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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 organisms to another. Such transfer is not limited to closely related organisms; it can also take place between organisms of different evolutionary origins and/or ecological niches. Thus, antimicrobial drug usage and resistance in one ecological compartment can have consequences for the occurrence of resistance in another compartment. When addressing antimicrobial resistance – the occurrences, causes, consequences and preventive measures – a holistic approach is needed, encompassing both data on usage and resistance in human and veterinary medicine, as well as organisms in the food production chain.

In response to the growing concern about antimicrobial resistance, the Norwegian Ministry of Health and Social Affairs issued a national action plan against antimicrobial resistance in March 2000. The importance of monitoring the human and animal health sectors as well as food production, was emphasised. The action plan recognised the need for ongoing surveillance as a fundamental component of the strategy. The NORM and NORM-VET programmes were consequently established in order to provide and present data on the occurrence and distribution of antimicrobial resistance over time. The national action plan formally expired by the end of 2004. However, the need for continued surveillance of both resistance and antimicrobial usage was emphasised at subsequent consultations and an integrated national strategy for prevention of infections in the health service and antibiotic resistance (2008-2012) was issued in the summer of 2008. Following the renewed effort of the WHO in recent years, the Norwegian government launched a new national strategy (2015-2020) 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. Mapping of reservoirs of antimicrobial resistant bacteria will also be carried out in the most relevant animal populations and plants important to food safety. Due to the coronavirus pandemic, the expiry of this strategy has been postponed until 2021, 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 2020. The editors would like to thank all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Oslo, September 2021

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 2020. 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 2020 utgjorde salget av antibakterielle veterinærpreparater til landdyr totalt 5 019 kg som er på samme nivå som i 2019.

Salget av antibakterielle veterinærpreparater til matproduserende landdyr, inkludert hest, var på 4 659 kg. Data rapportert til Veterinært legemiddelregister (VetReg) viser at til gris, storfe, sau, geit og fjørfe ble det i all hovedsak brukt penicilliner og av disse var det nesten utelukkende beta-laktamseømfintlige penicilliner (benzylpenicillinprokain) som ble benyttet. Fra 2013 til 2020 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 23 % målt i kg aktivt stoff. Når salget relateres til størrelsen av dyrepopulasjonen, var nedgangen i forbruket 18 %. Til hest ble det i hovedsak brukt trimetoprim-sulfa (oralpasta).

Salget av antibakterielle veterinærpreparater som kan benyttes til flokkbehandling, er fortsatt lavt; i 2020 representerte salg av slike preparater 3,6 % av totalsalget til matproduserende landdyr, inkludert hest. Forbruket av veterinære antibakterielle midler til oppdrettsfisk (forbruk til rensefisk inkludert) var fortsatt svært lavt i 2020 og utgjorde 223 kg. Dette utgjør en nedgang på over 99 % sammenlignet med 1987 da forbruket var på sitt høyeste. I 2020 ble det foretatt behandling med antibiotika av laks og regnbueørret i 0,8 % av sjølokalitetene.

Til kjæledyr (hund og katt) ble det i 2020 solgt 360 kg veterinære antibakterielle midler. Dette er en nedgang på 32 % sammenlignet med 2013. Data rapportert til VetReg for perioden 2015-2020 viser en gradvis reduksjon på 21 % i forskrivningen av antibakterielle humanpreparater til hund og katt, noe som indikerer at redusert salg av veterinære antibakterielle midler ikke har blitt erstattet med forskrivning av antibakterielle humanpreparater.

Det europeiske legemiddelbyrået (EMA) har anbefalt å begrense bruken av enkelte antibakterielle midler til dyr på grunn av den potensielle risikoen for folkehelsa, som 3.-4. generasjon cefalosporiner, kinoloner (fluorokinoloner og andre kinoloner) og polymyksiner. Av disse antibakterielle midlene selges det kun kinoloner til matproduserende landdyr og oppdrettsfisk i Norge. Salget av kinoloner utgjør en svært liten andel av totalsalget av veterinære antibakterielle midler til disse kategoriene og brukes hovedsaklig til oppdrettsfisk.

Narasin ble faset ut som fôrtilsetningsmiddel til slaktekylling sommeren 2016. Bruken av antibiotika til behandling av slaktekylling er fortsatt svært lavt; i 2020 ble det kun foretatt én behandling av to slaktekyllingflokker, og det ble kun brukt beta-laktamaseømfintlige penicilliner.

Forbruk av antibiotika hos mennesker

I 2020 var det totale salget av antibakterielle midler til systemisk bruk hos mennesker (J01 ekskl. metenamin) 11,5 definerte døgndoser (DDD)/1000 innbyggere/døgn. Siden 2012 har det vært en markant nedgang i total antibiotikabruk, i alt en reduksjon på 32 %. Under Covid-19 pandemien har det vært observert en signifikant reduksjon i bruken av systemiske antibiotika, hovedsakelig grunnet mindre forskrivning av antibiotika mot luftveisinfeksjoner i primærhelsetjenesten. Smitteverntiltak kan ha redusert forekomsten av infeksjoner, i tillegg til en høyere terskel for å gå til lege med symptomer på luftveisinfeksjon.

Rundt 84 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. I 2020 ble penicilliner (J01C) oftest forskrevet i primærhelsetjenesten; 37 % av all DDD og 52 % av reseptene i ATC-gruppe J01, ekskl. metenamin, etterfulgt av tetracykliner, J01A (19 %). De tre hyppigst forskrevne antibiotika i 2020 var fenoksymetylpenicillin, pivmecillinam og doksycyklin. Disse tre utgjorde 49 % av alle resepter og 52 % av all antibiotika DDD. I Norge er smalspektret penicillin førstevalg ved luftveisinfeksjoner. I 2020 ble andelen smalspektret penicillin (J01CE) redusert og utgjorde 24 % av det totale salget (J01, ekskl. metenamin). Metenamin benyttes som forebyggende medisin mot urinveisinfeksjoner og utgjorde 25 % av alle DDD i J01 (antibakterielle midler til systemisk bruk). Den jevne nedgangen i antibiotikabruk i primærhelsetjenesten de siste årene kan skyldes økt oppmerksomhet mot antimikrobiell resistens, både blant helsepersonell og i befolkningen generelt. Etter innføringen av regjeringens handlingsplan mot antibiotikaresistens i 2016 har en stor andel av allmennlegene 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 2020. Det har vært en nedgang på 11 % i DDD/1000 innbygger/døgn sammenlignet med 2019. Sykehusene omstrukturerte avdelingene sine og utsatte valgfri kirurgi som forberedelse til det forventede høye antallet 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 76 DDD/100 liggedøgn i 2020. Dette er en økning på 14 % siden 2012. DDD/sykehusinnleggelse (i 2020; 3,1 DDD/innleggelse) økte med 1 % i samme periode. Antibakterielt terapimønster på sykehus endrer seg ikke mye fra ett år til et annet, men det er en klar trend mot mer bruk av antibiotika anbefalt i retningslinjene. Bruken

av bredspektret antibiotika er redusert med 20 % sammenlignet med 2012 målt som DDD/100 liggedøgn. I sykehus ble penicilliner (J01C) mest brukt (ca halvparten av bruken målt i DDD) med cefalosporiner som den nest største antibiotikagruppen (20 % 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 pasientpopulasjon alene.

Resistens hos kliniske isolater fra dyr

I 2020 ble det undersøkt kliniske isolater fra infeksjoner med *Klebsiella pneumoniae* hos forskjellige dyrearter (n=74), samt *Actinobacillus pleuropneumoniae* (APP) fra gris (n=83).

Totalt 86,5 % av *K. pneumoniae* isolatene var fullt følsomme overfor alle de antibiotika de ble testet for. Multiresistens ble påvist hos fire (5,4 %) av isolatene. Ett av disse var resistent mot hele syv antibakterielle klasser, og to av isolatene mot fem antibakterielle klasser. To av isolatene fra hund var resistente mot 3. generasjons cefalosporinene cefotaxim og ceftazidim, og $bla_{\text{CTX-M-15}}$ genet ble påvist fra begge isolatene.

A. pleuropneumoniae (APP) har ikke tidligere vært sensitivitetstestet i NORM-VET. Dessverre var de konsentrasjonene isolatene ble testet for, ikke optimale for APP. Epidemiologiske brytningspunkter kunne derfor ikke bestemmes for alle de antibakterielle midlene inkludert i testpanelet, og dermed kunne heller ikke resistensforekomst for APP bestemmes for disse. Blant de antibakterielle midlene hvor forekomst av resistens kunne bestemmes, var resistens mot amfenikolet florfenikol og kinolonene danofloksacin og enrofloksacin vanligst forekommende.

Resistens hos indikatorbakterier fra dyr og mat

Resultatene fra 2020 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. Karbapenem-resistente *Enterobacteriaceae* (CRE) har ikke blitt påvist fra dyr eller mat i Norge. Dette gjelder også for 2020.

NORM-VET følger de krav til overvåking av antibiotika-resistens som er satt i EU-regelverket (2013/652/EU). *E. coli* og *Enterococcus* spp. benyttes som indikatorbakterier, dvs. sensitivitetstesting av *E. coli og Enterococcus* spp. benyttes som indikator for forekomst av antibiotika-resistens i bakteriepopulasjonen. Selektive metoder benyttes til overvåking av *E. coli* resistent mot ESC, CRE, og vankomycinresistente *Enterococcus* spp. (VRE).

Noen antibakterielle midler er definert av WHO som kritisk viktige for behandling av infeksjoner hos mennesker. Utvikling av et betydelig reservoar av slike resistente bakterier hos dyr og i matproduksjonskjeden vil være uønsket, da disse vil kunne ha en effekt på bakteriepopulasjoners resistensutvikling hos mennesker.

I 2020 ble det undersøkt blindtarmsprøver fra flokker av slaktekylling og kalkun for isolering og sensitivitets-undersøkelse av *E. coli* og *Enterococcus* spp., samt isolering av ESC resistente *E. coli*, CRE og VRE. Prøvene av mat i 2020 var kyllingkjøtt, og disse ble undersøkt for forekomst av ESC-resistente *E. coli* og CRE.

Majoriteten av de 247 *E. coli* isolatene fra slaktekylling var fullt følsomme for de antibakterielle midlene de ble testet for (79,8 %), og kun 0,4 % av isolatene var multiresistente. Antallet isolater fullt følsomme har vært relativt stabilt de siste årene (2014-2020), men det har vært en statistisk signifikant økning i kinolonresistens fra 3,4 % i 2014 til 12,6 % i 2020. ESC resistente *E. coli* ble påvist kun i én av blindtarmprøvene og i tre av kjøttprøvene (0,9 %) fra slaktekylling. Alle isolatene var bærere av $bla_{\text{CMY-2}}$ genet. Dette er i samsvar med resultatene fra 2018, og bekrefter at tiltakene iverksatt av fjørfenæringen for å redusere forekomsten av ESC resistente *E. coli* hos slaktekylling har vært vellykket.

Av *Enterococcus faecalis* isolatene (n=87) fra slakte-kyllingflokkene var 31 % fullt følsomme for de anti-bakterielle midlene de ble testet for, mens tilsvarende tall for *Enterococcus faecium* (n=237) var 82,7 %. Ingen av isolatene var multiresistente. Det har vært en statistisk signifikant økning i forekomst av tetrasyklinresistens hos *E. faecalis* siden 2018 fra 36,7 % til 66,7 %. Imidlertid var forekomsten i 2014 mer lik som i 2020, og videre overvåking må til for å følge dette i årene framover. Det ble påvist en statistisk signifikant nedgang i forekomst av narasinresistens hos *E. faecium* fra 24,7 % i 2018 til 15,6 % i 2020. Denne nedgangen var forventet da bruken av narasin som koksidiostatikum til slaktekylling ble faset ut i Norge i 2015-2016. Etter dette har norsk kylling vært fôret opp uten forebyggende bruk av koksidiostatika, og kun noen flokker har fått narasin i fôret ved utbrudd av sykdom (se kapittel om forbruk av antibiotika). VRE ble ikke påvist i 2020, og det er i samsvar med resultatene fra 2018.

Majoriteten (75,2 %) av *E. coli* (n=121) fra kalkun var fullt følsomme for de antibakterielle midlene som var inkludert i testpanelet. Denne situasjonen ser ut til å ha vært relativt stabil de siste årene (2016-2020). Totalt 4,9 % av isolatene var multiresistente. ESC resistente *E. coli* ble påvist fra ni (7,4 %) av kalkunprøvene, alle disse var forårsaket av kromosomale mutasjoner. Hos *E. faecalis* (n=24) var 54,2 %, og hos *E. faecium* (n=115) var 61,7 %, fullt følsomme for alle de antibakterielle midlene det ble testet for. Multiresistens ble påvist hos 0,9 % av *E. faecium* isolatene. Hos *E. faecium* fra kalkun var 78,3 % resistente mot narasin, noe som er i samsvar med resultatene fra 2018. Narasin har aldri vært benyttet til kalkun, og det er ukjent hva som er årsak til forekomsten av narasinresistens hos kalkun. VRE ble ikke påvist fra noen av prøvene fra kalkun, og dette er i samsvar med resultatene fra 2018.

Resistens hos zoonotiske bakterier og andre enteropatogene bakterier

Zoonosebakterier isolert fra dyr

Den norske husdyrpopulasjonen er regnet som tilnærmet fri for *Salmonella*. I 2020 ble det sensitivitetstestet 33 *Salmonella* isolater. Hele 23 av disse var *S.* Typhimurium, fra henholdsvis åtte katter, fem villsvin, fire storfe, fire hunder, en gris og en kylling. De resterende ti isolatene tilhørte åtte forskjellige serovarianter. Ni av isolatene var fullt følsomme for alle de antibakterielle midlene de ble testet for. Tjue isolater viste nedsatt følsomhet for kolistin. Imidlertid ble det ikke påvist hverken ervervede resistens-

gener eller punktmutasjoner som kunne forklare dette funnet, og siden det kan være serovariantforskjeller i naturlig følsomhet, ble alle disse ansett som følsomme for kolistin. Multiresistens (resistens mot tre eller flere antibakterielle klasser) ble påvist hos tre *S.* Typhimurium isolater.

Campylobacter spp. ble isolert fra blindtarmsprøver fra flokker av slaktekylling og fra flokker av kalkun. Kun noen svært få isolater av *C. coli* ble påvist. Forekomsten av antibiotikaresistens hos *C. jejuni* fra kylling var lav. Totalt var 90,8 % av 87 isolater fullt følsomme for alle de antibakterielle midlene de ble sensitivitetstestet for. Resistens mot kinoloner var mest vanlig, fulgt av resistens mot streptomycin. Ingen av isolatene var multiresistente.

Kliniske isolater av tarmpatogene bakterier fra mennesker

Etter omorganiseringen av Referanselaboratorium for Enteropatogene Bakterier (NRL) ved Folkehelseinstituttet (FHI), og det midlertidige opphøret i følsomhetstesting for antimikrobiell resistens i 2018, har NRL gjenopptatt antimikrobiell følsomhetstesting for tarmpatogene bakterier fra og med 2019. Fra 2020 blir alle *Enterobacterales* isolater undersøkt med genotypisk resistensscreening ved NRL.

For *Salmonella* Typhimurium og den monofasiske varianten av *S.* Typhimurium var det totale resistensnivået høyere for reiseassosierte stammer sammenlignet med innenlands ervervede stammer. Antimikrobiell resistens var høyest blant *Salmonella* Typhi, med en økende trend for resistens mot utvidet spektrum cefalosporiner. Multiresistens (MDR) var også en karakteristisk egenskap hos en betydelig andel av *S.* Typhi stammer (42,9%). Syv *Salmonella* isolater ble karakterisert som ESBL-produserenter og alle ble genotypet som $bla_{\text{CTX-M}}$. Fluorokinolonresistens i *Salmonella* ble hovedsakelig tilskrevet kjente mutasjoner i *gyrA*.

For *Campylobacter jejuni* var det totale resistensnivået mot ciprofloxacin og tetracyclin høyere for reiseassosierte stammer sammenlignet med innenlands ervervede stammer. En økende trend for resistens mot ciprofloxacin ble observert hos *Shigella sonnei*, og i tillegg en økende trend for resistens mot utvidet spektrum cefalosporiner hos *Shigella flexneri*. Fem *Shigella* spp. ble bekreftet som $ESBL_A$-produsenter og inneholdt $bla_{\text{CTX-M-15}}$. Forekomsten av antimikrobiell resistens i *Yersinia enterocolitica* er fortsatt lav.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2020. Det ble påvist 19 tilfeller av methicillinresistente *Staphylococcus aureus* (MRSA) blant 1 367 blodkulturisolater (1,4 %) som ble inkludert i NORM 2020. Resultatene samsvarer godt med tall fra laboratorienes datasystemer som rapporterte 35 MRSA isolater blant 1 993 *S. aureus* (1,8 %) fra blodkultur og spinalvæske i 2020. Dette er en økning fra 0,9 % i 2019. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 734 tilfeller av MRSA infeksjon i 2020 mot 905 i 2018 og 945 i 2019. De fleste tilfellene var fra pasienter med overfladiske sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (18 av 1 005; 1,8 %) slik de har gjort i tidligere år (1,7 % i 2018; 1,3 % i 2019). MSIS registrerte videre 1 148 tilfeller av MRSA-kolonisering i 2020 mot 1 631 i 2018 og 1 499 i 2019. I alt ble det meldt funn av MRSA hos 1 882 personer i 2020. Dette utgjør en insidensrate på 35/100 000 personår mot 46/100 000 i 2019. Det måndelige antall MRSA infeksjoner har ikke endret seg signifikant gjennom de siste syv 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 i de siste tre årene. En høy andel av tilfellene blir fortsatt smittet i utlandet, men det var en sterk reduksjon i 2020 som antagelig 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 2020. Andelen av gentamicinresistente isolater var 6,7 % i 2020 sammenliknet med 5,4 % i 2018 og 5,9% i 2019, mens forekomsten av resistens mot ciprofloxacin var stabil med 11,2 % i 2020 mot 11,3 % i 2019. *Klebsiella* spp. har omtrent samme forekomst av resistens mot gentamicin (5,2 %) og ciprofloxacin (8,1 %) 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 136/2 087 (6,5 %) *E. coli* og 70/967 (7,2 %) *Klebsiella* spp. fra blodkultur ble rapportert som ESBL-positive i 2020. Forekomsten er omtrent uendret for både *E. coli* (6,5 % i 2018 og 7,1 % i 2019) og *Klebsiella* spp. (6,6 % i 2018 og 5,7 % i 2019). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (6,5 %) enn fra urinprøver (3,4 %).

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 gikk ned fra 75 i 2019 til 57 i 2020. Antallet pasienter med karbapenemaseproduserende *P. aeruginosa* (n=4) var stabilt, mens antallet meldinger for *Acinetobacter* spp. gikk ned fra 23 i 2019 til 10 i 2020. Den mest sannsynlige forklaringen på disse endringene er den dramatiske reduksjonen av internasjonal reisevirksomhet som følge av koronaviruspandemien. Resultatene viser betydningen av importsmitte for epidemiologien til karbapenemaseproduserende Gram-negative bakterier i Norge.

Overvåkingen av resistens hos systemiske isolater av *Haemophilus influenzae* og *Neisseria meningitidis* ble tatt opp igjen ved referanselaboratoriet på Nasjonalt folkehelseinstitutt (FHI) i 2020, men som for andre luftveispatogener ble det diagnostisert svært få tilfeller (henholdsvis n=43 og n=3). *Neisseria gonorrhoeae* (n=442) viste utbredt resistens mot penicillin G (21,9 %), og bare 2,7 % var følsomme for standard dosering svarende til villtypepopulasjonen. Hele 54,8 % var resistente mot ciprofloxacin. Alle isolater var følsomme for ceftriaxon, mens i alt fem isolater (1,1 %) var resistente mot det perorale cefalosporinet cefixim. Alle isolater var fullt følsomme for spectinomycin.

Det ble ikke påvist enterokokkisolater fra blodkultur med klinisk signifikant vankomycinresistens (*vanA* eller *vanB*) i 2020. Forekomsten av resistens mot ampicillin i *E. faecium* ligger stabilt rundt 70-80 %. Høygradig gentamicinresistens holdt seg uendret hos *E. faecalis* på 12,0 % (13,6 % i 2019), men økte hos *E. faecium* til 43,8 % (32,4 % i 2019). 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 2020. Både VRE og LRE er meldepliktige til MSIS, og det ble bekreftet funn av 75 VRE (204 i 2019) og 10 LRE (16 i 2019) på referanselaboratoriet ved Nasjonal kompetansetjeneste for påvisning av antibiotikaresistens (K-res) på UNN i 2020. Ett isolat var i tillegg kombinert VRE og LRE. Forekomsten av VRE varierer med utbrudd fra år til år, mens antallet LRE er langsomt økende. Man kan spekulere på om den signifikante reduksjonen av antall VRE-tilfeller skyldes redusert reisevirksomhet og/eller bedre smitteverntiltak i sykehusene under koronaviruspandemien.

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 1,7% av pneumokokkisolatene fra blod og spinalvæske var resistente mot penicillin G, men i tillegg var 11,1 % kun følsomme for økt eksponering for dette middelet. Andelen kategorisert som I+R økte dermed fra 8,9 % i 2018 til 12,8 % i 2020. Åtte isolater ble i tillegg kategorisert som I for 3. generasjon cefalosporiner. Forekomsten av makrolidresistens var 8,4 % i 2020 sammenliknet med 6,0 % i 2018. *S. pneumoniae* fra luftveisprøver var generelt mer følsomme for penicillin G (91,4 % S) sammenliknet med systemiske isolater (87,2 % S), mens forekomsten av makrolidresistens var tilnærmet den samme (henholdsvis 9,8 % og 8,4 %). Alle isolater av *S. pyogenes* fra blodkultur var følsomme for penicillin G. Forekomsten av erytromycinresistens (6,7 %) er en økning fra 2017 (4,2 %). Systemiske isolater av *Streptococcus agalactiae* (beta-hemolytiske streptokokker gruppe B) var også følsomme for penicillin G, men hadde høy forekomst av resistens mot erytromycin (25,5% i 2019; 19,5 % i 2020) og tetracyklin (77,7% i 2019; 75,2 % i 2020).

Mer enn 900 anaerobe blodkulturisolater ble inkludert i NORM 2020. Det ble funnet utbredt resistens mot penicillin G, og for noen bakteriearter var det også betydelig forekomst av resistens mot piperacillin-tazobaktam og klindamycin. Leseren henvises til teksten for ytterligere detaljer.

I alt 160 pasienter med tuberkulose ble meldt til MSIS i 2020, og resistensresultater er tilgjengelige for 139 av dem. Et enkelt isolat (0,8 %) ble definert som multiresistent (MDR) mot både rifampicin og isoniazid, mens et annet isolat kun var resistent mot rifampicin (RR). Begge pasientene hadde ervervet sine infeksjoner i Asia.

Det ble utført resistensbestemmelse av 195 *Candida* blodkulturisolater av ni forskjellige species fra 185 ulike pasienter. De vanligste artene var *C. albicans* (n=129), *C. glabrata* (n=24), *C. tropicalis* (n=15), *C. dubliniensis* (n=14) og *C. parapsilosis* (n=6). Alle *C. albicans* var følsomme for de undersøkte midlene med unntak av to echinocandinresistente isolater (begge resistente mot micafungin og ett også mot anidulafungin). 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*. 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 husdyr-holdet og i helsevesenet. Det er imidlertid nødvendig med kontinuerlig innsats for å bevare den gunstige situasjonen slik at antibiotika også i fremtiden vil være effektive for de som trenger det. NORM/NORM-VET-rapporten er viktig for å dokumentere utviklingen av antibiotikaforbruk og resistens hos mennesker og dyr, og for å evaluere effekten av tiltak.

SUMMARY

This joint report from the surveillance programme for antimicrobial resistance in human pathogens (NORM) and the monitoring programme for antimicrobial resistance in bacteria from feed, food and animals (NORM-VET) presents data on the occurrence of antimicrobial resistance and the usage of antimicrobial agents in humans and animals for the year 2020. 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 5,019 kg antibacterial ingredients in 2020, which is at the same level as in 2019.

Sales of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,659 kg in 2020. Penicillins continued to be the most-selling antibacterial class for the major species – i.e. cattle, pigs, goats, sheep and poultry - and were almost exclusively accounted for by beta-lactamase sensitive penicillins. From 2013-2019, the estimated sales of antibacterial VMPs for cattle, pigs, poultry, sheep and goats declined by 23% when measured in kg and 18% 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 for group treatment of terrestrial food-producing animals in Norway continued to be very low; in 2020 such products accounted for only 3.6% of the total sales.

In 2020, the sales (kg) of antibacterial VMPs for farmed fish (cleaner fish included) were 223 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 only 0.8% of the on-grower locations were subjected to antibacterial treatment in 2020.

The sales (kg) of antibacterial VMPs marketed for companion animals were 360 kg in 2020. From 2013-2020 the sales of such VMPs for use in companion animals have been reduced by 32%. The prescriptions of human anti-bacterial medicinal products reported to the Veterinary Prescription Register declined gradually by 21% (kg) from 2015-2020. 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, including 3rd and 4th generation cephalosporins, quinolones (fluoroquinolones and other quinolones) and polymyxins. In Norway, only quinolones are sold for food-producing terrestrial animals and farmed fish. The proportion sold of quinolones of the total sales of antibacterial VMPs was very low 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 2020, only two broiler flocks were subjected to one such treatment each and only beta-lactamase sensitive penicillins were used.

Usage of antimicrobial agents in humans

In 2020, the total sales of antibacterial agents for systemic use in humans (J01 excl. methenamine) were 11.5 defined daily doses (DDD)/1,000 inhabitants/day. Since 2012 there has been a marked decline in total antibiotic use, a reduction of 32%. 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 has been raised.

Around 84% 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 2020 was penicillins (J01C); 37% of DDD and 52% of prescriptions in ATC group J01 excl. methenamine, followed by tetracyclines J01A (19%). The three most commonly prescribed antibiotics for outpatients in 2020 were phenoxymethylpenicillin, pivmecillinam and doxy-cycline. These three substances represented 49% of all prescriptions and 52% of all DDD sold. In Norway, the main indication for narrow-spectrum penicillins in primary care is respiratory tract infections, and in 2020 the proportion of narrow-spectrum penicillins (J01CE) was reduced and accounted for 24% of total sales (J01, excl. methenamine). The urinary antiseptic methenamine accounted for 25% of all DDD in the antibacterial J01 group. The steady decreased use in primary care over the latest years may be due to increased attention towards antimicrobial resistance, both among the general public and health professionals. 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 individualisation of doses or duration of course length and choice of antibiotics. One should therefore expect that it is possible to achieve a further lowering of consumption rate and a better narrow-spectrum profile.

In 2020, the antibacterial sales (in DDD) to hospitals represented 8% of total sales of antibacterials for human use in the country. There has been a decrease of 11% in DDD/1,000 inhibitants/day compared to 2019. The hospitals restructured their departments and postponed elective surgery as preparation for the expected high numbers of patients 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 2020, a mean use of 76 DDD/100 bed days was observed, an increase of 14% since 2012. The DDD/admission (2020; 3.1 DDD/admission) increased by 1% in the same period. The therapy pattern of antibacterials in hospitals does not

change much from one year to another but there is a clear trend towards more use of antibiotics recommended in national guidelines. The use of broad-spectrum antibiotics was reduced by 20% compared to 2012 (measured in DDD/100 bed days). In hospitals, around half of the use, measured in DDD, is penicillins (J01C). The second largest group is the cephalosporins with 20% of all DDD. There are large variations between the hospitals in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile. The variations cannot be accounted for by differences in activity or patient populations alone.

Resistance in animal clinical isolates

The clinical isolates included in NORM-VET 2020 were *Klebsiella pneumoniae* from infections in various animal species (n=74) and *Actinobacillus pleuropneumoniae* in pigs (n=83).

In total, 86.5% of the *K. pneumoniae* isolates were susceptible to all antimicrobial agents included in the susceptibility testing. Multi-drug resistance (MDR) was detected in four (5.4%) of the isolates. One of these MDR isolates was resistant to seven antimicrobial classes and two isolates were resistant to five antimicrobial classes. Two of them displayed resistance to the extended-spectrum cephalosporins (ESC) cefotaxime and ceftazidime due to presence of the $bla_{\text{CTX-M-15}}$ gene. Both isolates were from clinical infections in dogs.

This is the first time *A. pleuropneumoniae* has been included in NORM-VET. The antibiotic concentration ranges for several of the substances tested for were too narrow to define epidemiological cut-off values (ECOFFs) based on the available distributions. Therefore, the true occurrence of resistance could not be determined. Among the antimicrobial agents where occurrence of resistance could be determined, the most commonly detected resistances were to the amphenicol florfenicol and the quinolones dano-floxacin and enrofloxacin.

Resistance in indicator bacteria from animals and food

The 2020 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, are low. Carbapenem resistant *Enterobacteriaceae* (CRE) have never been isolated in samples from animals or food in Norway. This still applies for the 2020 results.

NORM-VET is following the requirements set in EU Commission Implementing Decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU). In addition, samples from sources that this legal act does not cover may also 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, CRE, and vancomycin resistant *Enterococcus* spp. (VRE).

Some antimicrobials are defined by WHO as critically important for treatment of human infections. A significant reservoir of such resistant bacteria in animals and the food production chain is of concern as they may interact with the human bacterial population and thus have an impact on resistance development in these.

In 2020, animal samples included caecal samples from broiler and turkey flocks for susceptibility testing of *E. coli* and *Enterococcus* spp., and detection of emerging resistant bacteria/resistance mechanisms such as ESC resistant *E. coli*, CRE and VRE. Food samples consisted of meat from broilers.

In samples from broiler flocks, the majority (79.8%) of the *E. coli* (n=247) were fully susceptible to the antimicrobial classes in the test panel, and only 0.4% were MDR. The number of fully susceptible isolates has been relatively stable around 80% the last years (2014-2020). There has, however, been a statistically significant increase in resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) from 3.4% in 2014 to 12.6% in 2020. ESC resistant *E. coli* were found in only one of the broiler caecal samples and in three (0.9%) of the broiler meat samples, and all were due to presence of the $bla_{\text{CMY-2}}$ gene. This is in concordance with the results from 2018, and confirms that the measures implemented by the industry to reduce the occurrence of ESC resistant *E. coli* in broilers have been successful. Full susceptibility to all antimicrobial classes included in the test panel was present in 31.0% of the *Enterococcus faecalis* (n=87) and in 82.7% of the *Enterococcus faecium* (n=237) isolates from broilers. None of the isolates were MDR. Compared to the data from 2018, there has been a significant increase in occurrence of tetracycline resistance among *E. faecalis* isolates from 36.7% to 66.7%. However, the occurrence in 2014 was more similar to 2020, and further monitoring is needed to follow this in the years to come. A significant decrease in occurrence of narasin resistance was detected in *E. faecium* from 24.7% in 2018 to 15.6% in 2020. A decrease was indicated in *E. faecalis* as well. This decrease in occurrence of narasin resistance was expected as the use of narasin as coccidiostat to broilers was phased out in Norway in 2015-2016. Since then, Norwegian broilers have been raised without the use of coccidiostats, though some flocks are given narasin in cases of outbreaks (see chapter on usage in animals). No VRE were detected, and this is in concordance with the 2018 results.

In turkey, the majority (75.2%) of the *E. coli* isolates (n=121) were fully susceptible to the antimicrobial agents in the test panel, and this seems to have been relatively stable over the last years (i.e. 2016-2020). Altogether, 4.9% of the isolates were MDR. ESC resistant *E. coli* were found in nine (7.4%) of the turkey caecal samples. All were due to chromosomal mutations. A total of 54.2% of *E. faecalis* (n=24) and 61.7% of *E. faecium* (n=115) isolates were susceptible to all antimicrobial classes included in the test panel. MDR was detected in 0.9% of *E. faecium* isolates. The occurrence of narasin resistance in *E. faecium* from turkey was 78.3%, and in concordance with the 2018 result. Narasin has never been used in the turkey production, and the reason behind this occurrence is unknown. No VRE were detected, and this is in concordance with the 2018 results.

Resistance in zoonotic bacteria and non-zoonotic enteropathogenic bacteria

Animal isolates

The Norwegian population of production animals is considered virtually free from *Salmonella* spp. In 2020, a total of 33 *Salmonella* spp. isolates from animals were susceptibility tested. In total, 23 of these isolates were *S.* Typhimurium and included one each from eight cats, five wild boars, four cattle, four dogs, one pig and one chicken, respectively. The remaining ten isolates belonged to eight different serovars. Nine of the isolates were fully susceptible to all antimicrobial classes tested for. Twenty isolates showed reduced susceptibility to colistin (MIC>2). However, no acquired resistance genes nor point mutations were found, and due to differences in natural susceptibility to colistin among serovars, these were regarded as susceptible to colistin. MDR was detected in three *S.* Typhimurium isolates.

Campylobacter spp. from both broiler and turkey flocks were included in 2020. Only a few isolates of *C. coli* were detected, i.e. four from broiler and one from turkey, and streptomycin resistance was detected in one of the broiler isolates. From turkey, only five *C. jejuni* isolates were detected, of which one was resistant to streptomycin. The prevalence of antimicrobial resistance among *C. jejuni* isolates from broilers is low. In total, 90.8% of the 87 *C. jejuni* isolates from broilers tested were susceptible to all antimicrobial agents included in the test panel. Resistance to quinolones were most common, followed by resistance to streptomycins. None of the isolates were MDR.

Human clinical enteropathogenic isolates

Following the reorganisation of the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) and the paused antimicrobial susceptibility testing for 2018, the NRL resumed antimicrobial susceptibility testing for enteropathogenic bacteria in 2019. From 2020 onwards, all *Enterobacterales* isolates received at the NRL are subjected to genotypic resistance screening.

For *Salmonella* Typhimurium and its monophasic variant, overall resistance levels were higher for travel-associated strains compared to domestically acquired strains. Antibiotic resistance was highest among *Salmonella* Typhi, with an observed increasing trend for resistance against extended-spectrum cephalosporins. Multi-drug resistance (MDR) was also a characteristic trait for a considerable propotion of the *S.* Typhi isolates (42.9%). Seven *Salmonella* isolates were characterised as ESBL producers and all were genotyped as $bla_{\text{CTX-M}}$. Fluoroquinolone resistance in *Salmonella* was mostly attributed to known mutations in *gyrA.*

For *Campylobacter jejuni*, overall resistance rates for ciprofloxacin and tetracycline were higher for travel-associated strains compared to strains domestically acquired. An increasing trend of resistance towards ciprofloxacin was observed in *Shigella sonnei* and also an increasing trend of resistance towards extended-spectrum cephalosporin in *Shigella flexneri.* Five *Shigella* spp. isolates were confirmed as ESBL_{A} producers encoding $bla_{\text{CTX-M-15}}$. Antimicrobial resistance rates in *Yersinia enterocolitica* remain low.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2020. Only 19 methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,367 strains included in NORM 2020 (1.4%). During 2020, the total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 1,993 including 35 MRSA strains (1.8%). This is an increase from 0.9% in 2019. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 734 cases of MRSA infections in 2020 compared to 905 in 2018 and 945 in 2019. 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 1.8% (18/1,005) and comparable to previous years (1.7% in 2018; 1.3% in 2019). Furthermore, MSIS registered 1,148 MRSA colonisations compared to 1,631 in 2018 and 1,499 in 2019. A total of 1,882 persons were reported with MRSA in 2020, corresponding to an incidence rate of 35/100,000 person years (46/100,000 in 2019). The monthly number of MRSA infections has not changed significantly over the last seven years, and the incidence of invasive disease has remained stable at a low level. The annual number of colonised persons reached a peak in 2017, and has declined significantly in the last three years. A large proportion of cases are still infected abroad, but a steep reduction was noted in 2020 and was presumably 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 un-changed in 2020. The prevalence of gentamicin resistance increased slightly from 5.9% in 2019 to 6.7% in 2020, while the prevalence of ciprofloxacin resistance remained stable at 11.2% compared to 11.3% in 2019. *Klebsiella* spp. isolates now demonstrate approximately the same rates of resistance to gentamicin (5.2%) and ciprofloxacin (8.1%) as *E. coli*.

Extended-spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 136/2,087 (6.5%) *E. coli* and 70/967 (7.2%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2020. The prevalence was at the same level as in previous years for both *E. coli* (6.5% in 2018; 7.1% in 2019) and *Klebsiella* spp. (6.6% in 2018; 5.7% in 2019). The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (6.5%) than in urinary tract isolates (3.4%).

Colonisation and/or infection with carbapenemase-producing *Enterobacterales* (CPE), *P. aeruginosa* and *Acinetobacter* spp. have been notifiable to MSIS since 2012. The number of CPE patients decreased from 75 in 2019 to 57 in 2020. The number of patients with carbapenemase-producing *P. aeruginosa* (n=4) remained stable, whereas *Acinetobacter* spp. notifications decreased from 23 in 2019 to 10 in 2020. The most probable explanation for this change is the dramatic reduction of international travel due to the coronavirus pandemic, thus demonstrating the role of import for the epidemiology of carbapenemase-producing Gram-negative bacteria in Norway.

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=43 and n=3, respectively). *Neisseria gonorrhoeae* isolates (n=442) displayed resistance to penicillin G (21.9%), and only 2.7% were susceptible to standard dosage corresponding to the wildtype population. Ciprofloxacin resistance was detected in 54.8% of isolates. Five isolates (1.1%) were resistant to cefixime, but sensitive to ceftriaxone. All isolates remained susceptible to spectinomycin.

No enterococcal blood culture isolates with clinically significant vancomycin resistance (*vanA* or *vanB*) were detected in 2020. The prevalence of ampicillin resistance in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) remained unchanged in *E. faecalis* at 12.0% (13.6% in 2019) but increased to 43.8% in *E. faecium* (32.4% in 2019), 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 2020. Both VRE and LRE should be reported to the national notification system (MSIS), and 75 VRE (204 in 2019) and 10 LRE (16 in 2019) were confirmed at the Reference Laboratory at K-res/UNN in 2020. One additional isolate was combined VRE and LRE. The prevalence of VRE varies over time due to outbreaks, whereas there is a gradually increasing number of LRE cases from one year to another. One may speculate that the significant reduction of VRE cases in 2020 was caused by reduced international travel and 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 2020. Only 1.7% of *S. pneumoniae* isolates from blood cultures and cerebrospinal fluids were resistant to penicillin G, but another 11.1% would require increased exposure to be susceptible to this agent. The I+R categories thus increased from 8.9% in 2018 to 12.8% in 2020. Eight isolates were also categorised as I for 3rd generation cephalosporins. The prevalence of macrolide resistance was 8.4% in 2020 compared to 6.0% in 2018. Respiratory tract *S. pneumoniae* isolates were generally more susceptible to penicillin G (91.4% S) compared to systemic isolates (87.2% S), but the prevalences of macrolide resistance were similar (9.8% and 8.4%, respectively). All *Streptococcus pyogenes* blood culture isolates were susceptible to penicillin G. The prevalence of erythromycin resistance (6.7%) is an increase from 2017 (4.2%). Systemic *Streptococcus agalactiae* isolates (beta-haemolytic group B streptococci) were similarly susceptible to penicillin G, but often resistant to erythromycin (25.5% in 2019; 19.5% in 2020) and tetracycline (77.7% in 2019; 75.2% in 2020).

More than 900 anaerobic blod culture isolates were included in NORM 2020. Resistance to penicillin G was commony found, and for some bacterial species there were also significant prevalences of resistance to piperacillin-tazobactam and clindamycin. The reader is referred to the text for further details.

A total of 160 patients with tuberculosis were reported to MSIS in 2020 and susceptibility test results were available from 139 of them. A single isolate (0.8%) was defined as multi-drug resistant (MDR) to both rifampicin and isoniazid (0.8%), whereas another isolate was only resistant to rifampicin (RR). Both patients acquired their infections in Asia.

Susceptibility testing was performed on 195 *Candida* spp. blood culture isolates of nine different species from 185 unique patients. The most common species were *C. albicans* (n=129), *C. glabrata* (n=24), *C. tropicals* (n=15), *C. dubliniensis* (n=14) and *C. parapsilosis* (n=6). All *C. albicans* were susceptible to the substances examined with the exception of two echinocandin resistant isolates (both resistant to micafungin and one also to anidulafungin). 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*. 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 01.01.2021. Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	282,960	145,601	137,359
5 to 14 years	638,631	327,655	310,976
15 to 24 years	654,620	337,208	317,412
25 to 44 years	1,453,799	745,609	708,190
45 to 64 years	1,395,617	712,227	683,390
65 years and older	965,742	450,959	514,783
All age groups	5,391,369	2,719,259	2,672,110

TABLE 2. Livestock population in Norway in 2020. Data provided by the Register of Production Subsidies as of 01.03.2020.

	Number* of	
Animal category	Herds	Animals
Cattle	13,100	876,800
Dairy cows only**	6,300	174,400
Suckling cow only**	4,800	86,500
Combined production (cow)**	950	45,100
Goats	1,270	72,500
Dairy goats**	280	35,700
Sheep	13,510	947,400
Breeding sheep > 1 year**	13,510	947,400
Swine	1,720	741,300
Breeding animal > 6 months**	1,281	42,600
Fattening pigs for slaughter**	1,540	416,830
Laying hen flocks > 250 birds	560	4,088,370
Broilers	490[1]	69,127,540[2]
Turkey, ducks, geese for slaughter (flock > 250 birds)	39	398,000

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

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2020. Data provided by the Norwegian Directorate of Fisheries updated by 09.06.2021.

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	0	515	1,524	2,134	12	10
2020[3]	1,377,185	96,633	152	501	1733	2,033	11	20

[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 2020 was 16,795 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 1993-2020 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 data analysis, including for supplementary information (see Appendix 1).

Usage of veterinary antibacterial agents

Overall, the sales in Norway of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals, including horses, and companion animals in 2019 were 5,008 kg. A decline of the annual sales of such VMPs of 46% in the period 1993-2019 is observed (Figure 1).

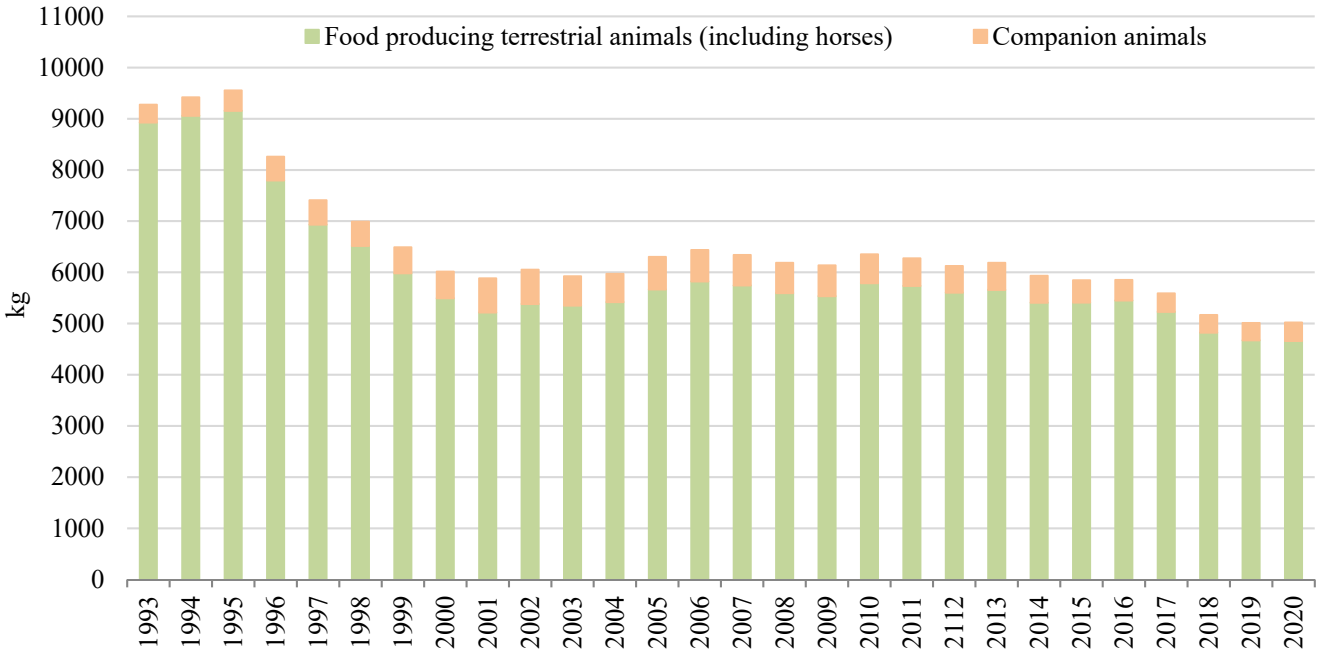

FIGURE 1. Total sales, in kg active substance, for food-producing terrestrial animals (including horses) and companion animals, of antibacterial veterinary medicinal products for therapeutic use in Norway in 1993-2020.

Food-producing terrestrial animals, including horses

In 2020 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,659 kg and compared to 1993 a decrease in the sales of such VMPs of 48% is observed (Figure 2). In total, 62% of the sales (kg) of antibacterial VMPs for this animal category contained penicillins only, of which 94% was accounted for by beta-lactamase sensitive penicillins (narrow-spectrum). Of the total sales to this animal category, 30% was accounted for by combination VMPs with trimethoprim-sulfa; of this combination 89% was sold as oral paste for horses.

The proportion of sales of VMPs containing only penicillins for this animal category increased from 19% to 62% during the period 1993-2020. This is mainly due to reduced sales of injectable and intramammary combination VMPs of penicillins and aminoglycosides (dihydrostreptomycin) that have been gradually replaced by VMPs containing penicillins as the sole antibacterial agents.

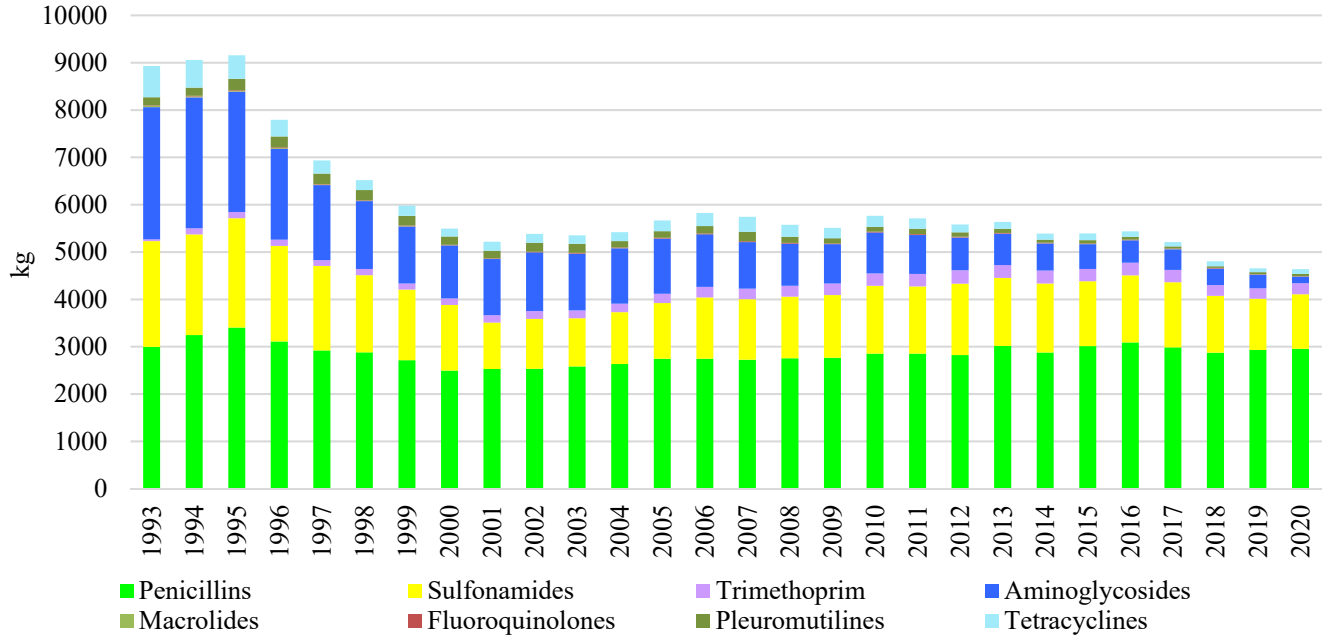

FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals (including horses) in Norway in 1993-2020. In addition, minor amounts of amphenicols VMPs were sold in 2008-2020 (range 16-27 kg). Minor amounts of baquiloprim were sold annually in 1994-2000.

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 cephalonsporins, polymyxins and quinolones (fluoroquinolones and other quinolones) (1,2), only fluoroquinolones are marketed in Norway for food-producing terrestrial animals. From 1993 to 2020, 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 1993-2020 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 3.6% of the sales of antibiotic VMPs for food-producing terrestrial animals were for VMPs for group treatment (oral treatment).

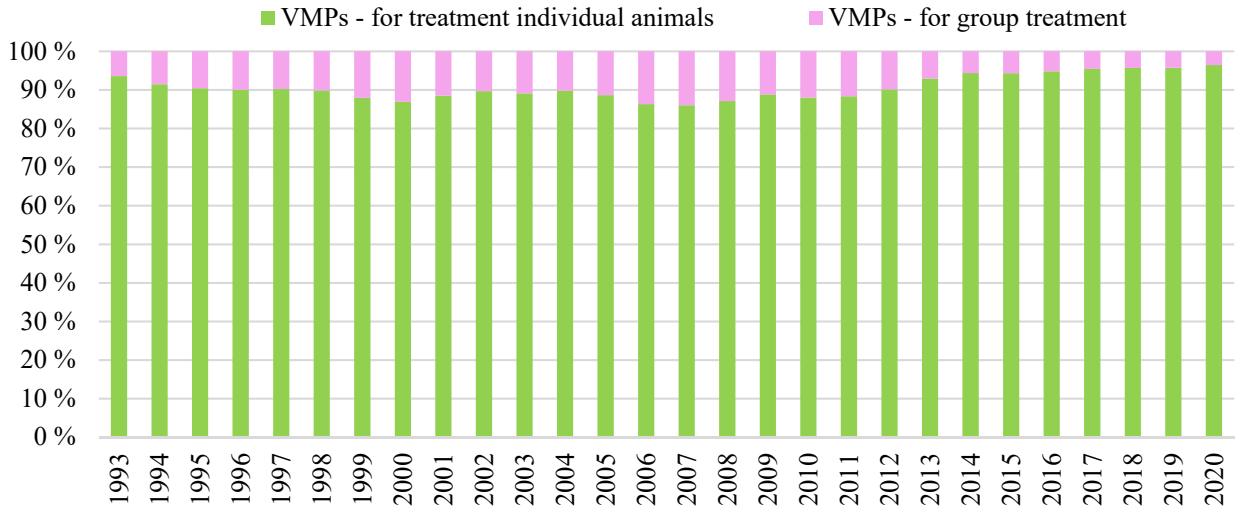

FIGURE 3. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals, including horses (bolus, injectables, intramammary preparations, intrauterine preparations, oral paste and some tablet VMP presentations – see Appendix 1) and 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 presented usage patterns represent the data reported to VetReg (see Appendix I) for 2020. The data were extracted from the VetReg database 2 March 2021. Of the reported amounts (kg) of antibacterial VMPs for cattle, pigs, sheep and goats, <0.5% was for goats and therefore data for this animal species are not presented. Of the amounts antibacterial VMPs and human medicinal products reported to VetReg for which EMA advice restriction of the use due to potential public health risks, the proportions acconted for by cattle, pigs and sheep were 0.2%, 0.1% and 0.03%, respectively, and of these only fluoroquinolones were used (Figure 4-6).

Cattle

Of the prescriptions (VetReg data) of antibacterial veterinary and human medicinal products for cattle in 2020, 89.4% was for penicillins (kg active substance); 87.6% was for beta-lactamase sensitive penicillins (intra-mammaries not included)) (Figure 4). This figure increased slightly from 2015-2020.

Of the prescriptions of intramammaries reported to VetReg specifying animal species, 99% (kg) was for cattle. For intrammaries the sales data are used to document the prescribing patterns (see explanation Appendix I); the sales of intramammaries in kg active substance containing penicillins only were 79% in 2020 and for combinations of penicillins and aminoglycosides this figure was 21%. Measured in number of intramammary injectors sold in 2020, the corresponding figures were 89% and 11%, respectively.

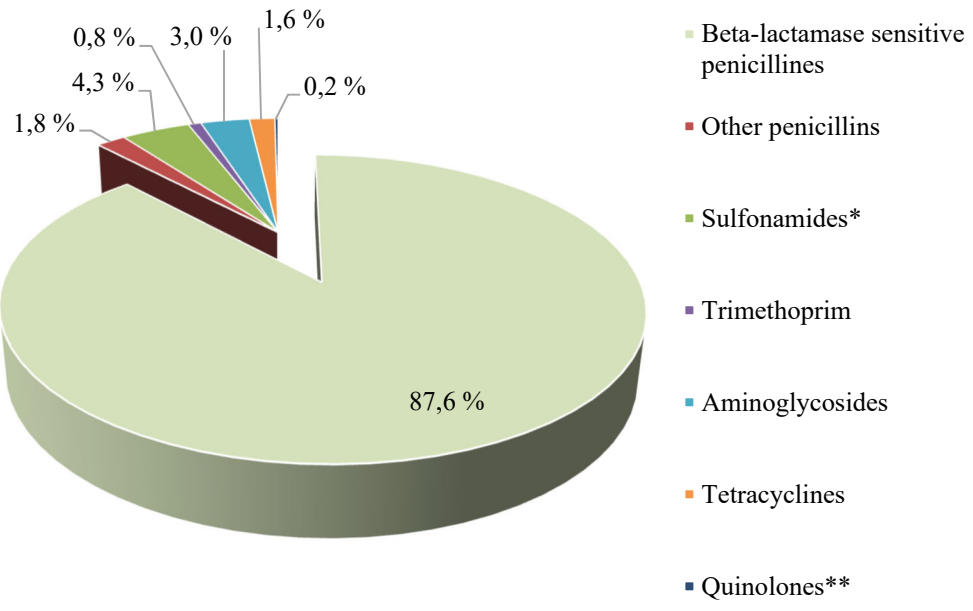

FIGURE 4. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for cattle in Norway in 2020. Data were obtained from the Veterinary Prescription Register (intramammaries not included in data in the figure); * In combination with trimethoprim only; ** Fluoroquinolones only. In addition, 0.07% of the prescribed amounts were for macrolides and 0.7 for others (ampenicols and lincosamides).

Pigs

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of pigs (Figure 5), 85% of the toal amount was accounted for by penicillins; 76.8% was for beta-lactamase sensitive penicillins only (Figure 5). These proportions were increasing slightly from 2015-2020.

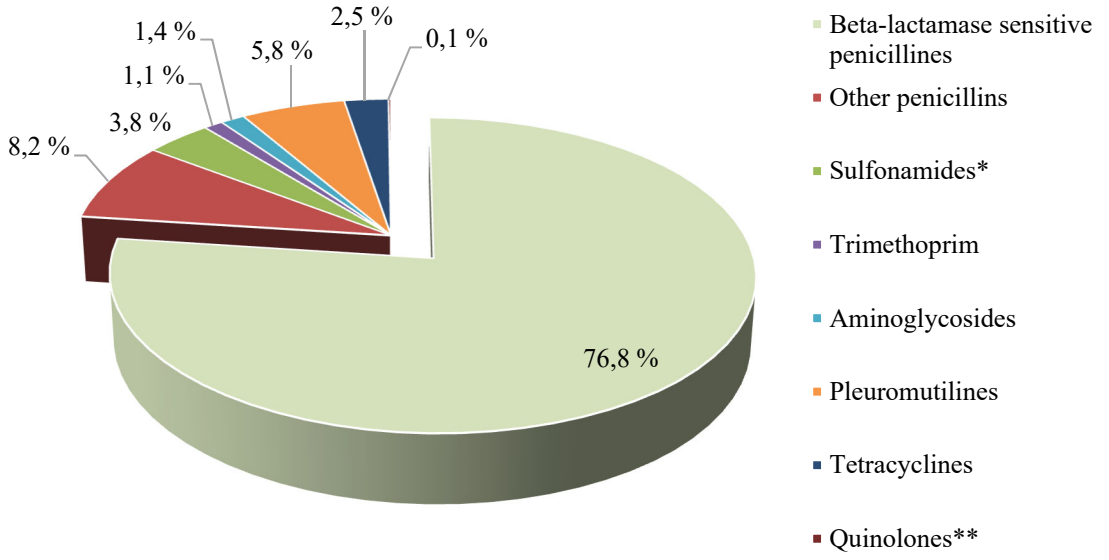

FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for pigs in Norway in 2020. Data were obtained from the Veterinary Prescription Register. *In combination with trimethoprim only; **Fluoroquinolones only.

Sheep

Of the antibacterial veterinary and human medicinal products reported to VetReg as prescribed for treatment of sheep (Figure 6), 75.9% of the toal amount reported to VetReg was accounted for by penicillins, 75.1% was for beta-lactamase sensitive penicillins only (Figure 6). This proportion increased slightly from 2015-2020.

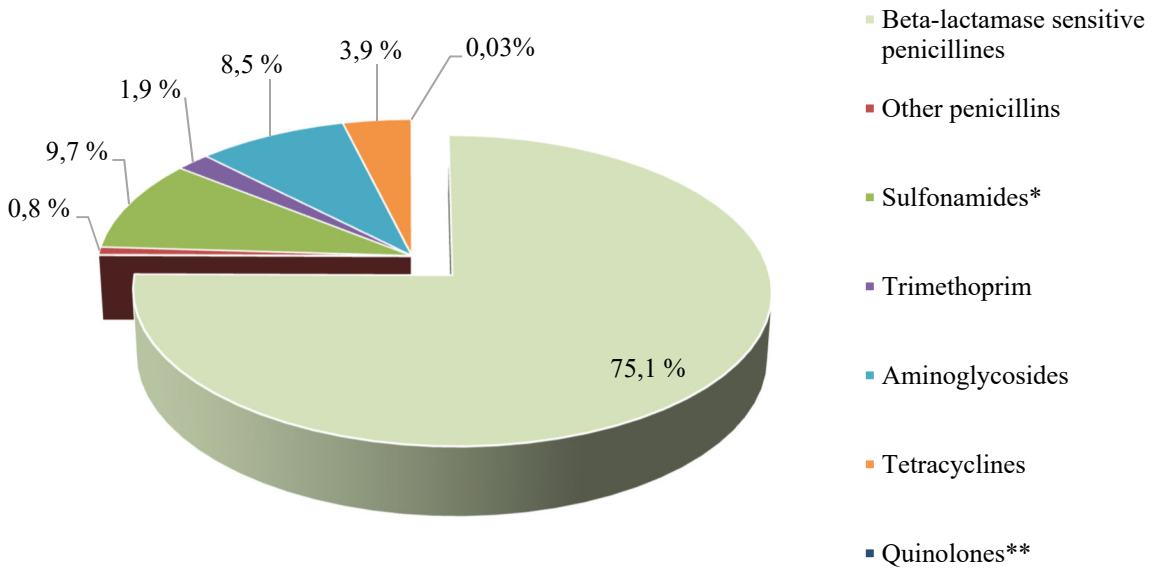

FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary and human medicinal products for sheep in Norway in 2020. Data were obtained from the Veterinary Prescription Register (intramammaries not included in data in the figure). *In combination with trimethoprim only; **Fluoroquinolones only. In addition, 0.017% of kg active substance prescribed was for amphenicols, lincosamides, macrolides and pleuromutilines.

Farmed fish

In 2020, the total amount of antibacterials prescribed for use in aquaculture in Norway was 223 kg (Table 4); of this 207 kg were prescribed for farmed fish intended for human consumption (cleaner fish excluded). This usage was approximately at the same level as in 2015, 2016 and 2019. The amounts (kg) of antibacterials prescribed for farmed fish in 2017 and 2018 were somewhat increased compared to the previous and following years. This was not due to an increase in the number of treatments of farmed fish with antibacterials for these years as the number of prescriptions for 2015-2020 were 61, 63, 63, 43 45 and 48, respectively (Figure 7). The reason for the increase observed in the 2017 and 2018 data in prescriptions measured in kg active substance was that both in 2017 and 2018 a few sea farms with Atlantic salmon with high weights were subjected to treatment with antibiotics while in 2015, 2016, 2019 and 2020 antibiotics were not prescribed for such sea farms.

Of the antibacterials for which restriction of use in animals is recommended at EU/EEA level due to potential public health risk (1, 2), only "other quinolones" are used for farmed fish. From 2011-2020, the proportion of sales of quinolones has fluctuated; in 2020 this proportion was 49% (115 kg) (Table 4).

TABLE 4. Usage, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2011-2020. For 2011-2012 the data represent sales data from feed mills and wholesalers collected by the Norwegian Institute of Public Health; for 2013-2020 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	2011	2012	2013	2014	2015[1]	2016[1]	2017	2018[1]	2019	2020
Tetracyclines										
Oxytetracycline	1	1	0	0	0	0	0	20	0	1
Amphenicols										
Florfenicol	336	191	236	399	188	136	269	858	156	115
Quinolones										
Flumequine	0	0	25	25	< 0.05	< 0.05	< 0.05	0	0	0
Oxolinic acid	212	1,399	599	99	84	66	343	54	66	107
Total	**549**	**1,591**	**860**	**523**	**273**	**201**	**612**	**931**	**222**	**223**

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

For the years 2013-2020, 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 was negligible during the period 2013-2020, despite that Atlantic salmon represents more than 95% of the farmed fish produced in Norway and the total annual production of farmed fish has been above 1.2 million tonnes in the period. This is a strong indication that the vaccines used are efficient and that the coverage of vaccination of fingerlings is very high.

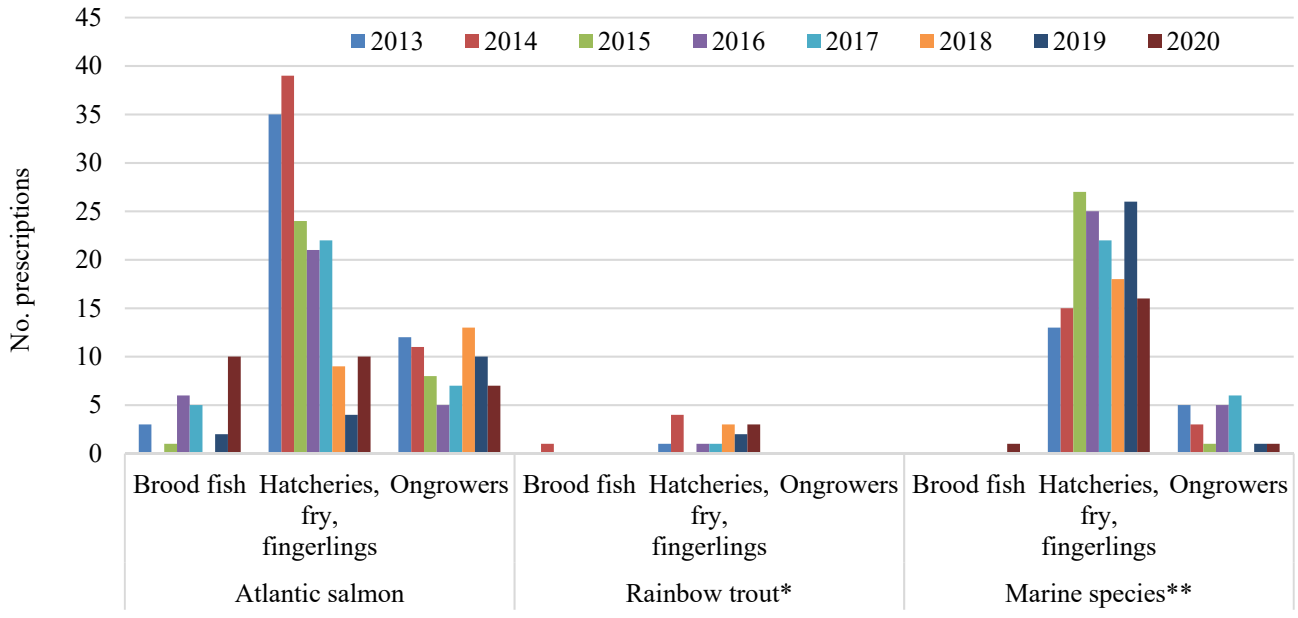

FIGURE 7. Number of prescriptions of antibiotics by fish species, split into production stages/types, in Norway in 2013-2020. Data were obtained from the Veterinary Prescription Register. *Includes two prescriptions for trout (*Salmo tutta*) fingerlings; **Cod, halibut, pollack, turbot and/or wolffish. Note that cleaner fish are not included.

The annual sales of antibacterial VMPs for use in aquaculture peaked in 1987 when it amounted to 48 tonnes (Figure 8) – i.e. 876 mg/population correction unit (PCU); the corresponding figure in 2020 was 0.15 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.

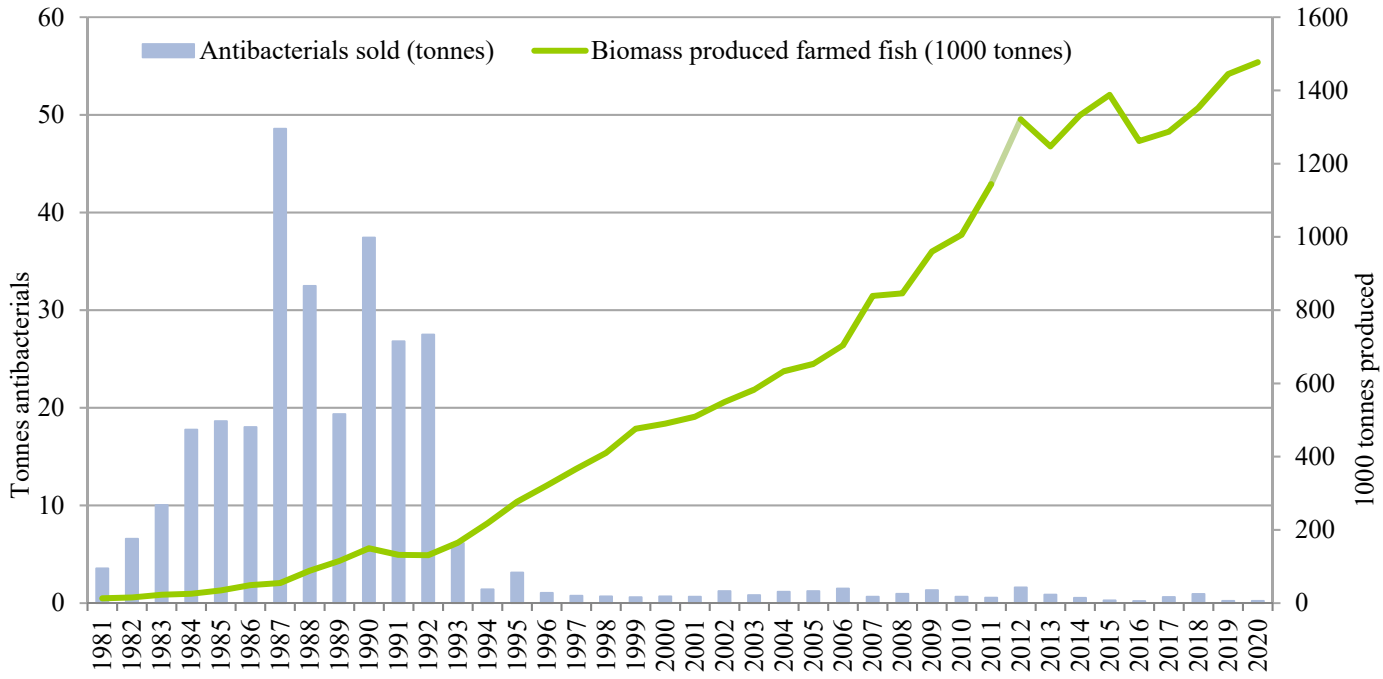

FIGURE 8. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish (including cleaner fish) in Norway in 1981-2020 versus tonnes produced (slaughtered) farmed fish. For the years 1981-2012 the data represent sales data provided by Norwegian Institute of Public Health; for 2013-2020 data represent prescription data obtained form the Veterinary Prescription Register. Data on slaughtered biomass farmed fish were obtained from Norwegian Directorate of Fisheries (https://www.fiskeridir.no/Akvakultur/Tall-og-analyse/Akvakulturstatistikk-tidsserier).

In a report from 2019 (3) it was shown that for Atlantic salmon and rainbow trout, fish in only 1.5%, 1.4%, 1.0%, 0.6% and 0.8% of the ongrowers locations were subjected to treatment in the years 2013-2017, respectively. For 2018, 2019 and 2020 these figures were 1.6%, 1.2% and 0.8%, respectively.

Companion animals (dogs and cats)

The sales in 2020 of antibacterial VMPs approved solely for companion animals (includes VMPs formulated as tablets, oral solution, injectable and oral paste) were 360 kg; in 2019 this figure was 335 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, antibacterial human medicinal products (HMPs) were likely prescribed for dogs and cats. In 1993, only eight antibacterial VMP presentations (name, pharmaceutical form, strength and pack size) were authorised in Norway for dogs and cats, while in 2001 the corresponding number was 36. The number of VMP presentations for dogs and cats amounted to 49 in 2015; in 2020 this figure had decreased to 30.

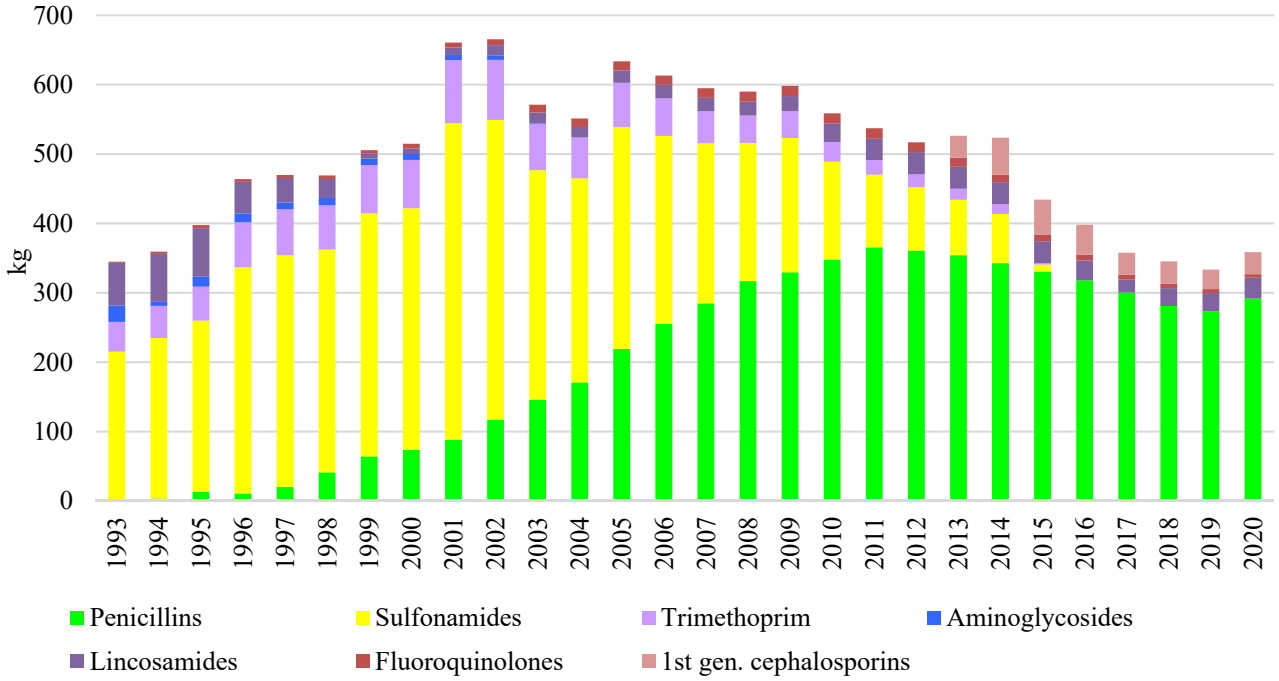

FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables, oral paste, oral solution and tablets; note the exceptions for tablets: see Appendix 1) in Norway for the period 1993-2020. Minor sales of an injectable 3rd generation cephalosporin VMP (range 0.4-1.1. kg) in 2008-2020 and of macrolide VMPs (0.4-5 kg) in 1996-2003 were observed.

The sales patterns of antibacterial VMPs marketed solely for companion animals (dogs and cats) have changed significantly during the period 1993-2020 (Figure 9). The first penicillin VMP as tablets – i.e. amoxicillin (an aminopenicillin) was marketed for dogs and cats in 1994; since then the proportion belonging to the penicillins (only aminopenicillin VMPs marketed) sold of total sales of antibacterial VMPs approved for such animals has increased from 1% to 81% (Figure 9). In 1997, a VMP with amoxicillin in combination with clavulanic acid was marketed for dogs and cats and since then the proportion of the combination amoxicillin and clavulanic acid increased steadily (Figure 10) peaking in the period 2009-2012 accounting for 88% of the sales of aminopenicillins. Since then a minor decrease in this proportion is observed (Figure 10).

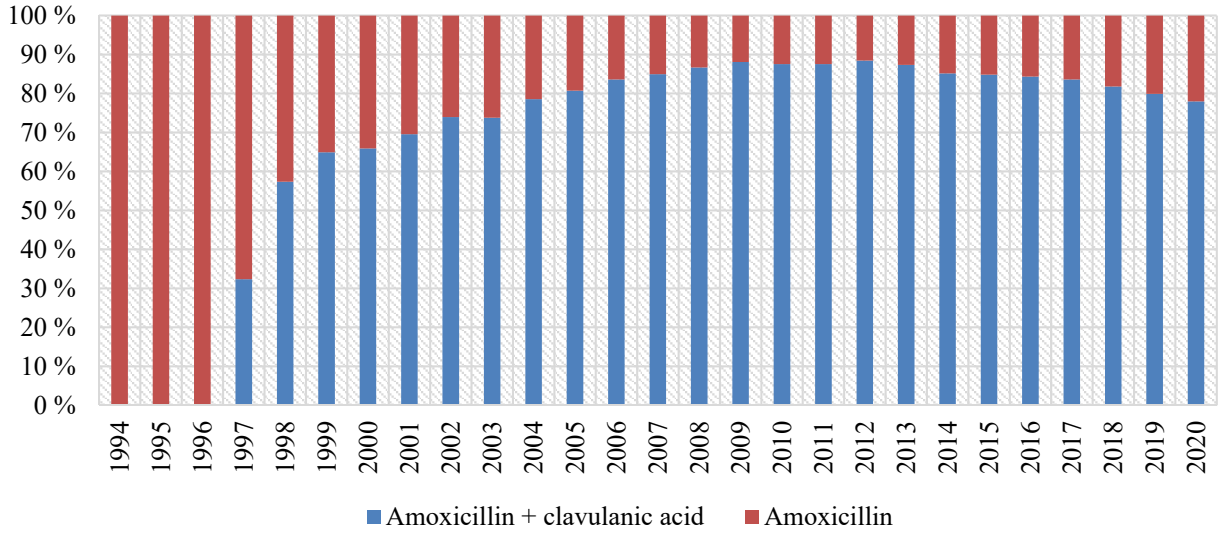

FIGURE 10. Proportions of sales (in kg active substance), of amoxicillin combined with clavulanic acid and of amoxicillin products for dogs and cats in Norway in 1994-2020.

From 1993-2020 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 1.4% in 2020 (Figures 9 and 11). The proportion of the total sales for dogs and cats of 3rd generation cephalosporins has been low since such VMPs were marketed in Norway; this figure was 0.2% in 2008 and declined to 0.1% in 2020 (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 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 anti-bacterials belonging to the categories AMEG advices to restrict the use of, compared to the total sales of antibacterial VMPs, stratified by animal categories. In total, 1.5% of the sales of antibacterial VMPs were accounted for by the AMEG category adviced to restrict use 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.

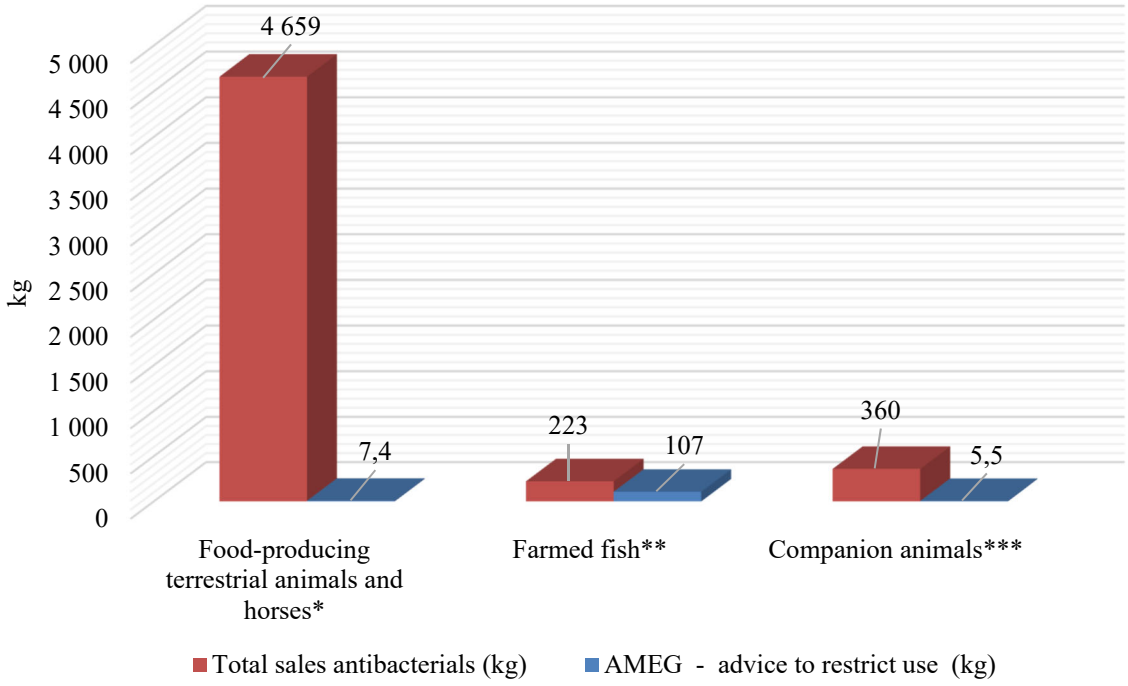

FIGURE 11. Total sales and sales of antibacterial veterinary medicinal products (VMPs) in 2020, for which the Antimicrobial Advice Ad Hoc Expert Group (AMEG) of the European Medicines Agency advises to restrict the use, stratified by animal category (1, 2). Of note, VMPs for topical treatment are not included. *Fluoroquinolones. **Other quinolones. ***3rd generation cephalosporins and fluoroquinolones.

References:

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

National Strategy against Antibiotic Resistance (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 – i.e. on average the sales for the period 1999-2012 was 39% lower than in 1995 (Figures 2 and 12).

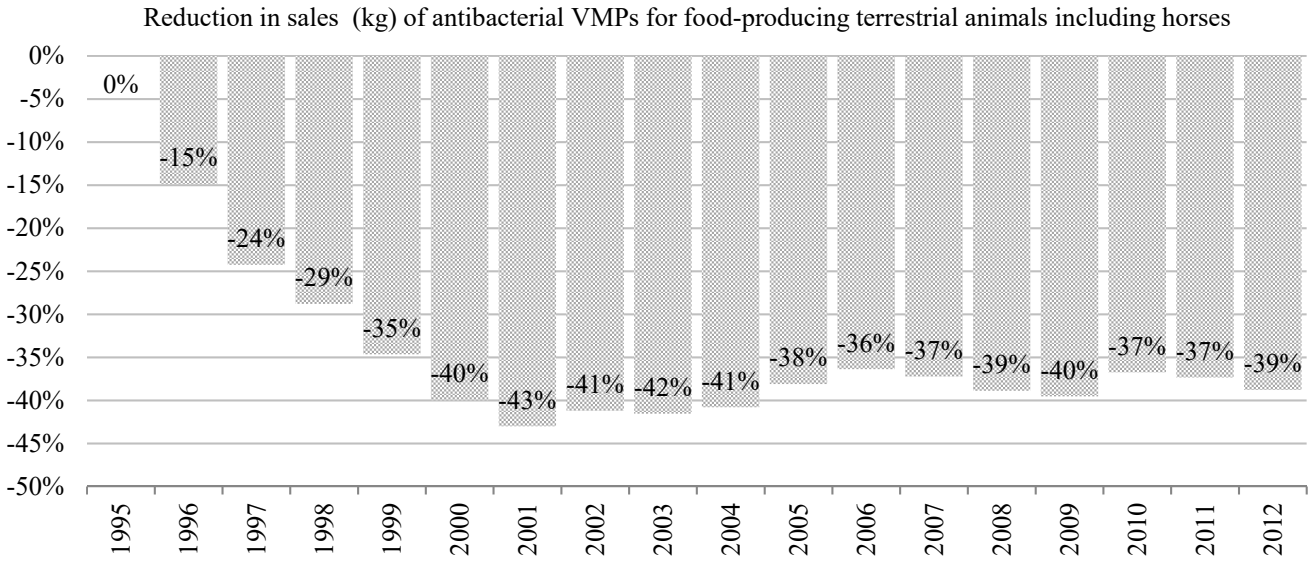

FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMPs) approved for use in food-producing terrestrial animals, including horses, 1995 being the reference year.

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

Approach – assessment of changes

To evaluate progress in terms of reaching the goals set down in the national strategy, sales data for 2013-2020 have been further refined in order to obtain estimates on the usage that are more accurate in terms of identifying changes across time by sector. Data on prescribing per animal species obtained from the Veterinary Prescription Register (VetReg) have been used as supportive information for this refinement (see Appendix 1).

Food-producing terrestrial animals

In order to achieve Target 1 of the national strategy Animalia, whose role is to provide Norwegian farmers with knowledge and expertise, initiated and coordinated the development and implementation of a joint action plan against antibiotic resistance (1). The suggested key measures to reduce the usage of antibacterials in the livestock industry are prevention of diseases and 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 usage 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 2013-2020 was 23% and 20% when measured in kg and in mg/PCU, respectively (Figure 13). The sales patterns (data from wholesalers) have been stable across the period 2013-2020, both in terms of proportion by antibacterial substances and by pharmaceutical forms. The figures are therefore assumed not to be biased by changes towards products/antibacterial classes with higher or lower dosing per treatment. The sales of injectable antibacterial VMPs are included in sales for food-producing terrestrial animals (horses excluded in Figure 13), but as the proportion of prescribing of such products for horses and companion animals (VetReg data) was relatively stable (and very low) across 2015-2020, the impact on the trends is thought to be minor. 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. Usage of HMPs, estimated by use of VetReg data, shows that for cattle, pig, sheep and goats (see Appendix 1 for estimation methodology; Table 5 on treatment of broilers) the usage of HMPs was very low for the years 2015-2020 (68 kg, 38 kg, 32 kg, 40 kg, 50 kg and 34 kg, respectively) and was mostly accounted for by benzylpenicillin for injection and primarily used in sheep.

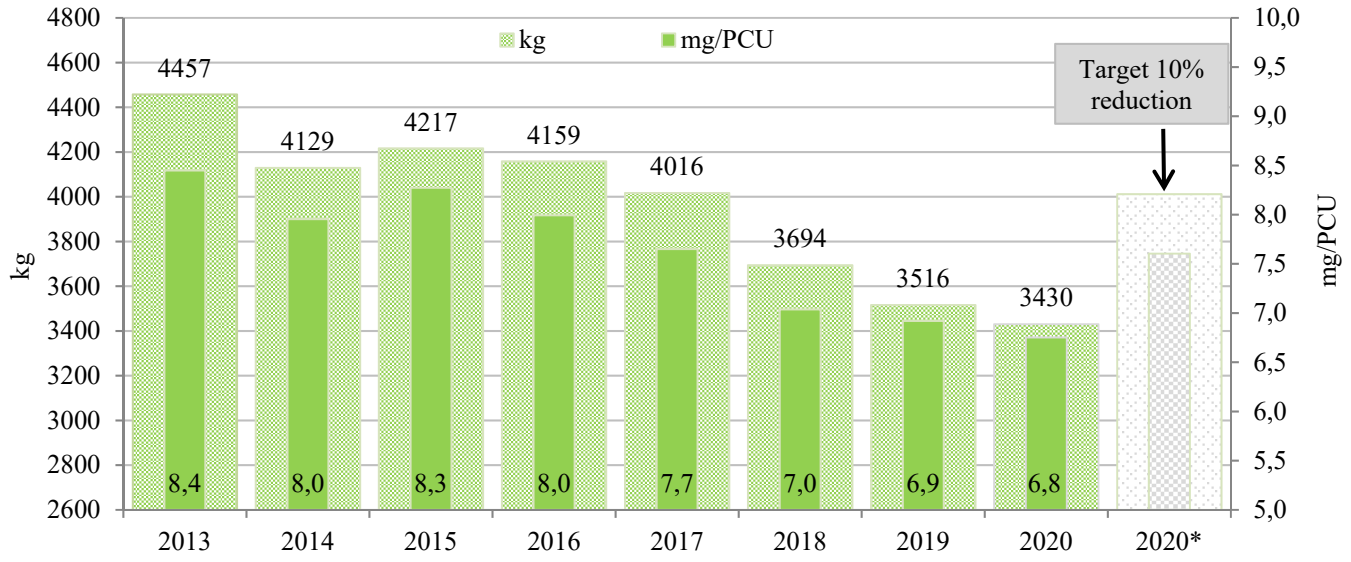

FIGURE 13. Estimated sales, in kg active substance and in mg/PCU, of antibacterial veterinary medicinal products for cattle, pigs, sheep, goats and poultry in Norway in 2013-2020 and the target according to the National Strategy. Sales data were obtained from Norwegian Institute of Public Health. Note 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 2015-2020.

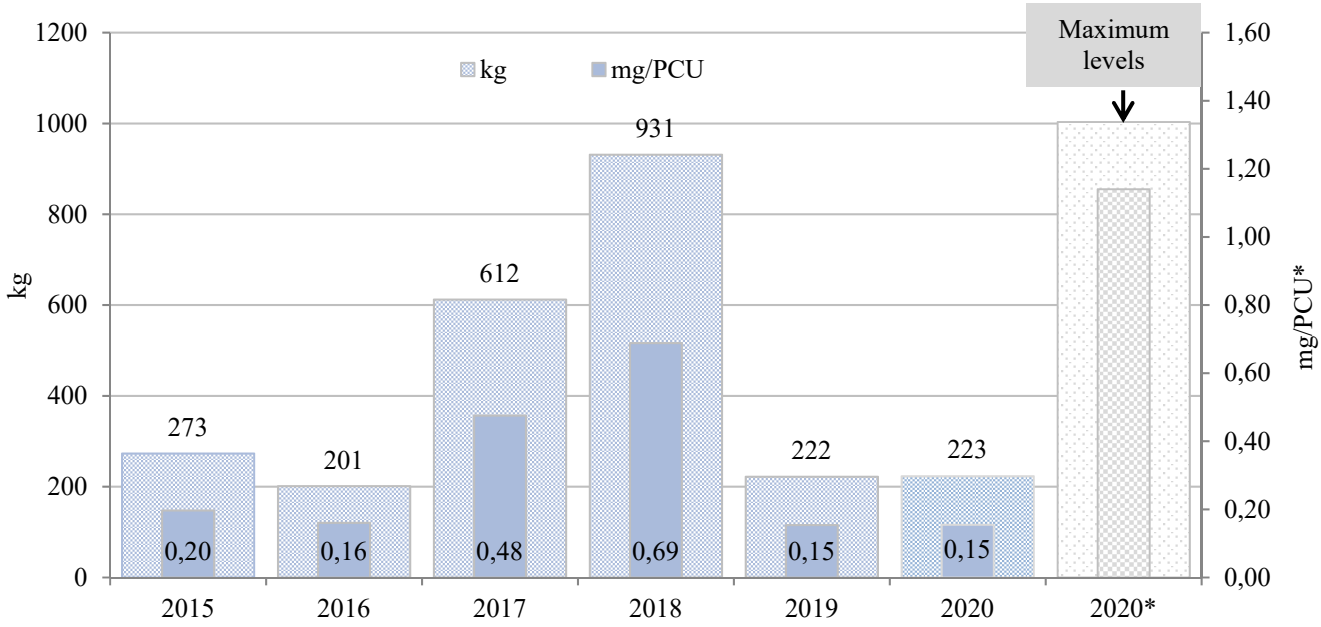

FIGURE 14. Prescription, in kg active substance and in mg/PCU, of antibacterial VMPs for farmed fish, in Norway in the period 2015-2020 and the target according to the National Strategy. Maximum levels are based on average for the period 2004-2014. Prescription data were obtained from the Veterinary 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 I for exception for tablets). From 2013-2020 a reduction in the sales of such antibacterial VMPs for companion animals of 34% is observed (Figure 15). The use of antibacterial HMPs for dogs and cats, reported to VetReg, declined gradually from 269 kg to 212 kg (21%) from 2015-2020 (see Appendix I for estimation methodology). This indicates that prescribing antibacterial VMPs for companion animals has not been substituted by prescribing antibacterial HMPs

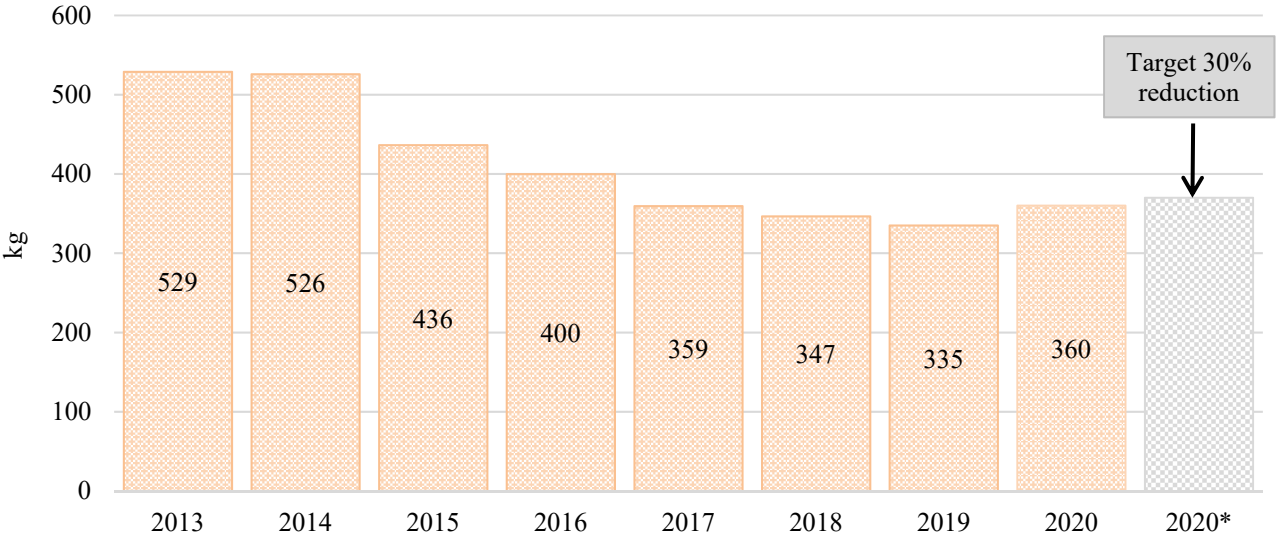

FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (oral paste, oral solution and tablets; exceptions for tablets - see Appendix 1) in the periode 2013-2020 and the target according to the National 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 anti-bacterials for therapeutic use. Due to the quality of the VetReg data for poultry in general - i.e. it was not possible to report to VetReg the VMPs typically used for broilers; data on number of treatments with antibiotics was obtained from Animalia (Thorbjørn Refsnes, personal communi-cation). Table 5 shows that the annual number of broiler flocks treated with antibiotics has been very low during the years 2013-2020.

TABLE 5. Number of broiler flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs)[1] in Norway in the period 2013-2020. Data were obtained from HelseFjørfe, Animalia.

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

[1]Mostly phenoxymethylpenicillin VMPs; minor use of amoxicillin VMPs up to 2017. [2]Treated with oxytetracycline. [3]Phasing out narasin as coccidiostat feed additive started February 2015. [4]Out-phasing of narasin finished June 2016. [5]Parents.

Narasin has been used in some cases of necrotic enteritis (*Clostridium perfringens*). In 2017, 2018, 2019 and 2020, a few of the broiler flocks were given narasin in 5-7 days, with the same daily dose as when used as coccidiostat feed additive and a withdrawal period of two days was applied (Bruce David, Nortura, personal communication).

References:

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

USAGE IN HUMANS

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

Overall antibiotic sales

In 2020, the total sales of antibacterials for systemic use in humans (J01, excl. methenamine) decreased by 13% compared to 2019; from 13.2 to 11.5 DDD/1,000 inhabitants/day (Table 6). The use has decreased every year since 2012 except for a small increase from 2018-2019. The overall consumption (J01, excl. methenamine) has decreased by 32% 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), see Figure 16.

Although a lot has been achieved there are probably still areas of 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 the 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 84% of the human use of antibacterials is used by patients outside healthcare institutions. In 2020, hospitals accounted for 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 total sales (J01, excl. methenamine) has been quite stable around 27%, but it was lower in 2020 (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 combined with increased infection control has led to lower incidence of infections, and especially respiratory tract infections have been sparsely reported. The reduced use of narrow-spectrum penicillins was observed for all age groups, but was most pronounced among small children.

During 2020 there have been several shortage situations for antibiotics, but generics have been available for the market and none of the shortage situations in 2020 were serious enough to impact the antibiotic consumption pattern.

TABLE 6. Human usage of antibacterial agents in Norway 2012, 2014, 2016, 2018 and 2020 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2019-2020 and 2012-2020. Data from the Norwegian Drug Wholesales Statistics Database. Methodology for collection of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2012	2014	2016	2018	2020	Change (%) 2019-2020	Change (%) 2012-2020
J01A	Tetracyclines	3.87	3.46	3.16	2.86	2.65	-10	-31
J01B	Amphenicols	<0.001	<0.001	<0.001	<0.001	<0.001	-	-
J01CA	Penicillins with extended spectrum	2.79	2.90	2.62	2.46	2.22	-12	-20
J01CE	Beta-lactamase sensitive penicillins	4.31	3.88	3.73	3.43	2.77	-22	-36
J01CF	Beta-lactamase resistant penicillins	0.90	0.91	0.90	0.90	0.95	+2	+5
J01CR	Combination of penicillins	0.04	0.07	0.10	0.08	0.11	+16	+208
J01D	Cephalosporins, monobactams, carbapenems	0.53	0.46	0.42	0.39	0.37	-	-31
J01E	Sulfonamides and trimethoprim	0.87	0.88	0.85	0.88	0.90	-3	+3
J01F	Macrolides, lincosamides and streptogramins	2.26	1.68	1.33	1.05	0.80	-23	-65
J01G	Aminoglycosides	0.08	0.08	0.08	0.09	0.10	-	+25
J01M	Quinolones	0.74	0.67	0.53	0.42	0.30	-16	-60
J01X*	Other antibacterials	0.47	0.43	0.38	0.32	0.33	+7	-29
J01	**Total excluding methenamine**	**16.9**	**15.4**	**14.1**	**12.9**	**11.5**	**-13**	**-32**
J01XX05	Methenamine	3.57	3.86	4.09	4.08	3.85	+13	+8
J01	**Total all antimicrobial agents**	**20.4**	**19.3**	**18.2**	**16.9**	**15.3**	**-7**	**-25**

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

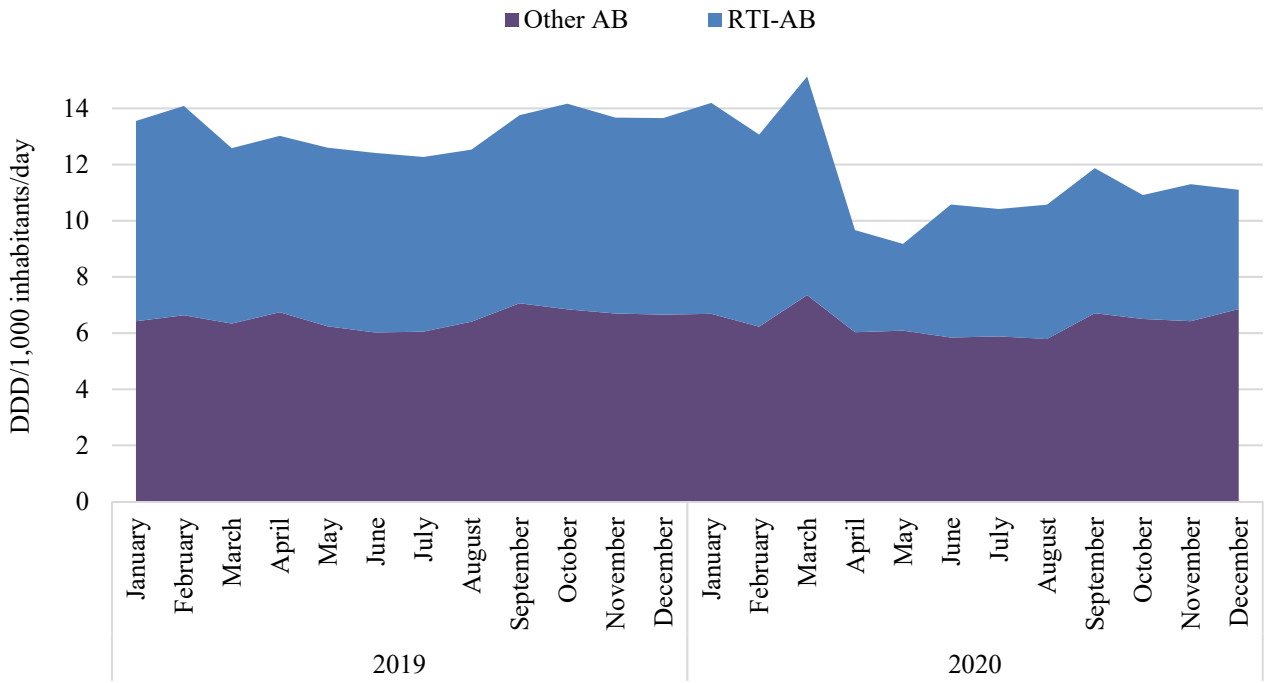

FIGURE 16. Monthly sales of antibiotics in 2019 and 2020 as measured in DDD/1,000 inhabitants/day. "Antibiotics for respiratory tract infections" (RTI-AB) is defined as amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline. "Other antibiotics" (AB) is defined as all other antibiotics in ATC group J01, excl. methenamine. Data from the Norwegian Drug Wholesales Statistics Database.

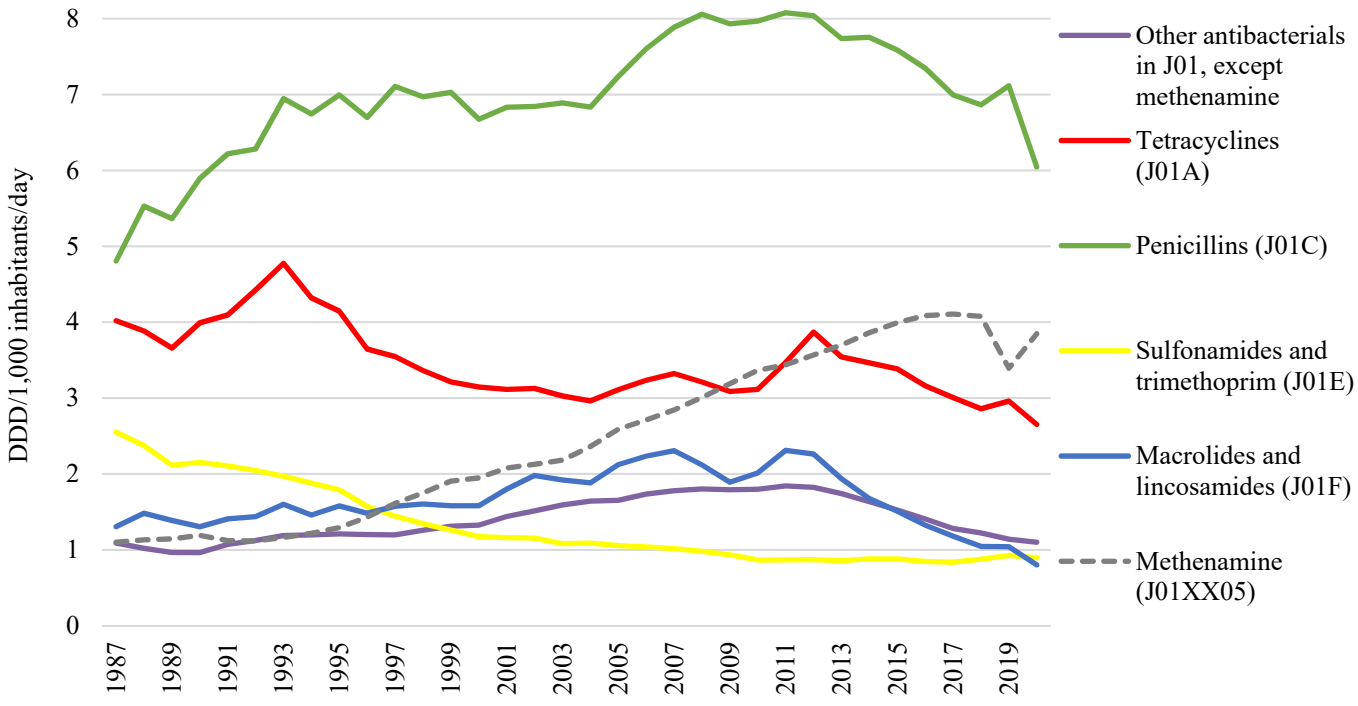

FIGURE 17. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine and other antibacterials in Norway 1987-2020. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05). Data from the Norwegian Drug Wholesales Statistics Database.

The beta-lactamase sensitive penicillin-group (J01CE), the tetracyclines (J01A) and penicillins with extended spectrum (J01CA) were the three most used antibacterial groups in Norway in 2020.

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 2020 the use was still lower than in 2016 (Figure 17, Table 6). Methenamine has the largest amounts of DDDs of all antibiotics used in Norway and accounted for 25% of total antibacterial use in 2020.

Of the tetracyclines (J01A), doxycycline is most frequently used, followed by lymecycline, a drug mainly indicated for acne (Table 7).

In 2020, 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-spectered penicillins. In 2020, beta-lactamase sensitive penicillins accounted for almost half of the penicillin group (46% share) measured in DDDs. This is lower than in earlier years, but is probably caused by the effects of Covid-19 as the 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 has been observed in the latest years (Table 6). 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, at the expense of trimethoprim, and possibly due to increasing resistance in *E. coli*.

The subgroup of sulfonamides and trimethoprim as a whole has decreased over the years, 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 the recurrent epidemics of *M. pneumoniae* in Norway, occurring with four- to six-year intervals. Furthermore, until 2014, azithromycin and doxycycline were both recommended for genital chlamydia infection in the primary care treatment guidelines, and since then doxycycline has been the only first-line treatment. The use of macrolides is now at the same level as in the 1970s.

In the latest years, sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased, mainly due to decreased use of 1st and 2nd gen. cephalosporins (Tables 6-7, Figure 18). In 2020 there was 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 was 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 95% of the quinolone group in 2020.

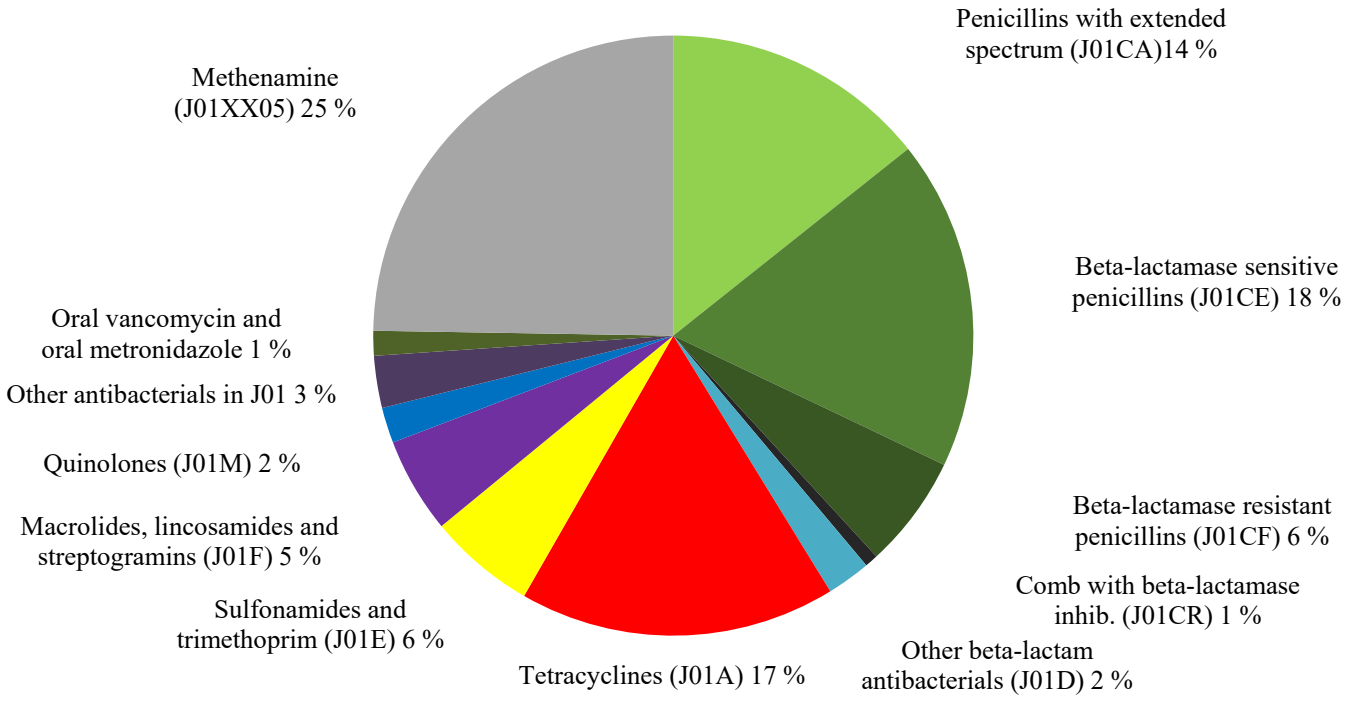

FIGURE 18. Relative amount of antibacterial agents for systemic use in 2020 in Defined Daily Doses (DDD) (total sales in the country). Data from the Norwegian Drug Wholesales Statistics Database.

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
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	1.99	1.82	1.60	1.38
	J01A A04	Lymecycline	0.90	0.96	0.94	0.93	1.09
	J01A A06*	Oxytetracycline	-	<0.001	<0.001	<0.001	<0.001
	J01A A07	Tetracycline	0.62	0.50	0.40	0.32	0.19
	J01A A08*	Minocycline	0.006	0.003	0.002	0.001	0.001
	J01A A12	Tigecycline	<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
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.03	0.04	0.04	0.05	0.05
	J01C A04	Amoxicillin	0.97	0.97	0.88	0.84	0.65
	J01C A08	Pivmecillinam	1.78	1.87	1.69	1.57	1.52
	J01C A11	Mecillinam	0.008	0.008	0.005	0.002	0.003
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.24	0.24	0.23	0.24	0.23
	J01C E02	Phenoxymethyl-penicillin	4.07	3.64	3.50	3.18	2.53
	J01C E08*	Benzathine benzylpenicillin	<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
	J01C F02	Cloxacillin	0.14	0.19	0.17	0.16	0.16
	J01C F05*	Flucloxacillin	<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	0.038	0.05
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.07	0.09	0.05	0.06
J01DB – first gen. cephalosporins	J01D B01	Cefalexin	0.18	0.14	0.10	0.09	0.07
	J01D B03	Cefalotin	0.08	0.09	0.09	0.07	0.02
	J01D B04	Cefazolin				0.03	0.08
J01DC – second gen. cephalosporins	J01D C02	Cefuroxime	0.08	0.06	0.04	0.03	0.03
J01DD – third gen. cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	0.11
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.01	0.01
	J01D D04	Ceftriaxone	0.03	0.02	0.02	0.02	0.04
	J01D D08*	Cefixime			<0.001	<0.001	<0.001
	J01D D52	Ceftazidime and avibactam				<0.001	<0.001
J01DF - Monobactams	J01D F01	Aztreonam	<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
	J01D H03	Ertapenem	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
J01DI – Other cephalo-sporins and penems	J01D I02	Ceftaroline fosamil		<0.001	<0.001	<0.001	<0.001
	J01DI54	Ceftolozane and enzyme inhibitor			<0.001	<0.001	0.001
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.46	0.38	0.34	0.33
	J01E C02*	Sulfadiazine			0.001	<0.001	<0.001
	J01E E01	Sulfamethoxazole and trimethoprim	0.36	0.40	0.44	0.53	0.57

ATC group	ATC code	Substance	2012	2014	2016	2018	2019
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.75	0.60	0.44	0.29
	J01F A02	Spiramycin	0.01	0.005	0.003	0.002	0.002
	J01F A06*	Roxithromycin		<0.001	<0.001	<0.001	<0.001
	J01F A09	Clarithromycin	0.39	0.23	0.14	0.11	0.09
	J01F A10	Azithromycin	0.48	0.35	0.30	0.24	0.19
	J01FS15	Telithromycin	<0.001	<0.001	<0.001	-	-
	J01F F01	Clindamycin	0.33	0.34	0.28	0.25	0.23
J01G - Aminoglycosides	J01GA01*	Streptomycin	<0.001	<0.001	<0.001	<0.001	<0.001
	J01G B01	Tobramycin	0.03	0.02	0.02	0.01	0.01
	J01G B03	Gentamicin	0.05	0.05	0.06	0.08	0.09
	J01G B06*	Amikacin	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
	J01M A02	Ciprofloxacin	0.71	0.64	0.51	0.39	0.28
	J01MA12	Levofloxacin	0.002	0.002	0.003	0.004	0.005
	J01MA14*	Moxifloxacin	0.004	0.007	0.009	0.011	0.009
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.02	0.02	0.02	0.02
	J01X A02	Teicoplanin	0.001	<0.001	<0.001	<0.001	-
	J01X B01	Colistin	0.004	0.005	0.006	0.006	0.008
	J01X C01	Fusidic acid	0.005	0.004	0.003	0.003	<0.001
	J01X D01	Metronidazole	0.07	0.05	0.03	0.04	0.04
	J01X E01	Nitrofurantoin	0.37	0.35	0.31	0.25	0.26
	J01XX01	Fosfomycin	<0.001	<0.001	<0.001	<0.001	<0.001
	J01X X05	Methenamine	3.57	3.86	4.09	4.08	3.85
	J01XX08	Linezolid	0.01	0.007	0.010	0.009	0.009
	J01XX09	Daptomycin	0.001	<0.001	0.001	0.001	0.001
	J01X X11	Tedizolid			<0.001	<0.001	0.001
Antibiotics in other ATC groups	A07A A09	Vancomycin	0.002	0.002	0.002	0.002	0.003
	A07A A11	Rifaximin	0.004	0.012	0.043	0.076	0.010
	A07A A12	Fidaxomicin	<0.001	<0.001	<0.001	<0.001	<0.001
	P01A B01	Metronidazole	0.23	0.24	0.23	0.21	0.21
	D06A X09/ R01A X06*	Mupirocin (grams)[1]	145	174	186	247	288

*Drugs not licensed in Norway in 2020. [1]Given as the total amount grams (g) mupirocin per year.

Antibiotic usage in primary care

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

The decrease in total use of antibacterials in 2020 was mainly due to decreased use in primary care. A decrease of 13% was seen from 2019-2020 as measured in DDD/1,000 inhabitants. For primary care, the most important antibiotic group in 2020 was the penicillins (J01C; 37% of DDDs and 52% of prescriptions in ATC group J01, excl. methenamine). Tetracyclines was the second most used group (J01A; 19% of DDDs and 10% of prescriptions) followed by macrolides and lincosamides (J01F; 5% of DDDs and 9% of prescriptions). The three antibiotic substances most often prescribed for outpatients in 2020 were phenoxymethylpenicillin, pivmecillinam and doxycycline. These three antibiotics represented 49% of all prescriptions and 52% of all DDDs of the antibacterial group J01, excluding methenamine. Of the whole ATC group J01 antibacterials for systemic use in primary care, the urinary antiseptic methenamine represented 28% of DDDs and 10% of prescriptions.

The steady decrease in primary care over the latest years may be due to an increased attention towards antimicrobial resistance, both among the general public and healthcare professionnals. 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 last year is probably due to the Covid-19 pandemic. Firstly, infection control measures may have decreased the incidence of other RTIs. Secondly, the threshold for seeing a general practitioner for symptoms of infections has been raised, as GPs' offices have been closed for these patients.

Geographical variation

The usage of antibacterials varies among the Norwegian counties. 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, the same counties seem to be high-use counties and low-use counties, respectively. However, the difference among counties was less in 2020 than in earlier years. Antibiotic use has decreased in all counties the latest years, but with certain differences between them. Oslo is the county with the largest decrease in use of antibiotics (J01, excl. methenamine) with 37% reduction since 2012 (green dots in Figure 21).

Females use more antibiotics than males; 20% of females purchased at least one antibiotic prescription (methenamine is excluded) in 2020 compared to 13% of 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 uses more; for those above 75 years; 2.2 prescriptions/user (same for males and females) are dispensed every year compared to around 1.5 prescriptions/user for younger persons (men and women together, Figure 23). The number of DDDs/user has increased by 1-2% from 2019-2020 in all age groups except in children 0-14 years, for which the DDD/user increased by approximately one DDD unit. This indicates that those being treated were treated either by higher doses or for longer periods of time. The mean number of DDDs/ prescription is 11.5 DDDs, which indicates a mean treatment length of 11-12 days.

Antibiotics prescribed by dentists

Physicians are the main prescribers to humans, but in 2020 dentists prescribed around 5.5% (measured in DDDs) of antibiotics (J01) to humans in ambulatory care. Moreover, they prescribe 20% of all DDDs of metronidazole oral forms. In 2020, dentists most often prescribed phenoxymethylpenicillin (78% of all antibiotic DDDs prescribed by dentists) followed by amoxicillin (8%), clindamycin (5%) and oral metronidazole (4%) (Figure 24).

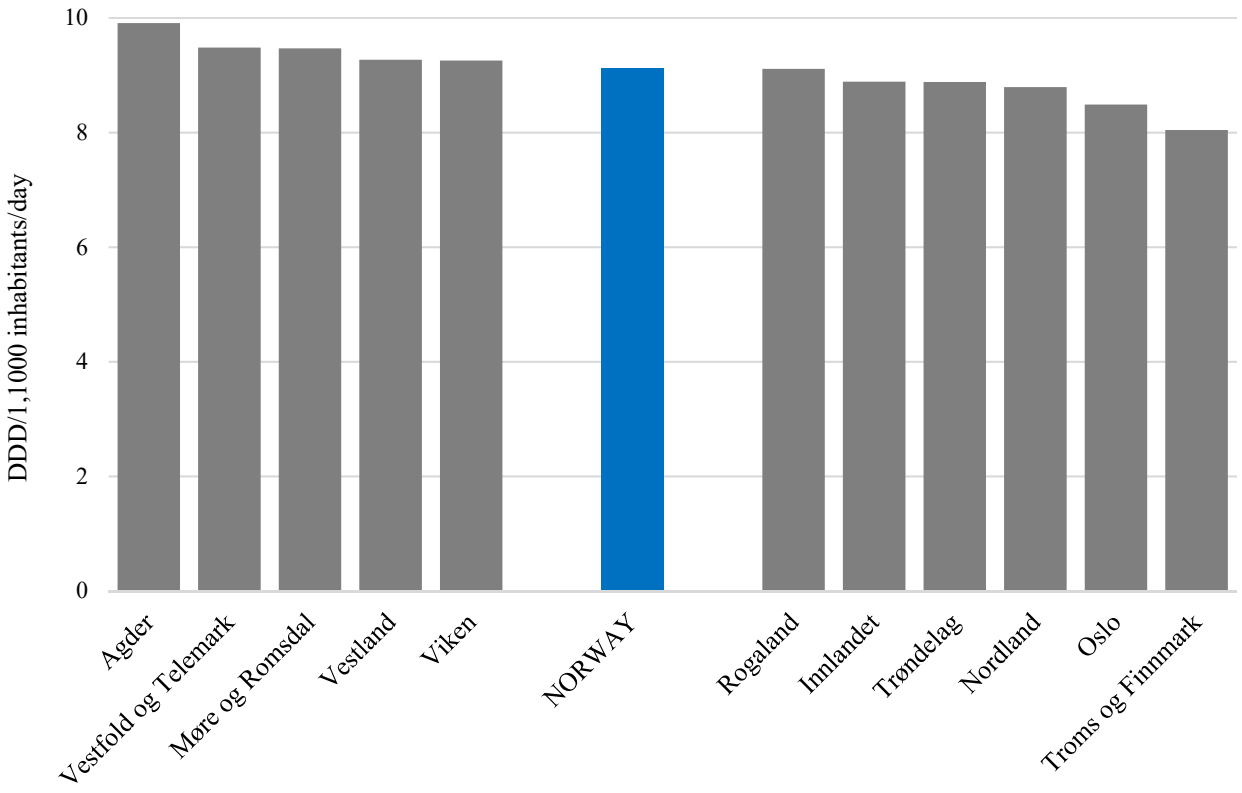

FIGURE 19. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2020 measured as the number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

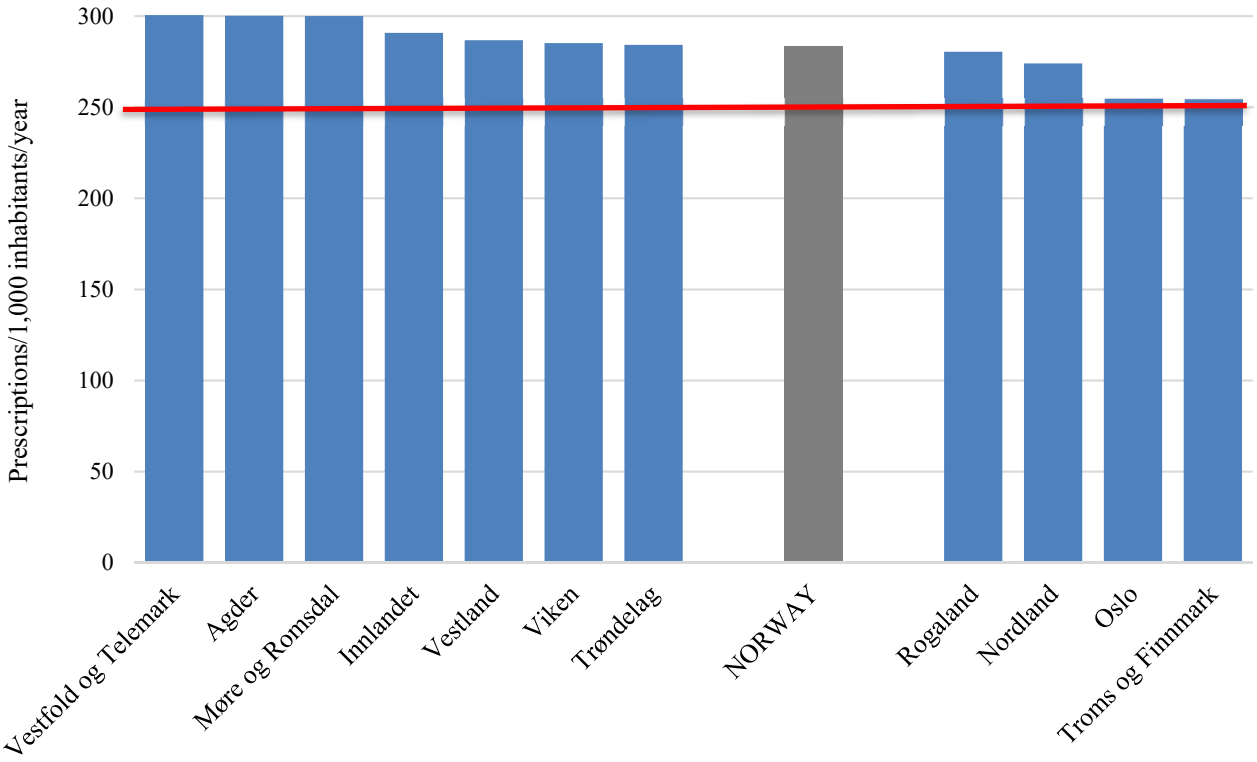

FIGURE 20. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2020 measured as number of prescriptions/1,000 inhabitants. Data from NorPD (excl. health institutions). The red line indicates the goal set by the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

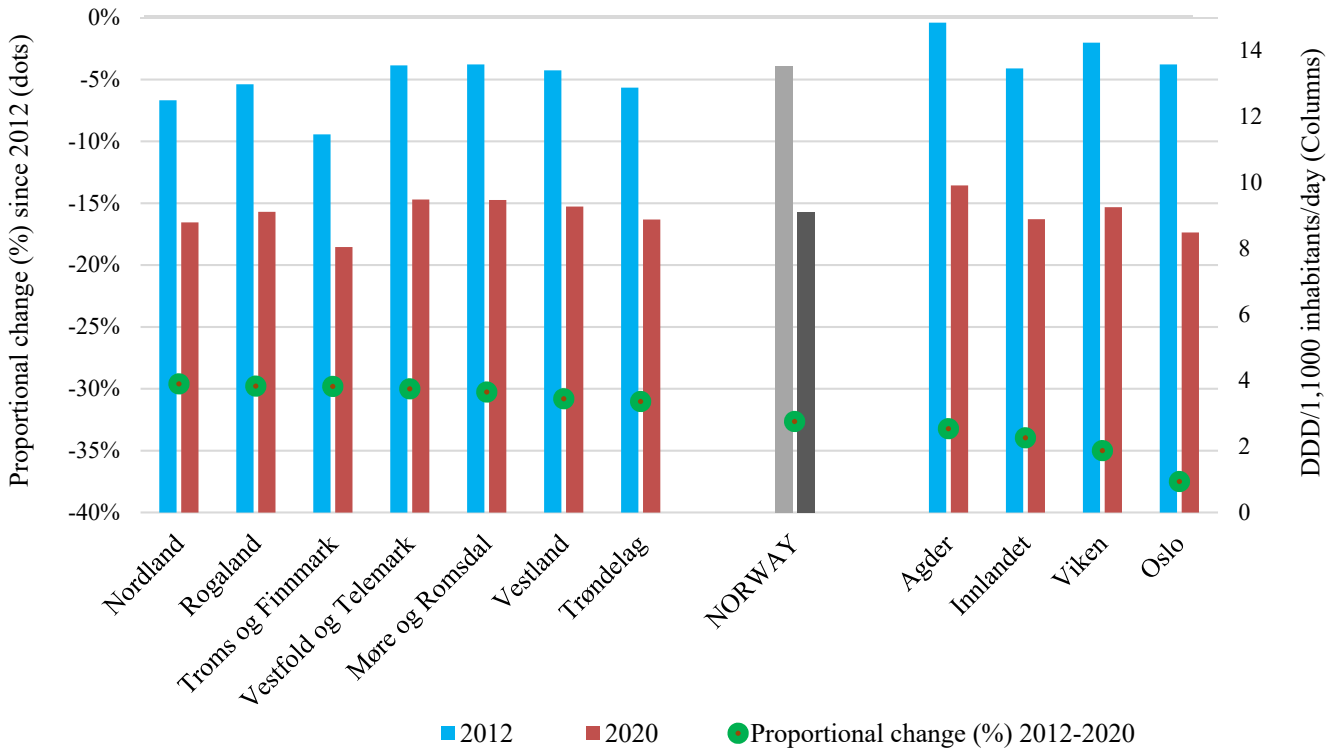

FIGURE 21. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2012 and 2020 measured as number of DDD/1,000 inhabitants/day (columns) and proportional change (reduction in %, green dots). Data from NorPD (i.e. 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 in 2020. 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.

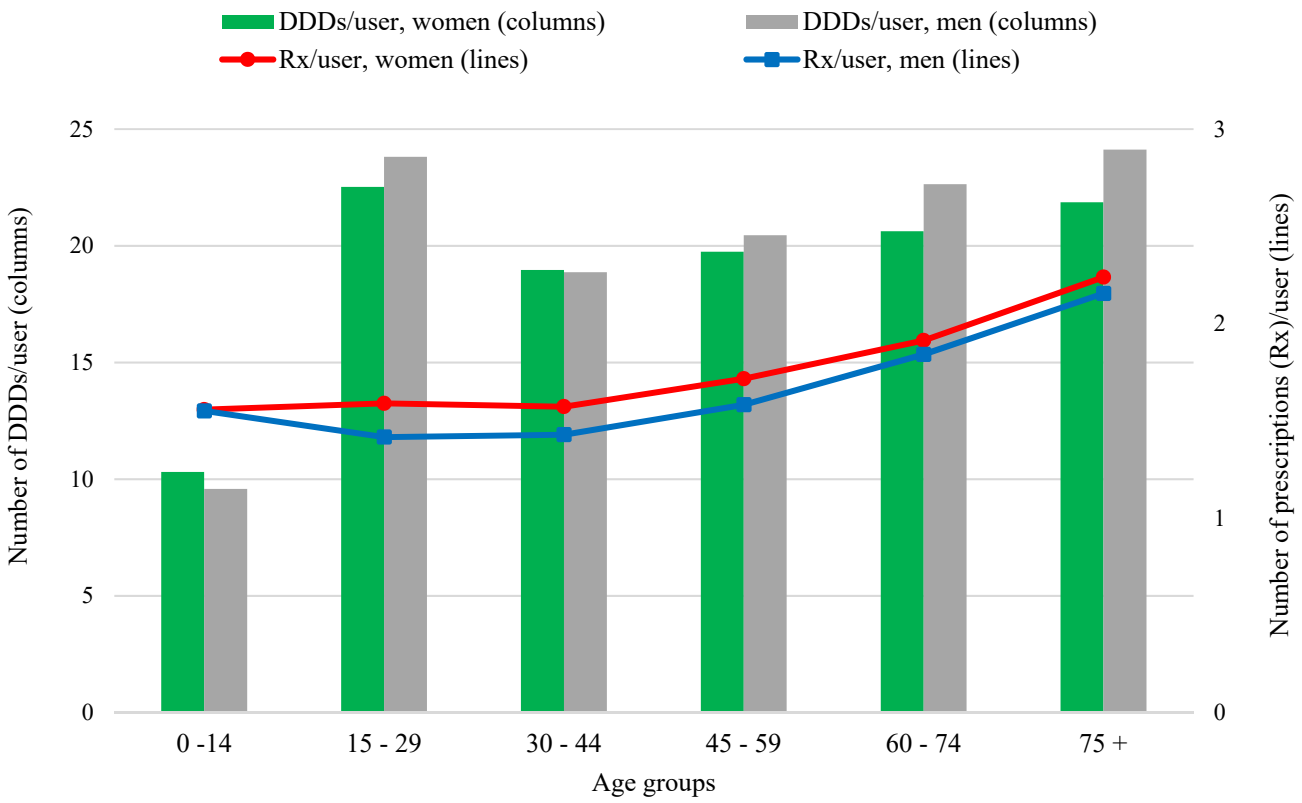

FIGURE 23. Mean number of prescriptions (Rx) per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway in 2020. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

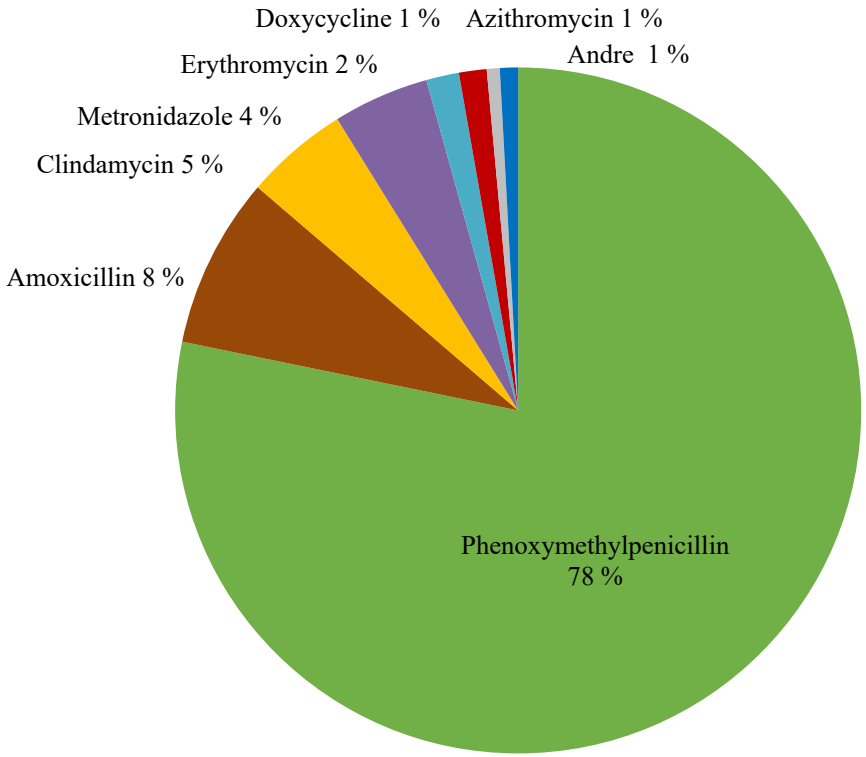

FIGURE 24. Relative amount of antibacterial agents for systemic use prescribed by dentists in 2020 as measured in Defined Daily Doses (DDD).

Antibiotic switch after treatment with UTI antibiotics in male patients

Urinary tract infection (UTI) is a common reason for antibiotic prescribing in Norwegian general practice [1]. Although UTIs are far more common in women than in men, it is estimated that approximately 20 % of UTIs occur in men [1, 2]. By definition, urinary tract infections in male patients are considered complicated infections, and treatment guidelines for these infections vary across Europe. In Norway, current treatment guidelines recommend treating non-febrile UTIs in male patients empirically with nitrofurantoin, pivmecillinam or trimethoprim for 5-7 days, whereas at-risk patients or men with suspected pyelonephritis or prostatitis should be treated empirically with trimethoprim-sulfamethoxazole (co-trimoxazole) or ciprofloxacin for 7-14 days [3].

We conducted an observational study with the aim to explore the rates of antibiotic switch as a proxy for treatment failure after treatment with UTI antibiotics in Norway between 2008-2018 [4]. Antibiotic switch was defined as a dispensed prescription of a different UTI antibiotic within 14 days after initial treatment. During the 11-year period, 476,423 men experienced 726,096 episodes of acute UTI. 13 % of the initialt prescriptions resulted in a new prescription within 14 days, where 7% (49,531/726,096) were another UTI antibiotic than the initial prescription.

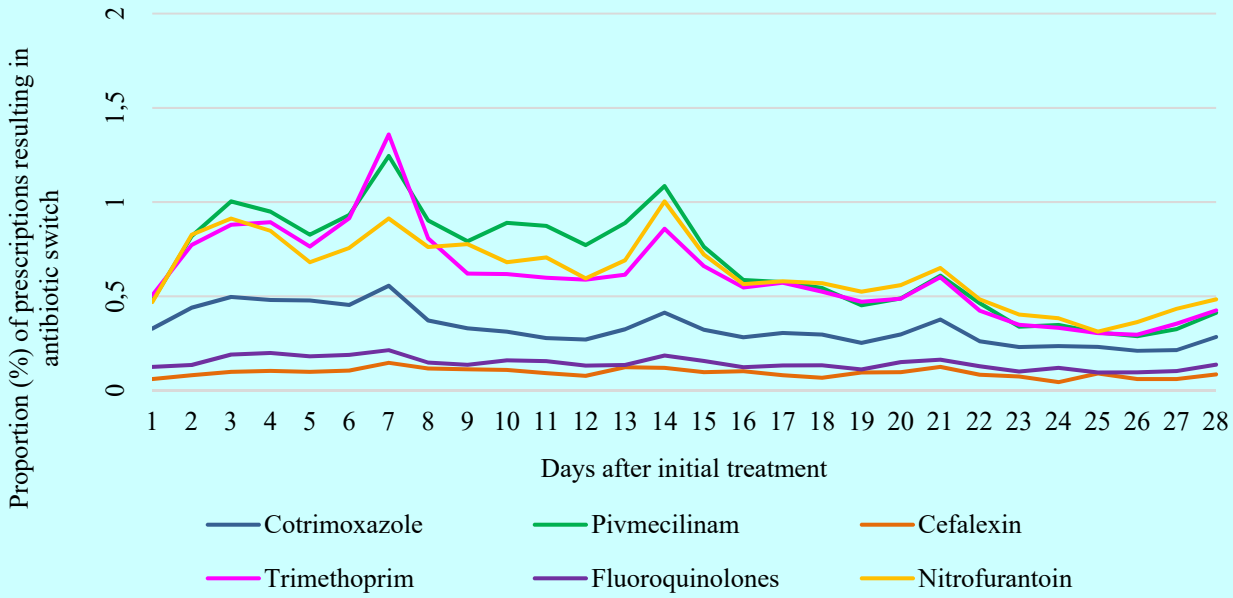

FIGURE 25. Proportion (%) of prescriptions of UTI antibiotic resulting in antibiotic switch by days after initial prescription.

Pivmecillinam, trimethoprim and nitrofurantoin had the highest rates of antibiotic switch with 12.5%, 10.8% and 10.6%, respectively. Cefalexin, fluoroquinolones and co-trimoxazole had lower rates of antibiotic switch with 1.5%, 2.3% and 5.5%, respectively (Figure 25). Longer treatments (>10 DDD) decreased switch rates for trimethoprim and nitrofurantoin, but increased switch rates for fluoroquinolones and pivmecillinam.

There is a lack of randomised controlled trials on treatment of male UTI, and a recent systematic review concluded that the available evidence is insufficient to make clear recommendations in relation to type and duration of antimicrobial treatment for male UTIs [5]. Our data suggest that the antibiotic treatment failure rate in men is relatively low, and comparable to the failure rate in women [6-8]. Hence, aiming to reduce the use of broad-spectrum antibiotics, current guideline recommendations seem safe.

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Antibiotic usage in hospital care

In 2020, the antibacterial sales (in DDDs) to hospitals represented around 8% of total sales of antibacterials for human use in the country. This was a decrease of 11% in DDD/1,000 inhibitants/day compared to 2019 (Figure 26). The 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. The last three years the total sales of antibiotics to hospitals have been stable when measured in DDD/1,000 inhabitants/ day, but a change in pattern of use has occurred with increased use of narrow-spectrum antibiotics. The narrow-spectrum penicillins are highly utilised, and for this group the theoretical DDD-value is lower than the therapeutic doses most commonly prescribed in Norway. Furthermore, combination regimens with a narrow-spectrum penicillin plus an aminoglycoside accounts for more DDDs than if monotherapy with a cephalosporin or carbapenem is used. This implies that the total count of DDDs will show artificially high values for volume.

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 hospital DDDs in 2020 compared to 26% in 2012. The share of beta-lactamase sensitive penicillins in 2020 was 17% of the total (Figure 26).

Penicillins (J01C) represent 47% of the use measured in DDDs in hospitals (J01CE 17%, J01CA 10%, J01CF 15% and J01CR 5%). The second largest group is the cephalosporins (20% of all DDDs), the dominant subgroup being 3rd generation cephalosporins (J01DD). In 2020, six substances accounted for 52% of all DDDs used in hospitals. These were benzylpenicillin, cloxacillin, cefotaxime, cefazolin, gentamicin and doxycycline. Three single substances accounted for 33% of all antibacterial DDDs in hospitals; benzylpenicillin (14%), cloxacillin (13%) and cefotaxime (7%).

Figure 27 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 has been 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. Reduced number of bed days in Norway over the latest years probably does not reflect reduced hospital activity in the country as a whole, but a shift from in-patient treatment to day-care and outpatient treatment. Figur 28 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 29. 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 an increase was observed. There was increased use of aminoglycosides, beta-lactamase resistant penicillins, sulfonamides and trimethoprim, but decreased use of 3rd and higher generation cephalosporins (not shown). This is probably due to implementation of antibiotic stewardship programmes in Norwegian hospitals from 2016. The use of aminoglycosides increased by 48% from 2016-2020, whereas the use of quinolones has decreased by 28%. 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. Figure 30 shows that the distribution between “preferred antibiotics” (which largely reflects standard treatment regimens in national guidelines) and “resistance driving antibiotics” for the different Norwegian hospitals. The proportion of preferred antibiotics varies from 54% to 81%.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between hospitals. Figure 31 shows the use of 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 populations alone.

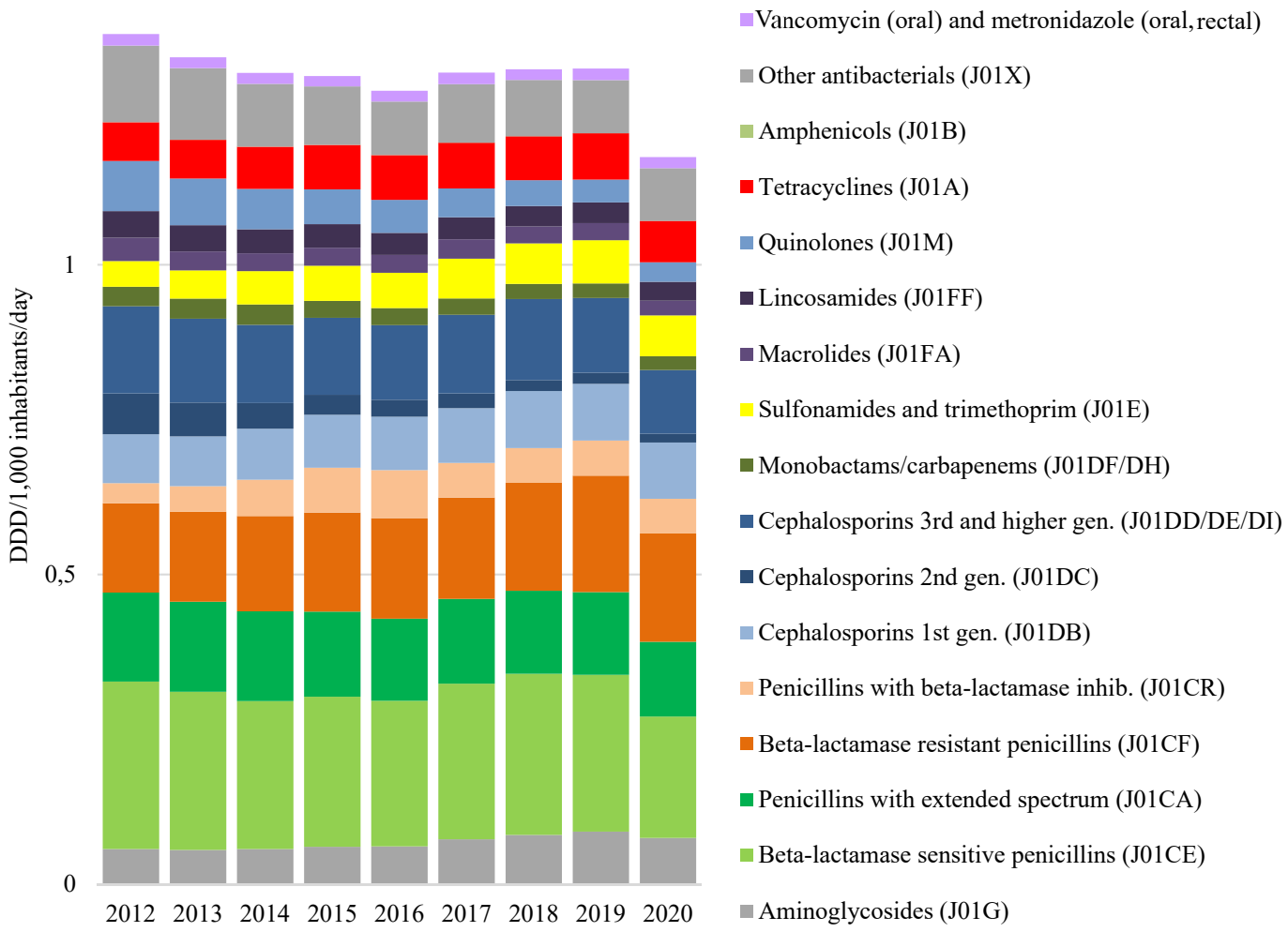

FIGURE 26. Proportions of antibacterial agents for systemic use (J01), vancomycin (A07AA09), and metronidazole (P01AB01) in Norwegian hospitals 2012-2020, measured in DDD/1,000 inhabitants/day.

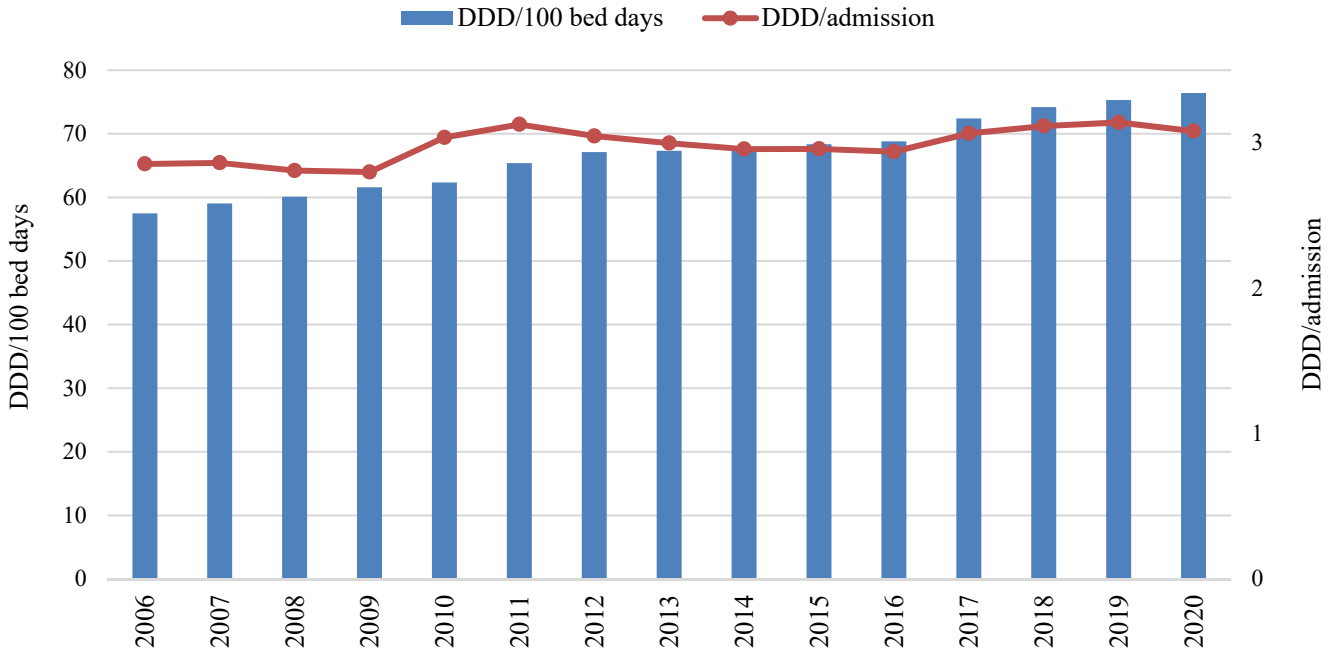

FIGURE 27. Total use of antibiotics in Norwegian hospital (somatic) 2006-2020, measured in DDD/100 bed days (blue bars) and DDD/admission (red line). Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

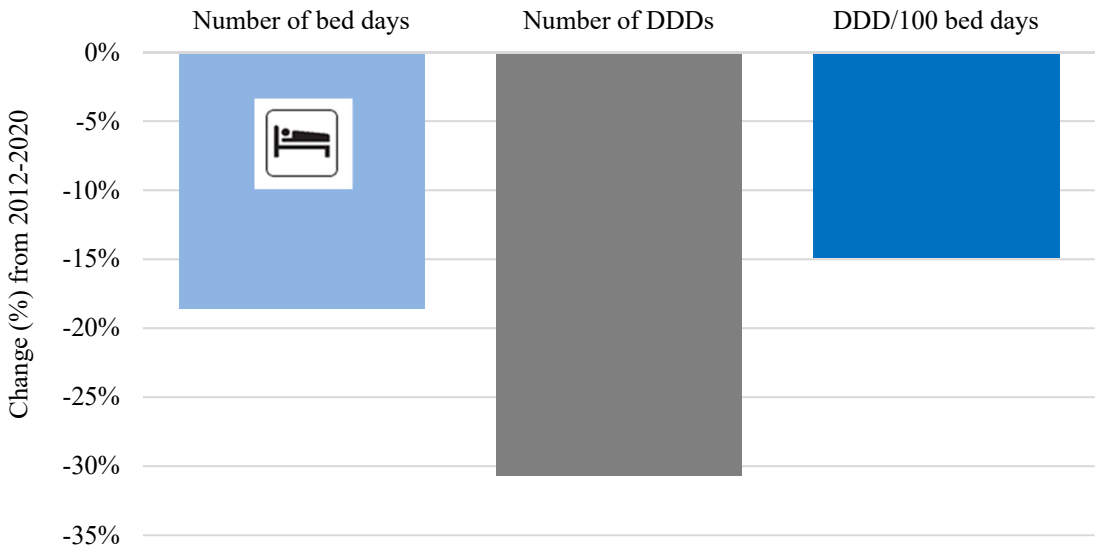

FIGURE 28. Proportional change will vary according to the measures used. Antibiotic usage in hospitals is often presented in DDD/100 bed days, but total number of DDDs may also be used as a measure. The number of bed days in Norway has been reduced by 19% since 2012. The figure visualises the impact of the reduction in bed days on antibiotic consumption statistics of broad-spectrum antibacterial agents for systemic use (ATC J01CR, J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2012-2020, measured as % change either as change of total DDDs (31% reduction - grey bar) or change of DDD/100 bed days (15% reduction - blue bar).

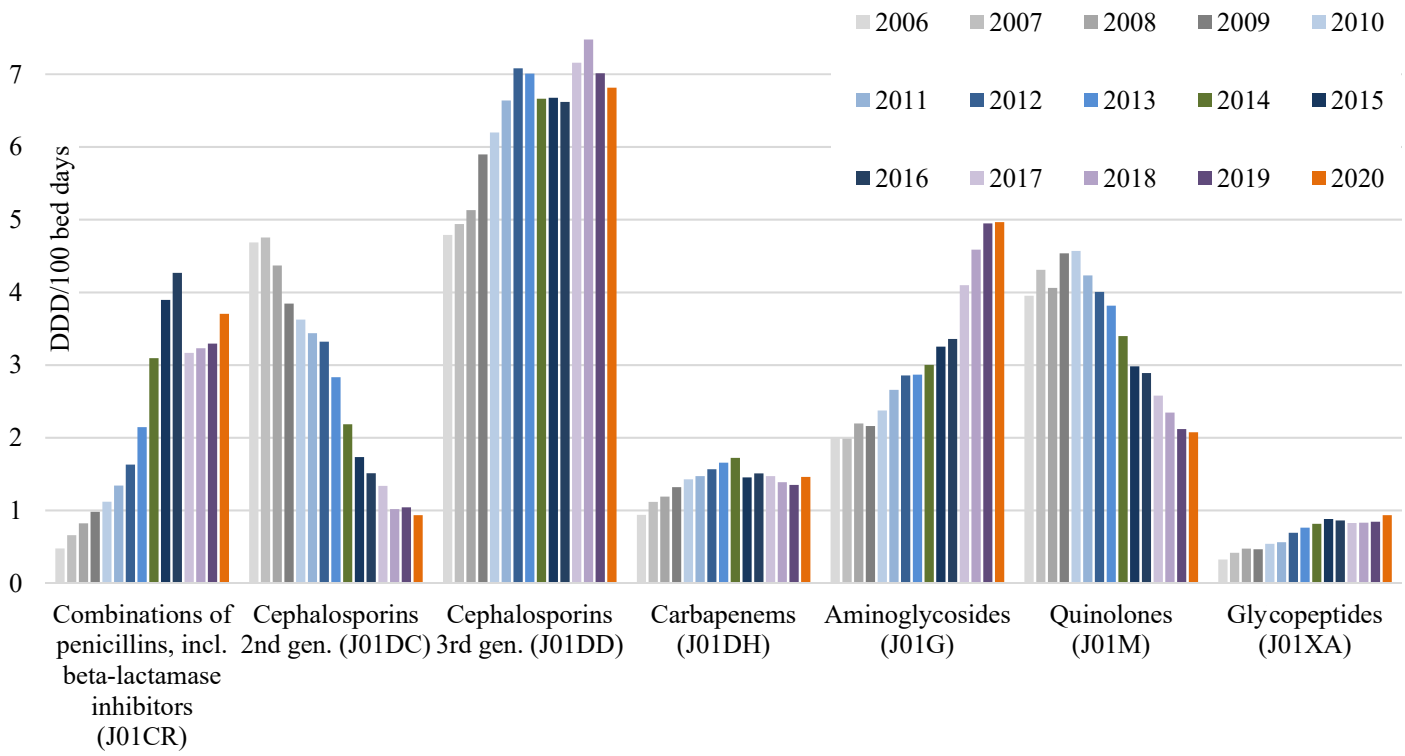

FIGURE 29. Proportions of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2020, measured in DDD/100 bed days.

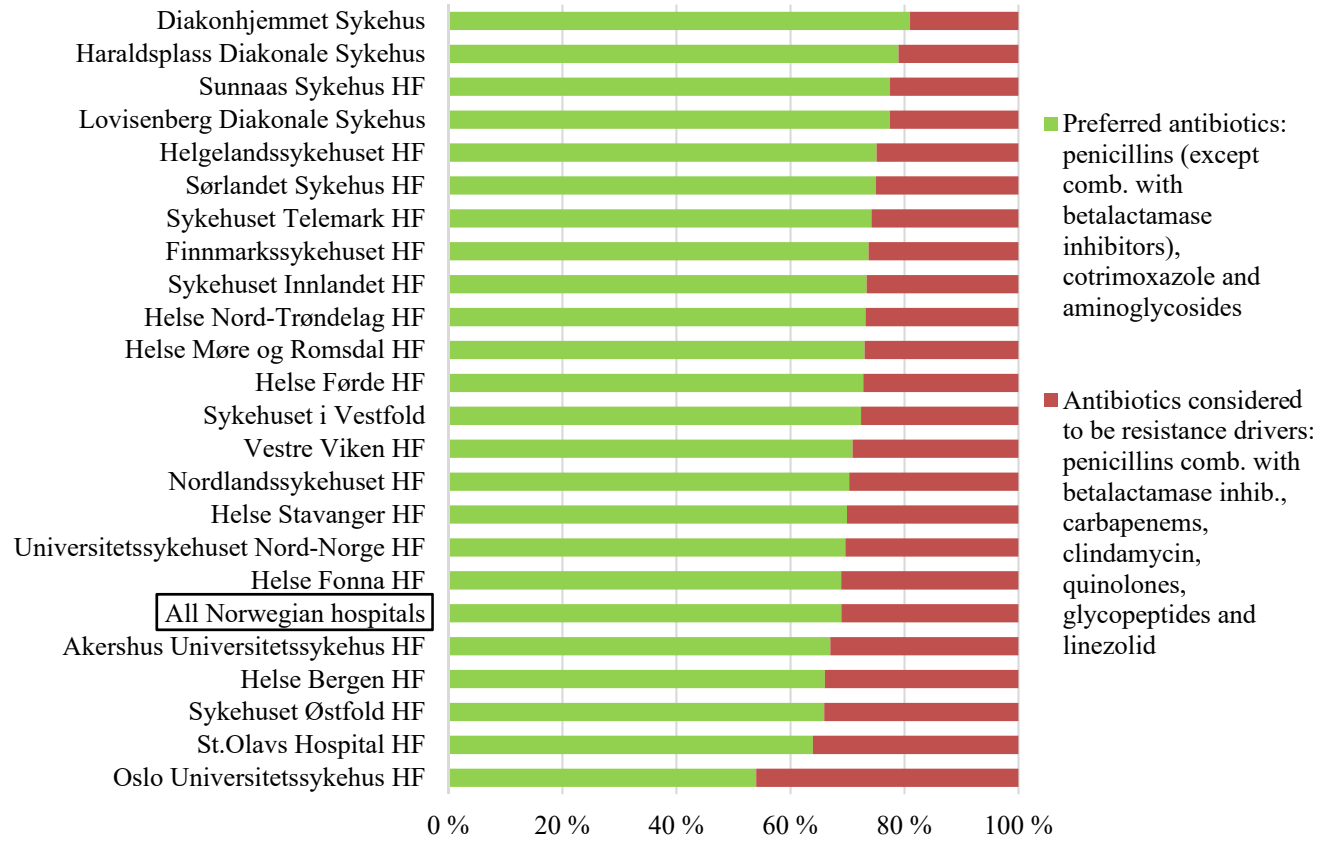

FIGURE 30. Proportions (% of DDDs) of preferred antibiotics (green part of the column) and antibiotics that are considered to be drivers of antibiotic resistance (red part i.e. belonging to ATC groups J01CR, J01DC, J01DD, J01DE, J01DI, J01DH, J01M, J01XA and J01XX08) in Norway, presented per hospital/health trust in 2020. 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 mainly targeting anaerobic bacteria.

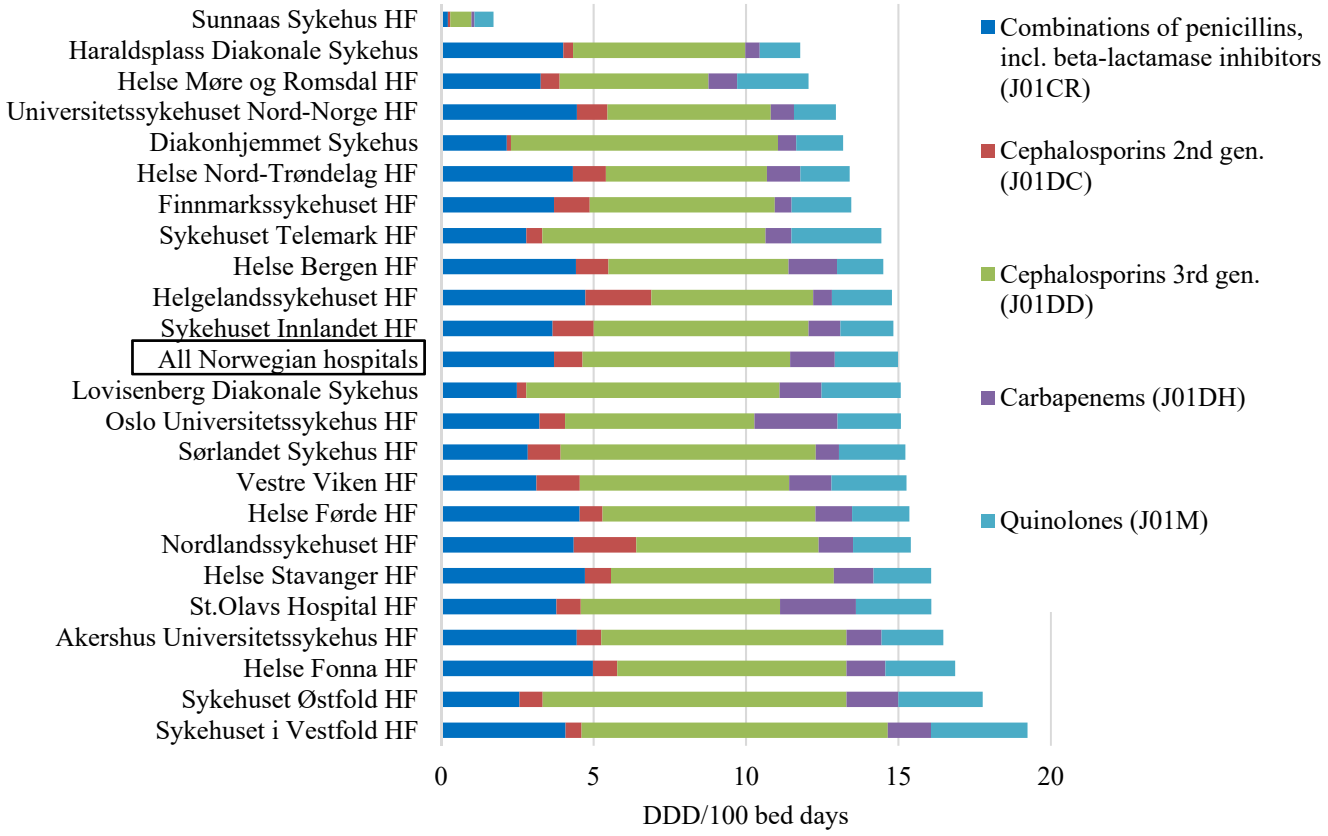

FIGURE 31. Proportions of selected antibacterial agents for systemic use (belonging to ATC groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2020, measured in DDD/100 bed days.

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. The Strategy was followed by a National Action Plan, issued January 2016, with suggested ways to reach the targets within 2020. 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 prescriptions per 1,000 inhabitants per year) and the reduction of antibiotics for respiratory tract infections by 20% (in DDD/1,000 inhabitants/day). Figure 32 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 has been reduced by 25% since 2012. When excluding methenamine, the reduction in use has been 32% (Table 6). There are county differences with some counties using more *Guidelines recommened antibiotics* (i.e. narrow-spectrum antibiotics), indicating a higher adherence rate to the national Guidelines (Figure 33). There were smaller county differences in propoportional use of *Guidelines recommened antibiotics* in 2020 compared to 2012. This may indicate that AMR awareness 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 to 282 Rx/1,000 inhabitants/year in 2020.

Between 2012 and 2019, there has been a reduced prevalence of use in all age groups with the largest reduction (around 33%) in small children (0-9 years) and the lowest reduction for elderly above 70 years (15%). Moreover, the use in men is reduced more than in women. There was a dramatic reduction during the pandemic in 2020, which is mainly due to lower prescribing of antibiotics for respiratory tract infections, Figure 34. The largest reduction in prescriptions per 1,000 during the pandemic was observed in children 0-9 years olds; 33% less prescriptions pr 1,000 and 41% less prescriptions with antibiotics mainly used for respiratory tract infections in 2020 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 35 shows the annual variation of total hospital use of these groups in the years 2006-2020 according to the national target. Figure 36 shows how the use of these five groups has changed in the different Norwegian hospitals/health trusts in relation to the national target. A reduction by 30% is marked by a black dotted line in the figure. For all hospitals in Norway together there was 14.8 % reduction in use of the five selected groups of broad-spectrum antibiotics from 2012-2020 when adjusting for activity (bed days). The number of bed days is going down every year and there is a large increase in outpatient consultations, therefore it is probably necessary to use more than one indicator of clinical activity in hospitals when assessing drug use data. Unadjusted sales data measured in DDDs show a reduction of 31% for the same period (see also Figure 28).

Norway has two national advisory units for antibiotic use, one for primary care (established in 2006); the Antibiotics Center for Primary Health 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 strengthened and appointed key roles in the National Action Plan. The Directorate of Health has issued National Antibiotic Treatment Guidelines for ambulatory care, nursing homes, dentists and hospitals in collaboration with the advisory units.

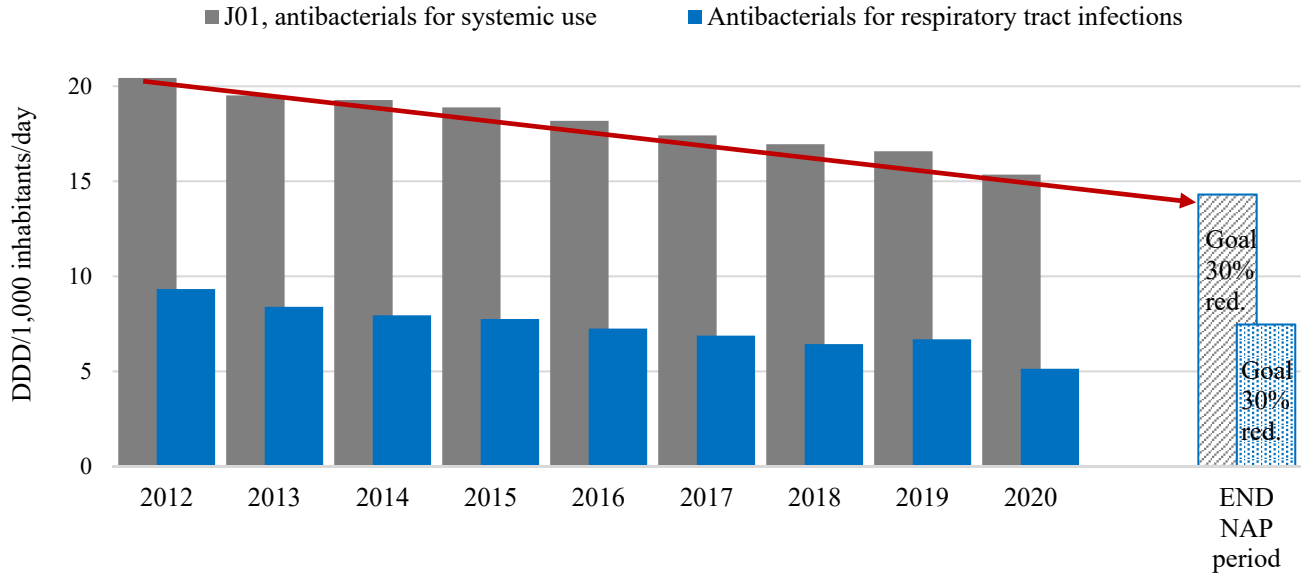

FIGURE 32. Total human sales of antibacterial agents for systemic use (ATC group J01) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2020 measured in DDD/1,000 inhabitants/day. According to the National Action Plan (NAP), the target for 2020 is 30% reduction of total use since 2012, measured in DDDs. Bars shows measured use 2012-2020 (grey; J01, blue; antibiotics for respiratory tract infections), red line and bars with pattern; targets set in the National Strategy against Antibiotic Resistance 2015-2020.

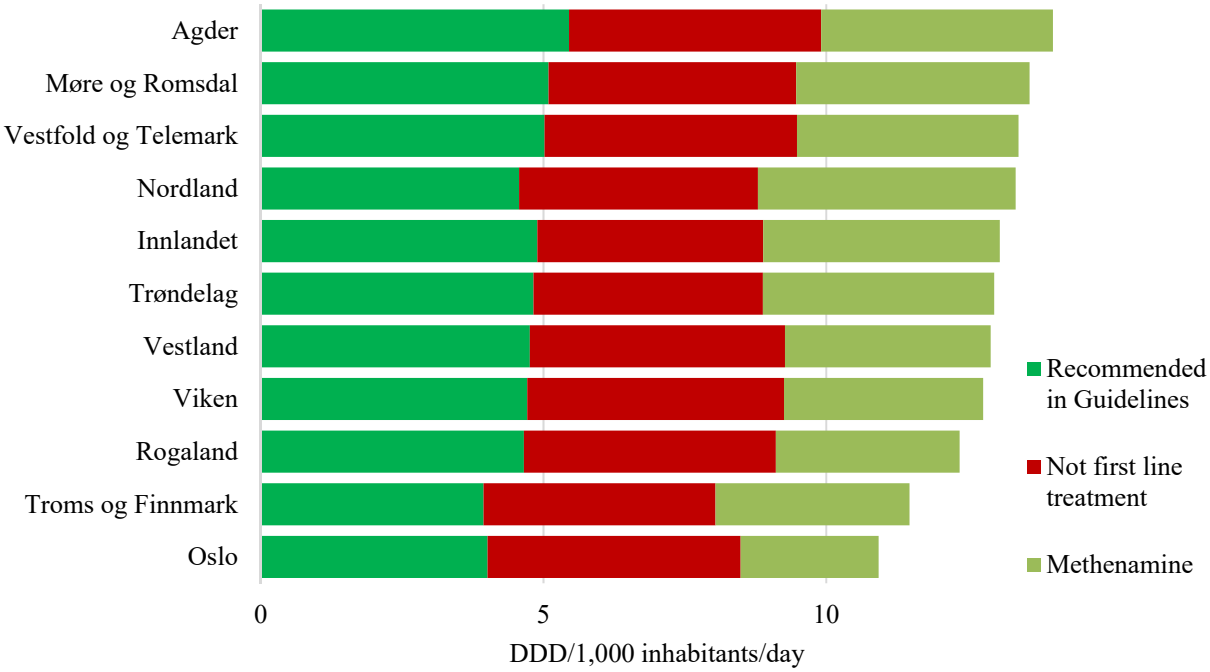

FIGURE 33. Consumption of antibacterial agents for systemic use (ATC group J01) in outpatients in the different counties of Norway in 2020 aggregated in three groups; a) recommended as first-line treatment in the Guidelines for primary care (phenoxymethylpenicillin for respiratory tract infections, pivmecillinam, trimethoprim and nitrofurantoin for urinary tract infections, and dicloxacillin for skin infections), b) not first-line treatment including all other antibiotics in J01. and c) methenamine. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers´ own practice not included).

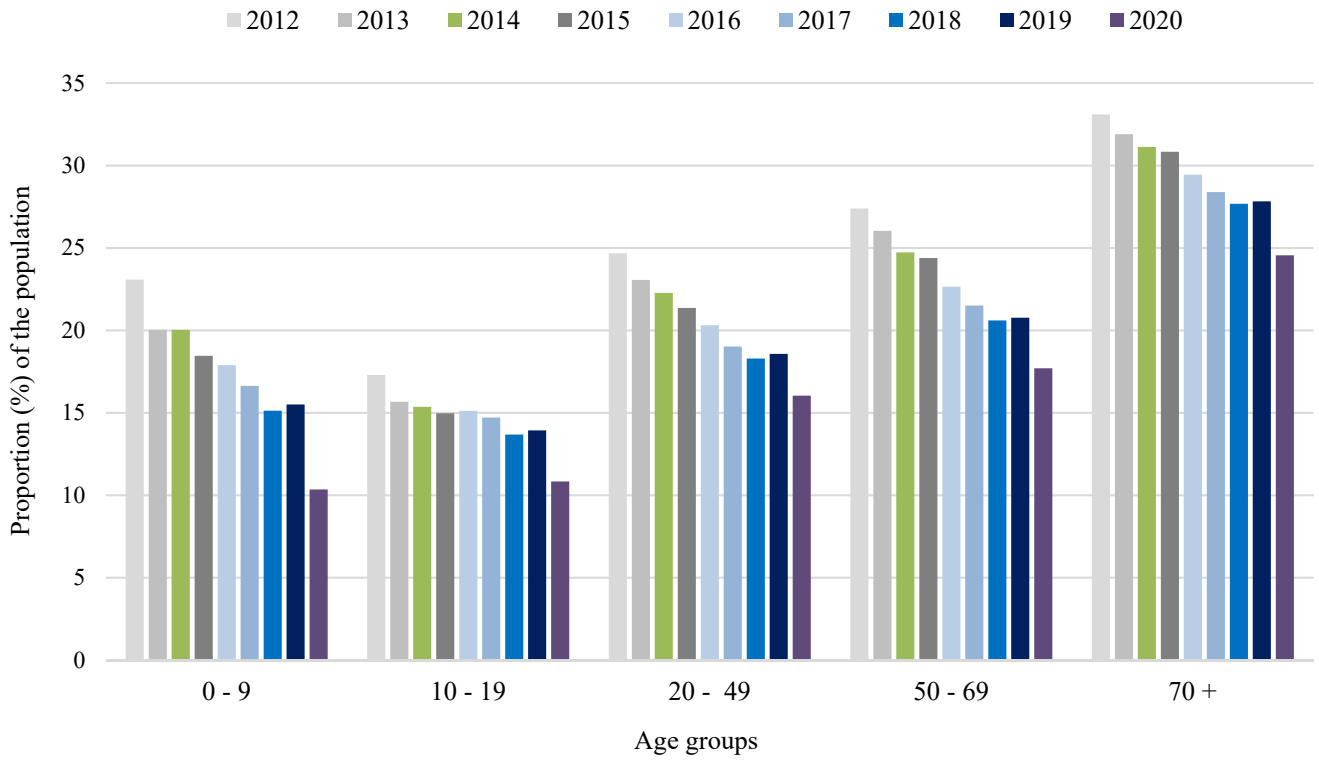

FIGURE 34. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one-year prevalence) in primary care in Norway 2012-2020. Antibiotics included are antibacterials for systemic use (ATC group J01, excl. methenamine).

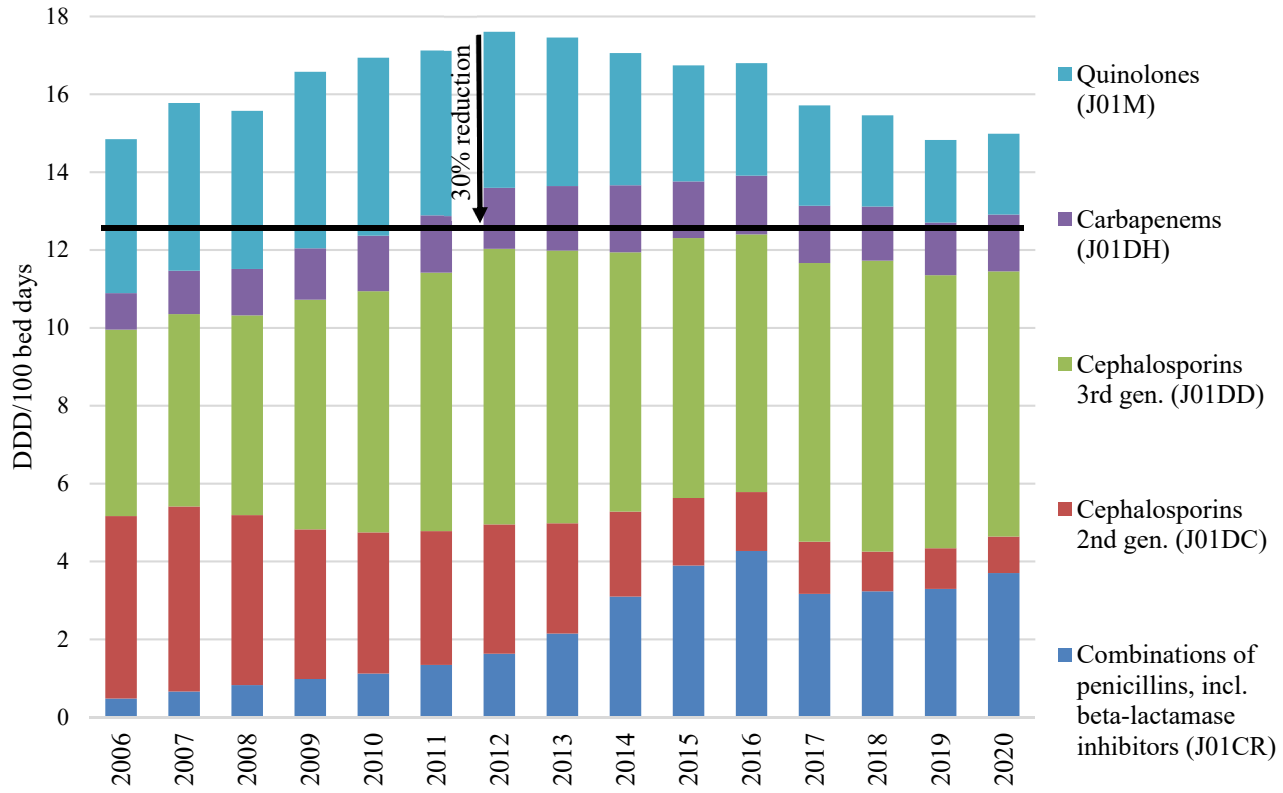

FIGURE 35. Consumption of selected antibacterial agents for systemic use (belonging to ATC-groups J01CR, J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2020, measured in DDD/100 bed days.

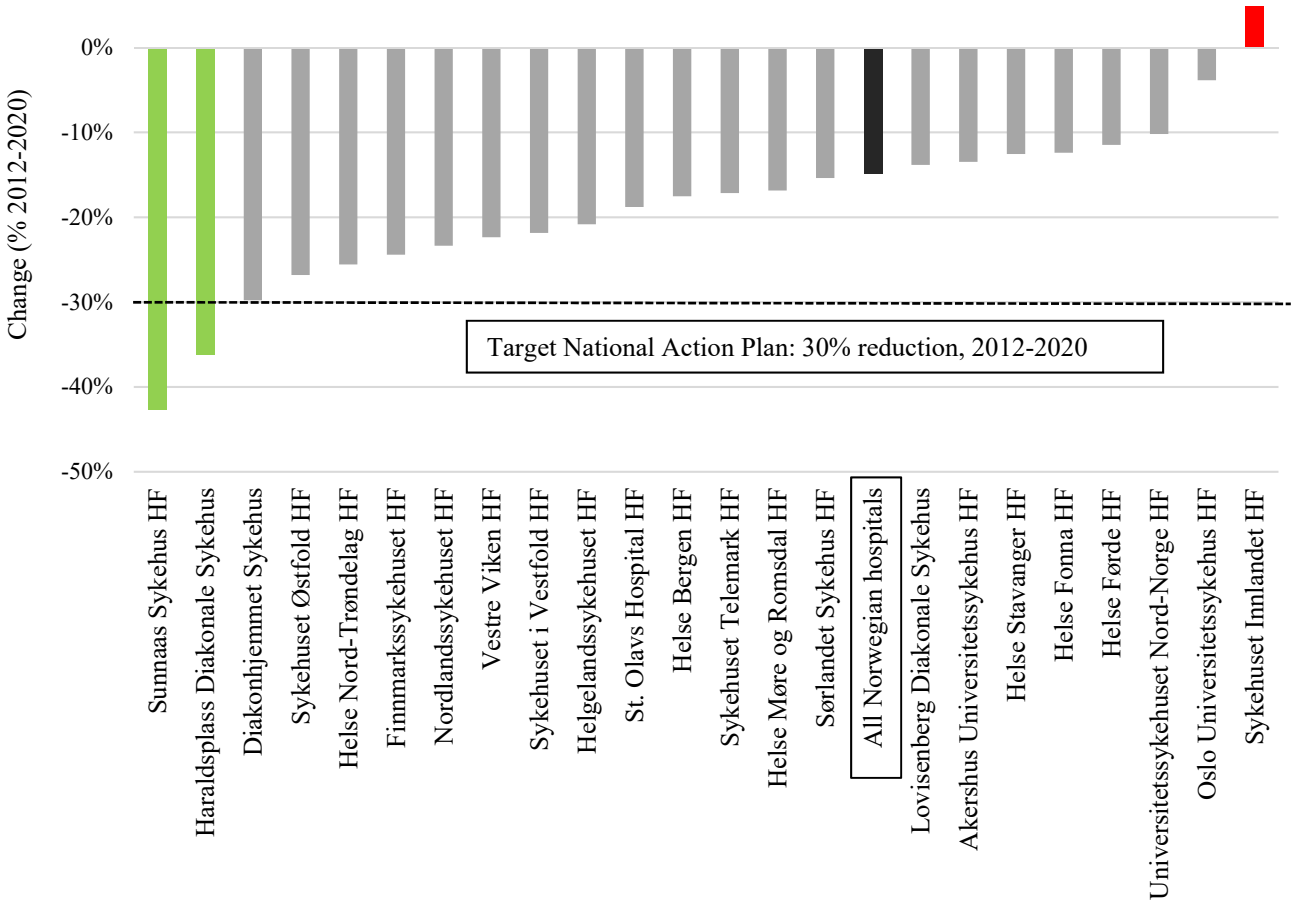

FIGURE 36. Change in consumption of selected antibacterials for systemic use (belonging to ATC-groups J01CR, J01DC, J01DD, J01DH and J01M) in Norway 2012-2020. The data are presented per hospital/health trust as measured in DDD/100 bed days.

OCCURRENCE OF ANTIMICROBIAL RESISTANCE

ANIMAL CLINICAL ISOLATES

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

The clinical isolates included in NORM-VET 2020 were *Klebsiella pneumoniae* from infections in various animal species and *Actinobacillus pleuropneumoniae* in pigs. Sampling, laboratory methods and data processing are described in Appendix 3. One isolate per submission was susceptibility tested.

Klebsiella pneumoniae from animals

A total of 74 isolates of *Klebsiella pneumoniae* from 65 clinical submissions in pigs, canines, turkeys, horses, bovines, felines, chickens, sheep, reindeer and goats (listed in descending order according to number of isolates per species) were susceptibility tested. The isolates were collected between 2017 and 2020 and originated from infections at various body sites. The results are presented in Table 8 and in the text.

TABLE 8. Antimicrobial resistance in clinical isolates of *Klebsiella pneumoniae* from ten different animal species (n=74) collected between 2017 and 2020.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*															
Substance	[95% CI]		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	2.7	[0.3-9.4]								94.6	1.4	1.4				2.7		
Tigecycline	0.0	[0.0-4.9]					48.6	47.3	4.1									
Chloramphenicol	4.1	[0.8-11.4]										94.6	1.4				4.1	
Ampicillin		NA										1.4	37.8	51.4	5.4	4.1		
Cefotaxime	2.7	[0.3-9.4]					97.3					2.7						
Ceftazidime	2.7	[0.3-9.4]						97.3					2.7					
Meropenem	0.0	[0.0-4.9]		91.9	8.1													
Trimethoprim	9.5	[3.9-18.5]					8.1	55.4	24.3	2.7			1.4		8.1			
Sulfamethoxazole	10.8	[4.8-20.2]										83.8	5.4					10.8
Azithromycin	0.0	[0.0-4.9]										17.6	78.4	4.1				
Gentamicin	2.7	[0.3-9.4]						97.3						1.4	1.4			
Ciprofloxacin	5.4	[1.5-13.3]	2.7	79.7	12.2			2.7				1.4	1.4					
Nalidixic acid	4.1	[0.8-11.4]									96.4	1.4			1.4		2.7	
Colistin	1.4	[0.0-7.3]							93.2	5.4	1.4							

*Bold vertical lines denote epidemiological cut-off values for resistance. NA=not applicable, due to inherently low susceptibility to ampicillin. 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 ECOFF, only ECOFFs are shown (i.e for tetracycline, gentamicin and colistin). Clinical breakpoints are not defined for tigecycline, ampicillin, sulfamethoxazole, azithromycin and nalidixic acid.

RESULTS AND COMMENTS

In total, 86.5% of the isolates were susceptible to all antimicrobial agents included in the susceptibility testing. *Klebsiella pneumoniae* has an inherently low susceptibility to ampicillin and this antibiotic was excluded from further assessment. The following proportions of isolates were resistant to one or more antimicrobial classes (ampicillin excluded): 4.1% were resistant to one, 4.1% to two and 5.4% to three or more antimicrobial classes, respectively. One of the isolates was resistant to seven antimicrobial classes and two isolates were resistant to five antimicrobial classes. Two of these multi-drug resistant isolates, both from infections in dogs, displayed resistance to the ESCs cefotaxime and ceftazidime. This was due to presence of the $bla_{\text{CTX-M-15}}$ gene. All isolates resistant to more than two antimicrobial classes were resistant to quinolones. None of the isolates displayed resistance to the carbapenem meropenem.

Clinical breakpoints are shown in dotted blue lines in Table 8. However, these clinical breakpoints are defined in order to indicate if treatment of a specific pathogen is likely to succeed or not, and factors like dosage and formulations will affect the result.

This is the first time *K. pneumoniae* is included in NORM-VET, and comparisons to previous years are therefore not possible. *K. pneumoniae* is probably not a particularly prominent pathogen among domesticated animals in Norway, as reflected by the long sampling period and low number of isolates. *K. pneumoniae* is an important human pathogen and is included in the NORM surveillance programme. It is also listed on the WHO Global Priority Pathogen List, in the critical priority category.

Actinobacillus pleuropneumoniae from pigs

A total of 83 isolates of *Actinobacillus pleuropneumoniae* from infections in pigs were susceptibility tested. The isolates were collected in the period between 2004 and 2020. The results are presented in Table 9 and in the text.

TABLE 9. Antimicrobial resistance in *Actinobacillus pleuropneumoniae* from infections in pigs (n=83) collected between 2004 and 2020.

			Distribution (%) of MIC values (mg/L)*															
Substance	Resistance (%)	[95% CI]	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Chlortetracycline	1.2	[0.0-6.5]						8.4	25.3	59.0	4.8	1.2	1.2					
Oxytetracycline	2.4	[0.3-8.4]						8.4	43.4	42.2	3.6		2.4					
Florfenicol	8.4	[3.5-16.6]					10.8	79.5	1.2	2.4	3.6		2.4					
Ampicillin	3.6	[0.8-10.2]					73.5	22.9		2.4				1.2				
Benzylpenicillin	1.2	[0.0-6.5]				7.2	30.1	41.0	20.5				1.2					
Ceftiofur	3.6	[0.8-10.2]					94.0	2.4	2.4				1.2					
Sulfadimethoxine	ND	ND															59.0	41.0
Trimethoprim/ Sulfamethoxazole**	ND	ND								83.1	16.9							
Tylosin***	ND	ND						1.2			2.4		4.8	21.7	69.9			
Tilmicosin	0.0	[0.0-4.3]									3.6	41.0	54.2	1.3				
Tulathromycin	0.0	[0.0-4.3]									1.2	1.2	45.8	50.6	1.2			
Clindamycin	0.0	[0.0-4.3]						1.2		10.8	44.6	42.2	1.2					
Gentamicin***	ND	ND								1.2		7.2	28.9	62.7				
Neomycin***	ND	ND									1.2		6.0	12.0	80.7			
Enrofloxacin	7.2	[2.7-15.1]				88.0	4.8	1.2	1.2	3.6	1.2							
Danofloxacin	8.4	[3.5-16.6]				85.5	6.0	2.4	1.2	4.8								
Tiamulin	0.0	[0.0-4.3]									2.4	9.6	60.2	25.3	2.4			
Spectinomycin***	ND	ND												2.4	32.5	65.1		

*Bold vertical lines denote epidemiological 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. **Range for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only. ***Range for testing was too narrow, giving an uncomplete MIC distribution, and ECOFFs were therefore not defined.

RESULTS AND COMMENTS

This is the first time *A. pleuropneumoniae* is included in NORM-VET. The range for several of the substances were too narrow to define ECOFFs based on the available distributions. Therefore, the true occurrence of resistance could not be determined. Among the antimicrobial agents where resistance could be determined, the most commonly detected resistances were to the amphenicol florfenicol and the quinolones danofloxacin and enrofloxacin.

The national recommendations for antimicrobial treatment of *A. pleuropneumoniae* infections in pigs list benzyl-penicillinprocain as the first-choice drug. Only one of the included isolates was classified as resistant to benzyl-penicillin, indicating a low occurrence of resistance to this first-choice antibiotic.

Antimicrobial resistance genes in Norwegian *Actinobacillus pleuropneumoniae* isolates

In the Norwegian pig population except for specific pathogen free (SPF) herds, *Actinobacillus pleuropneumoniae* occurs endemically and can on its own cause severe acute respiratory disease outbreaks (1). Therapeutic recommendations on porcine pleuropneumoniae are supported by updated phenotypic antimicrobial susceptibility data, as provided by the NORM/NORM-VET report. For *A. pleuropneumoniae*, genotypic testing of antimicrobial resistance (AMR) has shown to correlate nearly 100% with phenotypes for most relevant antimicrobial agents (2), hence genotyping will likely be of value to future surveillance of AMR in this important porcine pathogen. *A. pleuropneumoniae* serovar 8 (APP8) is the dominating clinical serovar in Norway (3,1). The genotypic AMR of Norwegian isolates was assessed in a study comparing occurrence of AMR genes in APP8 from Norway, Demark and the UK (4).

Methods

The collection of 123 Norwegian APP8 isolates originated from diagnostic sampling at the Norwegian Veterinary Institute (NVI) from 2004-2019 and a field study of respiratory disease in 2017-2018. Isolates from the same collection were tested for phenotypic AMR by NORM-VET for the 2020 report, however, due to different selection criteria it was impossible to compare the results. The isolates were whole genome sequenced using Illumina technology. The presence of AMR genes was investigated using ABRicate (https://github.com/tseemann/abricate) to search the assembled genomes for genes associated with AMR in the ResFinder database (5). The phylogenetic relationship between the isolates was assessed by maximum likelihood approach on pairwise Single Nucleotide Polymorphism distances.

Results

AMR genes were only identified in four out of 123 isolates (Table 10). The following AMR genes were identified: *aph(3'')-Ib* and *aph(6)-Id* (streptomycin resistance), *tet*(Y) (tetracycline resistance), $bla_{\text{ROB-1}}$ (beta-lactam resistance) and *sul2* (sulfonamide resistance). A combination of *aph(3'')-Ib*, *aph(6)-Id*, *tet*(Y) and *sul2* was found in three isolates. The isolates were disseminated in the phylogeny, which points to independent acquisition of these genes.

TABLE 10. Antimicrobial resistance genes identified in 123 isolates of *Actinobacillus pleuropneumoniae* serovar 8.

Country of origin	*aph(3'')-Ib/ strA*	*aph(6)-Id/ strB*	*tet*(Y)	$bla_{\text{ROB-1}}$	*sul2*	Total
Norway	3.3% (4)	2.4% (3)	2.4% (3)	0.8% (1)	3.3% (4)	3.3% (4)

aph(3'')-Ib and *aph(6)-Id* = streptomycin resistance genes (also called *strA* and *strB,* respectively); *tet*(Y) = tetracycline resistance genes; $bla_{\text{ROB-1}}$ = beta-lactam resistance gene; *sul2* = sulfonamide resistance gene. The number of isolates harboring the gene is given in parentheses.

Discussion

There was a low occurrence of AMR genes in APP8 isolates from the Norwegian pig population, differing significantly in comparison to other national APP8 populations (4). There was no evidence of emerging resistant genetic lines, for instance due to selective pressure from antimicrobial drug usage, likely explained by a prudent use of antimicrobial drugs in Norway. Independent acquisition of AMR genes could have happened through random mutations or horizontal transmission from other species in the environment. AMR genes can accumulate in special mobilisable genetic elements that facilitate horizontal transmission of these genes together, previously demonstrated in APP8 (6, 7). Whether the genes identified in this study are part of a common mobilisable element requires further investigation.

Geographic location and restrictions on live pig movements have been important for the molecular evolution of the APP8 populations (4). Regulation on livestock trade will likely be important to sustain a bacterial population widely susceptible to antimicrobial drugs, for instance by stopping an introduction of multi-resistant *A. pleuropneumoniae* strains from other pig populations.

Note that there may be a divergence between the phenotypic susceptibility results of the minimum inhibitory concentration testing and the identified AMR genes. The limitations of identifying AMR genes in ResFinder are tied to a lack in knowledge of genetic variants associated with the respective phenotypes.

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INDICATOR BACTERIA FROM ANIMALS

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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 in various populations. 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 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 is following the requirements set in Commission implementing decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU). In addition, NORM-VET includes antimicrobial 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.

In NORM-VET, *E. coli* and *Enterococcus* spp. are used as indicator bacteria. Selective methods are used for detection of *E. coli* resistant to extended-spectrum cephalosporins (ESC), carbapenem resistant *Enterobacteriaceae* (CRE) and vancomycin resistant *Enterococcus* spp. (VRE).

In 2020, animal samples included caecal samples from broiler and turkey flocks. These samples were analysed for *E. coli* and *Enterococcus* spp., including ESC resistant *E. coli*, CRE and VRE. The substances in the antimicrobial test panels are included due to their importance in human medicin, and are not necessarily relevant for use in veterinary medicine. 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 2020. Only data retrieved following the requirements set in decision 2013/652/EU are shown. For previous data, please see the respective annual reports. Sampling, laboratory methods and data processing are described in Appendix 3.

PRODUCTION ANIMALS

Escherichia coli from broiler and turkey

Caecal samples from 247 broiler flocks and 121 turkey flocks were examined and *E. coli* isolates were obtained from 247 (100%) and 121 (100%) samples, respectively. One isolate per positive sample was susceptibility tested. The results are presented in the text, in Table 11 and Figures 37-40.

TABLE 11. Antimicrobial resistance in isolates of *Escherichia coli* from caecal samples from broiler (n=247) and turkey (n=121) flocks in 2020.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample	[95% CI]		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Broiler	3.6	[1.7 - 6.8]								91.1	4.9	0.4		0.4	1.6	1.6		
	Turkey	8.3	[4.0 - 14.7]								83.5	8.3			1.7	4.1	2.5		
Tigecycline	Broiler	0.0	[0.0 - 1.5]					97.6	2.4										
	Turkey	0.0	[0.0 - 3.0]					99.2	0.8										
Chloramphenicol	Broiler	0.4	[0.0 - 2.2]										98.8	0.8	0.4				
	Turkey	1.7	[0.2 - 5.8]										92.6	5.8			0.8	0.8	
Ampicillin	Broiler	2.0	[0.7 - 4.7]							0.8	39.7	56.3	1.2				2.0		
	Turkey	19	[12.4 - 27.1]							0.8	17.4	61.2	1.7				19.0		
Cefotaxime	Broiler	0.0	[0.0 - 1.5]					100											
	Turkey	1.7	[0.2 - 5.8]					98.3			1.7								
Ceftazidime	Broiler	0.0	[0.0 - 1.5]						100										
	Turkey	1.7	[0.2 - 5.8]						98.3			1.7							
Meropenem	Broiler	0.0	[0.0 - 1.5]		100														
	Turkey	0.0	[0.0 – 3.0]		100														
Trimethoprim	Broiler	2.8	[1.1 - 5.8]					34.4	54.7	7.7	0.4					2.8			
	Turkey	6.6	[2.9 - 12.6]					35.5	51.2	6.6						6.6			
Sulfamethoxazole	Broiler	0.4	[0.0 - 2.2]										99.6						0.4
	Turkey	5.8	[2.4 - 11.6]										91.7	2.5					5.8
Azithromycin	Broiler	0.0	[0.0 - 1.5]								0.4	46.6	50.6	2.4					
	Turkey	0.0	[0.0 - 3.0]								1.7	59.5	38.8						
Gentamicin	Broiler	0.0	[0.0 - 1.5]						86.2	11.7	2.0								
	Turkey	0.8	[0.0 - 4.5]						78.5	14.9	5.8	0.8							
Ciprofloxacin	Broiler	12.6	[8.7 - 17.3]	83.0	3.6	0.8		2.4	1.6	7.7		0.4	0.4						
	Turkey	2.5	[0.5 - 7.1]	84.3	13.2				0.8	1.7									
Nalidixic acid	Broiler	12.1	[8.3 - 16.9]									87.4	0.4			0.4	1.2	10.5	
	Turkey	1.7	[0.2 - 5.8]									96.7	1.7					1.7	
Colistin	Broiler	0.0	[0.0 - 1.5]							96.4	3.6								
	Turkey	0.0	[0.0 - 3.0]							96.7	3.3								

*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.

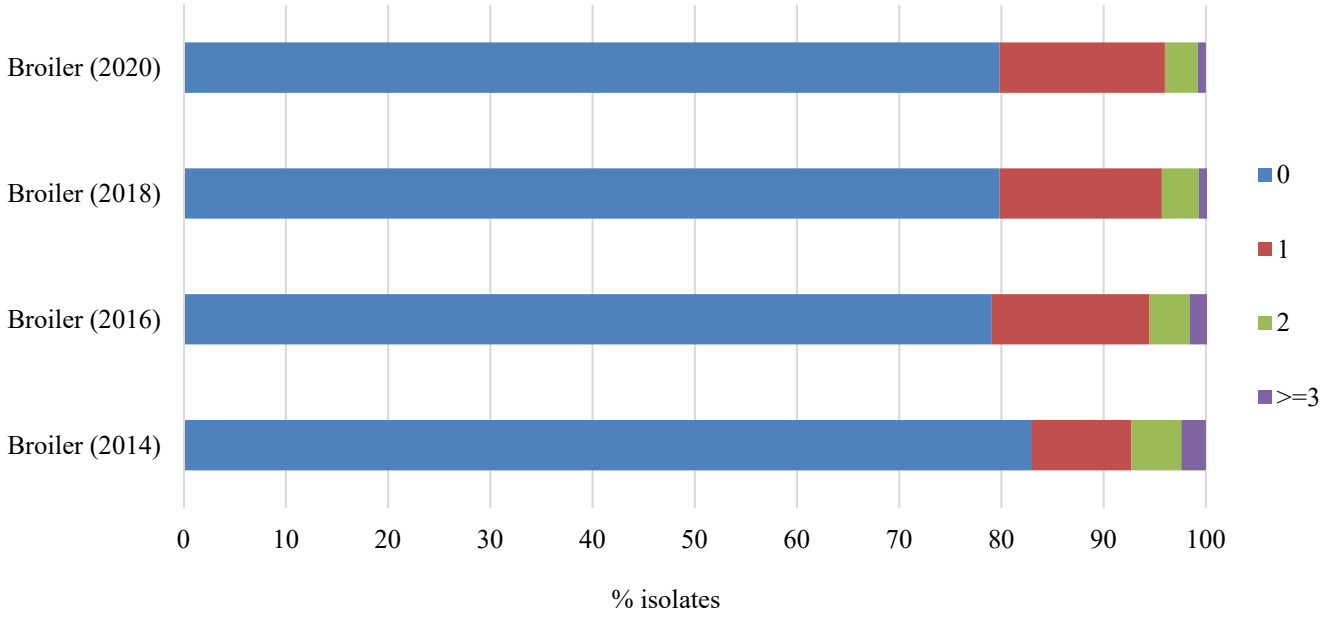

FIGURE 37. Antimicrobial resistance profile for *Escherichia coli* caecal isolates from broiler in 2014-2020. Proportions (%) of isolates susceptible to all (blue) or resistant to one (red), two (green), and three or more (purple) antimicrobial classes are illustrated.

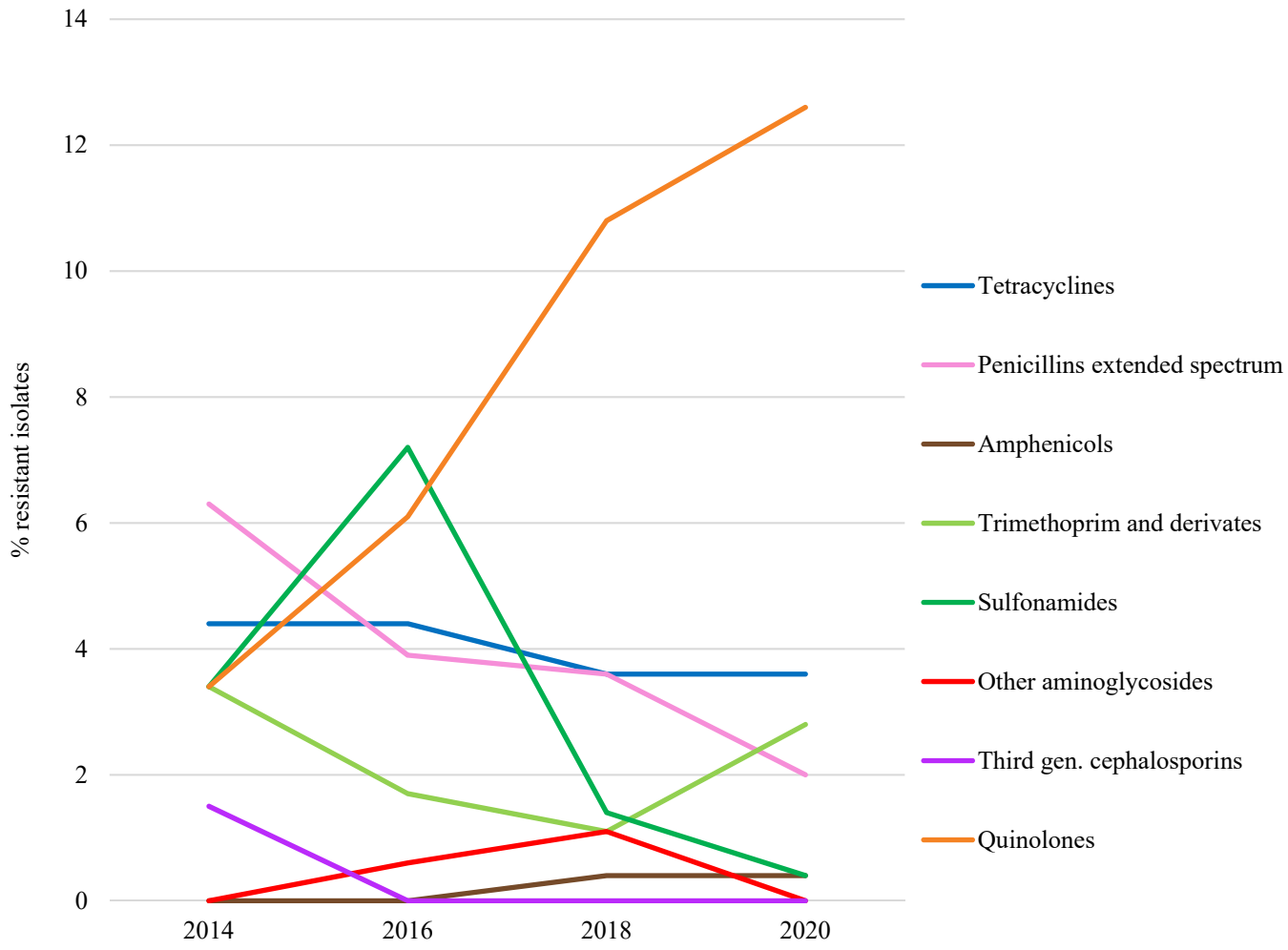

FIGURE 38. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* caecal isolates from broiler in 2014-2020. The cut-off values used in NORM-VET 2020 were applied.

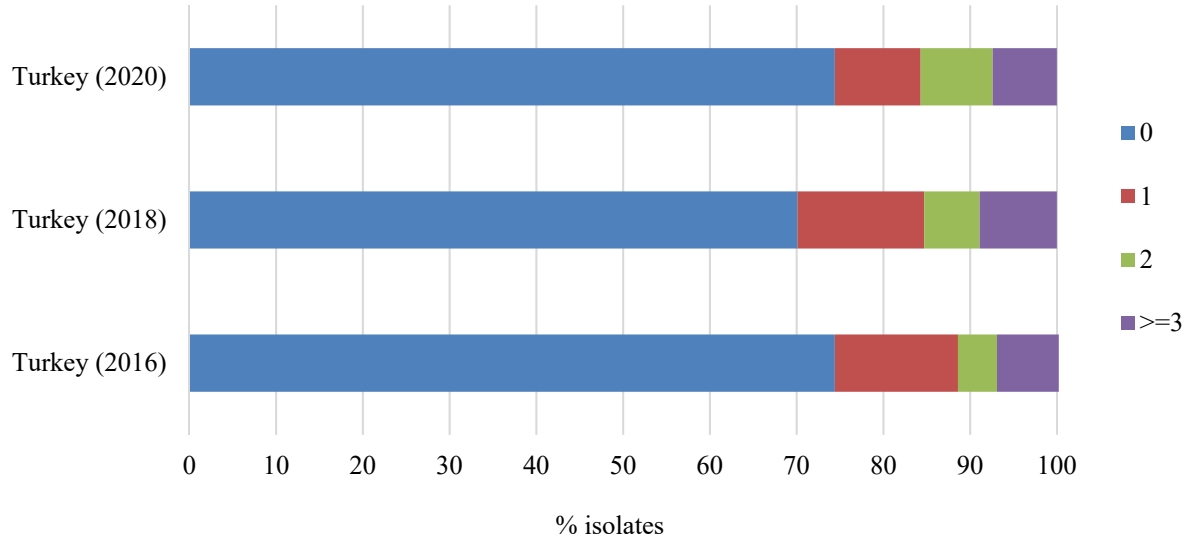

FIGURE 39. Antimicrobial resistance profile for *Escherichia coli* caecal isolates from turkey in 2016-2020. Proportions of isolates susceptible to all (blue) or resistant to one (red), two (green), and three or more (purple) antimicrobial classes are illustrated.

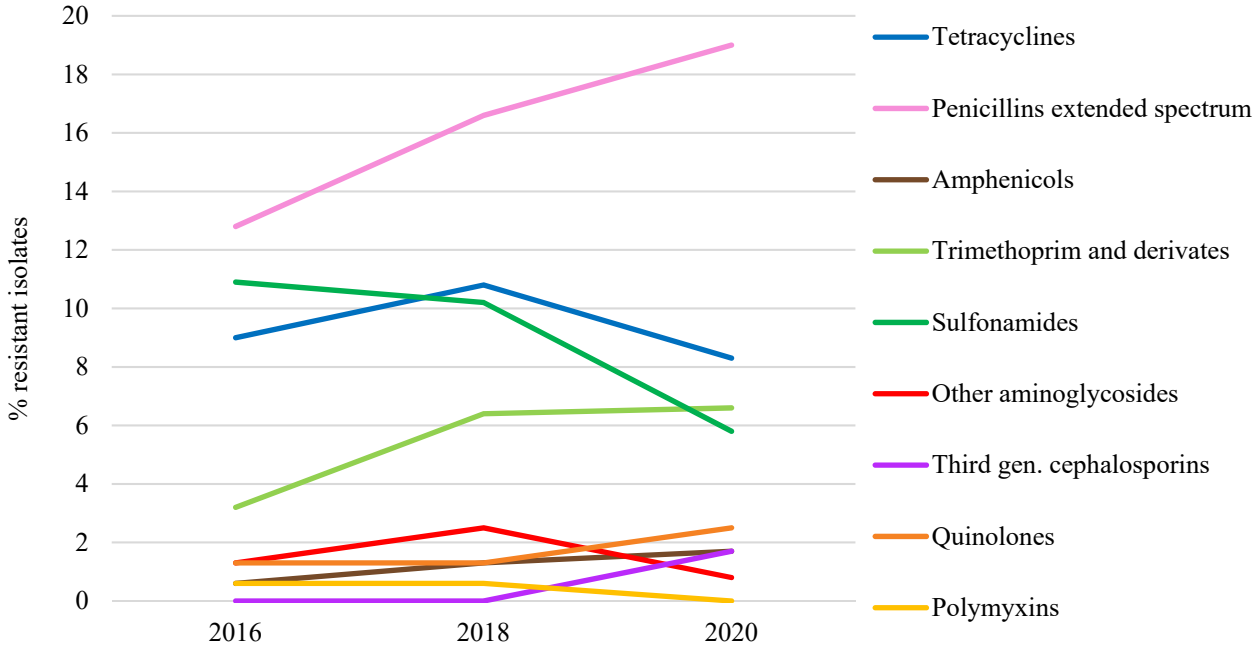

FIGURE 40. Prevalence of resistance to various antimicrobial classes in *Escherichia coli* caecal isolates from turkey in 2016-2020. The cut-off values used in NORM-VET 2020 were applied.

RESULTS AND COMMENTS

BROILER

The 2020 data showed that 79.8% of the *E. coli* isolates from broiler caecal samples were susceptible to all antimicrobial agents included. Altogether, 16.2% of the isolates were resistant to one antimicrobial class (predominantely quinolones), 3.2% to two and 0.8% to three antimicrobial classes (Figure 37). In total, 20.2% of the isolates were resistant to at least one antimicrobial, indicating a high occurrence of resistance in broilers according to the EFSA classification described in Appendix 6. Resistance to ciprofloxacin and nalidixic acid were the most frequently identified resistance determinants, followed by resistance to tetracycline, trimethoprim and ampicillin.

As shown in Figure 37, the number of isolates being fully susceptible has been relatively stable around 80% over the years 2014-2020. The antimicrobial classes for which the isolates show resistance have changed over these years (Figure 38). There has been an increase in resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) from 2014-2020 (p=0.002). In 2014, quinolone resistance was identified in 3.4% [95% CI: 1.4-6.9] of the isolates, while 12.6% [95% CI: 8.7-17.3] of the isolates in 2020 were quinolone resistant. In the years inbetween, i.e. in 2016 and 2018, 6.1% [95% CI: 3.1-10.5] and 10.8% [95% CI: 7.4-15.0] of the isolates were quinolone resistant, respectively. For sulfonamides and penicillins with extended spectrum (i.e. for sulfamethoxa-zole and ampicillin, respectively), however, a decrease in resistance over these years is indicated in Figure 38. Observed resistance to sulfamethoxazole has decreased from 3.4% [95% CI: 1.4-6.9] to 0.4% [95% CI: 0.0-2.2], and observed resistance to ampicillin from 6.3% [95% CI: 2.5-10.6] to 2.0% [95% CI: 0.7-4.7]. These changes are, however, not statistically significant.

None of the *E. coli* isolates from broilers displayed resistance to the extended-spectrum cephalosporins (ESC) cefotaxime or ceftazidime [95% CI: 0.0-1.5]. This is in concordance with the results from 2016 and 2018. In addition, a selective method was used to investigate the occurrence of ESC resistant *E. coli* in the same broiler caecal sample material (see next page).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian broilers is low, though the occurrence varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance levels (EFSA and ECDC Summary report 2018/2019). This favorable situation is probably due to the very limited use of antibiotics in Norwegian broiler production.

TURKEY

The 2020 data showed that 74.4% of the *E. coli* isolates were susceptible to all antimicrobial agents included. Altogether, 9.9% of the isolates were resistant to one antimicrobial class (predominantly ampicillin), 8.3% to two and 7.4% to three or more antimicrobial classes (Figure 39). In total, 25.6% of the isolates were resistant to at least one antimicrobial agent, indicating a high occurrence of resistance in turkey according to the EFSA classification described in Appendix 6. Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to tetracycline, trimethoprim and sulfa-methoxazole.

As shown in Figure 39, the number of isolates being fully susceptible has been relatively stable around 71-74% over the years 2016-2020. The antimicrobial classes for which the isolates show resistance have, however, changed over these years (Figure 40). The figure indicates that there has been an increase in resistance to penicillins with extended spectrum (i.e. ampicillin) from 12.8% [95% CI: 8.0-19.1] in 2016 to 19.0% [95% CI: 12.4-27.1] in 2020. The observed change is, however, not statistically significant and further monitoring is needed to assess whether this is a truly increasing trend. Resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) was detected in 2.5% [95% CI: 0.5-7.1] of the isolates. These results are in concordance with results from previous years.

Two of the isolates displayed resistance to ESC (i.e. cefotaxime and ceftazidime) [95% CI: 0.2-5.8]. Both had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and genotyping showed that the resistance was due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. These two were also detected by the use of a selective method to investigate the occurrence of ESC resistant *E. coli* in the same turkey caecal sample material (see next page).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian turkey is low, though the occurrence varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance levels (EFSA and ECDC Summary report 2018/2019).

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

A total of 242 broiler and 121 turkey flocks were investigated for the presence of *E. coli* resistant to extended-spectrum cephalosporins (ESC). The results are presented in the text and and in Figures 41-42.

RESULTS AND COMMENTS

BROILER

ESC resistant *E. coli* were found in one (0.4% [95% CI: 0.0-2.3]) of the 242 broiler caecal samples. As described above, no cephalosporin resistant isolates were found by using the standard non-selective procedure, indicating that the within-flock prevalence is low. Quantification of *E. coli* resistant to ESC and total *E. coli* in the positive sample, showed that the level of resistant bacteria was below the detection point of 100 CFU/g and the total *E. coli* number was between 10^5-10^6 CFU/g (performed as previously described in textbox, page 52, in NORM/NORM-VET 2016).

The identified isolate carried the bla_{CMY-2} gene and was resistant to quinolones in addition to the ESCs cefotaxime and ceftazidime. The isolate did not show reduced susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance.

As shown in Figure 41, these results are in concordance with the results from 2018, and confirms that the measures implemented by the industry to reduce the occurrence of ESC resistant *E. coli* in broilers have been successful.

Also, in a European perspective, this prevalence of ESC resistant *E. coli* in broilers is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary report 2018/2019). The South-Eastern, South-Central and South-Western countries tended to report a higher prevalence than the Nordic countries and, to a lesser extent, than countries from Western Europe. There are also variations in prevalence between the Nordic countries, with Norway having the lowest reported prevalence.

TURKEY

ESC resistant *E. coli* were found in 7.4% [95% CI: 3.5-13.7] of the 121 turkey caecal samples. As described above, two ESC resistant isolates were found by using the non-selective procedure, indicating that the within-flock prevalence is low. These were from the same samples as detected by this selective method. All nine isolates were only resistant to beta-lactams, i.e. ampicillin and the ESCs cefotaxime and ceftazidime. None of the isolates showed reduced susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance.

All the isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and whole genome sequencing showed that the resistance was due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. Compared to previous results, it appears to have been a decrease in occurrence of ESC resistant *E. coli* due to presence of the plasmid mediated bla_{CMY-2} gene from 5.1% [95% CI: 2.2-9.9] in 2016 to 0% in 2018 [95% CI: 0.0-2.3] and 2020 [95% CI: 0.0-3.0] (Figure 42). This change, however, is statistically non-significant. ESC resistance due to chromosomal mutations in the promoter region of the chromosomal *ampC* gene, appears to be relatively stable between 5-8% (Figure 42). Further monitoring is necessary to follow this situation in the future.

In an international perspective, the occurrence of ESC resistant *E. coli* in Norwegian turkey is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary report 2018/2019).

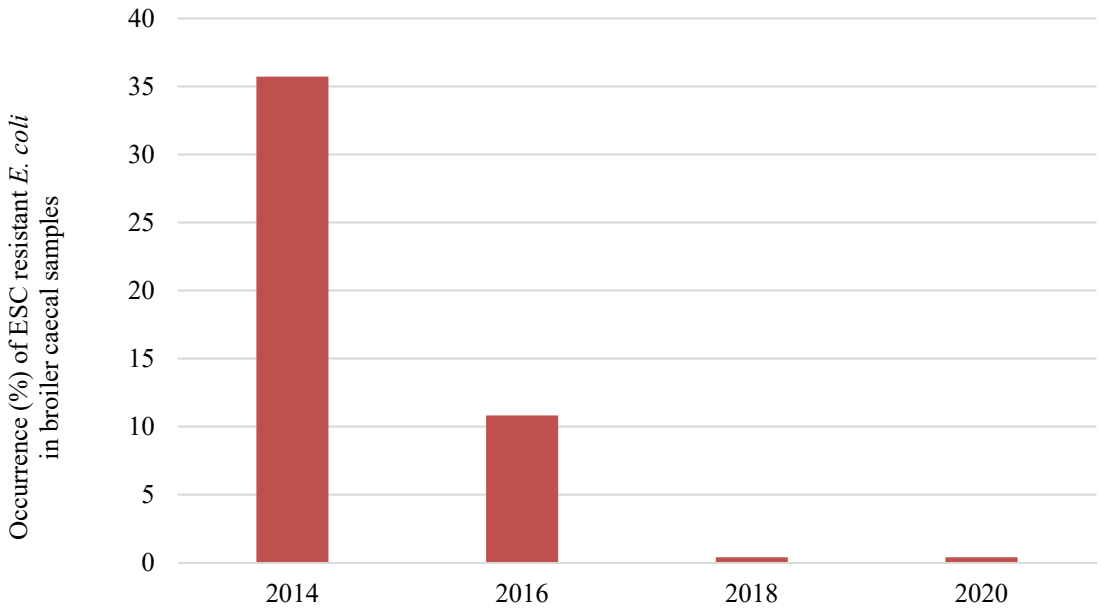

FIGURE 41. Occurrence (%) of ESC resistant *E. coli* in caecal samples from broiler flocks in 2014-2020. All isolates with genotype bla_{CMY-2}.

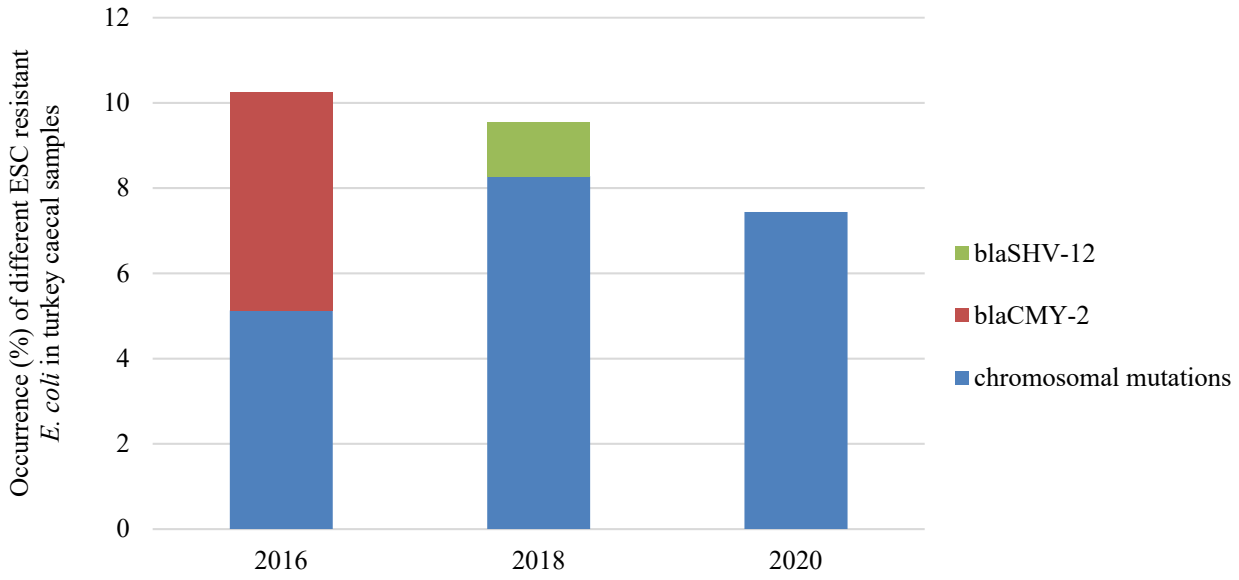

FIGURE 42. Occurrence (%) of different ESC resistant *E. coli* in caecal samples from turkey flocks 2016-2020.

Carbapenem resistant *Enterobacteriaceae* from broiler and turkey

Selective screening for carbapenem resistant *Enterobacteriaceae* (CRE) was performed on caecal samples from a total of 224 broiler and 109 turkey flocks. No CRE were detected. Carbapenems are not approved for use in food-producing animals in EU and EEA countries. Nevertheless, resistance to these critically important antimicrobial agents has sporadically been reported from animals in some of the EU/EEA countries, and further monitoring is recommended to follow the situation in the years to come.

Population structure and uropathogenic potential of extended-spectrum cephalosporin-resistant *Escherichia coli* from retail chicken meat

Escherichia coli (*E. coli*) resistant to extended-spectrum cephalosporins (ESC) were detected in Norwegian retail chicken meat samples included in NORM-VET in 2012, 2014 and 2016 (1-3). Food-producing animals and their food products are considered a plausible source for human acquisition of antimicrobial resistant (AMR) bacteria (4). However, the zoonotic potential of ESC-resistant *E. coli* from broiler production and their potential role as extraintestinal pathogens is unclear. The aim of the current study was to characterise ESC-resistant *E. coli* isolated from Norwegian retail chicken meat in 2012-2016 with regard to population structure, presence of virulence-associated geno- and phenotypes and carriage of AMR genes to evaluate their uropathogenic potential.

We included all ESC-resistant *E. coli* (n=141) isolated from retail chicken meat in NORM-VET from 2012-2016 and performed whole genome sequencing. All isolates harboured the bla_{CMY-2} gene, responsible for ESC resistance (1-3). The population structure was evaluated using multilocus sequence type (MLST) and core-genome MLST (cgMLST), and the presence of AMR- and virulence genes determined using the ARIBA programme (antimicrobial resistance identification by assembly) and the ResFinder, VirulenceFinder and vfdb databases (5-9). In addition, a selection of 18 isolates were included in *in vitro* experiments to determine their phenotypic characteristics relating to expression of type 1 fimbriae, adhesion and invasion, bacterial growth, serum resistance, colicin production, biofilm production and motility.

The isolates were genetically diverse, with 19 different sequence types (STs) observed. There were temporal variations in the distribution of STs. In general, a limited number of virulence genes were present in the isolates. Five of the STs, namely ST131, ST117, ST38, ST10 and ST69 are commonly associated with extraintestinal pathogenic *E. coli* (ExPEC) infections (10). Among the 18 isolates selected for phenotypic testing, we observed a high diversity in virulence-associated phenotypes, suggesting highly variable uropathogenic potential as well. None of the isolates belonging to traditional ExPEC-associated STs appeared to have a higher uropathogenic potential compared to other STs. The high diversity of virulence-associated traits among the isolates suggests that the uropathogenic potential of ESC-resistant *E. coli* from retail chicken meat is dependent on the isolate. However, the susceptibility of the host may also have a possible impact.

In conclusion, the uropathogenic potential of ESC-resistant *E. coli* from Norwegian broiler production seems to be limited, and the risk of exposure to ESC-resistant *E. coli* with uropathogenic potential through handling and consumption of retail chicken meat in Norway appears to be low.

The work presented here was performed in the NoResist project (NoResist – combating antimicrobial resistance in the Norwegian food production chain), and was financed by the Research Council of Norway (project number 250212), the Norwegian University of Life Sciences and the Norwegian Veterinary Institute.

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The text above is a summary of the main findings in the publication "Population structure and uropathogenic potential of extended-spectrum cephalosporin-resistant *Escherichia coli* from retail chicken meat" published in BMC Microbiology 21, 94 (2021). https://doi.org/10.1186/s12866-021-02160-y

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Comparative genomics of quinolone resistant *Escherichia coli* from wild animals and livestock species

The occurrence of quinolone resistance in *Escherichia coli* is low in Norwegian livestock [1–6]. This is likely due to a low usage of antimicrobials, including quinolones, but also a consequence of good animal health. Despite low usage of quinolones, quinolone resistant *E. coli* (QREC) can been detected in a high proportion of samples from broilers and pigs [7]. As the selective pressure is expected to be low, the finding was somewhat surprising. Therefore, investigations to explore the level of QREC among several animal species, identify their quinolone resistance determinants, and to identify their origins were conducted.

QREC isolates (n=285) from broilers, pigs, red foxes, and wild birds were subjected to whole genome sequencing [8]. Wild animal species were included to be able to identify possible wild reservoirs of QREC. A phylogenetic approach was used to investigate the evolutionary relationships between the isolates.

The overall occurrence of QREC among the four animal species was low, but a significantly higher occurrence was detected in broilers [8]. The results revealed that mutations in the chromosomal DNA gyrase gene *gyrA* was the major resistance determinant among all included isolates, and a low level of plasmid-mediated quinolone resistance was identified. The initial phylogenetic analysis revealed a high diversity of QREC among the included animal species. Major sequence types overlapped for both production- and wild animal species, but the overall evolutionary distance was too great to determine a clonal transmission. A denser aggregation was observed for isolates from broilers compared to the rest of the animal species. The phylogenetic analysis also revealed potential dissemination within the broiler and pig production chains separately, and possible persistence in the broiler production chain [8]. This initiated further investigations to identify the origin of QREC in broilers. Comparing QREC to wildtype *E. coli* from broilers showed that commensal *E. coli* rarely develop resistance in the broiler production environment [9]. However, the same sequence types as previously described in other Nordic countries were detected [10], supporting the hypothesis that import of parent animals may be a source of QREC. This highlights the importance of biosecurity measures at the top of the broiler production pyramid, to prevent dissemination of QREC.

The studies summarised here are more thoroughly discussed in the cited papers and PhD Thesis [11].

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Enterococcus spp. from broiler and turkey

Caecal samples from a total of 247 broiler flocks and 120 turkey flocks were investigated. *E. faecalis* was obtained from 91 (36.8%) and *E. faecium* from 239 (96.8%) of the broiler samples. From turkey, *E. faecalis* was obtained from 24 (20.0%) and *E. faecium* from 116 (96.7%) of the samples. Of these, 87 and 24 *E. faecalis* from broiler and turkey, respectively, were susceptibility tested. Of the *E. faecium* isolates that were subjected to susceptibility testing, 237 were from broiler and 115 from turkey. The results are presented in Tables 12-14, Figures 43-47, and in the text.

TABLE 12. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from broiler flocks (n=87) in 2020.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	66.7	[55.7 - 76.4]						32.2	1.1				21.8	33.3	10.3	1.1	
Tigecycline	0.0	[0.0 - 4.2]		21.8	63.2	14.9											
Chloramphenicol	0.0	[0.0 - 4.2]								20.7	79.3						
Ampicillin	0.0	[0.0 - 4.2]						80.5	18.4	1.1							
Erythromycin	11.5	[5.7 - 20.1]						50.6	14.9	23	1.1	3.4	3.4	3.4			
Quinupristin - Dalfopristin	ND	ND								13.8	62.1	24.1					
Gentamicin	0.0	[0.0 - 4.2]									9.2	67.8	23.0				
Ciprofloxacin	0.0	[0.0 - 4.2]						81.6	17.2	1.1							
Vancomycin	0.0	[0.0 - 4.2]						69.0	29.9	1.1							
Teicoplanin	0.0	[0.0 - 4.2]					100										
Linezolid	0.0	[0.0 - 4.2]						4.6	93.1	2.3							
Daptomycin	1.1	[0.0 - 6.2]						13.8	70.1	14.9	1.1						
Narasin	1.1	[0.0 - 6.2]				3.4	86.2	8.0	1.1	1.1							

*Bold vertical lines denote microbiological cut-off values for resistance. ND=cut-offs not defined by EUCAST. 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 13. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from turkey flocks (n=24) in 2020.

		Distribution (n) of MIC values (mg/L)*														
Substance	Resistance (n)	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	7						15	2				2	2	3		
Tigecycline	0		6	17	1											
Chloramphenicol	0								6	18						
Ampicillin	0						24									
Erythromycin	7						11	3	3		2				5	
Quinupristin - Dalfopristin	ND									14	10					
Gentamicin	0									7	14	3				
Ciprofloxacin	0					1	19	4								
Vancomycin	0						15	8	1							
Teicoplanin	0					24										
Linezolid	0						3	21								
Daptomycin	0						5	17	2							
Narasin	2				5	10	2	5	2							

*Bold vertical lines denote microbiological cut-off values for resistance. ND=cut-offs not defined by EUCAST. 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 14. Antimicrobial resistance in *Enterococcus faecium* from caecal samples from broiler (n=237) and turkey (n=115) flocks in 2020.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*													
Substance	Sample	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Broiler	4.2	[2 - 7.6]						95.8					0.4	3.0	0.8		
	Turkey	20.0	[13.1 - 28.5]						78.3	0.9	0.9	0.9	1.7		13	4.3		
Tigecycline	Broiler	0.0	[0.0 - 1.5]	18.6	59.9	21.1	0.4											
	Turkey	0.0	[0.0 - 3.2]	29.6	52.2	18.3												
Chloramphenicol	Broiler	0.0	[0.0 - 1.5]								25.3	73.4	0.4	0.8				
	Turkey	0.0	[0.0 - 3.2]								29.6	68.7	1.7					
Ampicillin	Broiler	0.8	[0.1 - 3]					32.1	29.5	23.6	13.9	0.4	0.4					
	Turkey	7.8	[3.6 - 14.3]					10.4	28.7	12.2	40.9	7.8						
Erythromycin	Broiler	11.0	[7.3 - 15.7]						65.0	16.0	8.0	2.1	5.9	3.0				
	Turkey	16.5	[10.3 - 24.6]						67.8	9.6	6.1	2.6	8.7	2.6	0.9		1.7	
Quinupristin –	Broiler	ND	ND					11.0	24.5	32.1	32.1	0.4						
Dalfopristin	Turkey	ND	ND					6.1	9.6	29.6	54.8							
Gentamicin	Broiler	0.0	[0.0 - 1.5]									81.4	16.1	2.5				
	Turkey	0.0	[0.0 - 3.2]									84.3	13	2.6				
Ciprofloxacin	Broiler	1.3	[0.3 - 3.7]				2.1		14.8	35	41.8	5.1	1.3					
	Turkey	0.0	[0.0 - 3.2]					0.9	17.4	30.4	40.0	11.3						
Vancomycin	Broiler	0.0	[0.0 - 1.5]						90.7	7.6	1.7							
	Turkey	0.0	[0.0 - 3.2]						89.6	9.6	0.9							
Teicoplanin	Broiler	0.0	[0.0 - 1.5]					99.2	0.8									
	Turkey	0.0	[0.0 - 3.2]					100										
Linezolid	Broiler	0.8	[0.1 – 3.0]						0.4	60.3	38.4	0.8						
	Turkey	0.9	[0.0 - 4.7]							59.1	40.0	0.9						
Daptomycin	Broiler	0.0	[0.0 - 1.5]				1.3	2.5	13.1	34.6	45.6	3.0						
	Turkey	0.0	[0.0 - 3.2]				6.1	13.9	13.9	36.5	27.8	1.7						
Narasin	Broiler	15.6	[9.8-19.0]				1.7	19.8	60.8	2.1	3.8	11.8						
	Turkey	78.2	[60.6-85.4]					5.2	15.7	0.9	59.1	19.1						

*Bold vertical lines denote microbiological cut-off values for resistance. ND=cut-offs not defined by EUCAST. 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.

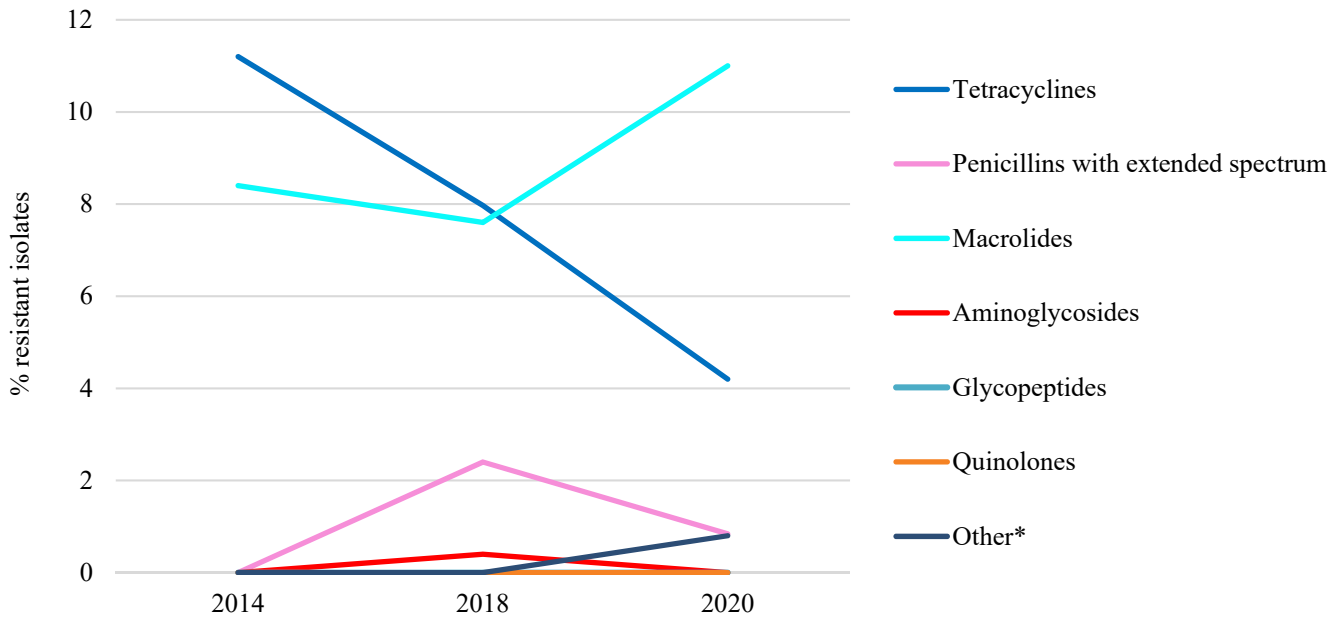

FIGURE 43. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* isolates from caecal samples from broiler 2014-2020. The epidemiological cut-off values used in NORM-VET 2020 were applied. Narasin is not included in this figure. *i.e. Daptomycin.

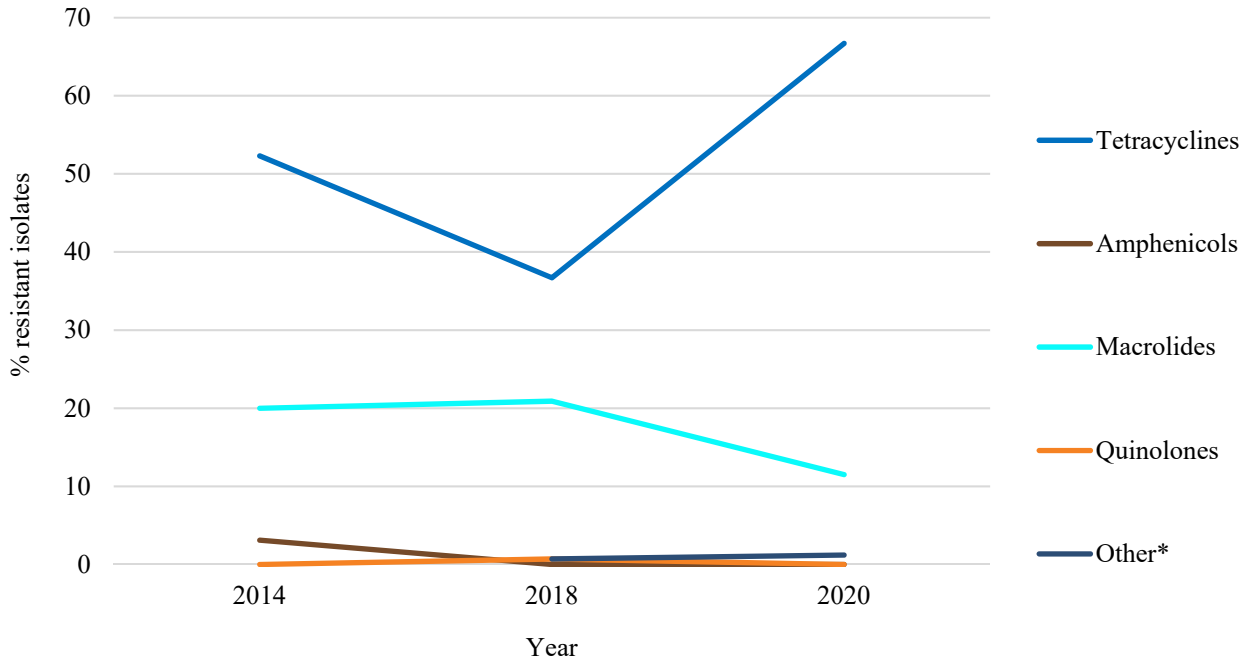

FIGURE 44. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecalis* isolates from caecal samples from broiler 2014-2020. The epidemiological cut-off values used in NORM-VET 2020 were applied. Narasin is not included in this figure. *i.e. Daptomycin.

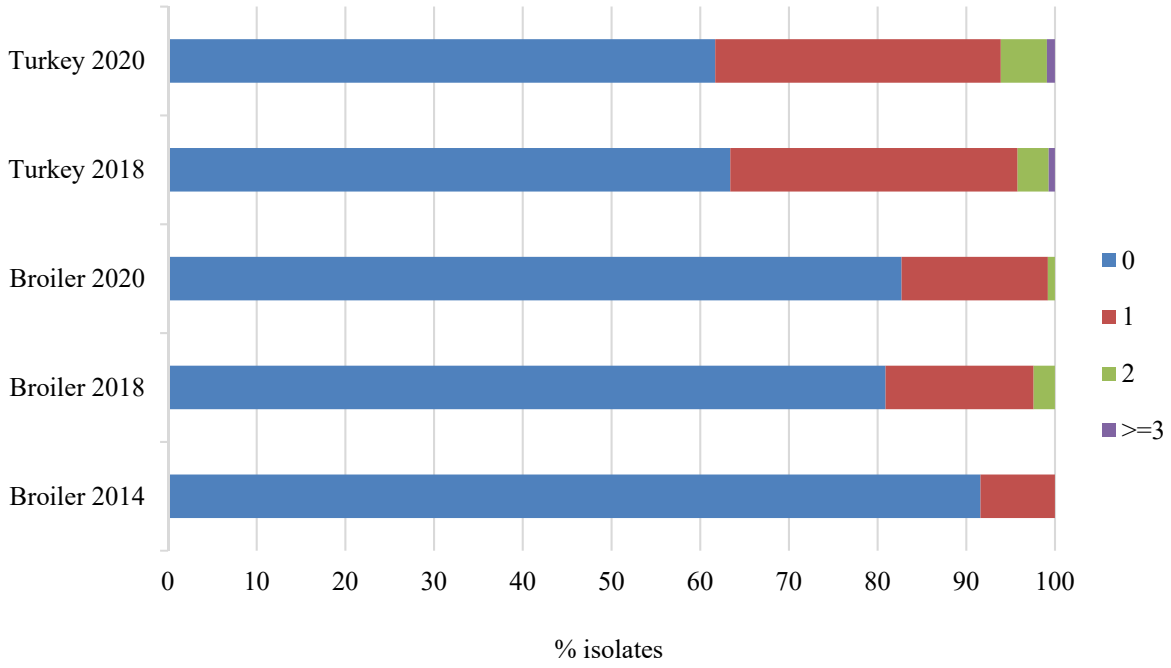

FIGURE 45. Antimicrobial resistance profile for *Enterococcus faecium* caecal isolates from broiler and turkey in 2014-2020. Proportions of isolates (%) susceptible to all (blue), resistant to one (red), two (green) or three or more (purple) antimicrobial classes are illustrated. Resistance to narasin is not included.

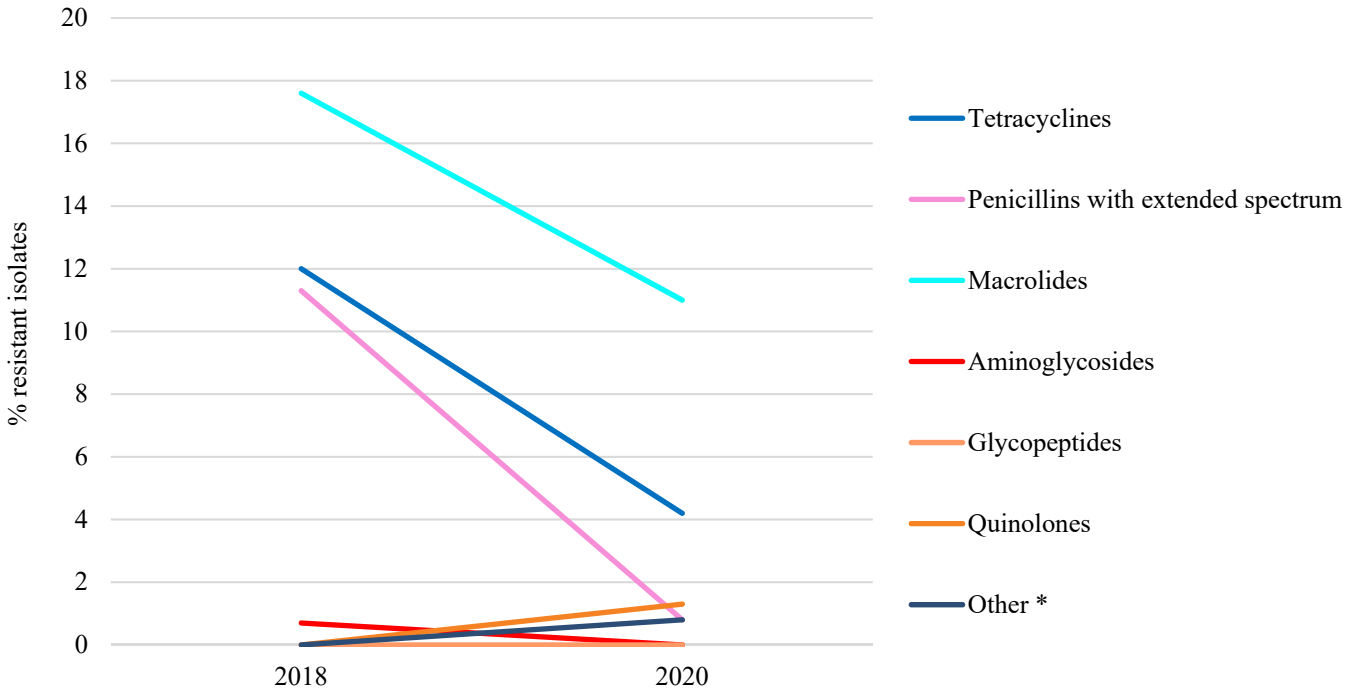

FIGURE 46. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecium* isolates from caecal samples from turkey 2018-2020. The epidemiological cut-offs used in NORM-VET 2020 were applied. Narasin is not included in this figure. *i.e. Daptomycin.

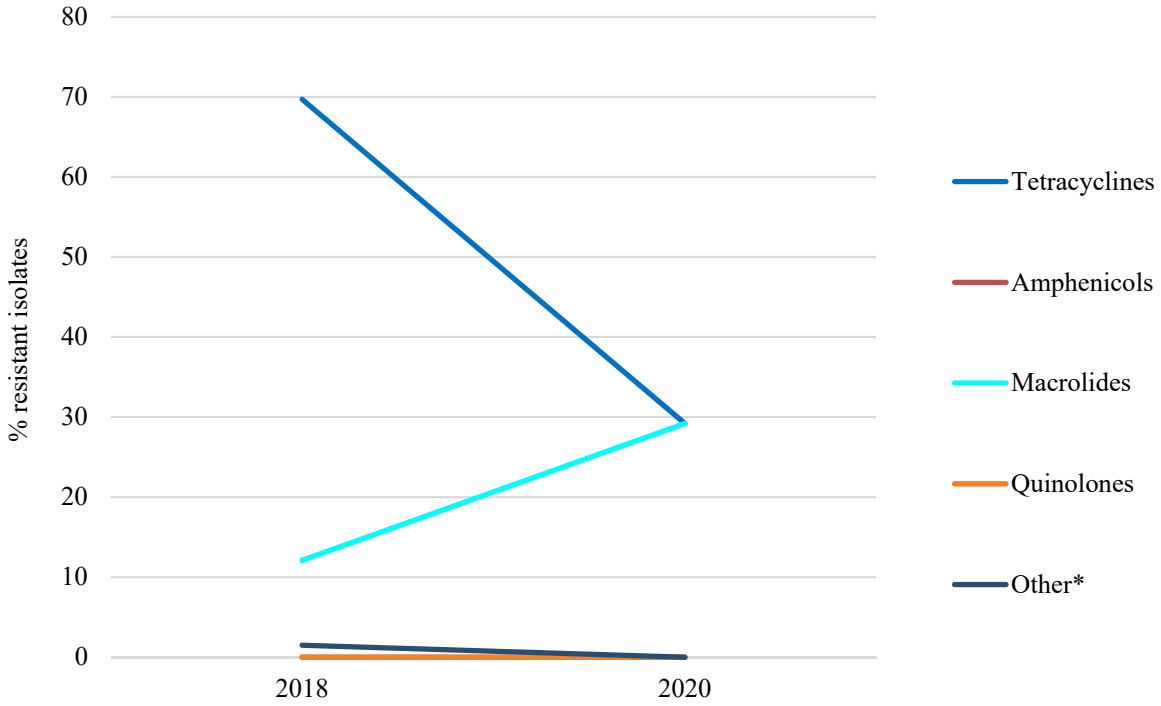

FIGURE 47. Prevalence of resistance to various antimicrobial classes in *Enterococcus faecalis* isolates from caecal samples from turkey 2018-2020. The epidemiological cut-off values used in NORM-VET 2020 were applied. Narasin is not included in this figure. *i.e. Daptomycin.

RESULTS AND COMMENTS

BROILER

The 2020 data showed that 31.0% of the *E. faecalis* and 82.7% of the *E. faecium* isolates from broiler caecal samples were susceptible to all antimicrobial classes included in the test panel. Narasin was not included in these calculations, and is commented separately below.

E. faecalis: Altogether, 58.6% of the isolates were resistant to one antimicrobial class (mainly tetracycline) and 10.3% to two (mainly tetracycline and erythromycin).

E. faecium: Altogether, 16.5% of the isolates were resistant to one antimicrobial class (mainly erythromycin) and 0.8% to two antimicrobial classes. Reduced susceptibility to linezolid was observed in two of the isolates. However, no acquired resistance genes nor point mutations were detected.

In total, 69.0% of the *E. faecalis* isolates and 17.3% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a very high and moderate occurrence of resistance, respectively, according to the EFSA classification described in Appendix 6.

Compared to the data from 2018, there has been an increase in occurrence of tetracycline resistance among *E. faecalis* from 36.7% [95% CI: 28.7-45.3] to 66.7% [95% CI: 55.7-76.4]. However, the occurrence in 2014 was more similar to 2020 with 52.3% [95% CI: 39.5-64.9], and further monitoring is needed to follow this in the years to come. The prevalence of tetracycline resistance among *E. faecalis* is surprising, as there is insignificant use of oxytetracycline for clinical purposes in Norwegian broiler production.

Resistance to narasin was identified in 1.1% of the *E. faecalis* and 15.6% of the *E. faecium* isolates. The results indicate a decreasing trend in occurrence of narasin resistance in both *E. faecalis* and *E. faecium* from broilers. In 2018, narasin resistance was detected in 3.6% of the *E. faecalis* and in 24.7% of the *E. faecium*. The observed change in *E. faecium* is statistically significant ($p<0.02$). This decrease in occurrence is expected as the use of narasin as coccidiostat to broilers was phased out in Norway in 2015-2016, and since then Norwegian broilers have been raised without the use of coccidiostats. Though some flocks have been treated with narasin in cases of outbreak (see chapter on usage in animals). This has been possible due to implementation of coccidia vaccines for all broilers.

None of the *E. faecium* or *E. faecalis* isolates displayed resistance to vancomycin. This is in concordance with results from 2014 and 2018. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. The use selected for a reservoir of vancomycin resistant enterococci (VRE) in Norwegian broiler production that persisted for many years after the ban was implemented.

TURKEY

The 2020 data showed that 54.2% of the *E. faecalis* and 61.7% of the *E. faecium* isolates from turkey caecal samples were susceptible to all antimicrobial classes included in the test panel. Narasin was not included in these calculations, and is commented separately below.

E. faecalis: Altogether, 33.3% of the isolates were resistant to one antimicrobial class (mainly tetracyclines or erythromycin), 12.5% to two (tetracyclines and eythromycin) antimicrobial classes.

E. faecium: Altogether, 32.2% of the isolates were resistant to one antimicrobial class (mainly tetracyclines), 5.2% to two (mainly erythromycin and ampicillin), and 0.9% to three or more antimicrobial classes. Reduced susceptibility to linezolid was observed in one of the isolates. However, no acquired resistance genes nor point mutations were detected.

In total, 45.8% of the *E. faecalis* isolates and 38.3% of the *E. faecium* isolates were resistant to at least one antimicrobial class (narasin not included), indicating a high occurrence of resistance, according to the EFSA classification described in Appendix 6.

Resistance to narasin was identified in 8.3% of the *E. faecalis* and 78.2% of the *E. faecium* isolates. In contrast to the result for broilers, the occurrence of narasin resistance in *E. faecalis* and *E. faecium* from turkey has not changed. The occurrence in *E. faecium* has been relatively stable around 80%. Due to high toxicity in turkeys, narasin has never been used in the turkey production. Instead the coccidiostat monensin is used. There is no indication of cross-resistance between narasin and monensin, and the reason behind the occurrence of narasin resistance in *E. faecium* from turkey is therefore not clear.

None of the *E. faecium* or *E. faecalis* isolates displayed resistance to vancomycin. This is in concordance with results from 2018. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. The use selected for a reservoir of vancomycin resistant enterococci (VRE) in Norwegian broiler production that persisted for many years after the ban was implemented.

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

A total of 247 caecal samples from broiler flocks and 121 caecal samples from turkey flocks were screened for the presence of vancomycin resistant *Enterococcus* spp. (VRE). No VRE were detected in the broiler [95% CI: 0.0-1.5] or turkey [95% CI: 0.0-3.0] samples. This is in concordance with the result from 2018. For broilers a statistically significant decrease from 2014 when 6.7% [95% CI: 3.7-10.9] of the flocks were VRE positive.

Characterisation of a narasin resistance mechanism in *Enterococcus faecium*

Feed used for conventional rearing of poultry has historically been supplemented with antimicrobial substances to reduce serious diseases in the poultry population. Between 1986 and 1995 (Norway; 1997 in the EU), poultry feed was supplemented with the glycopeptide avoparcin. However, use of avoparcin selected for vancomycin resistant enterococci (VRE) in European livestock and VRE was detected in the community. When use of avoparcin was discontinued in Norway in 1995, and Europe in 1997, poultry feed was supplemented with polyether ionophores to control coccidiosis and reduce occurrence of necrotising enteritis. As a result, occurrence of VRE in poultry was drastically reduced, but surveillance data revealed that enterococci resistant to the polyether ionophore narasin were prevalent and a reservoir of VRE persisted in the Norwegian as well as European poultry populations.

The prophylactic use of polyether ionophores was phased out of the Norwegian broiler production in 2015 as part of an intervention strategy to reduce antibiotic use, occurrence of antibiotic resistance and maintain animal health in poultry production, and since 2016 broilers have been reared on feed free of polyether ionophores. Since then, occurrence of narasin resistant enterococci has been reduced and VRE have not been detected in the Norwegian broiler population [1, 2]. Although it is not possible at this time to conclude that the inability to detect VRE in Norwegian poultry is a direct consequence of the discontinuation of narasin as a broiler feed additive, a number of facts support this notion. Firstly, all of the VRE isolated from Norwegian poultry in 2006-2014 are also narasin resistant suggesting co-selection of resistance to narasin and vancomcyin [2]. Secondly, narasin resistance has been shown to be co-localised on mobile plasmids and both resistance mechanisms have been shown to be transferred between bacteria by conjugation [3, 4]. Genetic analysis found an association between narasin resistance and a two gene operon encoding a putative membrane transporter [4].

In a recent study performed by the University of Oslo and the Norwegian Veterinary Institute, this operon was cloned under the native promoter and the ability to confer resistance to a panel of antibiotics was assessed [3]. It was for the first time definitely confirmed that the two genes confer resistance to narasin, and cross-resistance was demonstrated against the polyether ionophores salinomycin, and maduramicin. The two genes were named narasin resistance genes A and B, and the resistance mechanism is referred to as NarAB [3]. Interestingly, NarAB did not provide resistance against the polyether ionophore monensin or any of the clinically used antimicrobials tested in the study, including vancomycin. This proves that the observed selection of vancomycin resistant transconjugants during conjugation experiments was due to co-selection of physically linked narasin and vancomycin resistance on mobile plasmids. This experiment specifically and the study in general support that use of polyether ionophores as feed additives can select for vancomycin resistance and that use of in-feed narasin has contributed to persistence of VRE in poultry.

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INDICATOR BACTERIA FROM FOOD

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NORM-VET is following the requirements set in Commission implementing decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistant bacteria in food (2013/652/EU). In addition, NORM-VET includes antimicrobial testing of bacteria from sources other than those covered by this legal act and uses 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.

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 treatment of human infections. Monitoring the occurrence of bacteria resistant to these substances in different foods is therefore of special interest. A reservoir of such resistant bacteria in the food chain is of concern as they may have an impact on resistance development in human bacterial populations.

In NORM-VET, *Escherichia coli* are used as indicator bacteria from food sources. Selective methods for detection of *E. coli* resistant to extended-spectrum cephalosporins were included in NORM-VET from 2011. From 2015 a selective method for detection of carbapenem resistant *Enterobacteriaceae* was implemented as well. In 2020, food samples included broiler meat.

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 2020. Sampling, laboratory methods and data processing are described in Appendix 3.

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

A total of 323 broiler meat samples were analysed for the presence of *E. coli* resistant to extended-spectrum cephalosporins (ESC). Results are presented in Figure 48 and in the text.

RESULTS AND COMMENTS

ESC resistant *E. coli* were found in three (0.9%) [95% CI: 0.2-2.7] of the 323 meat samples. The isolates were only resistant to beta-lactams, i.e. ampicillin and the ESC cefotaxime and ceftazidime. The isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and whole genome sequencing showed that the isolates contained the $bla_{\text{CMY-2}}$ gene. The isolates did not show decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance. There was a significant reduction of *E. coli* resistant to ESC in broiler meat in 2018 ($p<0.001$) as compared to previous years (Figure 48). The result from 2020 is in concordance with results from 2018.

In a European perspective, the occurrence of 0.9% *E. coli* resistant to ESC in broiler meat in Norway is very low, although the occurrence varied markedly between countries reporting to EFSA in 2018 (EFSA and ECDC Summary report 2018/19). A decrease in prevalence has also been observed in several other European countries. The South-Eastern, South-Central and South-Western countries tended to report a higher prevalence than the Nordic countries and, to a lesser extent, than countries from Western Europe. There are also variations in prevalence between the Nordic countries, with Norway having the lowest prevalence.

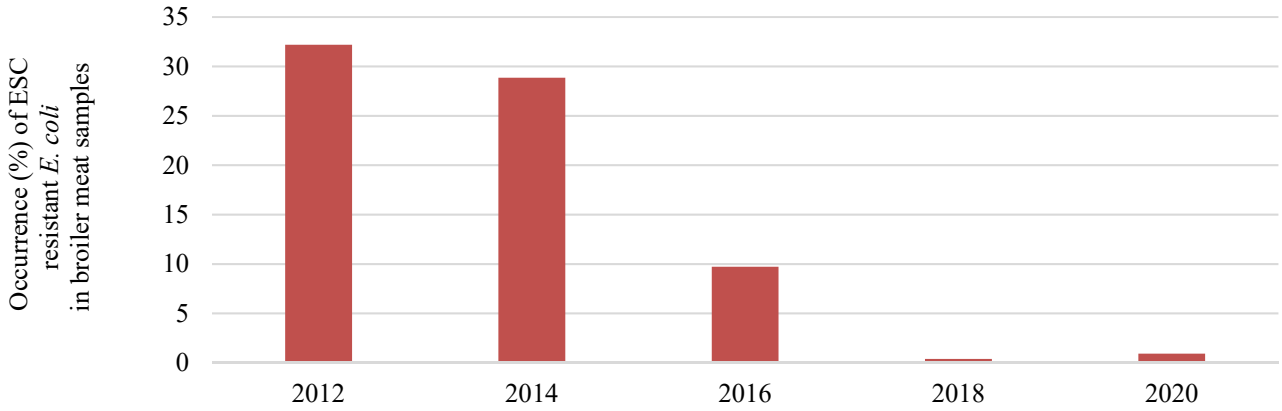

FIGURE 48. Occurrence (%) of ESC resistant *E. coli* in broiler meat samples in 2012-2020. All isolates had genotype $bla_{\text{CMY-2}}$.

Carbapenem resistant *Enterobacteriaceae* from broiler meat

A total of 323 broiler meat samples were screened for the presence of carbapenem resistant *Enterobacteriaceae* (CRE). No CRE were detected. 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.

Methicillin resistant *Staphylococcus aureus* (MRSA) in pig in Norway in 2020

There are several variants 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 (2-7). In 2020, a total of 641 herds were included, of which 81 were genetic nucleus or multiplier herds, 12 herds were central units of the sow pool herds, 18 were of the largest farrow to grower or farrow to finish herds, and the remaining 530 were herds with more than 10 sows. The surveillance programme did not detect any pig herds with MRSA. Further details can be found in the report "The surveillance programme for methicillin resistant *Staphylococcus aureus* in pig in Norway 2020" (8).

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 15 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 we define LA-MRSA 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 (9).

TABLE 15. MRSA positive pig herds 2013-2020. Table shows total number of MRSA positive herds, herds detected by the MRSA surveillance programme, and results from the MRSA typing.

Year	MRSA positive herds (detected by the MRSA surveillance prog.)	Herds investigated in the MRSA surveillance prog.	MRSA typing*
2014	5 (1)	986	CC398 t034 (2), CC398 t011 (3)
2015	34 (4)	821	CC398 t034 (25), CC1 t177 (9)
2016	8 (1)	872	CC398 t034 (8)
2017	6 (2)	826	CC7 t091 (2), CC8 t024 (2), CC130 t843 (1), CC425 t6292 (1)
2018	0	716	
2019	9 (1)	722	CC398 t034 (3), CC398 t011 (5), CC130 t843 (1)
2020	0	641	
Total	62 (9)		CC398 t034 (38), 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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ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

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Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health 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.

Salmonella isolates from control programmes concerning feed samples, animals and food products, as well as diagnostic samples from animals are monitored for antimicrobial resistance every year. In addition, *Campylobacter* spp. from broiler and turkey were included in 2020.

Bacteria recovered from human clinical specimens including *Salmonella*, *Shigella*, *Yersinia enterocolitica* and a representative selection of *Campylobacter* spp. are included for monitoring of antimicrobial resistance.

Sampling, laboratory methods and data processing are described in Appendix 4.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food production 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 runs an extensive surveillance programme that covers both live animals (cattle, pigs and poultry) and meat samples. The *Salmonella* isolates examined in NORM-VET include those that are detected in this programme, as well as isolates detected by clinical submissions to the Norwegian Veterinary Institute. The data are presented in Table 16 and in the text.

TABLE 16. Antimicrobial resistance in *Salmonella* spp. (n=33) from animals (cat=8, dog=4, wild boar=9, swine=3, cattle=8, one chicken); *S.* Typhimurium (n=23) and other *Salmonella* spp. (n=10) in 2020.

Substance	Resistance (n)	Distribution (n) of MIC values (mg/L)*																
		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥1024
Tetracycline	3								30				3					
Tigecycline	0					30	3											
Chloramphenicol	4										29					4		
Ampicillin	3							18	12						3			
Cefotaxime	0					33												
Ceftazidime	0						33											
Meropenem	0		20		13													
Trimethoprim	0					30	3											
Sulfamethoxazole	3										11	11	8					3
Azithromycin	0									24	7	2						
Gentamicin	0						31	1	1									
Ciprofloxacin	0	11		19		3												
Nalidixic acid	3									30						3		
Colistin	20							11	2	12	8							

*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 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.

RESULTS AND COMMENTS

In 2020, a total of 33 *Salmonella* spp. isolates from animals were susceptibility tested. In total, 23 of these isolates were *S.* Typhimurium including one each from eight cats, five wild boars, four cattle, four dogs, one pig and one chicken, respectively. The remaining ten isolates belonged to eight different serovars; one isolate each of *S.* Agona, *S.* Umbilo, *S.* Hessarek, and *S. enterica* subsp. *diarizonae* from cattle, one isolate each of *S.* Derby and *S. enterica* subsp. *diarizonae* from swine, and two isolates of *S. enterica* subsp. *diarizonae* and one isolate each of *S. bongori* and *S. enterica* subsp. *enterica* from wild boars.

Nine of the isolates were fully susceptible to all antimicrobial classes tested for, 21 were resistant to one (mainly colistin) and three isolates from cattle (*S.* Typhimurium) were resistant to five different antimicrobial classes (tetracyclines, amphenicols, penicillins with extended spectrum, sulfonamides and quinolones).

The colistin resistant isolates were subjected to whole genome sequencing for further characterisation of the responsible resistance mechanisms. No acquired resistance genes nor point mutations were found. Due to differences in natural susceptibility to colistin among serovars, there is no general *Salmonella* ECOFF, and these isolates should therefore probably be considered susceptible to colistin.

Salmonella from human clinical specimens

In 2020, 439 human cases of nontyphoidal salmonellosis and 7 cases of typhoid fever were notified to the Norwegian Surveillance System for Communicable Disease (MSIS). The majority of these cases were infected abroad (40%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 412 unique *Salmonella* isolates from primary diagnostic laboratories in Norway. All isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on all *Salmonella* Typhimurium, *Salmonella* Typhi and *Salmonella* Paratyphi A isolates, and based on information at the point of reception, all other non-travel associated *Salmonella* isolates. In addition, antimicrobial susceptibility testing was performed on all *Salmonella* isolates recovered from blood cultures. Information on place of acquisition was completed and updated for all isolates by data from MSIS. A total of 354 unique *Salmonella* spp. isolates were tested (Table 17). 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 17. Number of antimicrobial susceptibility tested *Salmonella* isolates recoved from human clinical specimens in Norway 2020, by serovar and place of acquisition.

Salmonella serovars	No. of isolates tested in 2020	Place of acquistion		
		Norway	Abroad	Unknown
S. Typhimurium	60	41	8	11
S. Typhimurium monophasic (4,[5],12:i-)	20	10	6	4
S. Enteritidis	129	31	66	32
S. Typhi	7	0	4	3
S. Paratyphi A	5	0	4	1
Other *Salmonella*	133	68	28	37
Total	354	150	116	88

A total of 51 isolates were recovered form blood cultures representing 12% of all *Salmonella* isolates submitted to NRL. This included five of the seven *S.* Typhi (71.4%), four of the five *S.* Paratyphi A (80%), 16 of the 129 *S.* Enteritidis (12.4%), three of the 60 *S.* Typhimurium (5%), two of the 20 *S.* Typhimurium monophasic (4,[5],12:i-) (10%) and the rest from other *Salmonella* species (n=21, 15.8%). The results from the antimicrobial susceptibility testing and genomic resistance screening for *Salmonella* isolates are presented in Tables 18-29, Figures 49-59 and in the connected text.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHIMURIUM

TABLE 18. Percentage distributions of antimicrobial susceptibility categories of domestically acquired *Salmonella* Typhimurium (n=41) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	87.8	-	12.2
Cefotaxime	≤ 1	> 2	97.6	0.0	2.4
Ceftazidime	≤ 1	> 4	97.6	0.0	2.4
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	85.4	-	14.6
Tetracycline[2]	≥ 17 mm	< 17 mm	82.9	-	17.1
Chloramphenicol	≤ 8	> 8	90.2	-	9.8

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. 11.0).[2]Breakpoints according to national zone distributions.

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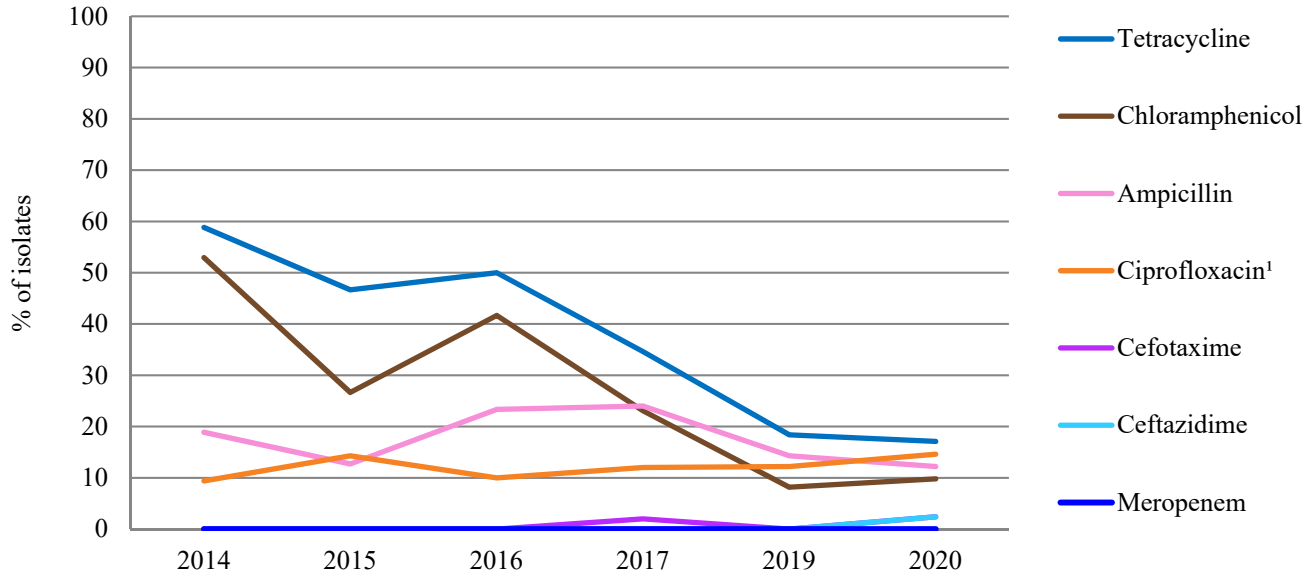

FIGURE 49. Percentage of domestically acquired *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway, trend 2014-2020. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 19. Percentage distributions of antimicrobial susceptibility categories of travel-associated *Salmonella* Typhimurium (n=8) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	87.5	-	12.5
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	62.5	-	37.5
Chloramphenicol	≤ 8	> 8	87.5	-	12.5

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. 11.0).[2]Breakpoints according to national zone distributions.

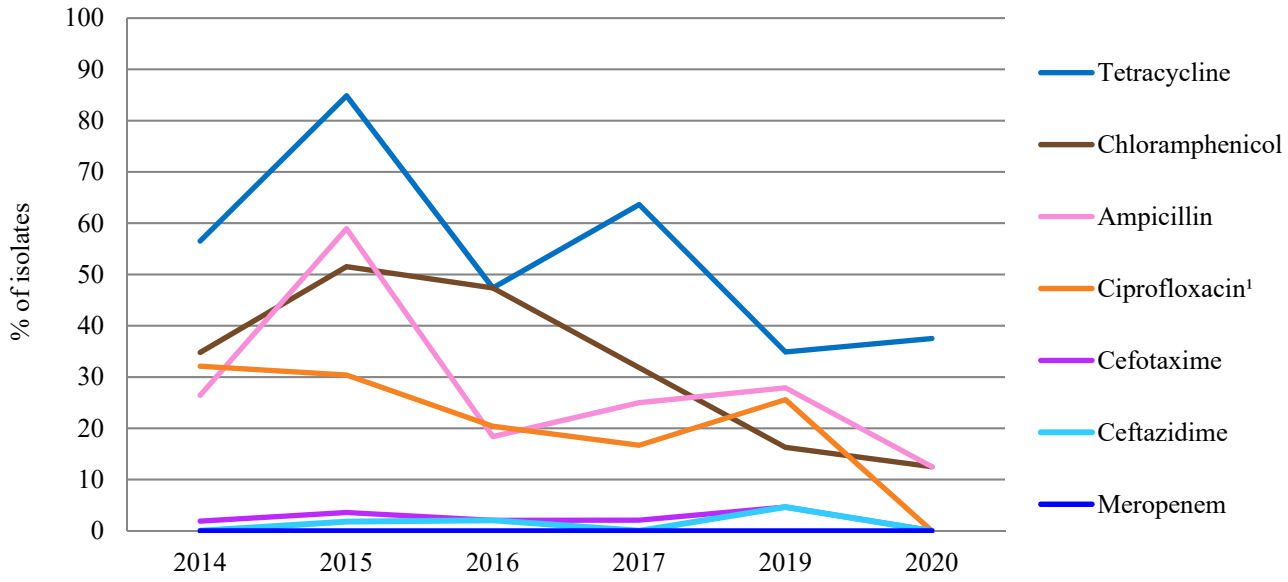

FIGURE 50. Percentage of travel-associated *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway, trend 2014-2020. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 20. Percentage distributions of genotypic resistant *Salmonella* Typhimurium (n=60) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 4	> 4	90.0	10.0
Cefotaxime[2]	≤ 0.5	> 0.5	98.3	1.7
Ceftazidime[2]	≤ 2	> 2	95.5	4.5
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Pefloxacin[3]	≥ 24 mm	< 24 mm	95.0	5.0
Tetracycline	≤ 8	> 8	91.7	8.3
Chloramphenicol	≤ 16	> 16	93.3	6.7
Gentamicin	≤ 2	> 2	100.0	0.0
Trimethoprim	≤ 2	> 2	96.7	3.3

[1]Epidemiological cut-off values (ECOFF) retrieved from EUCAST for *Salmonella enterica* (last accessed 02.07.21). WT=wildetype, NWT=non-wildetype. [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion.

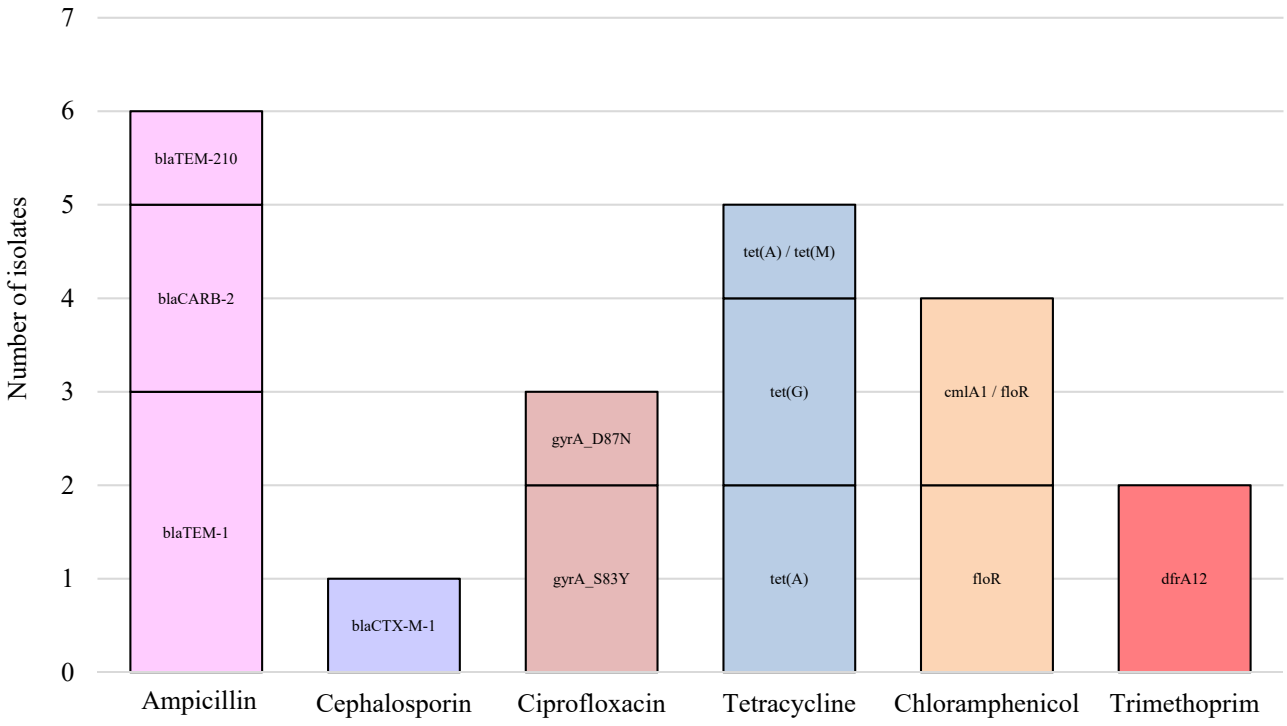

FIGURE 51. Identified resistance determinants in genotypic resistant *Salmonella* Typhimurium to selected antimicrobial agents in Norway 2020.

ANTIMICROBIAL RESISTANCE IN MONOPHASIC SALMONELLA TYPHIMURIUM

TABLE 21. Percentage distributions of antimicrobial susceptibility categories of domestically acquired monophasic *Salmonella* Typhimurium (n=10) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	30.0	-	70.0
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	10.0	-	90.0
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. 11.0).[2]Breakpoints according to national zone distributions.

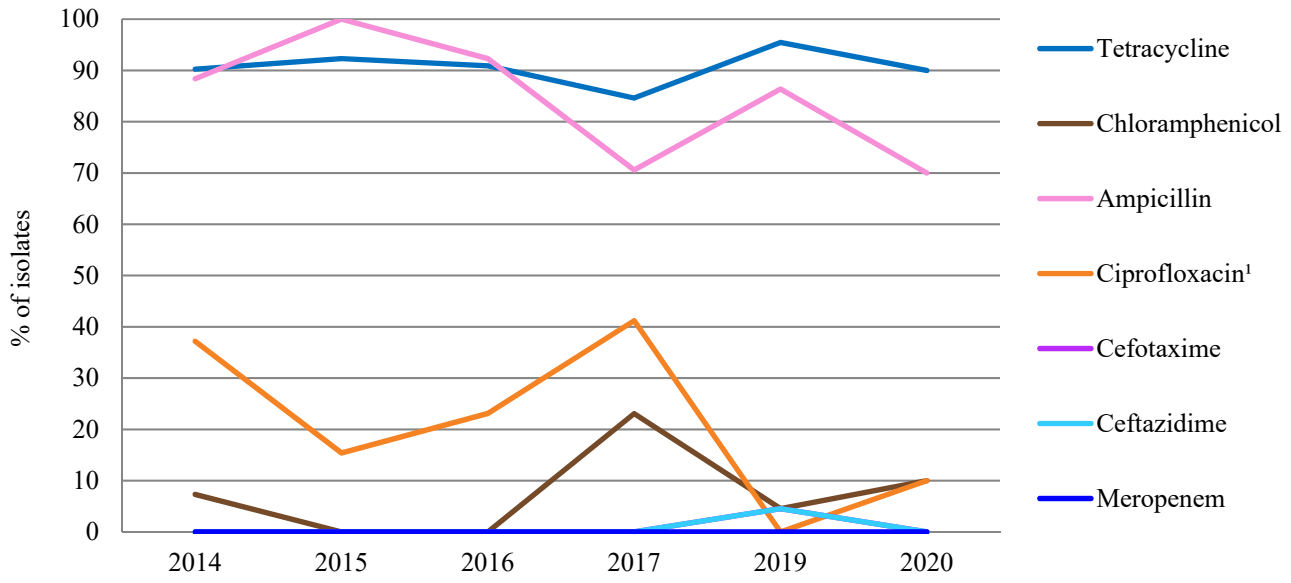

FIGURE 52. Percentage of domestically acquired monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway, trend 2014-2020. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 22. Percentage distributions of antimicrobial susceptibility categories of travel-associated monophasic *Salmonella* Typhimurium (n=6) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	16.7	-	83.3
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.5	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	66.7	-	33.3
Tetracycline[2]	≥ 17 mm	< 17 mm	0.0	-	100.0
Chloramphenicol	≤ 8	> 8	100.0	-	0.0

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. 11.0).[2]Breakpoints according to national zone distributions.

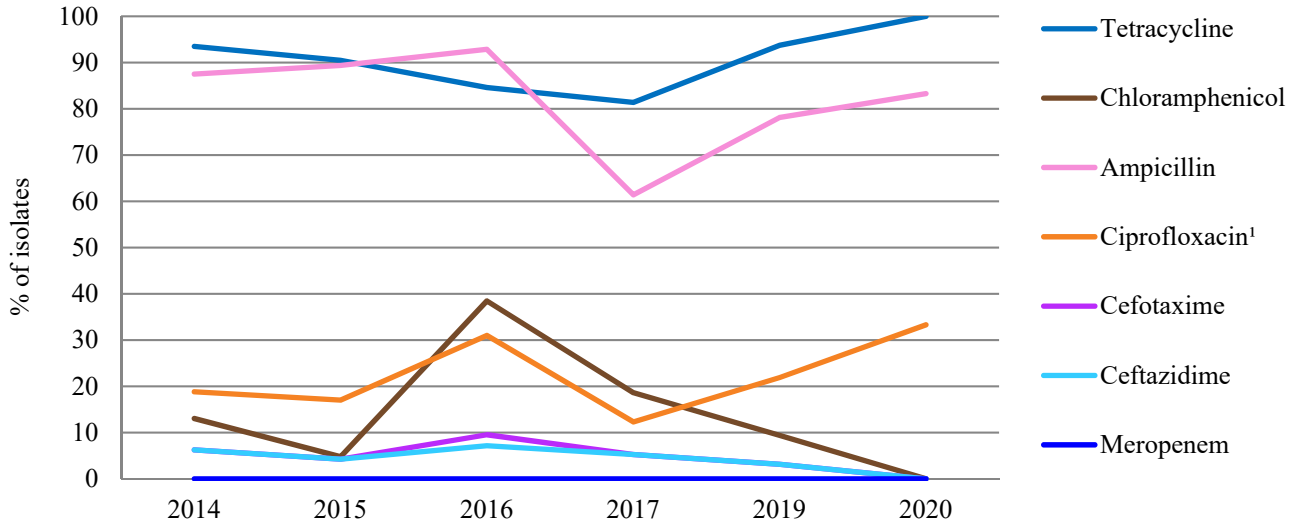

FIGURE 53. Percentage of travel-associated monophasic *Salmonella* Typhimurium resistant to selected antimicrobial agents in Norway, trend 2014-2020. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 23. Percentage distributions of genotypic resistant monophasic *Salmonella* Typhimurium (n=20) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 4	> 4	20.0	80.0
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2	95.5	4.5
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Pefloxacin[3]	≥ 24 mm	< 24 mm	85.0	15.0
Tetracycline	≤ 8	> 8	15.0	85.0
Chloramphenicol	≤ 16	> 16	90.0	10.0
Gentamicin	≤ 2	> 2	90.0	10.0
Trimethoprim	≤ 2	> 2	85.0	15.0

[1]Epidemiological cut-off values (ECOFF) retrieved from EUCAST for *Salmonella enterica* (last accessed 02.07.21). WT=wildetype, NWT=non-wildetype. [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion.

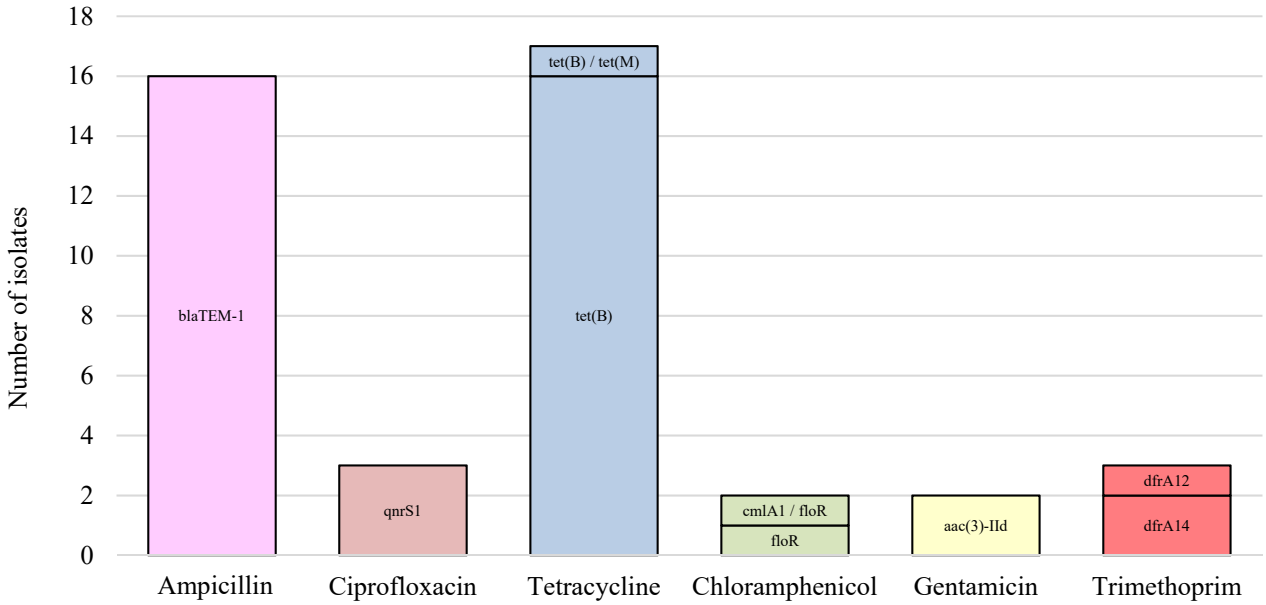

FIGURE 54. Identified resistance determinants in genotypic resistant monophasic *Salmonella* Typhimurium to selected antimicrobial agents in Norway 2020.

ANTIMICROBIAL RESISTANCE IN SALMONELLA ENTERITIDIS

TABLE 24. Percentage distributions of antimicrobial susceptibility categories of *Salmonella* Enteritidis (n=129) from human clinical specimens irrespective of place of acquisition in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	94.6	-	5.4
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	98.4	1.6	0.0
Pefloxacin[1]	≥ 24 mm	< 24 mm	83.7	-	16.3
Tetracycline[2]	≥ 17 mm	< 17 mm	96.1	-	3.9
Chloramphenicol	≤ 8	> 8	100.0	-	0.0

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. 11.0).[2]Breakpoints according to national zone distributions.

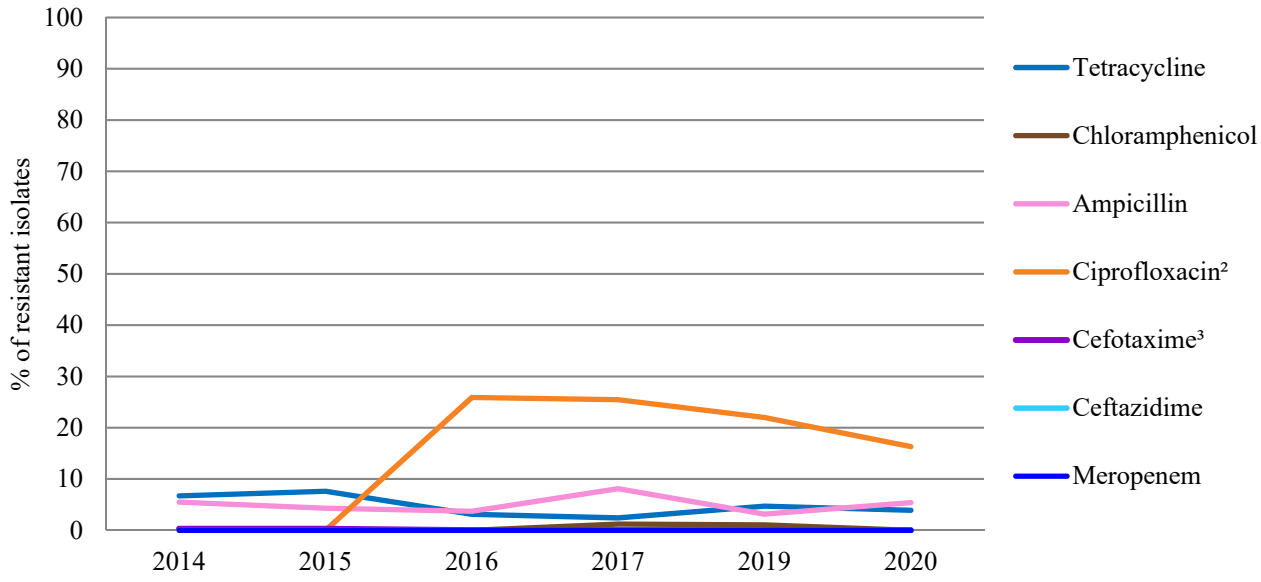

FIGURE 55. Percentage of *Salmonella* Enteritidis resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2014-2020. [1]Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 25. Percentage distributions of genotypic resistant *Salmonella* Enteritidis (n=144) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 4	> 4	94.4	5.6
Cefotaxime[2]	≤ 0.5	> 0.5	100.0	0.0
Ceftazidime[2]	≤ 2	> 2	95.5	4.5
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Pefloxacin[3]	≥ 24 mm	< 24 mm	81.2	18.8
Tetracycline	≤ 8	> 8	99.3	0.7
Chloramphenicol	≤ 16	> 16	100.0	0.0
Gentamicin	≤ 2	> 2	100.0	0.0
Trimethoprim	≤ 2	> 2	100.0	0.0

[1]Epidemiological cut-off values (ECOFF) retrieved from EUCAST for *Salmonella enterica* (last accessed 02.07.21). WT=wildetype, NWT=non-wildetype. [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion.

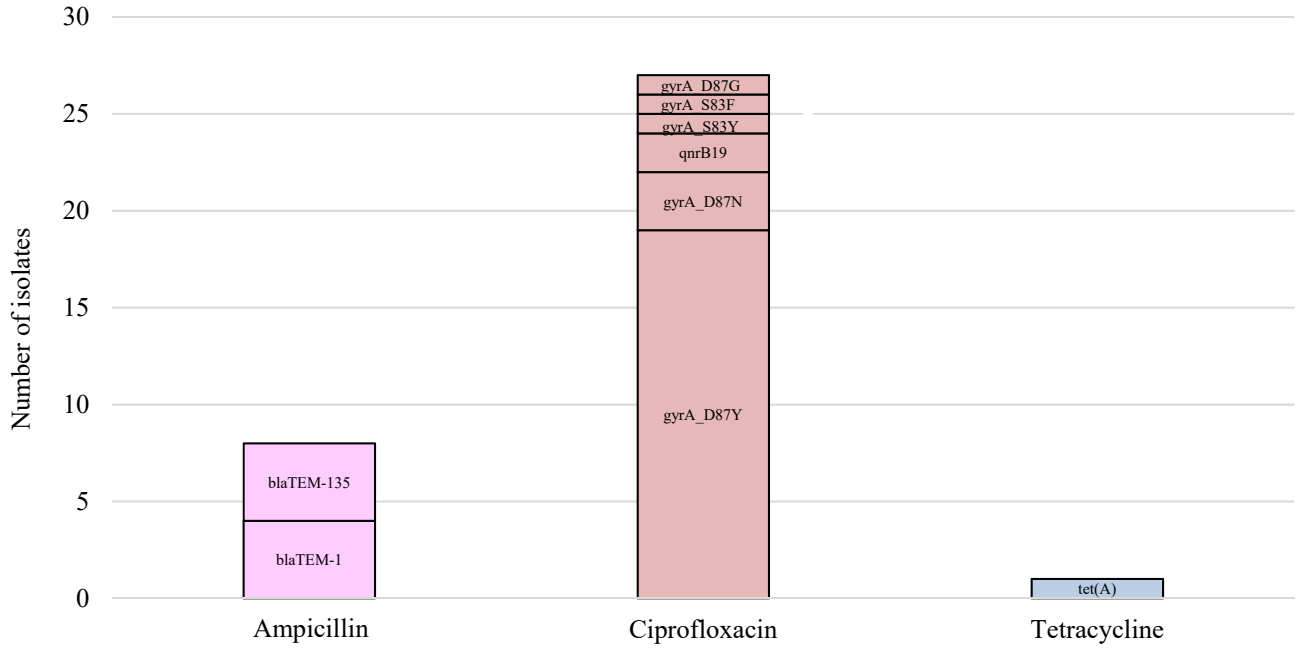

FIGURE 56. Identified resistance determinants in genotypic resistant *Salmonella* Enteritidis to selected antimicrobial agents in Norway 2020.

ANTIMICROBIAL RESISTANCE IN SALMONELLA TYPHI

TABLE 26. Percentage distributions of antimicrobial susceptibility categories of *Salmonella* Typhi (n=7) from human clinical specimens irrespective of place of acquisition in Norway 2020.

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

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. 11.0).[2]Breakpoints according to national zone distributions.

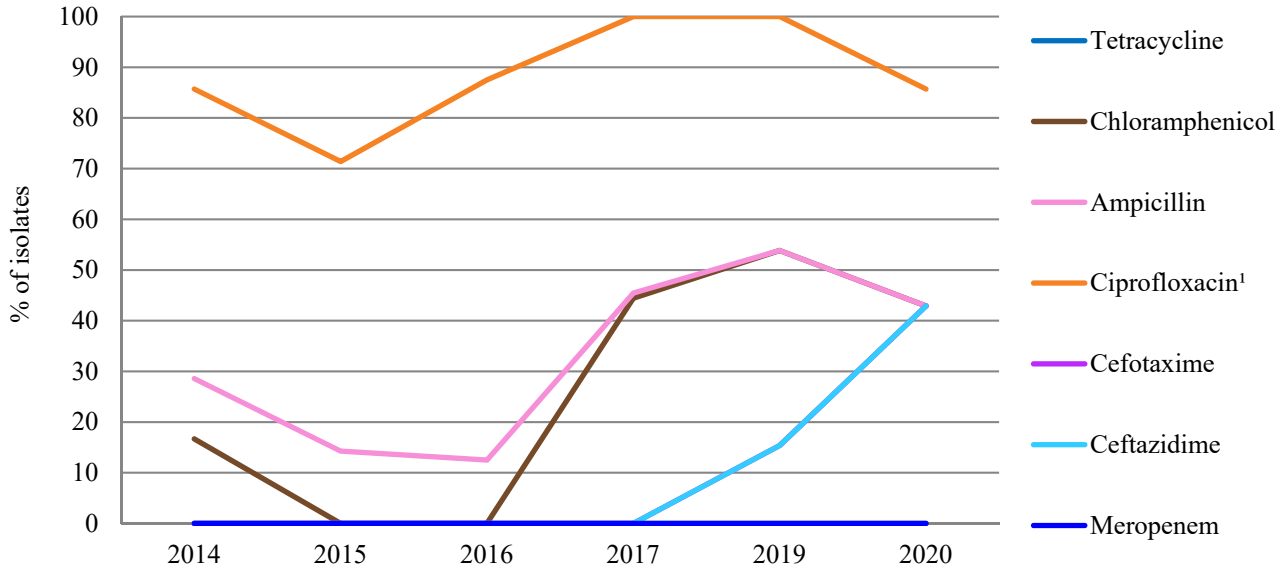

FIGURE 57. Percentage of *Salmonella* Typhi resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2014-2020. [1] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion 2016 onwards.

TABLE 27. Percentage distributions of genotypic resistant *Salmonella* Typhi (n=7) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 4	> 4	57.1	42.9
Cefotaxime[2]	≤ 0.5	> 0.5	57.1	42.9
Ceftazidime[2]	≤ 2	> 2	95.5	4.5
Meropenem	≤ 0.06	> 0.06	100.0	0.0
Pefloxacin[3]	≥ 24 mm	< 24 mm	14.3	85.7
Tetracycline	≤ 8	> 8	100.0	0.0
Chloramphenicol	≤ 16	> 16	57.1	42.9
Gentamicin	≤ 2	> 2	100.0	0.0
Trimethoprim	≤ 2	> 2	57.1	42.9

[1]Epidemiological cut-off values (ECOFF) retrieved from EUCAST for *Salmonella enterica* (last accessed 02.07.21). WT=wilde-type, NWT=non wilde-type. [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion.

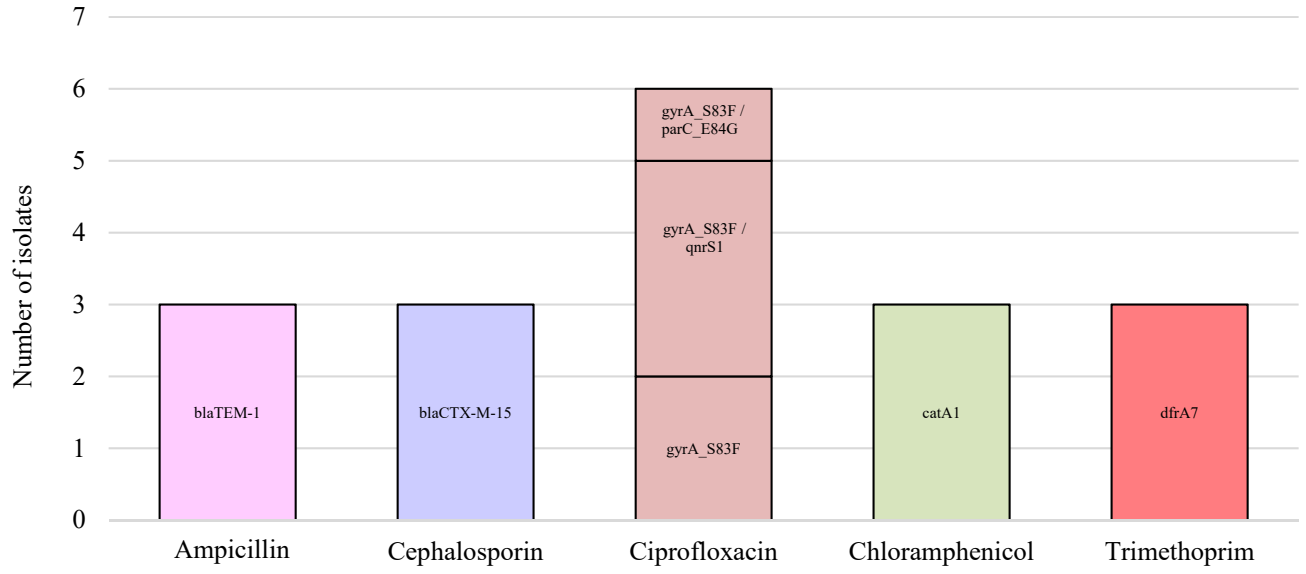

FIGURE 58. Identified resistance determinants in genotypic resistant *Salmonella* Typhi to selected antimicrobial agents in Norway 2020.

MULTI-DRUG RESISTANCE IN SALMONELLA

TABLE 28. Number of multi-drug resistant *Salmonella* isolates identified in Norway 2020, stratified according to serovar and resistance to antibiotic categories.

		Antibiotic[1]	Total	*Salmonella* Typhimurium	*Salmonella* Typhimurium (monophasic)	*Salmonella* Enteritidis	*Salmonella* Typhi	*Salmonella* Other
Multi-drug resistant		NS ≥ 3 categories	25	5	4	2	3	11
Antibiotic categories	Pencillins	AMP	23	5	4	2	3	9
	Extended-spectrum cephalosporins	CTX/CTZ	5	1	0	0	3	1
	Carbapenems	MEM	0	0	0	0	0	0
	Fluoroquinolones	CIP	21	3	3	2	3	10
	Tetracyclines	TET	20	5	4	2	0	9
	Phenicols	CAM	17	5	2	0	3	7

[1]NS:non-suscetiblility, AMP:Ampicillin, CTX:Cefotaxime, CTZ:Ceftazidime, MEM:Meropenem, CIP:Ciprofloxacin (inferred from pefloxacin), TET:Tetracycline, CAM:Chloramphenicol.

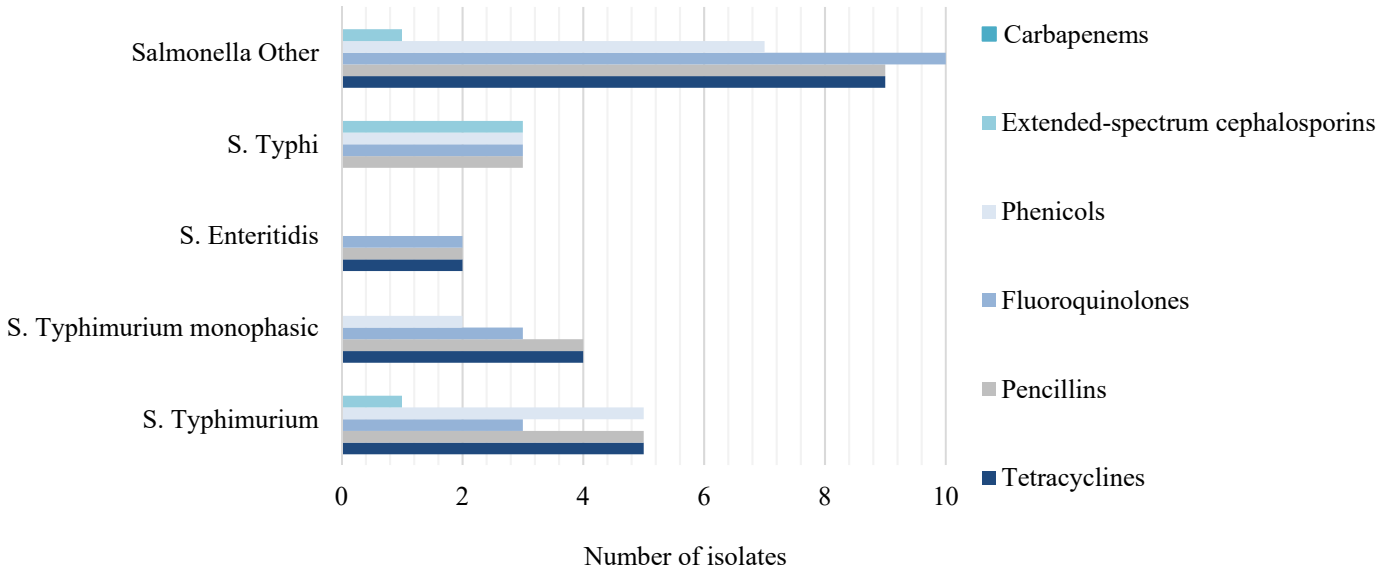

FIGURE 59. Multi-drug resistant *Salmonella* isolates identified in Norway 2020, stratified according to serovar and resistance to antibiotic categories.

GENOTYPIC RESISTANCE IN SALMONELLA

TABLE 29. Concordance between phenotypic and genotypic resistance to selected antibiotic categories in *Salmonella* isolates identified in Norway 2020.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	354	1	309	43	1	97.7	99.7
Extended-spectrum cephalosporins	354	1	348	4	1	80.0	99.7
Carbapenems	354	0	352	0	2	-	99.4
Fluoroquinolones	354	2	289	46	17	95.8	94.4
Tetracycline	354	1	289	34	30	97.1	90.6
Phenicols	354	0	333	16	5	100.0	98.5

[1]Wildtype (WT) and non-wildtype (NWT) according to ECOFF for *Salmonella enterica* determined by EUCAST (last accessed 02.07.21).

RESULTS AND COMMENTS

Following the reorganisation of the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the NIPH and paused antimicrobial susceptibility testing for 2018, the NRL resumed antimicrobial susceptibility testing for a selection of the received *Salmonella* isolates from 2019. Selection criteria were set to ensure inclusion of important *Salmonella* serovars and antibiotics for the monitoring of emergence and dissemination of antimicrobial resistance in Norway. Additionally, in 2020 the NRL screened all submitted *Salmonella* isolates for antimicrobial resistance determinants following whole genome sequencing to identify genotypic resistance.

For *S.* Typhimurium isolates, overall resistance rates were higher for travel-associated strains when compared to domestically acquired strains. A stable decreasing trend in resistance to tetracycline and chloramphenicol irrespective of place of acquisition was observed. A single isolate was identified as susceptible to extended-spectrum chephalosporins, genotypic resistance confirmed the presence of $bla_{\text{CTX-M-1}}$ gene.

For the monophasic variant of the *S.* Typhimurium, overall resistance rates are higher than for *S.* Typhimurium. We observed stable resistance rates over the last five years for the tested antibiotics, although resistance rates are high for both ampicillin and tetracycline, in both domestically acquired and travel-associated strains. Few isolates were identified as resistant to ciprofloxacin, genotypic resistance confirmed the presence of plasmid-mediated *qnrS1* gene in these isolates.

Antibiotic resistance in *S.* Enteritidis in 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 confirmed the presence of mutations in *gyrA* known to confer resistance to ciprofloxacin.

The overall prevalence of antibiotic resistance in *S.* Typhi is high, with an observed rising trend for resistance against extended-spectrum cephalosporins. Multi-drug resistance (MDR) was also a characteristic feature of a considerable proportion of the *S.* Typhi isolates (42.9%). The MDR phenotype in *S.* Typhi was largely attributed to resistance towards ampicillins, fluoroquinolones, extended-spectrum cephalosporins and phenicols. Screening for genotypic resistance confirmed the presence of the $bla_{\text{CTX-M-15}}$ gene in all MDR isolates.

In total, seven isolates were genotypically resistant to extended-spectrum cephalosporins; *S.* Typhi (n=3), *S.* Typhimurium (n=1), *S.* Schwarzengrund (n=1) *S.* Infantis (n=1) and *S.* Amsterdam (n=1). Of these, five (*S.* Typhi (n=3), *S.* Typimurium (n=1) and *S.* Amsterdam (n=1)) were susceptibility tested and four displayed phenotypic resistance. Six were classified as ESBL_{A}, encoding different $bla_{\text{CTX-M}}$ genes, and one was classified as ESBL_{M}, encoding $bla_{\text{DHA-1}}$.

The overall sensitivity of phenotypic versus genotypic resistance ranged between 80-100% for the selected antibiotics. Lowest sensitivity was recorded for extended-spectrum cephalosporins, where one isolate was categorised as phenotypic WT when encoding the $bla_{\text{DHA-1}}$ gene. Gene expression analysis was not performed to confirm this discrepancy. The overall specificity of phenotypic versus genotypic resistance ranged between 90.6-99.7% for the selected antibiotics. Lowest specificity was recorded for tetracycline, where no known resistance determinants were identified for thirty phenotypic NWT isolates. All but three of these isolates displayed low level of resistance (zone ≥12 mm), with a median inhibition zone of 15 mm (disc diffusion).

CAMPYLOBACTER SPP.

Campylobacter jejuni and Campylobacter coli from broilers and turkey

Caecal samples from a total of 113 broiler flocks were examined. These were flocks identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks in Norway in 2020, or flocks that for some reasons had not been tested in the *Campylobacter* surveillance programme. In total the *Campylobacter* surveillance programme examined 1,893 flocks from 490 producers (Pettersen *et al.* 2021). *C. jejuni* isolates were obtained from 92 of the 113 flocks, and 87 of these were susceptibility tested. Only four *Campylobacter coli* were identified. In addition, caecal samples from 117 turkey flocks were examined. *C. jejuni* isolates were obtained from five flocks (4.3%) and *C. coli* from only one flock (0.8%). The isolates were susceptibility tested, and the results fro *C. jejuni* are presented in Table 30, Figures 60-61 and in the text. The results for *C. coli* are not shown in table and figure due to few isolates.

TABLE 30. Antimicrobial resistance in *Campylobacter jejuni* from broiler (n=87) in 2020.

	Resistance		Distribution (%) of MIC values (mg/L)*												
Substance	(%)	[95% CI]	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Tetracycline	1.1	[0.0-6.2]				97.7	1.1						1.1		
Erythromycin	0.0	[0.0-4.2]					100								
Streptomycin	4.6	[1.3-11.4]						60.9	34.5			4.6			
Gentamicin**	0.0	[0.0-4.2]				5.7	74.7	19.5							
Ciprofloxacin	4.6	[1.3-11.4]		88.5	6.9					3.4	1.1				
Nalidixic acid	5.7	[1.9-12.9]						3.4	80.5	10.3		1.1		4.6	

*Bold vertical lines denote epidemiological cut-off values. CI=confidence interval. White fields denote range of dilutions tested for each antimicrobial agent. MIC values higher than the highest concentration tested are given as the lowest MIC value above the range. MIC values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. **Distribution for gentamicin skewed to the right compared to previous years, EFSA cut-off values have been used not to get unlikely high resistance to gentamicin.

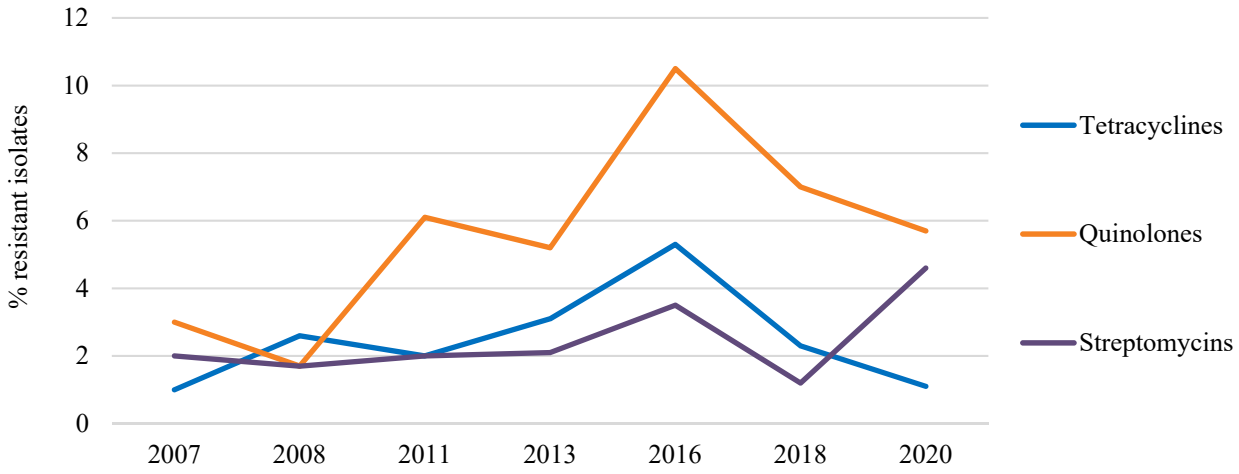

FIGURE 60. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers 2007-2020. The cut-off values used in NORM-VET 2020 were applied.

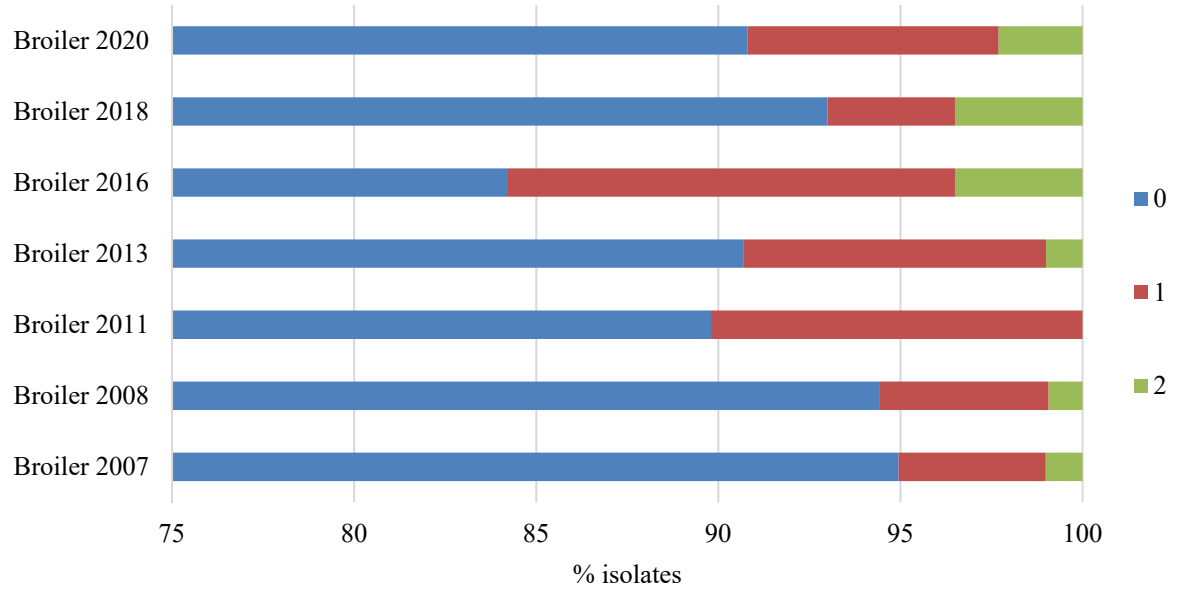

FIGURE 61. Antimicrobial resistance profiles for *Campylobacter jejuni* isolates from broilers in 2007-2020. Proportions of isolates susceptible to all (blue), or resistant to one (red) or two (green) antimicrobial classes are illustrated.

RESULTS AND COMMENTS

BROILER

The prevalence of antimicrobial resistance among *C. jejuni* isolates from Norwegian broilers is low. In total, 90.8% of the 87 isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to one antimicrobial class was detected in 6.9% of the isolates, while resistance to two antimicrobial classes was detected in 2.3% of the isolates. Only four isolates of *C. coli* were detected, and resistance to streptomycin was detected in one of these. Among the *C. jejuni* isolates, resistance to quinolones (i.e. ciprofloxacin and nalidixic acid) were the most frequently identified resistance determinants, closely followed by resistance to streptomycin.

The 2016 results indicated an increasing trend in prevalence of resistance since 2007. This was mainly due to an observed increase in resistance to quinolones. The 2018 and 2020 results, however, show that the fraction of resistant isolates has decreased after 2016 (Figure 60), and that this is due to a decrease in resistance both to quinolones and tetracyclines (Figure 60). An increase in resistance to quinolones, as well as tetracyclines and streptomycins, in *C. jejuni* from broilers is observed in several of the countries reporting to EFSA (EFSA and ECDC Summary Report 2018/2019). In a European perspective, the occurrence of resistance in *C. jejuni* (including quinolone resistance) from Norwegian broilers is quite low, although the occurrence varies between countries reporting to EFSA with the Nordic countries having the lowest resistance rates. Further monitoring is needed to follow the situation in Norway in the years to come.

TURKEY

In total, four of the five *C. jejuni* isolates were susceptible to all antimicrobial agents included in the test panel. One isolate displayed resistance to streptomycin. The single *C. coli* isolate was fully susceptible.

Campylobacter spp. from turkey caecal samples have only been susceptibility tested twice before, in 2007 and 2018. All these three years, there has been a limited number of isolates and comparisons are therefore not possible. The data show that there is a low prevalence of *Campylobacter* in turkey.

In a European perspective, the overall prevalences of resistance to ciprofloxacin, nalidixic acid and tetracycline in *C. jejuni* from turkey are very high, while resistance to erythromycin, streptomycin and gentamicin are low to very low according to the EFSA classification described in Appendix 6. Complete susceptibility was observed for only 17.2% of the isolates reported by European countries in 2018 (EFSA and ECDC Summary Report 2018). Compared to these European data, the occurrence of resistance in *C. jejuni* from turkey flocks in Norway is among the lowest.

Campylobacter spp. from human clinical cases

In 2020, 2,422 human campylobacteriosis cases were notified to MSIS. The majority of cases were infected in Norway (62%). 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 (Table 31).

Antimicrobial susceptibility testing was performed on a total of 327 *Campylobacter jejuni* and *Campylobacter coli* isolates against four different antibiotic groups: macrolides (erythromycin), aminoglycosides (gentamicin), fluoroquinolones (ciprofloxacin), and tetracycline. The results from the antimicrobial susceptibility testing is presented in Tables 14-17, Figures 12-14, and in the text.

TABLE 31. Number of antimicrobial susceptibility tested *Campylobacter* spp. isolates recoved from human clinical specimens in Norway 2020, by species and place of acquisition.

Campylobacter spp.	No. of isolates tested in 2020	Place of acquistion		
		Norway	Abroad	Unknown
Campylobacter jejuni	320	194	48	78
Campylobacter coli	7	1	6	0
Total	327	195	54	78

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER JEJUNI

TABLE 32. Percentage distributions of antimicrobial susceptibility categories of domestically acquired *Campylobacter jejuni* (n=194) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	95.9	-	4.1
Erythromycin	≤ 4	> 4	99.5	-	0.5
Gentamicin[1]	≤ 2	> 2	99.5	-	0.5
Ciprofloxacin	≤ 0.5	> 0.5	85.6	-	14.4

[1]Breakpoints according to national zone distributions.

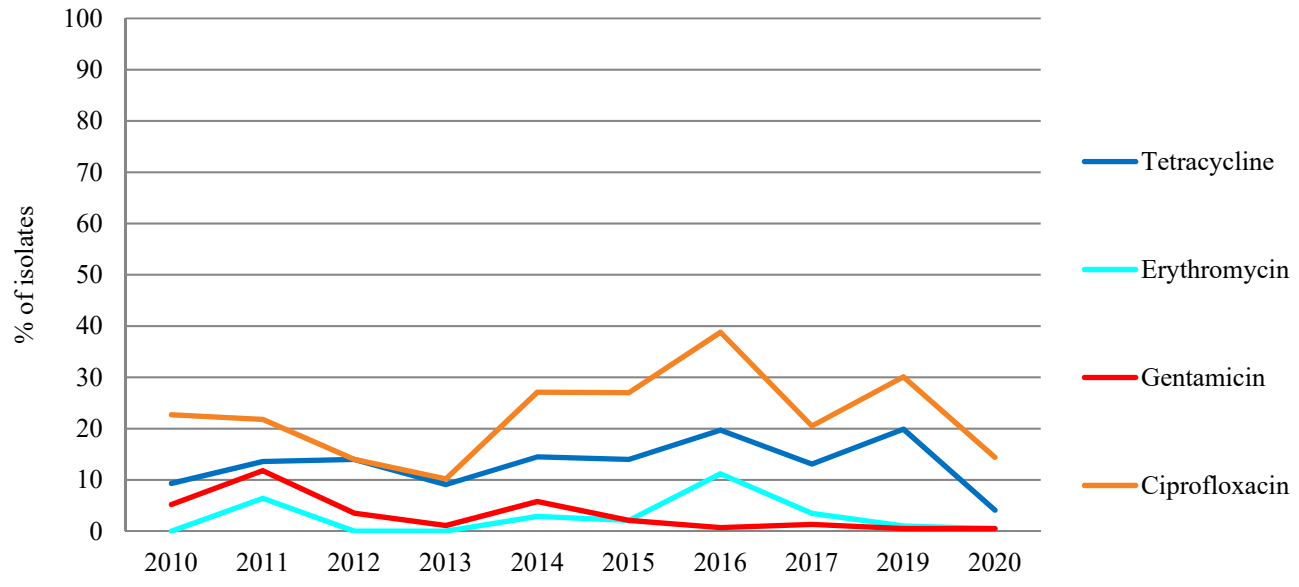

FIGURE 62. Percentage of domestically acquired *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway, trend 2010-2020.

TABLE 33. Percentage distributions of antimicrobial susceptibility categories of travel-associated *Campylobacter jejuni* (n=48) from human clinical specimens in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	39.6	-	60.4
Erythromycin	≤ 4	> 4	95.8	-	4.2
Gentamicin[1]	≤ 2	> 2	97.9	-	2.1
Ciprofloxacin	≤ 0.5	> 0.5	14.6	-	85.4

[1]Breakpoints according to national zone distributions.

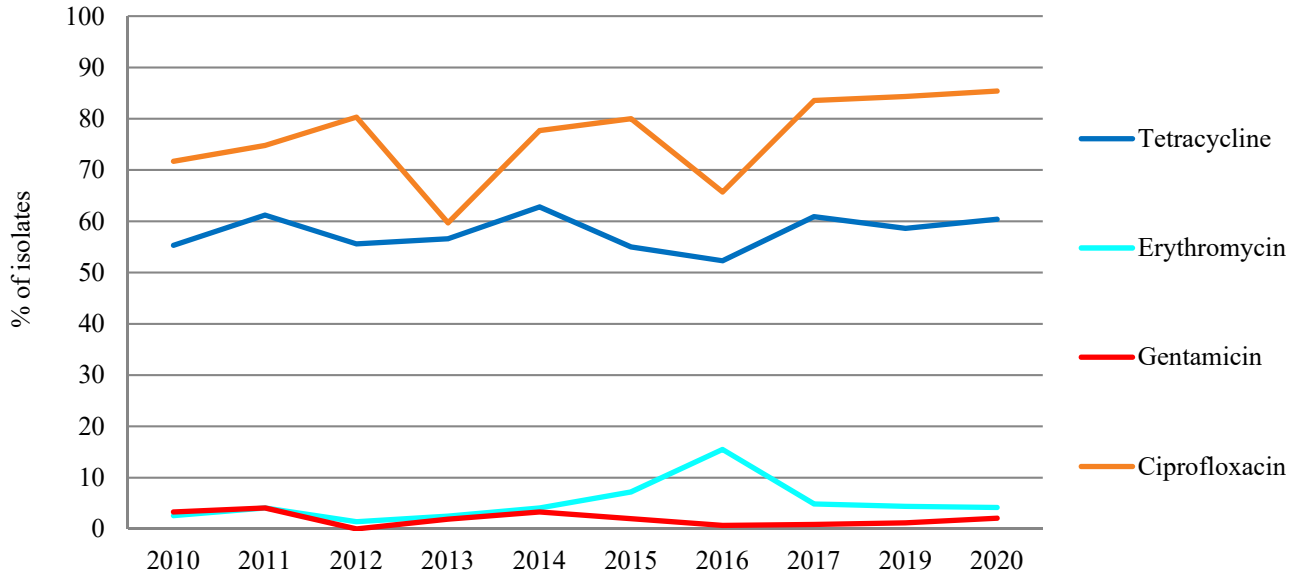

FIGURE 63. Percentage of travel-associated *Campylobacter jejuni* resistant to selected antimicrobial agents in Norway, trend 2010-2020.

ANTIMICROBIAL RESISTANCE IN CAMPYLOBACTER COLI

TABLE 34. Percentage distributions of antimicrobial susceptibility categories of *Campylobacter coli* (n=7) from human clinical specimens irrespective of place of acquisition in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Tetracycline	≤ 2	> 2	28.6	-	71.4
Erythromycin	≤ 8	> 8	85.7	-	14.3
Gentamicin[1]	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin	≤ 0.5	> 0.5	28.6	-	71.4

[1]Breakpoints according to national zone distributions.

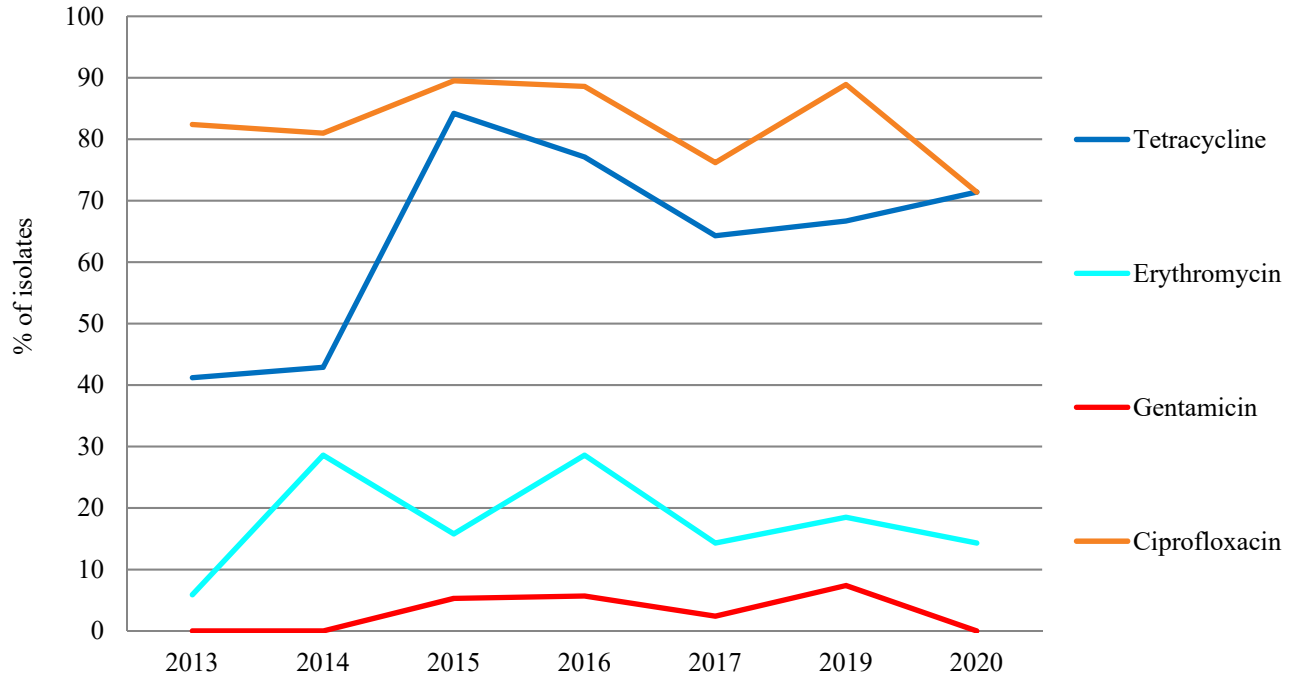

FIGURE 64. Percentage of *Campylobacter coli* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2013-2020.

RESULTS AND COMMENTS

Following the reorganisation of the NRL for Enteropathogenic Bacteria at the NIPH and paused antimicrobial susceptibility testing for 2018, the NRL resumed antimicrobial susceptibility testing for all *C. jejuni* and *C. coli* isolates received in 2019.

For the *C. jejuni* isolates, overall resistance rates against ciprofloxacin and tetracycline were higher for travel-associated strains when compared to domestically acquired strains. Resistance in *C. coli* follow similar patterns as *C. jejuni*, although *C. coli* were observed to be more resistant to erythromycin.

An MDR phenotype was observed in 21 isolates, 16 *C. jejuni* and five *C. coli*. All, but three isolates were associated to travel. MDR was recorded against all tested antibiotic classes in three isolates, and to fluoroquinolones, tetracycline and macrolides in 15 isolates.

YERSINIA ENTEROCOLITICA

Yersinia enterocolitica from human clinical specimens

In 2020, 83 human yersiniosis cases were notified to MSIS. The majority of cases were domestically acquired (61.4%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 82 unique isolates of pathogenic *Yersinia* from primary diagnostic laboratories in Norway. All isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on all isolates against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolone (ciprofloxacin), tetracycline and chloramphenicol. The results are presented in Tables 35-38 and Figures 65-66.

TABLE 35. Number of antimicrobial susceptibility tested *Yersinia enterocolitica* isolates recoved from human clinical specimens in Norway 2019, by serotype and place of acquisition.

Yersinia enterocolitica	No. of isolates tested in 2020	Place of acquistion		
		Norway	Abroad	Unknown
Y. enterocolitica O:3	71	42	3	26
Y. enterocolitica O:9	6	6	0	0
Y. entericolitica (other serotypes)	5	3	0	2
Total	82	51	3	28

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

TABLE 36. Percentage distributions of antimicrobial susceptibility categories of *Yersinia enterocolitica* O:3 and O:9 (n=77) from human clinical specimens irrespective of place of acquisition in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	1.3	-	98.7
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	96.1	1.3	2.6
Tetracycline[1]	≥ 17 mm	< 17 mm	98.7	-	1.3
Chloramphenicol	≤ 8	> 8	89.6	-	10.4

[1]Breakpoints according to national zone distributions.

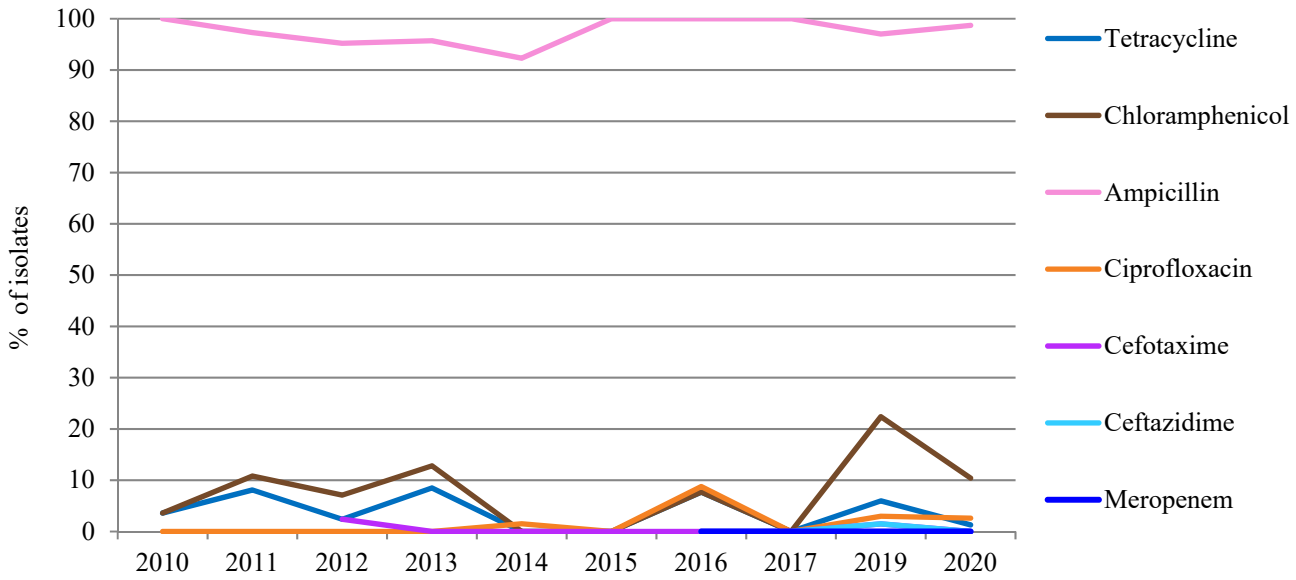

FIGURE 65. Percentage of *Yersinia enterocolitica* O:3 and O:9 resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2010-2020.

TABLE 37. Percentage distributions of genotypic resistant *Salmonella* Typhi (n=7) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 8	> 8	0.0	100.0
Cefotaxime[2]	≤ 1	> 2	100.0	0.0
Ceftazidime[2]	≤ 1	> 4		
Meropenem	≤ 2	> 8	100.0	0.0
Ciprofloxacin	≥ 0.25	< 0.5	100.0	0.0
Tetracycline[3]	≥ 17 mm	< 17 mm	100.0	0.0
Chloramphenicol	≤ 8	> 8	87.0	13.0
Gentamicin	≤ 2	> 2	100.0	0.0
Trimethoprim	≤ 4	> 4	100.0	0.0

[1]Wildtype (WT) and non-wildtype (NWT) categorised accorindg to EUCAST clinical breakpoints for *Yersinia enterocolitica* in absence of ECOFFs (v. 11.0). [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3]Breakpoints according to national zone distributions.

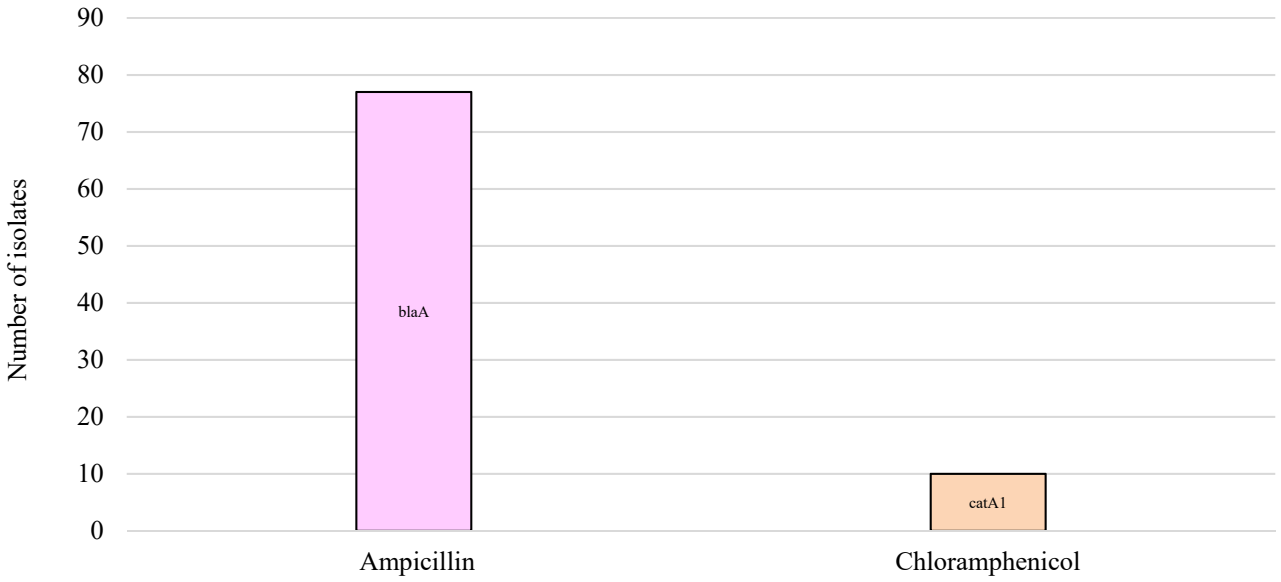

FIGURE 66. Identified resistance determinants in genotypically resistant *Yersinia enterocolitica* O:3 and O:9 to selected antimicrobial agents in Norway 2020.

GENOTYPIC RESISTANCE IN YERSINIA

TABLE 38. Concordance between phenotypic and genotypic resistance to selected antibiotic categories in *Yersinia enterocolitica* O:3 and O:9 isolates identified in Norway 2020.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	77	76	0	1	0	98.7	-
Extended-spectrum cephalosporins	77	0	77	0	0	-	100.0
Carbapenems	77	0	77	0	0	-	100.0
Fluoroquinolones	77	0	75	0	2	-	97.4
Tetracycline	77	0	76	0	1	-	98.7
Phenicols	77	2	67	8	0	80.0	100.0

[1] Wildtype (WT) and non-wildtype (NWT) categorised accorindg to EUCAST clinical breakpoints for *Yersinia enterocolitica* in absence of ECOFFs (v. 11.0).

RESULTS AND COMMENTS

Following the reorganisation of the NRL for Enteropathogenic Bacteria at the NIPH and paused antimicrobial susceptibility testing for 2018, the NRL resumed antimicrobial susceptibility testing for human pathogenic *Yersinia enterocolitica* in 2020. Additionally, in 2020 the NRL screened all submitted pathogenic *Yersinia enterocolitica* for antimicrobial resistance determinants following whole genome sequencing to identify genotypic resistance.

Antimicrobial resistance in *Yersinia enterocolitica* serotypes O:3 and O:9 has been combined and presented without differentiation of place of acquisition. All but one isolate of pathogenic *Y. enterocolitica* did not express intrinsic resistance to ampicillin, with little or no resistance to other antibiotic groups. However, all *Y. enterocolitica* isolates were genotypically positive for *blaA*. In addion, all isolates that were phenotypically resistant to chloramphenicol were genotypically positive for the *catA1* gene. In addition, two isolates that were phenotypically sensitive to chloramphenicol were genotypically positive for *catA1*.

Shigella spp. from human clinical specimens

In 2020, 38 human cases of shigellosis were notified to MSIS. The majority of cases were infected abroad (44.7%). The National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) received 38 unique *Shigella* spp. isolates from primary diagnostic laboratories in Norway. All isolates were screened for antimicrobial resistance determinants following whole genome sequencing. Antimicrobial susceptibility testing was performed on all *Shigella sonnei*, *Shigella flexneri* and S*higella boydii* isolates (Table 39). All 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 39-44 and Figures 67-70.

TABLE 39. Number of antimicrobial susceptibility tested *Shigella* spp. isolates recoved from human clinical specimens in Norway 2019, by species and place of acquisition.

Shigella spp.	No. of isolates tested in 2020	Place of acquistion		
		Norway	Abroad	Unknown
S. sonnei	17	8	5	4
S. flexneri	17	5	8	4
S. boydii	4	0	4	0
Total	38	13	17	8

ANTIMICROBIAL RESISTANCE IN SHIGELLA SONNEI

TABLE 40. Percentage distributions of antimicrobial susceptibility categories of *Shigella sonnei* (n=17) from human clinical specimens irrespective of place of acquisition in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	76.5	-	23.5
Cefotaxime	≤ 1	> 2	88.2	0.0	11.8
Ceftazidime	≤ 1	> 4	94.1	0.0	5.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	64.7	0.0	35.3
Tetracycline[1]	≥ 17 mm	< 17 mm	5.9	-	94.1
Chloramphenicol	≤ 8	> 8	100.0	-	0.0

[1]Breakpoints according to national zone distributions.

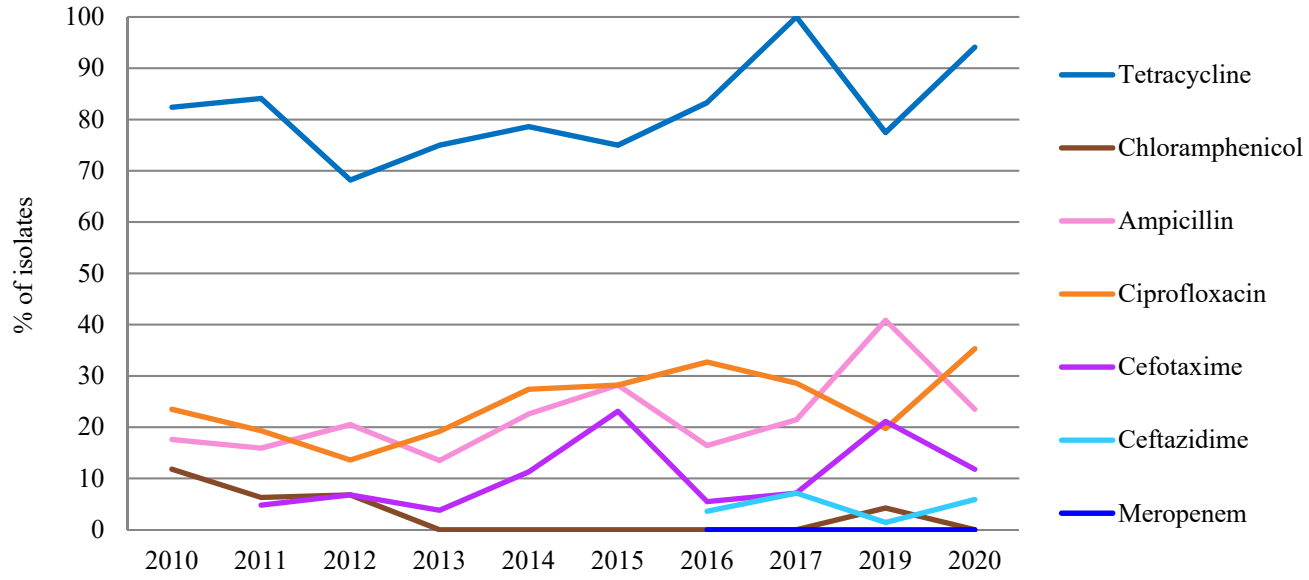

FIGURE 67. Percentage of *Shigella sonnei* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2010-2020.

TABLE 41. Percentage distributions of genotypic resistant *Shigella sonnei* (n=17) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 8	> 8	88.2	11.8
Cefotaxime[2]	≤ 1	> 2	88.2	11.8
Ceftazidime[2]	≤ 1	> 4		
Meropenem	≤ 2	> 8	100.0	0.0
Ciprofloxacin	≥ 0.25	< 0.5	47.1	52.9
Tetracycline[3]	≥ 17 mm	< 17 mm	17.6	82.4
Chloramphenicol	≤ 8	> 8	100.0	0.0
Gentamicin	≤ 2	> 2	94.1	5.9
Trimethoprim	≤ 4	> 4	0.0	100.0

[1] Wildtype (WT) and non-wildtype (NWT) categorised accorindg to EUCAST clinical breakpoints for *Shigella sonnei* in absence of ECOFFs (v. 11.0). [2] Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3]Breakpoints according to national zone distributions.

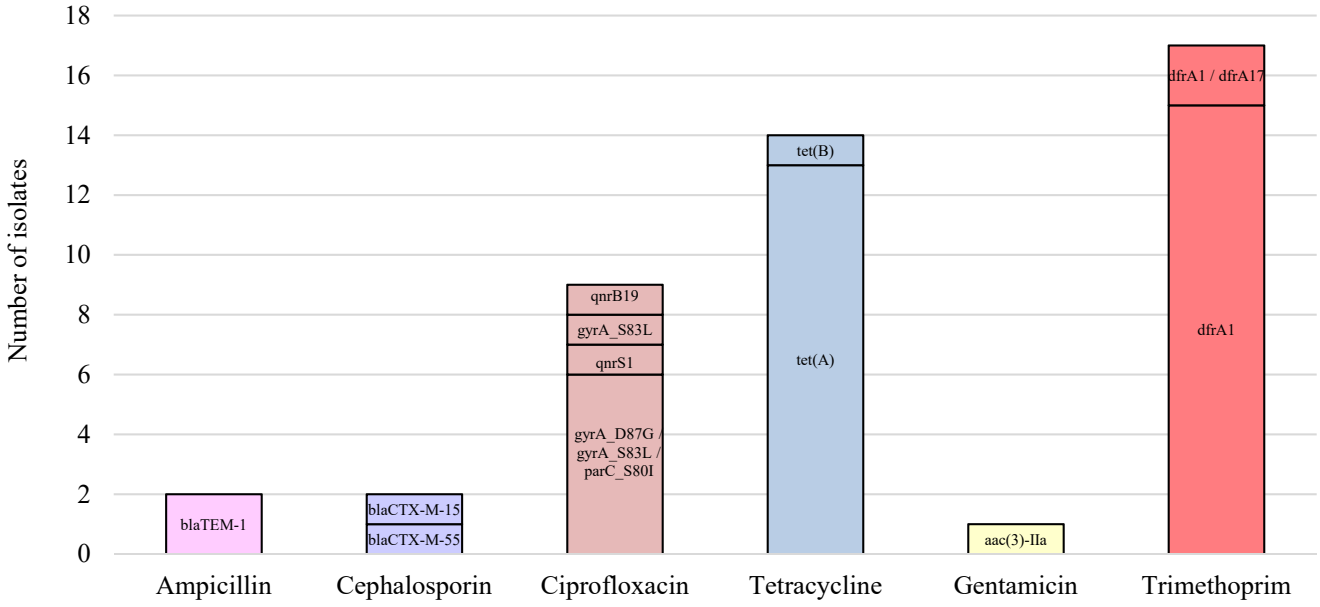

FIGURE 68. Identified resistance determinants in genotypic resistant *Shigella sonnei* to selected antimicrobial agents in Norway 2020.

ANTIMICROBIAL RESISTANCE IN SHIGELLA FLEXNERI

TABLE 42. Percentage distributions of antimicrobial susceptibility categories of *Shigella flexneri* (n=17) from human clinical specimens irrespective of place of acquisition in Norway 2020.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	47.1	-	52.9
Cefotaxime	≤ 1	> 2	82.4	0.0	17.6
Ceftazidime	≤ 1	> 4	94.1	0.0	5.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	70.6	0.0	29.4
Tetracycline[1]	≥ 17 mm	< 17 mm	11.8	-	88.2
Chloramphenicol	≤ 8	> 8	64.7	-	35.3

[1] Breakpoints according to national zone distributions.

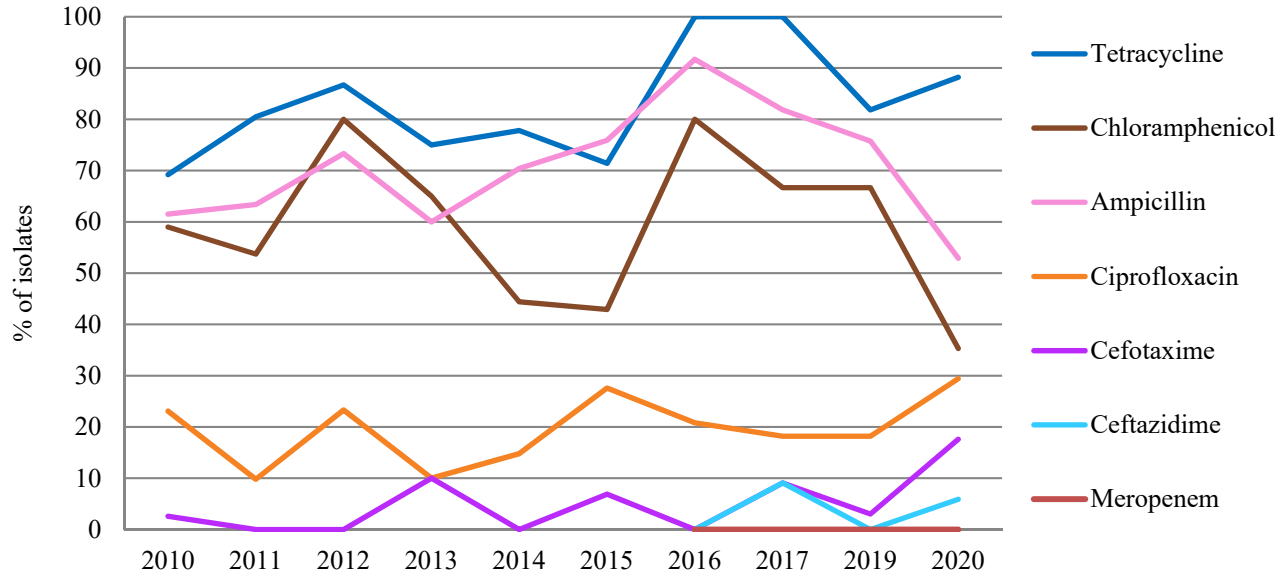

FIGURE 69. Percentage of *Shigella flexneri* resistant to selected antimicrobial agents irrespective of place of acquisition in Norway, trend 2010-2020.

TABLE 43. Percentage distributions of genotypic resistant *Shigella flexneri* (n=17) from human clinical specimens in Norway 2020.

	ECOFF[1] (mg/L)		Proportion of isolates (%)	
	WT	NWT	S	R
Ampicillin	≤ 8	> 8	35.3	64.7
Cefotaxime[2]	≤ 1	> 2	82.4	17.6
Ceftazidime[2]	≤ 1	> 4		
Meropenem	≤ 2	> 8	100.0	0.0
Ciprofloxacin	≥ 0.25	< 0.5	47.1	52.9
Tetracycline[3]	≥ 17 mm	< 17 mm	23.5	76.5
Chloramphenicol	≤ 8	> 8	47.1	52.9
Gentamicin	≤ 2	> 2	100.0	0.0
Trimethoprim	≤ 4	> 4	17.6	82.4

[1]Wildtype (WT) and non-wildtype (NWT) categorised accorindg to EUCAST clinical breakpoints for *Shigella sonnei* in absence of ECOFFs (v. 11.0). [2]Genotypic resistance to cefotaxime and ceftazidime is combined as genotypic resistance against extended-spectrum cephalosporins. [3]Breakpoints according to national zone distributions.

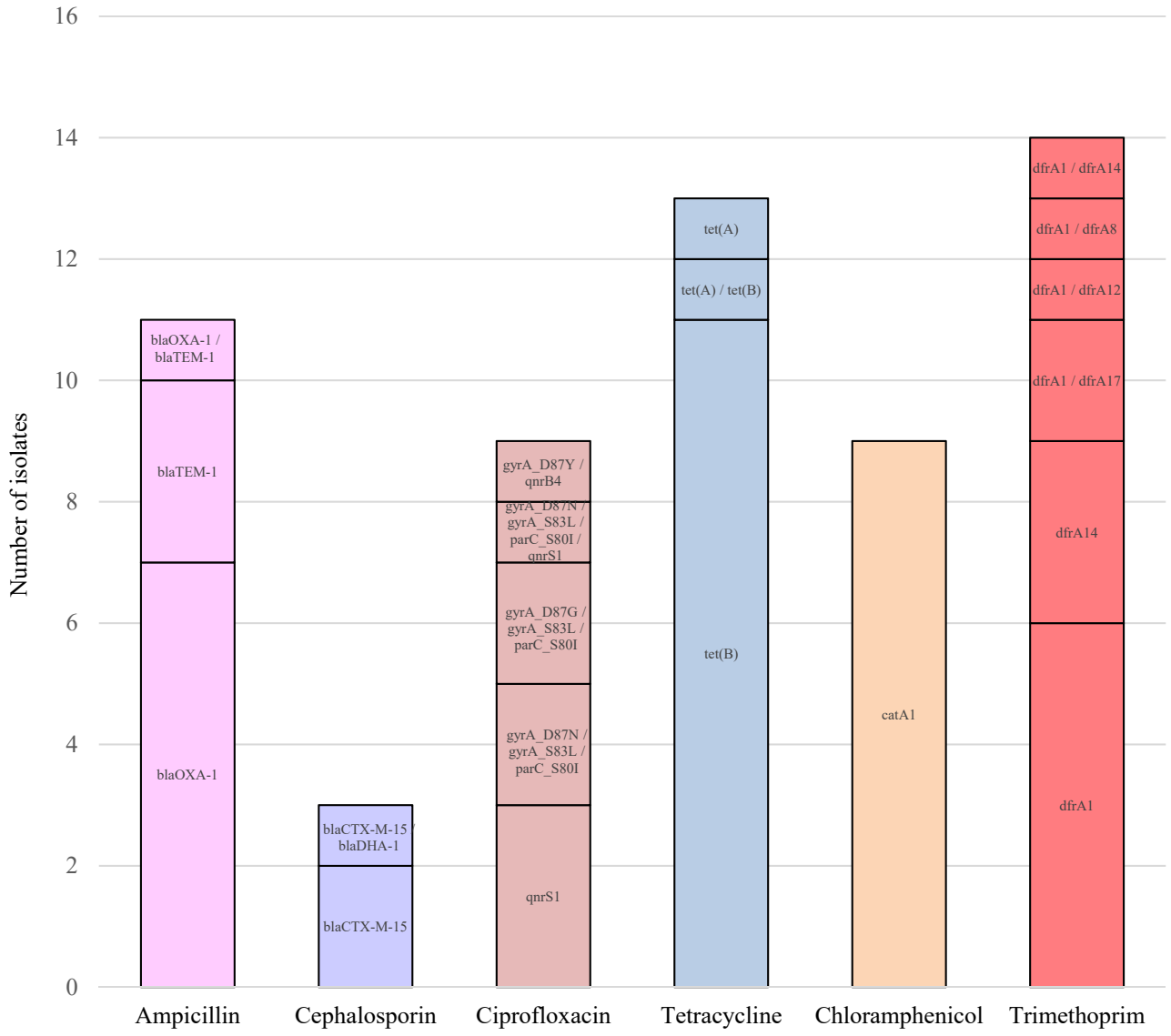

FIGURE 70. Identified resistance determinants in genotypic resistant *Shigella flexneri* to selected antimicrobial agents in Norway 2020.

GENOTYPIC RESISTANCE IN SHIGELLA

TABLE 44. Concordance between phenotypic and genotypic resistance to selected antibiotic categories in *Shigella spp*. (n=38) isolates identified in Norway 2020.

		Phenotype WT[1]		Phenotype NWT[1]			
Antibiotic categories	Tested	Genotype R	Genotype S	Genotype R	Genotype S	Sensitivity (%)	Specificity (%)
Penicillins	38	1	19	14	4	93.3	82.6
Extended-spectrum cephalosporins	38	0	33	5	0	100.0	100.0
Carbapenems	38	0	38	0	0	-	100.0
Fluoroquinolones	38	7	20	11	0	61.1	100.0
Tetracycline	38	1	4	30	3	96.8	57.1
Phenicols	38	0	26	11	1	100.0	96.3

[1]Wildtype (WT) and non-wildtype (NWT) categorised according to EUCAST clinical breakpoints for *Yersinia enterocolitica* in absence of ECOFFs (v. 11.0)

RESULTS AND COMMENTS

Following the reorganisation of the NRL for Enteropathogenic Bacteria at the NIPH and paused antimicrobial susceptibility testing for 2018, the NRL resumed antimicrobial susceptibility testing for all *Shigella* spp. in 2019. Additionally, in 2020 the NRL screened all submitted *Shigella* spp. isolates for antimicrobial resistance determinants following whole genome sequencing to identify genotypic resistance. Antimicrobial resistance profiles and trends are only presented for *S. sonnei* and *S. flexneri*.

A stable and high proportion (81.8%) of *S. sonnei* were observed resistant to tetracycline over the last decade. In addition, an increasing trend of resistance towards ciprofloxacin was recorded.

Also, in *S. flexneri* a stable and high proportion of isolates were observed resistant to tetracycline over the last decade (83.1%). In addition, a high proportion of *S. flexneri* isolates were resistant to chloramphenicol and ampicillin. An increasing trend of resistance to extended-spectrum cephalosporins was observed in 2020.

Three *S. flexneri* and two *S. sonnei* isolates displayed reduced susceptibility to extended-spectrum cephalosporins. All were classified as $ESBL_A$, encoding $bla_{CTX\text{-}M\text{-}15}$. In additional, one *S. flexneri* isolate also encoded $bla_{DHA\text{-}1}$.

The overall sensitivity of phenotypic versus genotypic resistance ranged between 61-100% for the selected antibiotics. Lowest sensitivity was recorded for fluoro-quinolones, where seven isolates categorised as phenotypic WT were identified as genotypically resistant. Six of these isolates encoded a *qnr* gene (*qnr*S1: n=4), whereas all isolates that were phenotypically resistant were identified with known mutations in the *gyrA* gene conferring quinolone resistance. When using pefloxacin to infer ciprofloxacin resistance, we could correctly identify ciprofloxacin resistance for six of these seven isolates. The overall specificity of phenotypic versus genotypic resistance ranged between 57-100% for the selected antibiotics. Lowest specificity was recorded for tetra-cycline, where no known resitance genes were identified in three isolates.

HUMAN CLINICAL ISOLATES

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Distribution of bacterial species in blood cultures

Surveillance of antimicrobial resistance is usually based on prevalences of reduced susceptibility and resistance to certain combinations of antimicrobials and bacterial species in clinical samples. The NORM surveillance programme generally follows this approach. However, there is a serious limitation to the model because a transition in the distribution from susceptible bacterial species to inherently more resistant ones will represent de facto emergence of resistance which is not easily detected. In order to complement the surveillance of individual species, NORM collects data on all positive blood cultures from the laboratory information systems of the participating institutions. A patient with a given microbial isolate was excluded from registration with a new isolate of the same species within a month from the first entry. This rule was applied irrespectively of changes in the organism´s susceptibility pattern. Isolates of a different species from the same patient were included in the surveillance. It proved difficult to systematically evaluate the clinical significance of species which are commonly part of the normal skin flora. In Table 45, 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 45. Number of blood culture isolates in 2020, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) 2016-2020. The table is based on data from the information systems of all laboratories in Norway.

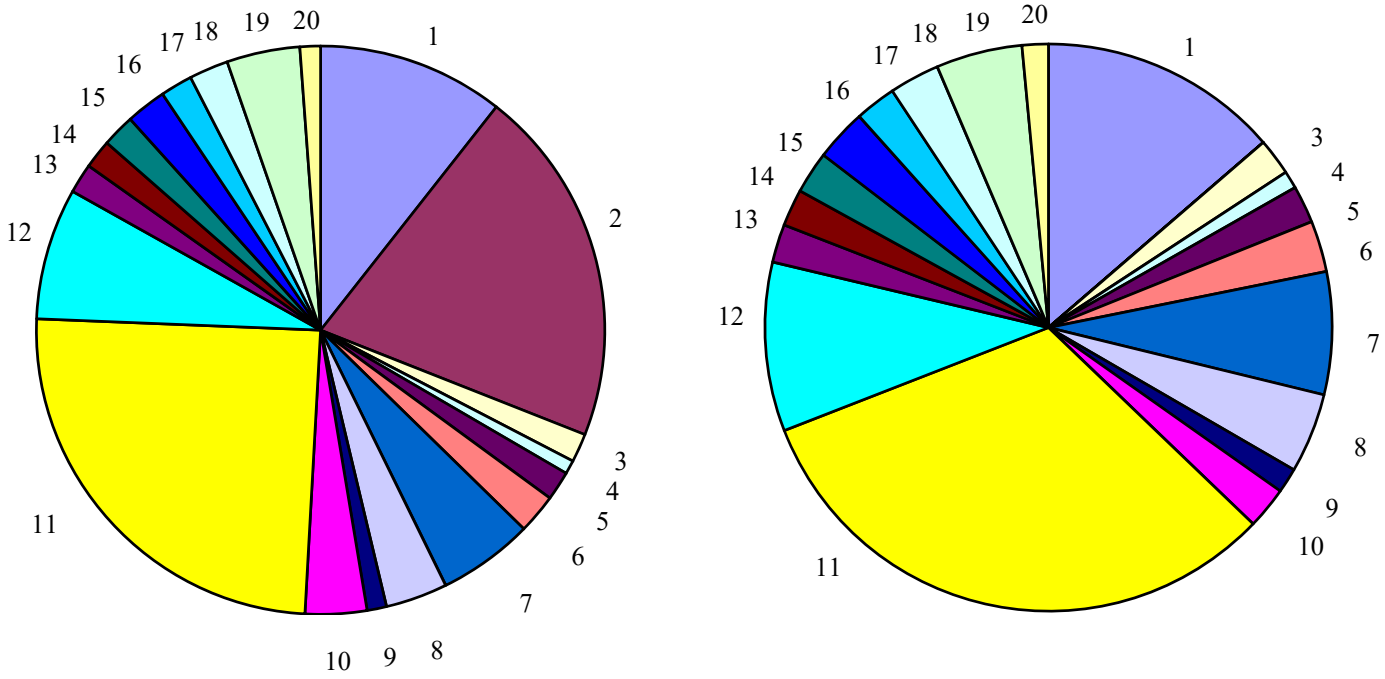
Species	No. of isolates 2020	% of all isolates					% of all isolates excluding skin flora				
		2016	2017	2018	2019	2020	2016	2017	2018	2019	2020
Staphylococcus aureus	1,955	10.5	10.1	11.1	11.0	10.6	13.6	13.1	14.2	13.9	13.7
Coagulase negative staphylococci	3,753	20.7	20.9	19.5	18.7	20.4	-	-	-	-	-
Streptococcus pneumoniae	300	3.4	2.7	3.3	3.1	1.6	4.4	3.6	4.2	4.0	2.1
Streptococcus pyogenes	144	1.1	1.2	1.2	1.0	0.8	1.4	1.5	1.5	1.2	1.0
Streptococcus agalactiae	305	1.6	1.4	1.5	1.8	1.7	2.1	1.8	1.9	2.2	2.1
Beta-haemolytic streptococci group C and G	417	1.3	1.5	2.0	2.0	2.3	1.7	2.0	2.5	2.5	2.9
Viridans- and non-haemolytic streptococci	999	5.0	5.5	5.1	5.0	5.4	6.5	7.2	6.4	6.4	7.0
Enterococcus faecalis	650	3.6	3.6	3.4	3.4	3.5	4.6	4.7	4.4	4.3	4.5
Enterococcus faecium	203	1.4	1.4	1.2	1.3	1.1	1.9	1.9	1.5	1.7	1.4
Other Gram-positive aerobic and facultative anaerobic bacteria	645	3.3	3.5	3.1	3.7	3.5	2.3	2.2	2.0	2.3	2.4
Escherichia coli	4,562	24.9	24.9	25.5	25.4	24.7	32.2	32.2	32.6	32.2	32.0
Klebsiella spp.	1,378	7.1	7.0	6.8	7.4	7.5	9.2	9.1	8.7	9.4	9.6
Enterobacter spp.	311	1.7	1.9	1.9	1.7	1.7	2.2	2.4	2.4	2.1	2.2
Proteus spp.	302	1.6	1.5	1.6	1.6	1.6	2.1	2.0	2.0	2.0	2.1
Other *Enterobacteriaceae*	423	1.8	2.3	3.4	2.2	2.3	2.3	3.0	4.3	2.7	3.0
Pseudomonas spp.	344	1.6	1.4	1.7	1.8	1.9	2.0	1.8	2.1	2.3	2.4
Other Gram-negative aerobic and facultative anaerobic bacteria	336	2.4	2.0	1.0	2.1	1.8	3.0	2.6	1.3	2.6	2.3
Bacteroides spp.	410	1.9	2.3	1.9	1.9	2.2	2.4	2.9	2.4	2.4	2.9
Other anaerobic bacteria	768	3.8	3.7	3.7	3.8	4.2	4.4	4.4	4.2	4.4	4.9
Yeasts	214	1.3	1.2	1.1	1.1	1.2	1.7	1.6	1.4	1.4	1.5
Total	**18,419**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 45 and Figure 71, aerobic and facultative Gram-positive and Gram-negative bacteria represented 50.9% and 41.5% 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 20.4%. This is an increase from 18.7% in 2019, 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 37.1% aerobic Gram-positives and 53.6% 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% in 2020 may be linked to the on-going coronavirus pandemic with reduced incidence of all respiratory tract pathogens. The reduction corresponds to a drop from 604 cases in 2019 to 300 cases in 2020. The proportions of other aerobic Gram-positives have remained stable over many years.

E. coli (32.0%) and other *Enterobacteriaceae* (16.9%) accounted for the vast majority of aerobic Gram-negative isolates, but the proportions have remained relatively unchanged over the years. *Pseudomonas* spp. (2.4%) has been fairly stable after a peak in 2005 (2.8%), all figures excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 6.4% (7.8% excluding skin flora). Yeasts accounted for 1.2% (1.5% excluding skin flora), which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (2.2%/2.9%) and among yeasts *Candida albicans* (0.7%/1.0%). However, a multitude of other species were also represented.



1. *Staphylococcus aureus*
2. Coagulase negative staphylococci
3. *Streptococcus pneumoniae*
4. *Streptococcus pyogenes*
5. *Streptococcus agalactiae*
6. Betahaemolytic streptococci group C and G
7. Non-haemolytic and viridans streptococci
8. *Enterococcus faecalis*
9. *Enterococcus faecium*
10. Other Gram-positive bacteria
11. *Escherichia coli*
12. *Klebsiella* spp.
13. *Enterobacter* spp.
14. *Proteus* spp.
15. Other *Enterobacteriaceae*
16. *Pseudomonas* spp.
17. Other Gram-negative bacteria
18. *Bacteroides* spp.
19. Other anaerobic bacteria
20. Yeasts

FIGURE 71. Distribution of all blood culture isolates (left, n=18,419) and blood culture isolates excluding common skin contaminants (right, n=14,298) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp. Data for 2020 were retrieved from the information systems of all Norwegian laboratories.

Escherichia coli in blood cultures

TABLE 46. *Escherichia coli* blood culture isolates in 2020 (n=2,087). 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	58.4	-	41.6
Amoxicillin-clavulanic acid*	≤ 8	> 8	74.9	-	25.1
Piperacillin-tazobactam	≤ 8	> 8	94.6	-	5.4
Cefuroxime	≤ 0.001	> 8	0.0	90.7	9.3
Cefotaxime	≤ 1	> 2	93.1	0.2	6.7
Ceftazidime	≤ 1	> 4	93.0	1.2	5.8
Cefepime	≤ 1	> 4	92.9	1.4	5.7
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	93.3	-	6.7
Tobramycin	≤ 2	> 2	92.3	-	7.7
Amikacin	≤ 8	> 8	96.7	-	3.3
Ciprofloxacin	≤ 0.25	> 0.5	85.7	3.1	11.2
Tigecycline	≤ 0.5	> 0.5	99.6	-	0.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	76.7	0.2	23.1
ESBL	Negative	Positive	93.5	-	6.5

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.

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 (93.3%), ceftazidime (94.2%), gentamicin (93.3%), cefepime (94.3%), piperacillin-tazobactam (94.6%), tigecycline (99.6%) and meropenem (100.0%) (Table 46). There were no significant changes in resistance rates from 2019-2020.

The prevalence of resistance to gentamicin increased slightly to 6.7% in 2020 compared to 5.4% in 2018 and 5.9% in 2019 (Figure 72). The data were interpreted according to the breakpoints for systemic urinary tract infections, although NordicAST/EUCAST no longer consider gentamicin sufficient for monotherapy in infections originating from other sources. A high proportion of gentamicin resistant isolates (55/139, 39.6%) 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 7.6%, North 6.5%, West 5.5% and Middle 5.0%). Tobramycin and amikacin were surveyed to broaden the perspective on aminoglycoside resistance. Both substances displayed widespread susceptibility of 92.3% and 96.7%, respectively.

The prevalence of resistance to ciprofloxacin was 11.2% in 2020 compared to 11.3% in 2019. 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 73. A similar association between quinolone use and resistance in systemic *E. coli* isolates is also reported internationally. The resistance rates for ampicillin (43.3% in 2019, 41.6% in 2020) and trimethoprim-sulfamethoxazole (24.6% in 2019, 23.1% in 2020) are stable.

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 136 isolates (6.5%) were reported as ESBL positive, which is a slight reduction from 2019 (7.1%) (Figure 75). 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; South-East (7.3%), North (6.9%), West (6.4%) and Middle (3.3%). Most of the ESBL isolates were phenotypically resistant to cefuroxime (n=136), cefotaxime (n=134), cefepime (n=113) and ceftazidime (n=113), whereas many were susceptible to piperacillin-tazobactam (n=116). Forty-nine isolates were susceptible to amoxicillin-clavulanic acid using breakpoints for non-urinary tract infections, whereas 87 were resistant. The ESBL isolates displayed high rates of co-resistance to ciprofloxacin (n=80), trimethoprim-sulfamethoxazole (n=90) and/or gentamicin (n=55), but many ESBL+/gentamicin R isolates remained susceptible to amikacin (45/55). All isolates were fully susceptible to meropenem according to clinical breakpoints, but 21 isolates (1.0%) had zone diameters less than the screening breakpoint of 28 mm and required further examination. A single OXA-48 carbapenemase-producing isolate was detected.

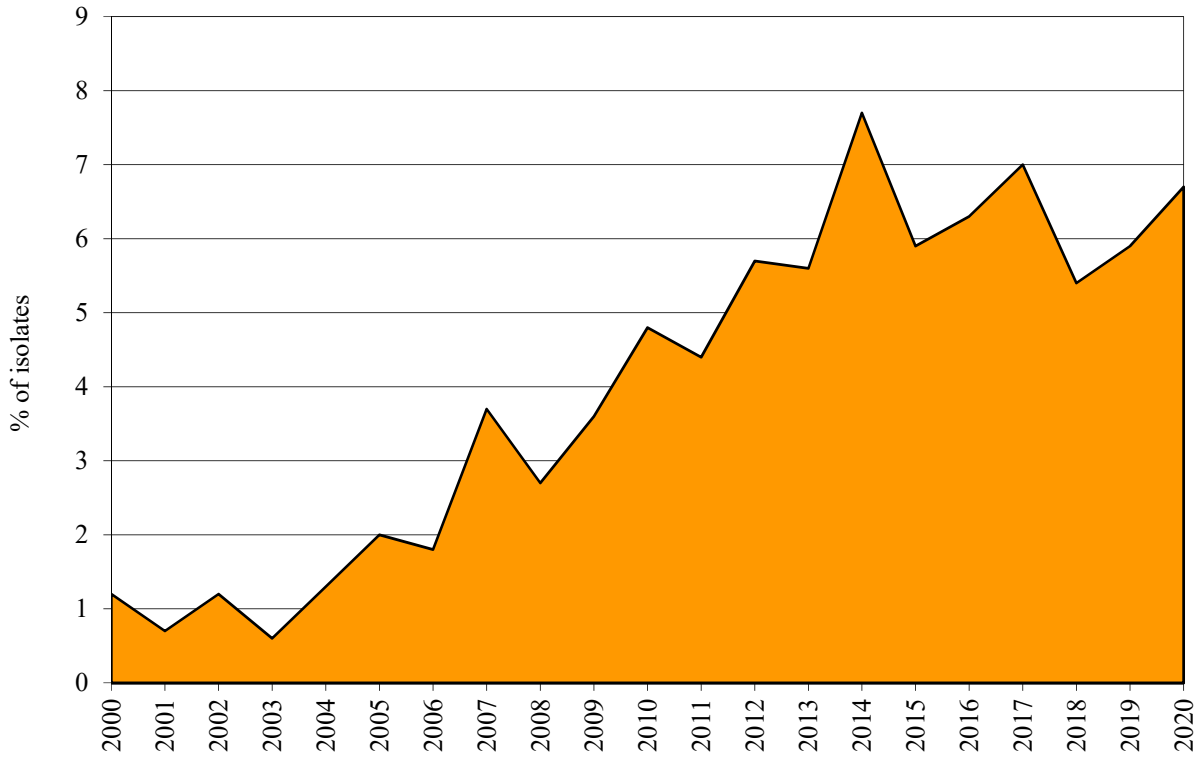


FIGURE 72. Prevalence of resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2020.

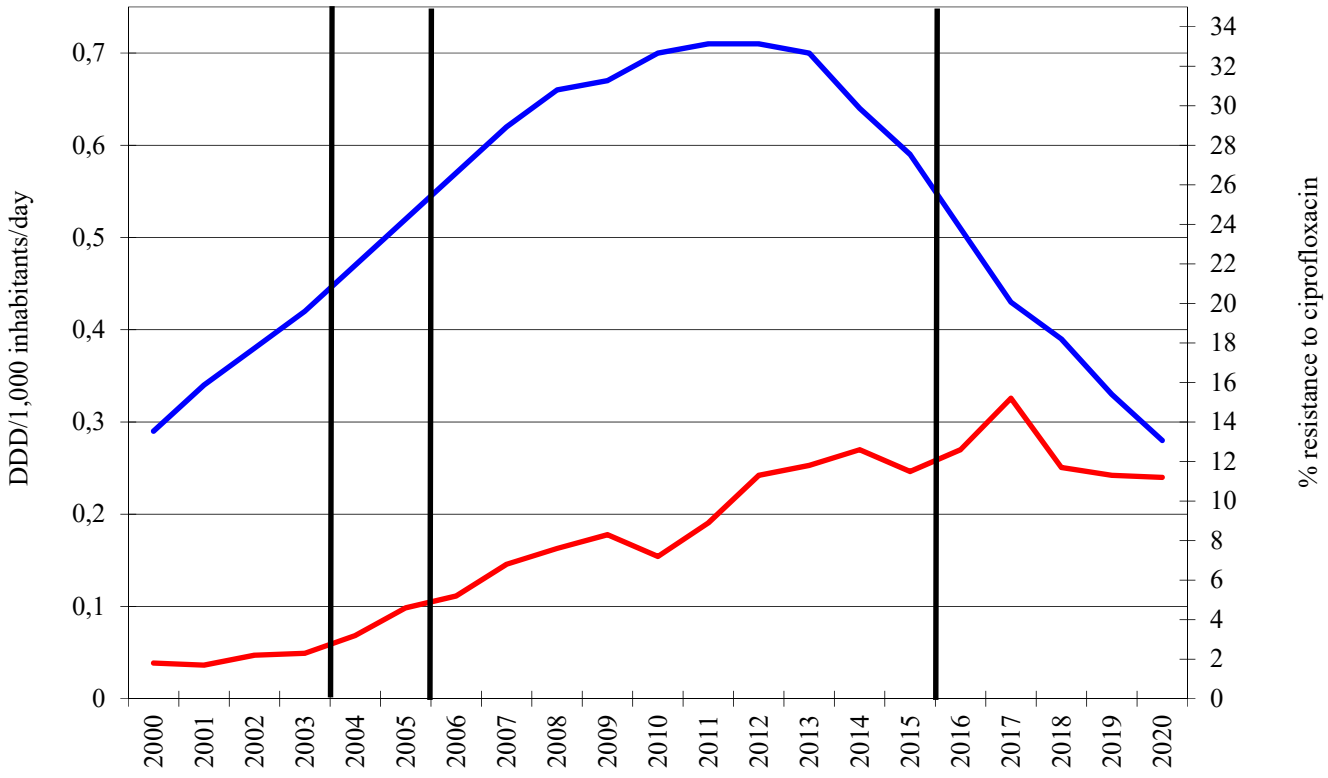


FIGURE 73. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates (red) as defined by MIC > 4 mg/L (2000-2003), MIC > 2 mg/L (2004-2005), MIC > 1 mg/L (2006-2015), and MIC > 0.5 mg/L (2016-2020). The breakpoints cannot be calibrated over the entire time period due to changes in susceptibility test methodology.

Escherichia coli in urine

TABLE 47. *Escherichia coli* urinary tract isolates in 2020 (n=2,520). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	62.2	-	37.8
Mecillinam	≤ 8	> 8	94.7	-	5.3
Amoxicillin-clavulanic acid*	≤ 32	> 32	92.0	-	8.0
Cefotaxime	≤ 1	> 2	96.1	0.4	3.5
Ceftazidime	≤ 1	> 4	96.4	1.0	2.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	96.0	-	4.0
Tobramycin	≤ 2	> 2	96.3	-	3.7
Amikamicin	≤ 8	> 8	98.5	-	1.5
Ciprofloxacin	≤ 0.25	> 0.5	89.1	2.8	8.1
Nitrofurantoin	≤ 64	> 64	99.0	-	1.0
Fosfomycin	≤ 8	> 8	96.4	-	3.6
Trimethoprim	≤ 4	> 4	75.5	-	24.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	78.1	0.6	21.3
ESBL	Negative	Positive	96.6	-	3.4

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 2020 is shown in Table 47 and the rates of resistance for 2000-2020 are shown in Figure 74. 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 is slowly increasing for most antibiotics. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to 38%. Resistance to trimethoprim and trimethoprim-sulfamethoxazole has remained stable around 20-25%. The prevalence of resistance to mecillinam was 5.3% in 2020 compared to 4.4% in 2018 and 3.9% in 2019. 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 73), the prevalence of resistance has remained stable around 8-9% over the last five years. In 2020, 8.1% of the isolates were resistant to ciprofloxacin in addition to 2.8% 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 11.2% resistance and 3.1% 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 wildtype normal flora.

The prevalence of resistance to amoxicillin-clavulanic acid was 8.0% in 2020 compared to 4.4% in 2018 and 6.4% in 2019. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (99.0%) remained susceptible to nitrofurantoin. Fosfomycin has been included in NORM since 2017. The vast majority of isolates were categorised as susceptible (96.4%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Eighty-five isolates (3.4%) were reported as ESBL producers. This is at the same level as 3.7% in 2018 and 3.0% in 2019. As seen in Figure 75, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (6.5%). The ESBL positive strains were isolated at 19 different laboratories in all parts of the country. Fifty-eight isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=12) or patients in nursing homes (n=6), outpatient clinics (n=7) or unspecified locations (n=2). The ESBL isolates were all resistant to ampicillin, and the majority were also resistant to cefotaxime (82/85) and ceftazidime (57/85). Almost all isolates (80/85) were registered as *in vitro* susceptible to mecillinam. Recent data suggest that this may be a viable treatment option provided a dosage of 400 mg x 3. Many of the ESBL isolates were resistant to ciprofloxacin (47/85), trimethoprim (51/85) and trimethoprim-sulfamethoxazole (44/85), but remained susceptible to nitrofurantoin (82/85), fosfomycin (74/85) and gentamicin (67/85). All ESBL isolates were clinically susceptible to carbapenems. Twelve isolates had zone diameters below the meropenem screening breakpoint of 28 mm, but most of these were susceptible to piperacillin-tazobactam. A single isolate containing an OXA-48 like carbapenemase was detected.

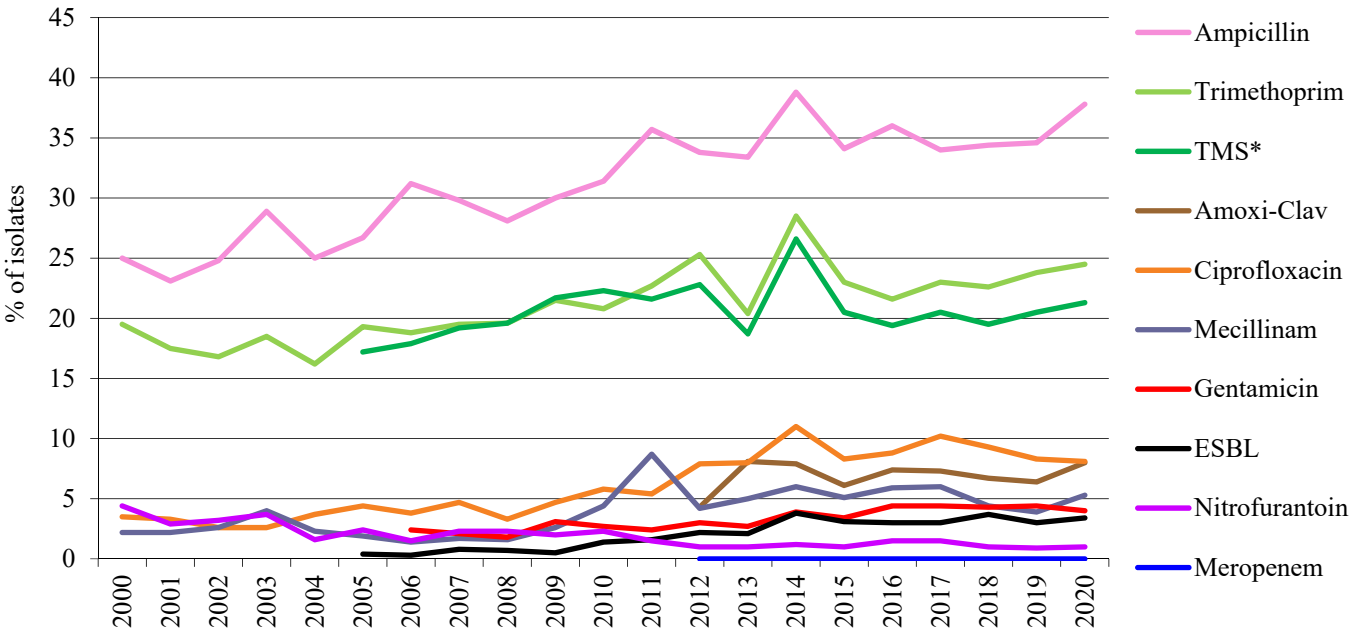


FIGURE 74. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2020. Isolates are categorised according to the breakpoints at the time of analysis for each year.
*TMS=Trimethoprim-sulfamethoxazole.

TABLE 48. Antimicrobial resistance (%) in *Escherichia coli* urinary tract isolates in 2020, by location of sampling (n=2,479).

	General practitioner (n=1,804)	Outpatient clinic (n=119)	Nursing home (n=151)	Hospital ward (n=405)
Ampicillin	37.1	38.4	41.2	39.0
Mecillinam	4.3	6.6	10.1	7.9
Amoxicillin-clavulanic acid*	7.8	7.3	9.2	8.9
Cefotaxime	3.3	5.3	5.0	3.2
Ceftazidime	2.2	5.3	5.0	2.5
Meropenem	0.0	0.0	0.0	0.0
Gentamicin	4.0	3.3	3.4	4.2
Tobramycin	3.7	3.3	3.4	4.0
Amikamicin	1.6	0.0	3.4	1.2
Ciprofloxacin	8.0	6.6	8.4	8.9
Nitrofurantoin	0.7	2.6	0.8	2.0
Fosfomycin	2.9	2.6	10.1	4.7
Trimethoprim	24.1	26.5	27.7	24.4
Trimethoprim-sulfamethoxazole**	20.7	23.2	24.4	21.5
ESBL	3.2	4.6	5.0	3.0

*Breakpoints for uncomplicated urinary tract infections. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

Table 48 presents the resistance rates of urinary tract *E. coli* by location of sampling. Overall, there is no clear pattern with higher or lower occurrence of resistance in certain locations. Mecillinam resistance is apparently more common in nursing homes (10.1%) than in hospital (7.9%) and general practitioner (4.3%) patients, and fosfomycin resistance is surprisingly high among urinary tract isolates from nursing homes (10.1%). There in no obvious reason for this difference in terms of antibiotic usage pattern, and it may be due to selective sampling of refractory or recurrent infections. For antibiotics commonly used for uncomplicated (trimethoprim, trimethoprim-sulfamethoxazole and nitrofurantoin) or complicated (ciprofloxacin) urinary tract infections there are only minor differences.

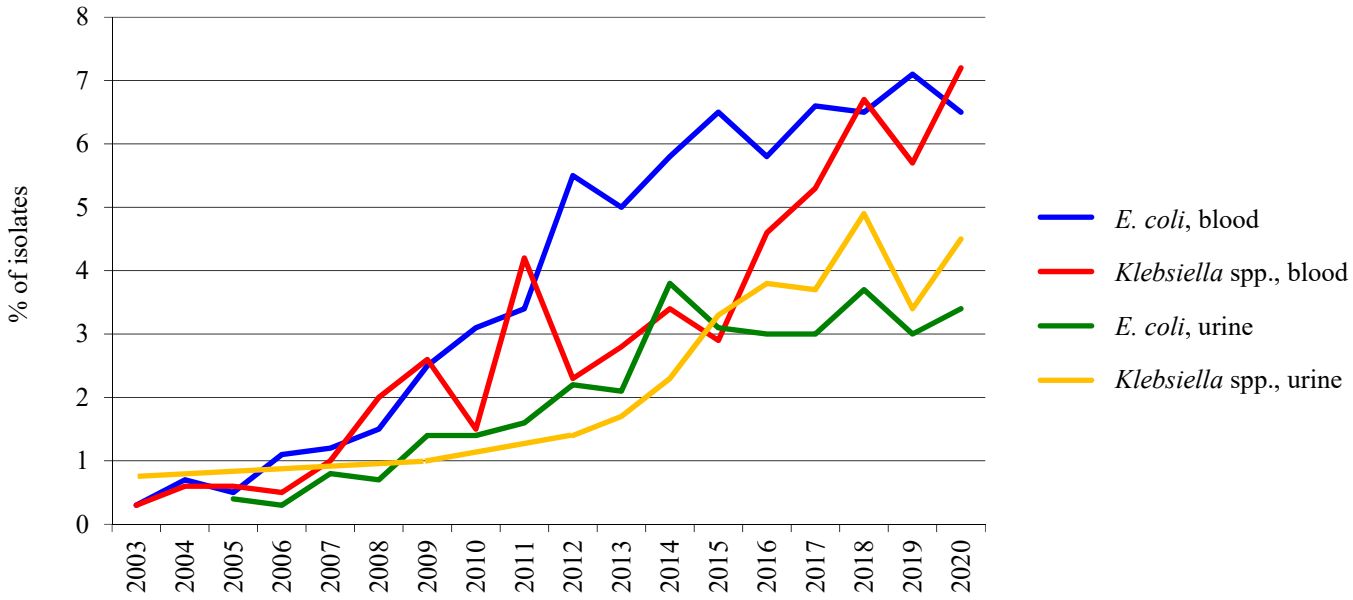


FIGURE 75. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2020.

A nationwide, longitudinal, microbial population genomic study of *Escherichia coli* causing bloodstream infections in Norway in 2002-17

Surveillance of antimicrobial resistance has multiple purposes including identifying the extent of the problem, monitoring changes over time, guidance of empirical therapy, identification of emerging resistance phenotypes/genotypes and devising intervention or prevention strategies. Surveillance systems also provide a valuable resource for in-depth research on specific topics. However, there are several limitations for the use of surveillance data in research such as the use of different protocols/methods for susceptibility testing, data only from sentinel sites and lack of storage and access to isolates. Moreover, current surveillance systems frequently do not include molecular typing methodologies like whole genome sequencing which offer the possibility to investigate emergence of "high-risk" clones, specific resistance/virulence determinants and population structure changes over time.

Escherichia coli associated with bloodstream infections is a subset of extraintestinal pathogenic *E. coli* (ExPEC) which constitutes a diverse set of clones (1). Previous studies have shown that a small number of globally disseminated ExPEC clones are responsible for most infections and that specific clones like CC131 are associated with multi-drug resistance (1,2). In Norway, bloodstream infections caused by *E. coli* have been increasing as well as the prevalence of ESBL-producing and fluoroquinolone non-susceptible *E. coli* (3).

To investigate the clonal diversity underpinning the trends in multi-drug resistant *E. coli*, we took advantage of the strengths of the NORM surveillance system which includes nationwide coverage, standardised protocols and storage of isolates by participating laboratories. In collaboration with 15 out of 22 laboratories, 3,397 *E. coli* bloodstream isolates from 2002-17 were collected and 3,254 were successfully sequenced, representing the largest genomic survey of *E. coli* to date. This allowed us to investigate the clonal diversity, emergence of clones and their contribution to increasing rates of bloodstream infections and antimicrobial resistance in Norway and compare it with other countries.

The results from the study show that *E. coli* causing bloodstream infection in Norway are relatively diverse (Figure 76), represented by the identification of 136 clonal groups, but that four clones, CC73, CC95, CC69 and CC131 are most common representing 54.1% of the population. All four clones are well-known globally disseminated clones with various degrees of association to antimicrobial resistance (1). Using 2002 as a baseline, CC131 showed the largest proportional sustained increase in the collection. CC131 is a known high-risk clone associated with ESBL production and fluoroquinolone resistance (4). Concurrently, we observed that CC131 was the single largest contributor to ESBL production and fluoroquinolone non-susceptibility in the collection. Fifty-nine percent of $bla_{\text{CTX-M}}$ positive isolates and 39.2% of ciprofloxacin non-susceptible isolates belonged to CC131. CC131 can be delineated into multiple clades (e.g. A, B, C1 and C2) with different associations with antimicrobial resistance (4). As expected, the multi-drug resistant C2 clade was most strongly associated with ESBL production with 72.5% of the isolates being $bla_{\text{CTX-M}}$ positive compared to 40% of clade C1 and 14.7% of clade A isolates. A similar scenario was observed for fluoroquinolone non-susceptibility. This shows that the globally disseminated "high-risk" CC131 clone is the main contributor to the increase in multi-drug resistant *E. coli* bloodstream infections in Norway.

To investigate in more detail the expansion of CC131 we estimated the effective population sizes and rates of expansion of the CC131 clades. Interestingly, we observed a higher effective population size and growth rate of the predominantly susceptible clade A compared to the more resistant clades C1 and C2. We also found that clade A was established in 2002 while clade C2 emerged in 2007. This is in contrast to data from a UK longitudinal study (2) where clade C2 dominated. Moreover, the increase in CC131 in Norway was a gradual process compared to a more rapid expansion in the UK. The data also show that contributions of the different clades to resistance in the countries are different. Finally, the modelling indicated that expansion of the susceptible clade B happened already a decade earlier compared to the other clades. Overall, this indicates that acquisition of resistance is not a prerequisite for clonal success but that other factors are also contributing.

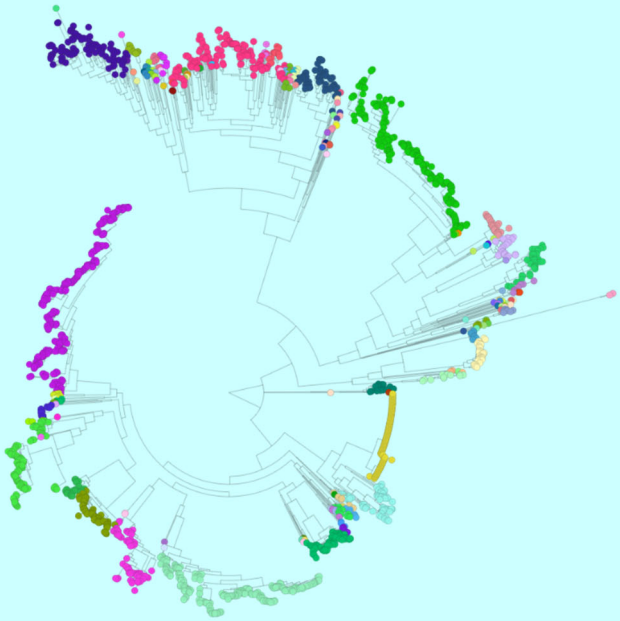


FIGURE 76. Species-wide phylogeny of the collection coloured according to clonal groups. Interactive view is available at: https://microreact.org/project/EcoliBSINorway/14b916b0.

The study highlights the possibilities of surveillance structures for genomic surveillance studies to elucidate the ecology underlying the expansion of multi-drug resistance and that the epidemiology of *E. coli* is variable between countries. These observations have implications for our efforts to implement strategies and interventions to control the spread of high-risk multi-drug resistant clones.

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Klebsiella spp. in blood cultures

TABLE 49. *Klebsiella* spp. blood culture isolates in 2020 (n=967). 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	79.5	-	20.5
Piperacillin-tazobactam	≤ 8	> 8	88.8	-	11.2
Cefuroxime	≤ 0.001	> 8	0.0	85.9	14.1
Cefotaxime	≤ 1	> 2	91.5	0.7	7.8
Ceftazidime	≤ 1	> 4	91.1	1.9	7.0
Cefepime	≤ 1	> 4	87.8	3.9	8.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	94.8	-	5.2
Tobramycin	≤ 2	> 2	94.1	-	5.9
Amikacin	≤ 8	> 8	99.0	-	1.0
Ciprofloxacin	≤ 0.25	> 0.5	87.3	4.6	8.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	87.2	0.6	12.2
ESBL	Negative	Positive	92.8	-	7.2

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 50. *Klebsiella pneumoniae* blood culture isolates in 2020 (n=632). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	88.6	-	11.4
Piperacillin-tazobactam	≤ 8	> 8	88.0	-	12.0
Cefuroxime	≤ 0.001	> 8	0.0	84.7	15.3
Cefotaxime	≤ 1	> 2	90.4	0.3	9.3
Ceftazidime	≤ 1	> 4	88.3	2.5	9.2
Cefepime	≤ 1	> 4	86.4	4.4	9.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	93.0	-	7.0
Tobramycin	≤ 2	> 2	92.4	-	7.6
Amikacin	≤ 8	> 8	98.6	-	1.4
Ciprofloxacin	≤ 0.25	> 0.5	82.1	6.3	11.6
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	83.6	0.9	15.5
ESBL	Negative	Positive	90.3	-	9.7

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 51. *Klebsiella oxytoca* blood culture isolates in 2020 (n=237). 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	84.6	-	15.2
Piperacillin-tazobactam	≤ 8	> 8	89.9	-	10.1
Cefuroxime	≤ 0.001	> 8	0.0	86.1	13.9
Cefotaxime	≤ 1	> 2	92.4	2.1	5.5
Ceftazidime	≤ 1	> 4	95.8	0.8	3.4
Cefepime	≤ 1	> 4	89.9	2.1	8.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	97.5	-	2.5
Tobramycin	≤ 2	> 2	96.2	-	3.8
Amikacin	≤ 8	> 8	99.6	-	0.4
Ciprofloxacin	≤ 0.25	> 0.5	96.6	1.7	1.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	92.8	0.0	7.2
ESBL	Negative	Positive	96.2	-	3.8

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

RESULTS AND COMMENTS

The surveillance of *Klebsiella* spp. in blood cultures included 632 *K. pneumoniae* (65.4%), 237 *K. oxytoca* (24.5%), and 98 (10.1%) isolates not identified to the species level, giving a total of 967 *Klebsiella* spp. isolates (Tables 49-51).

The majority of *Klebsiella* spp. isolates was susceptible to aminoglycosides, and the prevalence of gentamicin resistance remained stable at 5.2% compared to 5.2% in 2018 and 4.4% in 2019. The prevalence of resistance to tobramycin was 5.9%, whereas almost all isolates (99.0%) were susceptible to amikacin. *K. pneumoniae* isolates were more often resistant to gentamicin (7.0%) than *K. oxytoca* isolates (2.5%). 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 septicemia 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 decreased to 6.1% in 2019 and 8.1% in 2020. 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* (11.6%) than in *K. oxytoca* (1.7%). Resistance to trimethoprim-sulfamethoxazole increased from 11.3% in 2019 to 12.2% in 2020. As for ciprofloxacin, the prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (7.2%) than in *K. pneumoniae* (15.5%).

A 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*. Most *Klebsiella* spp. isolates were susceptible (defined as S+I) to cefotaxime (92.2%), ceftazidime (93.0%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (88.8%), see Figure 77. The prevalence of resistance to 3rd generation cephalosporins increased by approximately one percentage point from 2019-2020. 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.

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 increased from 5.7% in 2019 to 7.2% in 2020 (9.7% in *K. pneumonia*), the highest prevalence ever recorded in NORM (Figure 75). The 70 ESBL isolates originated from 18 different laboratories and were identified as *K. pneumoniae* (n=61, 87%) or *K. oxytoca* (n=9, 13 %). ESBL isolates were generally resistant to cefuroxime (67/70), cefotaxime (66/70), ceftazidime (60/70) and cefepime (60/70), and co-resistance was frequently seen for trimethoprim-sulfamethoxazole (59/70), ciprofloxacin (45/70) and gentamicin (42/70). Many isolates were susceptible to piperacillin-tazobactam (38/70), tigecycline (52/70) and/or amikacin (64/70). Seventy-two isolates (7.4%) displayed a zone diameter below the meropenem screening breakpoint of 28 mm, but carbapenemase production was not confirmed in any of them.

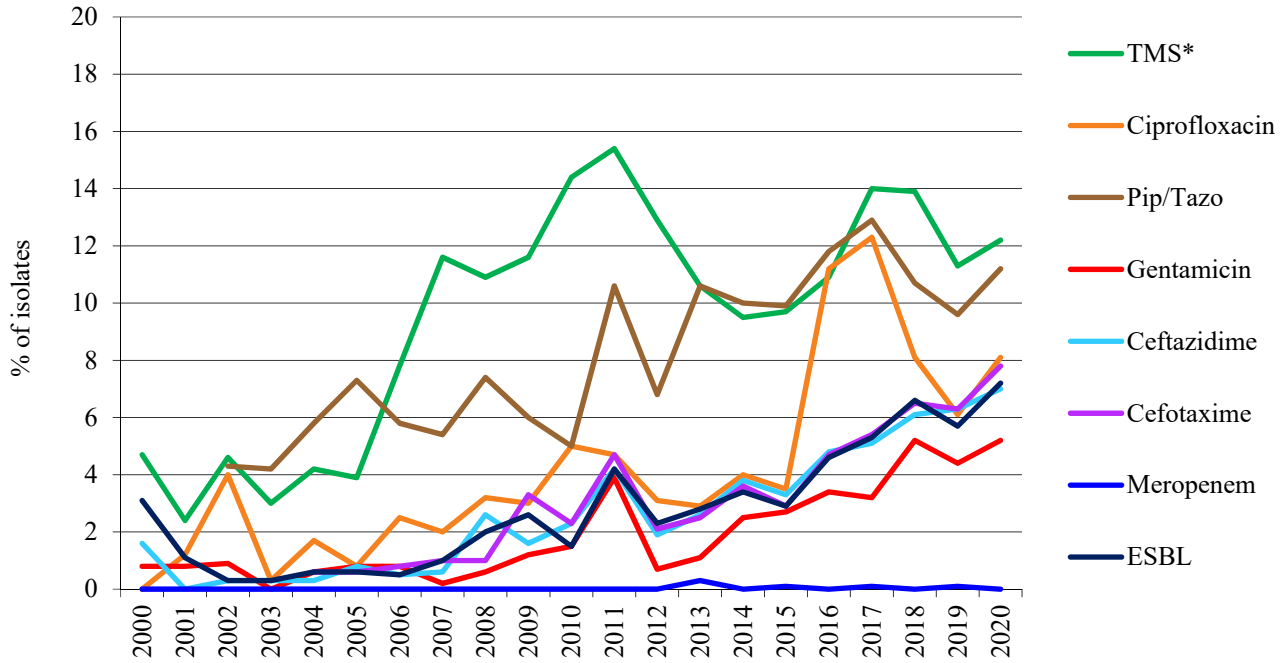

FIGURE 77. Prevalence of resistance to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2020. Isolates are categorised according to the breakpoints at the time of analysis. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 52. *Klebsiella* spp. urinary tract isolates in 2020 (n=1,003). 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	92.0	-	8.0
Amoxicillin-clavulanic acid*	≤ 32	> 32	92.0	-	8.0
Piperacillin-tazobactam	≤ 8	> 8	91.2	-	8.8
Cefotaxime	≤ 1	> 2	94.5	0.8	4.7
Ceftazidime	≤ 1	> 4	94.1	1.4	4.5
Cefepime	≤ 1	> 4	92.8	2.0	5.2
Meropenem	≤ 2	> 8	99.8	0.1	0.1
Gentamicin	≤ 2	> 2	96.2	-	3.8
Tobramycin	≤ 2	> 2	96.0	-	4.0
Amikacin	≤ 8	> 8	98.9	-	1.1
Ciprofloxacin	≤ 0.25	> 0.5	89.6	4.3	6.1
Trimethoprim	≤ 4	> 4	84.3	-	15.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	88.0	0.7	11.3
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.

RESULTS AND COMMENTS

Klebsiella spp. urinary tract isolates have previously been included in the NORM surveillance programme in 2001, 2003, 2009 and 2012-2019. 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 prevalence of resistance to urinary tract antibiotics was slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Tables 52-54). The majority of isolates remained susceptible to gentamicin at 96.2% compared to 96.6% in 2019. Among urinary tract *E. coli*, 96.0% were susceptible to gentamicin in 2020. The rates of resistance to ciprofloxacin in *Klebsiella* spp. increased from 4.2% in 2019 to 6.1% in 2020. The comparable rate for urinary tract *E. coli* in 2020 was 8.1%. Susceptibility to trimethoprim (81.3% in 2019; 84.3% in 2020) and trimethoprim-sulfamethoxazole (86.8% in 2019; 88.0% in 2020) was

higher than in *E. coli* (75.5% and 78.1% in 2020, respectively). Our data may indicate that the *E. coli* breakpoints for fosfomycin are not suitable for *Klebsiella* (72.7% resistance).

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. Forty-five isolates (4.5%) were reported as ESBL positive, of which 40 were *K. pneumoniae*, four were *K. oxytoca*, and one was not identified to the species level. They were retrieved from 17 different laboratories and originated from general practices (n=20), hospitals (n=14), outpatient clinics (n=4), nursing homes (n=4) or other locations (n=3). The 4.5% ESBL rate (5.7% in *K. pneumoniae*) was an increase from 2019 (3.4% for all *Klebsiella*, 4.2% in *K. pneumoniae*). The 45 ESBL isolates were often resistant to trimethoprim (n=40), trimethoprim-sulfamethoxazole (n=38), ciprofloxacin (n=27) and gentamicin (n=26), but many remained susceptible to mecillinam (n=38) and piperacillin-tazobactam (n=22). Two isolates were categorised as R and I to meropenem according to the clinical breakpoints, but only the latter was confirmed to contain a carbapenemase determinant (KPC). No additional carbapenemase-producing isolates were detected by the screening breakpoint.

TABLE 53. *Klebsiella pneumoniae* urinary tract isolates in 2020 (n=699). 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	92.1	-	7.9
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.6	-	6.4
Piperacillin-tazobactam	≤ 8	> 8	89.6	-	10.4
Cefotaxime	≤ 1	> 2	93.7	0.4	5.9
Ceftazidime	≤ 1	> 4	92.9	1.4	5.7
Cefepime	≤ 1	> 4	92.2	1.9	5.9
Meropenem	≤ 2	> 8	99.8	0.1	0.1
Gentamicin	≤ 2	> 2	95.0	-	5.0
Tobramycin	≤ 2	> 2	94.7	-	5.3
Amikacin	≤ 8	> 8	98.9	-	1.1
Ciprofloxacin	≤ 0.25	> 0.5	87.3	5.0	7.7
Trimethoprim	≤ 4	> 4	81.0	-	19.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.0	1.0	14.0
ESBL	Negative	Positive	94.3	-	5.7

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

TABLE 54. *Klebsiella oxytoca* urinary tract isolates in 2020 (n=161). 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	91.9	-	8.1
Amoxicillin-clavulanic acid*	≤ 32	> 32	91.3	-	8.3
Piperacillin-tazobactam	≤ 8	> 8	92.5	-	7.5
Cefotaxime	≤ 1	> 2	93.8	3.1	3.1
Ceftazidime	≤ 1	> 4	96.9	0.6	2.5
Cefepime	≤ 1	> 4	92.9	3.1	4.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 2	98.8	-	1.2
Tobramycin	≤ 2	> 2	98.1	-	1.9
Amikacin	≤ 8	> 8	100.0	-	0.0
Ciprofloxacin	≤ 0.25	> 0.5	96.3	0.6	3.1
Trimethoprim	≤ 4	> 4	93.2	-	6.8
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.0	0.0	5.0
ESBL	Negative	Positive	97.5	-	2.5

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.

Carbapenemase-producing Gram-negative bacteria in Norway 2020

Carbapenem resistance is a major contributor to the burden of antimicrobial resistance (1) mainly due to the global spread of carbapenemases associated with 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 carbapenemase-producing Gram-negatives is performed at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance. Here we summarise the findings in 2020.

57 cases of carbapenemase-producing *Enterobacterales* (CPE) were identified in 2020 (Figure 78). This is a reduction from 75 cases in 2019 and at a similar level as 2018 (n=54).

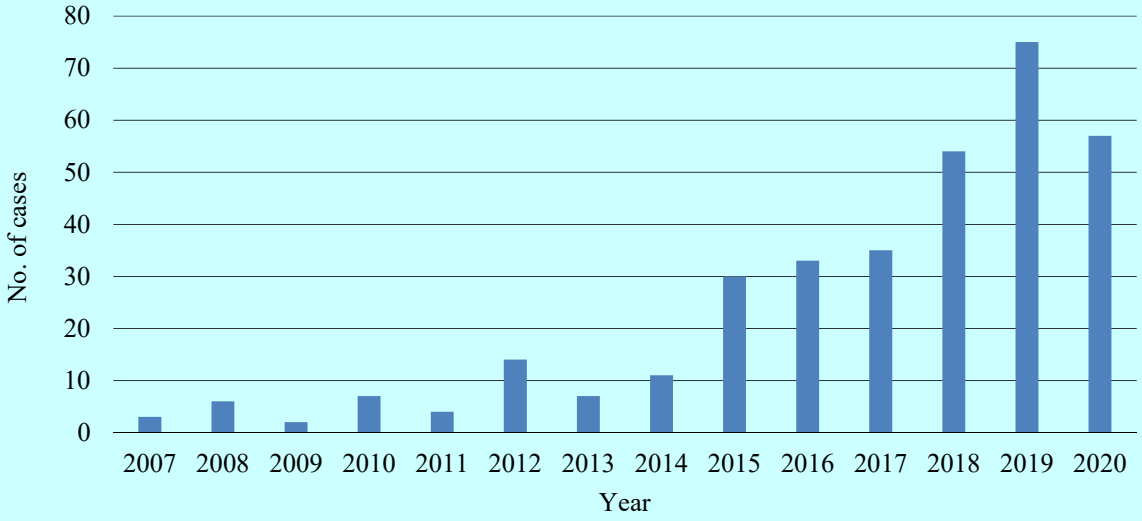

FIGURE 78. Number of cases with carbapenemase-producing *Enterobacterales* in Norway 2007-2020.

More than one CPE isolate, of either different species or the same species but different sequence type (ST)/carbapenemase gene, were identified in five cases leading to a total of 62 CPE isolates. The number of *Escherichia coli* in 2020 (n=45) was the same as in 2019 (n=44), while the number of *Klebsiella pneumoniae* went down from 28 isolates in 2019 to 13 isolates in 2020 (Figure 79). Two carbapenemase-producing *Enterobacter* sp. and single isolates of carbapenemase-producing *Proteus mirabilis* and *Kluyvera* sp. were identified.

In terms of carbapenemase variants the number of isolates with OXA-48-like variants was stable with 36 isolates in 2020 versus 35 in 2019 (Figure 80). In contrast, the number of isolates with NDM declined from 46 isolates in 2019 to 22 isolates in 2020. Two isolates harboured more than one carbapenemase – one *K. pneumoniae* with NDM-5 and OXA-232 and one *E. coli* with NDM-5 and KPC-3.

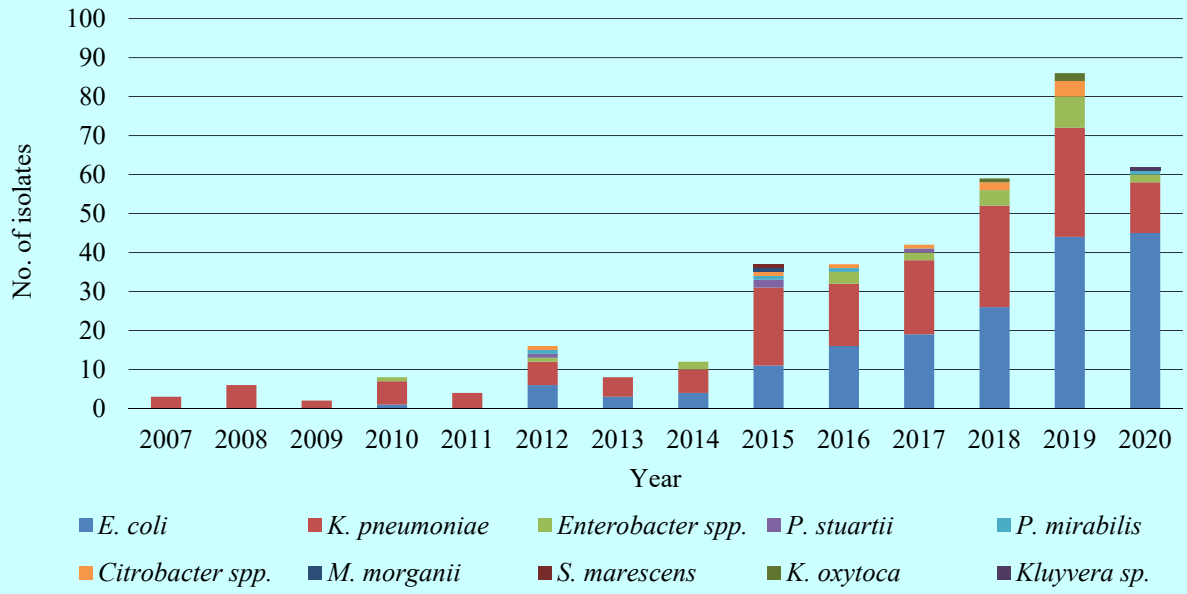

FIGURE 79. Number of carbapenemase-producing *Enterobacterales* isolates according to species.

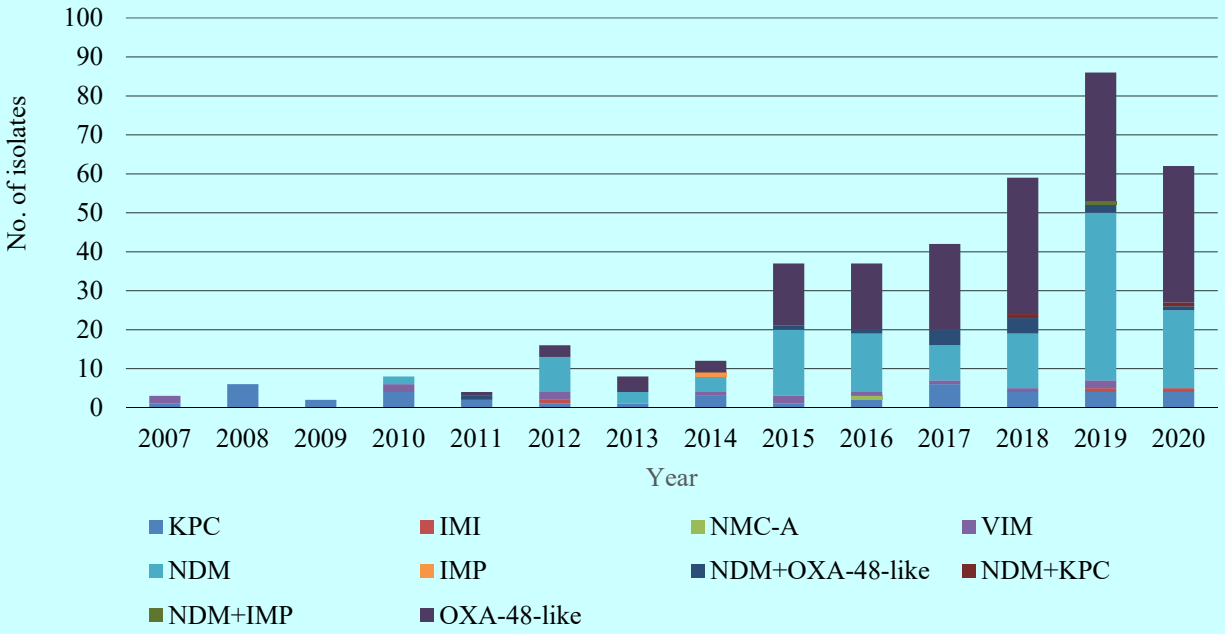

FIGURE 80. Number of carbapenemase variants among *Enterobacterales* isolates.

In general, genetic analysis showed a relatively large diversity in terms of ST and carbapenemase variants. Nineteen different STs were identified among the 45 *E. coli* isolates (Table 55).

TABLE 55. Sequence type (ST) and carbapenemase variant combinations among carbapenemase-producing *E. coli* (n=45) identified in 2020.

ST	Carbapenemase variant
ST38	OXA-244 (n=19); OXA-48 (n=2)
ST46	NDM-5 (n=1)
ST69	OXA-244 (n=2)
ST90	OXA-181 (n=1)
ST129	NDM-5 (n=1)
ST131	OXA-181 (n=1)
ST167	NDM-5 (n=2)
ST205	OXA-181 (n=1)
ST294	OXA-48 (n=1)
ST361	NDM-5+KPC-3 (n=1); NDM-5 (n=1)
ST405	NDM-5 (n=1)
ST617	NDM-5 (n=1); OXA-244 (n=1)
ST1643	NDM-1 (n=1)
ST1702	NDM-5 (n=1)
ST2851	NDM-5 (n=1)
ST5415	NDM-5 (n=1)
ST8346	NDM-5 (n=1)
ST-novel	NDM-5 (n=2)

The dominant combination was *E. coli* ST38-OXA-244 identified in 19 cases. In addition, *E. coli* ST38-OXA-48 was identified in two cases. Phylogenetic analysis showed two clusters of closely related *E. coli* ST38-OXA-244 (Figure 81). The largest cluster represents an outbreak in the Western Health Region that involved three hospitals and 12 cases. Six isolates were from clinical specimens while six isolates were identified through screening. The second cluster of two cases was identified at the same laboratory with an approximately two-month interval. Epidemiological data did not reveal any relationship that could link the cases. The combination of *E. coli* ST38 and OXA-244 has emerged as a high-risk clone with increasing prevalence in Europe (2) and dissemination has been shown in several countries and across borders (3-6). OXA-244 is a one amino acid variant of OXA-48 which leads to reduced activity towards temocillin and carbapenems (7). This leads to diagnostic challenges in terms of phenotypic identification and screening approaches for the identification of OXA-244 producers (6, 8). No other closely related clusters of isolates were observed, but several of the identified STs belong to pandemic high-risk clones of extraintestinal pathogenic *E. coli* (ExPEC); ST69, ST131, ST167, ST405 and ST648 (9).

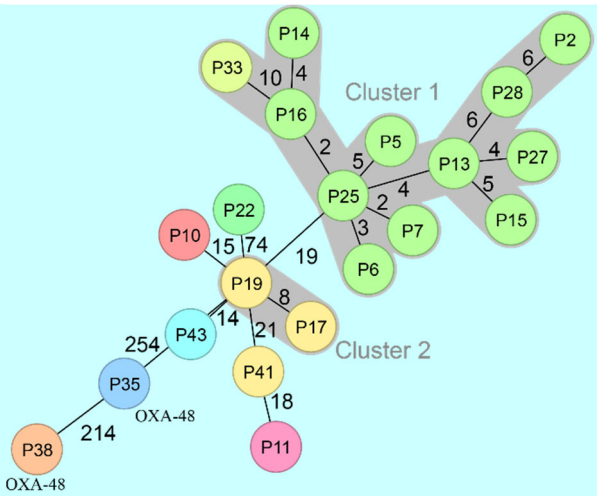

FIGURE 81. Minimum spanning tree based on the core genome allele profile of *E. coli* ST38 identified in Norway 2020, using Ridom-SeqSphere+ with integrated cgMLST scheme and *E. coli* K12 as reference. The isolates are coloured according to laboratory. Closely related isolates (≤10 allelic distance) are highlighted with grey shading.

The 13 carbapenemase-producing *K. pneumoniae* represented nine STs and five different carbapenemase variants (Table 56 and Figure 82). *K. pneumoniae* ST392-OXA-48 (n=3) and *K. pneumoniae* ST147-OXA-232 (n=2) were the only ST-carbapenemase variant combinations identified in more than one case. Epidemiological and phylogenetic analysis confirmed nosocomial transmission for two *K. pneumoniae* ST392-OXA-48 cases. The last case was identified in another health region and was not genetically related. *K. pneumoniae* ST392-OXA-48 has previously been identified in Norway and Sweden associated with import from Gran Canaria (10). The two *K. pneumoniae* ST392-OXA-48 cases were identified in two different laboratories and were not genetically related. As for *E. coli*, several of the STs identified belong to known high-risk clones (e.g. ST15, ST101, ST147, ST258, ST340 and ST392) associated with the dissemination of carbapenemases (11, 12).

TABLE 56. Sequence type (ST) and carbapenemase variant combinations among carbapenemase-producing *K. pneumoniae* (n=13) identified in 2020.

ST	Carbapenemase-variant
ST15	NDM-5+OXA-232 (n=1)
ST101	OXA-48 (n=1)
ST147	OXA-232 (n=2)
ST252	NDM-5 (n=1)
ST258	KPC-2 (n=1)
ST340	KPC-2 (n=1)
ST392	OXA-48 (n=3); NDM-1 (n=1)
ST485	KPC-3 (n=1)
ST505	OXA-48 (n=1)

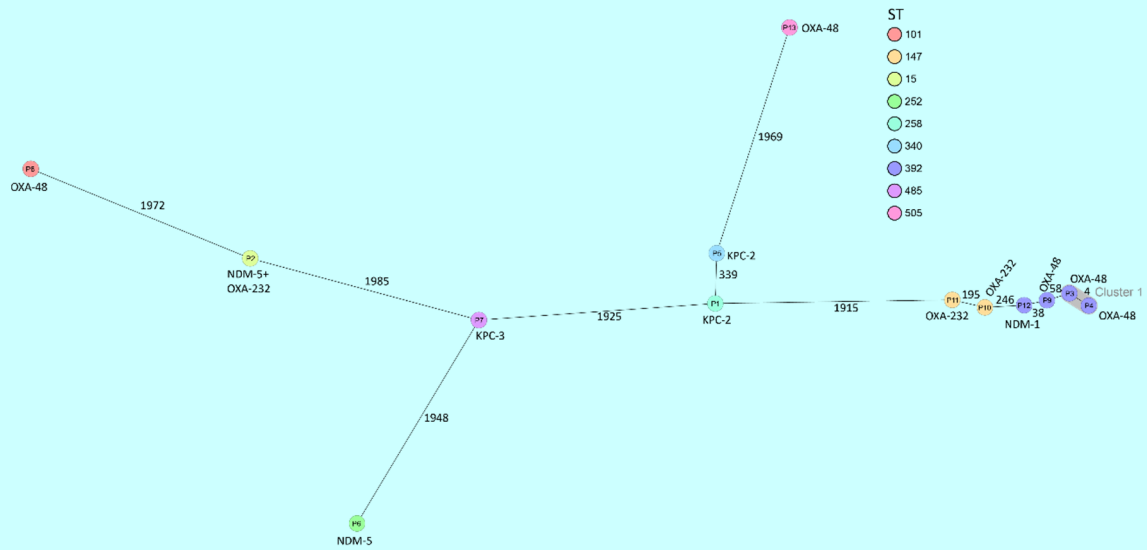

FIGURE 82. Minimum spanning tree based on the core genome allele profile of carbapenemase-producing *K. pneumoniae* identified in Norway 2020, using Ridom-SeqSphere+ with integrated cgMLST scheme and *K. pneumoniae* NTUH-K2044 as reference. The isolates are coloured according to sequence type (ST). Closely related isolates (≤15 allelic distance) are highlighted with grey shading.

Four other carbapenemase-producing *Enterobacterales* isolates were identified in 2020 compared to 14 in 2019 (Table 57). The *Enterobacter* sp. ST93-NDM-5 isolate was identified in a patient co-harbouring *K. pneumoniae* ST252-NDM-5. Both isolates harboured the plasmid-mediated colistin resistance gene *mcr-9.1*, but were susceptible to colistin. It is known that some *mcr*-variants including *mcr-9.1* do not confer clinical colistin resistance (13).

TABLE 57. Sequence type (ST) and carbapenemase variant combinations identified among carbapenemase-producing *Enterobacter* sp., *Kluyvera* sp. and *P. mirabilis* in 2020.

Species	ST-carbapenemase variant
Enterobacter sp. (n=2)	ST93-NDM-5 (n=1); ST-novel-IMI-1 (n=1)
Klyuvera sp. (n=1)[1]	KPC-2
P. mirabilis (n=1)[1]	NDM-1

[1]Multilocus sequence typing scheme not established.

Four cases of carbapenemase-producing *Pseudomonas aeruginosa* were identified in 2020 (Figure 83) which is at the same level as in previous years (2-7 cases/year). All cases were from clinical samples and associated with import. Four different ST-carbapenemase variant combinations were identified (ST111-NDM-1, ST348-IMP-8, ST773-NDM-1 and ST941-VIM-2).

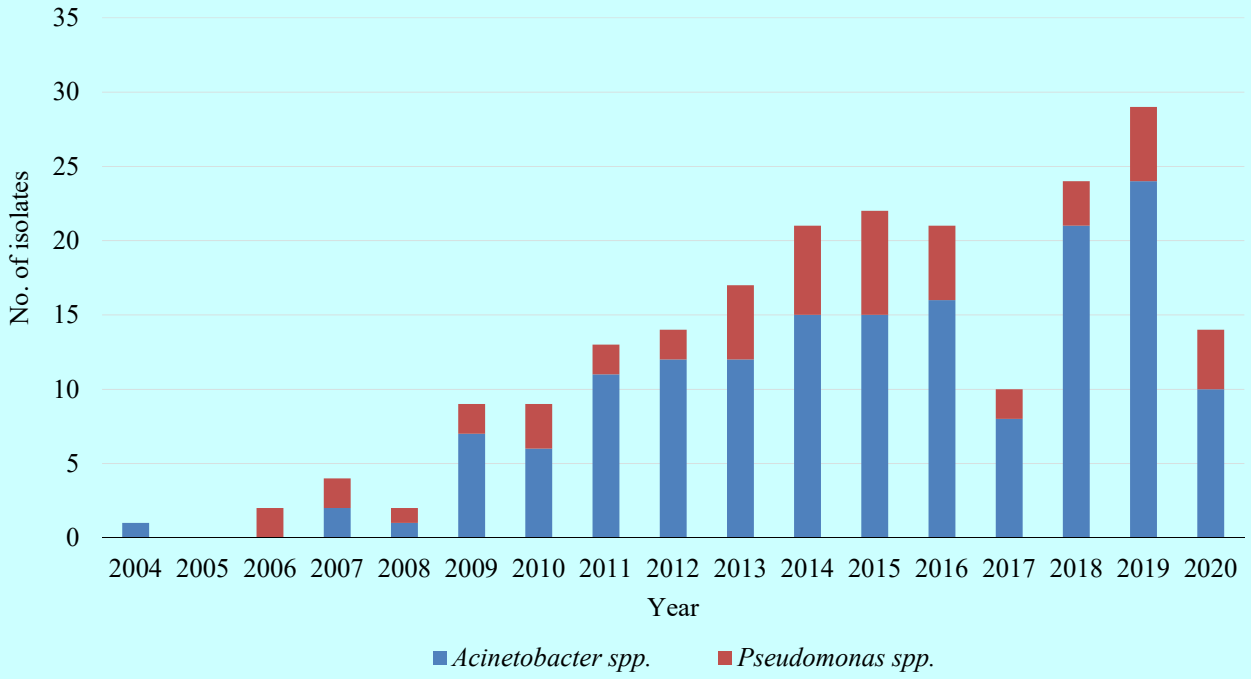

FIGURE 83. Number of carbapenemase-producing *Pseudomonas* sp. and *Acinetobacter* in Norway 2004-2020.

Ten cases of carbapenemase-producing *Acinetobacter baumannii* were identified in 2020, a reduction from 23 in 2019 (Figure 83). Six isolates belonged to the globally dominating ST2 clone (14), all harbouring OXA-23. OXA-23 was also identified in three other isolates, one ST1 isolate co-harbouring NDM-1, one ST16 isolate and one with a novel ST. OXA-72 (OXA-24/-40-variant) was identified in one ST1122 isolate. The isolates were submitted from seven different laboratories and association with import has been indicated for nine cases. Phylogenetic analysis showed that none of the isolates were closely related.

Conclusion

A reduction in the number of carbapenemase-producing Gram-negatives was observed in 2020 compared to 2019. The decline is likely linked to the travel restrictions due to the Covid-19 pandemic as cases of carbapenemase-producing Gram-negatives are frequently associated with import (15, 16). The observation is in line with reduction in other notifiable infectious diseases (17). Whole genome sequencing identified a diversity of clones and carbapenemase variants, including representatives of pandemic clones associated with specific carbapenemase variants (e.g. *E. coli* ST38-OXA-244, *P. aeruginosa* ST111-NDM-1 and *A. baumannii* ST2-OXA-23). This shows that Norway takes part in the global dissemination of antibiotic resistance. With the exception of the *E. coli* ST38-OXA-244 outbreak, only a few single cases of probable clonal spread in Norway were observed. Thus, there is no clear evidence of regional or interregional spread.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 58. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2020 (n=43). 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	83.7	-	16.3
Amoxicillin-clavulanic acid	≤ 2	> 2	95.3	-	4.7
Cefuroxime	≤ 1	> 2	58.2	30.2	11.6
Cefotaxime	≤ 0.125	> 0.125	97.7	-	2.3
Ceftriaxone	≤ 0.125	> 0.125	93.0	-	7.0
Meropenem*	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin	≤ 0.06	> 0.06	100.0	-	0.0
Chloramphenicol	≤ 2	> 2	100.0	-	0.0
Tetracycline	≤ 1	> 2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 0.5	> 1	65.1	4.7	30.2
Beta-lactamase	Negative	Positive	95.3	-	4.7

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 59. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2020 (n=43). 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
Ampicillin*						3	13	15	5	4	1		2			
Amoxi-clav**						1	4	13	19	4	2					
Cefuroxime			2			1		4	18	13	2	2			1	
Cefotaxime	1	4	19	15		3	1									
Ceftriaxone			37	3			1							2		
Meropenem*	1	1	2	7	21	8	2	1								
Ciprofloxacin	3	22	17	1												
Chloramph.								7	36							
Tetracycline							10	27	6							
TMS***			8	7	2	7	1	3	2	2		1		10		

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 analysis was limited 2018-2019 due to reorganisation of the laboratory. In 2020, 43 *H. influenzae* isolates were recovered from blood cultures (n=39) and unspecified specimens (n=4). One of the latter was also isolated in a blood culture, but the others represented unique patients (Tables 58-59). The results should be interpreted with caution due to a low number of isolates.

Beta-lactamase production was detected in only 2/43 isolates (4.7%), which is substantially lower than in 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 wildtype PBP3 sequence. Five isolates (11.6%) displayed this phenotype compared to 16.1% in 2017. Some of these isolates remained susceptible to ampicillin (2/5) and/or amoxicillin-clavulanic acid (3/5). All cefuroxime resistant isolates were beta-lactamase negative. One isolate was resistant to cefotaxime and ceftriaxone (both MIC 0.25 mg/L), whereas two additional isolates displayed high-level resistance to ceftriaxone (32 mg/L) but remained susceptible to cefotaxime. All isolates remained fully susceptible to meropenem according to EUCAST/NordicAST non-meningitis breakpoints, but a single isolate (MIC 0.5 mg/L) would have been classified as meropenem resistant in menigitis.

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=7) and cefuroxime (n=5) resistant isolates. Eighteen out of 41 (43.9%) beta-lactamase negative isolates were resistant to PCG1. Five of these isolates were resistant to both ampicillin and cefuroxime, and only five isolates remained fully susceptible to both agents.

As seen in previous surveys of systemic *H. influenzae* isolates, resistance to ciprofloxacin, tetracycline and chloramphenicol was at very low levels (all 0.0%). The 30.2% resistance to trimethoprim-sulfamethoxazole was an increase compared to 15.3% in 2017.

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 60. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2020 (n=4). 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	75.0	-	25.0
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 61. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2020 (n=4). 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*					3			1								
Ceftriaxone			4													
Ciprofloxacin	4															
Chloramph.								1	3							
Rifampicin	1	1	2													
Tetracycline							1	2	1							
Azithromycin						1	1	1	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 60-61.

Only five cases of systemic infections caused by *N. meningitidis* were reported in 2020. This is the lowest number of reported cases in Norway since surveillance was initiated in 1977, and must be seen in context with the ongoing coronavirus pandemic through most of the year. Four isolates were available for further analysis. All isolates were from unique patients and there were no known associations between the cases. The isolates belonged to serogroups B (n=2) and Y (n=2). The serogroup Y isolates belonged to the ST-23 clonal complex while the two serogroup B isolates belonged to two different clonal complexes, the ST-32 and ST-41/44 clonal complexes.

One isolate displayed a penicillin G MIC of 0.5 mg/L and was thus classified as resistant to this agent. The genetic basis for resistance was not determined, but was most likely caused by alterations in the penicillin-binding protein 2 (PBP2) encoded by *penA*. No clinical breakpoints have been established for azithromycin, but the MIC distribution does not indicate the presence of acquired macrolide resistance (Table 61).

Neisseria gonorrhoeae

TABLE 62. *Neisseria gonorrhoeae* from all specimen types in 2020 (n=442). 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	5.2	72.9	21.9
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	98.9	-	1.1
Ciprofloxacin	≤ 0.03	> 0.06	45.0	0.2	54.8
Tetracycline	≤ 0.5	> 1	61.6	16.7	21.7
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	81.2	-	18.8

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

TABLE 63. *Neisseria gonorrhoeae* from all specimen types in 2020 (n=442). 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*		0.2	1.4	1.1	2.5	19.2	31.2	14.7	7.7	7.9	7.7	4.1	0.7	1.6		
Ceftriaxone	28.1	17.9	43.9	8.6	1.1	0.5										
Cefixime			85.1	10.2	1.6	2.0	1.1									
Ciprofloxacin	27.8	13.3	3.4	0.5	0.2	0.2	2.7	5.0	5.9	16.5	10.9	3.4	1.6	8.6		
Tetracycline			0.2	0.5	3.4	10.6	25.6	21.3	16.7	7.9	1.8	3.8	5.0	2.9	0.2	
Spectinomycin							0.5		0.5	1.1	6.1	42.5	49.1	0.2		
Azithromycin			0.2	2.3	5.9	23.5	33.5	19.5	7.5	3.4	1.4	0.5	0.5	0.2		1.8

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *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. Only a single isolate from each disease episode was included from each patient. The microbiological data could not be linked to information in the Norwegian Surveillance System for Communicable Diseases (MSIS).

In 2020, a total of 442 isolates were available for analysis. The isolates were reported to originate from urethra (n=170), cervix uteri (n=52), anus (n=115), throat (n=64), eye (n=1) or "others/unknown" (n=40). A total of 348 (78.9%) isolates originated from men and 93 (21.1%) from women. The geographical location where the infection was 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 62-63. A majority of isolates were either susceptible only to increased exposure (72.9%) or resistant (21.9%) to penicillin G. The corresponding figures for 2019 were 80.1% and 18.6%, respectively. Eighty-three isolates (18.8%) produced beta-lactamase, which is a slight increase from 2019 (15.4%). Practically all beta-lactamase positive isolates (82/83, 98.8%) were also resistant to ciprofloxacin. Nineteen isolates (4.3%) were resistant, and 318 (71.9%) 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. Five 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 current European treatment guidelines recommend empirical combination treatment with ceftriaxone and azithromycin. It should be noted that 7.7% of the isolates displayed azithromycin MIC values above the EUCAST screening breakpoint for acquired resistance of 1 mg/L. The corresponding figure for 2019 was 19.4%. Ciprofloxacin was previously used for empirical treatment of gonorrhoeae acquired outside South-East Asia. The prevalence of ciprofloxacin resistance persisted at a high level (54.8%) in 2020. 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 64. *Staphylococcus aureus* blood culture isolates in 2020 (n=1,367). 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	93.9	0.2	5.9
Clindamycin	≤ 0.25	> 0.5	97.4	1.2	1.4
Fusidic acid	≤ 1	> 1	96.3	-	3.7
Ciprofloxacin	≤ 0.001	> 1	0.0	94.9	5.1
Gentamicin	≤ 1	> 1	99.5	-	0.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	98.6	1.0	0.4
Tetracycline	≤ 1	> 2	96.4	0.5	3.1
Tigecycline	≤ 0.5	> 0.5	98.0	-	2.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.8	0.1	0.1
Beta-lactamase	Negative	Positive	31.4	-	68.6
Cefoxitin screen	≥ 22	< 22	98.6	-	1.4
MRSA** (*mecA*)	Negative	Positive	98.6	-	1.4

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

Nineteen methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2020, corresponding to a prevalence of 1.4% (Table 64). This is an increase from 2018 and 2019 (both 0.8%). The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from eight different hospitals, but a single institution accounted for ten of them. 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 (7/19), ciprofloxacin (5/19), tetracycline (5/19), fusidic acid (3/19), tigecycline (n=2) and/or trimethoprim/sulfamethoxazole (1/19). All MRSA isolates were susceptible to gentamicin, linezolid, rifampicin and clindamycin (S=18; I=1). The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 67 on page 113. The NORM findings are at the same level as reported from the databases of the participating laboratories where 34 out of 1,968 (1.7%) *S. aureus* blood culture isolates were MRSA. One of the 17 *S. aureus* isolates recovered from cerebrospinal fluid was methicillin resistant, thus bringing the total number of systemic MRSA isolates to 35/1,993 (1.8%). This is an increase since 2018 (0.8%) and 2019 (0.9%).

Eighty-one *S. aureus* isolates (5.9%) were resistant to erythromycin. This is slightly higher than in previous years (5.3% in 2018; 5.4% in 2019). The macrolide resistance phenotypes of erythromycin resistant isolates were determined by the double disk diffusion (DDD) test. Seven isolates (9%) were constitutively MLS_B resistant, 56 (69%) were inducibly MLS_B resistant, and 18 (22%) displayed efflux mediated M-type resistance. These figures represent 0.5%, 4.1% and 1.3% of all *S. aureus* isolates from blood cultures, respectively. The distribution of MLS phenotypes was essentially unchanged from 2019-2020.

The prevalence of resistance to fusidic acid at 3.7% was at the same level as 3.0% in 2018 and 3.6% in 2019. The 5.1% prevalence of ciprofloxacin resistance was essentially unchanged from 4.6% in 2019. The breakpoint for susceptibility to ciprofloxacin was reduced from S ≤ 1 mg/L to S ≤ 0.001 mg/L in 2020, thus the wildtype 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 2020.

Figure 84 shows the prevalence of resistance to various antimicrobials. A total of 68.6% of the isolates were beta-lactamase positive, which is at the same level as 69.8% in 2018 and 70.6% in 2019. There were only minor differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

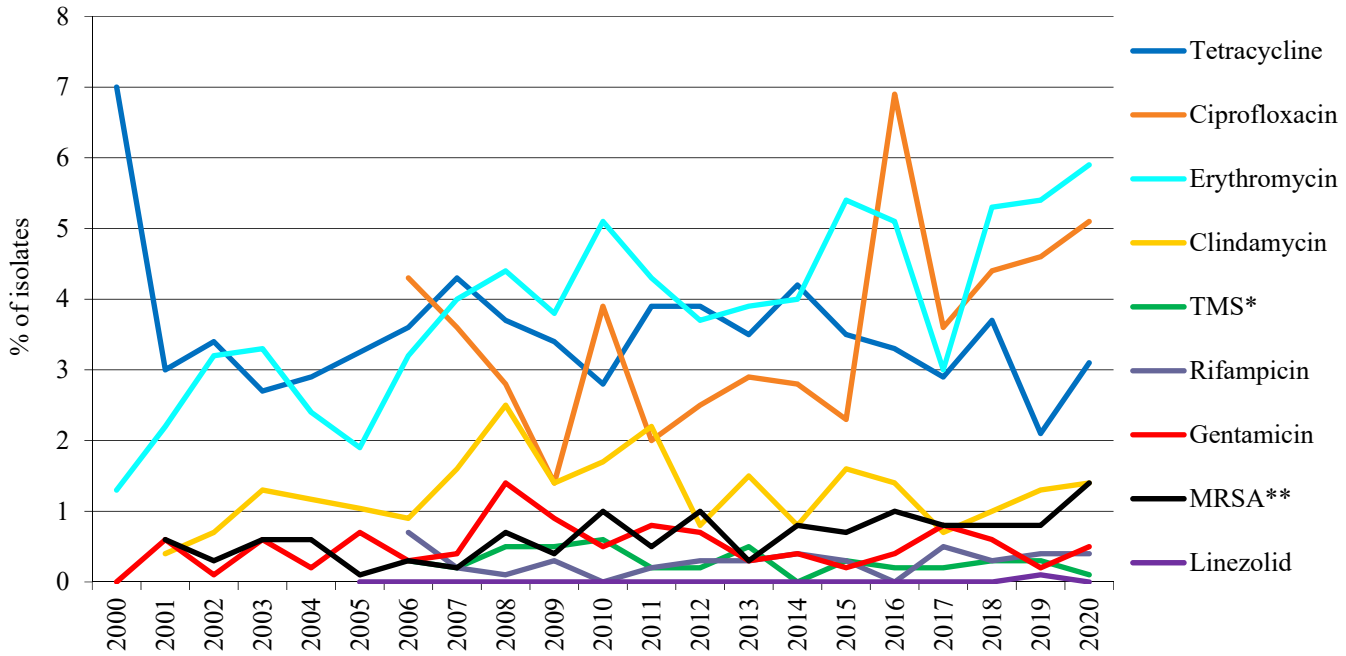

FIGURE 84. Prevalences of antimicrobial resistance among *Staphylococcus aureus* blood culture isolates 2000-2020. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Staphylococcus aureus in wound specimens

TABLE 65. *Staphylococcus aureus* isolates from wound specimens in 2020 (n=1,005). 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	94.8	0.0	5.2
Clindamycin	≤ 0.25	> 0.5	98.5	0.4	1.1
Fusidic acid	≤ 1	> 1	95.6	-	4.4
Ciprofloxacin	≤ 0.001	> 1	0.0	95.8	4.2
Gentamicin	≤ 1	> 1	99.7	-	0.3
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.3	0.4	0.3
Tetracycline	≤ 1	> 2	95.1	0.4	4.5
Tigecycline	≤ 0.5	> 0.5	99.5	-	0.5
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.3	0.4	0.3
Beta-lactamase	Negative	Positive	30.2	-	69.8
Cefoxitin screen	≥ 22	< 22	98.2	-	1.8
MRSA** (*mecA*)	Negative	Positive	98.2	-	1.8

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

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Eighteen out of 1,005 (1.8%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at approximately the same level as in 2018 (1.7%) and 2019 (1.3%). The MRSA isolates originated from patients visiting general practitioners (n=12), hospital wards (n=4) and outpatient clinics (n=2) in different parts of the country. Most MRSA isolates were co-resistant to tetracycline (11/18), erythromycin (8/18), ciprofloxacin (8/18), fusidic acid (2/18), gentamicin (2/18), clindamycin (2/18) and/or trimethoprim-sulfamethoxazole (1/18) in different combinations. All MRSA isolates were susceptible to tigecycline, rifampicin 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 113).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates decreased from 5.3% in 2019 to 4.4% in 2020 (Table 65 and Figure 85). 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 (3.7 %). For other antimicrobial agents such as trimethoprim-sulfamethoxazole, gentamicin, rifampicin, and tetracycline there were only minor changes from 2019-2020, 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. Fifty-two (5.2%) isolates were resistant to erythromycin, which is at the same level as 5.5% in 2018 and 5.9% in 2019. The isolates were further examined for determination of resistance phenotype and the majority were either inducibly (33/52, 63% of erythromycin resistant isolates) or constitutively (6/52, 12% 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 (13/52, 25% 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 69.8% of the isolates were beta-lactamase positive compared to 72.6% in 2018 and 75.0% in 2019. Beta-lactamase negative isolates were more likely to be resistant to erythromycin (5.9%) compared to beta-lactamase positive isolates (4.9%), whereas beta-lactamase positive isolates had a higher prevalence of resistance to tetracycline (5.3%) and ciprofloxacin (4.4%) than beta-lactamase negative isolates (2.6% and 3.6%, respectively). For other antimicrobials there were only minor differences.

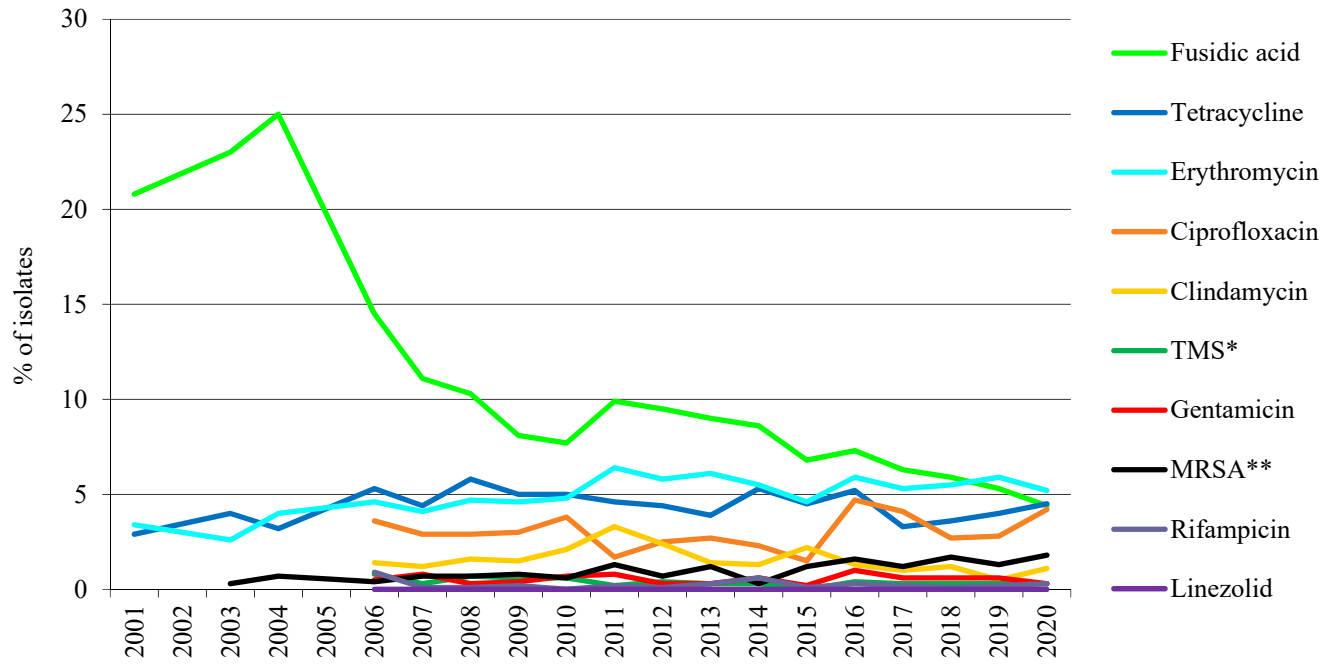

FIGURE 85. Prevalence of antimicrobial resistance among *Staphylococcus aureus* wound isolates 2001-2020. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole. **MRSA=Methicillin resistant *Staphylococcus aureus*.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2020

In total 1,882 persons were reported with MRSA to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2020, an incidence rate of 35 per 100,000 person-years (Figure 86). Of these, 734 (39%) were reported with clinical infections, while 1,148 were colonised.

The monthly number of infections has not changed significantly over the last seven years (IRR 1.00; 95% CI 0.999-1.003). The annual number of colonised persons reached a peak in 2017, and has decreased significantly in the last three years (IRR 0.99; 95% CI 0.986-0.993).

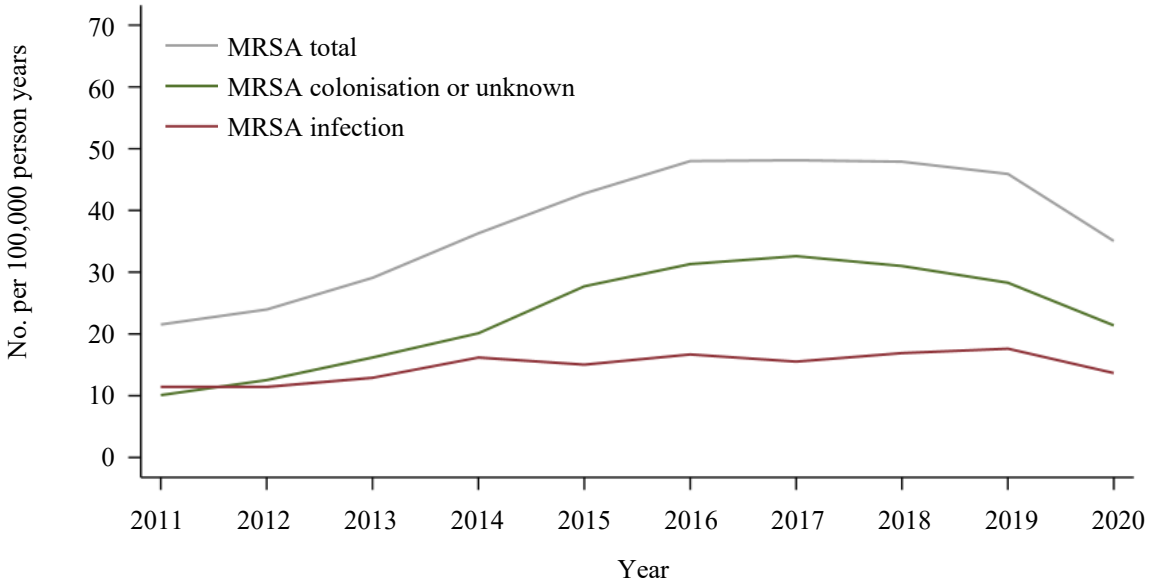

FIGURE 86. Number of persons notified with MRSA per 100,000 person-years in Norway in the last ten years, by infection and colonisation.

In 2020, a total of 475 (25%) persons were reported to have acquired MRSA during travel abroad or prior to coming to Norway. This is the lowest proportion of imported cases in ten years. However, it is important to note that over 1/3 of all cases are notified without information regarding possible place of infection (Figure 87).

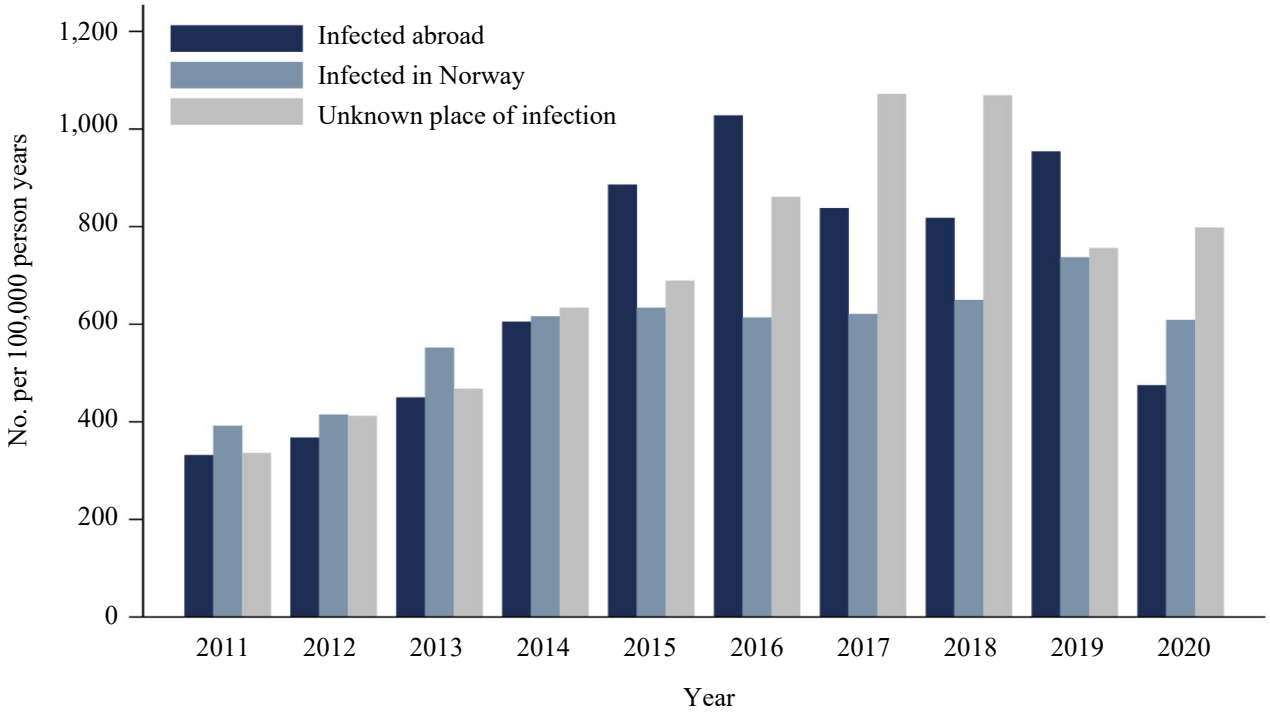

FIGURE 87. Number of persons notified with MRSA in Norway in the last ten years, by assumed place of infection.

The Norwegian Reference Laboratory for Methicillin-Resistant *Staphylococcus aureus* (MRSA) at St. Olavs hospital, Trondheim University Hospital, received 1,913 MRSA isolates in 2020. Staphylococcal protein A (*spa*) typing is still the main genotyping method, and 1,083 of 1,913 (56.6%) isolates were prioritised for genotyping. Additionally, 348 isolates were randomly selected for genotyping, and seven isolates were genotyped by request from referring microbiology laboratories. 255 different *spa*-types were identified, of which 112 *spa*-types were reported as single events and 114 *spa*-types were reported from two to ten times. Only 38 *spa*-types were reported more than ten times. Table 66 shows the ten most common *spa*-types in Norway 2020. Eight out of the ten most frequent *spa*-types detected in 2020 were also on the top-ten list for 2019.

TABLE 66. The ten most common *spa*-types in Norway in 2020.

spa-type	CC	No. of isolates	% of isolates genotyped
t002	5	160	11.1
t304	6	124	8.6
t008	8	84	5.8
t127	1	82	5.7
t019	30	81	5.6
t223	22	57	4.0
t034	398	33	2.3
t005	22	32	2.2
t3841	672	30	2.1
t105	5	28	1.9

The MRSA Reference Laboratory identified 17 livestock-associated MRSA (LA-MRSA) (CC398, PVL (Panton-Valentine Leucocidin) negative) in humans, of *spa*-types t034 (n=11), t011 (n=4), t571 (n=1) and t1451 (n=1). Twenty-four human isolates where identified as LA-MRSA (CC398, PVL positive), of *spa*-types t034 (n=20), t011 (n=2), t1793 (n=1) and t8290 (n=1). Two human isolates were positive for *mecC* (*spa*-types t843, CC130 and t6292, CC425).

Antimicrobial susceptibility testing was performed by the referring laboratories according to the EUCAST disc diffusion method and interpreted using the NordicAST 2021 breakpoints (Table 67). The MRSA Reference Laboratory received 1,720 complete antibiograms. Among these strains, 680 (39.5%) were sensitive to all antibiotics tested except beta-lactams (cefoxitin). The highest proportion of resistance was found for erythromycin (32.3%), followed by ciprofloxacin (24.7%) and tetracycline (24.2%). The lowest rates of resistance were found for mupirocin (0.6%), rifampicin (1%) and trimethoprim-sulfamethoxazole (1%). No isolates showed decreased susceptibility to linezolid or vancomycin. The results of susceptibility testing were similar to the results from 2019.

TABLE 67. MRSA isolates from human cases in 2020 (n=1,720). Distribution (% of isolates) of antimicrobial susceptibility by category.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 2	67.5	0.3	32.2
Clindamycin*	≤ 0.25	> 0.5	88.0	1.2	20.7
Fusidic acid	≤ 1	> 1	86.8	-	13.2
Ciprofloxacin	≤ 0.001	> 1	0.0	75.3	24.7
Gentamicin	≤ 1	> 1	87.2	-	12.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	98.4	0.6	1.0
Tetracycline	≤ 1	> 2	75.5	0.2	24.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	97.5	1.5	1.0
Mupirocin	≤ 1	> 256	96.8	2.6	0.6
Vancomycin	≤ 2	> 2	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Proportion of isolates resistant to clindamycin are given in total. Of these, 13.4 % were inducibly clindamycin resistant. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

Enterococcus spp. in blood cultures

TABLE 68. *Enterococcus* spp. blood culture isolates in 2020 (n=677). 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	83.6	0.9	15.5
Imipenem	≤ 0.001	> 4	0.0	82.3	17.7
Gentamicin HLR*	≤ 128	> 128	82.0	-	18.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	93.9	-	6.1
Vancomycin (any genotype)	≤ 4	> 4	98.5	-	1.5
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 69. *Enterococcus faecalis* blood culture isolates in 2020 (n=482). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Imipenem	≤ 0.001	> 4	0.0	98.5	1.5
Gentamicin HLR*	≤ 128	> 128	88.0	-	12.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	96.1	-	3.9
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 70. *Enterococcus faecium* blood culture isolates in 2020 (n=144). 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	26.4	2.1	71.5
Imipenem	≤ 0.001	> 4	0.0	21.5	78.5
Gentamicin HLR*	≤ 128	> 128	56.2	-	43.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	87.5	-	12.5
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.

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 68. The surveillance in NORM 2020 included 482 (71.2%) *E. faecalis* isolates (71.6% in 2019), 144 (21.2%) *E. faecium* isolates (22.1% in 2019), and 51 (7.5%) unspeciated or belonging to other species (6.3% in 2019). 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 stable at 3.0 in 2018, 3.2 in 2019 and 3.3 in 2020. The panel of antimicrobial agents examined was unchanged from 2019-2020.

E. faecalis was universally susceptible to ampicillin (Table 69). The prevalence of resistance to ampicillin in *E. faecium* was 71.5% in 2020 compared to 75.3% in 2018 and 75.9% in 2019 (Table 70). As expected, the results for imipenem closely mirrored those for ampicillin. The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 12.0%, which is a further decrease from 14.1% in 2018 and 13.6% in 2020 (Figure 88). The prevalence of HLGR in *E. faecium* increased from 32.4% in 2019 to 43.8% in 2020. Almost all (59/63) HLGR *E. faecium* isolates were concomitantly resistant to ampicillin and imipenem. Conversely, 59 of 103 (57.3%) ampicillin resistant *E. faecium* also displayed HLGR. High-level gentamicin

resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and beta-lactams often used for treatment of severe enterococcal infections.

Transferrable vancomycin resistance has not yet become endemically established in clinical enterococcal isolates in Norway, but recent outbreaks have occurred in different parts of the country. Ten blood culture isolates were reported as vancomycin resistant in NORM 2020 (1.5%), but none of them were confirmed by PCR to harbour transferrable vancomycin resistance. The phenotypically resistant isolates were either *E. gallinarum* (n=6) or *E. casseliflavus* (n=4), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All enterococcal isolates were susceptible to linezolid.

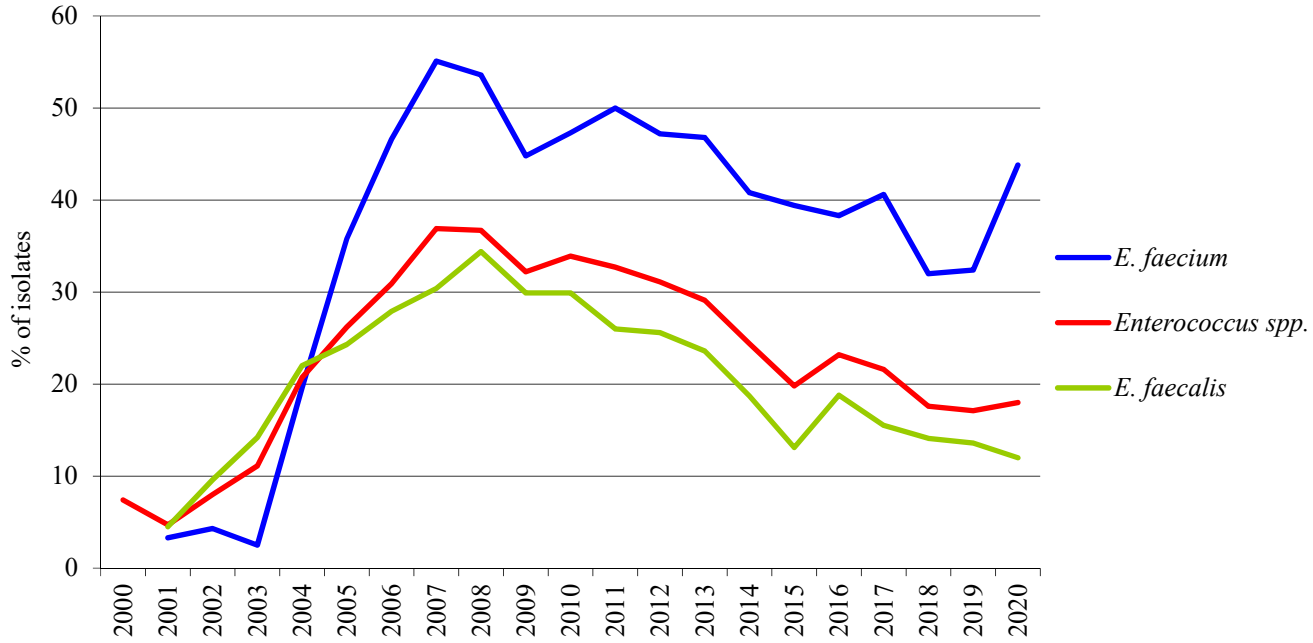

FIGURE 88. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2020. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Vancomycin and linezolid resistant enterococci in Norway 2020

Vancomycin resistant enterococci

Enterococci are the third 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 sidechain that prevents vancomycin from inhibiting crosslinking in the peptidoglycan cell wall (4). Currently, nine gene clusters are known to encode vancomycin resistance (*vanA*, *vanB*, *vanC*, *vanD*, *vanE*, *vanG*, *vanL*, *vanM* and *vanN*), 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).

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 the last years (6), while in Norway the incidence of VRE has varied during the last ten years. In 2020, 74 VRE plus one VRE that was also linezolid resistant (LVRE) were reported in Norway (Figure 89). This represents a decrease (63%) from 2019. K-res has received isolates and/or WGS data on 33 of these 75 (44%). Thus, this is not a complete picture of the VRE situation in Norway, even though some trends are observed. The distribution of VRE including LVRE in total and those analysed by WGS at K-res in 2020 by Health Regions is given in Table 71.

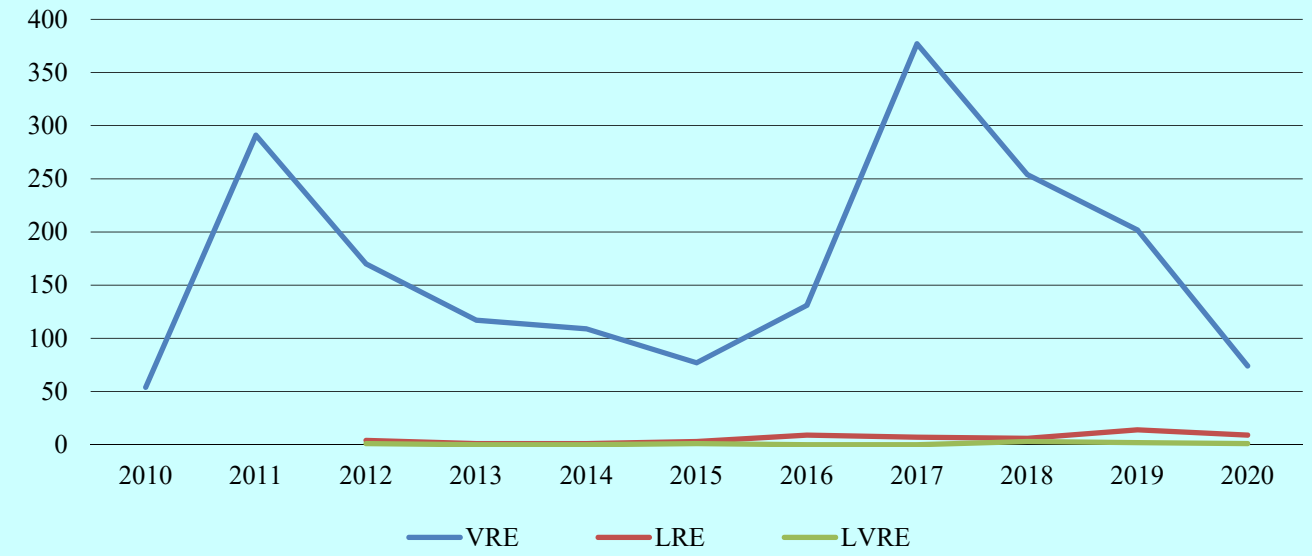

FIGURE 89. The number of vancomycin resistant (VRE), linezolid resistant (LRE) and both vancomycin and linezolid resistant (LVRE) enterococci in Norway 2010-2020. Combined data from MSIS.no and K-res.

TABLE 71. Total number of VRE+LVRE isolates in Norway for 2019 and 2020 as well as those analysed by WGS at K-res in 2020, distributed by Health Regions.

Health region	Number of VRE + LVRE 2019	Number of VRE + LVRE 2020	Number of VRE +LVRE with WGS data 2020
South-Eastern	99	44	13
Western	95	28	17
Central	1	5	1
Northern	8	6	2
Unknown	1	1	0

VanA (n=20) and *vanB* (n=12) *E. faecium* were the dominant VRE in Norway in 2020. One vancomycin resistant (*vanB*) *E. faecalis* was also detected (Figure 90). Worldwide vancomycin resistance is also much more prevalent in *E. faecium* than in *E. faecalis* (7,8), and *vanA* is more frequent than *vanB* (5). In Norway, both *vanA* and *vanB E. faecium* are to a large extent connected with smaller outbreaks/clusters in the Western and South-Eastern regions, but also occur as sporadic isolates (Figure 91).

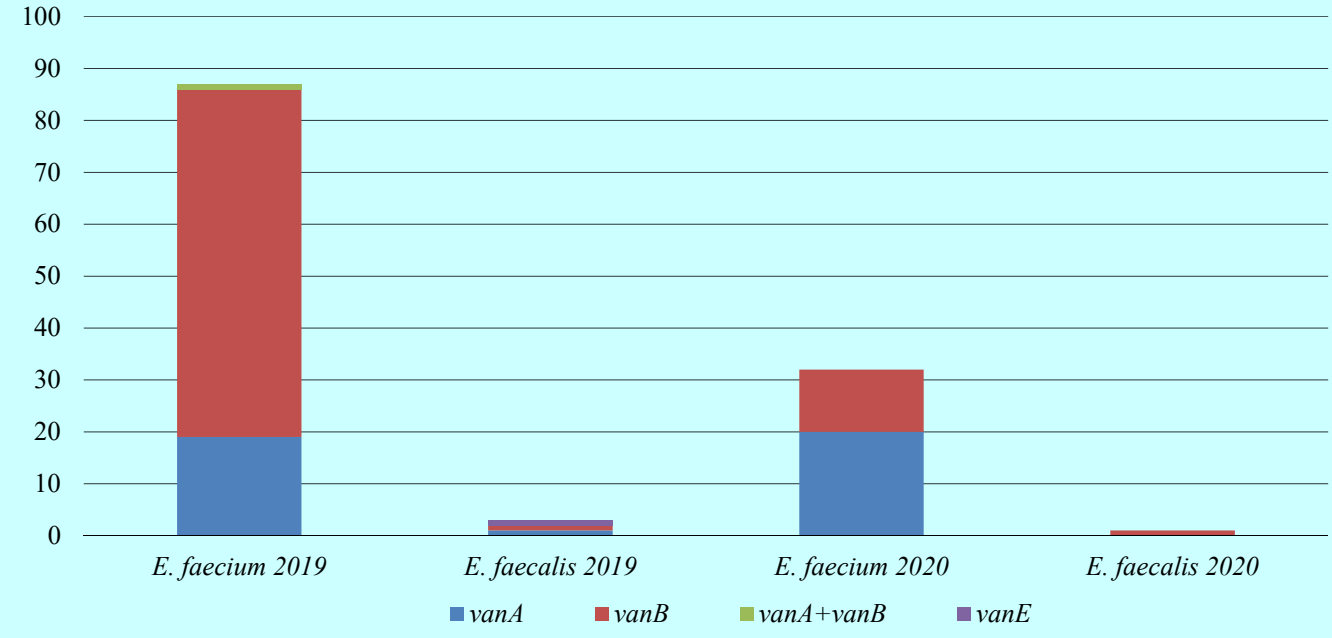

FIGURE 90. Species and genotype distribution of Norwegian VRE isolates (number) that K-res has WGS data on for 2019 and 2020. This also includes linezolid resistant VRE.

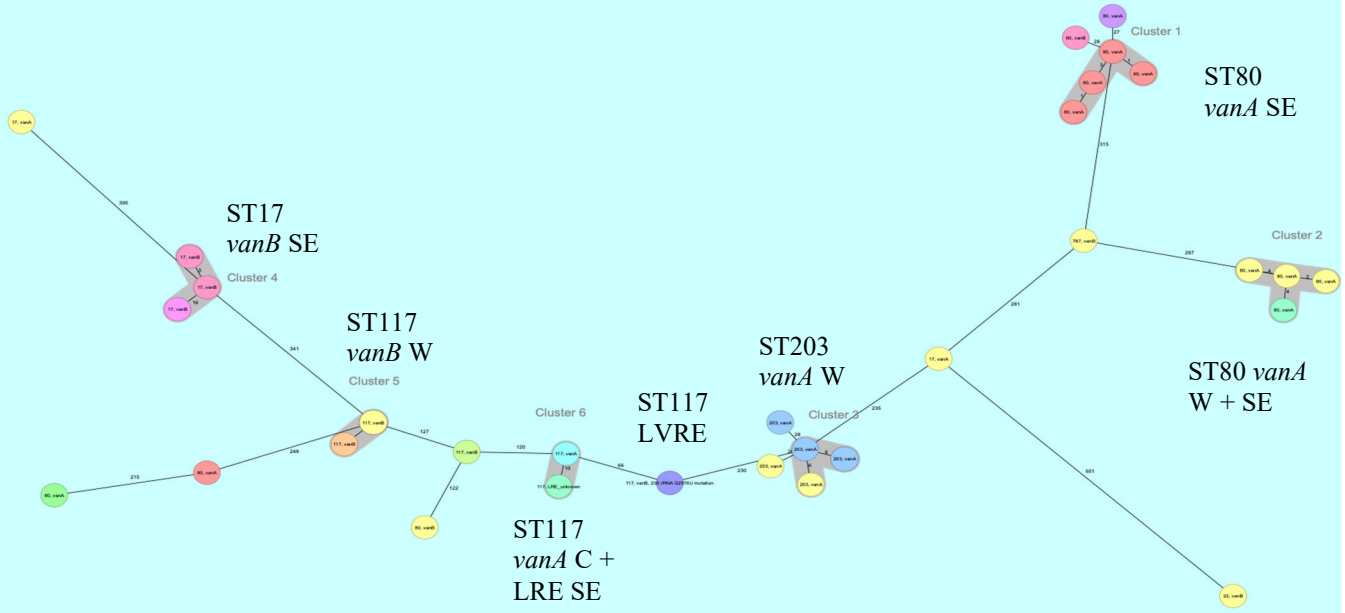

FIGURE 91. Minimum spanning network built form core genome allelic profiles of the 33 Norwegian *E. faecium* (VRE n=31, LVRE n=1, LRE n=1) 2020 isolates using Ridom-SeqSphere+ with integrated core genome (cg) MLST scheme with *E. faecium* Aus0004 as reference strain. The isolates are colour coded according to primary laboratory. Genetically closely related isolates (≤20 allelic distance) are highlighted in grey. SE=South-Eastern, W=Western, C=Central regions.

We have registered eight different sequence types (STs) of *E. faecium* in 2019 and six in 2020 (Figure 92). To a large extent, the same STs are found in 2020 and 2019. Some STs observed in 2019 (ST18, ST78 and ST789) are not detected in 2020. Except ST22 (n=1) that occurs in 2020, all STs in 2020 (ST17, ST80, ST117, ST203 and ST787) belong to known pandemic hospital adapted clones. ST22 has previously been associated with both patients in hospitals and different animals (9,10). The most predominant STs in *E. faecium* in 2020 are linked to outbreaks/clusters such as *vanB* ST17 in the South-Eastern region, two different clusters of *vanA* ST80 in the South-Eastern and Western regions, as well as *vanB* ST117 and *vanA* ST203 in the Western region (Figure 91). For *E. faecalis* two different STs were registered in 2019 of which ST6 often has been linked to clinical isolates and hospitals. The single VRE *E. faecalis* in 2020 was of a new ST (ST1117).

Conclusion

The number of patients with VRE (n=75) registered in MSIS in Norway in 2020 represents a large decrease (63%) from 2019. The decline was seen in the Western and South-Eastern regions. The number of patients with VRE in Norway varies depending on the incidence of hospital outbreaks. It may be that the infection control measures introduced in hospitals due to the pandemic also have reduced the spread of hospital associated VRE infections. In this report, we present WGS-data for 33 of these isolates. The majority of VRE were *E. faecium* with a *vanA* or *vanB* genotype. Both *vanA* and *vanB E. faecium* are to a large extent linked to smaller outbreaks/clusters in the Western and South-Eastern regions, but also occur sporadically. The majority of VRE *E. faecium* belong to dispersed hospital-adapted clones identified in several other countries (ST17, ST80, ST117, ST203 and ST787).

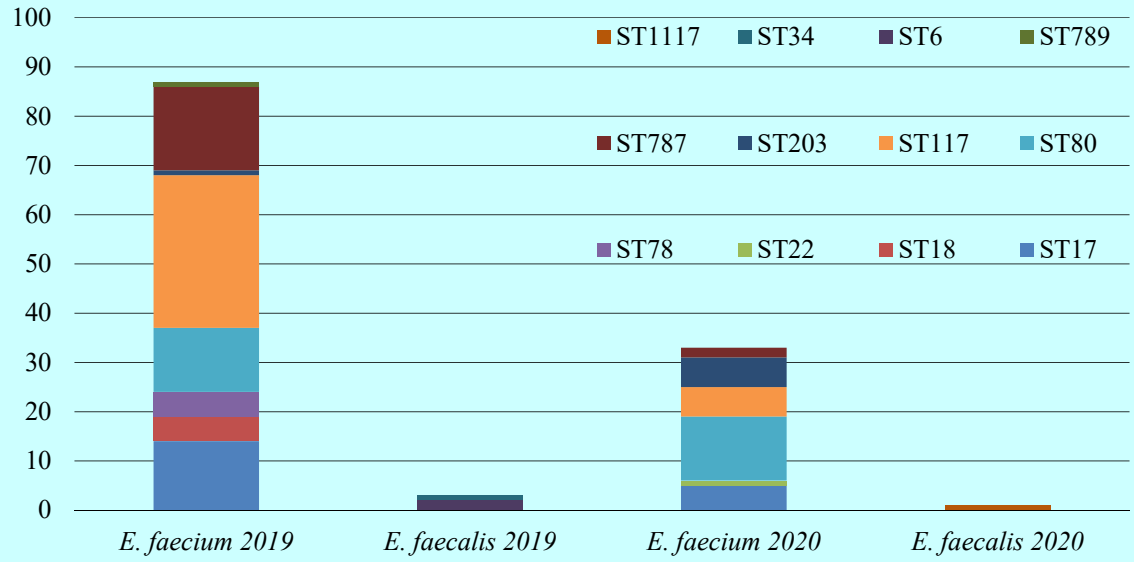

FIGURE 92. Distribution of species and ST in Norwegian VRE isolates from 2019 and 2020 that K-res has WGS data on.

Linezolid resistant enterococci

Linezolid is considered an antibiotic of last resort in the treatment of infections caused by multi-resistant enterococci, and in particular vancomycin resistant enterococci. 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. The *cfr*, *optrA* and *poxtA* genes can all be localised on mobile genetic elements (12,14,15).

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 antimicrobial susceptibility testing (AFA) recommend routine susceptibility testing for linezolid of clinical isolates of *Enterococcus* in Norway. All invasive *Enterococcus* isolates (n=1,271) were categorised as susceptible in the NORM report from 2019. 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.

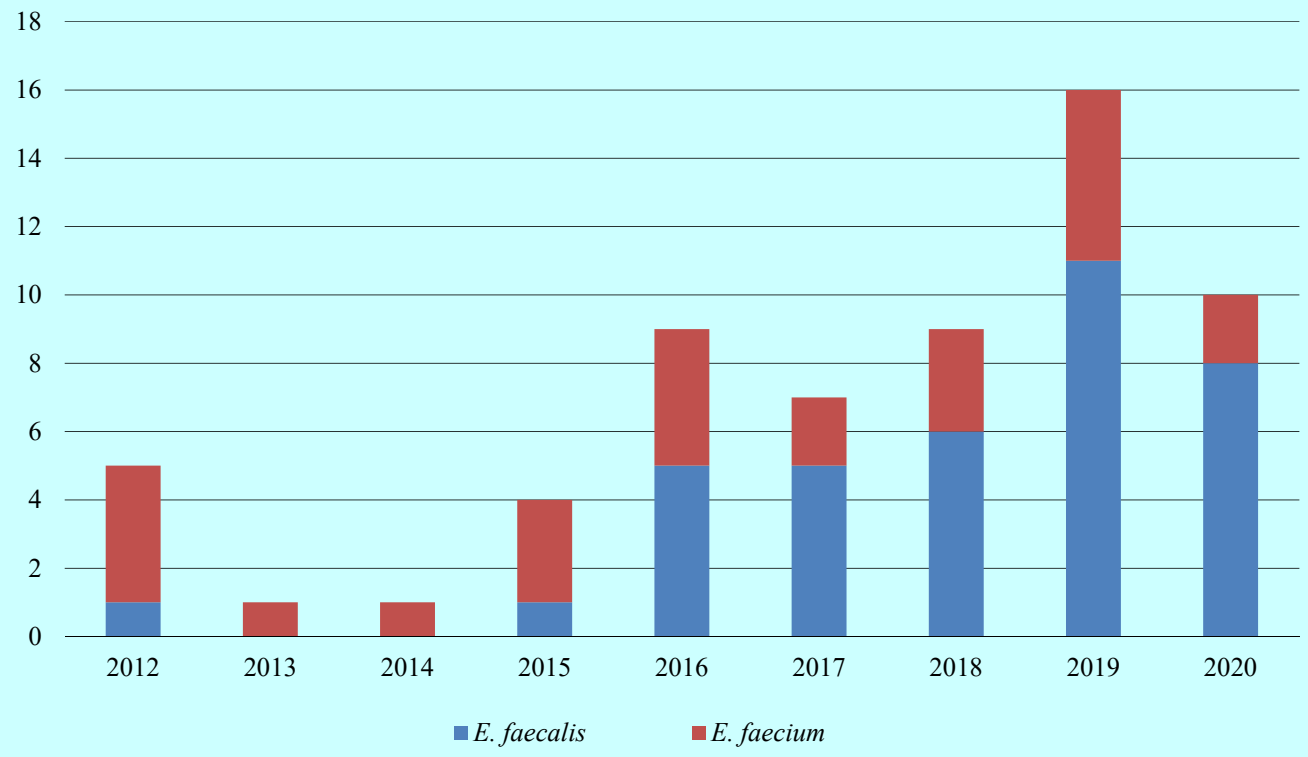

FIGURE 93. The number of linezolid resistant *E. faecium* and *E. faecalis* in Norway 2012-2020, including LRE that are vancomycin resistant.

In 2020, ten cases of LRE were detected in Norway, compared to 16 in 2019 (Figure 93). WGS analyses revealed no closely related isolates (Figures 91 and 94). 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 (Figure 93; n=35) is mainly due to non-clonal spread of isolates with *optrA* (Figure 95; n=32).

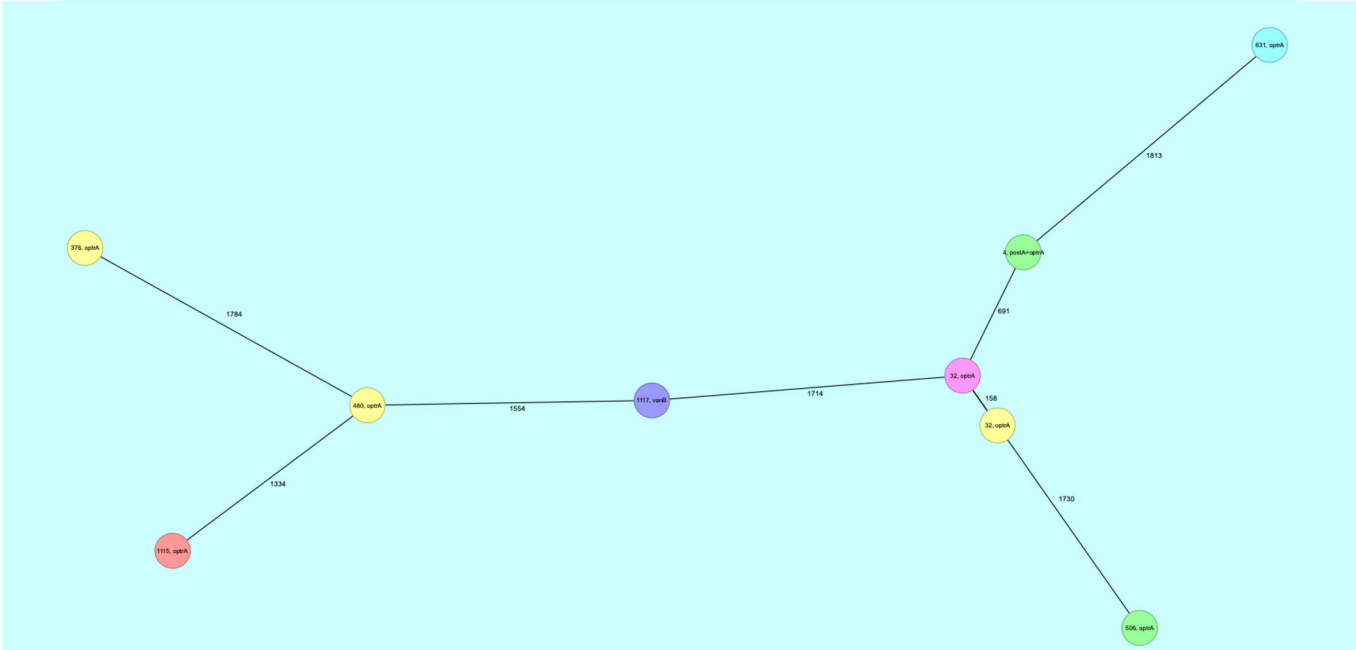

FIGURE 94. Minimum spanning network built from core genome allelic profiles of the nine Norwegian *E. faecalis* (LRE n=8, VRE n=1) 2020 isolates using Ridom-SeqSphere+ with integrated core genome (cg) MLST scheme with *E. faecalis* OG1RF as reference strain. The isolates are colour coded according to primary laboratory. None of the isolates are closely related (> 7 allelic distance). The two ST32 isolates showed 158 allelic differences.

Linezolid resistance in enterococci has traditionally mostly been mediated by point mutations in the chromosomal 23S rRNA regions, mainly the G2576U mutation. Mutations are known to occur after long-term exposure to linezolid (16). In 2020, two LRE were *E. faecium* of which one isolate had mutational based linezolid resistance and the other an unknown mechanism of resistance. Of the linezolid resistant *E. faecalis* (n=8), seven isolates had *optrA* and one both *optrA* and *poxtA* (Figure 95). Eight of the 2020 LRE isolates were from infections and six of these had *optrA*. One LRE isolate was associated with import, but information about import is lacking for seven isolates. Both *E. faecium* isolates belonged to ST117, a well-known pandemic hospital associated sequence type. The *E. faecalis* isolates (*n*=8) belonged to seven different STs of which ST32 was found in two isolates (Table 72).

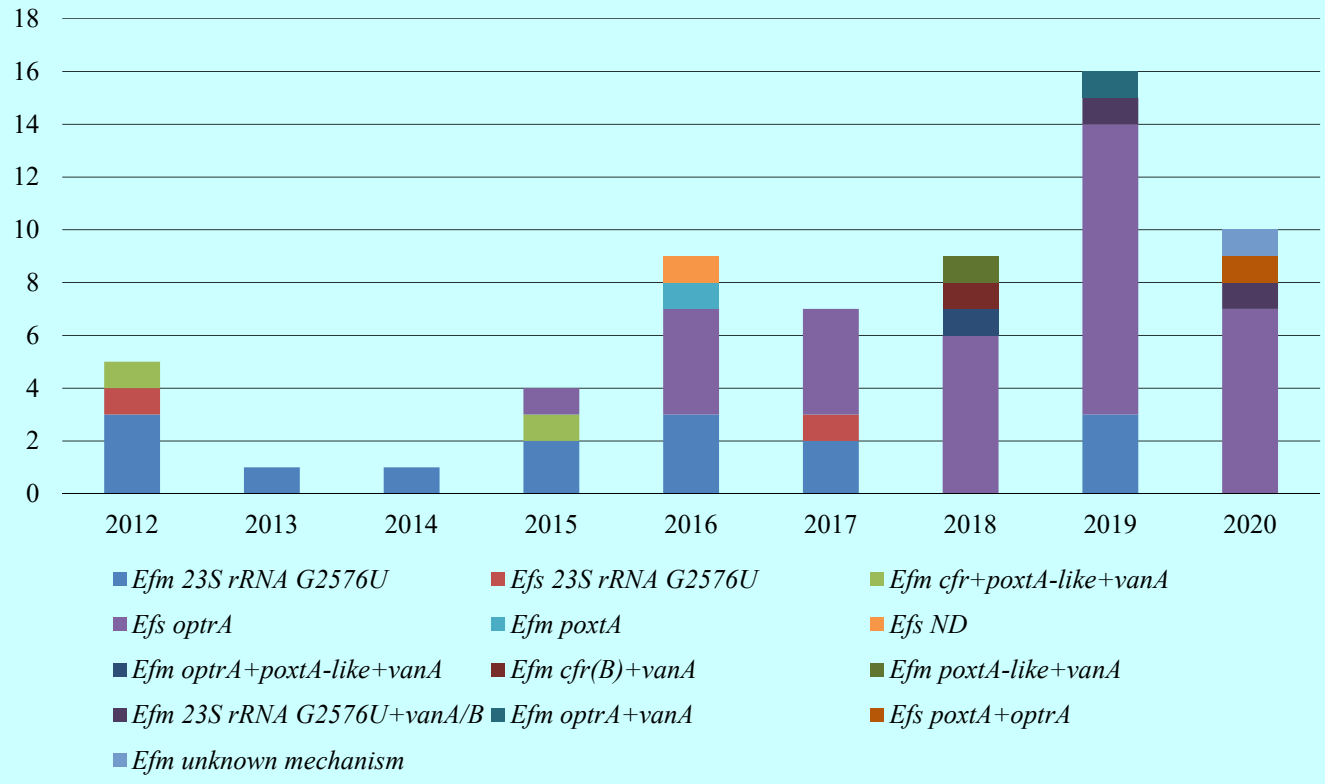

FIGURE 95. Number of linezolid resistant enterococci (LRE) according to resistance mechanisms per year. *Efm = E. faecium. Efs = E. faecalis*. ND = not determined genotype. This isolate was not sent to K-res or archived at the primary laboratory.

TABLE 72. Species, resistance mechanism and sequence type among LRE in Norway 2020.

Species	Resistance mechanism	ST
E. faecalis (n=8)	*optrA* (*n*=7)	ST32 (n=2); ST376 (n=1); ST480 (n=1); ST506 (n=1); ST631 (n=1); ST1115 (n=1)
	optrA + *poxtA* (n=1)	ST4 (n=1)
E. faecium (n=2)	23S rRNA G2576U mutation (n=1); unknown mechanism (*n*=1)	ST117 (n=2)

Conclusion:

The incidence of LRE is still low in Norway. In 2020 there were six fewer cases of LRE (n=10) compared to 2019. Since 2016 there has been a change from *E. faecium* with mutation-based linezolid resistance to *E. faecalis* with transferrable resistance mechanisms dominated by *optrA*. However, the numbers are still too small to exclude random effects. Phylogenetic analyses and epidemiological data do not support domestic spread of LRE in Norway. The majority of LRE isolates from 2020 were recovered from clinical samples.

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Kristin Hegstad, Jessin Janice and Arnfinn Sundsfjord, Norwegian National Advisory Unit on Detection of Antimicrobial Resistance, Department of Microbiology and Infection Control, University Hospital of North Norway and UiT – The Arctic University of Norway, Tromsø, Norway, and Petter Elstrøm and Oliver Kacelnik, Department of Antibiotic Resistance and Infection Prevention, Norwegian Institute of Public Health, Oslo, Norway.

Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 73. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2020 (n=297). 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	87.2	11.1	1.7
Cefotaxime*	≤ 0.5	> 2	98.0	2.0	0.0
Ceftriaxone*	≤ 0.5	> 2	97.3	2.7	0.0
Erythromycin	≤ 0.25	> 0.5	91.6	0.0	8.4
Clindamycin	≤ 0.5	> 0.5	93.3	-	6.7
Tetracycline	≤ 1	> 2	90.9	1.0	8.1
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	91.9	2.0	6.1
Chloramphenicol	≤ 8	> 8	100.0	-	0.0
Oxacillin screen (mm)	≥ 20	< 20	82.8	-	17.2

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 74. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2020 (n=297). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*		0.3	23.9	58.2	4.7	1.7	5.7	1.3	0.7	1.7	1.0	0.3	0.3			
Cefotaxime*		2.7	56.9	25.9	3.4	5.7	1.3	2.0	1.7	0.3						
Ceftriaxone*			77.1	8.8	4.4	4.4	1.3	1.3	2.4	0.3						
Erythromycin				0.7	24.9	63.3	2.7			1.0	0.3	0.3	0.7	0.3		5.7
Clindamycin			0.3	1.7	30.3	53.5	7.1	0.3	0.7		0.3					5.7
Tetracycline					5.1	52.5	32.7	0.3	0.3	1.0	1.0		1.7	4.0	1.3	
TMS**					0.7	28.3	58.6	2.7	1.7	2.0	2.7	0.7	1.3	1.3		
Chloramph.									11.4	78.8	9.4	0.3				
Norfloxacin							0.3		0.3	6.1	42.4	46.1	3.4	0.3	0.7	0.3
	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	17.2	1.0	3.0	6.7	9.1	15.5	16.5	9.8	8.8	6.4	3.4	2.0	0.7			

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 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 73-74 and Figures 96-97. Five strains were isolated from cerebrospinal fluids and seventeen were isolated from unspecified materials. 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 2020. 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 11.1% (33/297) of *S. pneumoniae* isolates were only susceptible to penicillin G with increased exposure (MIC 0.125-2 mg/L), and five isolates (1.7%) were classified as resistant (MIC > 2 mg/L). These rates have increased since 2018 (I + R combined were 8.9% and 12.8% in 2018 and 2020, respectively). The five penicillin G resistant isolates (MIC 4-16 mg/L) were categorised as S (n=1) or I (n=4) for cefotaxime and ceftriaxone (MIC 1-2 mg/L for both substances). Four additional isolates categorised as I to penicillin G (MIC 2 mg/L) were only susceptible to increased exposure to cefotaxime and/or ceftriaxone. Two isolates recovered from cerebrospinal fluids had penicillin G MICs of 0.25-0.5 mg/L and were thus resistant according to the meningitis breakpoint, but they were both susceptible to 3rd generation cephalosporins (S ≤ 0.5).

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 38 penicillin G I + R isolates were resistant to oxacillin.

Conversely, 13/259 penicillin G S isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 100% and 95.0%, respectively. Many of the *S. pneumoniae* isolates categorised as I+R to penicillin G were also resistant to tetracycline (21/38), erythromycin (20/38), clindamycin (16/38) and/or trimethoprim-sulfamethoxazole (13/38).

The prevalence of erythromycin resistance was relatively stable at 8.4% in 2020 compared to 7.8% in 2017 and 6.0% in 2018 (Figure 96). Most of these isolates (20/25) were resistant to both erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining five 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 2018. The results may suggest a continuing predominance of *erm*-encoded macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 97).

The 6.1% resistance rate to trimethoprim-sulfamethoxazole was at the same level as 5.4% in 2018. The prevalence of tetracycline resistance increased from 6.0% in 2018 to 8.1% in 2020 (Figure 96). All isolates were susceptible to chloramphenicol, which was earlier used for empirical treatment of meningitis in Norway. The low prevalence of high-level norfloxacin resistance (Table 74) may reflect the very limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

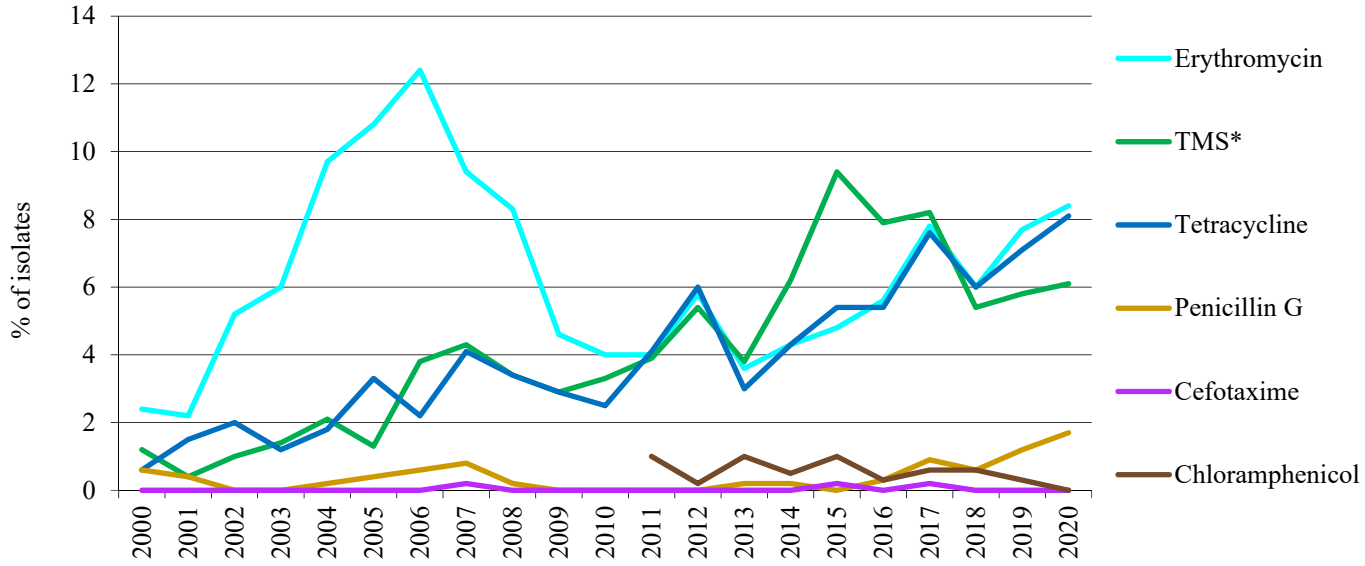

FIGURE 96. Prevalence (%) of resistance to antimicrobial agents in *Streptococcus pneumoniae* blood culture and cerebrospinal fluid isolates during 2000-2020. Doxycycline was substituted by tetracycline in 2005. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

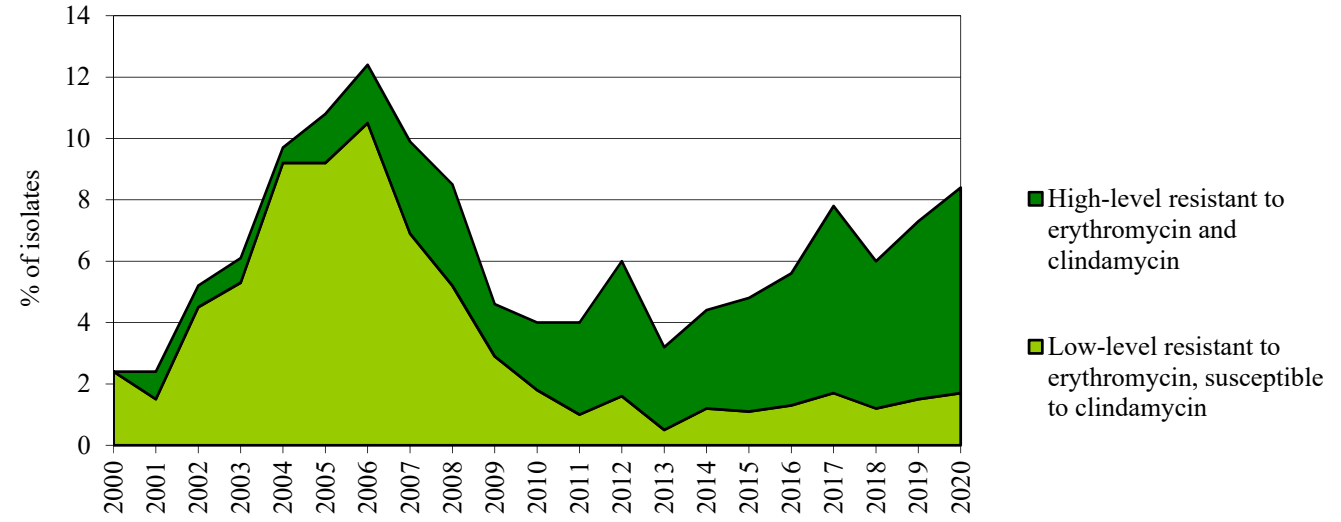

FIGURE 97. Prevalence of resistance (%) to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2020.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 75. *Streptococcus pneumoniae* in respiratory tract specimens in 2020 (n=326). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G*	≤ 0.06	> 2	91.4	8.3	0.3
Cefotaxime*	≤ 0.5	> 2	98.2	1.8	0.0
Ceftriaxone*	≤ 0.5	> 2	99.7	0.3	0.0
Erythromycin	≤ 0.25	> 0.5	88.7	1.5	9.8
Clindamycin	≤ 0.5	> 0.5	94.8	-	5.2
Tetracycline	≤ 1	> 2	88.7	0.9	10.4
Trimethoprim-sulfamethoxazole**	≤ 1	> 2	88.3	1.8	9.8
Chloramphenicol	≤ 8	> 8	99.1	-	0.9
Oxacillin screen (mm)	≥ 20	< 20	87.1	-	12.9

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. 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 76. *Streptococcus pneumoniae* in respiratory tract specimens in 2020 (n=326). 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*	13.8	44.5	25.2	4.9	3.1	3.1	2.8	0.3	1.5	0.6		0.3				
Cefotaxime*	0.3	18.1	57.4	11.7	2.8	6.1	0.6	1.2	1.5	0.3						
Ceftriaxone*	16.3	53.7	16.6	3.7	5.2	1.8	1.5	0.9	0.3							
Erythromycin					2.8	37.4	48.5	1.5			0.6	1.2	1.2	0.6	0.3	5.8
Clindamycin					6.1	50.6	33.7	4.3								5.2
Tetracycline	0.9	0.3		1.8	43.6	39.0	2.5	0.3	0.3	0.9		2.1	5.8	2.5		
TMS**				0.3	2.8	18.1	46.9	14.7	5.5	1.8	3.1	1.8	1.8	3.1		
Chloramph.									0.6	47.5	44.5	6.4	0.3	0.6		
Norfloxacin										8.0	32.5	52.5	6.1	0.6		0.3

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	12.9	0.6	1.2	1.2	1.5	5.5	7.4	12.0	12.9	12.9	7.1	12.6	3.4	5.8	1.2	1.8

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

S. pneumoniae isolates from respiratory tract specimens were last surveyed in NORM in 2018. The rates of resistance to various antimicrobials are shown in Tables 75-76 and Figure 98.

The prevalence of resistance to penicillin G was still very low (0.3%) according to the non-meningitis breakpoint of R > 2 mg/L. A single isolate with a penicillin G MIC of 8 mg/L remained fully susceptible to cefotaxime and ceftriaxone. A considerable proportion of isolates (6.9% in 2018, 8.3% in 2020) would require increased exposure for treatment with penicillin G as they had MICs in the 0.125-2 mg/L range. These 27 isolates should be categorised as penicillin G resistant in the context of clinical meningitis, and six of them would have required increased exposure to cefotaxime and/or ceftriaxone.

Almost all (27/28) isolates with penicillin G MIC > 0.06 mg/L were detected by the oxacillin screening test (sensitivity 96.4%), whereas fifteen fully penicillin susceptible isolates were classified as oxacillin resistant (specificity 95.0%). Isolates with elevated penicillin G MICs were commonly cross-resistant to other antimicrobial agents such as tetracycline (17/28), erythromycin (15/28) and trimethoprim-sulfamethoxazole (15/28).

The rate of resistance to erythromycin was 9.8% in 2020 compared to 8.2% in 2018. Macrolide resistance was thus at the same level in respiratory tract isolates as in isolates from blood and sterile sites (8.4%). The MLS fenotype of 28/32 erythromycin resistant isolates was determined by double disk diffusion. Twelve isolates (43% of erythromycin resistant isolates, 4.2% of all isolates) displayed constitutive MLS_B resistance to erythromycin and clindamycin, whereas two isolates (7%) were inducibly resistant to clindamycin. Low-level M-type resistance was detected in 14 isolates (50% of erythromycin resistant isolates, 4.9% of all isolates).

Tetracycline resistance increased from 6.9% in 2018 to 10.4% in 2020, whereas trimethoprim-sulfamethoxazole resistance increased from 8.2% in 2018 to 9.8% in 2020. The norfloxacin MIC distribution did not change significantly in the period 2018-2020.

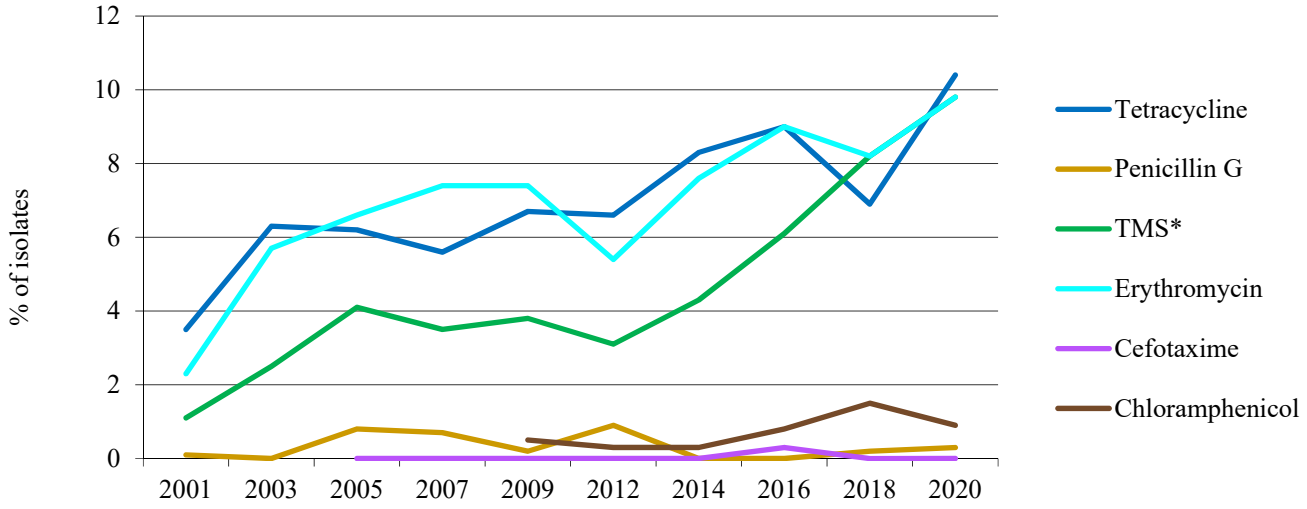

FIGURE 98. Prevalence of antimicrobial resistance in *Streptococcus pneumoniae* from respiratory tract samples 2001-2020. Isolates are categorised according to the breakpoints at the time of analysis for each year. Doxycycline was replaced by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole. Please note that the x-axis is not to scale.

Streptococcus pyogenes in blood cultures

TABLE 77. *Streptococcus pyogenes* in blood cultures in 2020 (n=134). 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	93.3	0.0	6.7
Clindamycin	≤ 0.5	> 0.5	94.8	-	5.2
Tetracycline	≤ 1	> 2	83.6	0.7	15.7
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	99.3	0.0	0.7

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 78. *Streptococcus pyogenes* in blood cultures in 2020 (n=134). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G	0.7	2.2	77.6	17.9	1.5											
Erythromycin				3.0	43.3	46.3	0.7			0.7				0.7		5.2
Clindamycin			0.7	5.2	61.9	26.1	0.7									5.2
Tetracycline					10.4	68.7	4.5			0.7	0.7		1.4	8.2	5.2	
TMS*					26.1	39.6	31.3	2.2						0.7		

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. *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 for 2018-2019 as the laboratory was reorganised during that period.

As expected, all isolates were fully susceptible to penicillin G (Tables 77-78). There were no isolates resistant to erythromycin or clindamycin in 2018, but the rates for 2020 (6.7% and 5.2%) have increased since 2017 (4.2% and 2.5%, respectively). However, the results should be interpreted with caution due to small numbers. Most erythromycin resistant isolates (7/9) were concomitantly high-level resistant to clindamycin, thus indicating the presence of constitutive MLS_B resistance. The prevalence of tetracycline resistance increased from 10.9% in 2017 to 15.7% in 2020, whereas the prevalence of resistance to trimethoprim-sulfamethoxazole remained stable at 0.7% in 2020 compared to 0.8% in 2017.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 79. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2020 (n=303). 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	80.5	0.0	19.5
Clindamycin	≤ 0.5	> 0.5	87.5	-	12.5
Tetracycline	≤ 1	> 2	24.1	0.7	75.2
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 80. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2020 (n=303). Distribution (%) of MICs (mg/L).

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G*			4.3	60.7	34.7	0.3										
Erythromycin				0.3	15.2	51.8	13.2			2.0	5.0	4.3	2.6	0.3		5.3
Clindamycin			0.3	1.0	18.2	62.4	3.0	2.6	1.0	0.7	0.7	0.7	0.7			8.9
Tetracycline				1.7	18.8	2.6	0.3	0.3	0.3	0.7	0.3	10.6	39.9	23.4	1.0	
Vancomycin				1.0	5.3	53.5	38.0	2.3								
Gentamicin												0.7	5.0	39.9	50.9	3.6

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method 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 303 isolates were retrieved from invasive infections (bacteremia and cerebrospinal infections) in 2020. Thirty-five isolates originated from neonates and small children < 1 year of age. Most isolates (99.3%) were recovered from blood cultures, but there were also two isolates from cerebrospinal fluids.

As seen in Tables 79-80 there were no isolates with reduced susceptibility to penicillin G or vancomycin. Fifty-nine isolates (19.5%) were resistant to erythromycin compared to 22.6% in 2018 and 25.5% in 2019. They were all analysed by double disk diffusion for MLS_B resistance phenotype. Constitutive MLS_B resistance was found in 45 isolates (76%), while inducible MLS_B resistance was detected in six isolates (10%). The remaining eight isolates (14%) had results in accordance with the efflux-mediated M phenotype encoded by *mef* genes. A single isolate was recorded as clindamycin resistant (MIC 2 mg/L) in spite of being susceptible to erythromycin (MIC 0.125 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 3.6% of the isolates. The prevalence of resistance to tetracycline (75.2%) was at the same level as in 2019 (77.7%) with the majority of isolates displaying MIC values of 8-32 mg/L (Table 80).

Resistance against empiric antibiotic combinations in the treatment of bloodstream infections – 2020 update

Narrow-spectrum antibiotic combinations are frequently used in Norway for empirical treatment of bloodstream infections (BSIs), often preferred over mono-therapy with broad-spectrum drugs [1]. In 2016, combinations of beta-lactam and gentamicin were shown to provide good coverage against many common BSI pathogens in Norway [2], thus it is of interest to see if this still is true. Table 81 shows the frequency of resistance among key pathogens in bloodstram infections (BSI) against common drugs and drug combinations used in Norwegian hospitals in the empirical treatment of sepsis in 2020 [1].

Among Gram-positive microbes, rates of resistance remain low. Notably, in *Staphylococcus aureus*, the prevalence of MRSA remains around 1% and gentamicin resistance is still less than 1%. Benzylpenicillin (penicillin G) resistance in *Streptococcus pneumoniae* is only 1.7%, but the rate of isolates only susceptible to increased exposure of this agent are increasing (11.1% in 2020). Whilst susceptible to high-dose benzylpenicillin, these isolates are resistant to phenoxymethylpenicillin, frequently used as peroral step-down therapy.

ESBL rates in *Escherichia coli* and *Klebsiella* spp. continue to rise, both rates now above 6.5 % for the last three years. Worryingly, this is largely driven by multi-drug resistant clones frequently resistant to gentamicin [3-5]. For now, cefotaxime and gentamicin still provide acceptable coverage, where half of all ESBL isolates are susceptible to gentamicin. Piperacillin/tazobactam resistance rates are higher than in 2016 due to adjustment of the breakpoint in 2020 [6]. When applying the new breakpoint to 2016 data, the resistance rates are similar to 2020.

For *Haemophilus influenzae* there are no breakpoints for benzylpenicillin, but wildtype isolates are likely susceptible to high dosage. By using benzylpencillin 1-unit screening [7], 46.5% of isolates are characterised as non-wildtype, likely rendering them resistant to benzylpenicillin. Thus, benzylpenicillin/gentamicin should be used with caution in clinical settings with a high prevalence of *H. influenzae*.

TABLE 81. Resistance (%) to broad-spectrum antibiotics and antibiotic combinations in key bloodstream infection pathogens.

Antibiotic drug combiantions		Proportion of invasive isolates resistant (%)									
		E. coli (n=2,087)	*Klebsiella* spp. (n=967)	ESBL *Enterobacterales** (n=206)	*H. influenzae* (n=43)	*Enterococcus* spp. (n=677)	*S. pneumoniae* (n=297)	*S. pyogenes* (n=134)	*S. agalactiae* (n=303)	*S. aureus* (n=1,367)	MRSA* (n=1,720)
Benzylpenicillin	Gentamicin	6.7	5.2	47.1	46.5[1]	-	1.7	0.0	0.0	0.4	12.8
Benzylpenicillin	Ciprofloxacin	11.2	8.1	60.7	0.0	-	1.7	0.0	0.0	3.1	24.3
Clindamycin	Gentamicin	6.7	5.2	47.1	100.0	100.0	6.7	5.2	12.5	0.1	1.5
Ampicillin	Gentamicin	6.2	5.2	47.1	16.3	15.5[3]	X	0.0[4]	0.0[4]	0.4	12.8
Piperacillin/tazobactam	Gentamicin	1.2	2.9	17.5	4.7[2]	15.5[3]	X	0.0[4]	0.0[4]	0.0	12.8
Cefotaxime		6.7	7.8	97.1	2.3	100.0	0	0.0[4]	0.0[4]	1.4[5]	100.0
Piperacillin/tazobactam		5.4	11.2	25.2	4.7[2]	15.5[3]	X	0.0[4]	0.0[4]	1.4[5]	100.0
Meropenem		0.0	0.0	0.0	0.0	100.0	X	0.0[4]	0.0[4]	1.4[5]	100.0

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

In conclusion, betalactam/gentamicin combinations still provide good coverage in many clinical settings. Resistance levels in Gram-positives remain favourable, while rising ESBL rates among *E. coli* and *Klebsiella* spp. are a continuing cause for concern.

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Anaerobic bacteria in blood cultures

TABLE 82. Anaerobic Gram-negative bacteria in blood culture 2020 (n=516). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Penicillin G	≤ 0.25	> 0.5	14.3	3.1	82.6
Piperacillin-tazobactam	≤ 8	> 16	82.5	7.4	10.1
Meropenem	≤ 2	> 8	96.0	1.7	2.3
Clindamycin	≤ 4	> 4	84.1	-	15.9
Metronidazole	≤ 4	> 4	98.1	-	1.9

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

TABLE 83. Distribution (n) of MICs (mg/L) for *Bacteroides fragilis* group (n=326), *Bacteroides* non-*fragilis* group (n=54) and *Fusobacterium* spp. (n=50) from blood culture 2020.

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Bacteroides fragilis group (n=326)																
Penicillin G	1				1	1	2	4	5	7	15	31	37	222		
Pip-Tazo*			2		7	14	42	88	54	29	26	18	20	15	5	6
Meropenem				2	24	142	89	37	8	6	3	5		10		
Clindamycin			9	11	24	30	33	41	58	45	18	7	2	3	1	44
Metronidazole						1	19	59	149	81	15	2				
Bacteroides non-*fragilis* group (n=54)																
Penicillin G						1		1		1	1	6	9	35		
Pip-Tazo**					1				7	6	8	16	9	5		2
Meropenem				1	3	10	27	11	2							
Clindamycin			1				1	4	13	17	6	2				10
Metronidazole					1	4		4	23	17	4					1
Fusobacterium spp. (n=50)																
Penicillin G	13	9	17	7					1					3		
Pip-Tazo*			28	11	4	1	3						1	1		1
Meropenem	14	14	17	3		1				1						
Clindamycin			9	15	17	6	1			1		1				
Metronidazole			23	4	2	5	8	4	3	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. *Pip-Tazo=Piperacillin-Tazobactam

TABLE 84. Anaerobic Gram-positive bacteria in blood culture 2020 (n=365). *Cutibacterium* spp. are not included. Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	S	I	R
Penicillin G	≤ 0.25	> 0.5	73.7	8.5	17.8
Piperacillin-tazobactam	≤ 8	> 16	88.8	3.0	8.2
Meropenem	≤ 2	> 8	98.9	0.8	0.3
Clindamycin	≤ 4	> 4	88.8	-	11.2
Metronidazole	≤ 4	> 4	87.7	-	12.3

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

TABLE 85. Distribution (n) of MICs (mg/L) for *Clostridium* spp. (n=169) and *Cutibacterium* spp. (n=25) from blood culture 2020.

	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Clostridium spp. (n=169)																
Penicillin G	2		6	32	53	15	21	19	12	4				5		
Pip-Tazo*			7	24	40	26	14	17	15	8	7	6	3	1		1
Meropenem	22	21	24	13	15	14	17	13	23	7						
Clindamycin			3	2	14	37	7	16	15	29	16	16	6	3		5
Metronidazole			3	4	2	6	7	14	44	64	23			1		1
Cutibacterium spp. (n=25)																
Penicillin G	3	3	7	8	3	1										
Pip-Tazo*			3		2	4	3	4	8	1						
Meropenem	1	2	3	5	6	7		1								
Clindamycin			1	12	8	1	1		1							1
Metronidazole																25

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. *Pip-Tazo=Piperacillin-Tazobactam

RESULTS AND COMMENTS

Anaerobic bacteria from blood cultures were previously surveyed in NORM in 2014. There are a number of methodological challenges with surveillance of anaerobes. In order to ensure clinical relevance of the material, only blood culture isolates were included. Furthermore, only laboratories using MALDI-TOF and/or 16S rDNA sequencing for identification submitted data, as inconsistent speciation is a major obstacle for meaningful interpretation of data. Finally, the reproducibility of antibiotic susceptibility test results may be a problem due to subtle variations in agar composition and incubation conditions. The EUCAST/NordicAST clinical breakpoints for anaerobes have remained unchanged since 2014 for the agents included in the survey.

The data for Gram-negative and Gram-positive bacteria are presented in Tables 82-83 and 84-85, respectively. The SIR distributions are combined for all genera/species in the two groups, except for *Cutibacterium* (formerly *Propioni-bacterium* spp.) which is excluded from Table 84. The MIC distribution data in Tables 83 and 85 are only presented for selected genera/species as specified.

A total of 516 Gram-negative isolates were included in the survey. The majority belonged to the *Bacteroides fragilis* group (n=326), defined as either *B. fragilis, B. ovatus, B. thetaiotaomicron* or *B. vulgatus.* All other Gram-negative isolates were classified as *Bacteroides* non-*fragilis* group (n=54), *Fusobacterium* spp. (n=50) and "others" (n=86). The latter group included isolates belonging to the genera *Dialister, Parabacteroides, Veillonella, Prevotella, Anaerotruncus, Tissirella, Gabonibacter, Odoribacter, Bilophila, Alistipes, Hungatella, Sutterella, Leptotrichia, Desulfovibrio,* and also a number of unspecified isolates.

Beta-lactamase testing was not included in the protocol, but as seen in Tables 82-83 the vast majority of Gram-negative isolates were clearly resistant to penicillin G including practically all *Bacteroides* spp. strains. The rate of Gram-negative isolates susceptible to standard dosage of piperacillin-tazobactam (82.5%) was at the same level as in 2014 (76.2%). As seen in Table 83, the *B. fragilis* group appeared more sensitive to this combination drug than other members of the same genus. Clindamycin resistance was detected in 15.9% of Gram-negative anaerobes in 2020 compared to 18.1% in 2014. *Fusobacterium* spp. isolates were generally suscpeptible to all the examined agents. Twelve isolates (2.3%) were resistant to meropenem (MIC ≥ 32 mg/L), ten belonging to the *B. fragilis* group and two identified as *Desulfovibrio* spp. Five additional *B. fragilis* group isolates were only susceptible to meropenem at increased dosage (MIC 8 mg/L). Ten isolates (1.9%) of various genera (*Bacteroides*, *Veillonella*, *Dialister* and *Sutterella*) were reported as resistant to metronidazole (MIC 8-256 mg/L).

Among the 390 Gram-positive isolates included in the survey, about 50% belonged to the genera *Clostridium* (n=169) and *Cutibacterium* (formerly *Propionibacterium*) (n=25). The latter is not generally considered a true anaerobe and the isolates are therefore omitted from Table 84. The remaning 196 isolates represented a wide variety of genera, including *Eubacterium, Eggerthella, Parvimonas, Trueperella, Actinomyces, Actinotignum, Atopobium, Peptoniphilus, Anaerococcus, Bifidobacterium, Blautia, Ruminococcus, Solobacterium, Peptostreptococcus, Lactobacillus, Bulleidia, Finegoldia, Catenibacterium, Anaerotruncus, Slackia, Lachnoanaerobaculum, Dielma, Paeniclostridium* and *Eggerthia.* As expected, *Cuti-bacterium* spp. isolates were highly resistant to metronidazole and susceptible to all other agents (Table 85). Forty-five other isolates (12.3%) of various species similarly displayed metronidazole resistance. A single *Lactobacillus rhamnosus* isolate was resistant to meropenem (MIC ≥ 32 mg/L), whereas three *Bifido-bacterium breve* isolates were only susceptible to increased dosage of this agent (MIC 4-8 mg/L). Piperacillin-tazobactam generally had high activity among all anaerobic Gram-positive species (88.8% S), whereas many species had a high prevalence of inherent or acquired resistance to penicillin G (17.8%). Clindamycin resistance (11.2%) was lower than in 2014 (17.5%).

Mycobacterium tuberculosis

In 2020 (2019 in parenthesis), 160 (162) persons were reported with tuberculosis disease (TB) to the Norwegian Surveillance System for Communicable Diseases (MSIS). Of these, 30 (17) were born in Norway. 130 (128) had TB for the first time, of which one (4) had received preventive treatment. 16 (11) had had previous TB, of which 15 (10) had been treated with anti-TB drugs previously. The rest, 14 (23) cases, were categorised as uncertain if they had received TB treatment previously.

132 (135) cases were confirmed with *M. tuberculosis*-complex (MTBC) by culture. One of these was identified as *M. africanum,* the rest were *M. tuberculosis*. Resistance results reported to MSIS are shown in Table 86. Results from testing of both isolates and direct samples are included. There was one MDR- and one RR-TB case in 2020 (two MDR-TB cases in 2019). The MDR case had low-level resistance to ethambutol, but was sensitive to pyrazinamide, fluoroquinolones, amikacin, linezolide, clofazimine, bedaquiline and cycloserine. The RR case was only resistant to rifampicin and susceptible to all other drugs mentioned above. Both cases had TB for the first time, but the RR-TB patient had received preventive TB treatment previously. In addition to the MDR case, 14 cases had strains resistant to isoniazid, six of them only with low-level resistance. Seven patients with negative culture result or without culture result had results from molecular/ genotypic tests showing MTBC and sensitivity to rifampicin (no *rpoB* mutation). One patient without culture confirmation showed resistance to isoniazid.

TABLE 86. Antimicrobial resistance for MTBC reported to MSIS (not *M. bovis* BCG) from human infections in 2020. Figures from 2019 in parentheses.

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents				
			Isoniazid	Rifampicin	Ethambutol	Pyrazinamide	MDR-TB
			133 (130)	139 (133)	133 (129)	133 (127)	133 (130)
Norway	30 (17)	24 (11)	2 (0)	0 (0)	1 (0)	0 (0)	0 (0)
Europe excl. Norway	10 (25)	9 (22)	0 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Asia	57 (58)	46 (48)	7 (3)	2 (2)	1 (2)	2 (5)	1 (2)
Africa	62 (60)	52 (52)	6 (5)	0 (0)	0 (0)	0 (1)	0 (0)
America	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oseania	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (1)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	160 (162)	132 (135)	15 (10)	2 (2)	2 (2)	2 (6**)	1 (2)
Proportion resistant isolates (%)*			11.3 (7.2)	1.4 (1.5)	1.5 (1.6)	1.5 (4.7)	0.8 (1.5)

*Result either from isolates or from genotypic tests without culture. **Of these, one *M. bovis* isolate in 2019 with inherent resistance to pyrazinamide.
MDR-TB: Multi-drug resistant tuberculosis, resistant to at least rifampicin and isoniazid. RR-TB: Rifampicin resistant tuberculosis, without isoniazid resistance.

Resistance in human scabies mites and head lice

A variety of pesticides have been used successfully to treat infestations of arthropod pests both on humans and animals. However, as is the case with antibiotics, frequent use of these drugs has led to treatment failure and development of resistance in many important medical and veterinary parasites. In fact, drug resistance has now been observed in more than 600 species of arthropod pests (1). Resistance to multiple drugs is observed in many species, making them very difficult to treat. Resistance to pesticides (ectoparasiticides) is the selection of a specific heritable trait (or traits) in an ectoparasite population as a result of exposure of that population to an active substance, resulting in a significant increase in the percentage of the population that will fail to respond to a standard dose of that chemical when used as recommended (2).

Ectoparasitic infestations with scabies mites (*Sarcoptes scabiei* var. *hominis*) and head lice (*Pediculus humanus capitis*) are common in humans. These infestations are rarely serious or fatal, but they do have debilitating symptoms and often come with a social stigma attached. Furthermore, the economic costs of repeated treatments can be excessive for many people.

There are estimated to be more than 300 million cases of scabies worldwide each year (3). In Norway, the number of cases of scabies has increased between 2012 and 2019 (4) (Figure 99). Surprisingly, unpublished data reveal a further increase in scabies cases in 2020 during the pandemic. The prevalence of head lice has been thoroughly examined in Norway, and among elementary school students the prevalence was as low as 1.6%. However, more than one-third of the households had previously experienced pediculosis, demonstrating that many people are affected by head lice infestations over time (5).

Scabies treatment in Norway includes either topical drugs (permethrin or benzylbenzoat) or in more complicated cases an oral drug (ivermectin). There are some reports of treatment failure, and possible explanations include:

1. Poor compliance - incorrect use of the drugs
2. Reinfestation due to incomplete management of surroundings, such as contact persons and items (clothing, bedding, towels etc.), although the latter is believed to be of only minor importance
3. Insensitivity/resistance of scabies mites to the drugs
4. Incorrect diagnosis

In vitro trials performed before 1994 with 5% permethrin cream indicated that human scabies mites died within an hour. More recent studies indicate increased tolerance to the drug with 25% survival of the mites after 12 hours (6). There are, however, no scientific papers confirming clinical resistance against permethrin among human scabies mites (7), but a confirmed case of resistant scabies mites on dogs is reported (8). Clinical resistance of human scabies mites against ivermectin is reported (9, 10). Studies have identified four different mechanisms that might contribute to scabicide resistance (11): voltage-gated sodium channels, glutathione S-transferase (GST), ATP-binding cassette transporters, and ligand-gated chloride channels.

In clinical practice, patients are often seen with persisting head lice infestation despite repeated and prolonged treatments. Thus, pediculicide resistance has been an increasing concern for effective control of this ectoparasite. As for scabies, treatment failure of head lice infestations can often be explained by poor compliance and/or reinfestation, but resistance to the pediculicide used are also a probable reason. The current preferred treatment of pediculosis is dimeticone containing products, which are shown to be very effective (12, 13). Dimeticone is a physically acting pesticide that covers the body surface and respiratory system of head lice, and the development of resistance against products with this active ingredient is unlikely (14). However, resistance against drugs with chemically acting compounds, like permethrin, is frequently reported in head lice, and such drugs are therefore considered less effective (12, 15, 16). Frequent combing with a lice comb is a time-consuming treatment method, but it can nevertheless be effective if performed properly (17).

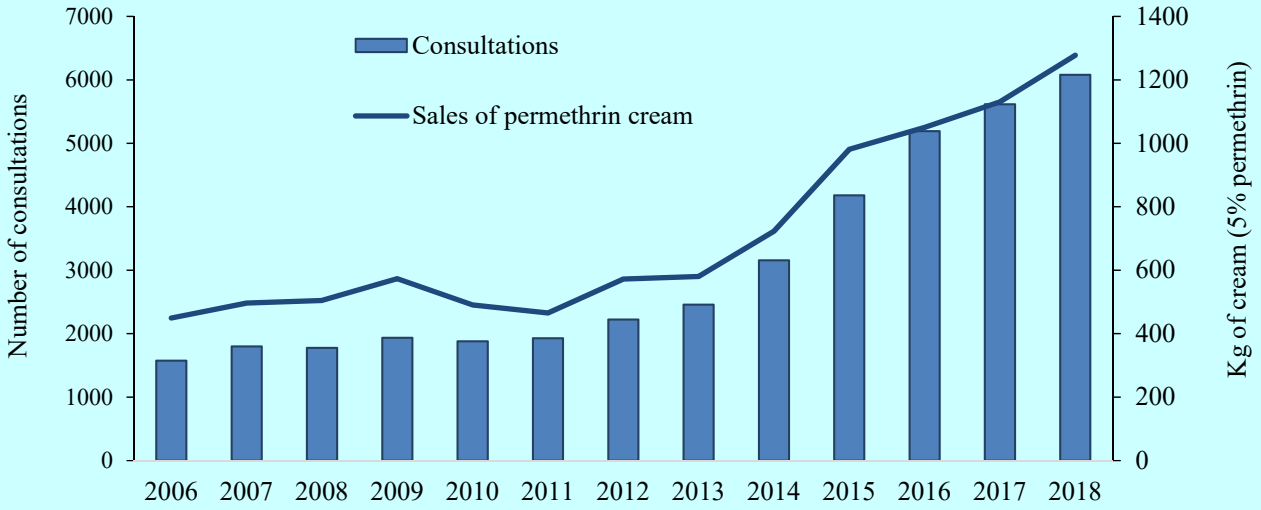

FIGURE 99. Number of scabies consultations versus sales of permethrin 2006-2018 in Norway (from Amato *et al.* 2019).

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Candida spp. in blood cultures

TABLE 87. Antimicrobial susceptibility of *Candida albicans* blood culture isolates in 2020 (n=129). 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
Anidulafungin*	≤ 0.03	> 0.03	99.2	-	0.8
Micafungin*/**	≤ 0.016	> 0.016	98.4	-	1.6

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2020. The revised breakpoints and necessary changes to match the new EUCAST definitions of S, I and R were released in February 2020. *There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible. **With EUCAST revised BP 2020-02-04, micafungin MIC 0.03 mg/L is defined as an area of technical uncertainty (ATU). Two isolates with this MIC were anidulafungin susceptible and were therefore categorised as suseptible to micafungin.

TABLE 88. *Candida albicans* blood culture isolates in 2020 (n=129). 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						14.0	69.8	16.3									
Fluconazole						3.1	51.9	39.5	4.7	0.8							
Voriconazole	12.4	62.0	22.5	3.1													
Anidulafungin	69.7	26.4	1.6	1.6		0.8											
Micafungin **/***	2.4	31.0	63.6	1.6			0.8	0.8									
Caspofungin**	0.8	0.8	3.9	13.2	43.4	33.3	2.3	1.6	0.8								

*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. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin as well as micafungin are considered susceptible. ***With EUCAST revised BP 2020-02-04, micafungin MIC 0.03 mg/L is defined as an area of technical uncertainty (ATU). Two isolates with this MIC were anidulafungin susceptible and were therefore categorised as suseptible to micafungin.

TABLE 89. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates in 2020 (n=24). 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	≤ 0.002	> 16	0.0	87.5	12.5
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. The revised breakpoints and necessary changes to match the new EUCAST definitions of S, I and R were released in February 2020. *There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible. 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.

TABLE 90. *Candida glabrata* blood culture isolates in 2020 (n=24). 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	≥ 256
Ampho. B				1	1	1	5	15	1								
Fluconazole								1		2	6	8	4				3
Voriconazole**			1	1	2	3	9	4	1	1	1	1					
Anidulafungin	1	5	16		2												
Micafungin		4	19	1													
Caspofungin***					2	10	11	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 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 91. Antimicrobial susceptibility of *Candida parapsillosis* blood culture isolates in 2020 (n=6). 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	66.7	0.0	33.3
Voriconazole	≤ 0.125	> 0.25	66.7	0.0	33.3
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. The revised breakpoints and necessary changes to match the new EUCAST definitions of S, I and R were released in February 2020. *There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 92. *Candida parapsilosis* blood culture isolates in 2020 (n=6). 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	≥ 256
Ampho. B								5	1								
Fluconazole						1		3									2
Voriconazole		1		3						1	1						
Anidulafungin									3	2	1						
Micafungin**								5	1								
Caspofungin**								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 are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin.

TABLE 93. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates in 2020 (n=15). 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. The revised breakpoints and necessary changes to match the new EUCAST definitions of S, I and R were released in February 2020. *There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible to caspofungin. **There is insufficient evidence whether the wildtype population of *C. tropicalis* can be considered susceptible to micafungin.

TABLE 94. *Candida tropicalis* blood culture isolates in 2020 (n=15). 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	≥ 256
Ampho. B							1	8	6								
Fluconazole							1	7	6	1							
Voriconazole		1	1	9	1	3											
Anidulafungin	1	7	7														
Micafungin**			7	8													
Caspofungin***					5	9	1										

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Non-shaded cells represent MIC values that are not covered by the standard test method. **There is insufficient evidence whether the wildtype 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 95. Antimicrobial susceptibility of *Candida dubliniensis* blood culture isolates in 2020 (n=14). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B	≤ 1	> 1	100.0	-	0.0
Fluconazole	≤ 2	> 4	100.0	0.0	0.0
Voriconazole	≤ 0.06	> 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. The revised breakpoints and necessary changes to match the new EUCAST definitions of S, I and R released in February 2020. There are currently no European breakpoints for anidulafungin, micafungin or caspofungin.

TABLE 96. *Candida dubliniensis* blood culture isolates in 2020 (n=14). 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	≥ 256
Ampho. B				1	3	3	6	1									
Fluconazole					1	6	5	2									
Voriconazole	4	5	5														
Anidulafungin**	4	8	2														
Micafungin **	1	4	7	2													
Caspofungin**				3	8	3											

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

RESULTS AND COMMENTS

In 2020 the National Mycology Reference Laboratory received 195 isolates from unique candidemias, compared to 199 isolates in 2019. Four infections in four patients were infections with the same species more than four weeks apart and six infections were mixed infections with more than one *Candida* spp. One patient had four different species in blood cultures over a two months period (*Candida albicans, C. dubliniensis, C. lusitaniae* and *Rhodotorula mucilaginosa*). We received nine different *Candida* species from 184 patients with bloodstream infections. The species distribution is still favourable and acquired resistance in *Candida* spp. is rare.

Candida albicans is the most common species (n=129, 66.1%) compared to 58.3% last year and 65.7 % in 2018. The number of *Candida glabrata* isolates is lower (n=24, 12.3 %) than in 2019 (n=29). Interestingly the number of *C. parapsilosis* declined from 19 to six, and no sibling species (*C. metapsilosis* and *C. orthopsilosis*) were referred this year. *C. tropicalis* is, as in 2019, the third most prevalent species (n=15). *Candida dubliniensis* increased further from 5.5% to 7.1% (n=14), but the number of non-albicans isolates is still low.

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). 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 87-96. Species identification still predicts the susceptibility pattern of *Candida* spp. in patients without long-term antifungal treatment.

To implement the new definition of the "I" category from "Intermediate" to "Susceptible, Increased exposure" and "Area of Technical Uncertainty" (ATU) for the antifungal agents, the EUCAST-AFST (Subcommittee on Antifungal Susceptibility Testing) has reviewed all, and revised some, clinical antifungal breakpoints. From 2020 *C. albicans* with micafungin MIC 0.03 mg/L and anidulafungin MIC 0.016 mg/L is regarded sensitive and EUCAST-AFST recommend reporting such isolates as "sensitive" with 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". The changes were released in a revised breakpoint table v. 10.0 in February 2020 and are adopted in this report.

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

Two *C. albicans* isolates were echinocandin resistant, one micafungin resistant isolate with *fks* mutations R647G, and one micafungin- and anidulafungin resistant isolate with *fks* mutations F641S. Two *C. albicans* with micafungin MIC 0.032 mg/L were both regarded sensitive according to the evaluation of ATU as they were anidulafungin sensitive.

All *C. parapsilosis* (n=6) belonged to the wild-type, now 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* have been changed given that the clinical response is not statistically different from that for other agents despite the intrinsic target gene alteration. The two azole resistant *C. parapsilosis* isolates were from one patient on previous long-term treatment, two months apart.

Acquired fluconazole resistance was otherwise only observed in one *C. glabrata* isolate (MIC 256 mg/L). The *C. glabrata* wild-type is considered within the "I" category. Fluconazole breakpoints in *C. glabrata* are redefined ("I " ≤ 16 mg/L) to acknowledge the use of fluconazole in a high dose in some clinical situations and the susceptible category (≤ 0.001 mg/L) is set to avoid misclassification of "I" strains as "S" strains. *C. krusei* (n=1) is inherently resistant to fluconazole. There are no breakpoints for *C. guillermondii* (n=3) but all isolates in 2020 displayed high fluconazole MIC values (8-16 mg/L).

C. dubliniensis (n=14) is closely related to *C. albicans*. Breakpoints were established for itraconazole, posaconazole and voriconazole in 2018 and from 2020 breakpoints of amphotericin B and fluconazole against *C. albicans* are adopted for *C. dubliniensis*. The MIC distribution is now shown in Table 96.

The wild-type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible to voriconazole and all isolates with defined breakpoints, with the exception of the two fluconazole resistant *C. parapsilosis* isolates, were found susceptible to voriconazole in 2020. The intermediate category for voriconazole was introduced for *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* in 2018 to acknowledge that increased exposure can be obtained by intravenous dosing. There is insufficient evidence that *C. glabrata* and *C. krusei* are good targets for therapy with voriconazole and no breakpoints have been set. Breakpoints for isavuconazole have not been established.

Decreased susceptibility to different antifungal classes is common in some of the species not shown in the tables; *C. guillermondii* (n=3) *C. lusitaniae* (n=2), *C. krusei* (n=1) and *C. kefyr* (n=1).

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

Data sources

Sales data at wholsalers level

In Norway, all medicinal products for animals are prescription-only medicines – this includes both veterinary medicinal products (VMPs) and human medicinal products (HMPs). The latter can be prescribed 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 HMP have to be dispensed through pharmacies that are supplied by wholesalers. Medicated feed (manufactured from premix VMPs) is supplied to the end user by feed mills and is currently only used for farmed fish; this is due to the small size of livestock herds in Norway and the low use of group/flock treatments. Group treatment of livestock (terrestrial animals) with anti-bacterial 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 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; antibacterials for farmed fish for the years 2013-2020 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 1 January 2011 and for terrestrial animals 1 January 2012. The veterinarians are mandated to report any administration and deliveries of VMPs and HMPs to VetReg for all terrestrial food-producing animals and horses while it is voluntary for all other animal species such as companion animals. Pharmacies and feed mills have to report all deliveries, i.e. for all terrestrial animals and farmed fish, to veterinarians or animal owners, including medicines prescribed for companion animals and HMPs.

For farmed fish the reporting of prescription of antibacterials has been shown to be complete for the years 2013-2018 (1) and this was the case also for 2019 and 2020 data data; VetReg data are used for farmed fish for these years. For 2012-2014 data from VetReg on antibacterials for terrestrial food-producing animals, the quality of the prescription data was unsatisfactory (unpublished data). For oral paste and intramammaries data quality was unsatisfactory for the entire period 2012-2020, with the result that amounts used could not be calculated. The number of prescriptions was used to obtain a picture of the prescribing per species for these formulations. In this analysis only 2015-2020 data for injectables, oral powders and oral solution from VetReg have been used (2); these were calculated to express kg antibacterials prescribed/used and the outputs were compared to sales data for the corresponding forms obtained from NIPH for the years 2015-2020: The results show that the VetReg data cover around two third of the sales data for VMP injectables**,** oral powders and oral solution. It could not be identified whether the data are represenative for the prescribing of VMPs by animal species, but the VetReg data are nevertheless believed to give a rough picture of the prescription of antibacterial classes by formulation and animal species. VetReg data have therefore been used as an additional souce in order to assess changes according to targets set in the National Strategy against Antibiotic Resistance (2015-2020) (3).

Antibacterial included in the data set

The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to identify the VMPs to be included in the data. Sales of VMPs belonging to the ATCvet codes shown in the table below were collected from the NIPH for terrestrial animals, for farmed fish data for QJ01 were 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

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 are detailed in the ESVAC 2016 report (3). The PCU for each terrestrial animal category is calculated by multiplying numbers of livestock animals (dairy cows, sheep, sows and horses) and slaughtered animals (cattle, goats, pigs, sheep, 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, fish biomass live-weight slaughtered is used as PCU in ESVAC reports. Data on animal population, including farmed fish, used to calculate PCU were obtained from Statistics Norway (https://www.ssb.no).

Indicators
The National Strategy against Antibiotic Resistance (2015-2020) (3) does not specify which indicators to be used in order to measure progress in terms of reduction of usage of antibacterials in animals. In 2017, ECDC, EFSA and EMA jointly established a list of harmonised outcome indicators to measure progress in reducing the usage of antimicrobials and antimicrobial resistance both in humans and food-producing animals. In order to measure the overall effect of policy interventions/management measures to reduce the consumption for food-producing animals the proposed indicator is overall sales in mg/PCU (mg active substance/population correction unit) (5). Therefore, the indicators used to report the usage of antibacterials in the current report are kg active substance and for food-producing animals also mg/PCU.

Analysis of the overall sales data
The sales data for each VMP presentation were calculated to express weight of active substance. In order to comply with the ESVAC standards, sales of prodrugs - e.g. procaine benzylpenicillin and penethamate hydriodide - have been converted to the corresponding values for the active ingredient, here benzylpenicillin (4).

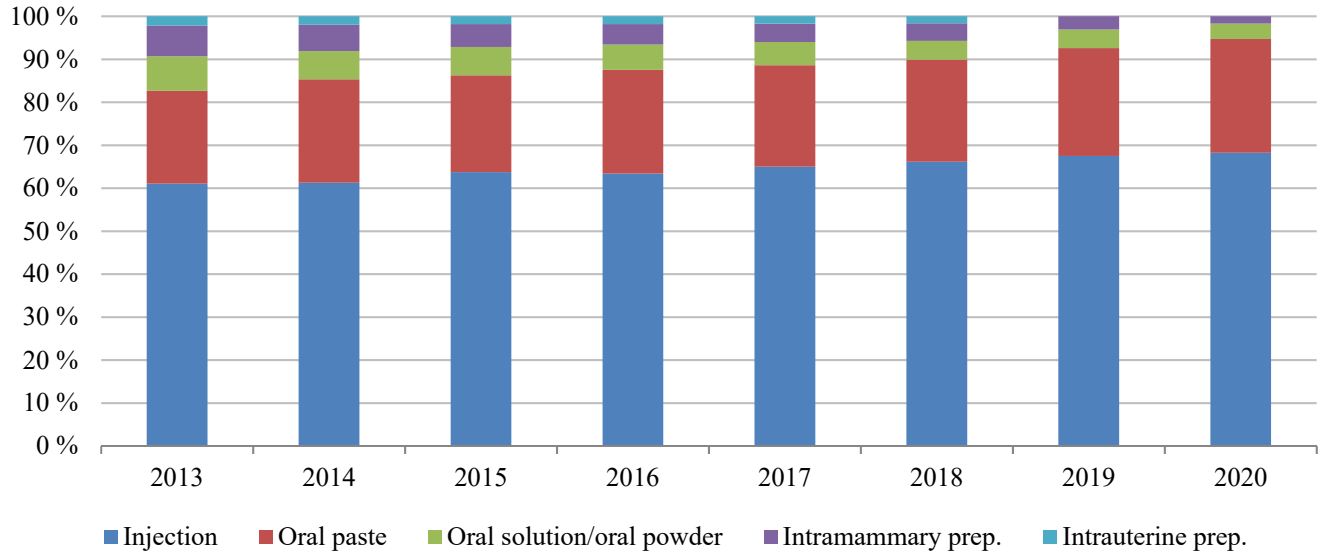
The sales data of antibacterial VMPs for terrestrial animals have been split into sales for food-producing animals (including horses) and companion animals. Sales of antibacterial VMPs for companion animals refer to sales of tablets, oral solution and oral paste that are approved solely for companion 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 therefore 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 2020 (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 2013-2020 have been further refined in order to obtain estimates on the usage in cattle, pigs, sheep, goats and poultry that are more accurate in terms of identifying changes over time. Of the total annual sales of antibacterial VMPs for terrestrial food-producing animals, oral paste approved for horses accounted for 21% in 2013. That figure increased to 26% in 2020, see figure below. Data on prescribtions per animal species obtained from the Veterinary Prescription Register (VetReg) have been used as supportive information to the sales data for this refinement.

VetReg data show that for the years 2015-2020, on average 97% (range 96.4%-97.3%) of the number of prescriptions of antibacterial oral paste VMPs was for horses showing that off-lable use for other animal species of oral paste was negligible. Oral paste (numerator) and PCU for horses (denominator) has been excluded from the analysis of data for the estimation of usage of antibacterial VMPs for cattle, pigs, sheep, goats and poultry. Intramammaries have been excluded from the analysis of the VetReg data regarding prescribed amounts (kg) due to data quality issues (2).



Proportion of kg sold in Norway of antibacterial veterinary medicinal products (VMPs) approved for one or more of the food-producing animal species, including horses, by pharmaceutical forms in the period 2013-2020. Of note, there were no sales of antibacterial VMP intrauterine devices in 2020.

The usage of HMPs for cattle, pigs, sheep, goats and poultry was estimated by use of the following data from VetReg:

- Delivery to animal owners from pharmacies of antibacterial HMPs for use in these species, plus
- Veterinarians' use/delivery of antibacterial HMP for these species. Note that due to underreporting by veterinarians the data represents an underestimate.

Estimation of sales of HMPs for dogs and cats

Veterinarians reported almost no use of HMPs for companion animals to VetReg; this is due to the fact that veterinarians are not mandated to report use of medicines for companion animals to VetReg. It should be noted that the sales from pharmacies to veterinarians of antibacterial HMPs applicable for use in dogs and cats were negligible. The amounts, in kg active substance, of usage of antibacterial HMPs for companion animals were estimated by use of the following data from VetReg:

- Delivery from pharmacies to animal owners of antibacterial HMPs for use in dogs and cats
- Delivery from pharmacies to veterinarians of antibacterial HMP tablets and of oral solution and oral powder for solution suitable for companion animals.

References:

1. Kari Grave and Kari Olli Helgesen. Antibacterials for farmed fish – prescribing, usage and diagnoses 2013 - 2017 (In Norwegian: Antibakterielle midler til oppdrettsfisk – rekvirering, forbruk og diagnose 2013 - 2017). Rapport 5: Veterinærinstituttet, 2018.
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, 2019. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Web Based Sales Data and Animal Population Data Collection Protocol (version 3) (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 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 SLS - Sykehusapotekenes Legemiddelstatistikk (Hospital Pharmacies Drug Statistics Database) which is a cooperation of LIS - Legemiddelinnkjøpssamarbeid (Drug Purchasing Cooperation) and the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. SLS 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. Nasjonal kompetansetjeneste for antibiotikabruk i spesialisthelsetjenesten (Norwegian Advisory Unit for Antibiotic Use in Hospitals) has analysed the data according to activity (admission and bed days).

Population statistics per 1 January are collected from Statistics Norway. Information on bed days and admissions are collected from the Norwegian Patient Register 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 outpatients 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 2021 is used for all years.

Unit of measurement
The ATC/DDD system is recommended by the WHO to serve as a tool for drug utilisation research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels.

The use of defined daily dose – DDD – as a unit of measurement, simplifies and improves the evaluation of drug consumption over time, nationally and internationally. The DDD is a theoretical unit of measurement, and does not necessarily reflect the recommended or Prescribed Daily Dose.

The basic **definition** of the unit is:
The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

The DDDs for the antibacterials are as a main rule based on the use in infections of moderate severity. Some antibacterials are only used in severe infections and their DDDs are assigned accordingly. The DDDs assigned are based on daily treatment.

Inclusion criteria
The antibacterials for human use included in this report belong to ATC group J01 "antibacterials for systemic use". Oral vancomycin (A07AA09), fidaxomycin (A07AA12) and oral and rectal metronidazole (P01AB01) are also included in some figures. Antibacterials used in dermatological preparations (ATC group D) and preparations intended for sensory organs (ATC group S) are not included in the material, except for mupirocin, which is included in one table.

References
1. WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs 2021. 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

Klebsiella pneumoniae was collected from clinical submissions (n=65) of diverse infectious conditions in ten different species (pigs, canines, turkeys, horses, bovines, felines, chickens, sheep, reindeer and caprines (listed in descending order according to number of isolates per species) submitted to the Norwegian Veterinary Institute (NVI) between 2017-2020. Altogether, 74 *K. pneumoniae* isolates were included for susceptibility testing. In total, 83 *Actinobacillus pleuropneumoniae* (APP) isolates from pigs were collected from both clinical submissions (including autopsies) submitted to the NVI and from a research project. All isolates were collected between 2004-2020.

The rest of the samples included in 2020 were collected by the Norwegian Food Safety Authority (NFSA). Caecal samples of broiler and turkey flocks were collected at slaughter for isolation of the indicator bacteria *Escherichia coli*, *Enterococcus faecalis* and *Enterococcus faecium* (as well as zoonotic bacteria, see Appendix 4). From each poultry flock ten caecal samples were collected. A total of 247 pooled samples from broiler and 121 pooled samples from turkeys were included, only one sample per flock. In addition, 323 broiler meat samples were collected at retail in all regions of Norway following the specifications set by the European Food Safety Authority (EFSA journal 2014; 12(5):3686). Samples were to be taken without taking place of origin into consideration. All the caecal and meat samples were also used for selective isolation of *E. coli* resistant to extended-spectrum cephalosporins (ESC) and carbapenem resistant *Enterobacteriaceae* (CRE). In addition, selective isolation for vancomycin resistant *Enterococcus* spp. (VRE) was performed on the caecal samples.

Isolation and identification of bacteria

Clinical isolates of *K. pneumoniae* and APP

The strains were cultured from frozen stocks stored at -80°C. *K. pneumoniae* was cultured on blood agar (Blood Agar Base No.2 (Oxoid, Oslo, Norway)) with 5% bovine blood and APP on blood agar in the presence of a *Staphylococcus aureus* isolate. After incubation of the agar plates at 37±1°C for 18-24 hrs, the strains were confirmed as *K. pneumoniae* or APP by matrix-assisted laser desorption/ionisation time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany).

Indicator isolates of *E. coli*

Sample material, i.e. caecal content from ten broilers or turkeys per flock were pooled and plated directly onto MacConkey agar (Difco) and incubated at 44±0.5°C for 20±2h. Typical colonies were subcultured on blood agar and incubated at 37±1°C for 20±2h. Colonies were identified as *E. coli* by typical colony appearance and a positive indole reaction before further phenotypical testing.

Indicator isolates of *E. faecalis* and *E. faecium*

Sample material, i.e. caecal content from ten broilers or turkeys per flock were pooled and plated directly onto Slanetz and Bartley agar (Oxoid) and incubated at 44±0.5°C for 24-48h. Typical colonies were subcultured on blood agar incubated at 37±1°C for 20±2h. Colonies were identified as *E. faecalis* or *E. faecium* using MALDI-TOF MS.

Vancomycin resistant *Enterococcus* spp.

Sample material, i.e. caecal content from ten broilers or turkeys per flock were pooled and plated directly onto Slanetz and Bartley agar containing 4 mg/L vancomycin (Oxoid) and incubated at 44±0.5°C for 24-48h. Typical colonies were subcultured on Slanetz and Bartley agar containing 4 mg/L vancomycin and blood agar containing 5% bovine blood and incubated at 37±1°C for 20±2h. Presumptive colonies were identified as *E. faecalis* or *E. faecium* by typical colony appearance and verified using MALDI-TOF MS before further phenotypical testing.

Enrichment of caecal and broiler meat samples

All samples were enriched prior to plating onto selective media. A total of 1±0.1 g caecal sample material from broiler or turkey was homogenised with 9 mL of buffered peptone water which is compliant to the ISO 6579 formulation (BPW-ISO). A total of 25 g broiler meat was homogenised with 225 mL of BPW-ISO. Samples were incubated at 37±1°C for 20±2 h according to the protocol from the EURL-AR (http://www.eurl-ar.eu/233-protocols.htm). From the overnight enrichment broth, 10-20 µL were plated on selective media as described in the sections below.

E. coli resistant to extended-spectrum cephalosporins (ESC)

Aliquots from the overnight BPW-ISO broth from all caecal and meat samples were plated onto MacConkey agar containing 1 mg/L cefotaxime and MacConkey agar containing 2 mg/L ceftazidime. The agar plates were incubated at 44±0.5°C for 24-48h. Presumptive ESC resistant *E. coli* were subcultured on MacConkey agar containing 1 mg/L cefotaxime and blood agar, and confirmed as *E. coli* using MALDI-TOF MS before further tested for cephalosporinase production.

Carbapenem resistant *Enterobacteriaceae* (CRE)

Aliquots from the overnight BPW-ISO broth from all caecal and meat samples were plated onto CHROMID® CARBA and CHROMID® OXA-48 agar (bioMérieux, Marcy l'Etoile, France). Plates were incubated at 35±2°C for 24-48 h. Presumptive CRE were subcultured on respective selective CHROMID® agar and blood agar, and species were confirmed using MALDI-TOF MS before further phenotypical testing.

Genotyping

DNA was extracted using QIAamp® DNA Mini Kit (QIAGEN) and whole genome sequencing (WGS) was performed at the NVI on an Illumina® MiSeq (Illumina, San Diego, California, USA). The WGS data were quality controlled by adapter and quality trimming using Trimmomatic (Bolger *et al.* 2014), and assembled using SPAdes v3.11.0 (Bankevich *et al.* 2012) using the "--careful" parameter and a contigs cut-off of "500". For the quality checking and assembly procedure, the Bifrost pipeline developed at the NVI was applied (https://doi.org/10.5281/zenodo.4043861). Assemblies or

paired end reads were subjected to analysis using ResFinder V.4.1 for both aquired genes and chromosomal point mutations (PointFinder) using the online tool at the Centre for Genomic Epidemiology web site (https://cge.cbs. dtu. dk/services/ResFinder/).

Susceptibility testing

Isolates were tested for antimicrobial susceptibility using a broth microdilution method at NVI. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the tested bacteria. Narasin MIC values for *Enterococcus* spp. were obtained using custom made plates from VetMIC™ (Statens veterinärmedicinska anstalt, Sweden). The Sensititre® TREK panels BOPO6F (VFM medium) and EUVSEC were used for the clinical APP and *K. pneumoniae* isolates, respectively. Epidemiological cut-off (ECOFF) values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 20.03.2021) were used, though with some exceptions as described in Appendix 6 and Appendix 7. Overview of the antimicrobial classes and agents tested for with corresponding ECOFFs are shown in Appendix 7.

Quality assurance systems

The following susceptible bacteria were included as quality control on a regular basis: *E. coli* ATCC 25922 and *E. faecalis* ATCC 25922. In addition to the regular susceptible bacteria, the following bacteria received from EURL-AR were included: *Acinetobacter baumanii* 2012-70-100-69 (EUVSEC and EUVSEC2 panel), and *E. faecium* 2012-70-76-8 and *E. faecalis* 2012-70-103-3 (EUVENC panel). The resistant bacterial strain *E. faecium* CCUG 36804 was tested on a regular basis. The results were approved according to reference values given by EUCAST when available. Additional control strains were included when necessary. The laboratories at 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), respectively.

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. Mainly Chi-square tests (when applicable) were performed for comparing resistance levels between years or groups and p-values < 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
Samples from animals were collected according to the Norwegian *Salmonella* control programme for live animals. Additional isolates were obtained from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). One isolate of each serovar per incident was included for susceptibility testing.

Campylobacter coli* and *Campylobacter jejuni
Caecal samples were collected by the Norwegian Food Safety Authority at slaughter. For turkey, these samples are those described in Appendix 3. For broilers, ten caecal samples were collected from flocks identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks, as well as flocks with unknown *Campylobacter* status. Caecal contents from ten samples per flock were plated directly onto mCCDA agar (Oxoid) and incubated under microaerobic conditions at 41.5±1°C for 44±4h. Typical colonies were subcultured on blood agar (Oxoid) and confirmed as *C. jejuni* and/or *C. coli* using MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany).

Susceptibility testing
Animal isolates were tested for antimicrobial susceptibility using broth microdilution. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacterial species to be tested. Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 20.03.2021) were used, except for sulfamethoxazole, colistin and azithromycin for *Salmonella* spp. where EFSA recommended cut-off values were used. For additional antimicrobial agents not defined in the EUCAST recommendations, cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also Appendix 6 and Appendix 7).

Quality assurance systems
The following susceptible bacterial strains were included as quality controls on a regular basis: *E. coli* ATCC 25922, *Acinetobacter baumanii* 2012-70-100-69, *C. coli* 2012-70-443-2 and *C. jejuni* ATCC 33560. NVI has a quality assurance system according to the requirements of NS-EN ISO/IEC 17025. The participating laboratories at 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), respectively.

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

NORM – enteropathogenic bacteria

Sampling strategy – humans

All human isolates of *Salmonella, Yersinia enterocolitica* and *Shigella* were obtained from clinical cases. One isolate per patient or one isolate per recognised outbreak was included for susceptibility testing. *Campylobacter* isolates from a selection of a little less than 10% of registered campylobacteriosis cases were submitted in the following way: Five regional laboratories submitted the first five independent isolates each month to the NRL for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Identification of bacteria – human isolates
The reference analyses on human clinical isolates of enteropathogenic bacteria were performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th edition ASM-Press, Washington 2003 and Ewing WH: Edwards and Ewing's Identification of *Enterobacteriaceae*, 4. edition, Elsevier, New York 1986).

Susceptibility testing human isolates
Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the National Reference Laboratory (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 (Liofilchem).
For human isolates, EUCAST clinical or epidemiological breakpoints for *Enterobacteriaceae*, version 10.0 2020 were used if defined. In absence of clinical breakpoints, ECOFFs based on 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 (BD Sensidisc), and for the presence of $ESBL_M$ by an AmpC detection test (Liofilchem MIC-test strips). 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
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 1.1.04) in Ridom SeqSphere+ (v. 7.0.6).

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 stored 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 septicaemiae. Surveillance schemes 2000-2020 are presented in the table below, for enteric infections see Appendix 4. In 2020, 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 2020 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. from blood cultures (9 months); *Streptococcus agalactiae*, anaerobic bacteria and *Candida* spp. from blood cultures (12 months); *Streptococcus pneumoniae*, *Streptococcus pyogenes, Haemophilus influenzae* and *Neisseria meningitidis* from blood cultures and cerebrospinal fluids (12 months); *S. aureus* from wound specimens (1 week); *S. pneumoniae* from respiratory tract samples (3 weeks); *E. coli* (1 week) and *Klebsiella* spp. (3 weeks) from urinary tract infections; *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* from all samples (12 months). *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 OUS/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. gonorrhoese* 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. Anaerobic bacteria, *S. pneumoniae*, *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*), or Brucella blood agar (anaerobic bacteria). 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 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* and *S. pyogenes* isolates was analysed using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

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, *Bacteroides fragilis* ATCC 25285, *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. All isolates of the same species 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
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
	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
	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
	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
	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
	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
	N. menigitidis														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
	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
	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
	S. pyogenes (GAS)						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
	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
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
	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

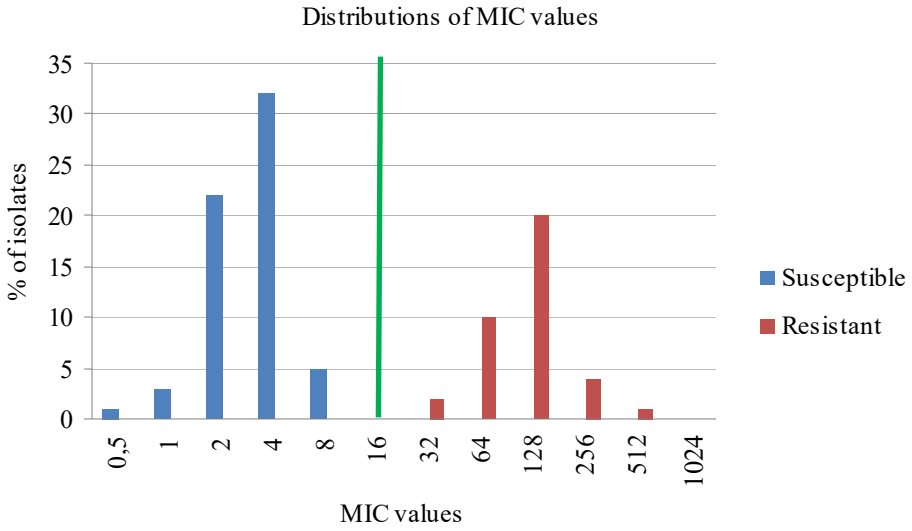
Surveillance at reference laboratories in red. d = days; w = weeks; m = months.

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 wildtype distribution whereas the curve to the right (red) shows the resistant or non-wildtype 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-wildtype 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 on the basis of 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 *Actinobacillus pleuropneumoniae* and *Klebsiella pneumoniae* to define ECOFFs 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 2018/2019 (EFSA Journal 2021;19(4):6490), as follows:

Rare:	<0.1%
Very Low:	0.1% to 1%
Low:	>1% to 10%
Moderate:	>10% to 20%
High:	>20% to 50%
Very high:	>50% to 70%
Extremely high:	>70%

Appendix 7: Cut-off values NORM-VET

Epidemiological cut-off (ECOFF) values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 20.03.2021) 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 *Actinobacillus pleuropneumoniae*, and for chloramphenicol, trimethoprim, sulfamethoxazole and nalidixic acid for *Klebsiella pneumoniae* isolates. The range for testing of *A. pleuropneumoniae* was too narrow for several of the included antimicrobials, thereby resulting in an uncomplete MIC distribution. For these cases, the ECOFFs were not defined.

Overview of the antimicrobial classes and agents tested for with corresponding epidemiological MIC cut-off values (mg/L) used in NORM-VET 2020:

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella* spp.	*Klebsiella pneumoniae*	*Campylobacter coli* / *C. jejuni*	*Enterococcus faecalis* / *E. faecium*	*Actinobacillus pleuropneumoniae***
Tetracyclines	Chlortetracycline						>8
	Oxytetracycline						>4
	Tetracycline	>8	>8	>8	>2 / >1	>4	
	Tigecycline	>0.5	>1[#]	>2		>0.25	
Amphenicols	Chloramphenicol	>16	>16	>16		>32	
	Florfenicol						>1
Penicillins with extended spectrum	Ampicillin	>8	>8	NA		>4	>1
	Temocillin	(>16)					
Beta-lactamase sensitive penicillins	Benzylpenicillin						>2
2nd generation cephalosporins	Cefoxitin	(>8)					
	Cefuroxime						
3rd generation cephalosporins	Cefotaxime	>0.25	>0.5	>0.25			
	Ceftazidime	>0.5	>2	>0.5			
	Ceftiofur						>0.5
Combinations of 3rd generation cephalosporins and clavulanic acid	Cefotaxime/clavulanate	(>0.25)					
	Ceftazidime/clavulanate	(>0.5)					
4th generation cephalosporins	Cefepime	(>0.25)					
Carbapenems	Meropenem	>0.125	>0.125	>0.125			
	Ertapenem	(>0.03)					
	Imipenem and enzyme inhibitor	(>0.5)					
Trimethoprim and derivatives	Trimethoprim	>2	>2	>2			

Antimicrobial class	Antimicrobial agents	*Escherichia coli*	*Salmonella* spp.	*Klebsiella pneumoniae*	*Campylobacter coli / C. jejuni*	*Enterococcus faecalis / E. faecium*	*Actinobacillus pleuropneumoniae***
Sulfonamides	Sulfadimethoxine						ND
	Sulfamethoxazole	>64[#]	>256[#]	>16			
Combinations of sulfonamides and trimethoprim, incl. derivates	Sulfamethoxazole and trimethoprim						ND
Macrolides	Erythromycin				>8 / >4	>4	
	Azithromycin	>16	>16[#]	>32			
	Tylosin						ND
	Tilmicosin						>64
	Tulathromycin						>64
Lincosamides	Clindamycin						>32
Streptogramins	Quinupristin and dalfopristin					ND	
Streptomycins	Streptomycin				>4		
Other aminoglycosides	Gentamicin	>2	>2	>2	>2[#]	>64 / >32	ND
	Neomycin						ND
Fluoroquinolones	Ciprofloxacin	>0.064	>0.064	>0.125	>0.5	>4 / >8	
	Enrofloxacin						>0.25
	Danofloxacin						>0.25
Other quinolones	Nalidixic acid	>8	>8	>8	>16		
Glycopeptid antibacterials	Vancomycin					>4	
	Teicoplanin					>2	
Polymyxins	Colistin	>2	>2[#]	>2			
Pleuromutilins	Tiamulin						>64
Other antibacterials	Spectinomycin						ND
	Linezolid					>4	
	Daptomycin					>4 / >8	
	Narasin					>2*	

ND = not defined, NA = not applicable, ( ) = only ESBL/AmpC suspected isolates tested as described in Commission Implementing Decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU), data not shown in the report tables.
[#]Cut-offs defined by EFSA. *Cut-offs defined by the MIC distributions obtained in NORM-VET. **Range for testing was too narrow for several included antimicrobial substances, giving an uncomplete MIC distribution, and ECOFFs were therefore not defined.

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.

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*	Anaerobic bacteria	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Amikacin	≤ 8	> 8	■	■																			
Amphotericin B	≤ 1	> 1																	■	■	■	■	■
Ampicillin	≤ 1	> 1			■																		
	≤ 4	> 8												■									
	≤ 8	> 8	■					■	■	■													
Amoxi-Clav*	≤ 2	> 2			■																		
	≤ 8	> 8	■	■																			
	≤ 32	> 32	■	■																			
Anidulafungin	≤ 0.03	> 0.03																	■				
	≤ 0.06	> 0.06																		■	■		
	≤ 4	> 4																				■	
Cefepime	≤ 1	> 4	■	■																			
Cefixime	≤ 0.125	> 0.125					■																
Cefoxitin	≥ 22 mm	< 22 mm											■[1]										
Cefotaxime	≤ 0.125	> 0.125			■																		
	≤ 0.5	> 2													■								
	≤ 1	> 2	■	■				■	■	■													
Ceftazidime	≤ 1	> 4	■	■				■	■	■													
Ceftriaxone	≤ 0.125	> 0.125			■	■	■																
	≤ 0.5	> 2													■								
Cefuroxime	≤ 0.001	> 8	■	■																			
	≤ 1	> 2			■																		
Chloramphenicol	≤ 2	> 2			■	■																	
	≤ 8	> 8						■	■	■					■								
Ciprofloxacin	≤ 0.001	> 1											■										
	≤ 0.03	> 0.03				■																	
	≤ 0.03	> 0.06					■																
	≤ 0.06	> 0.06			■																		
	≤ 0.25	> 0.5	■	■					■	■													
	≤ 0.5	> 0.5									■	■											
Clindamycin	≤ 0.25	> 0.5											■										
	≤ 0.5	> 0.5													■	■	■						
	≤ 4	> 4																■					
Erythromycin	≤ 0.25	> 0.5													■	■	■						
	≤ 1	> 2											■										
	≤ 4	> 4									■												
	≤ 8	> 8										■											

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*	Anaerobic bacteria	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
Fluconazole	≤ 0.002	> 16																		■			
	≤ 2	> 4																	■		■	■	■
Fosfomycin	≤ 8	> 8	■																				
Fusidic acid	≤ 1	> 1											■										
Gentamicin	≤ 1	> 1											■										
	≤ 2	> 2	■	■							■[2]	■[2]											
	≤ 128	> 128												■									
Imipenem	≤ 0.001	> 4												■									
Linezolid	≤ 4	> 4											■	■									
Mecillinam	≤ 8	> 8	■	■																			
Meropenem	≤ 2	> 2			■																		
	≤ 2	> 8	■	■				■	■	■								■					
Metronidazol	≤ 4	> 4																■					
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						■[3]															
Pip-Tazo**	≤ 8	> 8	■	■																			
	≤ 8	> 16																■					
Rifampicin	≤ 0.06	> 0.5											■										
	≤ 0.25	> 0.25				■																	
Spectinomycin	≤ 64	> 64					■																
Tetracycline	≤ 0.5	> 1					■																
	≤ 1	> 2			■								■		■	■	■						
	≤ 2	> 2				■					■	■											
	≥ 17 mm	< 17 mm						■[2]	■[2]	■[2]													
Tigecycline	≤ 0.25	> 0.25												■									
	≤ 0.5	> 0.5	■										■										
Tobramycin	≤ 2	> 2	■	■																			
Trimethoprim	≤ 4	> 4	■	■																			

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*	Anaerobic bacteria	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida dubliniensis*
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 based on the wildtype distribution by EUCAST. [2] Breakpoints according to national zone distributions. [3] 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. 10.0).

Appendix 9:
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