidulafungin susceptible and they were therefore regarded suseptible to micafungin. ATU; If S to anidulafungin, report as S and add the following comment: "Isolates susceptible to anidulafungin with micafungin MIC of 0.03 mg/L do not harbour an *fks* mutation conferring resistance to the echinocandins". If not S to anidulafungin, report as R and refer to reference laboratory for fks sequencing and confirmation of MICs. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 94. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates in 2021 (n=36). 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	88.9	11.1
Anidulafungin	≤ 0.06	> 0.06	100.0	-	0.0
Micafungin	≤ 0.03	> 0.03	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020 v.10.0. There is insufficient evidence that *C. glabrata* is a good target for therapy with voriconazole and no clinical breakpoints are available. An MIC with comment without an accompanying S, I or R categorisation may be reported. There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 95. *Candida glabrata* blood culture isolates in 2021 (n=36). 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						5.6	41.7	50.0	2.8								
Fluconazole								2.8	11.1	2.8	25.0	25.0	22.2		2.8	5.6	2.8
Voriconazole*				11.1	5.6	8.3	27.8	25.0	11.1	8.3				2.8			
Anidulafungin		19.4	75.0		2.8	2.8											
Micafungin		16.7	75.0	2.8	2.8	2.8											
Caspofungin**					8.3	41.7	45.8	4.2									

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. *There is insufficient evidence that *C. glabrata* is a good target for therapy with voriconazole and no clinical breakpoints are available. An MIC with comment without an accompanying S, I or R categorisation may be reported. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin as well as micafungin are considered susceptible.

TABLE 96. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates in 2021 (n=13). 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. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020 v.10.0. There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin are considered susceptible to caspofungin.

TABLE 97. *Candida tropicalis* blood culture isolates in 2021 (n=13). 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							6.7	53.3	40.0								
Fluconazole							6.7	46.7	40.0	6.7							
Voriconazole		6.7	6.7	60.0	6.7	20.0											
Anidulafungin	6.7	46.7	46.7														
Micafungin*			46.7	53.3													
Caspofungin**					33.3	60.0	6.7										

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined. *There is insufficient evidence whether the wild type population of *C. tropicalis* can be considered susceptible to micafungin. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin are considered susceptible to caspofungin.

TABLE 98. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates in 2021 (n=14). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	85.7	0.0	14.3
Voriconazole	≤ 0.125	> 0.25	92.9	0.0	7.1
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. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020 v.10.0. There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 99. *Candida parapsilosis* blood culture isolates in 2021 (n=14). Distribution (%) of MICs (mg/l).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B							14.3	57.1	28.6								
Fluconazole							21.4	14.3	21.4	28.6							14.3
Voriconazole			35.7	21.4	21.4	7.1				7.1	7.1						
Anidulafungin								7.1	14.3	50.0	21.4		7.1				
Micafungin							7.1	57.1	28.6	7.1							
Caspofungin*							7.1	57.1	28.6	7.1							

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined. *There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 100. Antimicrobial susceptibility of *Candida dubliniensis* blood culture isolates in 2021 (n=11). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	100.0	0.0	0.0
Voriconazole	≤ 0.06	> 0.25	100.0	0.0	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020 v.10.0. There are currently no European breakpoints for anidulafungin, micafungin or caspofungin.

TABLE 101. *Candida dubliniensis* blood culture isolates in 2021 (n=11). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥256
Ampho. B					18.2	45.5	36.4										
Fluconazole						54.5	45.5										
Voriconazole	9.1	90.9															
Anidulafungin*	27.3	63.6	9.1														
Micafungin*		18.2	45.5	36.4													
Caspofungin*				18.2	45.5	27.3	9.1										

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined. *There are currently no European breakpoints for anidulafungin, micafungin or caspofungin.

RESULTS AND COMMENTS

All systemic fungal isolates in Norway are referred to the National Mycology Reference Laboratory at Oslo University Hospital where confirmatory identification and susceptibility testing is performed. Only *Candida* isolates from blood culture are included in the NORM surveillance.

A total of 212 unique candidemia isolates from 193 patients were included in the survey in 2021, compared to 195 isolates in 2020. Twelve infections in nine patients were reinfections with the same species more than four weeks apart. Two patients experienced two and three reinfections with the same species, and one patient had reinfection with two different species. Six mixed infections with more than one *Candida* spp. were observed.

Candida albicans is still by far the most common species (n=128, 60%), compared to 129 of 195 (66%) last year. The number of *Candida glabrata* isolates is still rising (n=36, 17%) compared to 24 isolates (12.3%) in 2020, but the total number of other non-albicans isolates is still very low; *C. parapsilosis* (n=14), *C. tropicalis* (n=13). *C. dubliniensis* (n=11), *C. guillermondii* (n=3), *C. lusitaniae* (n=2), *C. krusei* (n=2), *C. bracarensis* (n=1), *C. palmioleophila* (n=1) and *C. kefyr* (n=1).

All isolates were susceptibility tested for 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 92-101.

All tested isolates were susceptible to amphotericin B, but amphotericin B is not recommended treatment for *C. lusitaniae* (n=2) infections as *C. lusitaniae* has high MICs or develop resistance during treatment.

With the exception of one fluconazole resistant *C. albicans* isolate (MIC 8 mg/L) from a patient on long-term fluconazole treatment, all *C. albicans* isolates were susceptible to all antifungal agents. Four anidulafungin sensitive *C. albicans* with micafungin MIC 0.03 mg/L were regarded micafungin sensitive according to the evaluation of ATU.

Thirteen of 14 *C. parapsilosis* (85.7%) belonged to the wild type, since 2020 regarded as echinocandin sensitive. The new definition of the "I" category from "Intermediate" to "Susceptible, Increased exposure" is not applicable for the echinocandins and *C. parapsilosis* as there is no dose escalation option for the echinocandins. Breakpoints for micafungin and anidulafungin against *C. parapsilosis* were changed in 2020, given that the clinical response is not statistically different from that of other agents despite the intrinsic target gene alteration. The two fluconazole resistant *C. parapsilosis* isolates were isolated from two patients on long-term antifungal treatment (Tables 98-99).

Acquired fluconazole resistance was observed in four *C. glabrata* isolates (MIC 64-256 mg/L). Fluconazole break-points in *C. glabrata* were redefined in 2020 and the wild type considered within the "I" category (MIC ≤ 16 mg/L) to acknowledge the use of fluconazole in a high dose in some clinical situations. Two *C. glabrata* isolates were classified as micafungin resistant, of whom one isolate also was classified as anidulafungin resistant. Both isolates had mutations in the hot spot region.

Of the ten isolates not shown in the tables, three isolates were regarded fluconazole resistant; *C. krusei* (n=2) is inherently resistant to fluconazole and *C. palmioleophila* (n=1, MIC 64 mg/L) is an emerging pathogen with known fluconazole resistance. *C. bracarensis* (n=1) is closely related to *C. glabrata* and with a MIC of 4 mg/L categorised as susceptible, increased exposure (I). There are no break-points defined for *C. guillermondii,* but two of the three isolates also displayed fluconazole MIC values of 4 mg/L.

The wild type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible to voriconazole, and with exception of the two fluconazole resistant *C. parapsilosis* isolates, all isolates with defined breakpoints were found susceptible to voriconazole in 2021. There is insufficient evidence that *Candida* spp. is a good target for therapy with isavuconazole and breakpoints have not been set.

In conclusion, the species distribution in blood culture isolates in Norway continues to be dominated by *C. albicans* and acquired resistance is rare. Species identification still predicts the susceptibility pattern of *Candida* spp. in patients without previous long-term antifungal treatment.

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

Data sources

Sales data at wholesalers 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 (Directive 2001/82/EC, Article 10) – 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 HMPs 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 exception is for antibacterials for farmed fish for the years 2013-2021 which were obtained from the 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 January 1st 2011 and for terrestrial animals January 1st 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 2019, 2020 and 2021 data. For the period 2013-2021 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 2012-2021, 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 2015-2021 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 representative for the prescribing of VMPs by animal species, but as the prescribing patterns were relatively stable across this period the data is believed to give a rough picture of the prescription patterns of antibacterial classes by animal species. VetReg data have therefore been used as an additional source in order to assess changes according to targets set in the National Strategy against Antibiotic Resistance (2015-2020) (3).

Antibacterials included in the data set

The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to identify the VMPs to be included in the data set. 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); for farmed fish data on slaughtered biomass was obtained from the Norwegian Fish Directorate (https://www.fiskeridir.no/Akvakultur/Tall-og-analyse/Akvakulturstatistikk-tidsserier).

Indicators

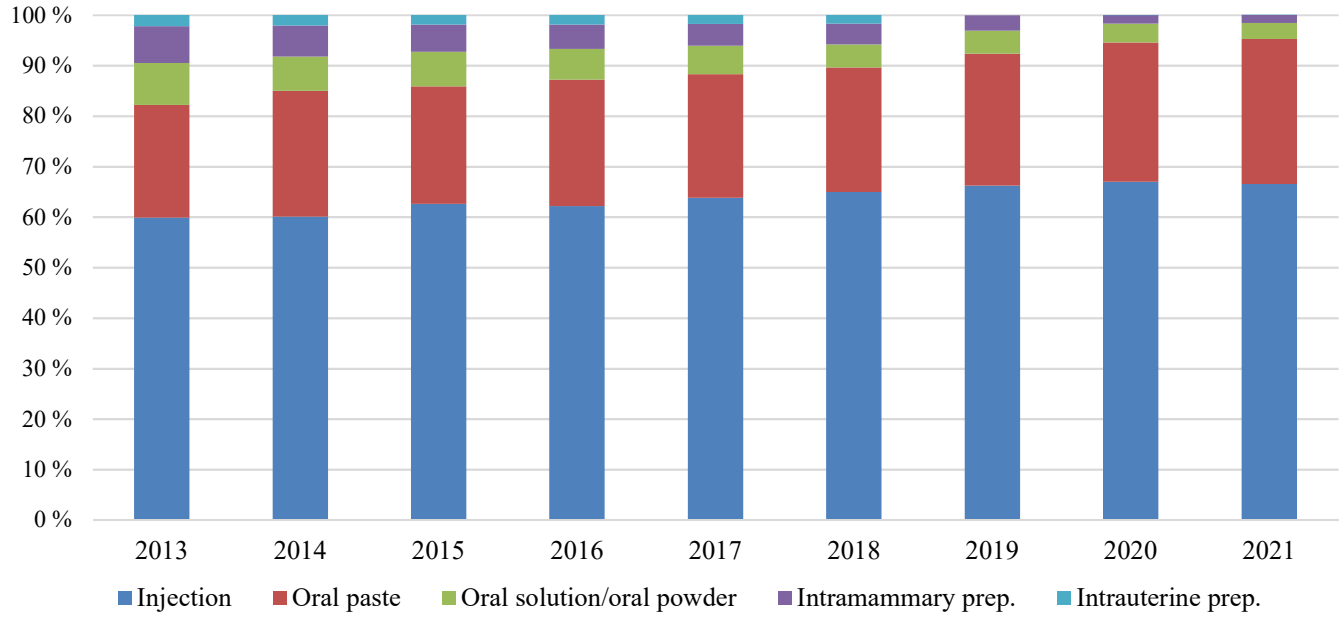
The sales data for each antibacterial VMP presentation were calculated to express weight of active substance. In order to comply with the ESVAC protocol (4), sales of derivatives (in previous report referred to as prodrugs) - e.g. procaine benzylpenicillin and penethamate hydriodide - has been calculated 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 list (values) for both types of conversion factors was updated for some antibacterials in 2021 and these conversion factors have been used to calculate the amounts (weights) sold both for 2021 as well as for the historical data. This has led to slightly lower sales figures of antibacterials for terrestrial food-producing animals compared to the values presented in the previous reports (range 2.1%-3.9%).

The sales data of antibacterial VMPs for terrestrial animals have been split into sales for food-producing animals (including horses) and companion animals. Sales of antibacterial VMPs for companion animals refer to sales of tablets, oral solution and oral paste that are approved solely for companion animals; in addition, dihydrostreptomycin tablets of pack size 10 pieces have been included in the data on sales for companion animals (no sales after 2004). The other antibacterial VMPs are assumed sold for use only in food-producing animals (including horses). There is some use of injectable 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, intramammary 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 2021 (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 2013-2021 have been refined in order to obtain estimates on the usage aggregated for 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 2015-2021, on average 96.9% (range 96.3% to 97.4%) of the number of prescriptions of antibacterial oral paste VMPs was for horses showing that off-label use for other animal species of oral paste was negligible. Of note is that of 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 2021 (see figure below). 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. Intra-mammaries 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 2013-2021. Of note, there were no sales of antibacterial VMP intrauterine devices in 2020 and 2021.

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.

References:

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2. Kari Grave and Petter Hopp. Veterinary Prescription Register – data quality for antibacterials (In Norwegian: Veterinært legemiddelregister (VetReg) – datakvalitet for antibakterielle midler). Rapport 29: Veterinærinstituttet, 2017.
3. National Strategy against Antibiotic Resistance (2015-2020) (in Norwegian). Nasjonal strategi mot Antibiotikaresistens 2015 – 2020. (https://www.regjeringen.no/contentassets/5eaf66ac392143b3b2054aed90b85210/strategi_antibiotikaresistens_230615.pdf).
4. EMA, 2021. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Sales Data and Animal Population Data Reporting Protocol (version 4). (https://www.ema.europa.eu/en/documents/other/european-surveillance-veterinary-antimicrobial-consumption-esvac-web-based-sales-animal-population_en.pdf).
5. EMA, 2017. Joint ECDC, EFSA and EMA scientific opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals. (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500237745.pdf).

Appendix 2:
Collection and analysis of data on usage of antimicrobial agents in humans

Data sources
In Norway, antimicrobials are prescription only medicines, and only allowed sold through pharmacies. These data are collected from three databases: the Norwegian drug wholesales statistics database, the hospital pharmacies drug statistics database and the Norwegian prescription database (NorPD).

The Norwegian Institute of Public Health collects data on drug use from wholesalers. The wholesales database covers total sales of antimicrobials 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 between the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. *Sykehus-apotekenes Legemiddelstatistikk* collects sales data from each pharmacy delivering drugs to hospitals. Data are collected as sales from the pharmacy to hospital wards. Data have been available since 2006. The national centre for the use of antibiotics in hospitals (*Nasjonal kompetanse-tjeneste for antibiotikabruk i spesialisthelsetjenesten*) has analysed the data according to activity (admission and bed days).

Population statistics per January 1st are collected from Statistics Norway. Information on bed days and admissions are 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 classification system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2022 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.
Use of the 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 dermato-logical 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.

References
1. WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs 2022. WHO Collaborating Centre, Oslo
2. Definitions Norwegian Directorate of Health https://volven.helsedirektoratet.no/begrep.asp?id=452&catID=12

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

Sampling strategy
The clinical isolates included in NORM-VET 2021 were *Escherichia coli*, *Streptococcus dysgalactiae* and *Streptococcus uberis*. All isolates were retrieved through submissions to TINE Mastittlaboratoriet. The *E. coli* (n=168), *S. dysgalactiae* (n=153) and *S. uberis* (n=174) were from clinical mastitis in cattle and sampled throughout 2020 (*E. coli* and *S. dysgalactiae*) and 2021 (*S. uberis*). One isolate per submission was susceptibility tested.

Caecal samples from cattle less than one year of age and fattening pigs were collected at slaughter throughout the year by the Norwegian Food Safety Authority (NFSA), following the specifications set by the European Food Safety Authority (EFSA; EFSA Journal 2019;17(6):5709). One individual caecal sample was included per herd, in total 295 and 321 samples from cattle and pigs, respectively, except from one cattle and two pig herds where samples were collected twice. The included indicator bacteria *E. coli*, *Enterococcus faecalis* and *E. faecium* were retrieved from these samples. The caecal samples were also used for selective isolation of *E. coli* resistant to extended spectrum cephalosporins (ESC), and carbapenemase-producing *Enterobacterales* (CPE). In addition, the caecal samples were used for isolation of *Salmonella* spp. and *Campylobacter coli* and *Campylobacter jejuni* (see Appendix 4).

Faecal and nasal swabs from 203 horses were collected by veterinarians. The horses sampled were from all over the country, and were between one and 33 years old. The faecal samples were used for retrieving indicator *E. coli*, and for selective isolation of *E. coli* resistant to ESC, CPE, and quinolone resistant *E. coli* (QREC). The nasal swabs were used for selective isolation of methicillin resistant *Staphylococcus aureus* (MRSA).

All food samples were collected by the NFSA. Beef and pork samples, 313 and 312, respectively, were collected at retail in all regions of Norway following the specifications set by EFSA (EFSA Journal 2019;17(6):5709). Samples were collected without taking place of origin into account. All the food samples were analysed using selective isolation for *E. coli* resistant to ESC and CPE.

Indicator isolates of *E. coli*
Sample material, i.e. caecal content from one cattle and one fattening pig per herd and faecal material from one horse, were plated directly onto MacConkey agar (Difco) and incubated at 44±0.5 °C for 20±2h. From all sample types, typical colonies were subcultured on blood agar (Heart infusion agar, Difco) containing 5% bovine blood and incubated at 37±1° C for 20±2h. Colonies were identified as *E. coli* by typical colony appearance and a positive indole reaction.

Indicator isolates of *E. faecalis* and *E. faecium*
Sample material, i.e. caecal content from one cattle and one fattening pig per herd and faecal material from one horse were plated directly onto Slanetz and Bartley agar (Oxoid, Oslo, Norway) and incubated at 44±0.5 °C for 24-48h. From all sample types, typical colonies were subcultured on blood agar incubated at 37±1 °C for 20±2h. Colonies were identified as *E. faecalis* and/or *E. faecium* using Matrix Assisted Laser Desorption/Ionisation - Time of Flight Mass Spectrometry (MALDI-TOF MS) (Bruker Daltonics GmbH, Bremen, Germany).

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 horses were inoculated in 5 mL of BPW-ISO. A total of 25±0.5 g sample material of beef and pork were homogenised with 225 mL of BPW-ISO. Samples were incubated at 37±1 °C for 20±2h according to the protocol from the EURL-AR (https://www.eurl-ar.eu/protocols.aspx). After incubation, 10 µL of the enrichment broth was plated onto selective media as described in the sections below.

***E. coli* resistant to extended spectrum cephalosporins**
Aliquots from the overnight BPW-ISO broth from all caecal, faecal, beef, and pork samples were plated onto MacConkey agar (Difco) containing 1 mg/L cefotaxime and MacConkey agar (Difco) containing 2 mg/L ceftazidime. The agar plates were incubated at 44±0.5 °C for 20±2h. Presumptive *E. coli* resistant to ESC were subcultured onto MacConkey agar (Difco) containing 1 mg/L cefotaxime and blood agar, and confirmed as *E. coli* using MALDI-TOF MS before further testing for cephalosporinase production.

Quinolone resistant *E. coli*
Aliquots from the overnight BPW-ISO broth from faecal samples were plated onto MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin. Plates were incubated at 44±0.5 °C for 20±2h. Presumptive QREC were subcultured onto MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin and blood agar and confirmed as *E. coli* using MALDI-TOF MS before further phenotypical testing.

Carbapenemase-producing *Enterobacterales*
Aliquots from the overnight BPW-ISO broth from all caecal, faecal, beef, and pork 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 24-48 h. Presumptive CPE were subcultured on respective selective CHROMID® agar and blood agar, and species confirmed using MALDI-TOF MS before further phenotypical testing.

Methicillin resistant *Staphylococcus aureus*
Nasal swabs from horses were analysed for methicillin resistant *Staphylococcus aureus* (MRSA). Sample material were 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) (EFSA journal 2012:10 (10):2897). Suspected colonies were subjected to species identification using MALDI-TOF MS before further phenotypical testing.

E. coli, S. dysgalactiae* and *S. uberis
All isolates retrieved from clinical samples were species identified using MALDI-TOF MS.

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 mutations using the online tool ResFinder V.4.1 at the Center for Genomic Epidemiology web site (https:// cge.food.dtu.dk/ services/ResFinder/).

Susceptibility testing
Isolates were tested for antimicrobial susceptibility using a broth microdilution method at the NVI, Oslo. 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 recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 16.02.2022) 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.

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

Clinical isolate tested	**Sensititre® TREK panel**
Escherichia coli	EUVSEC3
Streptococcus dysgalactiae	DNKDTUV1
Streptococcus uberis	DNKDTUV1

The clinical streptococci isolates were susceptibility tested using cation adjusted Mueller Hinton broth containing lysed horse blood (CAMHBT-LHB, TREK Diagnostic LTD) and 100 µL was pipetted in each well of the plate.

Quality assurance systems
The following susceptible bacteria were included as quality controls on a regular basis: *E. coli* ATCC 25922, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619. 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 4.0.3 Copyright (C) 2020 (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.**
Caecal samples from cattle less than one year of age and fattening pigs decribed in Appendix 3, were used for isolation of *Salmonella* spp.. In addition, isolates of *Salmonella* spp. were retrieved from the Norwegian *Salmonella* control programme for live animals, and from the surveillance of wild boars. Additional isolates were 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.

Campylobacter jejuni* and *C. coli
Caecal samples from cattle less than one year of age and fattening pigs decribed in Appendix 3, were used for isolation of *Campylobacter coli* and *Campylobacter jejuni*. Sample material, i.e. caecal content from one fattening pig per herd and one bovine less than one year of age as described in Appendix 3, were plated directly onto mCCDA agar and Bützler agar and incubated under microaerophilic conditions at 41.5±0.5 °C for 48h. Typical colonies were subcultured on blood agar and confirmed as *Campylobacter jejuni* or *Campylobacter coli* using Matrix Assisted Laser Desorption/Ionisation - Time of Flight Mass Spectrometry (MALDI-TOF MS) (Bruker Daltonics GmbH).

Susceptibility testing – animal isolates
Isolates were tested for antimicrobial susceptibility at the NVI, Oslo. 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. Epidemiological cut-off (ECOFF) values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 16.02.2022) were used, with some exceptions as explained further in Appendix 7.

Overview of the Sensititre® TREK panel that were 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 bacterium received from EURL-AR was included: *C. coli* 2012-70-443-2 (EUCAMP3 panel). The NVI and the Reference Laboratory for Entero-pathogenic 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 in 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 v.4.0.3 Copyright (C) 2020 (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 campylo-bacteriosis cases registered were submitted in the following way: Five regional laboratories submitted the first five independent isolates each month to the NRL for Entero-pathogenic 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.12.0 2022 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.*

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) in Ridom SeqSphere+ (v.8.3.4). Discrepancies between phenotype and genotype were re-screened using the ResFinder 4.1 software and database online with default threshold and length settings. (https://cge.cbs.dtu.dk/services/ResFinder/).

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 2000-2021 are presented in the table below, for enteric infections see Appendix 4. In 2021, all 22 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 2021 were as follows: *E. coli* from blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. 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); *E. coli* (3 days) and *Klebsiella* spp. (3 weeks) from urinary tract infections; *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* from all samples (12 months) as well as *S. pneumoniae*, *S. pyogenes*, *H. influenzae* and *N. meningitidis* 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* isolates were analysed at OUS/ Rikshospitalet. MRSA and *S. agalactiae* isolates were analysed at St. Olav University Hospital in Trondheim. *M. tuberculosis* isolates were analysed at NIPH, OUS/Ullevål and Rikshospitalet.

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp. 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 mm 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 was analysed using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

Molecular typing and characterization of isolates

Included in the NORM report is specific molecular analysis 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 analysis includes 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
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				
	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
	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
	Enterococcus spp.	50	50									2 w					3 w			3 w			
	Enterobacter spp.						50											3 w					
	Proteus spp.							25											3 w				
	P. aeruginosa																				3 w		
Wounds	*S. aureus*		50		50	50		50	2 w	2 w	2 u	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w	1 w
	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
	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
	Enterobacter spp.				12 m	12 m	12 m	12 m	12 m	9 m			12 m					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
	N. menigitidis														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
	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
	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
	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
	S. agalactiae (GBS)							50		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
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
	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

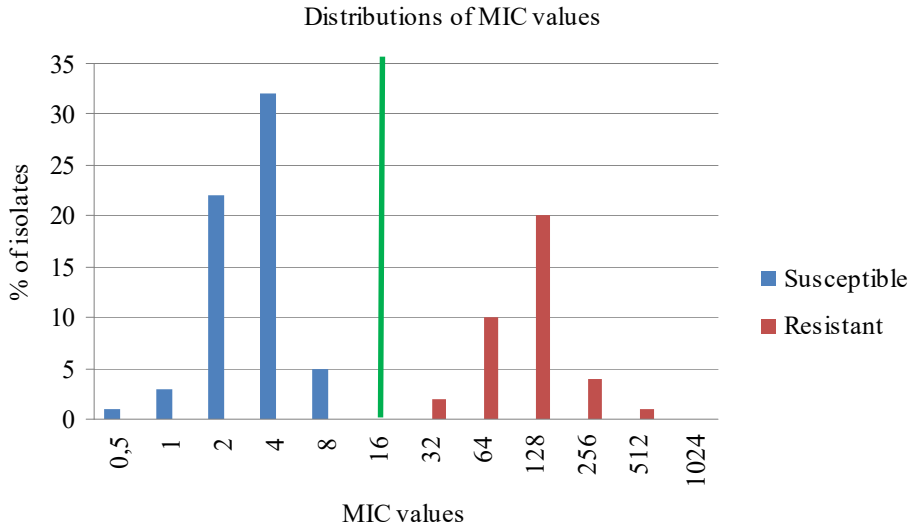
Surveillance at reference laboratories in red. d=days; w=weeks; m=months.

Appendix 6:
Definitions and classification of resistances used in this report

General guidelines for the reader of this report

The results presented in the NORM and NORM-VET programmes are not directly comparable. This is because the sampling and also the classification of resistance differs between the programmes. Clinical breakpoints are used for the classification within NORM, while epidemiological cut-off values (ECOFF) are used for the classification of resistance within NORM-VET.

The terms and usage of these two ways of classification of resistance are further explained below. The ECOFF would normally be lower for minimum inhibitory concentration (MIC) values and higher for disk diameters than the clinical breakpoints. However, this is not always the case.



Epidemiological cut-off values

Based on the distribution of the MIC values, or the inhibition zone diameter distribution, each bacterial population could (in an ideal case) be divided into two sub-populations by a biphasic curve as shown in the example above. The curve to the left (blue) shows the susceptible or wild type distribution whereas the curve to the right (red) shows the resistant or non-wild type distribution. 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 programmes were made available through courtesy of P. Smith, W. Finnegan, and G. Kronvall and were applied on the clinical isolates of *Streptococcus dysgalactiae* and *S. uberis* to define cut-off values (CO_{WT}) in cases where EUCAST ECOFFs were missing.

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 2019-2020, 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 16.02.2022) were used. For additional antimicrobial agents not defined in the EUCAST recommendations, EFSA recommended cut-off values were used or cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme as described in Appendix 6. This was applied to the clinical isolates of *Streptococcus dysgalactiae* and *S. uberis*.

Overview of the antimicrobial classes and agents tested for with corresponding epidemiological MIC cut-off values (mg/L) used in NORM-VET 2021:

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella* enterica	*Campylobacter coli* / *C. jejuni*	*Enterococcus faecalis* / *E. faecium*	*Streptococcus dysgalactiae**	*S. uberis**
Tetracyclines	Oxytetracycline					>16	>1
	Tetracycline	>8	>8	>2 / >1	>4		
	Tigecycline	>0.5	ND		>0.25		
Amphenicols	Chloramphenicol	>16	>16	>16	>32		
Penicillins with extended spectrum	Ampicillin	>8	>4		>4 / >8		
	Amoxicillin					>0.06	>0.12
	Temocillin	(>16)					
Beta-lactamase sensitive penicillins	Benzylpenicillin					>0.015	>0.12
Beta-lactamase resistent penicillins	Cloxacillin					>0.25	>1
1st generation cephalosporins	Cefalexin					>1	>1
	Cefapirin					>0.25	>0.12
2nd generation cephalosporins	Cefoxitin	(>8)					
3rd generation cephalosporins	Cefotaxime	>0.25	>0.5				
	Ceftazidime	>0.5	>2				
Combinations of 3rd generation cephalosporins and clavulanic acid	Cefotaxime/clavulanate	(>0.25)					
	Ceftazidime/clavulanate	(>0.5)					
4th generation cephalosporins	Cefepime	(>0.25)					
Carbapenems	Meropenem	>0.06	>0.06				
	Ertapenem	(>0.03)		ND			
	Imipenem and enzyme inhibitor	(>0.5)					
Trimethoprim and derivatives	Trimethoprim	>2	>2				

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella* enterica	*Campylobacter coli* / *C. jejuni*	*Enterococcus faecalis* / *E. faecium*	*Streptococcus dysgalactiae**	*S. uberis**
Sulfonamides	Sulfamethoxazole	>64[#]	ND				
Combinations of sulfonamides and trimethoprim, incl. derivates	Sulfamethoxazole and trimethoprim					0.25	>0.5
Macrolides	Erythromycin			>8 / >4	>4		
	Azithromycin	>16	>16				
	Tylosin					>0.5	>4
Lincosamides	Lincomycin					>0.5	>0.5
Streptogramins	Quinupristin and dalfopristin				ND		
Streptomycins	Streptomycin					>64	ND
Other aminoglycosides	Gentamicin	>2	>2	>1	>64 / >32		
	Amikacin	>8					
Fluoroquinolones	Ciprofloxacin	>0.064	>0.064	>0.5	>4 / >8		
Other quinolones	Nalidixic acid	>8	>8				
Glycopeptid antibacterials	Vancomycin				>4		
	Teicoplanin				>2		
Polymyxins	Colistin	>2	ND				
Other antibacterials	Linezolid				ND / >4		
	Daptomycin				>4 / >8		

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) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* 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*
Amikacin	≤ 8	> 8	■																			
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											■									
	≤ 0.03	> 0.03				■																
	≤ 0.03	> 0.06					■															
	≤ 0.06	> 0.06			■			■[1]														
	≤ 0.25	> 0.5	■	■					■	■												

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* 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											■									
	≤ 0.25	> 0.5											■[3]									
	≤ 0.5	> 0.5													■	■	■					
	≤ 4	> 4																				
Colistin	≤ 2	> 2							■[1]	■[1]												
	≤ 16	> 16						■[1]														
Erythromycin	≤ 0.25	> 0.5													■	■	■					
	≤ 1	> 2											■									
	≤ 4	> 4									■											
	≤ 8	> 8										■										
Fluconazole	≤ 0.002	> 16																	■			
	≤ 2	> 4																■		■	■	■
Fosfomycin	≤ 8	> 8	■																			
Fusidic acid	≤ 1	> 1											■									
Gentamicin	≤ 1	> 1											■									
	≤ 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											■									
	≤ 0.06	> 0.5											■[4]									
	≤ 0.25	> 0.25				■																
Spectinomycin	≤ 64	> 64					■															
Streptomycin	≤ 16	> 16						■[1]														

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* 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	> 2											■		■	■	■					
	≤ 2	> 2			■	■					■	■										
	≤ 4	> 4							■[1]	■[1]												
	≤ 8	> 8						■[1]														
	≥ 17 mm	< 17 mm						■[5]	■[5]	■[5]												
Tigecycline	≤ 0.25	> 0.25												■								
	≤ 0.5	> 0.5	■										■									
Tobramycin	≤ 2	> 2	■	■																		
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]Clindamycin breakpoint of R > 0.5 mg/L only used on MRSA isolates. [4]Rifampicin breakpoint of R > 0.5 mg/L only used on MRSA isolates. [5] Epidemiological cut-off value (ECOFF) based on national distribution.

Appendix 9: References used in this report

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