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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. Moreover, resistance can be disseminated through the spread of resistant pathogenic bacteria themselves or by horizontal transfer of resistance genes from one type of bacteria to another. Such transfer is not limited to closely related bacteria; it can also take place between bacteria 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 microbes in food production.

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 veterinary 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 is 10% and 30% reduction in the usage, respectively, by 2020, with 2013 as reference year.

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 eighteenth annual joint report from NORM and NORM-VET, presents data on resistance and usage for 2017. 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 2018

SAMMENDRAG

Dette er den attende felles rapporten fra Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM) og Norsk overvåkingsprogram for antibiotikaresistens i mikrober fra fôr, dyr og næringsmidler (NORM-VET). Rapporten presenterer data om forekomst av antibiotikaresistens og forbruk av antibiotika til mennesker og dyr i 2017. 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 som ble offentliggjort i 2000. NORM koordineres av Avdeling for mikrobiologi og smittevern, Universitetssykehuset Nord-Norge i Tromsø. NORM-VET koordineres av Veterinærinstituttet i Oslo. Programmene utgir en felles årsrapport.

Forbruk av antibiotika til dyr

I 2017 utgjorde salget av antibakterielle veterinærpreparater til landdyr 5587 kg aktivt stoff. Dette var en nedgang på 265 kg sammenlignet med 2016.

Til matproduserende landdyr som gris, storfe, sau, geit og fjørfe ble det i all hovedsak brukt penicilliner, og av disse var det nesten utelukkende benzylpenicillin som ble benyttet. I perioden 2013-2017 var det en nedgang i forbruket av antibakterielle veterinærpreparater til de viktigste matproduserende artene (storfe, gris, sau, geit og fjørfe) på ca 10 % målt i kg aktivt stoff. Hvis en tar hensyn til at det har skjedd en liten reduksjon i dyrepopulasjonen i samme tidsperiode, blir nedgangen i forbruket 9 %. Det er fortsatt lavt forbruk av antibakterielle midler som Verdens helseorganisasjon har definert som de høyest prioriterte av de kritisk viktige antibakterielle midlene (CIA) for humanmedisinen. Salget av antibakterielle veterinærpreparater som kan brukes til flokkbehandling, er fortsatt lavt; i 2017 representerte salg av slike produkter 5 % av totalsalget. Til hest ble det i hovedsak brukt trimetoprim-sulfa (oral pasta).

Forbruket av veterinære antibakterielle midler til oppdrettsfisk som går til matproduksjon (forbruk til rensefisk utelatt), var fortsatt svært lavt; i 2017 utgjorde det 535 kg. Dette representerer en nedgang på over 99 % sammenlignet med toppåret 1987. I 2017 ble det foretatt behandling med antibiotika av laks og regnbueørret i 0,8 % av sjølokalitetene.

Det er en nedgang i forbruket av veterinære antibakterielle midler på 32 % til kjæledyr (hund og katt) fra 2013. Nedgangen er på 20 % når man regner med bruk av humane antibakterielle midler, estimert ved bruk av data fra Veterinært lege-middelregister.

Narasin ble faset ut som fôrtilsetningsmiddel til slaktekylling sommeren 2016. Bruken av antibiotika til behandling av slaktekylling er fortsatt svært lavt; i 2017 ble det foretatt behandling i 0,2 % av slaktekyllingflokkene og kun penicilliner ble brukt.

Forbruk av antibiotika hos mennesker

Den totale antibiotikabruken er kontinuerlig redusert siden 2012. Bruken er gått ned med 21 % siden 2012. Med total antibiotikabruk menes alt salg i Norge av antibakterielle midler til systemisk bruk hos mennesker (J01 ekskl. metenamin) i primærhelsetjenesten og i institusjoner. Også i 2017 fortsatte reduksjonen, med 5 % sammenliknet med i 2016. Det totale salget gikk ned fra 14,6 DDD/1000 innbyggere/døgn i 2016 til 13,8 DDD/1000 innbyggere/døgn i 2017. Andelen smalspektrede penicilliner (J01CE) var stabil – 26 % av totalt salg (J01, ekskl. metenamin), men redusert i forhold til tidligere år; i år 1997 (20 år siden) var andelen 35 % av det totale salget.

Rundt 82 % av totalt antall DDD av antibakterielle midler forskrives i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. I 2017 var penicilliner (J01C) mest brukt i primærhelsetjenesten; 54 % av alle DDD for antibakterielle midler til systemisk bruk (J01, ekskl. metenamin), etterfulgt av tetracykliner, J01A (22 %). De fire hyppigst brukte antibiotika i 2017 var fenoksymetylpenicillin, doksycyklin, pivmecillinam og amoxicillin. Disse fire representerte 57 % av alle antibiotikaresepter og 61 % av alle solgte DDD. Tannleger forskriver rundt 5 % av alle DDD i primærhelsetjenesten.

Antibiotikasalg (i DDD) til sykehus utgjorde 8 % av totalt salg av antibakterielle midler til mennesker i 2017. I norske sykehus ble det gjennomsnittlig brukt 79 DDD/100 liggedøgn i 2017, og dette er en økning på 9 % siden 2012. DDD/sykehusinnleggelse (i 2017; 3,3 DDD/innleggelse) økte med 2 % i samme periode. Terapimønster av antibakterielle midler i sykehus endres ikke mye fra år til år. I sykehus ble penicilliner (J01C) mest brukt (ca halvparten av bruken målt i DDD), cefalosporiner er den nest største antibiotikagruppen; 17 % av alle DDD. Det er store variasjoner mellom sykehus, både målt i volum (DDD/100 liggedøgn) og i terapiprofil. Variasjonene kan ikke forklares med forskjeller i aktivitet eller pasientsammensetning alene.

Resistens hos indikatorbakterier fra dyr, mat og fôr

Forekomst av antibiotikaresistens hos bakterier i normal tarmflora kan fungere som en indikator på det seleksjonspresset floraen i de forskjellige populasjonene utsettes for. I et land med lavt forbruk av antibiotika til dyr og generelt lave nivåer av antibiotikaresistens vil det imidlertid kunne være andre faktorer som påvirker forekomst og spredning av antibiotikaresistens.

NORM-VET følger de krav til overvåking av antibiotikaresistens som er satt i EU-regelverket. I tillegg overvåkes/kartlegges bakterier og resistensformer ut i fra nasjonale hensyn. Eksempler på dette er målrettede selektive undersøkelser av spesielle resistensformer slik som f.eks. meticillinresistente *Staphylococcus aureus* (MRSA), *E. coli* med resistens mot tredje generasjons cefalosporiner eller karbapenemer, og kinolonresistente *E. coli*.

I 2017 ble det undersøkt avføringsprøver fra storfe, svin og hest. Det ble også undersøkt nesesvaber fra hest. I tillegg ble det undersøkt prøver fra flokker med fjørfe avlsdyr, både sokkeprøver og fuktede kluter. Fra mat ble det undersøkt kjøtt fra storfe og svin, samt bladsalat og ferske krydderurter. I tillegg blir resultatene fra overvåkingsprogrammet for MRSA hos svin beskrevet.

Resultatene fra 2017 bekrefter at forekomsten av antibiotika-resistens hos bakterier fra dyr og mat i Norge er lav. Dette vises av resultatene for indikator *E. coli* og fra selektiv screening for *E. coli* med resistens mot tredje generasjons cefalosporiner, kinoloner, karbapenemase-produserende enterobakterier og meticillinresistente *Staphylococcus aureus* (MRSA).

Majoriteten av *E. coli* isolater fra storfe, hest og svin var fullt følsomme for alle de antibiotika det ble testet for. Blant de isolatene som viste nedsatt følsomhet, var det i hovedsak resistens mot ampicillin, sulfamethoxazol, tetracyklin og trimetoprim som ble påvist. Dette er i samsvar med tidligere resultater.

I den selektive screeningen for *E. coli* med resistens mot tredje generasjons cefalosporiner hos storfe, svin og hest ble det kun påvist noen få isolater med plasmidmediert resistens. Dette viser at det fortsatt er en svært lav forekomst av disse overførbare resistensformene hos storfe, svin og hest i Norge. Resistens mot tredje generasjons cefalosporiner kan også være forårsaket av mutasjoner i bakterienes kromosom, og fra storfe og svin ble det påvist slike *E. coli* isolater. *E. coli* med resistens mot tredje generasjons cefalosporiner ble ikke påvist fra kjøttprøvene, mens det fra bladsalaten og krydderurtene kun ble påvist i en enkelt prøve.

Karbapenemaseproduserende enterobakterier har aldri vært påvist fra dyr eller mat i Norge. Den selektive screeningen for karbapenemaseproduserende enterobakterier ble utført på alle de undersøkte kategorier av dyr og mat, uten at slike bakterier ble påvist. Det ble heller ikke påvist kolistin-resistente *E. coli* i den selektive screeningen som ble gjort på prøvene fra bladsalat og krydderurter.

Kinolonresistente *E. coli* ble i de selektive undersøkelsene påvist kun fra noen få av prøvene fra hest, og fra prøvene fra bladsalat og ferske krydderurter. Av disse var det bare i enkelte isolater mistanke om plasmidmediert resistens. Prøvene fra storfe og svin, samt kjøttprøvene ble ikke undersøkt ved selektiv metodikk. Kinolonresistente *E. coli* er mer vanlig hos fjørfe, og ble påvist i ca. halvparten av de undersøkte prøvene fra fjørfe avlsdyr. I majoriteten av isolatene er resistensen forårsaket av mutasjoner i *gyrA* genet som ligger på kromosomet, mens det kun i to isolater antas at det forårsakes av plasmidmediert resistens.

Det er begrensede funn av MRSA i den norske dyre-populasjonen. Årlig gjennomføres det et omfattende overvåkingsprogram for MRSA i svinepopulasjonen. I 2017 ble det ikke påvist noen svinebestninger med LA-MRSA CC398, som er den MRSA typen det er mest vanlig å finne hos svin. Det ble imidletid påvist andre MRSA; MRSA CC7, CC130 og CC425 fra hhv. en formerings-besetning og i to smågrisproduserende besetninger. MRSA ble ikke påvist i noen av de undersøkte flokkene av fjørfe avlsdyr, noe som indikerer at avlsdyrene er fri for MRSA. Hest ble også undersøkt for MRSA i 2017. Det ble påvist MRSA CC398 *spa*-type t011 fra en hest. Dette er en MRSA type som tidligere er assosiert med funn fra hest.

Resistens hos zoonotiske bakterier og andre enteropatogene bakterier

Zoonosebakterier isolert fra dyr

Den norske husdyrpopulasjonen er regnet som fri for *Salmonella* spp. I 2017 ble kun 15 *Salmonella* spp. isolater fra dyr sensitivitetsundersøkt. De 15 isolatene var fra tre villfugler, en fjørfeflokk, to hunder, to svin, fire sauer, en hjort og to pinnsvin. Alle 15 isolatene var fullt følsomme for de antibiotika de ble testet for.

I 2017 ble svin undersøkt for *Campylobacter coli*, og resultatene indikerer en høy forekomst av resistens pga nedsatt følsomhet for streptomycin og kinoloner. Det har vært en økning i resistens hos *C. coli*, særlig kinolonresistens. Dette rapporteres også for *C. coli* fra både mennesker og dyr i andre europeiske land.

Kliniske isolater av tarmpatogene bakterier fra mennesker

For kliniske *Salmonella* isolater fra mennesker sett under ett var forekomsten av multiresistens (MDR) 8,0 %, mens forekomsten av bredspektrede beta-laktamaser (ESBL) holdt seg under 1 %. For blodkulturisolater (n=61) var forekomsten av MDR høyest for *Salmonella* spp. unntatt *S.* Typhi, Paratyphi, Typhimurium og Enteritidis. Forekomsten av resistens var høyere i *S.* Typhimurium-gruppen (inkludert *S. enterica* serovar 4,[5],12:i:-) enn hos andre *Salmonella* serovarer. Forekomsten av resistens mot tetracyklin og ampicillin var også økende i denne bakterie-gruppen.

Blant *Campylobacter* var det økende resistens mot tetracyklin og kinolon hos isolater ervervet ved utenlandssmitte, men forekomsten var betydelig lavere for innenlandssmittede isolater.

De fleste tilfeller av *Shigella* infeksjoner i Norge kan knyttes til smittekilder i utlandet. Antibiotikaresistens var følgelig utbredt blant *Shigella* isolater. Forekomsten av ESBL hos *Shigella* var 8 % i 2017.

Antibiotikaresistens hos *Yersinia enterocolitica* ligger stabilt lavt, bortsett fra artens iboende resistens mot ampicillin.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterie-isolater fra mennesker var fortsatt lav i 2017. Det ble påvist ti tilfeller av methicillinresistente *Staphylococcus aureus* (MRSA) blant 1312 blodkulturisolatene (0,8 %) som ble inkludert i NORM-protokollen. Dette samsvarer godt med tall fra laboratorienes datasystemer som rapporterte 18 MRSA-isolater blant 1767 *S. aureus* (1,0 %) fra blodkultur og spinalvæske i 2017. Andelen er på samme nivå som i 2015 (0,7 %) og 2016 (1,0 %). Meldesystemet for infeksjonssykdommer (MSIS) registrerte 763 tilfeller av MRSA-infeksjon i 2017 mot 785 i 2015 og 887 i 2016. De fleste tilfellene var fra pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus*-isolater fra sårprøver (13 av 1098; 1,2 %) slik de har gjort i tidligere år (1,2 % i 2015, 1,6 % i 2016). MSIS registrerte videre 1529 tilfeller av MRSA-kolonisering i 2017 mot 1448 i 2015 og 1651 i 2016. Det totale antallet MRSA-meldinger ble dermed redusert fra 2538 i 2016 til 2292 i 2017 (-10 %). Overvåkingen viser at det totale antallet MRSA-registreringer er stabilt, og dette skyldes

nedgang i antall infeksjoner og en svak økning av koloniseringsraten. Det påvises fortsatt svært få alvorlige MRSA-infeksjoner. Den økte prevalensen av MRSA-kolonisering kan skyldes en reell økning av MRSA-forekomsten, men kan også skyldes høyere testaktivitet.

Blodkulturisolater av *E. coli* og *Klebsiella* spp. viste en svakt økende forekomst av resistens mot bredspektrede antibiotika i 2017. Forekomsten av resistens og nedsatt følsomhet for gentamicin hos *E. coli* økte fra 6,4 % i 2015 og 6,7 % i 2016 til 7,1 % i 2017. Forekomsten av resistens og nedsatt følsomhet for ciprofloxacin i *E. coli* økte fra 17,1 % i 2016 til 18,0 % tross redusert forskrivning av ciprofloxacin i både sykehus og primærhelsetjenesten. *Klebsiella* spp. og *Proteus* spp. hadde lavere forekomst av resistens mot aminoglykosider og fluorokinoloner enn *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 140/2136 *E. coli* (6,6 %), 47/884 *Klebsiella* spp. (5,3 %) og 1/192 *Proteus* spp. (0,5 %) fra blodkultur ble rapportert som ESBL-positive i 2017. Forekomsten økte for både *E. coli* (6,5 % i 2015; 5,8 % i 2016) og *Klebsiella* spp. (2,9 % i 2015; 4,6 % i 2016). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (6,6 %) enn fra urinprøver (3,0 %). Karbapenemaseproduserende *Enterobacteriaceae* (CPE), *Pseudomonas aeruginosa* og *Acinetobacter* spp. har vært meldepliktige til MSIS siden juli 2012. Antallet meldte pasienter med CPE økte fra 33 i 2016 til 35 i 2017, mens antallet karbapenemase-produserende *P. aeruginosa* (n=2) og *Acinetobacter* spp. (n=8) ble signifikant redusert i 2017.

Blant *Haemophilus influenzae*-isolater fra systemiske infeksjoner (n=118) var 17,8 % beta-laktamase positive og 16,1 % resistente mot cefuroxim som ved kromosomal beta-laktamresistens. I alt 27,1 % av *Haemophilus influenzae*-isolater fra luftveisinfeksjoner (n=1028) var beta-laktamase positive (15,2 %) og/eller resistente mot cefuroxim (13,5 %). Fjorten isolater var resistente mot cefotaxim. Et enkelt *Neisseria meningitidis*-isolat hadde nedsatt følsomhet for penicillin G, men alle systemiske isolater var følsomme for andre relevante antibiotika. *Neisseria gonorrhoeae* (n=681) viste nedsatt følsomhet for penicillin G (98,1 %) og azitromycin (45,6 %). Hele 40,1 % var resistente mot ciprofloxacin, men dette er tross alt en nedgang fra 62,2 % i 2015 og 48,6 % i 2016. To isolater (0,3 %) var resistente mot cefixim, men alle var følsomme for ceftriaxon.

Det ble påvist syv enterokokkisolater fra blodkultur med klinisk signifikant vankomycinresistens i 2017 (alle VanB *E. faecium*). Forekomsten av nedsatt følsomhet for ampicillin i *E. faecium* ligger stabilt rundt 70-80 %. Høygradig gentamicinresistens ble påvist i 15,5 % av *E. faecalis* og 40,6 % av *E. faecium*, dette er på omtrent samme nivå som henholdsvis 18,8 % og 38,3 % i 2016. Alle *E. faecium*-isolater med høygradig gentamicinresistens hadde samtidig nedsatt følsomhet for ampicillin. Et enkelt *E. faecalis* isolat var resistent mot linezolid og inneholdt en *optr-A* kodet effluksmekanisme.

Det ble påvist nedsatt følsomhet for penicillin G hos 9,7 % av *Streptococcus pneumoniae* fra blodkultur/spinalvæske. Dette er en signifikant økning fra 5,1 % i 2016. Elleve blodkulturisolatisolater var penicillinresistente og hadde samtidig nedsatt følsomhet for cefalosporiner. Forekomsten av makrolidresistens var 7,8 % sammenliknet med 4,8 % i 2015 og 5,6 % i 2016.

Streptococcus pyogenes (betahemolytiske streptokokker gruppe A) fra blodkultur hadde uendret forekomst av erytromycinresistens (4,2 %). Forekomsten av resistens og nedsatt følsomhet for erytromycin blant *Streptococcus agalactiae* (betahemolytiske streptokokker gruppe B) var 22,7 % i 2017 sammenliknet med 21,7 % i 2016. Alle isolatene var følsomme for penicillin.

I alt 261 tilfeller av tuberkulose ble meldt til MSIS i 2017. Det ble utført resistensbestemmelse av 214 *Mycobacterium tuberculosis* isolater. Ni isolater (4,2 %) fra pasienter smittet i henholdsvis Afrika (n=5), Asia (n=1), Norge (n=1) og Europa utenom Norge (n=2) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 206 *Candida* blodkulturisolater av ti ulike species. De vanligste artene var *C. albicans* (n=127), *C. glabrata* (n=36), *C. tropicalis* (n=15) og *C. parapsilosis* (n=10). Alle *C. albicans* var fullt følsomme for de undersøkte midlene. Det ble kun påvist enkelte non-albicans isolater med ervervet resistens mot fluconazol, men som forventet var det høy forekomst av resistens mot azoler hos *C. glabrata*. Nøyaktig speciesbestemmelse er avgjørende for å forutsi iboende resistens og velge effektiv behandling. Resultatene er i samsvar med tidligere studier fra Norge.

Konklusjon

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

SUMMARY

This is the eighteenth joint report from the NORM surveillance programme for antimicrobial resistance in human pathogens and the NORM-VET monitoring programme for antimicrobial resistance in bacteria from feed, food and animals. The report presents data on the occurrence of antimicrobial resistance and the usage of antimicrobial agents in humans and animals for the year 2017. 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, Oslo. A joint NORM/ NORM-VET report is issued annually.

Usage of antimicrobial agents in animals

The overall sales of antibacterial veterinary medicinal products (VMPs) for terrestrial animals in Norway were 5,587 kg active substance in 2017; this is a reduction of 265 kg from 2016.

Penicillins continue to be the most-selling antibacterial class for the major terrestrial food-producing species – i.e. cattle, pigs, goat, sheep and poultry - and were almost exclusively accounted for by benzylpenicillin. The estimated sales, measured in kg and mg/PCU (population correction unit), of antibacterial veterinary medicinal products (VMPs) for cattle, pigs, poultry, sheep and goat declined by 10% and 9%, respectively, from 2013 to 2017. The sales of the antibacterial VMPs containing substances defined by the World Health Organization as highest priority critically important antimicrobials (CIA) for human medicine continue to be very low. Only 5% of the sales (kg) of antibacterial VMPs for terrestrial food-producing species in Norway were for group treatment. The usage for horses was mainly accounted for by trimethoprim-sulfa (oral paste).

In 2017, the sales (kg) of antibacterial VMPs for farmed fish for consumption (i.e. cleaner fish excluded) were 535 kg. This is a reduction of more than 99% compared to 1987, when the sales were at its highest. For Atlatic salmon and rainbow trout, fish in only 0.8% of the ongrowers locations were subjected to antibacterial treatment in 2017.

From 2013 to 2017 the sales (kg) of antibacterial VMPs marketed for companion animals have been reduced by 32%. When including prescription of antibacterial human medicinal products (estimated by use of data from the Veterinary Prescription Register) the observed reduction was 20%.

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 usages of antibiotics for broilers continue to be very low. In 2017, 0.2% of the broiler flocks were subjected to treatment with antibiotics and only penicillins were used.

Usage of antimicrobial agents in humans

The total antibiotic use in Norway has continuously been decreasing since 2012. The use is reduced by 21% since 2012. Total antibiotic use includes all sales of antibacterial agents for systemic use in humans (J01 excl. methenamine) in primary care and institutions. The decrease continued in 2017, by 5% compared with 2016. Total sales declined from 14.6 DDD/1,000 inhabitants/day in 2016 to 13.8 DDD/1,000 inhabitants/day. The proportion of narrow-spectrum penicillins (J01CE) remained stable at 26% of total sales (J01, excl. methenamine), but this proportion is lower than 20 years ago; in 1997 their share was 35% of total sales.

Around 82% of the total human sales of antibacterials are prescribed in primary care, i.e. outside health institutions. For ambulatory care, the most important antibiotic group in 2017 was penicillins (J01C; 54% of all DDDs of systemic antibacterials excluding methenamine), followed by tetra-cyclines (J01A; 22%). The four most commonly prescribed antibiotics for outpatients in 2017 were phenoxymethyl-penicillin, doxycycline, pivmecillinam, and amoxicillin. These four substances represented 57% of all prescriptions and 61% of all DDDs sold. Dentists prescribe around 5% of all DDDs in primary care.

In 2017, the antibacterial sales (in DDDs) to hospitals represented 8% of total sales of antibacterials for human use in the country. A mean use of 79 DDD/100 bed days was observed, which is an increase by 9% since 2012. The DDD/admission (2017; 3.3 DDD/admission) increased by 2 % in the same period. The therapy pattern of antibacterials in hospitals does not change much from one year to another. In hospitals, half of the use, measured in DDDs, is penicillins (J01C). The second largest group is the cephalosporins; 17% of all DDDs. There are large variations between the hospitals in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile. The variations cannot be accounted for by differences in activity or patient composition alone.

Resistance in indicator bacteria from animals, food and feed

The prevalence of antimicrobial resistance among bacteria of the normal enteric microflora can serve as an indicator for the selective antimicrobial pressure in various populations. However, in a country with low usage of antimicrobial veterinary medicinal products and generally low levels of antimicrobial resistance, the detected prevalence may be influenced by other factors as well.

In 2017, cattle, swine, horses and poultry breeder flocks were sampled to obtain indicator bacteria from the intestinal flora. From horses and poultry breeder flocks, nasal swabs and sterile moisted clothes, respectively, were also included. Food samples included beef and pork, as well as leafy greens and leafy herbs. In addition, the results from the surveillance programme for methicillin resistant *Staphylococcus aureus* in swine are described.

The 2017 data confirm that the prevalence of antimicrobial resistance in bacteria from animals and food in Norway is low. This is shown for indicator *E. coli*, as well as by the selective screenings for *E. coli* resistant to 3rd generation

cephalosporins, quinolones, carbapenemase-producing *Enterobacteriaceae* and methicillin resistant *Staphylococcus aureus* (MRSA).

The majority of the *E. coli* isolates from cattle, swine and horses were fully susceptible to the antimicrobial agents in the test panel. Among the isolates showing decreased susceptibility, resistance to the antimicrobial agents ampicillin, sulfamethoxazole, tetracycline and trimethoprim was most common. These results are in concordance with previous results.

Only a few isolates resistant to 3rd generation cephalosporins due to plasmid encoded resistance genes were detected in the selective screening in cattle, swine and horses, indicating that such plasmids still are rare. Similarly, these were not detected from any of the beef or pork samples. From the leafy greens and leafy herbs samples, resistance to 3rd generation cephalosporins due to plasmid encoded resistance genes, was detected from only one sample. From the cattle and swine samples, several isolates resistant to 3rd generation cephalosporins due to chromosmal mutations were detected.

Carbapenemase-producing *Enterobacteriaceae* have never been isolated in samples from animals or food in Norway. This still applies for the selective screening performed on all categories of samples in 2017. No colistin resistant *E. coli* were detected by selective screening on samples from leafy greens and fresh herbs.

Quinolone resistant *E. coli* was detected in only a few samples from horses and leafy greens and fresh herbs. Of these, the resistance in only single isolates from each category was suspected to be plasmid-mediated. Quinolone resistant *E. coli* is more common in poultry and was detected in about half of the poultry breeder samples. The majority of these isolates contained mutations in the chromosomally located *gyrA* gene, while only two were regarded as possible carriers of plasmid-mediated quinolone resistance genes.

Findings of MRSA in the Norwegian animal population are rare. The yearly MRSA surveillance programme, screening the Norwegian swine population for MRSA, did not detect any herds with LA-MRSA CC398 in 2017. However, MRSA CC7, CC130 and CC425 were detected in one multiplier herd and in two farrow to finish herds, respectively. MRSA was not detected in any of the genetic nucleus herds, nor in the central units of the sow pool herds. MRSA was not detected in any of the samples from poultry breeder flocks either, thereby indicating that the breeder production of broilers and turkey are free from MRSA. In addition, samples from horses were investigated for MRSA and one horse was found to carry MRSA CC398 *spa*-type t011, an MRSA type associated with findings in horses.

Resistance in zoonotic bacteria and non-zoonotic enteropathogenic bacteria

Animal isolates

The Norwegian animal production population is considered virtually free from *Salmonella* spp. In 2017, only 15 *Salmonella* spp. isolates from animals were susceptibility tested. The 15 isolates included one each from three wild birds, one poultry, two dogs, two swine, four sheep, one cervid and two hedgehogs. All isolates were fully susceptible to the tested antimicrobials.

Campylobacter coli from swine was included in 2017, and the results indicate a high occurrence of resistance among these due to decreased susceptibility to streptomycin and quinolones. Similar to what is being reported in both human and animal *C. coli* isolates by other European countries, there has been an increasing trend in resistance, especially with regard to quinolones.

Human clinical enteropathogenic isolates

The frequency of multi-drug resistance (MDR) in human clinical isolates of all *Salmonella* serovars was 8.0 %, and the frequency of ESBLs was less than 1 %. Among the 61 *Salmonella* blood culture isolates, the highest frequency of MDR was detected in *Salmonella* serovars other than *S.* Typhi, *S.* Paratyphi and the *S.* Typhimurium-group. Antimicrobial resistance in general was more prevalent in the *S.* Typhimurium-group (including *S. enterica* serovar 4,[5],12:i-) than in other serovars, and resistance to ampicillin and tetracycline was increasing in this group for infections that were acquired abroad.

For *Campylobacter*, isolates from infections acquired abroad were increasingly resistant to quinolones and tetracycline. However, resistance in isolates from infections acquired in Norway was lower and decreasing.

Most cases of shigellosis were acquired abroad and widespread resistance was observed. The prevalence of ESBLs in *Shigella* spp. was estimated to 8% in 2017 compared to 5% in 2016.

Antimicrobial resistance in *Yersinia enterocolitica* remained low despite the intrinsic resistance to ampicillin.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2017. Only ten methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,312 strains included in the NORM protocol (0.8%). During 2017, the total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 1,767, including 18 MRSA strains (1.0%). This prevalence is at the same level as in 2015 (0.7%) and 2016 (1.0%). The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 763 cases of MRSA infections in 2017, compared to 785 in 2015 and 887 in 2016. The majority of MRSA cases were reported as wound infections and/or abscesses. The prevalence of MRSA among non-invasive *S. aureus* isolates is still very low at 1.2% (13/1,098), as it was in 2015 (1.2%) and 2016 (1.6%). Furthermore, MSIS registered 1,529 reports from MRSA colonisations compared to 1,448 in 2015 and 1,651 in 2016. The total number of MRSA notifications thus decreased from 2,538 in 2016 to 2,292 in 2017 (- 10%). The results indicate a relatively stable rate of MRSA notifications caused by a decreasing number of infections and an increased rate of colonisation. The prevalence of invasive disease has remained stable at a low level. The increased rate of reported colonisation may reflect a higher prevalence in the population, but can also be a consequence of increased test activity.

Antimicrobial resistance to broad-spectrum antimicrobials in *E. coli* and *Klebsiella* spp. blood culture isolates increased slightly in 2017. The prevalence of gentamicin non-susceptibility in *E. coli* increased from 6.4% in 2015 and 6.7% in 2016, to 7.1% in 2016. The prevalence of *E.*

coli non-susceptibility to fluoroquinolones increased from 17.1% in 2016 to 18.0% in 2017 despite reduced ciprofloxacin prescription both in hospitals and in primary care. The prevalence of resistance to aminoglycosides and fluoroquinolones was significantly lower in *Klebsiella* spp. and *Proteus* spp. isolates than in *E. coli*.

Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 140/2,136 (6.6%) *E. coli*, 47/884 (5.3%) *Klebsiella* spp. and 1/192 (0.5%) *Proteus* spp. were reported with this phenotype in 2017. The prevalence increased for both *E. coli* (6.5% in 2015; 5.8% in 2016) and *Klebsiella* spp. (2.9% in 2015; 4.6% in 2016). The proportion of ESBL positive isolates is higher among *E. coli* from blood cultures (6.6%) than among urinary tract isolates (3.0%). Carbapenemase-producing Enterobacteriaceae (CPE), *Pseudomonas aeruginosa* and *Acinetobacter* spp. have been notifiable to MSIS since July 2012. The number of patients reported with CPE increased from 33 in 2016 to 35 in 2017. The numbers of carbapenemase-producing *P. aeruginosa* (n=2) and *Acinetobacter* spp. (n=8) were significantly reduced in 2017.
Among *Haemophilus influenzae* isolates from systemic infections (n=118), 17.8% displayed beta-lactamase production and 16.1% were resistant to cefuroxime, thus indicating chromosomal resistance to beta-lactam antibiotics. A total of 27.1% of *Haemophilus influenzae* isolates from respiratory tract specimens (n=1,028) were beta-lactamase positive (15.2%) and/or resistant to cefuroxime (13.5%). Fourteen isolates were cefotaxime resistant. A single *Neisseria meningitidis* isolate from a systemic infection displayed reduced susceptibility to penicillin G, but all isolates remained susceptible to other relevant antibiotics. *Neisseria gonorrhoeae* isolates (n=681) demonstrated non-susceptibility to penicillin G (98.1%) and azithromycin (45.4%). Resistance to ciprofloxacin was widespread (40.1%), but still lower than in 2015 (62.2%) and 2016 (48.6%). Two isolates (0.3%) were resistant to cefixime but remained susceptible to ceftriaxone.

Seven enterococcal blood culture isolates (1.0%) with clinically significant vancomycin resistance were detected in 2017 (all VanB *E. faecium*). The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) was detected in 15.5% of *E. faecalis* and 40.6% of *E. faecium* isolates. This is at the same level as 18.8% and 38.3% in 2016, respectively. All HLGR *E. faecium* isolates were also non-susceptible to ampicillin. A single *E. faecalis* isolate was resistant to linezolid due to an *optr-A* encoded efflux mechanism.

Non-susceptibility to penicillin G was detected in 9.7% of *Streptococcus pneumoniae* isolates from blood cultures and cerebrospinal fluids. This is a significant increase from 5.1% in 2016. Eleven blood culture isolates were non-susceptible to penicillin G and at the same time showed reduced susceptibility to cephalosporins. The prevalence of macrolide resistance was 7.8% compared to 4.8% in 2015 and 5.6% in 2016.

Streptococcus pyogenes (group A streptococcus) isolates from blood cultures had a stable prevalence of erythromycin resistance (4.2%). The prevalence of macrolide resistance in *Streptococcus agalactiae* (group B streptococcus) was 22.7% in 2017 compared to 21.7% in 2016. All isolates were susceptible to penicillin G.

A total of 261 cases of tuberculosis were reported to MSIS in 2017. Susceptibility testing was performed on 214 *Mycobacterium tuberculosis* isolates. Nine isolates (4.2%) originating from Africa (n=5), Asia (n=1), Norway (n=1) and Europe excluding Norway (n=2) were classified as multi-drug resistant (MDR).

Susceptibility testing was performed on 206 *Candida* spp. blood culture isolates of ten different species. The most common species were *C. albicans* (n=127), *C. glabrata* (n=36), *C. tropicals* (n=15) and *C. parapsilosis* (n=10). All *C. albicans* isolates were fully susceptible to the substances examined. 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 the report show that strategies for containment of antimicrobial resistance have been successful both in the food-producing animal sector and in the healthcare sector. Continous 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 January 1st, 2018.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	299,579	153,917	145,662
5 to 14 years	639,355	327,792	311,563
15 to 24 years	664,329	343,154	321,175
25 to 44 years	1,434,353	735,740	698,613
45 to 64 years	1,361,578	694,243	667,335
65 years and older	896,425	413,525	482,900
All age groups	5,295,619	2,668,371	2,627,248

TABLE 2. Livestock population in Norway in 2017.
Data provided by the Register of Production Subsidies as of 01.10.2017.

	Number* of	
Animal category	Herds	Animals
Cattle	14,000	885,500
Dairy cows only**	7,000	186,000
Suckling cow only**	4,500	81,400
Combined production (cow)**	860	38,600
Goat	1,200	65,600
Dairy goat**	300	33,900
Breeding sheep**	14,500	984,000
Breeding sheep > 1 year**	14,500	984,000
Swine	2300	835,000
Breeding animal > 6 months**	1,100	48,100
Fattening swine for slaughter**	2,100	479,000
Laying hen flocks > 250 birds	595	4,335,000
Broilers***	596	67,924,000
Turkey, ducks, geese for slaughter (flock > 250 birds)	49	512,000

*Numbers > 100 rounded to the nearest ten, numbers > 1000 rounded to the nearest hundred. **Included in above total from Register of Production Subsidies as of 01.10.2017, except for sheep where the numbers are from 01.05.2018. *** Included in the official surveillance programme of *Salmonella*.

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2017. *Data provided by the Norwegian Directorate of Fisheries updated by 18.06.2017.*

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[3]	1,219,235	63,350	117	362	1,623	2,420	29	17

[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 2017 was six cattle (including water buffalo), 19 camelids, 12 Mangalitsa pigs, 12 sheep and 26,505 day old chicks of hen, broiler, 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 1993-2017 for antibacterial veterinary medicinal products (VMPs) for terrestrial animal species obtained at wholesaler's level have been stratified into sales of antibacterial VMPs approved for terrestrial food-producing animals, including horses, and approved for companion animals, respectively (see Appendix 1). The data are based on sales from drug wholesalers of VMPs for therapeutic use to Norwegian pharmacies. This includes pharmaceutical formulations approved for food-producing terrestrial animals, including horses, and for companion animals (sees 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 and companion animals in 2017 were 5,587 kg. A decline of the annual sales of such VMPs of 40% in the period 1993-2017 was observed (Figure 1).

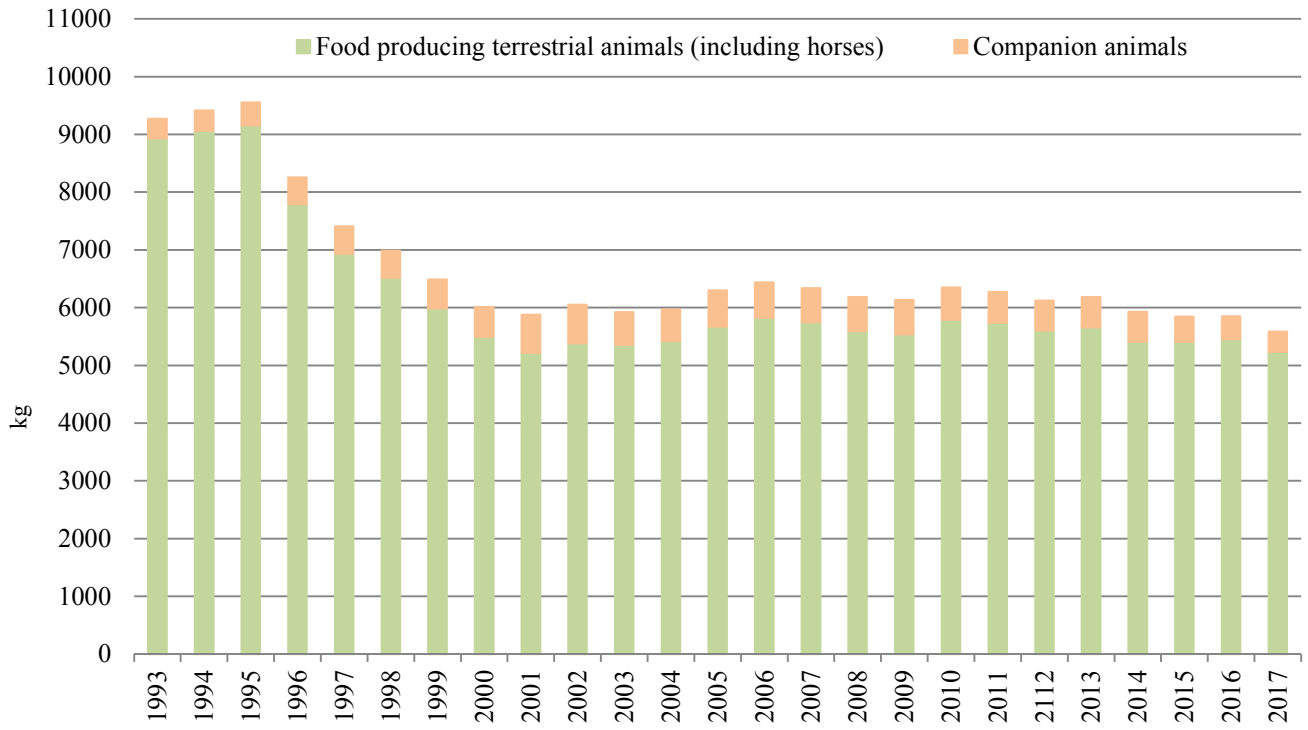

FIGURE 1. Total sales, in kg active substance, of antibacterial veterinary medicinal products for food-producing terrestrial animals (including horses) and companion animals, for therapeutic use in Norway in 1993-2017.

Food-producing terrestrial animals, including horses

In 2017 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 5,228 kg. A decrease in the sales of such VMPs of 41% is observed compared to 1993. The most-selling VMPs (kg) for this animal category in 2017 was containing only penicillins (55%); the second combination products of trimethoprim-sulfa (30%); of this combination 78% was sold as orale paste for horses (Figure 2).

In the period 1993-2017, the proportion of sales of VMPs containing only penicillins for this animal category increased from 19% to 55%. This is almost solely due to reduced sales of injectable and intramammary combination VMPs of penicillins and aminoglycosides (dihydro-streptomycin) that has been gradually replaced by products containing penicillin as the sole antibacterial agent.

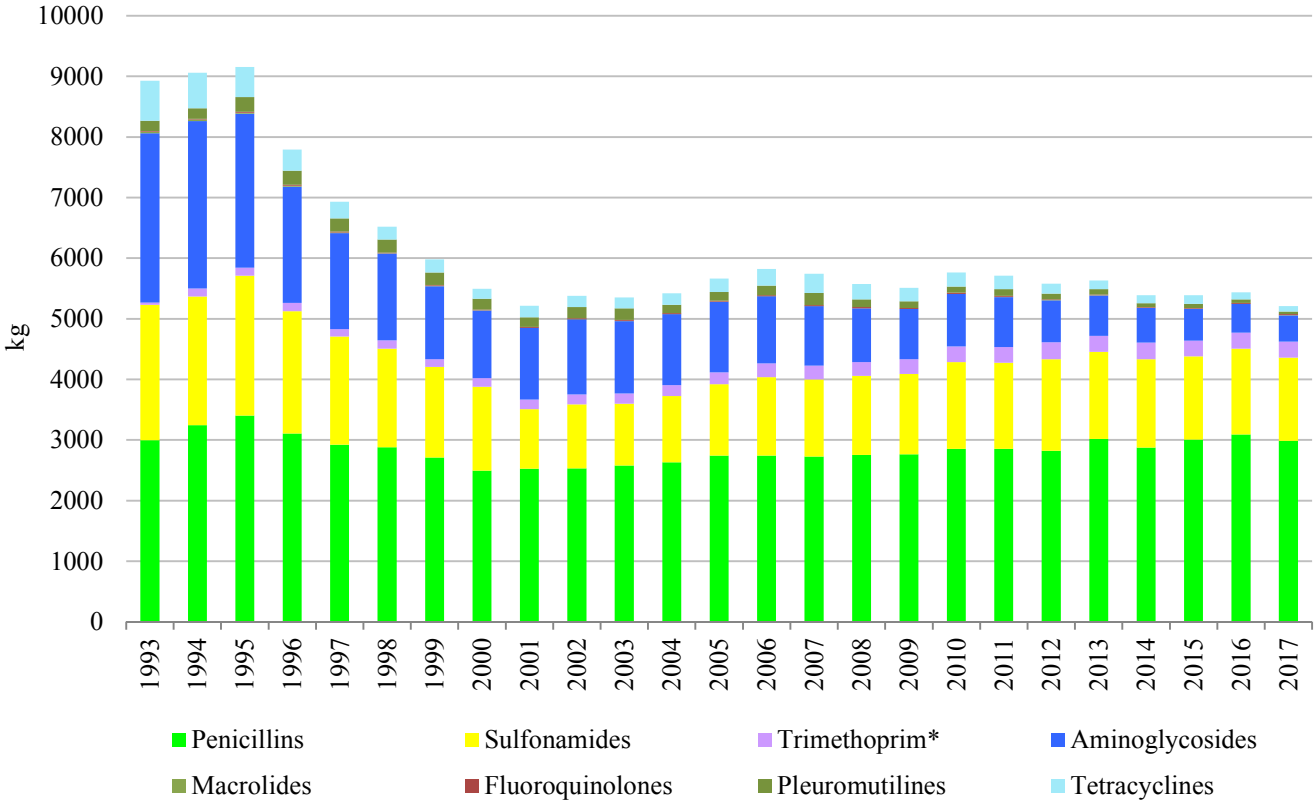

FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals (including horses) in Norway in 1993-2017. In addition, minor amounts of amphenicols VMPs were sold in 2008-2017 (range 16-27 kg). *Includes minor amounts of baquiloprim 1994-2000.

The sales (kg) for food-producing terrestrial animals (including horses) of the antibacterial VMPs defined by the World Health Organization (WHO) as critically important antimicrobials (CIA) with highest priority (HP) for human medicine have decreased substantially (56%) from 1993 to 2017 (Figure 3). This is mainly due to reduced sales of macrolides. The proportion of sales of the HP CIA of the total annual sales (kg) of antibacterial VMPs for food-producing animals was relatively stable during the years 1993-2017 accounting for 0.2-0.4% of the total sales of antibacterial VMP for this animal category. The Norwegian prudent use guidelines for antibacterial treatment of food-producing animals state that CIA should be last choice antibiotic. During 1993-2017 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 EU/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 (colistin) VMPs (Tonje Høy, Norwegian Medicines Authority, personal communication). Glycopeptides are not allowed for food-producing animals in EU/EEA countries.

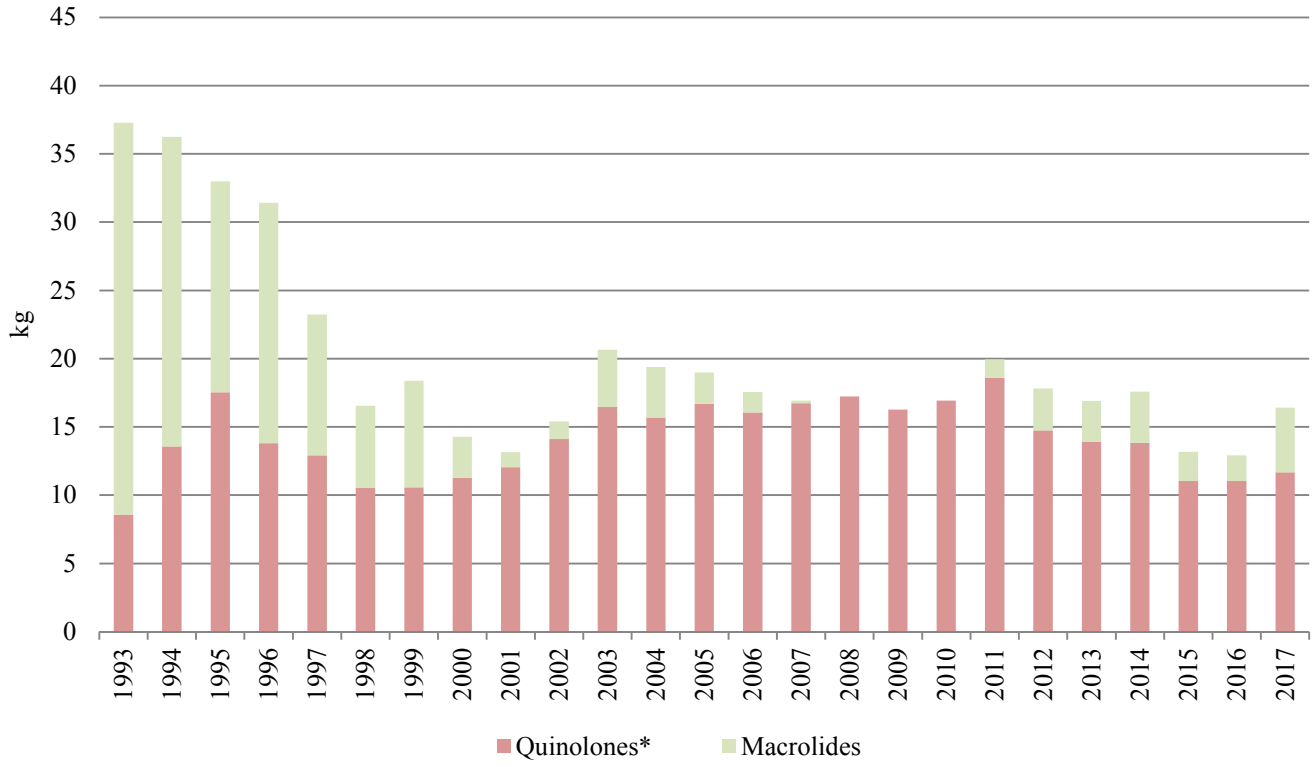

FIGURE 3. Overall sales, in kg of active substance, of antibacterial veterinary medicinal products (VMPs) containing the highest priority critically important antimicrobials for human medicine – i.e. quinolones (*only fluoroquinolones marketed) and macrolides, for therapeutic use in terrestrial food-producing animals (including horses) in Norway in 1993-2017.

In Norway, sales of antibacterial VMPs for treatment of food-producing terrestrial animals are dominated by pharmaceutical forms for treatment of individual animals (Figure 4) and were primarily injectables. This reflects that the production is characterised by small herds, but it can also partly be explained by therapeutic traditions. In 2017, only 5% of the sales of antibiotic VMPs for food-producing terrestrial animals were for VMPs for group treatment (oral treatment).

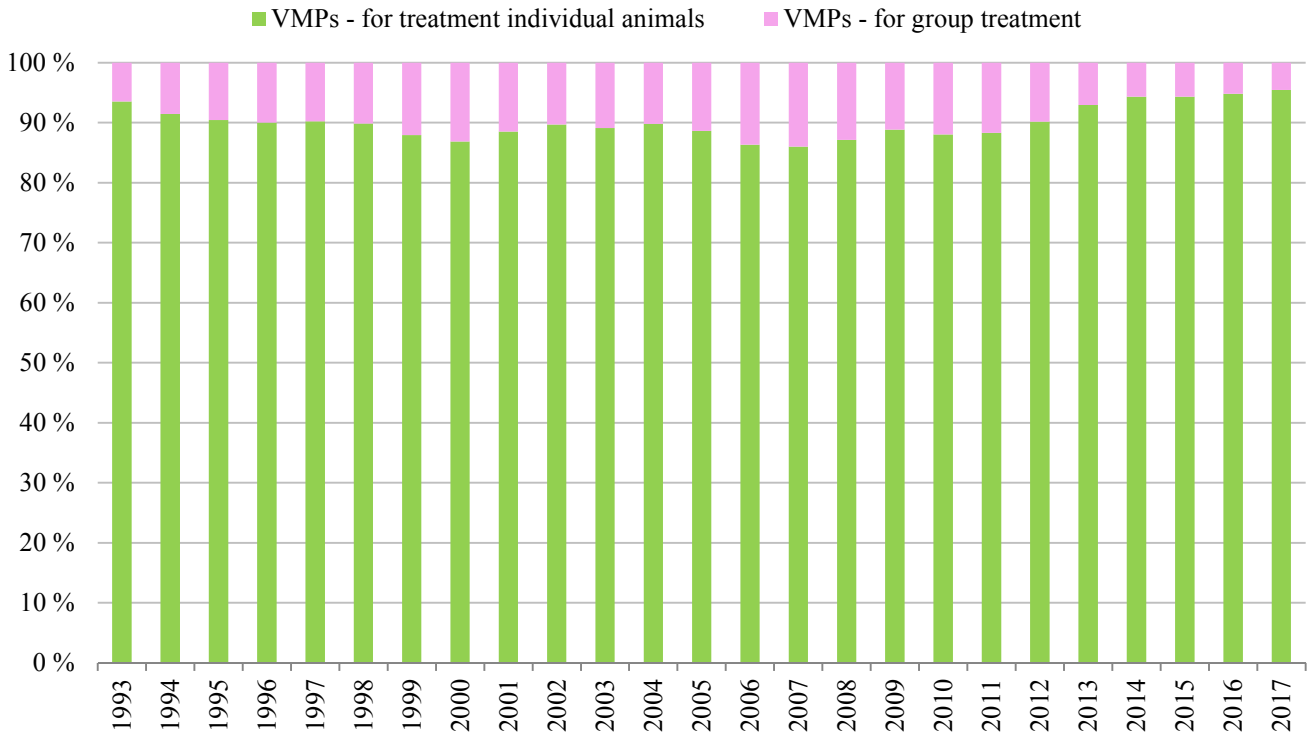

FIGURE 4. Sales in Norway, in proportions of kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals (bolus, injectables, intramammary, intrauterine, oral paste and some tablet VMP presentations – see Appendix 1) and for group treatment through feed or drinking water (oral solution and oral powder; no premixes are marketed for terrestrial food-producing animals) in 1993-2017.

Prescribing patterns for major food-producing species (VetReg data)

Of the amounts (kg active substance) of antibacterial VMPs reported to VetReg for cattle, goat, pigs and sheep, 85% were penicillins, 6% trimethoprim-sulfamethoxazole, 5% aminoglycosides and 2% tetracyclines. More than 99% of the penicillins was benzylpenicillin (as prodrugs). Note that intramammaries were not included (see Appendix 1).

Of prescriptions of VMPs for cattle, 88% was for penicillins (intramammaries not included); of these 99% was accounted for by benzylpenicillin (as prodrugs) (Figure 5). These figures were in the same order for 2015 and 2016. For intramammaries the sales data are used to document the prescribing patterns; the sales of intramammaries containing penicillins only were 28% in 2017 and combinations of penicillins and aminoglycosides (dihydrostreptomycin) were 72%.

Of the penicillins VMPs reported to VetReg as prescribed for treatment of pigs (Figure 6), 94% was accounted for by benzylpenicillin (as prodrugs).

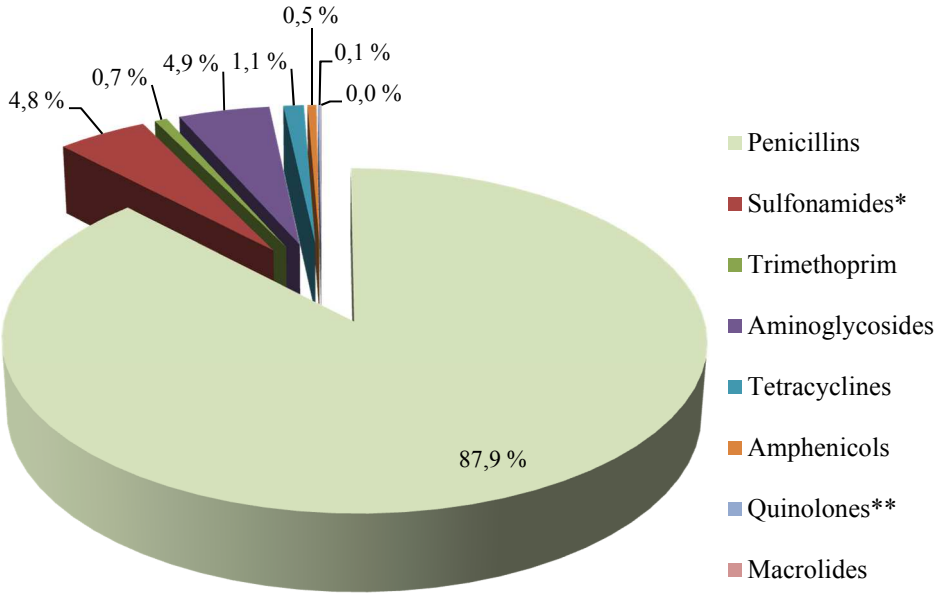

FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary medicinal products for cattle in Norway in 2017. Note that intramammaries are not included in the data. Data were obtained from the Veterinary Prescription Register. *In combination with trimethoprim only; **Fluoroquinolones only.

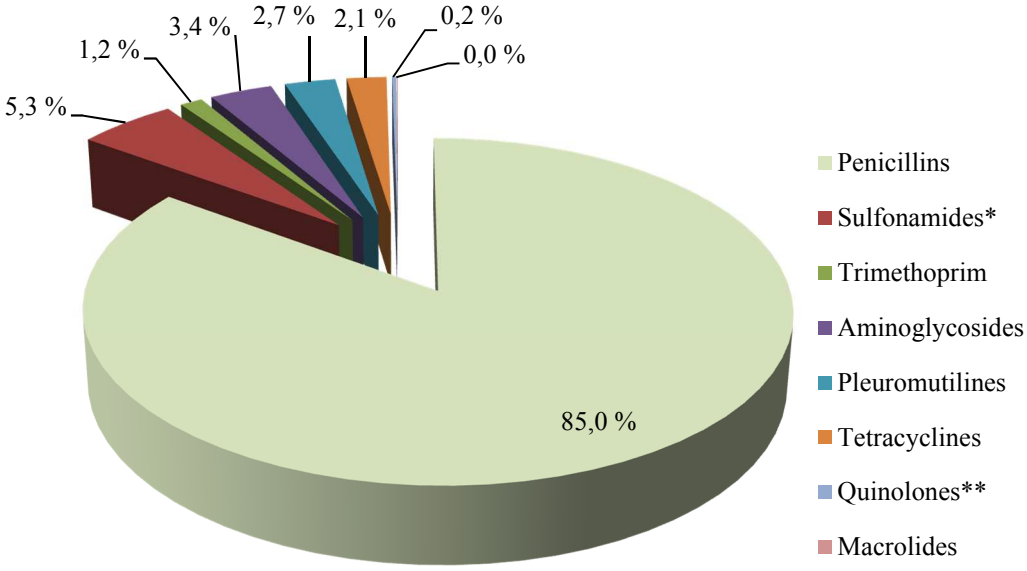

FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary medicinal products for pigs in Norway in 2017. Data are obtained from the Veterinary Prescription Register. *In combination with trimethoprim only. **Fluoroquinolones only.

Farmed fish

In 2017, the total amount of antibiotics prescribed for use in aquaculture in Norway was 612 kg (Table 4); of this 535 kg were prescribed for farmed fish for human consumption (cleaner fish excluded). The annual sales of antibacterial VMPs for use in farmed fish peaked in 1987 when it amounted to 48 tonnes (Figure 7) – i.e. 876 mg/PCU (population correction unit); the corresponding figure in 2017 was 0.5 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.

TABLE 4. Sales, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2008-2017. For 2008-2012 the data represent sales data from feed mills and wholesalers collected by the Norwegian Institute of Public Health. For 2013-2017 data represent prescription data obtained from the Veterinary Prescription Register (See Appendix 1). Note that data include sales for use in cleaner fish.

Active substance	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Tetracyclines										
Oxytetracycline	23	40	10	1	1	0	0	0	0	0
Amphenicols										
Florfenicol	166	303	275	336	191	236	399	189	135	269
Quinolones										
Flumequine	1	1	0	0	0	0	25	< 0.05	< 0.05	< 0.05
Oxolinic acid	681	926	308	212	1,399	599	99	84	66	343
Combinations										
Spectinomycin + lincomycin (2+1)	70	43	57	0	0	0	0	0	0	0
Total	**941**	**1,313**	**650**	**549**	**1,591**	**860**	**523**	**273**	**201**	**612**

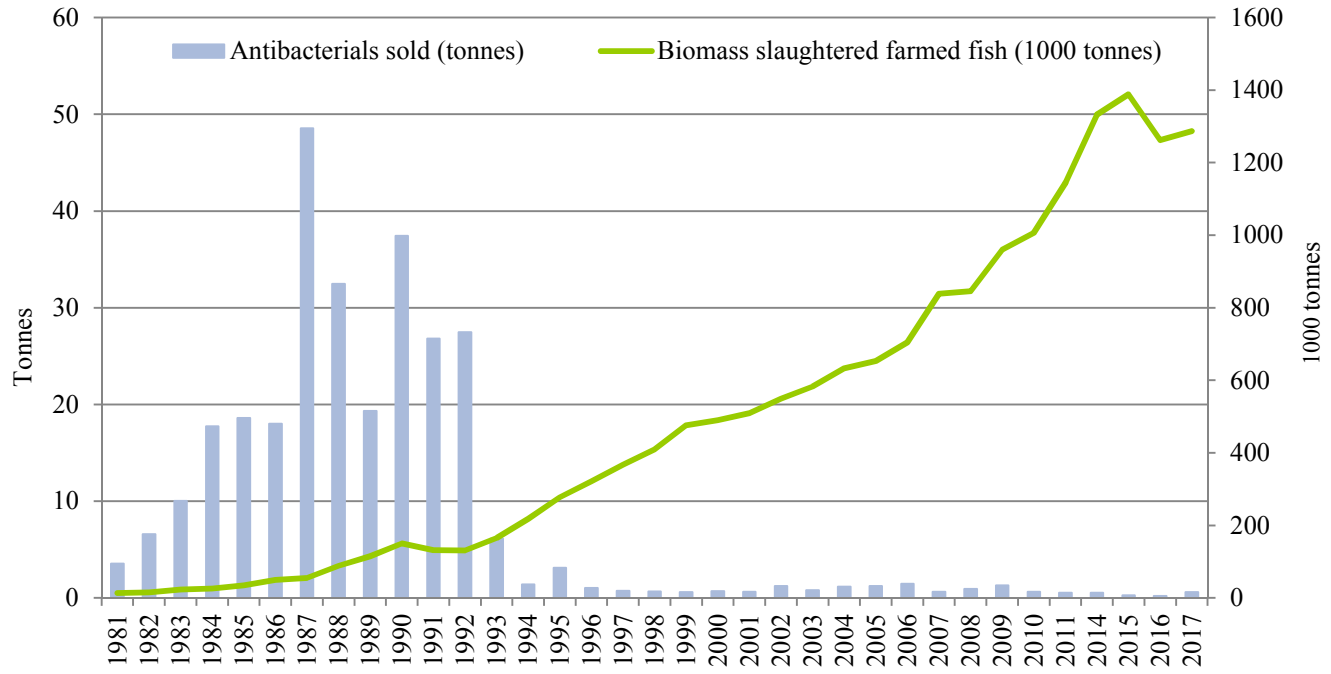

FIGURE 7. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish in Norway in 1981-2017 versus produced biomass (slaughtered) farmed fish. For 1981-2012 the data represent sales data provided by Norwegian Institute of Public Health. For 2013-2017 data represent prescription data obtained form the Veterinary Prescription Register. Data on slaughtered biomass farmed fish were obtained from Statistics Norway.

For the years 2013 to 2017, the major proportion of prescriptions was for farmed fish in the pre-ongrower phase (Figure 8). The number of prescriptions of antibacterial VMPs for Atlantic salmon ongrowers was negligible during the period 2013-2017, despite that Atlantic salmon represents approximately 95% of the farmed fish biomass produced in Norway. This is a strong indication that the vaccines used are efficient and that the coverage of vaccination of fingerlings is complete.

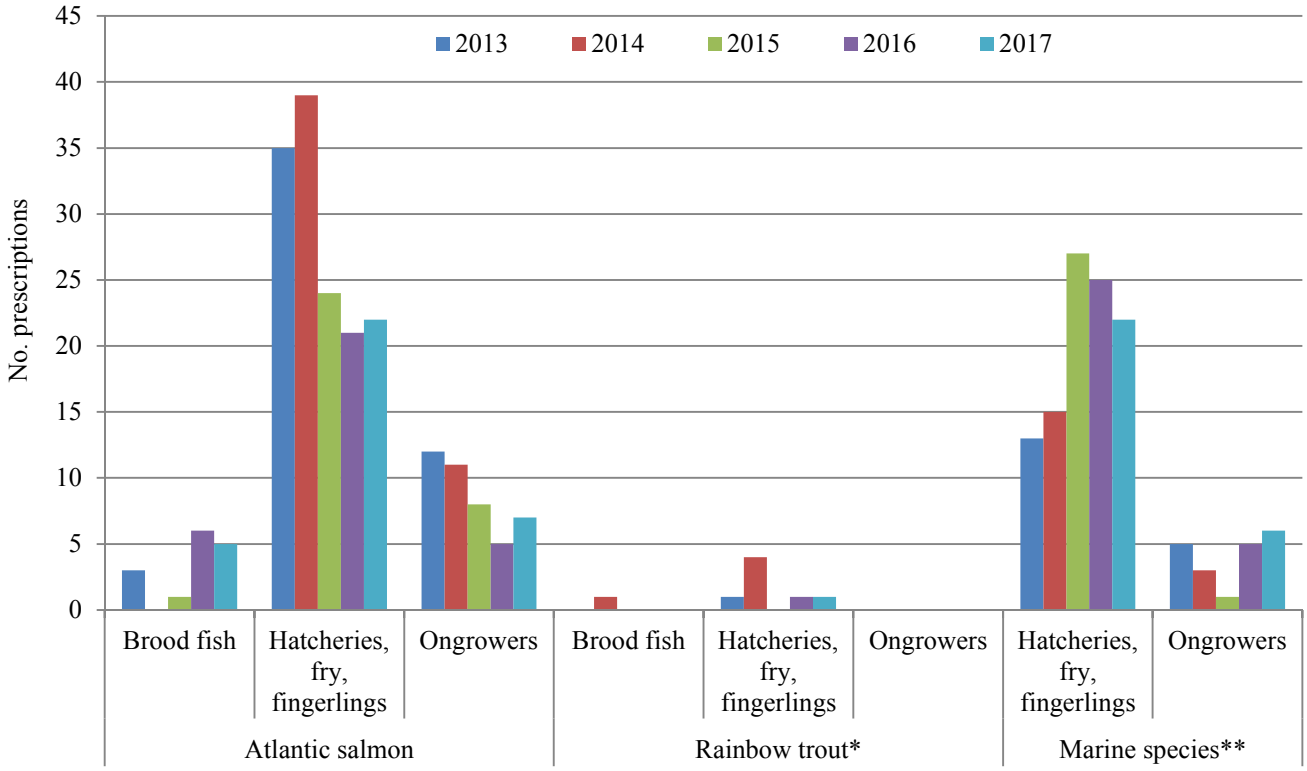

FIGURE 8. Number of prescriptions of antibacterials by fish species, split into production stages/types, in Norway in 2013-2017. Data were obtained from the Veterinary Prescription Register. *Includes two prescriptions for trout (*Salmo tutta*) fingelings. **Cod, halibut, turbot and wolffish.

In a recent report (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) it was shown that for Atlatic salmon and rainbow trout, 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 (1).

Companion animals (dogs and cats)

The sales in 2017 of antibacterial VMPs approved solely for companion animals (includes VMPs formulated as tablets, oral solution, injectable and oral paste) was 359 kg and thus sales of such VMPs were on the same level as in 1993 (345 kg) (Figures 1 and 9). As shown in Figure 9, a steady increase in the sales from 1993 to 2001 is 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 prescribed for dogs and cats. In 1993, only eight antibacterial VMP presentations (name, form, strength and pack size) were authorised 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 2017 this figure was 34. Since the sales of human antibacterials are not included in the statistics (Figure 9) the observed changes across the period 1993 to 2017 should be interpreted with caution (see chaper on National Strategy).

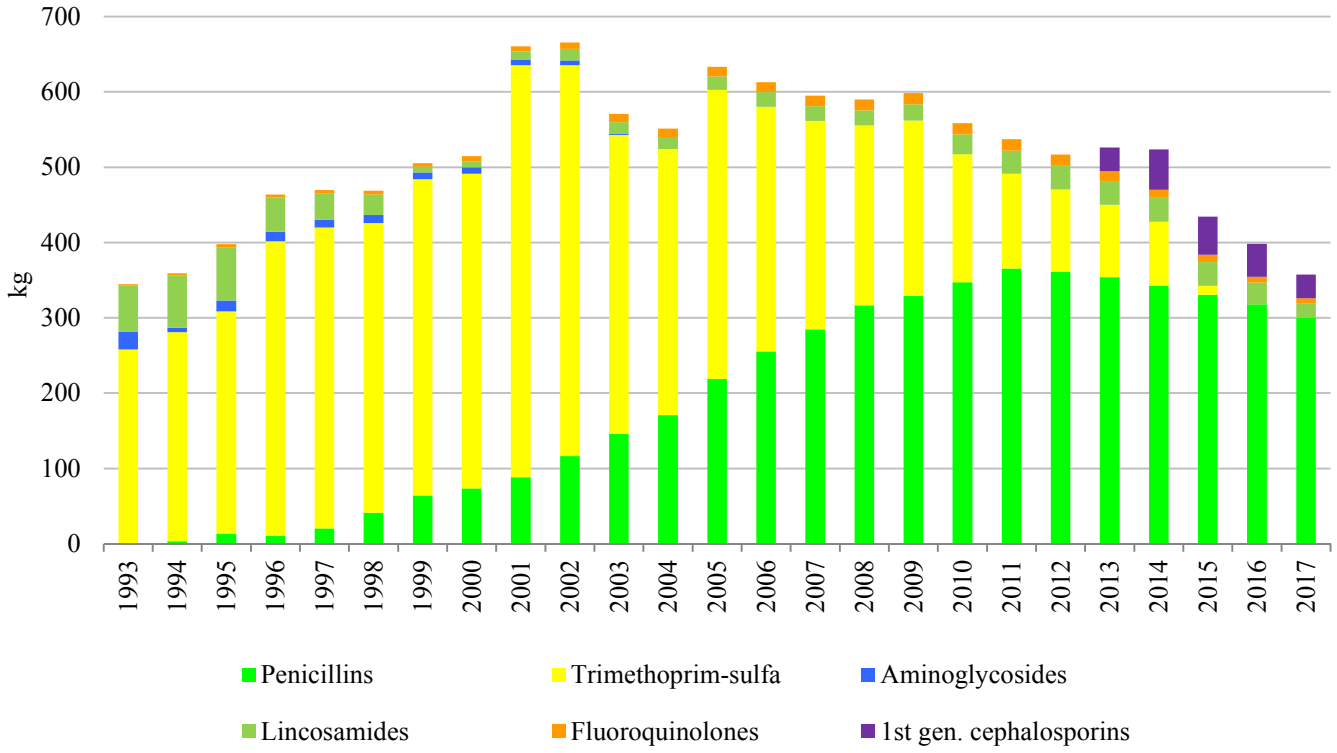

FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables oral paste, oral solution and tablets; exceptions for tablets: see Appendix 1) in Norway for the period 1993-2017. Minor sales of a 3rd generation injectable cephalosporin VMP (range 0.5-1.1 kg) in 2008-2017 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 1993-2017 (Figure 9). The first penicillin VMP tablets were marketed for companion animals in 1994; since then the proportion of penicillin sales of total sales of antibacterial VMPs approved for companion animals has increased from 1% to 84% (Figure 9). Of the sales of penicillin VMPs in 2017 approximately 84% were for the combination amoxicillin and clavulanic acid (Figure 10).

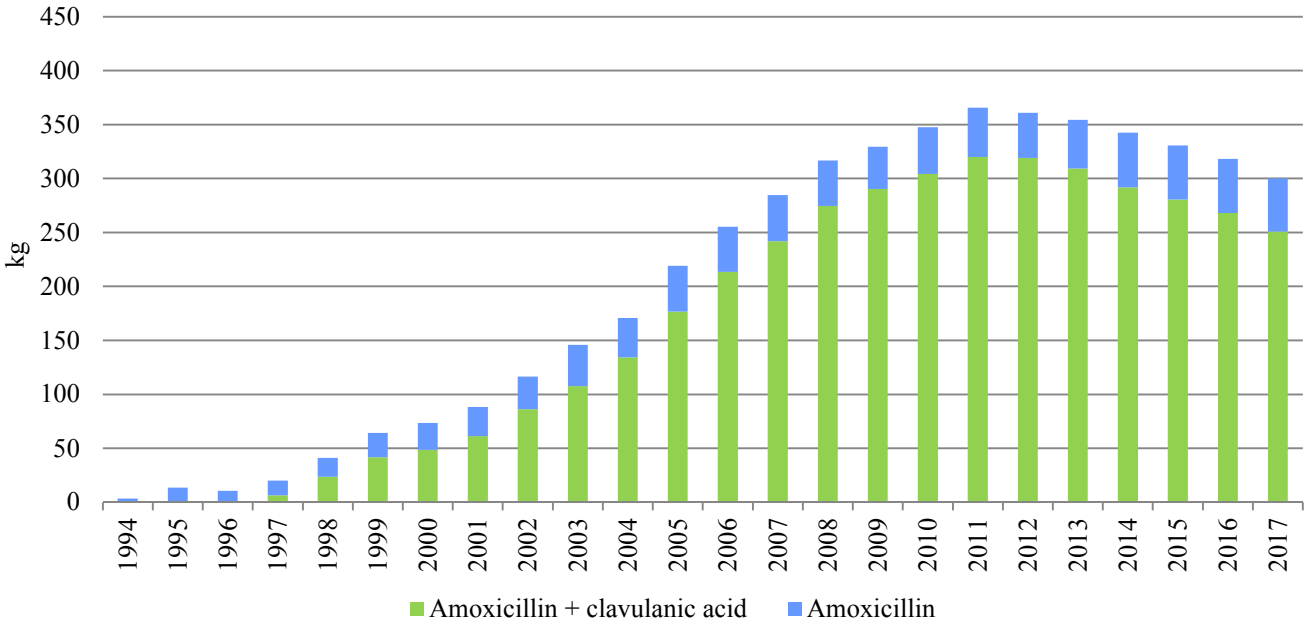

FIGURE 10. Sales, in kg active substance, of penicillin veterinary medicinal products for companion animals (dogs and cats), in Norway in 1994-2017.

The sales for companion aimals of VMPs belonging to the highest priority CIA for human medicine varied during 1993-2017 (Figure 11). The proportion of the total sales of antibacterial VMPs for companion animals accounted for by such CIAs was however low during this period (range 0.5% to 3.0%).

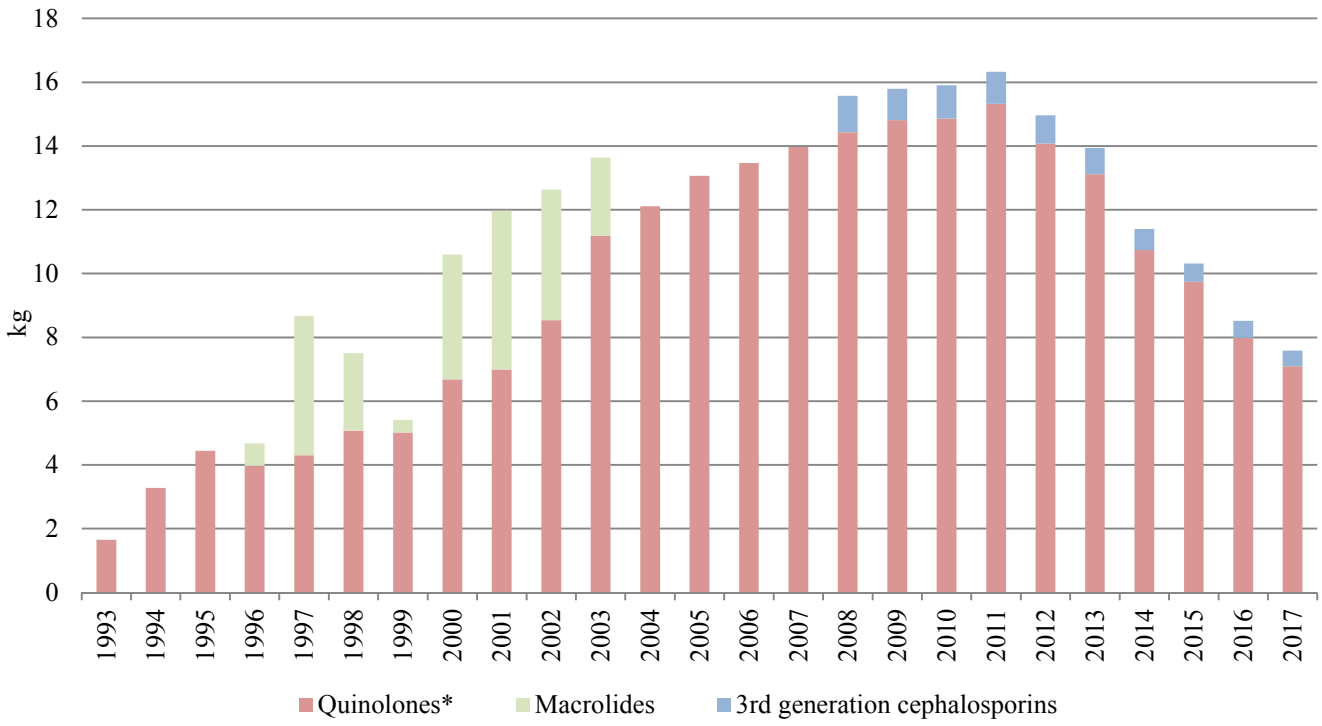

FIGURE 11. Sales, in kg active substance, of antibacterial veterinary medicinal products containing the highest priority critically important antimicrobials for human medicine – i.e. quinolones (*only fluoroquinolones marketed), macrolides and 3rd generation cephalosporins - for therapeutic use in companion animals (dogs and cats) in Norway in 1993-2017.

Antimicrobial and coccidiostat feed additives

Due to the reported association between use of avoparcin as antimicrobial growth promoter and the occurrence of vancomycin resistant enterococci in 1995, the Norwegian livestock industry immediately decided to phase out all use of antimicrobial growth promoters (AGPs) with instant stop of using avoparcin in May 1995 (Table 5). In 1996 and 1997, the sales of zinc bacitracin were only 64 kg and 27 kg, respectively; since 1997 no AGPs have been used for animals in Norway. Data in Table 5 on sales of AGPs in 1995 are given for historical reference.

TABLE 5. Sales, in kg of active substance, of ionophore coccidiostat feed additives in Norway in 2007-2017. Data for 1995 include antimicrobial growth promoters and are given for historical reference. Data were obtained from the Norwegian Food Safety Authority.

Active substance	1995	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Avoparcin	419*	0	0	0	0	0	0	0	0	0	0	0
Zincbacitracin	129	0	0	0	0	0	0	0	0	0	0	0
Total antimicrobial growth promoters	**548**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Lasalocid	996	17	16	63	0	0	0	0	0	164	0	0
Monensin	3,422	919	896	885	805	1,060	1,080	1,174	1,313	1,081	874	875
Salinomycin	214	0	0	0	0	0	0	0	0	0	0	0
Narasin	24	7,065	9,212	8,621	9,080	9,394	10,378	12,345	12,409	9,126	562	92**
Total ionophore coccidiostats	**4,656**	**8,001**	**10,124**	**9,569**	**9,885**	**10,454**	**11,458**	**13,519**	**13,722**	**10,371**	**1,436**	**967**

*Sold only part of the year; ** Used for control of necrotic enteritis (*Clostridium perfringens*) (Atle Løvland, Nortura, personal communication).

National Strategy against Antibiotic Resistance (2015-2020) - Targets for reduction of antibiotic usage in animals and farmed fish and changes according to targets

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

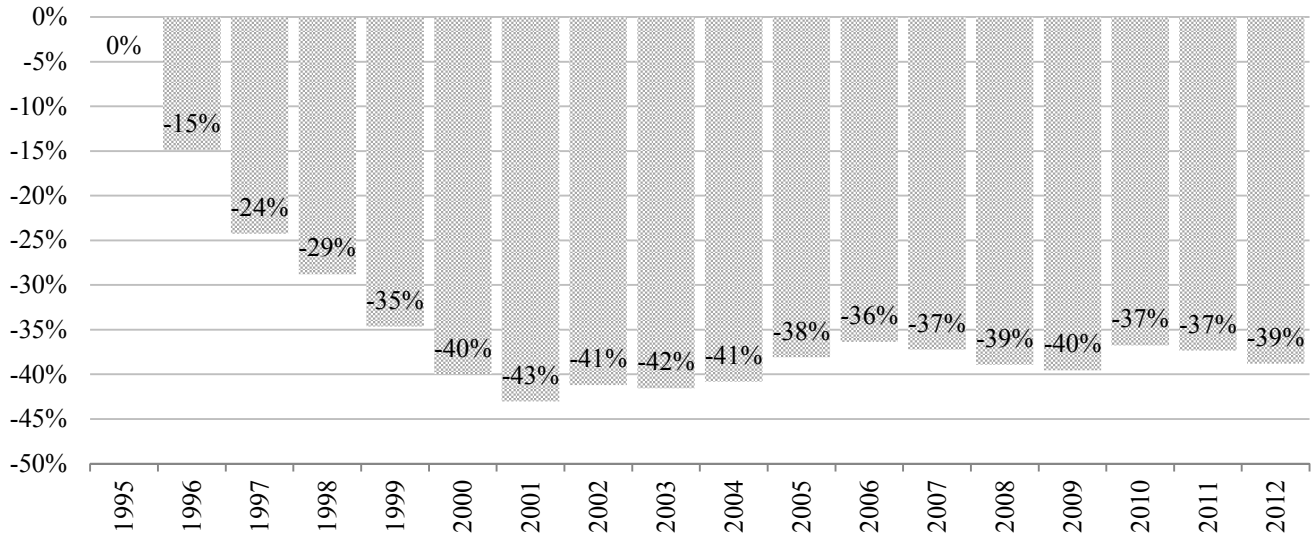

FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMPs) approved for use in food-producing terrestrial animals, including horses, 1995 being the reference year.

To evaluate progress in terms of reaching the goals set down in the National Strategy (2015-2020), sales data for 2013-2017 have been further refined in order to obtain estimates on the usage that are more accurate in terms of identifying changes across time. 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).

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

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 (https://www.animalia.no/en/animalia-in-a-brief/about-animalia/), 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, goat and poultry. The indicators used to express the usage are: kg (active substance) and mg/PCU (active substance/population correction unit), see Appendix 1.

The result of this analysis shows that in kg and mg/PCU the reduction in the usage of antibacterial VMPs for cattle, pigs, sheep, goat and poultry from 2013 to 2017 was 10% and 9%, respectively (Figure 13). As the sales patterns (data from wholesalers) have been stable across 2013 to 2017, the figures are not assumed 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), but as the prescribing of such products for horses (VetReg data) was relatively stable across 2015-2017, 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 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. Usage of HMPs, estimated by use of VetReg data, shows that for cattle, pig, sheep and goat (see Appendix 1 for estimation methodology; Table 6 on treatment of broilers) the usage of HMPs was low for the years 2015-2017 (68 kg, 38 kg and 32 kg, respectively) and was primarily accounted for by benzylpenicillin for injection that was almost exclusively prescribed for sheep. The impact on the trends by excluding HMPs from the material is thought to be minimal.

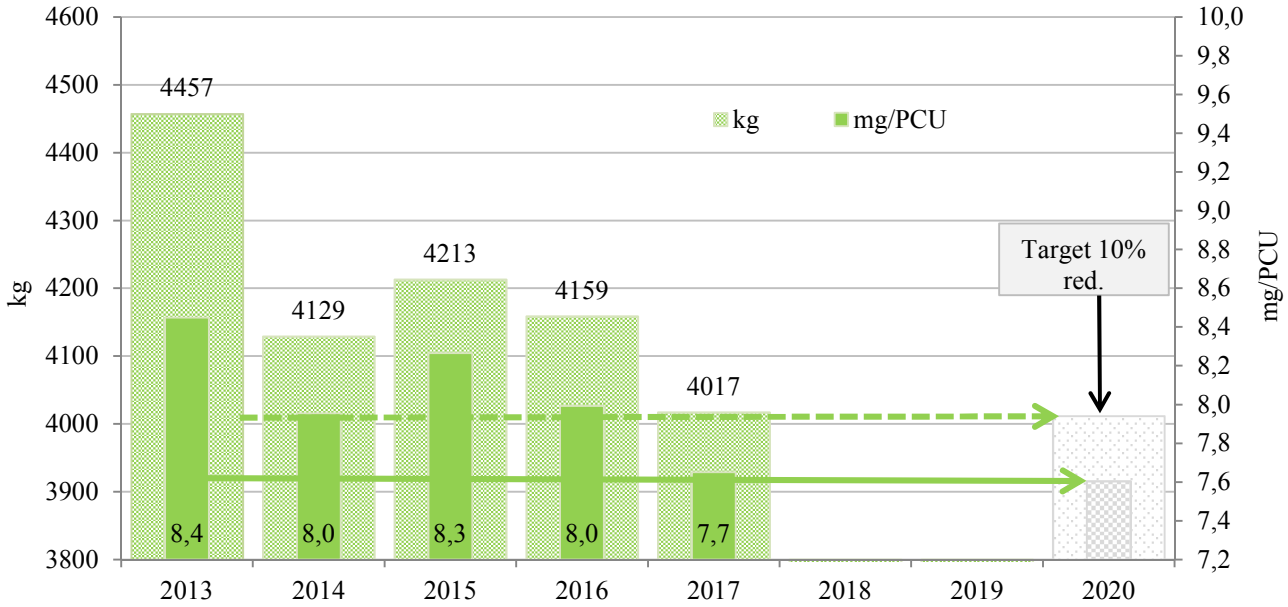

FIGURE 13. Estimated sales, in kg active substance and in mg/PCU, of antibacterial veterinary medicinal products for cattle, pigs, sheep, goat and poultry in Norway in 2013-2017 and the target according to the National Strategy. Sales data were obtained from Norwegian Institute of Public Health. Note 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 971 kg or 1.13 mg/PCU (maximum values), respectively, in 2020. Figure 14 shows that sales of antibacterial VMPs for farmed fish in 2017 were considerably lower than the maxium value set.

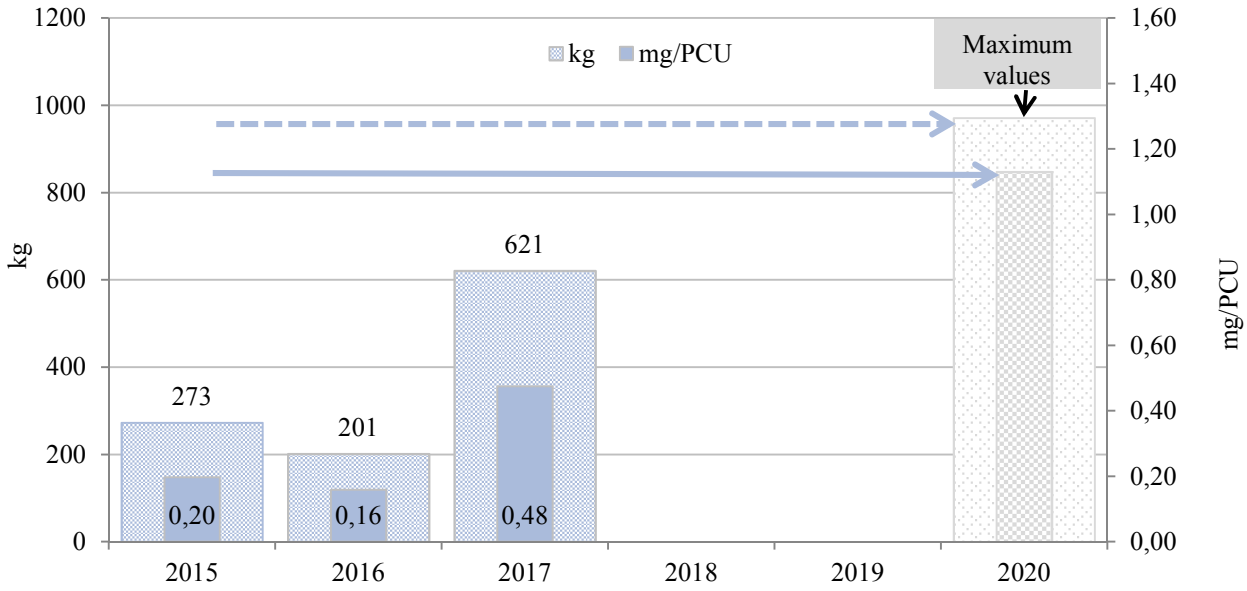

FIGURE 14. Prescription, in kg active substance and in mg/PCU, of antibacterial VMPs for farmed fish, in Norway in the period 2015-2017 and the target according to the National Strategy. Maximum values based on average of 2004-2014. Prescription data were obtained from the Veterinary Prescription Register and include prescription for cleaner fish. Note the differences in the scales of the Y-axes.

Companion animals (dogs and cats)

Sales of antibacterial VMPs for companion animals include tablets, oral solution, injectable and oral paste approved for dogs and cats only. From 2013-2017 a reduction in the sales of antibacterial VMPs for companion animals of 32% is observed (Figure 15). The usage of antibacterial HMPs for dogs and cats estimated by use of VetReg data for 2015, 2016 and 2017 was very stable; the average annual usage of HMPs was 288 kg (see Appendix 1 for estimation methodology). This indicates that the decline in the sales of VMPs for companion animals has not been substituted by prescribing of HMPs. Provided that the prescription of HMPs for companion animals was on the same level in 2013 the decline in the estimated sales of antibacterials (VMPs and HMPs) from 2013-2017 is 20%.

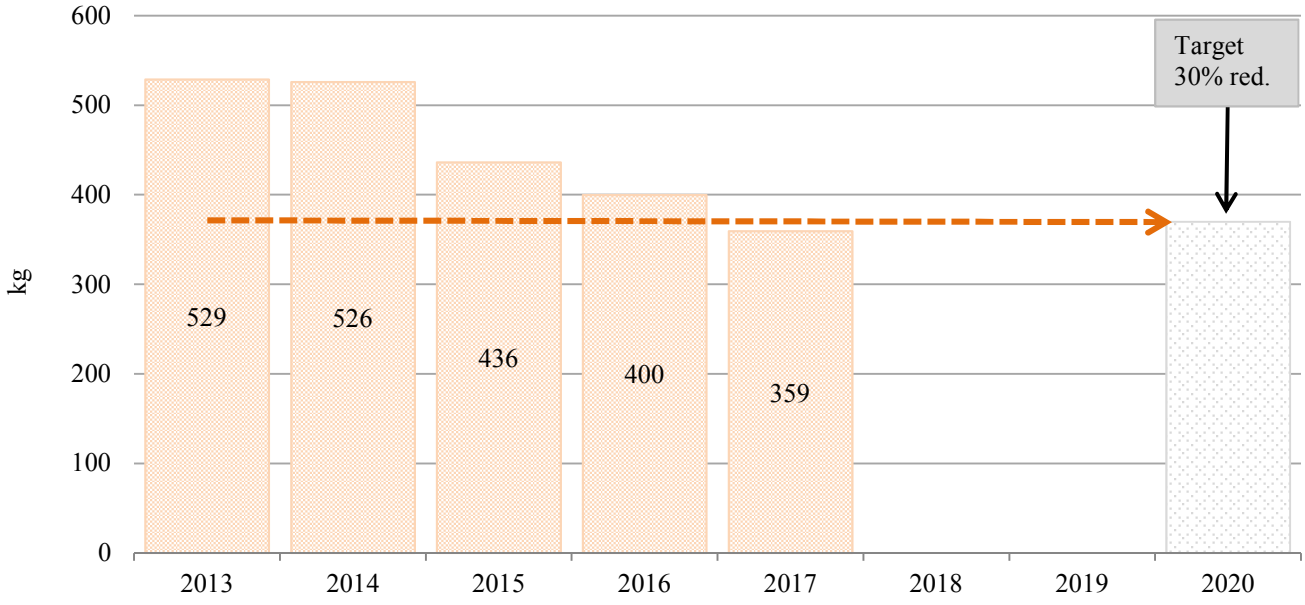

FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (oral paste, oral solution and tablets; exceptions for tablets - see Appendix 1) in the period 2013-2017 and the target according to the National 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 (Table 5, Figure 16). One of the targets stated in the National Strategy against Antibiotic Resistance is phasing out use of narasin as coccidiostat feed additive in the Norwegian broiler industry, without increasing the usage of antibacterials for therapeutic use. Due to the quality of the VetReg data for poultry in general - i.e. it was not possible to report to VetReg the VMP typically used – data for number of treatments with antibiotics were obtained from Animalia (Thorbjørn Refsnes, personal communication). Table 6 shows that the percentages of broiler flocks treated with antibiotics were very low in 2017.

TABLE 6. Number and percentages of flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs) in Norway in the period 2013-2017[1]. Data were obtained from HelseFjørfe, Animalia.

	2013	2014	2015[2]	2016[3]	2017
Broiler production	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)
Breeders P[4] (Rearing)	1 (1.1)	2 (2.2)	1 (1)	0 (-)	0 (-)
Breeders P[4] (Layers)	1 (1.1)	0 (-)	1 (1)	2 (2.1)	0 (-)
Broiler	8 (0.16)	2 (0.04)	1 (0.02)	3 (0.07)	7 (0.18)
No. flocks treated	10	4	3	5	7

[1] Phenoxymethylpenicillin and amoxicillin VMPs used only. [2] Phasing out narasin as coccidiostat feed additive started February 2015. [3] Out-phasing finished June 2016. [4] Parents.

Narasin has been used in some cases of necrotic enteritis (*Clostridium perfringens*). In 2017, 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).

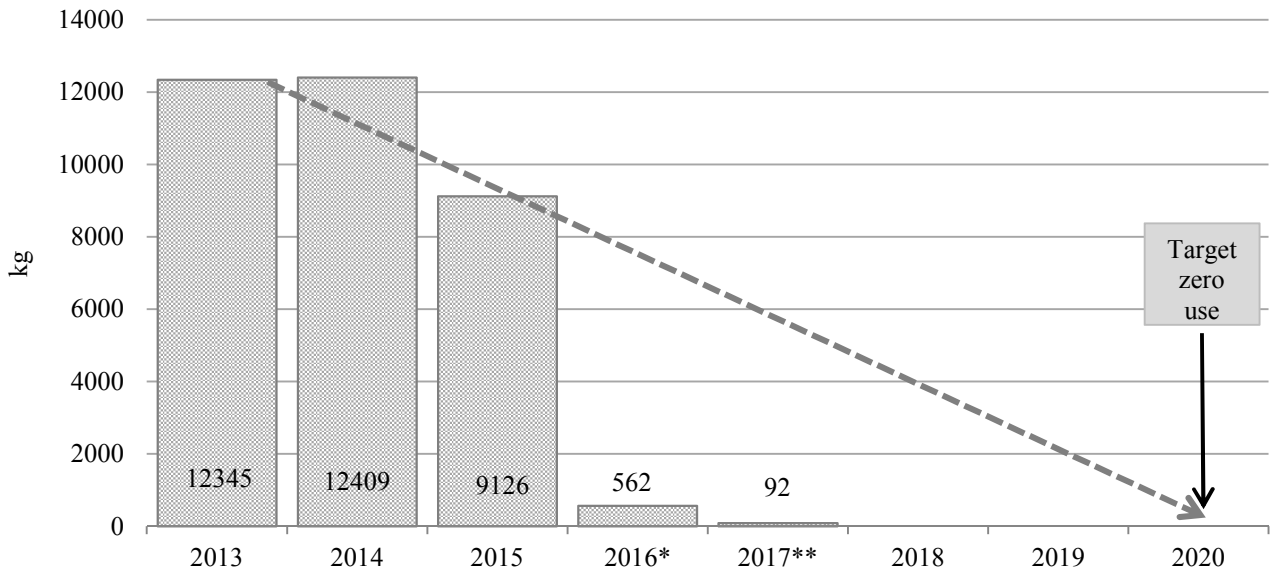

FIGURE 16. Sales of narasin as coccidiostat feed additive for use in broilers in Norway during the period 2013-2017. The data are obtained from Norwegian Food Safety Authority. *Sold until June 2016; **Used to control some cases of necrotic enteritis (*Clostridium perfringens*) (Bruce David, Nortura, personal communication).

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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, Morten Lindbæk

Overall antibiotic sales

In 2017, the total sales of antibacterials for systemic use in humans (J01, excl. methenamine) decreased by 5% compared to 2016 from 14.6 to 13.8 DDD/1,000 inhabitants/day. Antibiotics are prescription-only drugs in Norway. Overall antibiotic sales include all consumption in humans in Norway i.e. primary care and institutions. The overall consumption (J01) has decreased by 15% since 2012, when a *Mycoplasma pneumoniae* epidemic caused higher prescriptions of macrolides and tetracyclins. Increased sales of ATC group J01 (antibacterials) in the first decades of this century is mainly caused by increased use of the penicillins and the urinary antiseptic methenamine (Table 7, Figure 17). The proportion of narrow-spectrum penicillins (J01CE) of total sales (J01, excl. methenamine) was higher 20 years ago; in 1997, the proportion was 35% and in 2017, 26%.

TABLE 7. Human usage of antibacterial agents in Norway 2010-2017 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2016-2017. Methods for collection of data on human usage of antimicrobial agents are presented in Appendix 2.

ATC	Groups of substances	2010	2011	2012	2013	2014	2015	2016	2017	Change (%) 2016-2017
J01A	Tetracyclines	3.12	3.47	3.87	3.54	3.46	3.38	3.16	3.01	- 5
J01B	Amphenicols	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
J01CA	Penicillins with extended spectrum	3.19	3.21	3.34	3.35	3.46	3.27	3.14	3.00	- 5
J01CE	Beta-lactamase sensitive penicillins	4.44	4.47	4.30	4.09	3.88	3.88	3.73	3.61	- 3
J01CF	Beta-lactamase resistant penicillins	0.82	0.88	0.90	0.79	0.91	0.89	0.90	0.84	- 7
J01CR	Combination of penicillins	0.03	0.03	0.04	0.05	0.08	0.09	0.10	0.08	- 22
J01D	Cephalosporins, monobactams, carbapenems	0.55	0.56	0.55	0.52	0.48	0.45	0.43	0.40	- 8
J01E	Sulfonamides and trimethoprim	0.87	0.87	0.87	0.86	0.88	0.88	0.85	0.84	- 1
J01F	Macrolides, lincosamides and streptogramins	2.01	2.31	2.26	1.94	1.67	1.51	1.33	1.18	- 11
J01G	Aminoglycosides	0.07	0.07	0.08	0.07	0.08	0.08	0.08	0.09	+ 16
J01M	Quinolones	0.73	0.75	0.75	0.72	0.68	0.61	0.54	0.46	- 16
J01X*	Other antibacterials	0.47	0.49	0.47	0.45	0.43	0.41	0.38	0.36	- 5
J01	**Total exclusive of methenamine**	**16.3**	**17.1**	**17.4**	**16.4**	**16.0**	**15.5**	**14.6**	**13.8**	**- 5**
J01XX05	Methenamine	3.37	3.44	3.57	3.70	3.86	4.00	4.09	4.11	+ 1
J01	**Total all antimicrobial agents**	**19.7**	**20.6**	**21.0**	**20.1**	**19.9**	**19.4**	**18.7**	**18.0**	**- 4**

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

All main antibiotic groups have decreased since 2016. The beta-lactamase sensitive penicillin-group (J01CE), penicillins with extended spectrum (J01CA) and tetracyclines (J01A) were the three most used antibacterial groups in Norway in 2017.

Use of the prophylactic agent methenamine has been increasing for many years, but seems to level out in 2017. Methenamine has the largest amounts of DDDs of all antibiotics and accounts for 92% of subgroup J01X and 23% of total antibacterial use (Figures 17 and 18).

Among the tetracyclines (J01A), doxycycline is most frequently used, but lymecycline, mainly indicated for acne, is increasingly utilised (Figure 18 and Table 8).

In 2017, the penicillins (ATC group J01C) accounted for 42% of total antibacterial use in Norway (Figure 18). Over the years, there has been a shift towards use of more broad-spectered penicillins (Figures 18 and 19). Beta-lactamase sensitive penicillins represent approximately half of the penicillin group (48% share) measured in DDDs and this picture has been stable since 2012. Penicillins with extended spectrum (J01CA) represent 40% of the J01C group compared to 25% in 1996. The increase over years in J01CA has mainly been caused by increasing use of amoxicillin and pivmecillinam. Pivmecillinam is pre-scribed for urinary tract infections, and has been used at the expense of the subgroup of sulfonamides and trimethoprim, which has decreased over many years (Figure 17). Since 2014, amoxicillin and pivmecillinam have decreased. An increase of the penicillins with beta-lactamase inhibitors has been observed in the latest years, but in 2017 the sales decreased due to the global shortage of piperacillin/ tazo-bactam. Piperacillin/tazobactam is used in hospitals and has been the only penicillin with beta-lactamase inhibitor marketed in Norway. Oral co-amoxiclav has been available as an unlicenced product until May 2017 when it received marketing authorisation in Norway. A marked increase in sales is observed since then.

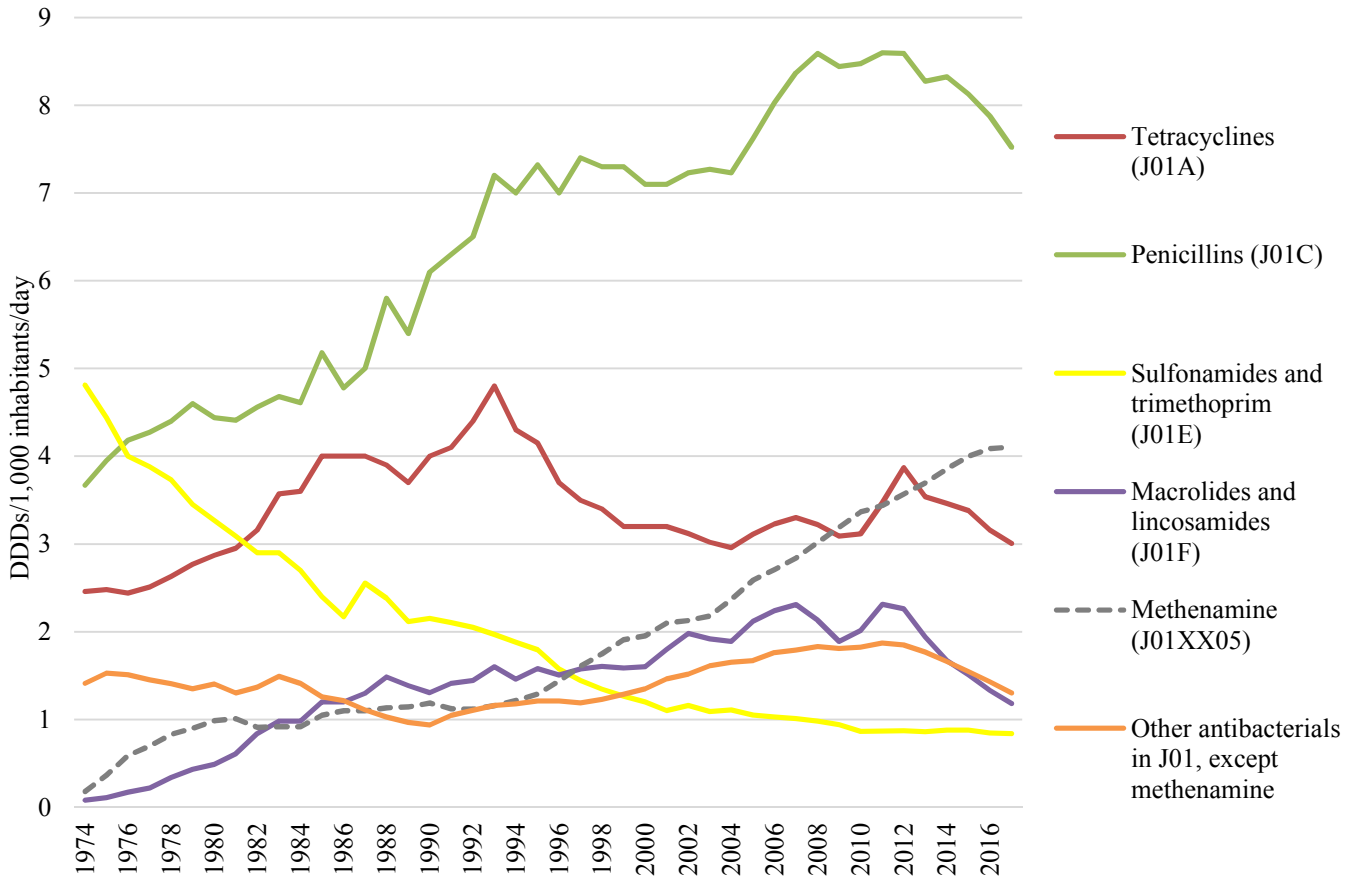

FIGURE 17. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine (J01XX05) and other antibacterials in Norway 1974-2017. Other types of antibacterials include all other antibacterials in ATC group J01.

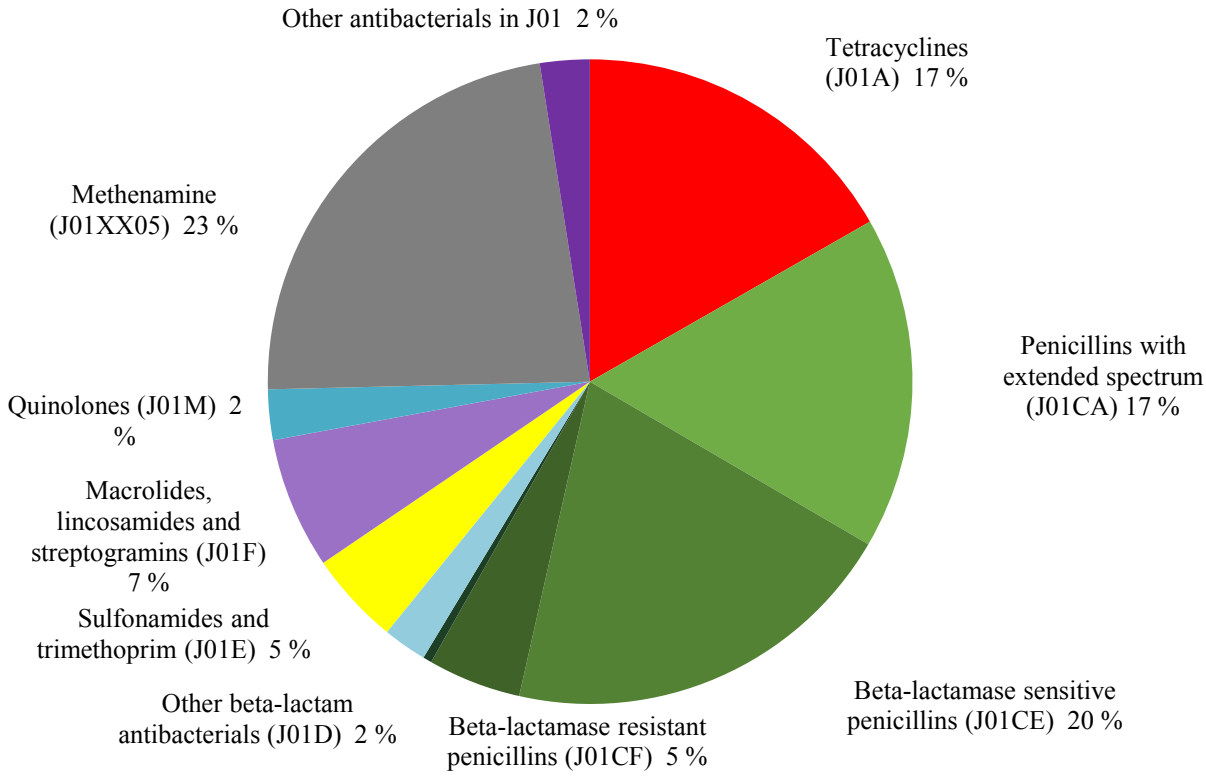

FIGURE 18. Relative amount of antibacterial agents for systemic use in 2017 in Defined Daily Doses (DDD) (total sale in the country).

Since 2012, use of macrolides has dropped markedly, while clindamycin (lincosamide) is increasingly utilised (Figures 18 and 20). Use of the group J01F macrolides, lincosamides and streptogramins has followed a wavy pattern over the years. The shifts in use could to some degree be explained by recurrent epidemics of *M. pneumoniae*, occurring with four- to six-years intervals. The last epidemic was in 2012. Furthermore, there has been a change in treatment guidelines for sexually transmitted diseases. Azithromycin is no longer recommended as first line treatment, and this could partly explain the decrease in macrolide use since 2012.

In the latest years, sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased. This is mainly due to decreased use of 1st and 2nd generation cephalosporins (Tables 7 and 8, Figures 18 and 21).

The quinolones represent only a small fraction (2%) of total antibacterial sales (Figure 18) and the use has steadily decreased since 2012. Ciprofloxacin is the main substance accounting for 95% of the quinolone group in 2017.

TABLE 8. Total human usage of antibacterial agents for systemic use in Norway 2012-2017. Sales are given in DDD/1,000 inhabitants/day. The methodology for collection of data on human usage of antibacterial agents is presented in Appendix 2.

ATC group	ATC code	Substance	2012	2013	2014	2015	2016	2017
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	2.02	1.99	1.97	1.82	1.69
	J01A A04	Lymecycline	0.90	0.97	0.96	0.96	0.94	0.95
	J01A A06*	Oxytetracycline	-	<0.001	<0.001	<0.001	<0.001	<0.001
	J01A A07	Tetracycline	0.62	0.54	0.50	0.45	0.40	0.36
	J01A A08*	Minocycline	0.006	0.009	0.003	0.002	0.002	0.001
	J01A A12	Tigecycline	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01B - Amphenicols	J01B A01	Chloramphenicol	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.09	0.10	0.12	0.11	0.13	0.13
	J01C A04	Amoxicillin	1.45	1.41	1.46	1.39	1.31	1.30
	J01C A08	Pivmecillinam	1.78	1.84	1.87	1.76	1.69	1.56
	J01C A11	Mecillinam	0.008	0.008	0.008	0.006	0.005	0.005
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.24	0.22	0.24	0.22	0.23	0.23
	J01C E02	Phenoxymethyl-penicillin	4.07	3.86	3.64	3.66	3.50	3.38
	J01C E08*	Benzathine benzylpenicillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CF - Beta-lactamase resistant penicillins	J01C F01	Dicloxacillin	0.76	0.58	0.72	0.73	0.74	0.70
	J01C F02	Cloxacillin	0.14	0.21	0.19	0.16	0.17	0.13
	J01C F05*	Flucloxacillin	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
J01CR - Combination of penicillins, incl. beta-lactamase inhibitors	J01C R02	Amoxicillin and enzyme inhibitor	0.004	0.007	0.012	0.013	0.016	0.025
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.04	0.07	0.08	0.09	0.05
J01DB – 1st gen. cephalosporins	J01D B01	Cefalexin	0.18	0.17	0.14	0.12	0.10	0.09
	J01D B03	Cefalotin	0.08	0.08	0.09	0.09	0.09	0.08
	J01D B04	Cefazolin						0.009
J01DC – 2nd gen. cephalosporins	J01D C02	Cefuroxime	0.08	0.07	0.06	0.04	0.04	0.03
J01DD – 3rd gen. cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	0.12	0.12
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.01	0.01	0.01
	J01D D04	Ceftriaxone	0.03	0.03	0.02	0.02	0.02	0.02
	J01D D08*	Cefixime					<0.001	<0.001
	J01D D52	Ceftazidime and avibactam						<0.001
J01DF - Monobactams	J01D F01	Aztreonam	<0.001	0.001	0.001	0.001	0.001	<0.001
J01DH - Carbapenems	J01D H02	Meropenem	0.05	0.05	0.05	0.04	0.04	0.04
	J01D H03	Ertapenem	0.002	0.002	0.002	0.003	0.002	0.002
	J01D H51	Imipenem and enzyme inhibitor	0.002	0.002	0.002	0.002	0.002	0.002

ATC group	ATC code	Substance	2012	2013	2014	2015	2016	2017
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
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.49	0.46	0.42	0.38	0.35
	J01E C02*	Sulfadiazine					0.001	0.001
	J01E E01	Sulfamethoxazole and trimethoprim	0.36	0.37	0.40	0.44	0.44	0.49
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.85	0.75	0.68	0.60	0.54
	J01F A02	Spiramycin	0.01	0.006	0.005	0.004	0.003	0.003
	J01F A06	Roxithromycin		<0.001	<0.001	<0.001	<0.001	<0.001
	J01F A09	Clarithromycin	0.39	0.30	0.23	0.18	0.14	0.13
	J01F A10	Azithromycin	0.48	0.41	0.35	0.33	0.30	0.26
	J01FS15	Telithromycin	<0.001	<0.001	<0.001	<0.001	<0.001	
	J01F F01	Clindamycin	0.33	0.37	0.34	0.31	0.28	0.25
J01G - Aminoglycosides	J01GA01*	Streptomycin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01G B01	Tobramycin	0.03	0.03	0.02	0.02	0.02	0.02
	J01G B03	Gentamicin	0.05	0.05	0.05	0.06	0.06	0.07
	J01G B06*	Amikacin	0.001	0.001	0.001	0.001	0.001	0.001
J01M - Quinolones	J01M A01	Ofloxacin	0.02	0.02	0.01	0.01	0.01	0.01
	J01M A02	Ciprofloxacin	0.72	0.70	0.65	0.59	0.52	0.43
	J01MA12	Levofloxacin	0.002	0.001	0.002	0.002	0.003	0.003
	J01MA14*	Moxifloxacin	0.004	0.005	0.007	0.008	0.009	0.01
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.01	0.02	0.02	0.02	0.02
	J01X A02	Teicoplanin	0.001	0.001	<0.001	<0.001	<0.001	<0.001
	J01X B01	Colistin	0.004	0.005	0.006	0.005	0.007	0.006
	J01X C01	Fusidic acid	0.005	0.004	0.004	0.004	0.003	0.003
	J01X D01	Metronidazole	0.07	0.06	0.05	0.04	0.03	0.04
	J01X E01	Nitrofurantoin	0.37	0.36	0.35	0.34	0.31	0.28
	J01XX01	Fosfomycin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01X X05	Methenamine	3.57	3.70	3.86	3.99	4.09	4.11
	J01XX08	Linezolid	0.01	0.007	0.007	0.009	0.01	0.009
	J01XX09	Daptomycin	0.001	0.001	<0.001	0.001	0.001	<0.001
	J01X X11	Tedizolid					<0.001	<0.001
Antibiotics in other ATC groups	J04A	Rifampicin**	0.13	0.13	0.13	0.12	0.12	0.11
	A07A A09	Vancomycin	0.002	0.002	0.002	0.002	0.002	0.002
	A07A A11	Rifaximin	0.004	0.007	0.012	0.028	0.043	0.058
	A07A A12	Fidaxomicin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	P01A B01	Metronidazole	0.23	0.24	0.24	0.24	0.23	0.22
	D06A X09/ R01A X06*	Mupirocin (grams)	145	174	174	225	185	213

*Drugs not licensed in the Norwegian market in 2017. **Given as the amount DDD/1,000 inhabitants/day of rifampicin (i.e. total amount in plain and combination products).

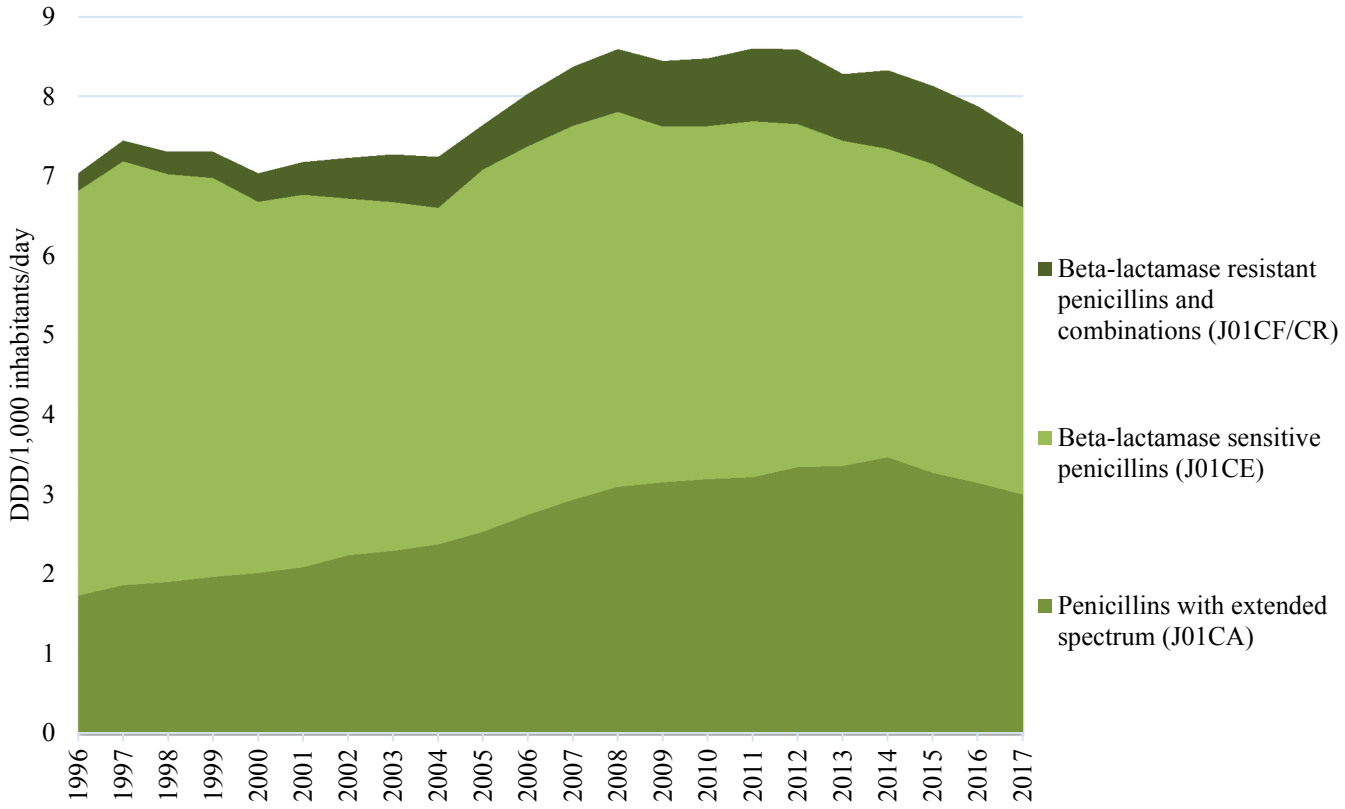

FIGURE 19. Sales of penicillins (J01C) in Norway 1996-2017 and changes between groups of penicillins.

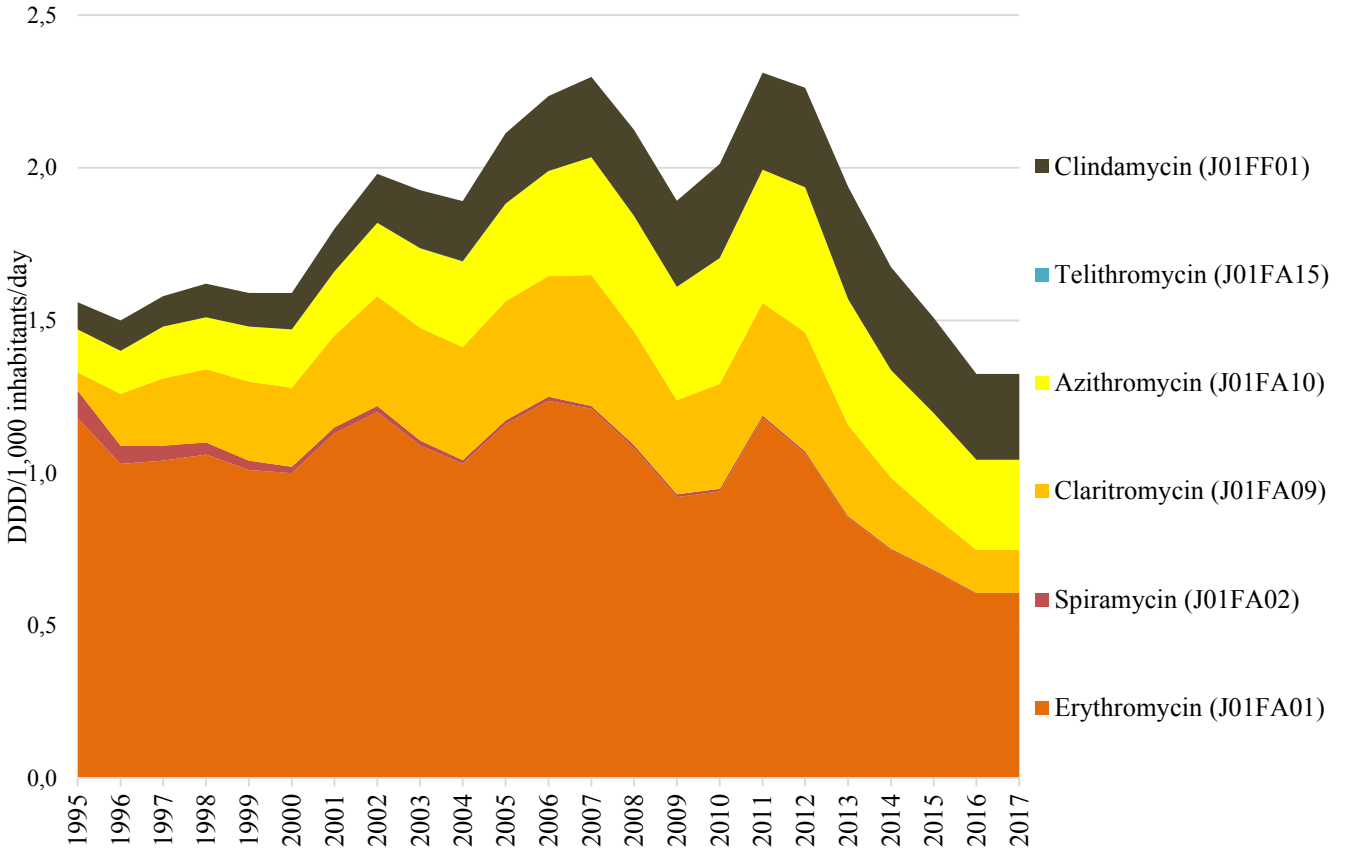

FIGURE 20. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1995-2017.

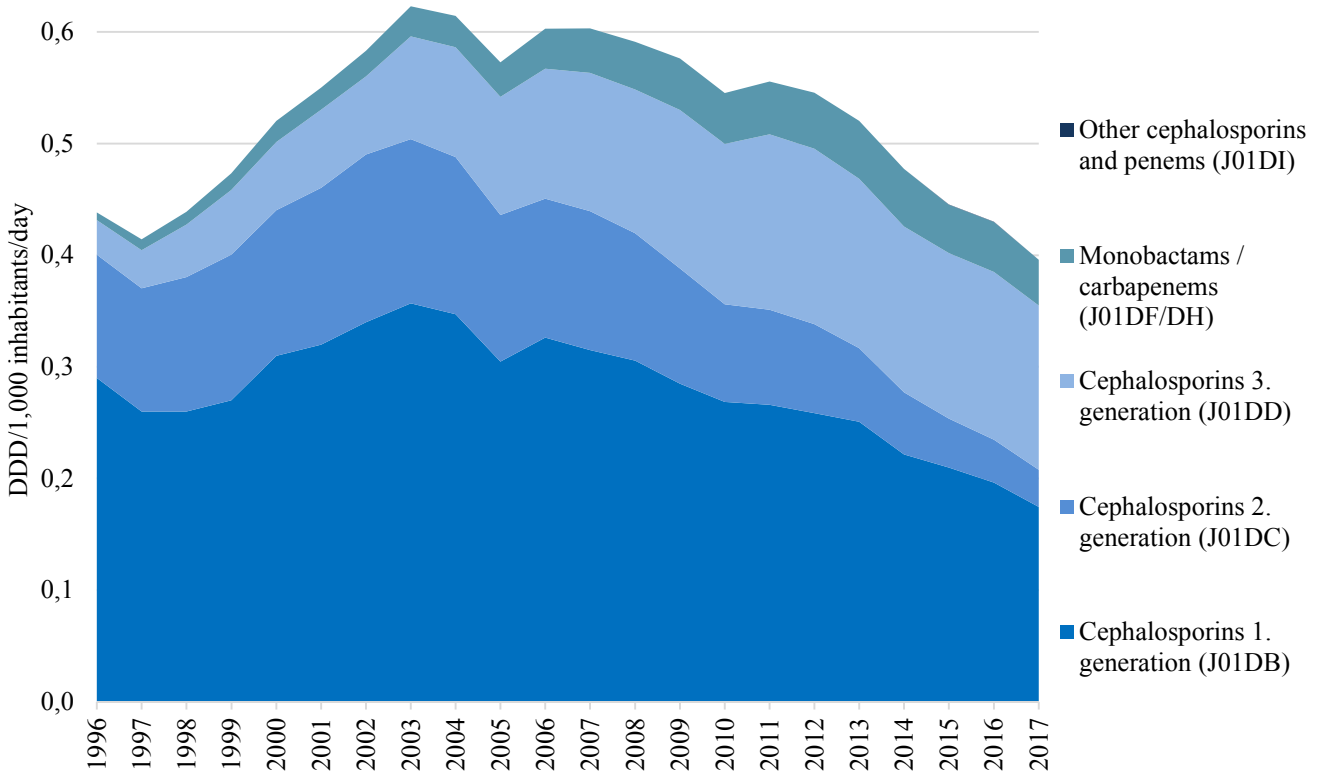

FIGURE 21. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2017 and changes between generations of cephalosporins and monobactams/carbapenems.

Antibiotic usage in primary care

Around 82% of the total human sales of antibacterials are used by patients in primary care, i.e. outside health institutions. Antibacterials are prescription-only drugs in Norway and all prescriptions (including those prescribed from hospitals to out-patients) to persons living in Norway are captured in these figures.

Sales of antibiotics to outpatients have decreased since 2012. For ambulatory care, the most important antibiotic groups in 2017 were penicillins (J01C; 54% of DDDs in J01 excl. methenamine), tetracyclines (J01A; 22%) and macrolides and lincosamides (J01F; 9%). The four most commonly prescribed antibiotics for outpatients in 2017 were phenoxymethylpenicillin, doxycycline, pivmecillinam and amoxicillin. These four represented 57% of all prescriptions and 61% of all DDDs of ATC group J01, excl. methenamine. The urinary antiseptic methenamine is the most used drug in ATC group J01 in ambulatory care. It represented 25% of all DDDs in the ATC group J01 and 9% of J01 prescriptions. Many outpatients, especially women, use methenamine over a long period, in spite of lack of documentation for long term use.

Geographical variation

The usage of antibacterials varies among the 19 Norwegian counties. The county using the least is using around 73%, in DDDs, of the county using the most (Figure 22). The same counties seem to be high-use and low-use counties over time. The pattern is almost the same when looking at the number of prescriptions/1,000 inhabitants/year. In the county with lowest prescribing, 25% fewer prescriptions per inhabitants are prescribed compared to the county with the highest prescription rate (Figure 23).

Females use more antibiotics than males; 24% of females purchased at least one antibiotic course (methenamine excluded) in 2017 compared to 15% of the males. The gender pattern is similar in all regions in the country (Figure 25). The highest use is found among young children, young women and the elderly (Figures 26 and 27). Among those who use antibacterials, the elderly population receive more prescriptions; for those above 75 years; 2.1 (males) and 2.2 (females) prescriptions/user are dispensed every year compared to around 1.5 prescriptions/user for younger persons (Figure 27).

Antibiotics prescribed by dentists

Physicians are the main prescribers to humans, but dentists prescribe around 5% (measured in DDDs) of antibiotics (J01) to humans in ambulatory care. In 2017, dentists most often prescribed phenoxymethylpenicillin (73% of all antibiotic DDDs prescribed by dentists) followed by amoxicillin (12%) and clindamycin (5%).

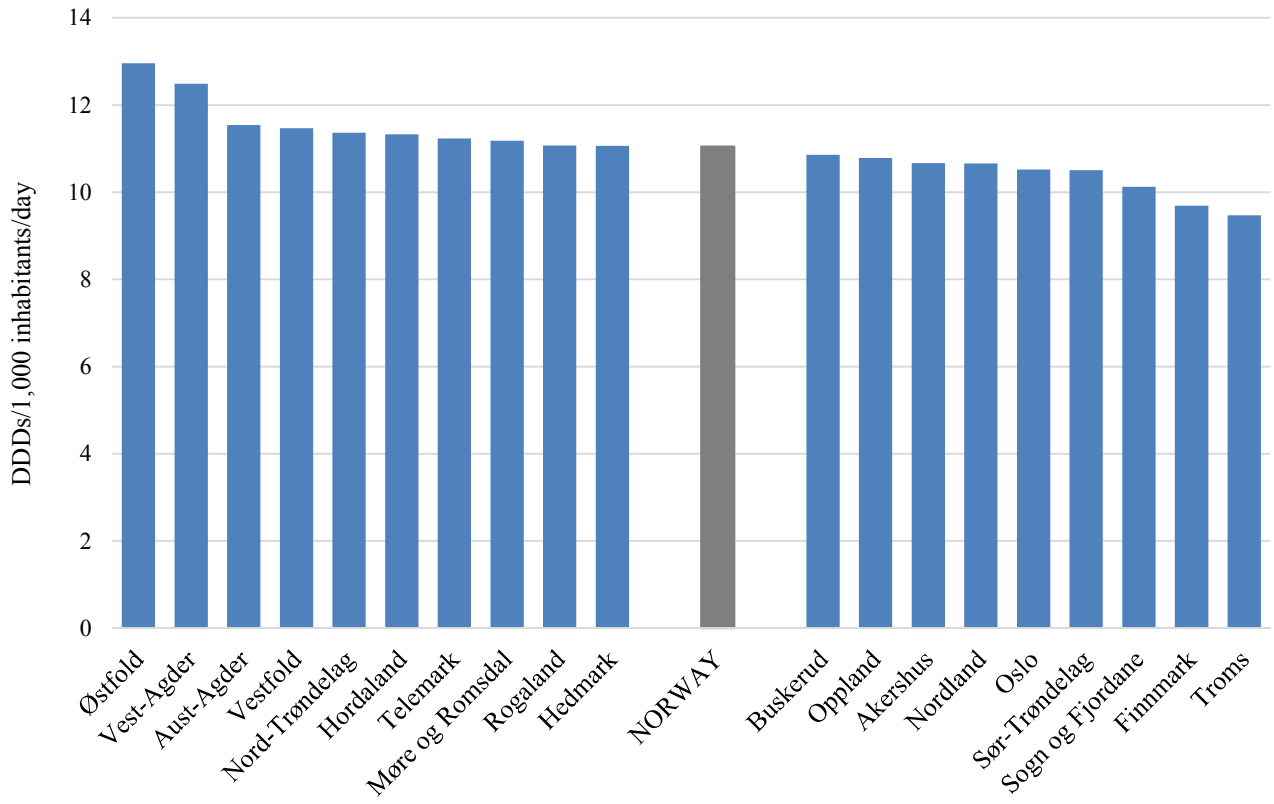

FIGURE 22. Sales of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2017. Measured as number of DDD/1,000 inhabitants/day. Data from the Norwegian Prescription Database (NorPD) (i.e. health institutions and sales to prescriber´s own practice not included).

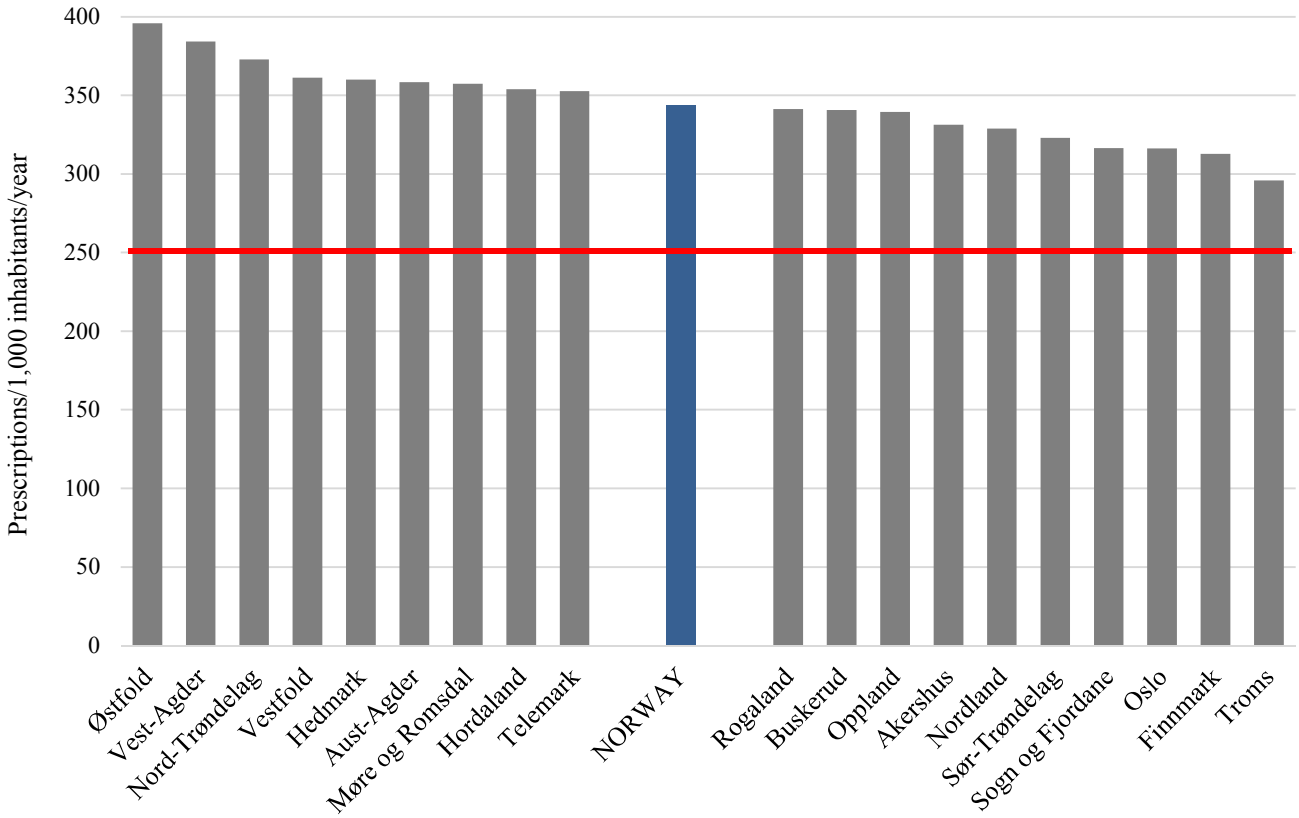

FIGURE 23. Sales of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2017. Measured as number of prescriptions/1,000 inhabitants/year. Data from the Norwegian Prescription Database (NorPD) (excl. health institutions). Red line denotes the goal set by the National Strategy against Antibiotic Resistance 2015-2020.

Methenamine treatment in urinary tract infections

Urinary tract infections (UTIs) are the most common bacterial infections in women of all age groups. An estimated 30-44% of women will have a recurrence within the first six months following an initial infection. The majority of patients with recurrent UTI are healthy women with normal urinary tracts. Methenamine hippurate is used in Norwegian primary care as preventive long-term treatment, especially among elderly women with recurrent UTI, and methenamine constituted 21% of the total antibiotic consumption in 2017.

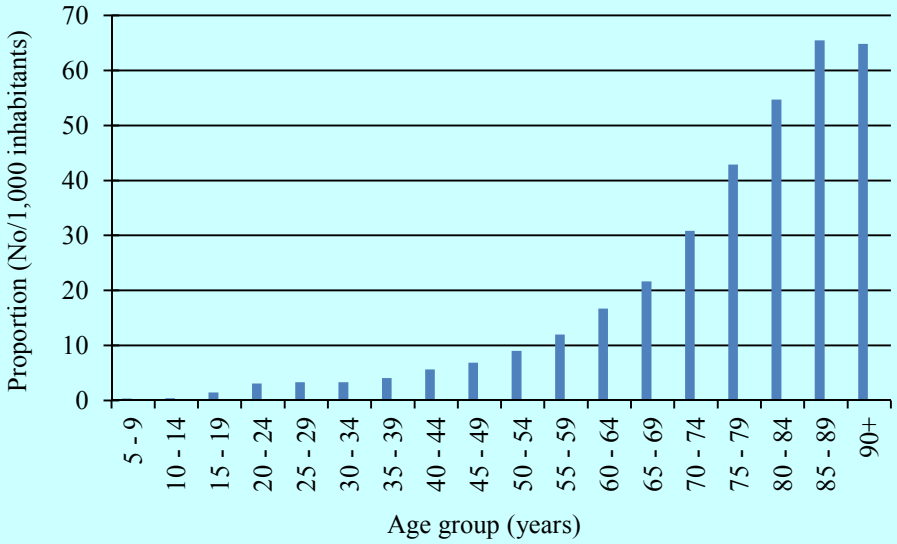

FIGURE 24. Proportion (No/1,000 women) by age-group having dispensed at least one prescription of methenamine (one year prevalence) in ambulatory care in Norway in 2017. Data from the Norwegian Prescription Database (NorPD) http://www.norpd.no/.

The proportion of the female population 60-80 years in Norway using antibacterials (J01) increased from 114,292 (31%) in 2004 to 155,013 (35%) in 2012. The number of methenamine users increased from 4,702 to 9,211 in the same period (1). Norway has a much higher consumption of methenamine than any other country and accounts for approximately 50% of the total consumption in Europe (2).

Methenamine was discovered by Aleksandr Butlerov in 1859. Hexamethylenetetramine is industrially manufactured by combining formaldehyde and ammonia. The reaction can be performed in gaseous phase or in solution. The molecule has a symmetrical tetrahedral cage-like structure. Hexamethylenetetramine was first introduced in a medical context in 1899 as a urinary tract antiseptic. It was only used in cases with acidic urine, whereas boronic acid was used for UTI cases with alkaline urine. The scientist De Eds found that there was a direct correlation between the acidity of the hexamethylenetetramine environment and the rate of decomposition. Consequently, the medical effectiveness was more dependent on the acidity of the urine than the amount of drug administered. Hexamethylenetetramine is totally inactive in an alkaline environment.

Methenamine is used prophylactially against UTIs. It decomposes at acidic pH to form formaldehyde and ammonia, and the formaldehyde component is bactericidal. The use of methenamine was reduced in the late 1990s due to adverse effects, especially chemically induced hemorrhagic cystitic when overdosed, but the usage is now escalating due to increasing antimicrobial resistance. Methenamine is assumed to be especially well suited for long-term prophylactic treatment of UTIs, as bacteria do not develop resistance to formaldehyde.

There is limited scientific research on prophylactic methenamine treatment of UTIs. A 2012 meta-analysis from the Cochrane Database evaluated the efficacy and benefits of prophylactic treatment of UTI. Thirteen studies were included with 2,032 participants in total. Six studies comprising 654 patients reported on treatment of symptomatic UTI, whereas eight studies with 796 patients analysed bacteriuria. Subgroup analyses found that methenamine could be effective in patients with no urinary tract/kidney abnormalities, but not in patients with such conditions. Short-term treatment (one week or less) gave a significant reduction in symptomatic UTI among patients without urinary tract/ kidney abnormalities. The authors concluded that methenamine may be effective for prevention of UTI, especially as short-term treatment. It does not appear to have any effect in patients with urinary tract/kidney abnormalities. There is a need for further large-scale randomised controlled trials to address these issues, especially in patients with neuropathic bladder (3). Several studies both in Norway and abroad are presently conducted to assess the effectiveness of methenamine. The results have not been presented yet, and the conclusions are at this stage uncertain.

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2. https://ecdc.europa.eu/en/home
3. Cochrane Database Syst Rev. 2012 Oct 17;10:CD003265. doi: 10.1002/14651858.CD003265.pub3.

Linda Rui, Skøyen Health Center and Antibiotic Centre for Primary Care, Institute of Health and Society, University of Oslo, Norway.

FIGURE 25. One year prevalence of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2013, 2015 and 2017. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine), vancomycin (A07AA09), rifaximin (A07AA11), fidaxomicin (A07AA12) and metronidazole (P01AB01).

FIGURE 26. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one year prevalence) in ambulatory care by gender and age in Norway in 2017. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine), vancomycin (A07AA09), rifaximin (A07AA11), fidaxomicin (A07AA12) and metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions.

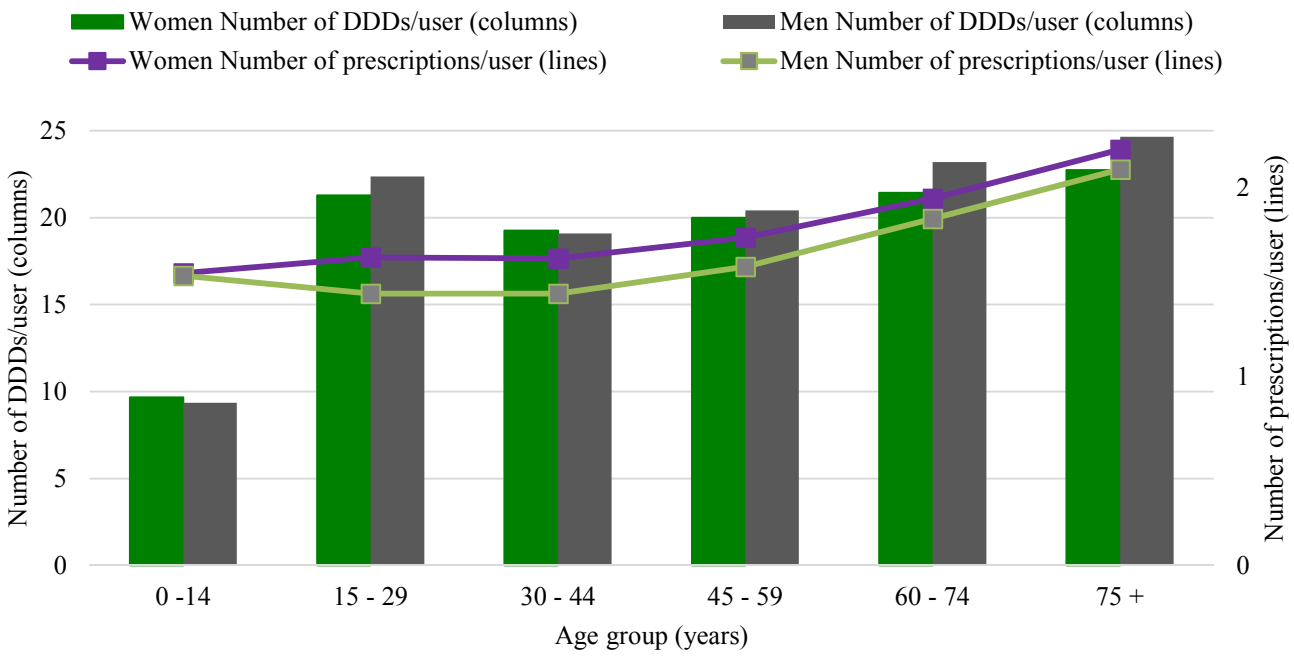

FIGURE 27. Mean number of prescriptions per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway, 2017. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

Antibiotic usage in hospital care

In 2017, the antibacterial sales (in DDDs) to hospitals represented around 8% of total sales of antibacterials for human use in the country. An increase in DDD/1,000 inhibitants/day of 6% compared to 2016 is observed (Figure 29). This is partially explained by an increased use of narrow-spectrum antibiotics, as the DDDs for these are lower than the doses most commonly used.

Penicillins (J01C) represent 50% of the use measured in DDDs in hospitals (J01CE 17%, J01CA 18%, J01CF 11% and J01CR 4%). The second largest group is the cephalosporins; 17% of all DDDs with 3rd generation cephalosporins (J01DD) being the dominant subgroup. In 2017, seven substances accounted for 54% of all DDDs used in hospitals. These are benzylpenicillin, cloxacillin, ampicillin, cefotaxime, cefalotin, doxycycline and gentamicin. Three single substances accounted for 32% of all antibacterial use in hospitals; benzylpenicillin (14%), cloxacillin (9%) and ampicillin (9%).

Figure 30 shows annual trends in national antibiotic use in hospitals corrected for hospital activity data (bed days and admissions) instead of population statistics. The two measurements together show the interplay between shorter hospital stays and intensity of antibiotic treatment.

Seven selected groups that are mainly used in hospitals are shown in Figure 31. The use of piperacillin/tazobactam has been increasing for many years, but was markedly reduced in 2017 due to a nationwide shortage. There was increased use of 3rd generation cephalosporins, aminoglycosides and metronidazole (not shown), probably as a result of the piperacillin/tazobactam shortage, as these drugs may be components of alternative regimens to piperacillin/tazobactam. The use of carbapenems peaked in 2014 after many years of increasing use, and seems to have reached a stable level. The use of quinolones is reduced by more than 1/3 since 2011, and the use of 2nd generation cephalosporins has been decreasing over many years. It should be noted that only parenteral formulations of 2nd and 3rd generation cephalosporins as well as carbapenems are licensed in Norway.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between hospitals. The variations cannot be accounted for by differences in activity or patient composistion alone. Figure 32 shows the use of the five selected groups of broadspectrum antibiotics targeted in the National Action Plan in all Norwegian hospitals/health trusts.

The national guidelines for hospitals recommend the use of narrow-spectrum antibiotics. Figure 33 shows the proportions of preferred antibiotics and antibiotics that are considered drivers of resistance. The preferred antibiotics constitute > 60% in all hospitals trusts except Oslo University Hospital. One factor that may partially explain higher relative use of antibiotics driving resistance in this hospital trust is that it has several national assignments and is the only hospital performing solid organ transplantation.

Antibiotic prescribing in dentistry

The sales of antibiotic to dentists and/or to dental clinics measured in DDDs decreased by 4% in 2017 compared with 2016. Phenoxymethylpenicillin is most commonly prescribed followed by amoxicillin, clindamycin and oral metronidazole. In 2017, these antibiotic substances represent 73%, 12%, 5% and 4% of all DDDs of antibiotics prescribed by dentists, respectively. There has been a shift towards more broad-spectrum antibiotics over the years; in 2008, the phenoxymethylpenicillin proportion (measured in DDDs) was higher (75%), while the proportion of amoxicillin was lower (9%). In dentistry, women are more often prescribed antibiotics than men. The age group 60-69 years accounts for the highest consumption of antibiotics (J01 and P01AB01) prescribed by dentists, around 4% of this age group were prescribed antibiotics in 2017. In the age groups younger and older, the proportions are around 2-3%.
Dentists account for approximately 5% of all antibiotics prescribed in outpatient care in 2017. Corresponding to outpatient medical care, there are great differences between the counties. The prevalence of use varies between 1.7% of the population in Finnmark to 3% in Vest-Agder. The total sales of antibiotics (J01 and metronidazole), measured as DDD/1,000 inhabitants/ year, decreased in 16 out of 19 counties in 2017 compared with 2016 (range +4% to -17%) .

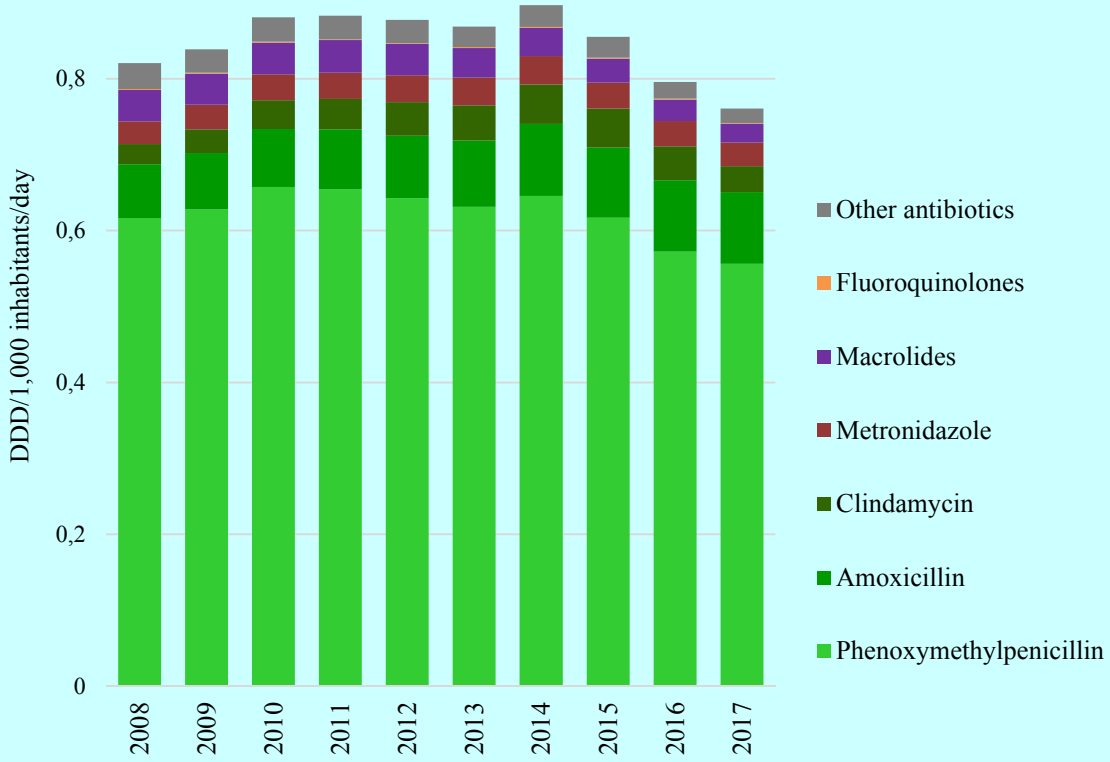

FIGURE 28. Antibiotics (J01 and oral metronidazole (P01AB01), prescribed in Norway for the years 2008-2017, measured in DDDs/1,000/inhabitants/day.

Hege Salvesen Blix, Department of Drug Statistics. Norwegian Institute of Public Health and Morten Enersen, Department of Oral Biology, Faculty of Dentistry, University of Oslo, Norway.

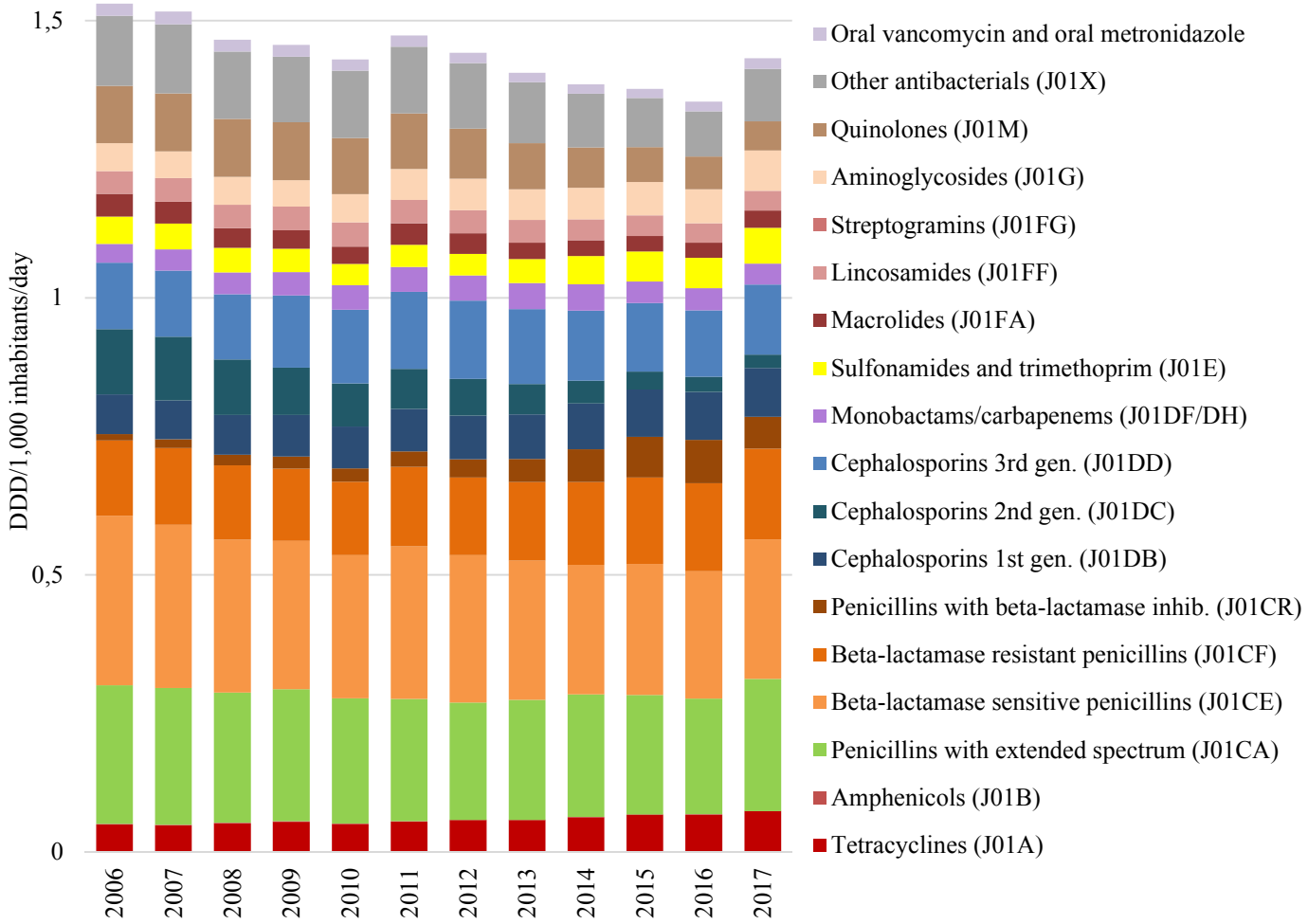

FIGURE 29. Consumption of antibacterial agents for systemic use in Norwegian hospitals 2006-2017, measured in DDD/1,000 inhabitants/day.

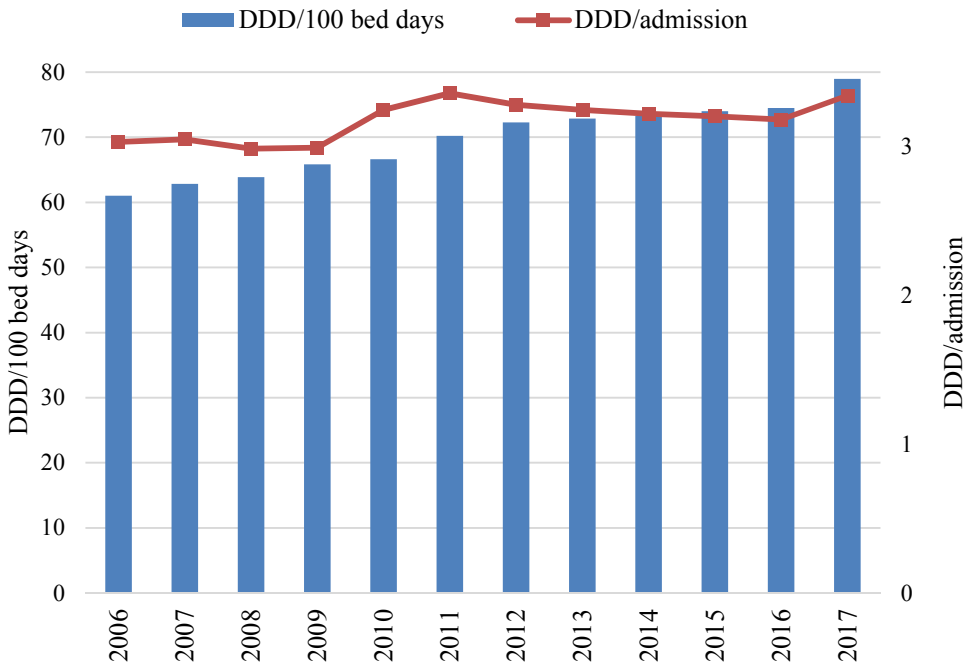

FIGURE 30. Total use of antibiotics in Norwegian hospitals (somatic) 2006-2017, measured in DDD/100 bed days (blue bars) and DDD/admission (red line). Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

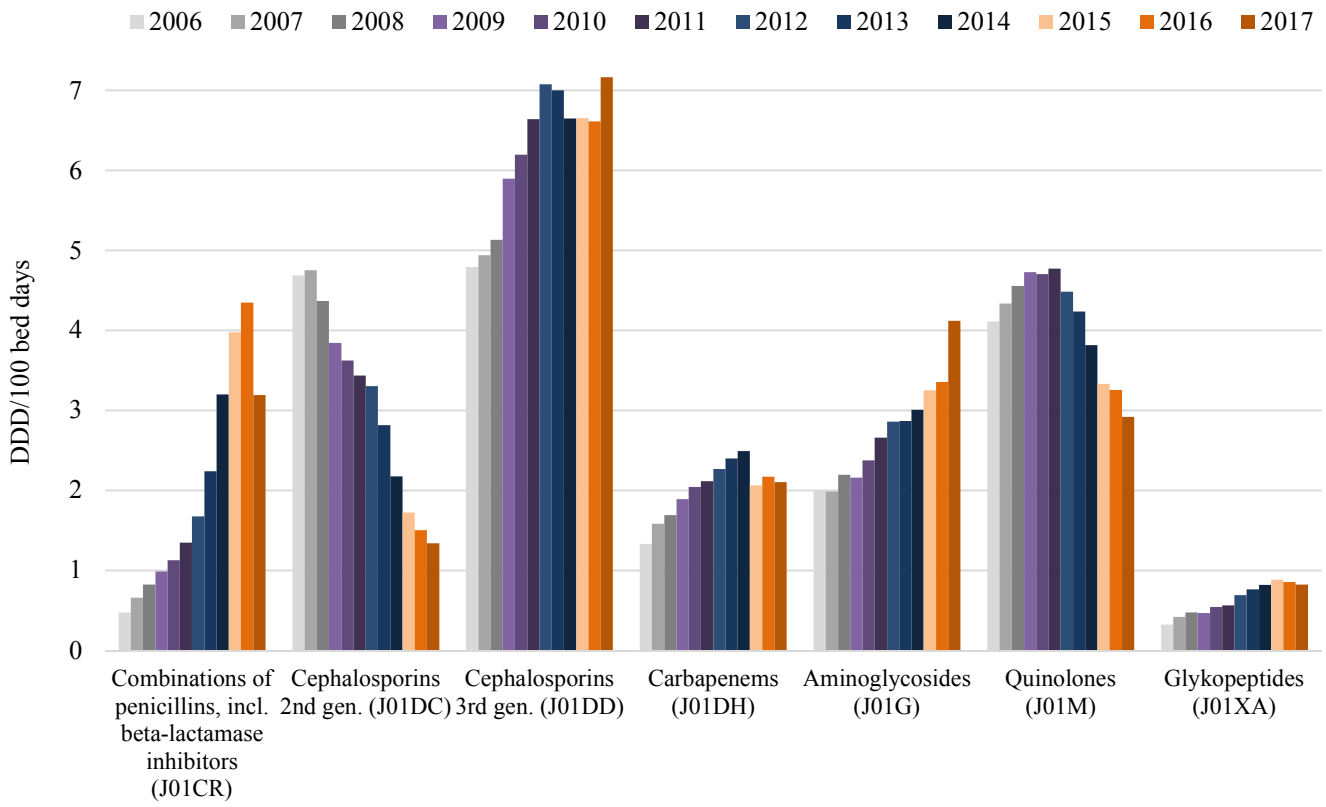

FIGURE 31. Consumption of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2017, measured in DDD/100 bed days.

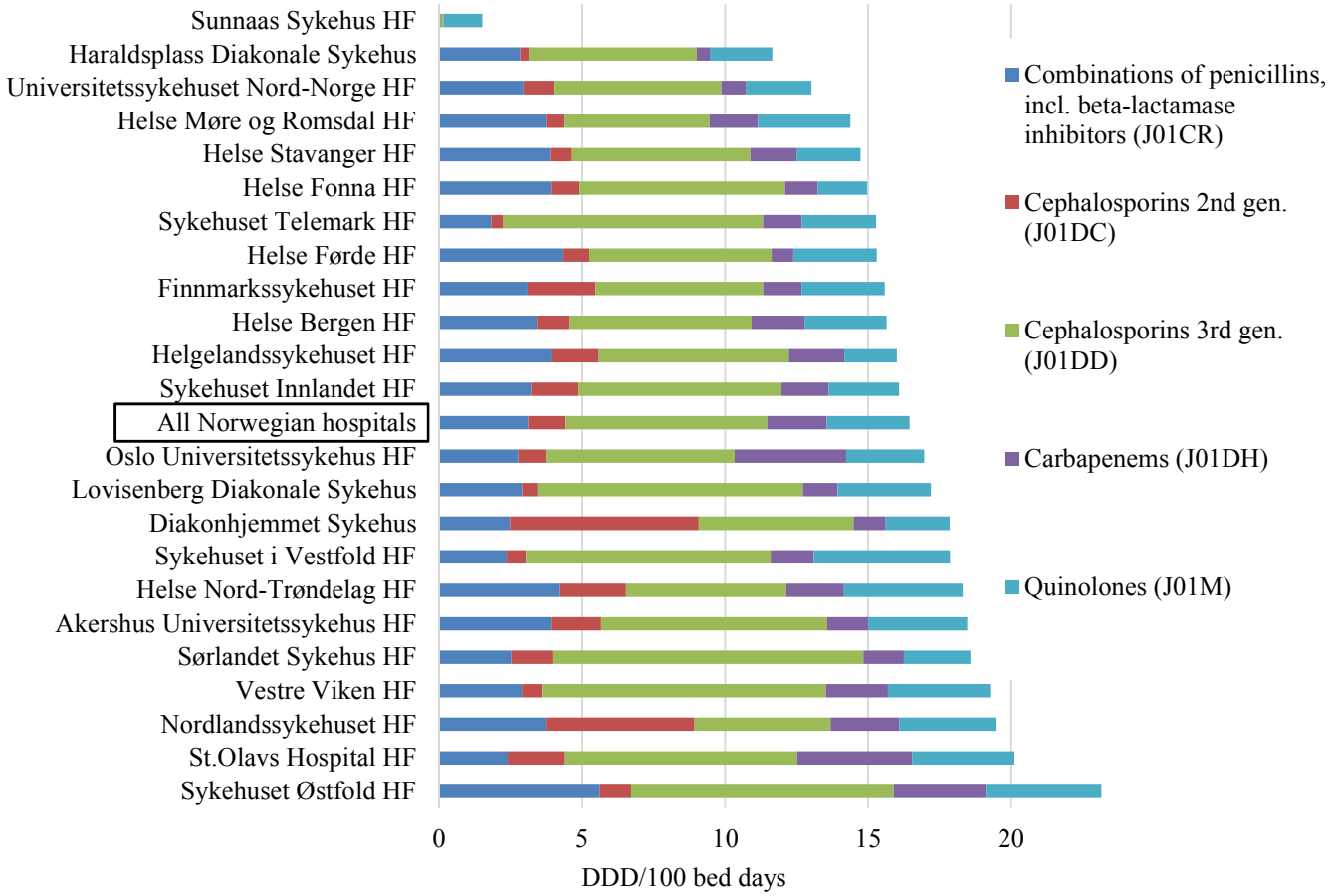

FIGURE 32. Consumption of selected antibacterial agents for systemic use (ATC group J01CR, J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2017, measured in DDD/100 bed days. Sunnaas Sykehus HF is a rehabilitation facility and not an acute care hospital.

FIGURE 33. Proportions (% DDDs) of preferred antibiotics and antibiotics that are considered drivers of antibiotic resistance (J01CR, J01DC, J01DD, J01DH, J01M, J01XA and J01XX08) in Norway, presented per hospital/health trust, in 2017.

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 (2015-2020) was agreed upon, aiming to reduce the total volume of antibiotics, 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 a reduction of DDDs by 30%. In 2017, the reduction since 2012 in J01, excl. methenamine has been 21%. In addition, there were two sector specific goals for ambulatory care; a reduction of average number of prescriptions to 250 precriptions per 1,000 inhabitants per year, and the reduction of antibiotics for respiratory tract infections by 20%. Figure 34 shows the reductions in total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to national targets. Precriptions per 1,000 inhabitants/year (J01, excl. methenamine) is reduced by 23% since 2012 from 444 to 340.

Figure 35 shows proportional change (2012-2017) in usage in ambulatory care in Norwegian municipalities with more than 5,000 inhabitants. In many municipalities the use of antibacterials has decreased since 2012, but in some, usage has increased. Furthermore, since 2012, there has been a reduced prevalence of use in all age groups with the largest reduction seen in small children and the lowest reduction in young adults and the elderly above 75 years. Moreover, prescriptions to men are reduced more than to women with 25% reduction in prescriptions per 1,000 men versus 20% in women. The largest reduction in prescriptions is observed in children 0-14 years old with approximately 32% fewer prescriptions/1,000 inhabitants/year in 2017 compared to 2012.

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 programs mandatory in Norwegian hospitals. Figure 36 shows the annual variation of total hospital use of these selected groups for the years 2006-2017 and according to the national target. Figure 37 demonstrates how the use of these five groups has changed in the different Norwegian hospitals/health trusts in relation to the national target, which is a reduction by 30% as marked by a grey line in the figure. In 2017, three hospitals had reached the target (green bars).

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

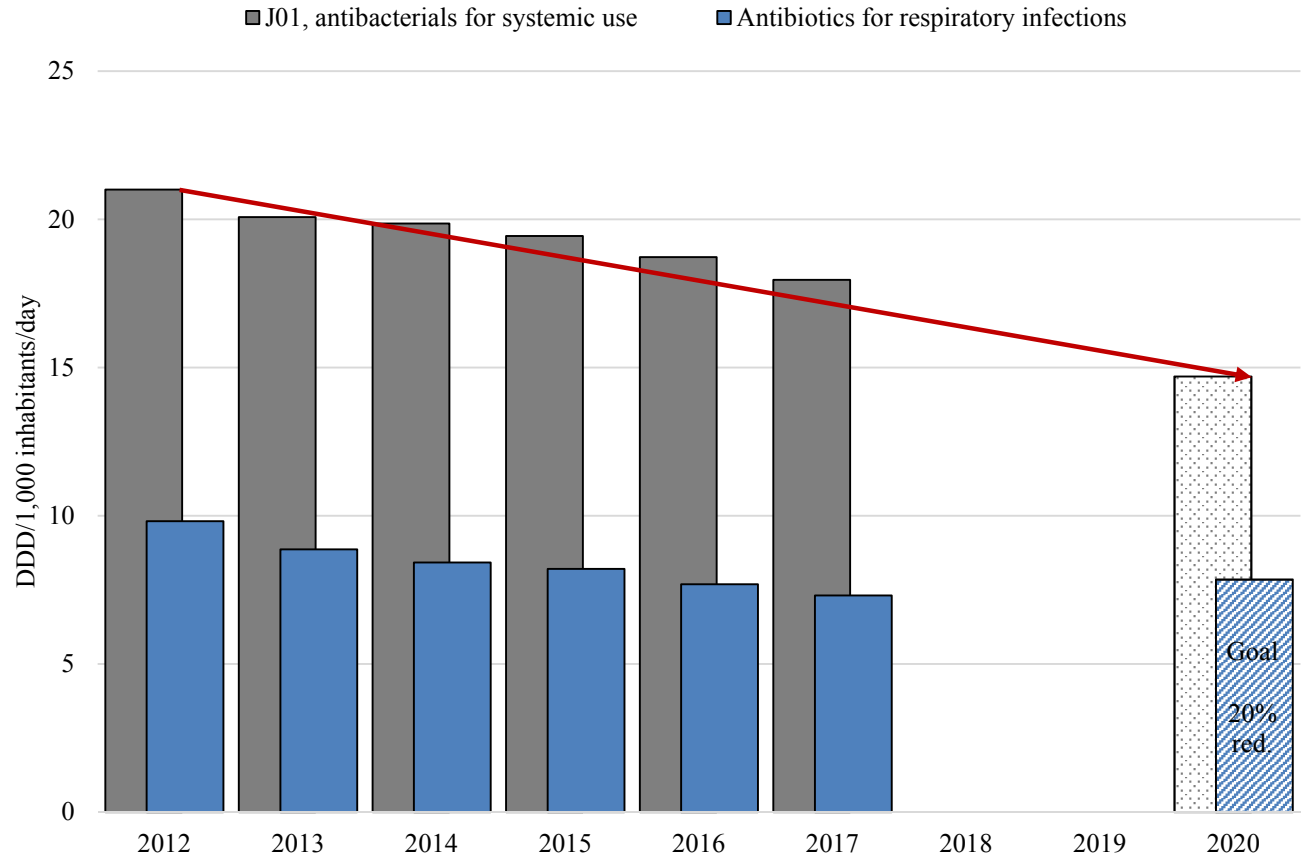

FIGURE 34. Total human sales of antibacterial agents for systemic use (ATC group J01, incl. methenamine) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2017 measured in DDD/1,000 inhabitants/day. According to the National Action Plan, the target for 2020 is a 30% reduction, as measured in DDDs. The grey and blue bars indicate measured use 2012-2017 (grey; J01, blue; antibiotics for respiratory tract infections), the red line and hatched bars indicate targets set in the National Strategy against Antibiotic Resistance (2015-2020).

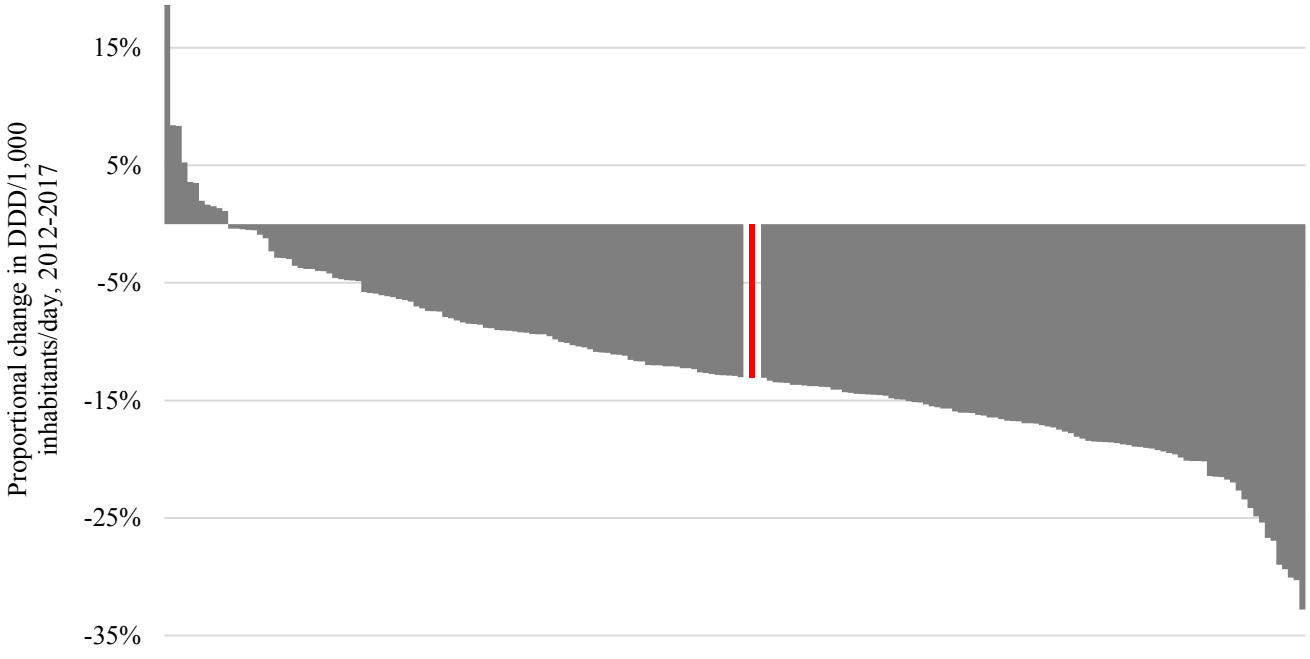

FIGURE 35. Proportional change (%), in DDD/1,000 inhabitants/day, of use of antibacterial agents for systemic use (ATC group J01) in outpatients in the 193 largest municipalities (more than 5,000 inhabitants) in Norway in 2017. Data from the Norwegian Prescription Database (NorPD) (i.e. excl. health institutions). The red line indicates the national average in 2017 of 13% reduction since 2012.

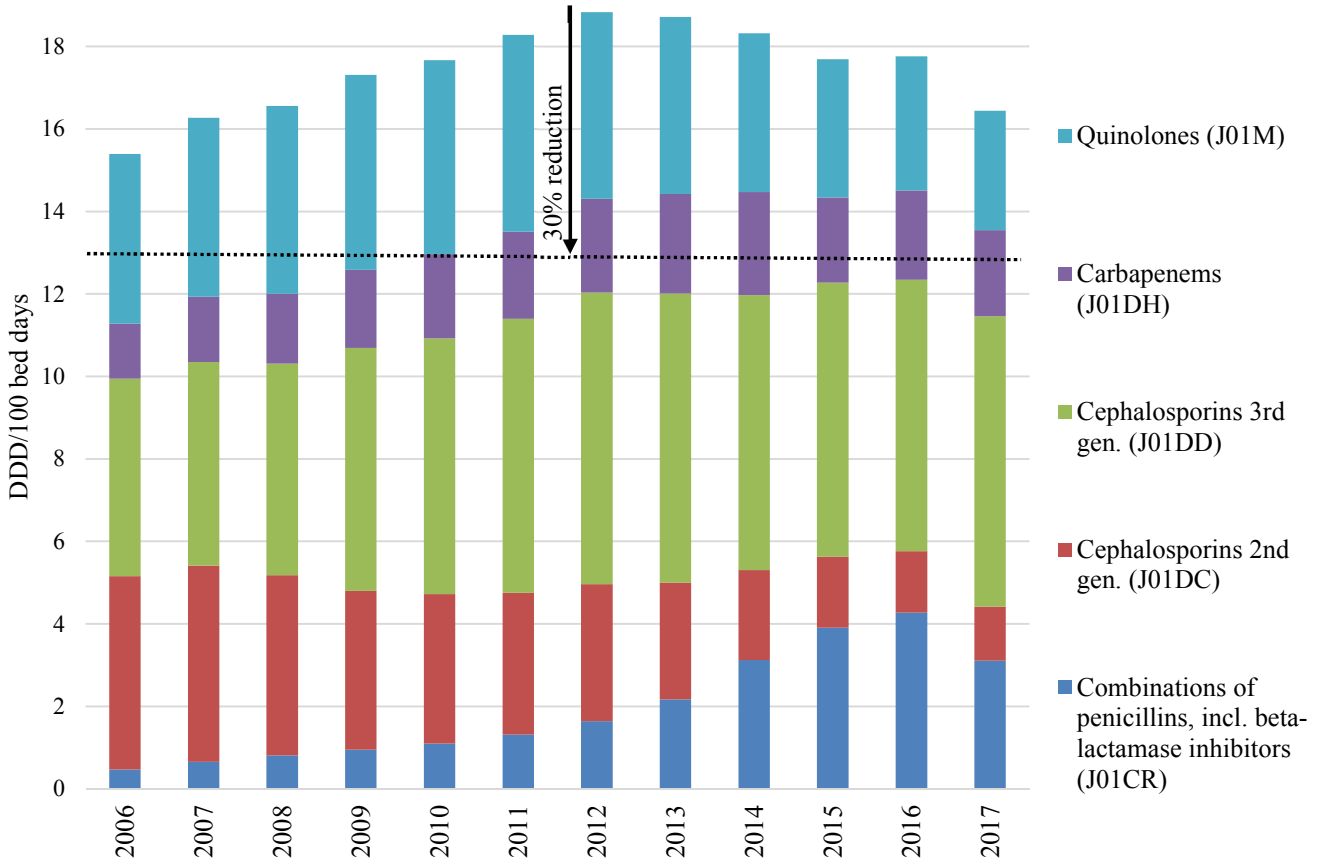

FIGURE 36. Consumption of selected antibacterial agents for systemic use (ATC J01CR05, ATC group J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2017, measured in DDD/100 bed days.

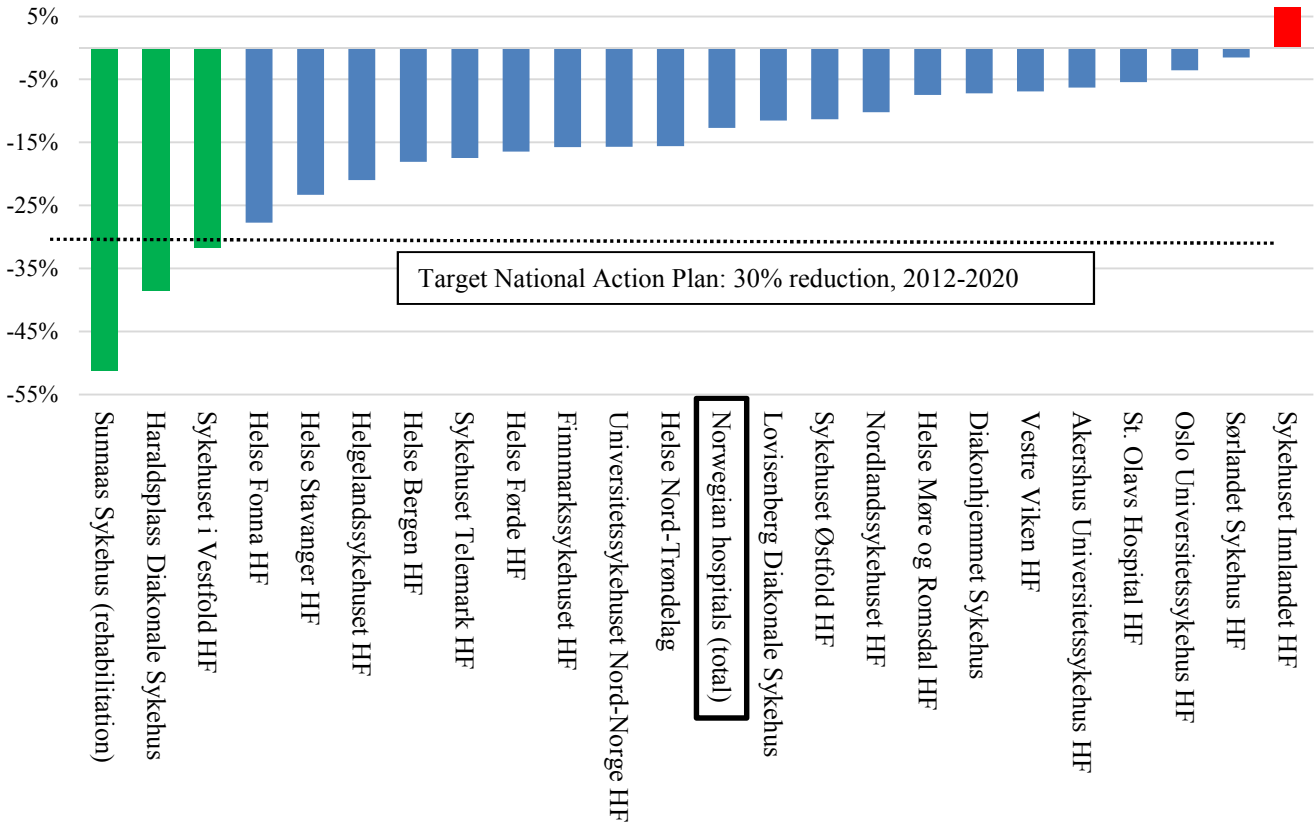

FIGURE 37. Change in consumption of selected antibacterial agents for systemic use (ATC group J01CR, J01DC, J01DD, J01DH and J01M) in Norway 2012-2017. The data are presented per hospital/health trust and measured in DDD/100 bed days.

Antimycotic usage in Norway

The use of antimycotics for systemic use has been increasing in Norway, more so in ambulatory care than in hospitals (Figure 38). In 2017, hospital use of antimycotics represented 20% of total antimycotic use measured in DDDs. Fluconazole is the most commonly prescribed agent in both settings. In July 2013, a warning regarding the use of oral ketoconazole was issued due to increased risk of liver damage. This resulted in decreased use of ketoconazole in ambulatory care (red section of bars in Figure 38). In ambulatory care, mainly oral formulations are utilized. Of total DDDs in ambulatory care, 2% of the DDDs were for parenteral use and in hospitals, 58 % was parenteral use.

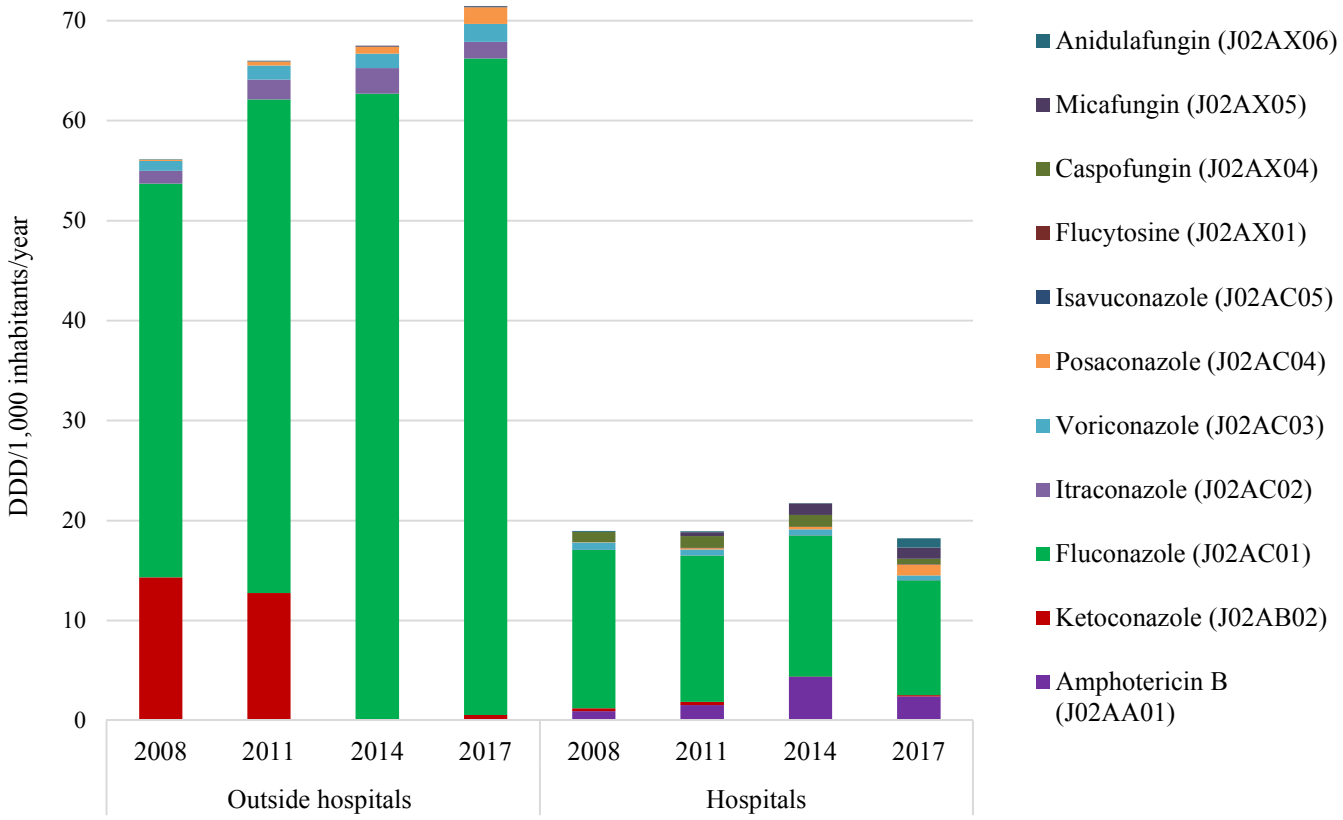

FIGURE 38. Consumption of antimycotics for systemic use (ATC group J02) in Norway for ambulatory care and hospitals 2008, 2011, 2014 and 2017, measured in DDD/1,000 inhabitants/year.

OCCURRENCE OF ANTIMICROBIAL RESISTANCE

INDICATOR BACTERIA FROM ANIMALS

Madelaine Norström, Jannice Schau Slettemeås, Cecilie Marie Mejdell and Anne Margrete Urdahl

The prevalence of acquired antimicrobial resistance among certain bacteria of the normal enteric microflora 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 transferable 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 microflora 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 3rd generation cephalosporins, quinolones and carbapenems, has received special attention over the last years. These are defined by the WHO as critically important for treatment of human infections, and 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 interact with the human bacterial population and thus have an impact on resistance development in these.

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, antimicrobial testing of bacteria from other sources than those included in this decision, or investigation of presence of specific antimicrobial resistant bacteria by selective methods, are included. The use of selective methods are especially relevant for low prevalent sources, as it enables early detection of important resistance mechanisms; thereby enabling these to be monitored.

In NORM-VET, *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria. Selective methods for detection of *E. coli* resistant to 3rd generation cephalosporins were included in NORM-VET from 2011, and for quinolone resistant *E. coli* from 2013. From 2015 a selective method for detection of carbapenemase-producing *Enterobacteriaceae*, and from 2016 a selective method for colistin resistant *E. coli* was implemented as well.

In 2017, animal samples included caecal samples from cattle and swine, as well as faecal swabs from horses. In addition, boot swabs were used for sampling poultry breeder flocks. Food samples included beef and pork, as well as leafy greens and leafy herbs. No feed samples were included in 2017. In addition, the results from the surveillance programme for methicillin resistant *Staphylococcus aureus* (MRSA) in swine are described (separate presentation), as well as MRSA screening of nasal swabs from horses, and boot swabs and cloths moistened with sterile saline water from poultry breeder flocks.

The substances included in the antimicrobial test panels might not always be those used in veterinary medicine, but are included because of their importance for human health. 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 2017. Sampling, laboratory methods and data processing are described in Appendix 3.

PRODUCTION ANIMALS

Escherichia coli from cattle and swine

Caecal samples from a total of 307 cattle < one year and 306 swine were examined. *E. coli* isolates were obtained from 296 (96.4%) of the cattle and 304 (99.3%) of the swine samples, respectively. One isolate per positive sample was susceptibility tested. The results are presented in Table 9 and Figures 39-41, and in the text.

TABLE 9. Antimicrobial resistance in *Escherichia coli* isolates from caecal samples of cattle < one year (n=296) and swine (n=304) in 2017.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample	[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	Cattle	3.4	[1.6-6.1]								95.3	1.4				1.4	2.0	
	Swine	6.6	[4.1-10.0]								92.1	1.3		0.7	0.3	3.3	2.3	
Tigecycline	Cattle	1.4	[0.4-3.4]					92.2	6.4	1.4								
	Swine	1.0	[0.2-2.9]					96.7	2.3	1.0								
Chloramphenicol	Cattle	0.7	[0.1-2.4]										98.3	1.0				0.7
	Swine	0.3	[0.0-1.8]										99.0	0.7	0.3			
Ampicillin	Cattle	1.7	[0.6-3.9]							0.3	31.1	61.8	5.1			0.3	1.4	
	Swine	6.9	[4.3-10.4]							5.9	36.8	49.3	1.0			0.3	6.6	
Cefotaxime	Cattle	0.7	[0.0-2.4]					99.3	0.3		0.3							
	Swine	0	[0.0-1.2]					100										
Ceftazidime	Cattle	0.7	[0.0-2.4]						99.3	0.3			0.3					
	Swine	0	[0.0-1.2]						100									
Meropenem	Cattle	0	[0.0-1.2]		100													
	Swine	0	[0.0-1.2]		100													
Sulfamethoxazole	Cattle	4.4	[2.4-7.4]										94.6	1.0				4.4
	Swine	8.9	[5.9-12.7]										89.5	1.6				8.9
Trimethoprim	Cattle	0	[0.0-1.2]					93.6	6.4									
	Swine	5.6	[3.3-8.8]					89.1	4.9	0.3						5.6		
Azithromycin	Cattle	ND	ND								8.1	60.5	30.4	1.0				
	Swine	ND	ND								11.5	59.2	28.3	1.0				
Gentamicin	Cattle	0.3	[0.0-1.9]						76.7	21.3	1.7	0.3						
	Swine	0.3	[0.0-1.8]						79.3	18.8	1.6				0.3			
Ciprofloxacin	Cattle	0	[0.0-1.2]	80.4	19.3	0.3												
	Swine	0	[0.0-1.2]	89.1	10.5	0.3												
Nalidixic acid	Cattle	0	[0.0-1.2]									99.7	0.3					
	Swine	0	[0.0-1.2]									100						
Colistin	Cattle	0	[0.0-1.2]							99.7	0.3							
	Swine	0	[0.0-1.2]							100								

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-off 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.

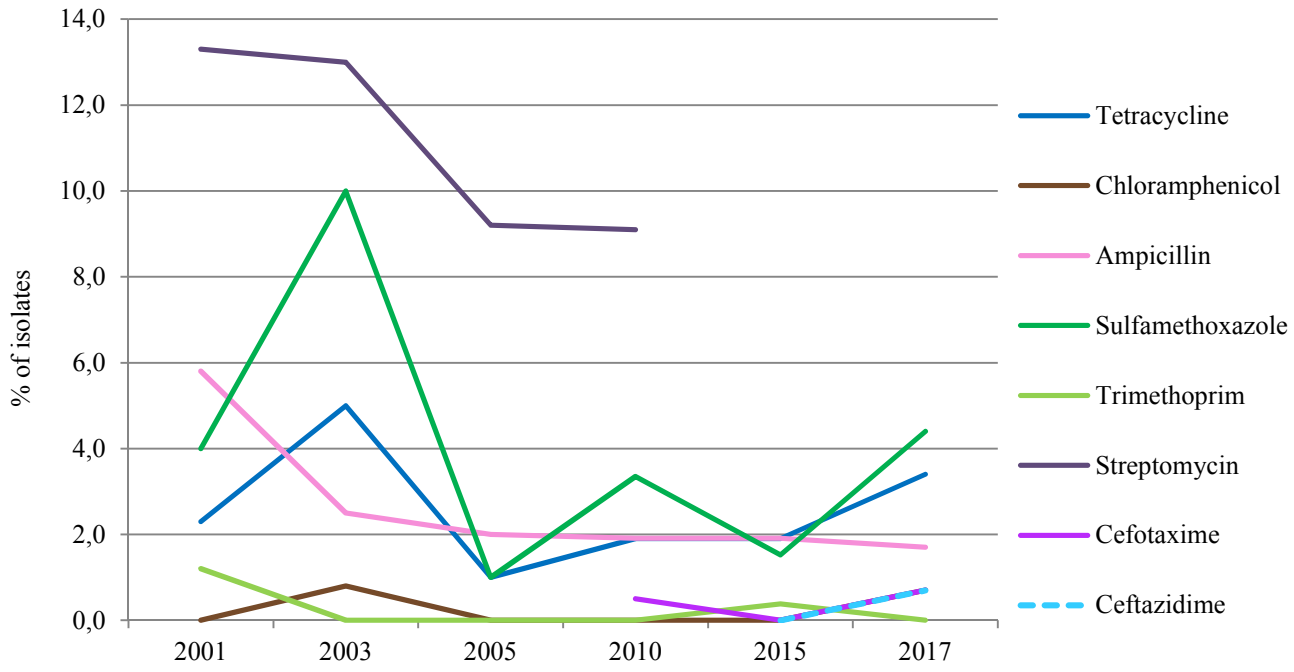

FIGURE 39. Prevalence of resistance to various antimicrobial agents in *Escherichia coli* from bovine faecal samples collected in 2001-2017. The breakpoints used in NORM-VET 2017 were applied. Oxytetracycline was used instead of tetracycline before 2005. Note irregular time intervals on the x-axis.

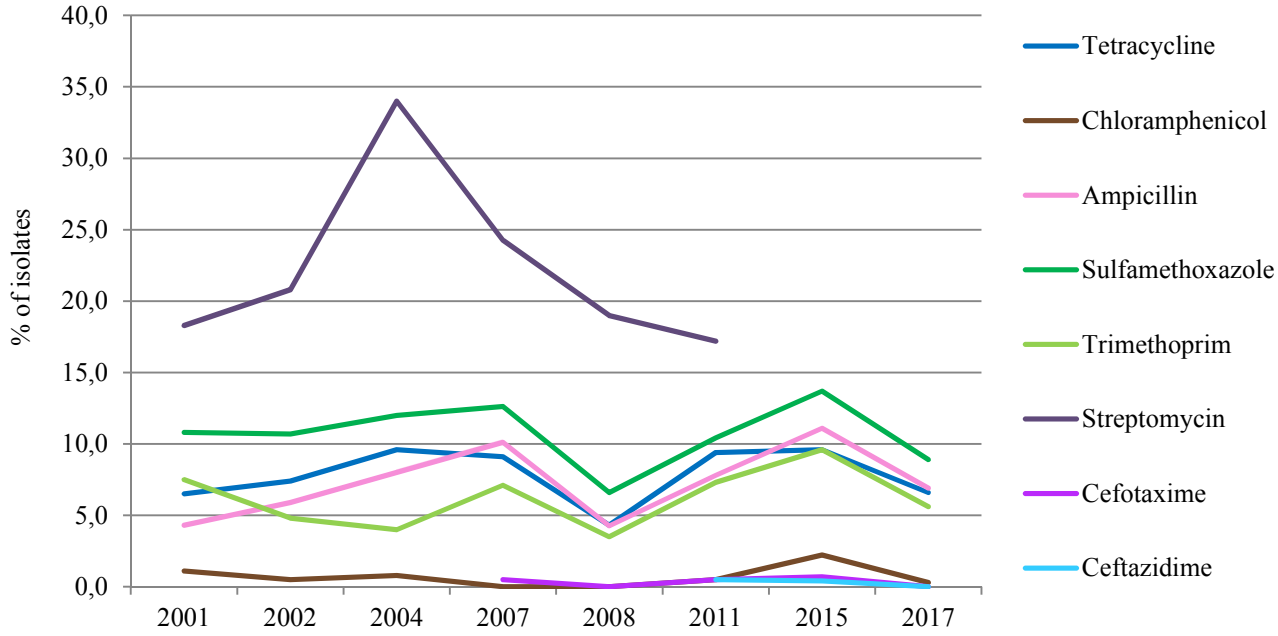

FIGURE 40. Prevalence of resistance to various antimicrobials in *Escherichia coli* from swine faecal samples 2001-2017. The breakpoints used in NORM-VET 2017 were applied. Oxytetracycline was used instead of tetracycline before 2005. Note irregular time intervals on the x-axis.

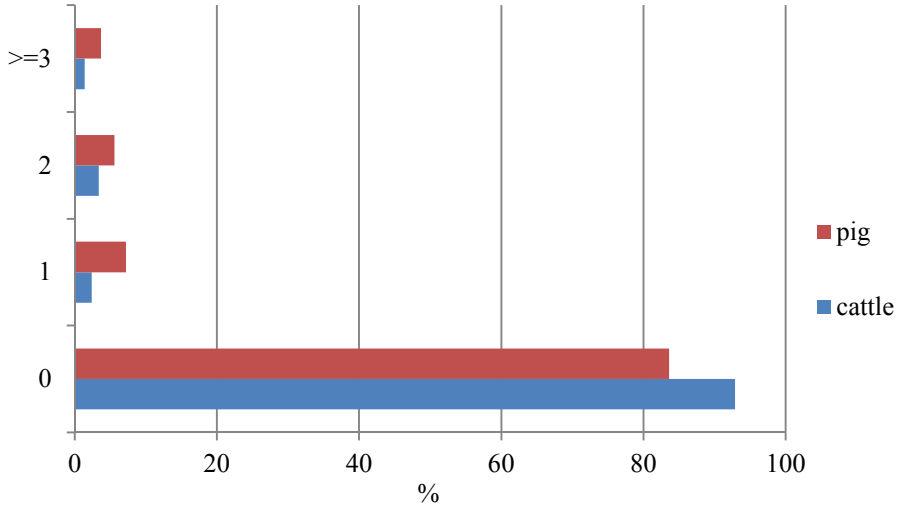

FIGURE 41. Antimicrobial resistance profile for *Escherichia coli* from caecal samples from swine and cattle in 2017. Proportions of isolates susceptible to all (0) or resistant to one (1), two (2), and three or more (≥ 3) antimicrobial agents are illustrated.

RESULTS AND COMMENTS

CATTLE

A total of 92.9% of the isolates were susceptible to all antimicrobial agents included in the test panel. The data indicate a low occurrence of resistance among *E. coli* from cattle caecal samples according to the EFSA classification described in Appendix 6. Resistance to one antimicrobial agent occurred in 2.4% of the isolates, while resistance to two and three antimicrobial agents occurred in 3.4% and 1.4% of the isolates, respectively. Resistance to sulfamethoxazole and tetracycline were the most frequently identified resistance determinants, followed by resistance to ampicillin.

The low detected occurrence is in concordance with the 2015 results, though 95.4% of the isolates back then were found fully susceptible. The resistance towards ampicillin, sulfamethoxazole and tetracycline was higher in 2017 than in 2015, when 1.9% 1.5% and 1.9% of the isolates were resistant towards ampicillin, sulfamethoxazole and tetracycline, respectively. However, the increases were not statistically significant, and further monitoring is needed to see whether any of these are true increases.

Two of the isolates displayed resistance to the 3rd generation cephalosporins cefotaxime and ceftazidime (0.7% [95% CI: 0.0 – 1.2%]). Both these isolates had an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene causing an upregulation. To investigate the reservoirs of resistance to 3rd generation cephalosporins further, selective methods were applied on the same sample material (see next page).

None of the isolates displayed any resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid), indicating a prevalence of these below 1.2%. This is in concordance with results from previous years.

In a European perspective, the occurrence of resistance among *E. coli* from cattle < one year in Norway is among the lowest, and in concordance with the results from Sweden (EFSA and ECDC Summary Report 2015). This situation is due to the limited use of antibiotics in the Norwegian cattle production.

SWINE

A total of 83.6% of the *E. coli* isolates from swine caecal samples were susceptible to all antimicrobial agents tested. Altogether, 7.2% of the isolates were resistant to one antimicrobial agent, 5.6% to two, 3.0% to three, and 0.7% to four or more antimicrobial agents. In total, 16.4% of the isolates were resistant to at least one of the tested antimicrobial agents, indicating moderate occurrence of resistance among swine caecal *E. coli* according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole was the most frequently identified resistance phenotype, followed by resistance to ampicillin, tetracycline and trimethoprim.

Compared to 2015, the proportion of isolates being fully susceptible has increased from 78.9% to 83.6%. However, this is not a statistically significant result, and further monitoring is needed to follow the situation. Comparisons to data from years before 2015 have to take into consideration changes made in the panel of antimicrobial agents tested. Resistance to streptomycin, which is no longer part of the panel, has traditionally been most frequently identified in isolates from swine with 17.2% resistant isolates in 2011 (NORM/NORM-VET 2011). After the panel changes, the most frequently identified antimicrobial agent has been sulfamethoxazole, previously the second most frequently identified (Figure 40).

None of the isolates displayed any resistance to the 3rd generation cephalosprins, nor to quinolones (i.e. ciprofloxacin and/or nalidixic acid), indicating a prevalence of these below 1.2%. This is in concordance with results from previous years. To investigate the occurrence of resistance to 3rd generation cephalosporins further, selective methods were applied on the same sample material (see next page).

In a European perspective, the occurrence of resistance among *E. coli* from swine in Norway is among the lowest (EFSA and ECDC Summary Report 2015). The occurrence varies markedly between countries reporting to EFSA, ranging from none susceptible isolates and up to nearly 80% fully susceptible, with the levels of full susceptibility decreasing in a north to south gradient. This favourable Norwegian situation is due to the rather limited use of antibiotics in the Norwegian swine production.

Cephalosporin resistant *Escherichia coli* from cattle and swine

In 2017, selective screening for *E. coli* resistant to 3rd generation cephalosporins was performed on samples from cattle < one year and swine. A total of 303 cattle caecal and 306 swine caecal samples were screened. Results are presented in the text and in Figure 42, page 57.

RESULTS AND COMMENTS

E. coli resistant to 3rd generation cephalosporins, i.e. cefotaxime and/or ceftazidime, were found in 16 of the cattle (5.3% [95% CI: 3.0-8.4]) and 43 of the swine (14.1% [95% CI: 10.4-18.5]) caecal samples, respectively.

The resistance genes responsible are shown in Figure 42, together with an overview of what other antimicrobial agents the isolates showed decreased susceptibility to. None of the isolates showed decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenemase production. All the 16 isolates from cattle caecal samples displayed an AmpC beta-lactamase phenotype. Of these, one was genotyped as $bla_{\text{CMY-2}}$ and in 14 isolates the resistance was due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene causing an upregulation. In one of the isolates, the genotype could not be resolved and further characterisation by whole genome sequencing will be conducted. Of the 43 isolates from swine caecal samples, 41 displayed an AmpC beta-lactamase phenotype. One of these was genotyped as $bla_{\text{CMY-2,}}$ while the remaining 40 harboured mutations in the promoter/attenuator region of the chromosomally located *ampC* gene causing an upregulation. The last two isolates displayed an ESBL phenotype and were genotyped as $bla_{\text{CTX-M-15}}$.

Compared to the results from 2015, there has been an increase in occurrence of *E. coli* resistant to 3rd generation cephalosporins in cattle from 0.4% in 2015 to 5.3% in 2017. The majority of the isolates causing this increase is due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene. The reason behind this increase is unknown. However, such an increase in *E. coli* resistant to 3rd generation cephalosporins due to chromosomal mutations has previously also been seen for swine (NORM-VET 2015). Further monitoring is necessary to see whether this is a limited peak or a continuing trend. For swine, the 2017 results are in concordance with the results from 2015, with the majority of isolates resistant being due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene.

In a European perspective, the occurrence of *E. coli* resistant to 3rd generation cephalosporins in cattle < one year and swine in Norway is among the lowest, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary Report 2015). This low prevalence reflects that use of this antimicrobial subclass for food-producing animal species is < 0.01 kg. Moreover, there is negligible numbers of import of live cattle and swine to Norway, which is also a preventive measure for importing *E. coli* resistant to 3rd generation cephalosporins from areas/countries with higher prevalence.

A scientific opinion published by EFSA in 2011 concluded that there is indirect evidence of transmission between food-producing animals/foods to humans (EFSA Journal 2011;9(8):2322). The situation regarding *E. coli* resistant to 3rd generation cephalosporins in Norwegian cattle and swine is rather similar to the situation in Sweden (SVARM 2015). A Swedish report from 2014 (Egervärn *et al.* 2014), concludes that food on the Swedish market is a limited contributor to the prevalence of cephalosporin resistant *E. coli* within the human healthcare sector for the time being. However, a continued awareness of animal bacterial reservoirs resistant to 3rd generation cephalosporins is of importance to be able to implement control measures if needed.

Carbapenemase-producing *Enterobacteriaceae* from cattle and swine

Selective screening for carbapenemase-producing *Enterobacteriaceae* was performed on a total of 303 cattle and 306 swine caecal samples. No carbapenemase-producing *Enterobacteriaceae* 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.

Antimicrobial resistance in bacteria from poultry breeders

Material and methods

In 2017, the poultry breeder flocks in Norway were planned to be sampled by the Norwegian Food Safety Authorities. The flocks were to be sampled twice a year about six months apart. From each flock and per sampling, one pair of boot swabs and one sterile cloth moistened with sterile saline were used for sampling. The cloth was used on about 15 control points (about 10x10 cm per location) representing furnishings, feeders, water nipples, window sills, door handles, tools, boots, ventilation system etc.

The samples were submitted to the Norwegian Veterinary Institute (NVI) laboratory in Sandnes and analysed for methicillin resistant *Staphylococcus aureus* (MRSA) by a modified method described by the EU reference laboratory on antimicrobial resistance (EURL-AR, DTU Food, National Food Institute, Copenhagen, Denmark). For pre-enrichment, samples were covered in 200-400 mL Mueller Hinton broth with 6.5% NaCl and incubated at 37±1°C for 18-24 h. From the overnight broth, 10 µL were streaked on Brilliance™ MRSA2 Agar (Oxoid) and incubated at 37±1°C for 18-24 h.

For analysis of faecal bacteria, a piece of one of the boot swabs was cut off and sent to the NVI laboratory in Oslo. The analyses for indicator *E. coli*, and the selective methods for detection of *E. coli* resistant to 3rd generation cephalosporins, for quinolone resistant *E. coli* (QREC), for carbapenemase-producing *Enterobacteriaceae* (CPE), and for colistin resistant *E. coli* were performed as follows; The piece of the boot swab was pre-enriched in Buffered Peptone Water (BPW-ISO) and incubated at 37±1°C for 20±2h according to the protocol from the EURL-AR (https://www.eurl-ar.eu/protocols.aspx). From the overnight broth, 10-20 µL were plated onto MacConkey agar (indicator *E. coli*), MacConkey agar (Difco) containing 1 mg/L cefotaxime and MacConkey agar (Difco) containing 2 mg/L ceftazidime (cephalosporin resistant *E. coli*), MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin (QREC), chromID™ CARBA and chromID™ OXA-48 agar (bioMérieux, Marcy l'Etoile, France) (CPE), and SuperPolymyxin agar (Oxoid) (colistin resistant *E. coli*). All agar plates were incubated at 41.5±0.5°C for 20±2h, except the chromID™ agars which were incubated at 37±1°C for 24-48 h. Presumptive positive colonies were selected, subcultured on blood agar and respective selective agar, and species confirmed using MALDI-TOF MS (Bruker Daltonics GmbH, Bremen, Germany).

Further susceptibility testing was performed using a broth microdilution method at NVI, Oslo. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the tested bacteria. Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 13.05.2018) were used, except for azithromycin for *E. coli* for which cut-off values are not defined and for tigecycline where cut-off values defined by EFSA were used. See Appendix 6 for definitions of cut-off values.

For the presumptive cephalosporin resistant *E. coli* displaying an AmpC phenotype, real-time PCR was performed for the identification of the plasmid-mediated AmpC gene bla_{CMY-2} (Schmidt et al. 2015).

Results and discussion

In total, at least 65 poultry breeder production sites (missing information from two sample submissions) were sampled between one (n=31), two (n=31), three (n=2), four (n=1) and six (n=1) times. Altogether, 111 sample submissions were recieved, 107 of these were from broiler production breeder flocks and four were from turkey breeder production sites. The sampling covers > 80% of the total number of poultry breeder production sites in Norway. In the following, the results are presented for the 111 received sample submissions, without adjusting for clustering at production site level.

MRSA was not detected in any of the 111 received samples, thereby indicating that the breeder production of broilers and turkey is free from MRSA. This was the first time samples from poultry flocks in Norway were investigated for the presence of MRSA, and further monitoring is recommended to follow the situation in the years to come.

TABLE 10. Antimicrobial resistance in *Escherichia coli* (n=100) isolates from > 80% of broiler and turkey breeder production sites in Norway in 2017.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	5.0	[1.6 - 11.3]								94.0	1.0				3.0	2.0		
Tigecycline	0	[0 - 3.6]					97.0	3.0										
Chloramphenicol	0	[0 - 3.6]										97.0	3.0					
Ampicillin	10.0	[4.9 - 17.6]							2.0	41.0	45.0	2.0			1.0	9.0		
Cefotaxime	1.0	[0 - 5.4]					99.0					1.0						
Ceftazidime	1.0	[0 - 5.4]						99.0					1.0					
Meropenem	0	[0 - 3.6]		100														
Sulfamethoxazole	8.0	[3.5 - 15.2]										92.0						8.0
Trimethoprim	6.0	[2.2 - 12.6]					91.0	3.0							6.0			
Azithromycin	ND	ND								12.0	51.0	36.0	1.0					
Gentamicin	1.0	[0 - 5.4]						63.0	32.0	4.0				1.0				
Ciprofloxacin	0	[0 - 3.6]	86.0	14.0														
Nalidixic acid	0	[0 - 3.6]									98.0	2.0						
Colistin	0	[0 - 3.6]							100									

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-off 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.

In total, 100 *E. coli* isolates were isolated from the 111 received samples. One of the isolates was from turkey, while the others were from broiler breeders. Of these, 86% were susceptible to all antimicrobial agents tested. In total, 14% of the isolates were resistant to at least one of the tested antmicrobial agents, indicating moderate occurrence of resistance among poultry breeder *E. coli* according to the EFSA classification described in Appendix 6. Altogether, 6% of the isolates were resistant to one antimicrobial agent, 2% to two, and 4% to three antimicrobial agents included in the test panel. Results from the susceptibility testing are presented in Table 10. Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to sulfamethoxazole, trimethoprim and tetracycline. One isolate displayed resistance to the 3rd generation cephalosporins cefotaxime and ceftazidime. The isolate displayed an AmpC beta-lactamase phenotypic profile and further genetic characterisation showed that it encoded the *bla*$_{CMY-2}$ gene. To investigate the reservoirs of resistance to 3rd generation cephalosporins further, selective methods were applied on the same sample material.

In the selective screening, *E. coli* resistant to 3rd generation cephalosporins, i.e. cefotaxime and/or ceftazidime, were found in seven of the 111 samples. The seven positive samples were taken at seven different production sites during the first two months of 2017. The isolates displayed an AmpC beta-lactamase phenotypic profile and further genetic characterisation showed that they all encoded the *bla*$_{CMY-2}$ gene. This is in concordance with what can be found further down in the broiler production line in Norway (NORM-VET 2016).

No carbapenemase-producing *Enterobacteriaceae* or any colistin resistant *E. coli* were detected, and this is in concordance with previous results from poultry in Norway (NORM-VET 2016). This indicates that the breeder production of broilers and turkey is free from carbapenemase-producing *Enterobacteriaceae* and colistin resistant *E. coli*.

Quinolone resistant *E. coli* were detected in 65 of the samples by the selective method. Results from susceptibility testing of these are presented in Table 11. In total, 52 of the isolates showed decreased sensitivity only to quinolones (ciprofloxacin and/or nalidixic acid). Among the others, additional resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to ampicillin. Twelve of the isolates were resistant to one additional antimicrobial agent (tetracycline (4), ampicillin (4), tigecycline (4)), one isolate was resistant to three (gentamicin, tetracycline, and sulfa-methoxazole) and one isolate to four additional antimicrobial agens (gentamicin, tetracycline, trimetoprim, chloramphenicol). The phenotypic characterisation of the isolates indicates that the majority contains mutations in the chromosomally located *gyrA* gene. Two isolates with low tolerance to ciprofloxacin (MIC 0.25 or 0.5 mg/L) were simultaneously sensitive to nalidixic acid (MIC < 16 mg/L). These isolates are regarded as possible carriers of a plasmid-mediated quinolone resistance genes based on the MIC profile, and whole genome sequencing showed that they both encoded *qnrS1*.

Selective methods for isolation of quinolone resistant *E. coli* have not been performed on samples from poultry breeders previously. However, it was performed on broiler samples in 2014 and mutations in the chromosomally located *gyrA* gene were suggested to be responsible for the observed quinolone resistance in the majority of the samples then as in the current investigations (NORM-VET 2014).

TABLE 11. Antimicrobial resistance in quinolone resistant *Escherichia coli* isolates (n=65) from > 80% of broiler and turkey breeder production sites in Norway in 2017.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*														
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256 ≥ 512
Tetracycline	9.2	[3.5-19.0]								80.0	10.8				3.1	6.2	
Tigecycline	4.6	[1 - 12.9]					87.7	7.7	3.1		1.5						
Chloramphenicol	1.5	[0 - 8.3]										96.9	1.5			1.5	
Ampicillin	7.7	[2.5 - 17]							3.1	26.2	60	3.1				7.7	
Cefotaxime	0	[0 - 5.5]					100										
Ceftazidime	0	[0 - 5.5]						100									
Meropenem	0	[0 - 5.5]		100													
Sulfamethoxazole	4.6	[1 - 12.9]										84.6	10.8				4.6
Trimethoprim	1.5	[0 - 8.3]					90.8	7.7							1.5		
Azithromycin	ND	ND								9.2	56.9	30.8	1.5	1.5			
Gentamicin	3.1	[0.4 - 10.7]						63.1	32.3	1.5			1.5		1.5		
Ciprofloxacin	100	[94.5 - 100]				3.1	49.2	44.6				3.1					
Nalidixic acid	95.4	[87.1-99.0]										3.1			3.1	47.7	44.6
Colistin	0	[0 - 5.5]							100								

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-off 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.

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Surveillance of methicillin resistant *Staphylococcus aureus* (MRSA) in swine in Norway in 2017

There are several varieties of methicillin resistant *Staphylococcus aureus* (MRSA), some of which are associated with animals (especially swine), and are collectively referred to as LA-MRSA (livestock associated MRSA). Within a few years, LA-MRSA has become widespread in swine populations around the world, thereby representing a risk for dissemination to the human population. LA-MRSA in European swine 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 swine as described in (1). The rationale behind this strategy was to prevent the swine population from becoming a domestic reservoir of MRSA with the potential of zoonotic transmission, as MRSA is not a significant cause of disease in swine.

A yearly surveillance programme on MRSA in the swine population was implemented from 2014. The first year, all sow herds with more than ten sows were examined (n=986 herds) and a single positive herd with MRSA CC398, t11 was identified (2). In 2015, a total of 821 herds were included, of which 86 were nucleus or multiplier herds and 735 were finishing herds (3). LA-MRSA was identified in four herds; three finishing herds and one multiplier herd. The isolates from two finishing herds were typed as CC1, t177 and further outbreak tracing showed that the two herds belonged to the same cluster of positive herds. The last two herds were not linked, but both were positive for MRSA CC398, t034 (3). In 2016, a total of 872 herds were investigated, of which 87 were genetic nucleus or multiplier herds, 12 sow pool herds and 773 herds with more than 10 sows (4). MRSA was not detected in any of the genetic nucleus, multiplier or sow pool herds. LA-MRSA CC398, t034 was, however, identified in one herd that had recently converted to a specialised finisher herd. Follow-up testing of contact herds revealed two additional herds positive for the same CC and *spa*-type, and eradication was initiated.

The surveillance programme in 2017 did not detect any herds with LA-MRSA CC398. However, MRSA CC7, CC130 and CC425 were detected in one multiplier herd and in two farrow to finish herds, respectively. MRSA was not detected in any of the genetic nucleus herds, nor in the central units of the sow pool herds. In total, 826 herds were included in the survey, of which 85 were genetic nucleus or multiplier herds. 12 herds were the central units of sow pool herds, and 729 were herds with more than 10 sows.

Further details of the surveillance can be found in the report “The surveillance programme for methicillin resistant *Staphylococcus aureus* in swine in Norway 2017” (5).

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SPORTS AND FAMILY ANIMALS

Escherichia coli from horses

Faecal swab samples from a total of 246 horses were examined, and *E. coli* isolates were obtained from 227 (92.3%) of the horses. One isolate per positive sample was susceptibility tested. The results are presented in the text and in Table 12.

TABLE 12. Antimicrobial resistance in *Escherichia coli* isolates (n=227) from faceal samples from horses in 2017.

	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	2.2	[0.7-5.1]								96.9	0.9				0.4	1.8		
Tigecycline	0	[0.0-1.6]					97.4	2.6										
Chloramphenicol	0	[0.0-1.6]										100						
Ampicillin	1.3	[0.3-3.8]							1.3	22	61.7	13.7				1.3		
Cefotaxime	0	[0.0-1.6]					100											
Ceftazidime	0	[0.0-1.6]						100										
Meropenem	0	[0.0-1.6]		100														
Sulfamethoxazole	12.8	[8.7-17.8]										85.9	1.3					12.8
Trimethoprim	12.8	[8.7-17.8]					84.1	3.1							12.8			
Azithromycin	ND	ND								19.8	60.8	19.4						
Gentamicin	0.4	[0.0-2.4]						62.6	33	4				0.4				
Ciprofloxacin	0	[0.0-1.6]	84.6	15.4														
Nalidixic acid	0	[0.0-1.6]									100							
Colistin	0	[0.0-1.6]							100									

*Bold vertical lines denote epidemiological cut-off values for resistance. ND = cut-off 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.

RESULTS AND COMMENTS

In total, 85.0% of the isolates were susceptible to all antimicrobial agents included. Altogether, 3.1% of the isolates were resistant to one antimicrobial agent (predominantly ampicillin), 10.6% to two, 0.4% to three, and 0.8% to four or more antimicrobial agents. In total, 15% of the isolates were resistant to at least one of the tested antimicrobial agents, indicating a moderate occurrence of resistance among *E. coli* from faecal samples of horses according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole and trimethoprim were the most frequently identified resistance determinants.

None of the isolates displayed any resistance to the 3rd generation cephalosporins cefotaxime or ceftazidime, nor to quinolones, indicating a prevalence of these below 1.5%. This is in concordance with previous results from 2009 (NORM-VET 2009). Selective methods were also used on the same sample material to investigate the occurrence of these substances with more sensitive methods.

Samples from horses have only been included in NORM-VET once before, in 2009. Since 2009 there has been a change in the panel of antimicrobial agents tested for and streptomycin is no longer part of the test panel. In 2009, 7.6% of the tested isolates displayed reduced sensitivity towards streptomycin. Due to this change in panel, comparison of overall resistance is difficult. However, the data do show an increase in resistance to sulfamethoxazole and trimethoprim from 7.6% and 8.8%, respectively, in 2009 to 12.8% each in 2017. Overall this may indicate an overall increase as well, though further monitoring is needed to explore this and follow the situation in the years to come.

Cephalosporin resistant *Escherichia coli* from horses

Selective screening for *E. coli* resistant to 3rd generation cephalosporins was performed on the samples from horses. A total of 246 samples were screened. *E. coli* resistant to 3rd generation cephalosporins were found in two (0.8% [95% CI: 0.1-2.9]) of the samples.

One isolate from the horse faecal samples displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene causing an upregulation. The last isolate displayed an ESBL phenotype and was genotyped as $bla_{\text{CTX-M}}$ group 1. An overview of the cephalosporin resistant genotypes and the isolates´ antimicrobial resistance patterns are shown in Figure 42, page 57.

Selective methods for isolation of *E. coli* resistant to 3rd generation cephalosporins have not been performed on horse samples previously, and comparison to previous years is therefore not possible.

Quinolone resistant *Escherichia coli* from horses

Selective screening for *E. coli* resistant to quinolones was performed on samples from 246 horses. *E. coli* resistant to fluoroquinolones were found in six (2.4% [95% CI: 0.9-5.2]) of the samples.
The phenotypic characterisation of the six isolates indicates that four contain mutations in the chromosome located in the *gyrA* gene. Two isolates with low tolerance to ciprofloxacin (MIC 0.25 mg/L and 0.5 mg/L) were simulatenously sensitive to nalidixic acid (MIC 8 mg/L). These isolates are regarded as possible carriers of plasmid-mediated quinolone resistance genes based on the MIC profiles. Based on whole genome sequencing they were found to encode *qnrB19* and *qnrS1*, respectively. One isolate had a ciprofloxacin MIC > 8 mg/L and nalidixic acid MIC > 128 mg/L, indicating more than one mutation on the chromosome and/or a possible plasmid-mediated quinolone resistance gene. The same isolate was simultaneously resistant to ampicillin, sulfamethoxazole, trimetoprim, gentamicin and had an azithromycin MIC > 128 mg/L. In total, three of the isolates showed decreased susceptibility only to quinolones (ciprofloxacin and nalidixic acid). The remaining three isolates showed additional resistance to trimethoprim and sulfamethoxazole, and two of the isolates also showed additional resistance to ampicillin and gentamicin.
Selective methods for isolation of quinolone resistant *E. coli* have not been performed on horse samples previously, and comparison to previous years are therefore not possible.

Carbapenemase-producing *Enterobacteriacae* spp. from horses

A total of 246 samples from horses were screened for the presence of carbapenemase-producing *Enterobacteriacae*.

No carbapenemase-producing *Enterobacteriaceae* isolates were detected.

Methicillin resistant *Staphylococcus aureus* (MRSA) from horses

A total of 246 samples from horses were screened for the presence of methicillin resistant *Staphylococcus aureus* (MRSA). MRSA was detected from only one of these horses (0.4% [95% CI: 0.01-2.2%]). This result is in concordance with previous screening results in NORM-VET in 2009, where no MRSA was detected among the 186 sampled horses.

The MRSA isolate belonged to clonal complex CC398 *spa*-type t011. MRSA CC398 *spa*-type t011 is associated with MRSA findings in horses as well as other animals including pigs, and has previously been detected from clinical cases in horses in several countries, including Norway.

Antimicrobial resistance in bacteria from wild roe deer and reindeer – a survey conducted for the Ministry of Climate and Environment

The importance of the environment for understanding the dynamics of antimicrobial resistance (AMR) has been the focus of growing scientific interest in the last decade. Sharing of common habitats and water resources may result in transfer of antimicrobial resistant bacteria between wildlife, food-producing animals and humans. The relative importance of such reservoirs and transfer routes of AMR remain unclear, with little data available.
In 2017, the Norwegian Veterinary Institute (NVI) was commissioned by the Norwegian Environment Agency to investigate the occurrence of AMR in terrestrial wild mammals, using bacteria isolated from wild, free-ranging roe deer and reindeer as an indicator. The two species have assumed different exposure to human activities (and AMR drivers) in Norway.
The survey indicated that there in general is a low occurrence of AMR among *E. coli* of the intestinal microbiota of wild reindeer and roe deer in Norway. *E. coli* was isolated and susceptibility tested from 230 out of 265 (86.8%) wild reindeer, and from 274 out of 301 (91%) roe deer. Among the isolates obtained from wild reindeer and from roe deer, 96.5% and 93.8%, respectively, were fully susceptible to all the tested substances. Resistance to more than one substance tested for was rare. Resistance to streptomycin was the most commonly occurring resistance form and was detected in 1.7% of the *E. coli* isolates from wild reindeer and in 5.1% of the *E. coli* isolates from roe deer. Resistance to streptomycin cannot be easily explained, except for contamination from livestock animals or humans, or it being a natural form of resistance.
The overall occurrence of *E. coli* resistant to 3rd generation cephalosporins was 0.3% in roe deer, and was mediated by $bla_{CTX\text{-}M\text{-}1}$. This is the first finding of an ESBL-producing *E. coli* from a wild cervid in Norway. This isolate originated from a roe deer hunted in an area near one of the largest cites in Norway. While ESBL has recently been reported in red foxes in Norway, its occurrence is surprising given the low selection pressure in Norway and highlights the existence of bacteria resistant to critically important antimicrobials in spite of absence of selection pressure.
Longitudinal and spatial broad studies should be prioritised in order to better understand this problem and elucidate the role of wildlife species in the spread of AMR in a One Health perspective, especially in ecosystems with relatively simple and well-characterised potential inputs of AMR, such as Norway.

Further details of the survey can be found in the report "Antibiotic resistance in terrestrial wild mammal species in Norway – roe deer and wild reindeer as indicators species" (ISSN 1890-3290) available at file:///C:/Users/VI1084/Downloads/2018_6_%20Antibiotic%20resistance%20in%20terrestrial%20wild%20mammal%20species%20in%20Norway.pdf

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INDICATOR BACTERIA FROM FOOD

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MEAT

Cephalosporin resistant *Escherichia coli* from beef and pork

Selective screening for *E. coli* resistant to 3rd generation cephalosporins was performed on 343 beef and 340 pork samples. Results are presented in the text and in Figure 42.

RESULTS AND COMMENTS

E. coli resistant to 3rd generation cephalosporins, i.e. cefotaxime and/or ceftazidime, was not detected in any of the beef samples, indicating a prevalence < 1.1%. From the pork samples, *E. coli* resistant to 3rd generation cephalosporins were found in one of the samples (0.3% [95% CI: 0.0-1.6]). This is in concordance with previous NORM-VET results from 2015 where *E. coli* resistant to 3rd generation cephalosporins were detected in 1.2% of the beef samples and 0.8% of the pork samples.

The pork isolate displayed an AmpC beta-lactamase phenotype and the resistance was due to mutations in the promoter/attenuator region of the chromosomally located *ampC* gene causing an upregulation. The resistance gene responsible is shown in Figure 42, together with an overview of what other antimicrobial agents the isolate showed decreased susceptibility to. The isolates did not show decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenemase production.

In a European perspective the occurrence of *E. coli* resistant to 3rd generation cephalosporins in Norwegian beef and pork are among the lowest reported to EFSA (EFSA and ECDC Summary report 2015). The reported occurrences vary between the countries, where the south-eastern, south central and south-western countries seem to have a higher occurrence of *E. coli* resistant to 3rd generation cephalosporins than the Nordic and the western countries.

A scientific opinion published by EFSA in 2011 concluded that there is indirect evidence for transmission between food-producing animals and food to humans (EFSA Journal 2011;9(8):2322). A Swedish report from 2014 (Egervärn *et al.* 2014), concluded that food on the Swedish market is a limited contributor to the prevalence of cephalosporin resistant *E. coli* within the human healthcare sector for the time being. The situation regarding *E. coli* resistant to 3rd generation cephalosporins in Norway is rather similar to the situation in Sweden. However, a continued awareness of animal/food bacterial reservoirs resistant to 3rd generation cephalo-sporins is of importance in order to be able to implement control measures if needed.

Carbapenemase-producing *Enterobacteriaceae* from beef and pork

A total of 343 beef and 340 pork samples were screened for the presence of carbapenemase-producing *Enterobacteriaceae*. No carbapenemase-producing *Enterobacteriaceae* 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.

VEGETABLES

Escherichia coli from leafy greens and leafy herbs

A total of 188 samples of leafy greens and leafy herbs were screened for the presence of indicator *E. coli*. *E. coli* was detected from 27 of these, and one isolate per sample was susceptibility tested. The results are presented in Table 13 and in the text.

TABLE 13. Antimicrobial resistance in *Escherichia coli* isolates (n=27) from leafy greens and leafy herbs in 2017.

		Distribution (n) of MIC values (mg/L)*															
Substance	Resistance (n)	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	1								24	2					1		
Tigecycline	0					27											
Chloramphenicol	0										26	1					
Ampicillin	3							1	9	14					3		
Cefotaxime	0					27											
Ceftazidime	0						27										
Meropenem	0		27														
Sulfamethoxazole	2										25						2
Trimethoprim	1					25	1							1			
Azithromycin	ND								6	10	11						
Gentamicin	0						24	3									
Ciprofloxacin	1	22	4			1											
Nalidixic acid	1									26						1	
Colistin	0							27									

*Bold vertical lines denote epidemiological cut-off values for resistance. ND=cut-off 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.

RESULTS AND COMMENT

In total, 85.2% of the 27 isolates were susceptible to all antimicrobial agents included. Altogether, 4% of the isolates were resistant to one antimicrobial agent, 7% to two and 4% to four antimicrobial agents. None of the isolates displayed any resistance to the 3rd generation cephalosporins cefotaxime or ceftazidime, nor to quinolones, carbapenems or colistin. Selective methods were also used on the same sample material to investigate the occurrence of these substances with more sensitive methods.

Leafy herbs have not previously been investigated in NORM-VET while leafy greens were investigated in 2015. Comparisons are however, difficult due to the limited number of isolates. Sampling of leafy greens and leafy herbs continues in 2018.

Leafy greens and leafy herbs can become contaminated with antimicrobial resistant bacteria from animal and human sources during primary production and harvesting. As these products typically are consumed raw and without any heat treatment, presence of antimicrobial resistant bacteria may be of concern, especially plasmid-encoded resistance due to its dissemination potential. Further monitoring is recommended to acquire more knowledge and to follow the situation on the presence of antimicrobial resistant bacteria in vegetables in general and especially in those consumed raw such as leafy greens and leafy herbs.

Cephalosporin resistant *Escherichia coli* from leafy greens and leafy herbs

Selective screening for *E. coli* resistant to 3rd generation cephalosporins was performed on a total of 188 samples. *E. coli* resistant to 3rd generation cephalosporins was detected from one (0.5% [95% CI: 0.01-2.9]) of these samples. The isolate displayed an ESBL phenotype and the resistance mechanism encoding the cephalosporin resistance was bla_{SHV-12}, and is shown in Figure 42, together with an overview of what other antimicrobial agents the isolate showed decreased susceptibility to.

The 2015 screening did not detect any *E. coli* resistant to 3rd generation cephalosporins.

Quinolone resistant *Escherichia coli* from leafy greens and leafy herbs

Selective screening for quinolone resistant *E. coli* was performed on a total of 187 samples. Quinolone resistant *E. coli* was detected in three (1.6% [95% CI: 0.3-4.6%]) of the samples. One isolate had a ciprofloxacin MIC of 16 mg/L and nalidixic acid MIC of 256 mg/L, indicating more than one mutation on the chromosome and/or a possible

plasmid-mediated quinolone resistance gene. This will be further explored through whole genome sequencing. The isolate was additionally resistant to cephalosporins and displayed an ESBL phenotype. The resistance mechanism encoding the cephalosporin resistance was bla_{SHV-12}. The isolate was isolated from the same sample as the cephalosporin resistant *E. coli* described above, was identical with regard to resistance pattern and genotype, and is probably the same bacterial clone detected through the two different screening procedures.

The screening in 2015 detected quinolone resistant *E. coli* in two of the investigated 243 samples of leafy greens. However, comparisons should be done with caution due to sample variabilities.

Colistin resistant *Escherichia coli* from leafy greens and leafy herbs

A total of 188 samples were screened for the presence of colistin resistant *E. coli*. None of the samples were positive.

Carbapenemase-producing *Enterobacteriaceae* from leafy greens and leafy herbs

A total of 184 samples were screened for the presence of carbapenemase-producing *Enterobacteriaceae*. None of the samples were positive. This is in concordance with the 2015 results.

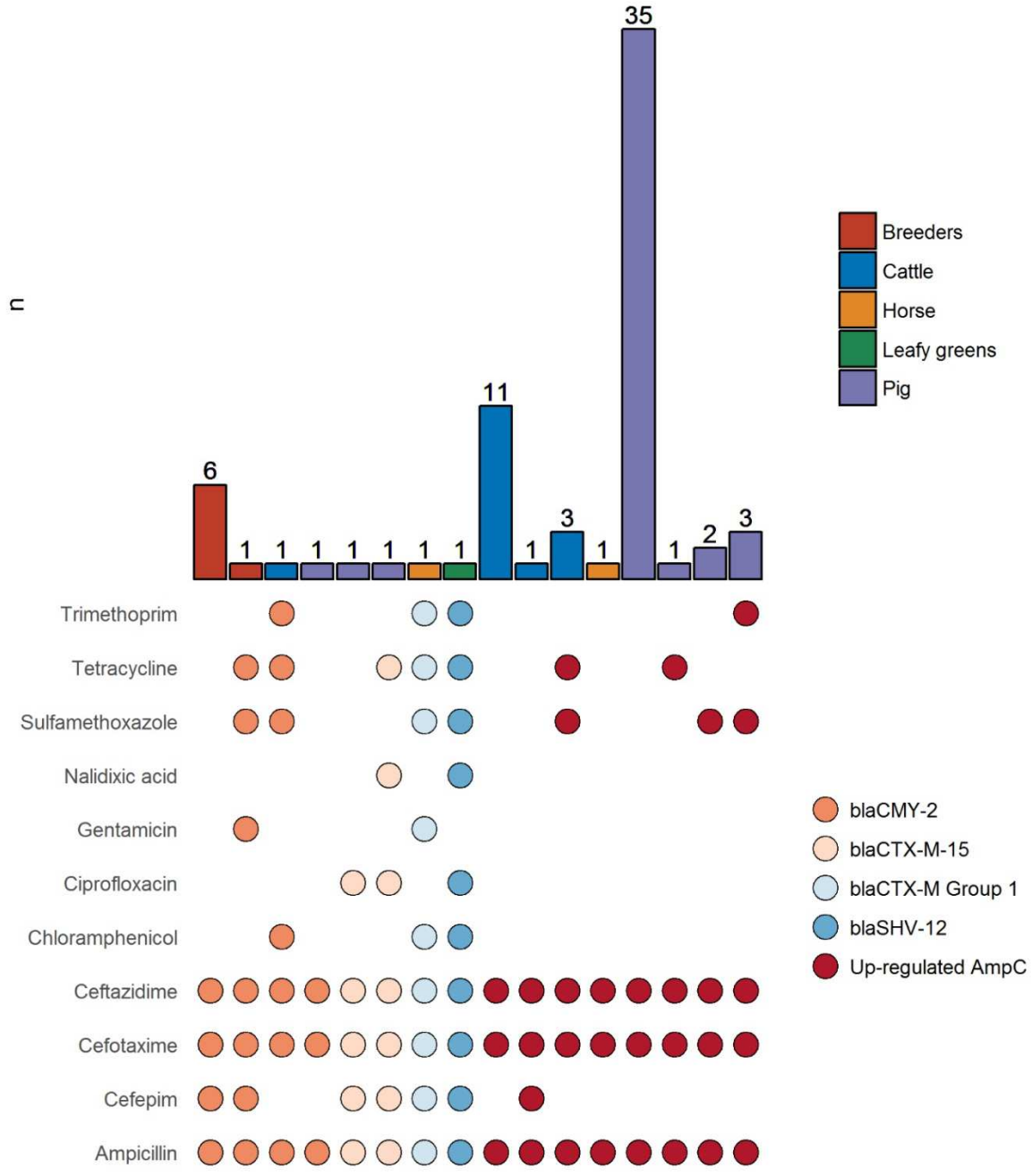

FIGURE 42. Overview of *Escherichia coli* resistant to 3rd generation cephalosporins identified in NORM-VET 2017, their genotype, antimicrobial resistant patterns and source of origin. Histogram shows number of isolates.

ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

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

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.

In Norway, *Salmonella* isolates from control programmes on animals and food products, as well as diagnostic samples from animals are monitored for antimicrobial resistance. In 2017, *Campylobacter coli* from swine was included.

Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates.

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

The NORM-VET results are interpreted according to the determined epidemiological cut-off values (ECOFFs) of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), while NORM results on human isolates of enteropathogenic *Enterobacteriaceae* are interpreted according to the clinical breakpoints set by EUCAST. In the absence of clinical breakpoints, ECOFFs as determined by EUCAST or national zone distribution evaluations are used to determine breakpoints. Multi-drug resistance (MDR) has been defined as non-susceptibility to three or more antimicrobial classes, in line with the 2011 ECDC/CDC joint definition.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food-producing animals in Norway is very favourable as such animal populations are considered virtually free from *Salmonella* spp. To document and maintain this favourable situation, Norway runs an extensive surveillance programme that covers both live animals (cattle, swine and poultry) and meat samples. The *Salmonella* isolates examined in NORM-VET include those that are detected in this programme, as well as those detected by clinical submissions to the Norwegian Veterinary Institute. The data are presented in Table 14 and in the text.

TABLE 14. Antimicrobial resistance in *Salmonella* spp. (n=15) from animals (three wild birds, one poultry, two dogs, two swine, two hedgehogs, four sheep and one cervid); *S.* Typhimurium (n=5), other *Salmonella* spp. (n=9) and one uncharacterised isolate in 2017.

Substance	n (resistance)	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	0								15									
Tigecycline	0					14	1											
Chloramphenicol	0										15							
Ampicillin	0							11	4									
Cefotaxime	0					15												
Ceftazidime	0						15											
Meropenem	0		13	2														
Sulfamethoxazole	0										7	8						
Trimethoprim	0					15												
Azithromycin	ND									9	6							
Gentamicin	0						15											
Ciprofloxacin	0	8	7															
Nalidixic acid	0									15								
Colistin	0							13	2									

*Bold vertical lines denote epidemiological cut-off values for resistance. ND = cut-off not defined by EUCAST. 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 2017, a total of 15 *Salmonella* spp. isolates from animals were susceptibility tested. The 15 isolates included one each from three wild birds, one poultry, two dogs, two swine, four sheep, one cervid and two hedgehogs. Five isolates were of *S.* Typhimurium, while nine isolates were of *S.* Entertitidis (n=2), *S.* Saintpaul (n=1), *S.* Stanley (n=1), *S. enterica* subsp. *diarizonae* (n=5). One isolate was not further characterised (swine). All of the 15 isolates were fully susceptible to the tested antimicrobial agents.

Salmonella from human clinical specimens

In 2017, the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) performed antimicrobial susceptibility testing on a total of 878 unique *Salmonella* isolates from human infections.
As indicated in Table 15, 24.7% were reported as acquired in Norway, 65.9% were acquired abroad, whereas the place of acquisition was unknown for 9.3% of the isolates.

All isolates were tested for resistance to four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), fluoroquinolones (ciprofloxacin and pefloxacin), gentamicin, and trimethoprim-sulfamethoxazole. In addition, 321 of the 878 isolates were tested for nalidixic acid, azithromycin, tetracycline and chloramphenicol.

TABLE 15. Distribution of human isolates of *Salmonella* serovars (n=878) in 2017 according to place of acquisition.

	Place of acquisition		
	Norway	Abroad	Unknown
S. Typhimurium including *S. enterica* serovar 4,[5],12:i- (n=188)	67	105	16
S. Enteritidis (n=271)	52	194	25
S. Typhi (n=11)	1	10	0
S. Paratyphi (n=4)	0	3	1
Other *Salmonella* (n=404)	97	267	40
Total (n=878)	**217 (24.7%)**	**579 (65.9%)**	**82 (9.3%)**

The major serovars were *S.* Typhimurium (n=107) and its monophasic variant (n=81), with 21.4% of all *Salmonella* isolates, and *S.* Enteritidis with 271 isolates (30.9%). The numbers of *S.* Typhi and *S.* Paratyphi isolates remained low. For 2017 their totals numbers were eleven and four, respectively.

The results of the antimicrobial susceptibility testing for 2017 *Salmonella* isolates are presented in Tables 16-19, Figures 43-50 and in the text.

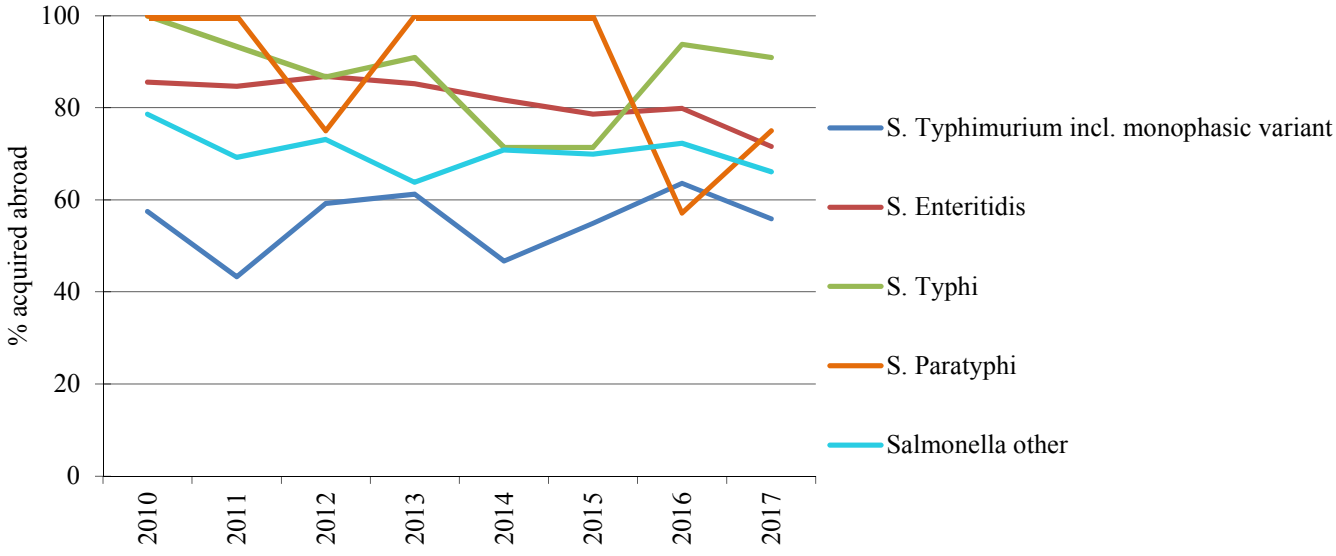

FIGURE 43. Proportions of unique *Salmonella* isolates acquired abroad stratified by serovars from 2010- 2017.

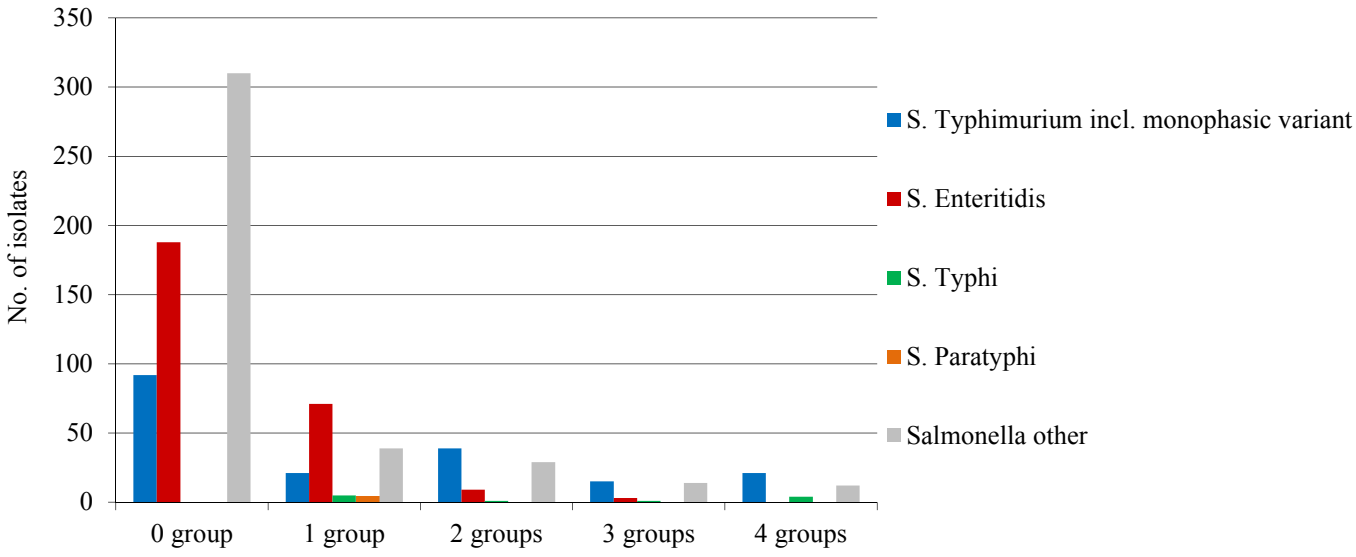

FIGURE 44. The number of antibiotic groups that *Salmonella* isolates in 2017 (n=878) were resistant to stratified by serovars. The four antibiotic classes tested were; beta-lactams, aminoglycosides, fluoroquinolones and trimethoprim-sulfamethoxazole.

ANITMICROBIAL RESISTANCE IN BLOOD CULTURE ISOLATES OF SALMONELLA

A total of 61 isolates were recovered from blood cultures, representing 7% of all *Salmonella* infections (seven *S.* Typhimurium and its monophasic variant (11.5%), 18 *S.* Enteritidis (29.5%), eight *S.* Typhi, three *S.* Paratyphi, and 25 (41%) of 17 different *Salmonella* serovars (Figure 45)).

Most isolates from blood cultures were tested against seven groups of antibiotics. The number that each group of *Salmonella* was resistant to is shown in FIGURE . The most frequent serovar in blood cultures was *S.* Enteritidis followed by isolates from the *Salmonella* other group.

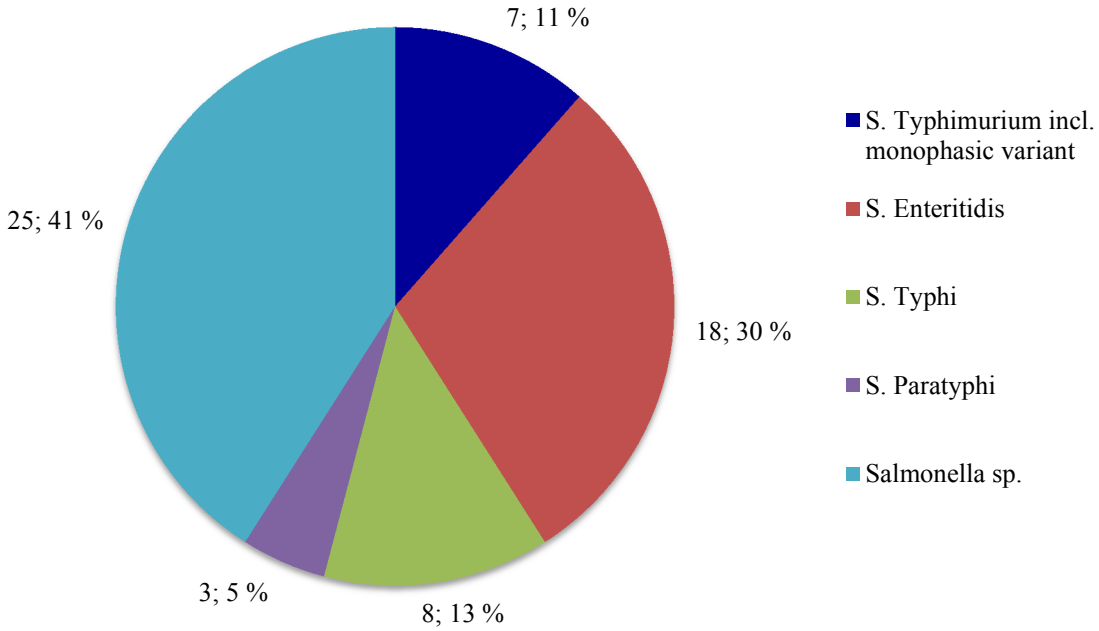

FIGURE 45. Distribution of blood culture isolates into different *Salmonella* serovars (n=61) in 2017.

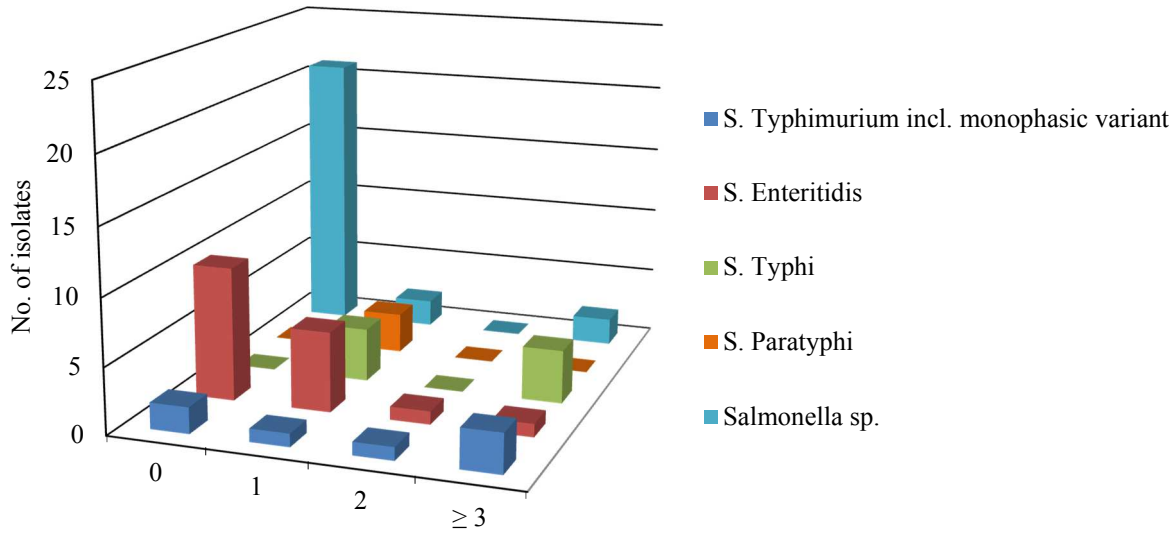

FIGURE 46. Antimicrobial resistance in *Salmonella* isolated from blood culture in 2017 tested against seven antibiotic groups displaying the number of isolates resistant to; none, one, two, and three or more antimicrobial groups. The seven antibiotic groups tested were beta-lactams, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, macrolides, tetracycline and chloramphenicol.

RESISTANCE IN SALMONELLA IRRESPECTIVE OF SAMPLE MATERIAL

TABLE 16. Distribution (%) of antimicrobial susceptibility categories of human isolates of domestically acquired *Salmonella* Typhimurium-group (n=50) and *S. enterica* serovar 4,[5],12:i:- (n=17) in 2017. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	64.2	-	35.8
Cefotaxime	≤ 1	> 2	98.5	0.0	1.5
Ceftazidime	≤ 1	> 4	98.5	1.5	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin/Pefloxacin[1]	≥ 24	< 21	80.6	9.0	10.4
Nalidixic acid[2]*	≥ 16	< 16	89.7	-	10.3
Gentamicin	≤ 2	> 4	97.0	1.5	1.5
Azithromycin[3]*	≥ 12	< 12	100.0	-	0.0
Tetracycline[3]*	≥ 17	< 17	48.7	-	51.3
Chloramphenicol*	≤ 8	> 8	76.9	-	23.1
Trimethoprim-sulfamethoxazole	≤ 2	> 4	92.5	0.0	7.5

[1] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion; EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. Susceptibility to ciprofloxacin is therefore inferred from pefloxacin disk diffusion susceptibility with breakpoints based on epidemiological cut-off values on national zone distribution evaluations in line with EUCAST recommendation. [2] Breakpoints based on EUCAST ECOFFs (accessed June 2018). [3] Epidemiological cut-off values based on national zone distribution evaluations. *Only tested in 39/67 isolates.

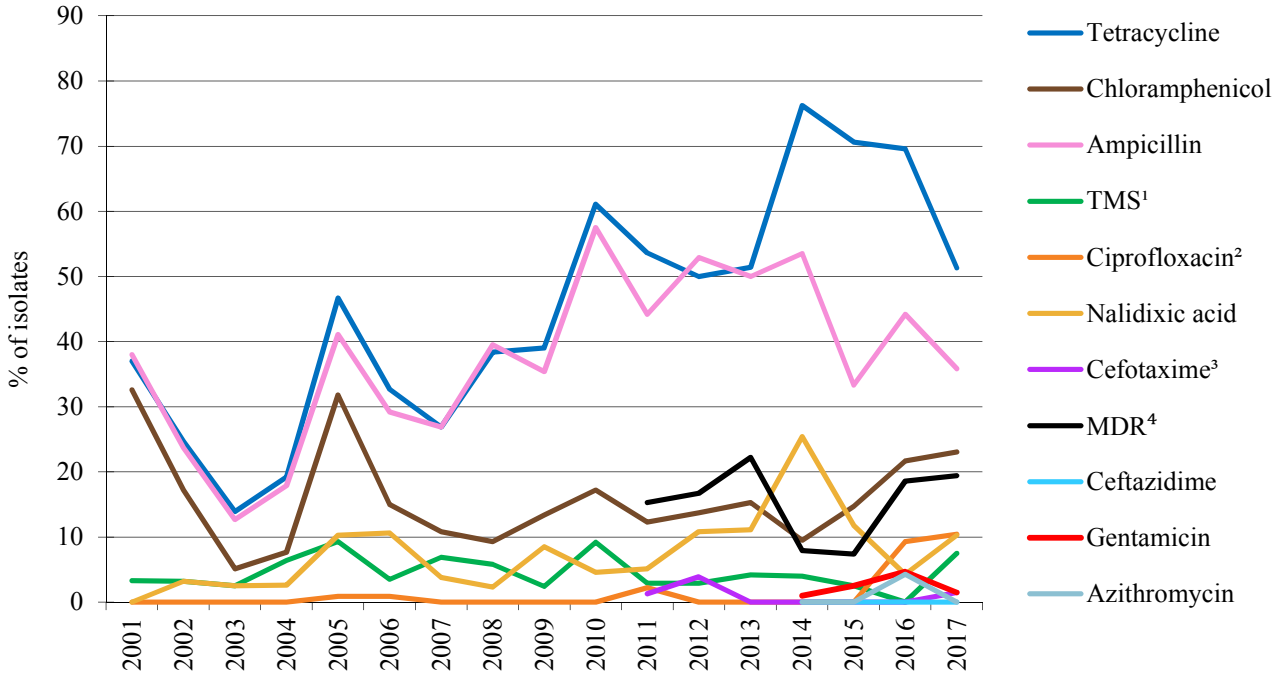

FIGURE 47. Percentage of resistance to various antimicrobial agents in the *Salmonella* Typhimurium-group including *S. enterica* serovar 4,[5],12:i:- from humans infected in Norway 2001-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion susceptibility from 2016 onwards. [3] Cefpodoxime was tested before 2014. [4] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

TABLE 17. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Salmonella* Typhimurium-group (n=48) and *S. enterica* serovar 4,[5],12:i:- (n=57) acquired abroad in 2017. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	55.2	-	44.8
Cefotaxime	≤ 1	> 2	96.2	0.0	3.8
Ceftazidime	≤ 1	> 4	97.1	0.0	2.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin/Pefloxacin[1]	≥ 24	< 21	85.7	2.9	11.4
Nalidixic acid[2]*	≥ 16	< 16	92.3	-	7.7
Gentamicin	≤ 2	> 4	93.3	0.0	6.7
Azithromycin[3]*	≥ 12	< 12	95.4	-	4.6
Tetracycline[3]*	≥ 17	< 17	24.6	-	75.4
Chloramphenicol*	≤ 8	> 8	76.9	-	23.1
Trimethoprim-sulfamethoxazole	≤ 2	> 4	89.5	0.0	10.5

[1] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. Susceptibility to ciprofloxacin is therefore inferred from pefloxacin disk diffusion susceptibility with breakpoints based on epidemiological cut-off values on national zone distribution evaluations in line with EUCAST recommendation. [2] Breakpoints based on EUCAST ECOFFs (accessed June 2018). [3] Epidemiological cut-off values based on national zone distribution evaluations. *Only tested in 23/43 isolates.

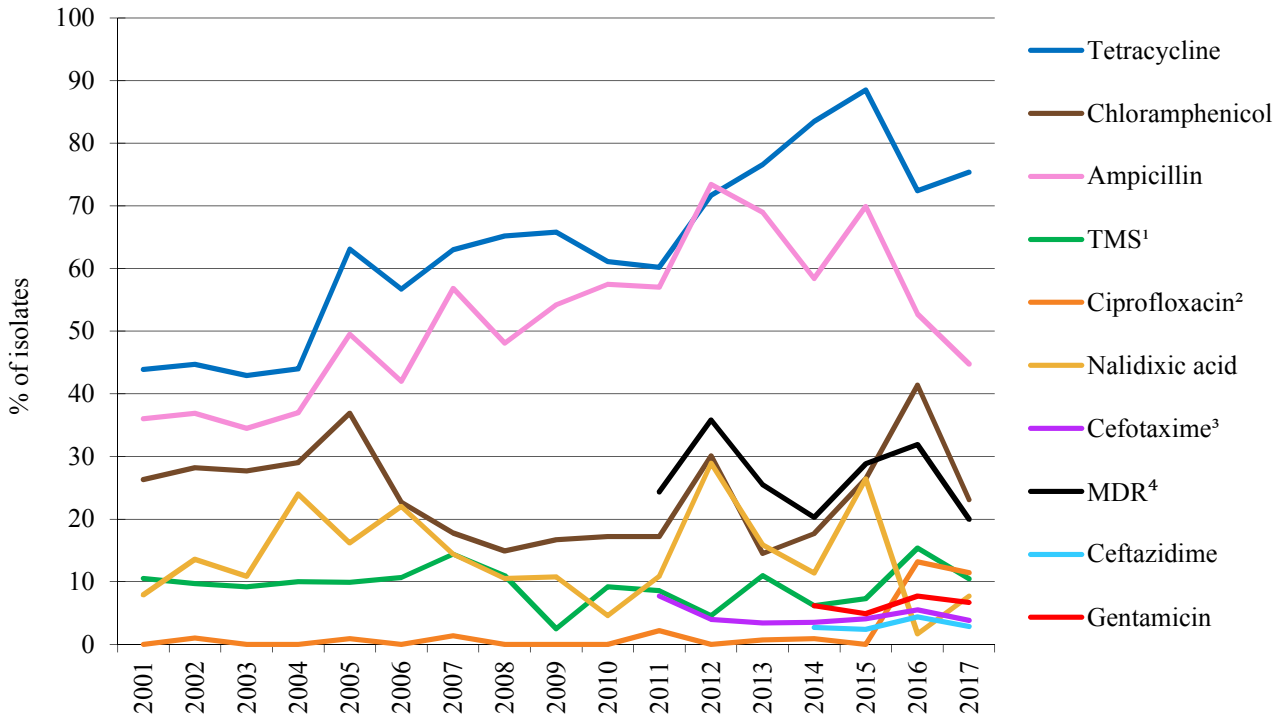

FIGURE 48. Percentage of resistance to various antimicrobial agents in *Salmonella* Typhimurium-group including *S. enterica* serovar 4,[5],12:i:- from humans infected outside Norway 2001-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion susceptibility from 2016 onwards. [3] Cefpodoxime was tested before 2014. [4] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

TABLE 18. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Salmonella* Enteritidis (n=271), acquired during 2017, irrespective of place of acquisition (Norway (n=52); abroad (n=194); unknown (n=25)). Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	91.9	-	8.1
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/Pefloxacin[1]	≥ 24	< 21	73.8	0.7	25.5
Nalidixic acid[2]*	≥ 16	< 16	71.1	-	28.9
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin[3]*	≥ 12	< 12	100.0	-	0.0
Tetracycline[3]*	≥ 17	< 17	97.6	-	2.4
Chloramphenicol*	≤ 8	> 8	98.8	-	1.2
Trimethoprim-sulfamethoxazole	≤ 2	> 4	99.3	0.0	0.7

[1] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. Susceptibility to ciprofloxacin is therefore inferred from pefloxacin disk diffusion susceptibility with breakpoints based on epidemiological cut-off values on national zone distribution evaluations in line with EUCAST recommendation. [2] Breakpoints based on EUCAST ECOFFs (accessed June 2018). [3] Epidemiological cut-off values based on national zone distribution evaluations. *Only tested in 83/271 isolates.

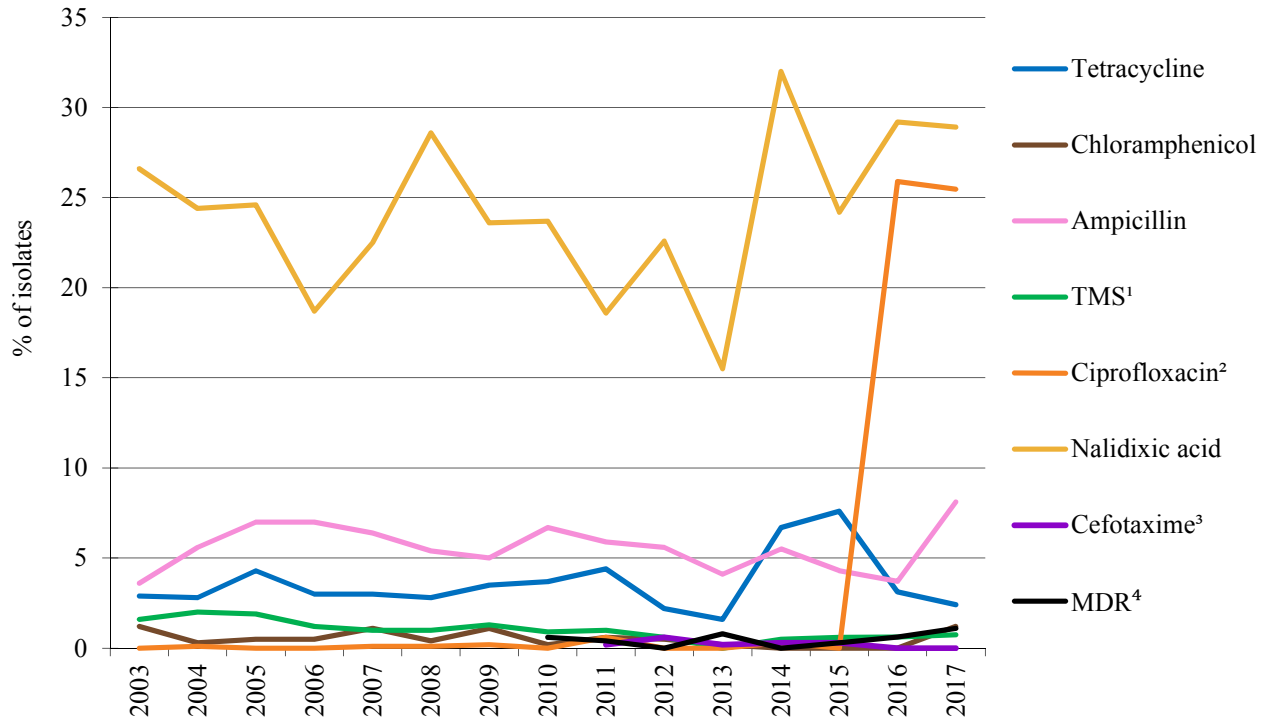

FIGURE 49. Percentage of resistance to various antimicrobial agents in *Salmonella* Enteritidis from humans irrespective of place of infection 2003-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion susceptibility from 2016 onwards. [3] Cefpodoxime was tested before 2014. [4] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

TABLE 19. Distribution (%) of antimicrobial susceptibility categories on human isolates of *Salmonella* spp. including *S.* Paratyphi B variant Java, excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi (n=404), acquired in 2017, irrespective of place of acquisition (Norway (n=97); abroad (n=267); unknown (n=40)). Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	87.4	-	12.6
Cefotaxime	≤ 1	> 2	99.5	0.0	0.5
Ceftazidime	≤ 1	> 4	99.0	0.5	0.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin/Pefloxacin[1]	≥ 24	< 21	84.4	2.0	13.6
Nalidixic acid[2]*	≥ 19	< 19	91.1	-	8.9
Gentamicin	≤ 2	> 4	96.5	0.2	3.2
Azithromycin[2]*	≥ 12	< 12	100.0	-	0.0
Tetracycline[2]*	≥ 17	< 17	83.0	-	17.0
Chloramphenicol*	≤ 8	> 8	95.5	-	4.5
Trimethoprim-sulfamethoxazole	≤ 2	> 4	91.3	0.5	8.2

[1] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. Susceptibility to ciprofloxacin is therefore inferred from pefloxacin disk diffusion susceptibility with breakpoints based on epidemiological cut-off values on national zone distribution evaluations in line with EUCAST recommendation. [2] Epidemiological cut-off values based on national zone distribution evaluations. *Only tested in 112/404 isolates.

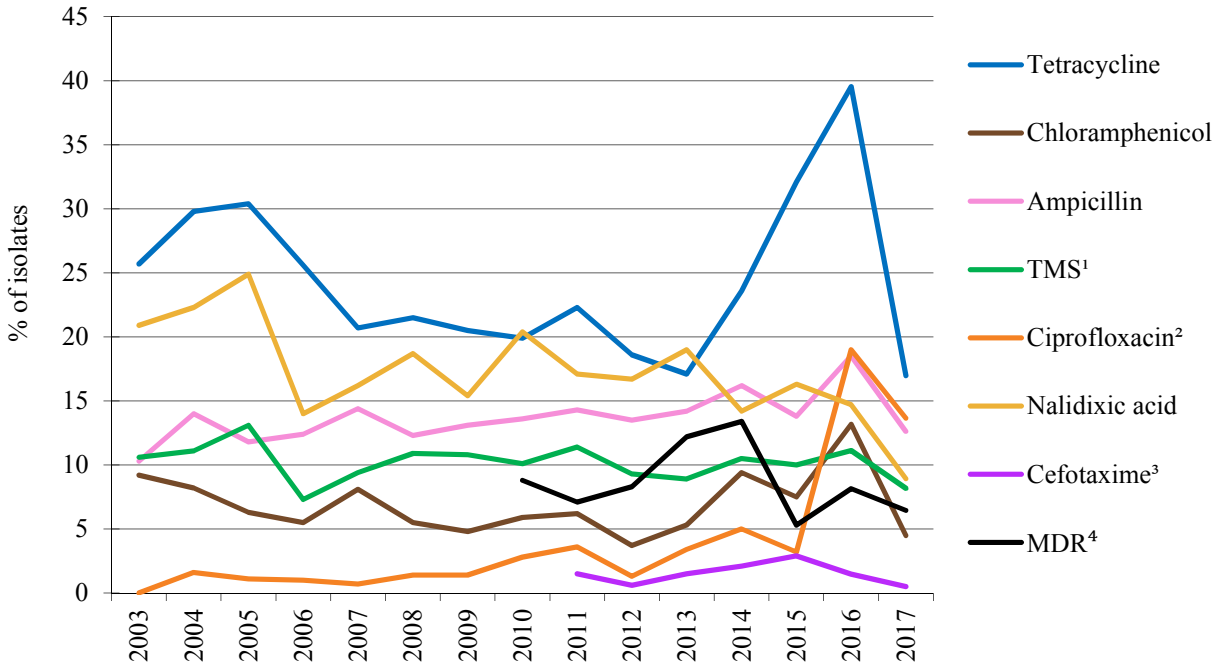

FIGURE 50. Percentage of resistance to various antimicrobial agents in *Salmonella* spp. including *S.* Paratyphi B variant Java; excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi, from humans in 2003-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Resistance to ciprofloxacin is inferred from pefloxacin disk diffusion susceptibility from 2016 onwards. [3] Cefpodoxime was tested before 2014. [4] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

RESULTS AND COMMENTS

As previously recorded, the overall level of resistance was higher among *S.* Typhimurium and its monophasic variant group, and the "*Salmonella* other" group than *S.* Enteritidis (Figure 44). In previous years, ciprofloxacin resistance was inferred from disk diffusion susceptibility according to local breakpoints in the absence of breakpoints defined by EUCAST. Consequently low-level ciprofloxacin resistance was probably underestimated. As in 2016, ciprofloxacin resistance in *Salmonella* isolates in 2017 was inferred from pefloxacin disk diffusion in accordance with EUCAST guidelines. Breakpoints used were set in accordance with locally observed pefloxacin zone distributions in 2016 (Appendix 4).

For infections acquired in Norway of *S.* Typhimurium and its monophasic variant group, resistance to ampicillin and tetracycline was still high although with a decreasing trend since 2014 (Figure 47). Also for infections acquired abroad, a slight reduction in resistance to both these drugs was observed (FIGURE 48). Within this group the monophasic variant accounted for 9% of all the domestically acquired infections and 30% of all the infections acquired abroad. The overall level of resistance to all antibiotics was much higher in the monophasic variant of *S.* Typhimurium.

Antibiotic resistance in *S.* Enteritidis isolates was stable over the years (Figure 49). An increase in ciprofloxacin resistance followed the change in methodology in 2016, and is unchanged in 2017 at around 25.5% regardless of place of acquisition.

In the "*Salmonella* other" group, in addition to the jump in prevalence of resistance to ciprofloxacin, a significant increase was observed in resistance to tetracycline in 2016. In 2017, the level of tetracycline resistance was again seen to revert back to 2014 (Figure 50). The non-identification of *S.* Stanley and *Salmonella enterica* subspecies enterica of different O-groups, both non-motile and monophasic variants, were the probable cause of the observed reduction.

A total of eight isolates carried extended spectrum beta-lactamases (ESBL) among the recovered *Salmonella* isolates in 2017. $ESBL_A$ was identified in five isolates of *S.* Typhimurium and its monophasic variant, and in one *S.* Kentucky isolate. $ESBL_M$ was found in one isolate of *S.* Typhimurium and its monophasic variant, and in one isolate of *S.* Heidelberg.

CAMPYLOBACTER SPP.

Campylobacter coli from swine

Caecal samples from a total of 300 swine were examined. *C. coli* isolates were obtained from 273 of these (91%). while only 255 isolates were used for sensitivity testing, one per herd. The results are presented in Table 20, Figure 51 and in the text.

TABLE 20. Antimicrobial resistance in *Campylobacter coli* isolates (n=255) from swine caecal samples in 2017.

	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	0	[0.0-1.4]				97.6	2.4								
Erythromycin	0	[0.0-1.4]					99.2	0.4	0.4						
Streptomycin	31.0	[25.3-37.0]			0.4	0.4		7.8	60.4	1.2		29.8			
Gentamicin	0	[0.0-1.4]		1.2		43.1	55.7								
Ciprofloxacin	18.9	[14.2 – 24.2]		81.2					6.3	11.0	1.6				
Nalidixic acid	19.2	[14.6-24.6]						0.4	32.2	47.1	1.2	0.4	5.1	13.7	

*Bold vertical lines denote microbiological cut-off values. 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.

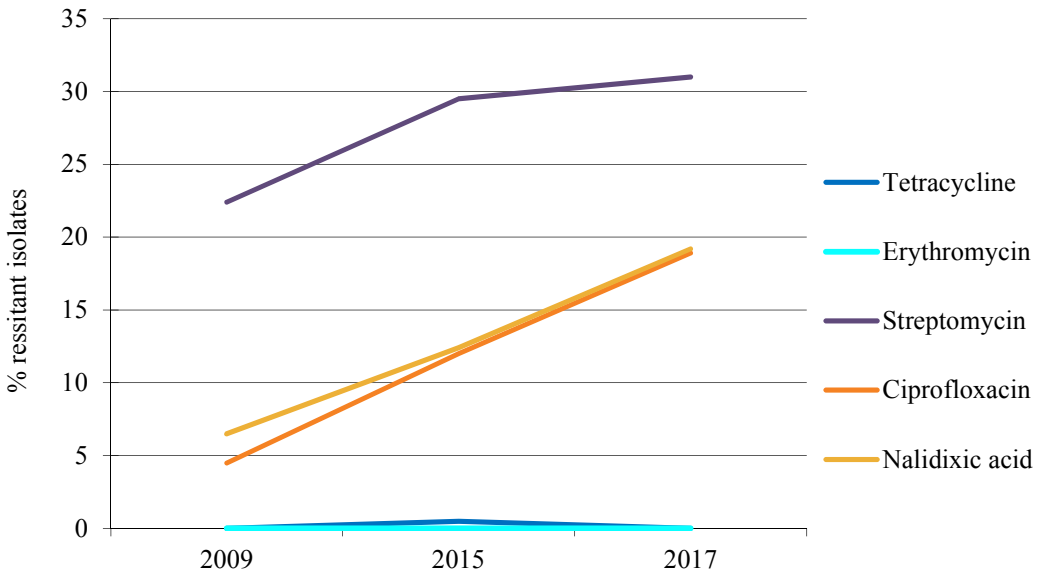

FIGURE 51. Prevalence of resistance to various antimicrobials in *Campylobacter coli* from faecal swine samples 2009-2017. The breakpoints used in NORM-VET 2017 were applied.

RESULTS AND COMMENTS

The data indicate a high occurrence of resistance among *C. coli* from swine. A total of 54.5% of the isolates were susceptible to all antimicrobial agents tested. Altogether, 24.7% were resistant to one antimicrobial agent, 12.2% to two, and 6.7% to three of the antimicrobial agents tested. Resistance to streptomycin was the most frequently identified resistance determinant (31.0%), followed by resistance to nalidixic acid (19.2%) and ciprofloxacin (18.9%). Resistance to erythromycin and gentamicin was not detected.

C. coli has been investigated only twice before, in 2009 and 2015. In this time period there has been a significant increase in resistance to quinolones from 4.5% and 6% resistance to ciprofloxacin and nalidix acid, respectively, in 2009, to 18.9% and 19.2% to ciprofloxacin and nalidixic acid, respectively, in 2017. This increasing trend is also reported by others, both in human and animal *C. coli* isolates. In the EFSA and ECDC Summary report from 2015, resistance to quinolones among *C. coli* is reported to be > 60%. The occurrence varies, however, markedly between the reporting countries (EFSA and ECDC Summary report 2016). The results from Norway are still among the lowest reported. This situation is most likely due to the rather limited use of antibiotics in the Norwegian swine production. The causes for increasing quinolone resistance, despite the limited use of antibiotics, are unknown.

Campylobacter spp. from human clinical cases

Of the 3,884 human campylobacteriosis cases registered in Norway in 2017, 44.4% were reported as acquired abroad. Based on epidemiological data from patients, the vast majority of cases were judged as sporadic. However, only a fraction of the isolates were forwarded to the National Reference Laboratory. Consequently, quality-assured species diagnoses, complete AMR data and molecular epidemiological data on *Campylobacter* isolates are lacking due to resource limitations. Outbreaks with less clear epidemiological links may very well have been overlooked, and the antimicrobial susceptibility testing results presented may therefore be underestimated or overestimated.

Susceptibility testing was performed on a total of 494 *C. jejuni* isolates from 229 patients infected in Norway, 225 infected abroad and 40 where the place of acquisition was unknown, as well as 42 *C. coli* isolates. The results for *C. jejuni* are presented in Tables 21-22, Figures 52-54, and in the text.

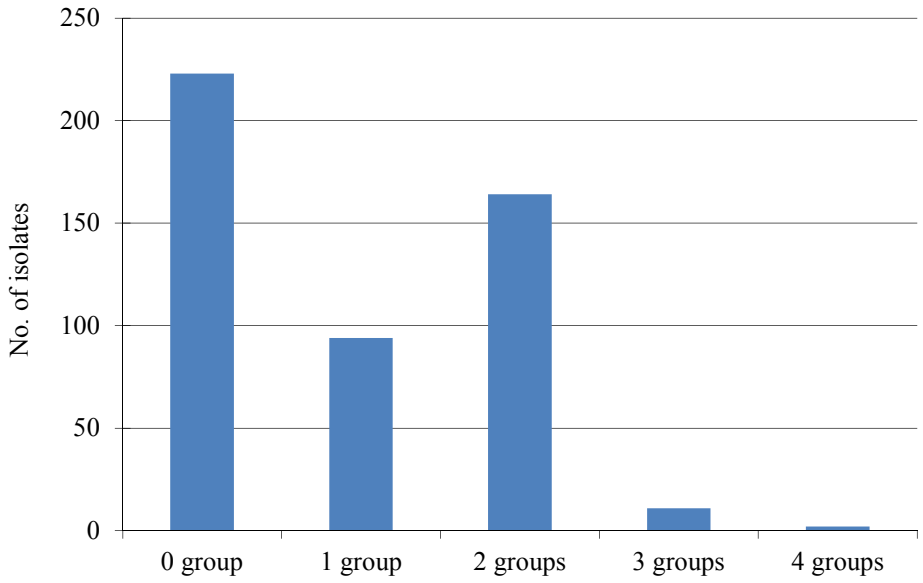

FIGURE 52. The number of antimicrobial groups *Campylobacter jejuni* isolates were resistant to in 2017. The four antibiotic groups tested were tetracycline, fluoroquinolones, aminoglycosides and macrolides.

TABLE 21. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Campylobacter jejuni* from patients infected in Norway in 2017 (n=229).

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	86.9	-	13.1
Erythromycin	≤ 4	> 4	96.5	-	3.5
Gentamicin [1]	≤ 2	> 2	98.7	-	1.3
Nalidixic acid [1]	≤ 16	> 16	79.0	-	21.0
Ciprofloxacin	≤ 0.5	> 0.5	79.5	-	20.5

[1] Epidemiological cut-off values according to EUCAST (accessed June 2018).

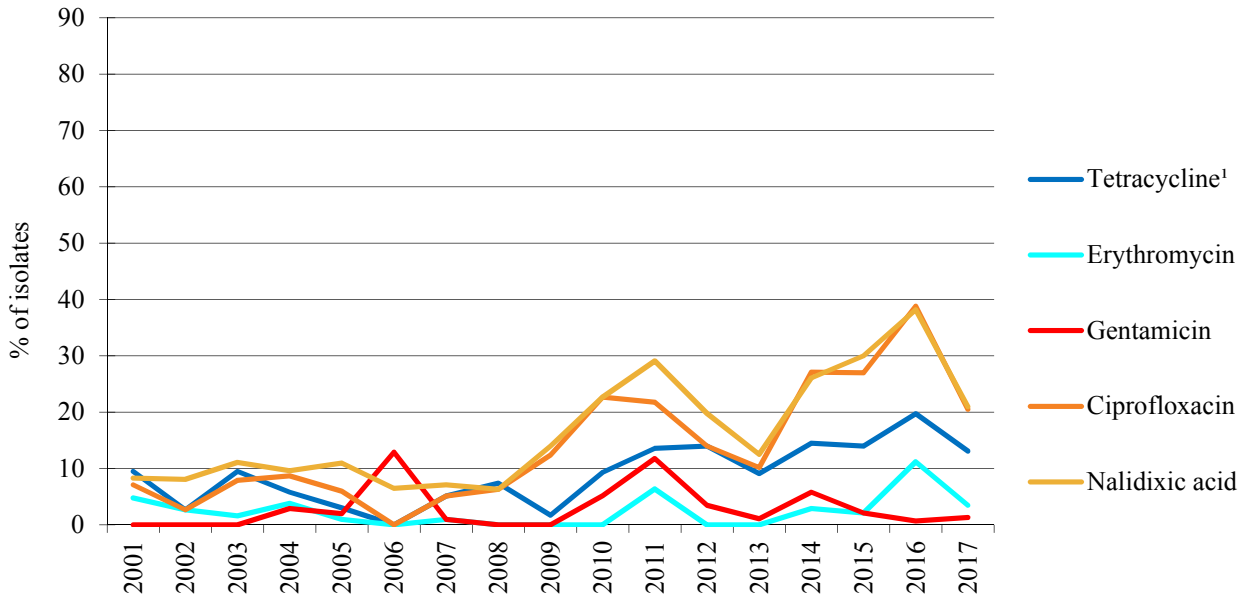

FIGURE 53. Percentage of resistance to various antimicrobial agents in *Campylobacter jejuni* isolated from humans infected in Norway 2001-2017. [1] Doxycycline was tested before 2006.

TABLE 22. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Campylobacter jejuni* from patients infected outside Norway in 2017 (n=225).

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	39.1	-	60.9
Erythromycin	≤ 4	> 4	95.1	-	4.9
Gentamicin [1]	≤ 2	> 2	99.1	-	0.9
Nalidixic acid [1]	≤ 16	> 16	17.3	-	82.7
Ciprofloxacin	≤ 0.5	> 0.5	16.4	-	83.6

[1] Epidemiological cut-off values according to EUCAST (accessed June 2018).

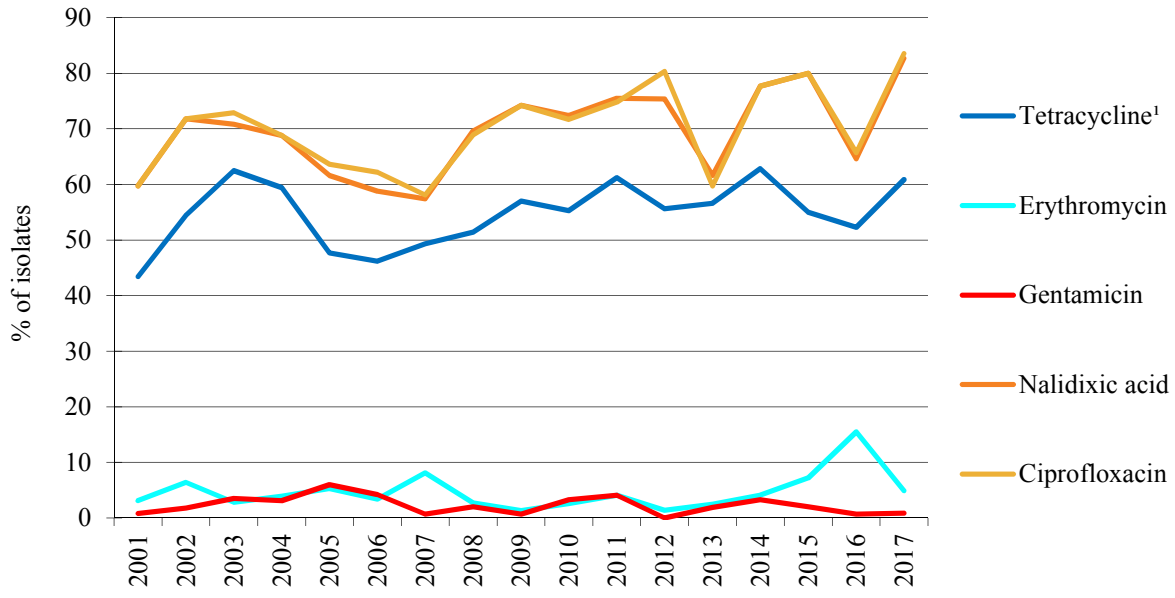

FIGURE 54. Percentage of resistance to various antimicrobial agents in *Campylobacter jejuni* isolated from humans infected outside Norway 2001-2017. [1] Doxycycline was tested before 2006.

RESULTS AND COMMENTS

The data show that resistance was more widespread among *C. jejuni* isolates recovered from patients infected abroad than from patients infected in Norway. Only 14.7% of the isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 74.2% of the isolates from patients infected in Norway. The main difference between the two groups was seen for ciprofloxacin, nalidixic acid and tetracycline. There was a statistically significant difference in levels of resistance between those isolates acquired abroad compared to those acquired in Norway ($p < 0.001$ for both antimicrobial groups).

For isolates from patients infected in Norway the upward trend recorded in 2016 seems to have been reversed. For infections acquired in Norway and acquired abroad, a decrease in resistance to macrolides (erythromycin) was observed.

No isolates were identified as ESBL producers. An MDR phenotype was observed in four isolates acquired in Norway (1.6%) and in 14 isolates acquired aborad (5.4%)

Thirty-two of the 42 *C. coli* isolates were acquired abroad. The level of resistance to macrolides was the major difference between *C. coli* acquired in Norway (0.0%) and abroad (36.0%).

Yersinia enterocolitica from human clinical cases

A total of 67 unique isolates of pathogenic *Yersinia enterocolitica* were analysed in 2017. Forty-seven belonged to serogroup 3 including 20 acquired in Norway, 17 acquired abroad, and 10 with an unknown place of acquisition. Fourteen isolates were of serogroup 9, of which eight were acquired in Norway. Two isolates were acquired abroad and four isolates were acquired at an unknown location. Three *Y. pseudotuberculosis* isolates were recovered in 2017. All *Y. enterocolitica* isolates were tested for susceptibility to four antimicrobial groups (beta-lactams, quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole) whereas only seventeen isolates were tested against all seven groups. The results are presented in Table 23 and Figures 55-56.

The crude number of isolates was considered low, and judgements should consequently be more conservative regarding AMR results for *Y. enterocolitica* than for other enteropathogenic bacteria.

TABLE 23. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Yersinia enterocolitica* serogroups O:3 and O:9 from patients infected in 2017 (n=61). Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	0.0	-	100.0
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Nalidixic acid [1]*	≥ 16	< 16	94.1	-	5.9
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1]*	≥ 12	< 12	100.0	-	0.0
Tetracycline [1]*	≥ 17	< 17	100.0	-	0.0
Chloramphenicol *	≤ 8	> 8	100.0	-	0.0
Trimethoprim-sulfamethoxazole	≤ 2	> 4	100.0	0.0	0.0

[1] Epidemiological cut-off values based on zone distribution evaluations. *Only tested in 17/61 isolates.

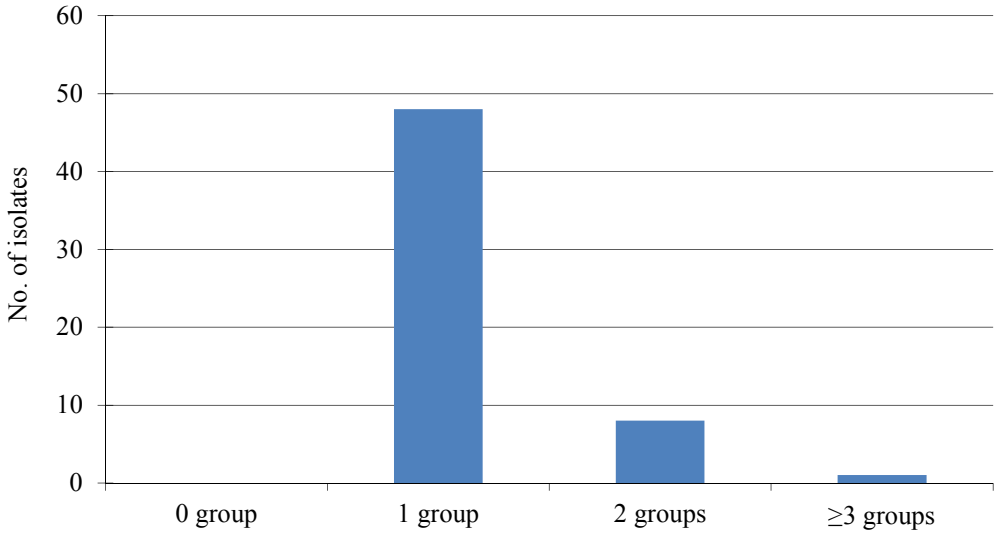

FIGURE 55. The number of antimicrobial groups that *Yersinia enterocolitica* isolates were resistant to in 2017.

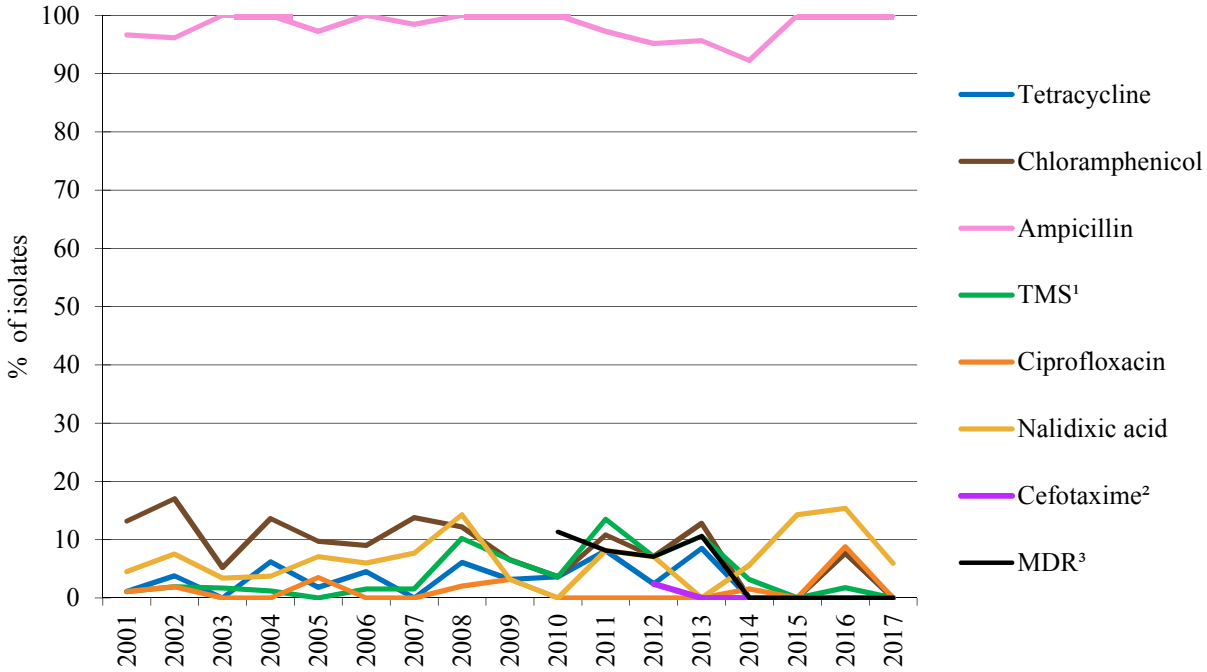

FIGURE 56. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Cefpodoxime was tested before 2014. [3] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

RESULTS AND COMMENTS

The prevalence of resistance to all antimicrobial agents appeared stable during the years 2001-2017. All isolates of pathogenic *Yersinia enterocolitica* expressed intrinsic resistance to ampicillin.

Shigella spp. from human clinical cases

In 2017, only 25 (21.9%) of the 114 unique isolates of *Shigella* were domestically acquired, and the prevalence of resistance presented in this report predominantly relates to isolates from infections acquired abroad. The species distribution of the 114 *Shigella* isolates that were tested for drug susceptibility was as follows: *S. sonnei* 65 (57.0%); *S. flexneri* 39 (34.2%); *S. boydii* 8 (7.0%); *S. dysenteriae* 2 (1.8%). The numbers of antimicrobial agents that *Shigella* isolates were resistant to are shown in Figure 57. All isolates were tested for resistance to four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime, and meropenem), ciprofloxacin, gentamicin and trimethoprim-sulfamethoxazole. In addition, nine isolates were also tested for resistance to nalidixic acid, azithromycin, tetracycline, and chloramphenicol. The results for *S. sonnei* and *S. flexneri* are presented in Table 24 and Figure 58, and in Table 25 and Figure 59, respectively.

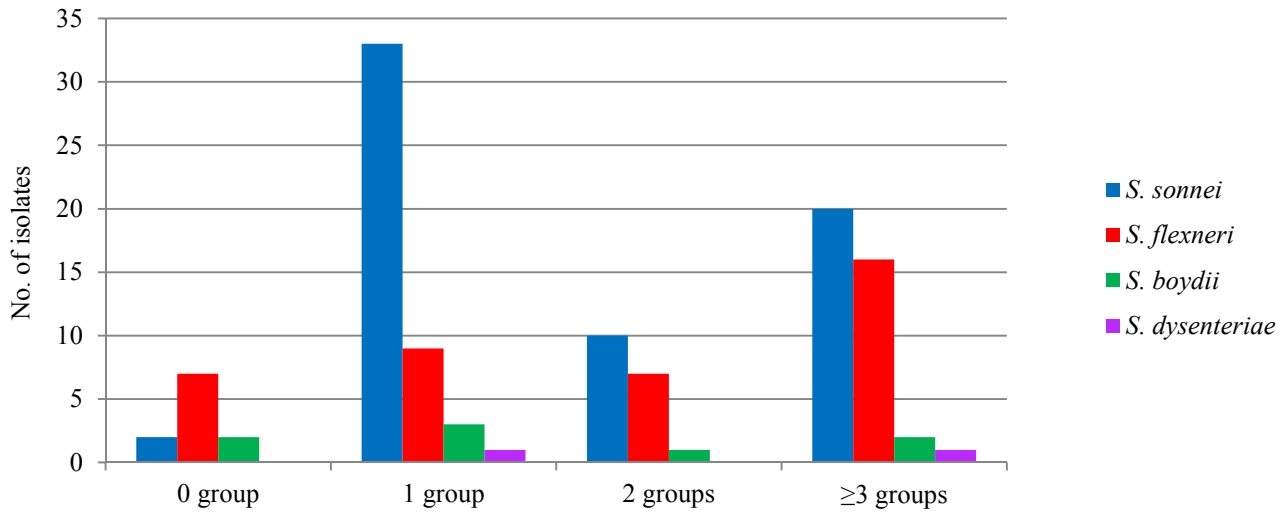

FIGURE 57. The number of antibiotic groups that *Shigella* isolates were resistant to stratified by species.

TABLE 24. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Shigella sonnei* in 2017 (n=65). Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	72.3	-	27.7
Cefotaxime	≤ 1	> 2	89.2	0.0	10.8
Ceftazidime	≤ 1	> 4	95.4	0.0	4.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	56.9	6.2	36.9
Nalidixic acid [1]*	≥ 16	< 16	44.4	-	55.6
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1]*	≥ 12	< 12	84.4	-	15.6
Tetracycline [1]*	≥ 17	< 17	0.0	-	100.0
Chloramphenicol *	≤ 8	> 8	100.0	-	0.0
Trimethoprim-sulfamethoxazole	≤ 2	> 4	18.5	0.0	81.5

[1] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 9/65 isolates.

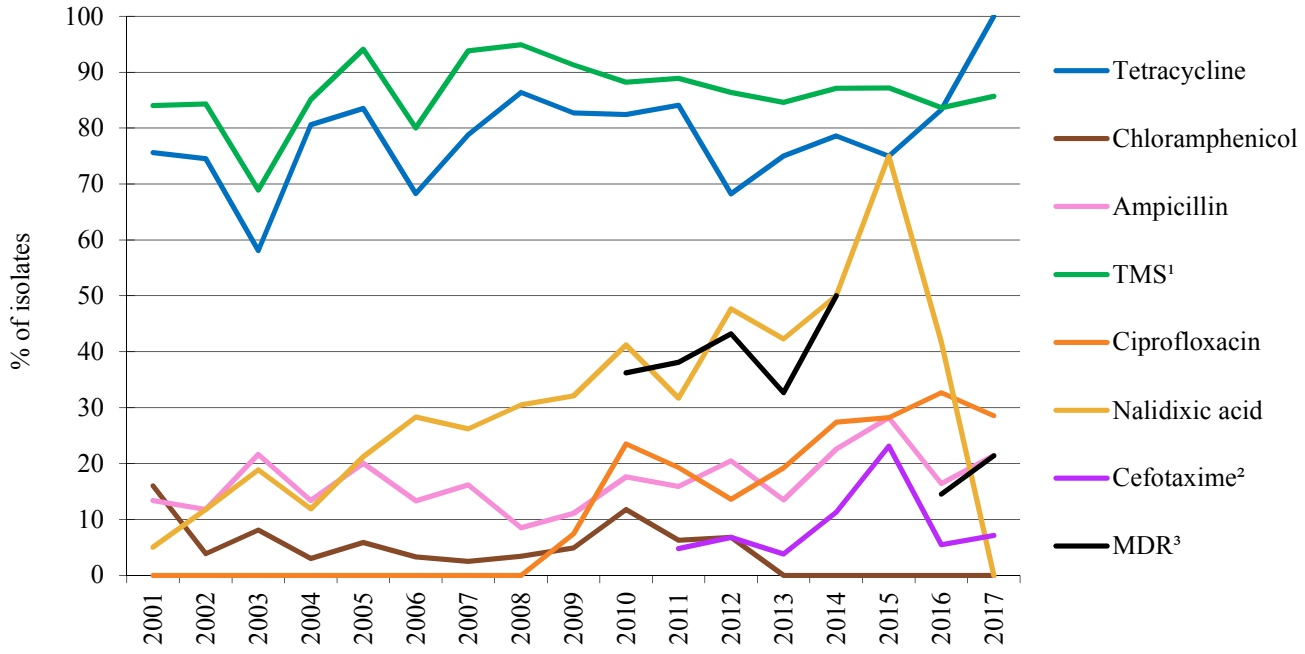

FIGURE 58. Prevalence of resistance to various antimicrobial agents in *Shigella sonnei* from humans in Norway 2001-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Cefpodoxime was tested before 2014. [3] MDR was based on five antibiotic groups tested from 2011-2013 and seven groups tested from 2014 onwards.

TABLE 25. Distribution (%) of antimicrobial susceptibility categories of human isolates of *Shigella flexneri* in 2016 (n=39). Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	30.8	-	69.2
Cefotaxime	≤ 1	> 2	92.3	0.0	7.7
Ceftazidime	≤ 1	> 4	94.8	2.6	2.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	66.7	7.7	25.6
Nalidixic acid [1]*	≥ 16	< 16	53.8	-	46.2
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1] *	≥ 12	< 12	85.7	-	14.3
Tetracycline [1] *	≥ 17	< 17	15.4	-	84.6
Chloramphenicol *	≤ 8	> 8	30.8	-	69.2
Trimethoprim-sulfamethoxazole	≤ 2	> 4	41.0	0.0	59.0

[1] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 13/39 isolates.

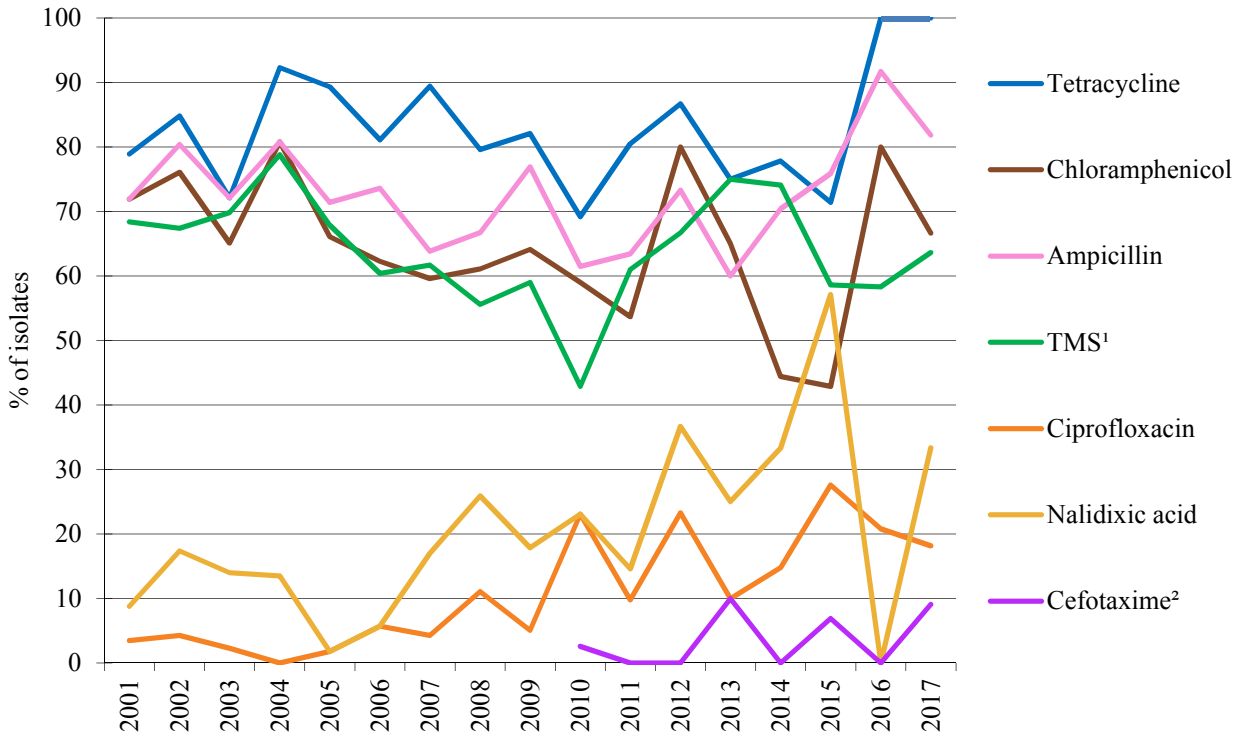

FIGURE 59. Prevalence of resistance to various antimicrobial agents in *Shigella flexneri* from humans in Norway 2001-2017. [1] TMS; trimethoprim-sulfamethoxazole. [2] Cefpodoxime was tested before 2014.

RESULTS AND COMMENTS

The resistance patterns for *S. sonnei* have been fairly stable during the period from 2001 to 2017. However, resistance to the fluoroquinolones has been on an upward trend since 2001 although a drop in resistance to nalidixic acid was observed in 2017, probably attributable to the low number of isolates tested. A similar observation for resistance to nalidixic acid and ciprofloxacin was recorded for *S. flexneri* isolates. The proportion of multi-drug resistance in both *S. sonnei* and *S. flexneri* (30.8% and 41.0%, respectively) was higher than in *Salmonella* as a whole (8.0%).

Six *S. sonnei* (9.2%), two *S. flexneri* and 1 *S. boydii* isolates were phenotypically identified as $ESBL_A$ producers. Additionally, one *S. sonnei* isolate was an $ESBL_M$ producer.

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 26, 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 *Propionibacterium* 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 26. Number of blood culture isolates in 2017, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) 2013-2017. The table is based on data from the information systems of all laboratories in Norway.

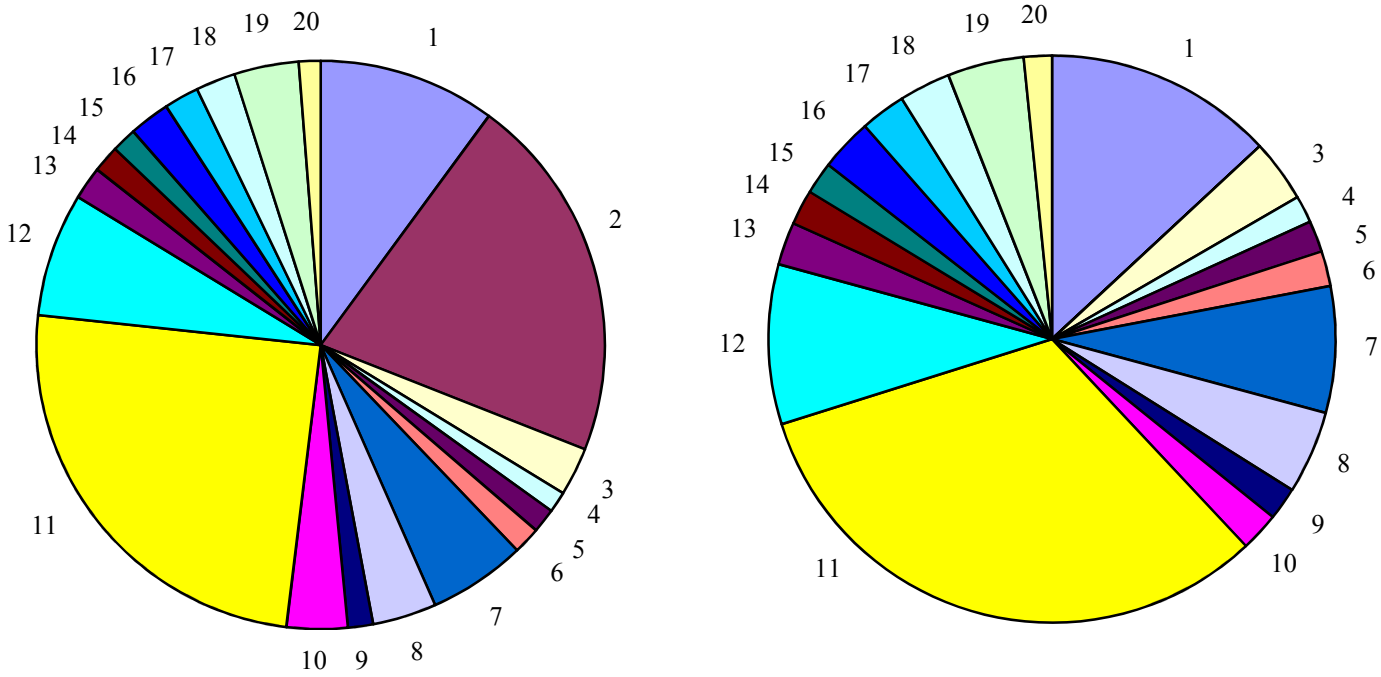
Species	No. of isolates 2017	% of all isolates					% of all isolates excluding skin flora				
		2013	2014	2015	2016	2017	2013	2014	2015	2016	2017
Staphylococcus aureus	1,751	11.5	11.0	11.1	10.5	10.1	14.3	14.2	14.4	13.6	13.1
Coagulase negative staphylococci	3,628	17.4	20.4	21.1	20.7	20.9	-	-	-	-	-
Streptococcus pneumoniae	477	4.2	3.6	3.2	3.4	2.7	5.2	4.6	4.2	4.4	3.6
Streptococcus pyogenes	207	1.3	1.1	1.3	1.1	1.2	1.6	1.4	1.7	1.4	1.5
Streptococcus agalactiae	240	1.7	1.6	1.7	1.6	1.4	2.1	2.0	2.2	2.1	1.8
Beta-haemolytic streptococci group C and G	268	1.2	1.2	1.5	1.3	1.5	1.5	1.6	2.0	1.7	2.0
Viridans- and non-haemolytic streptococci	963	5.5	4.6	4.6	5.0	5.5	6.8	5.9	6.0	6.5	7.2
Enterococcus faecalis	632	4.1	3.8	3.1	3.6	3.6	5.1	5.0	4.0	4.6	4.7
Enterococcus faecium	250	1.8	1.6	1.4	1.4	1.4	2.2	2.1	1.8	1.9	1.9
Other Gram-positive aerobic and facultative anaerobic bacteria	599	3.3	3.5	3.6	3.3	3.5	2.0	2.0	2.3	2.3	2.2
Escherichia coli	4,299	24.4	24.4	24.8	24.9	24.9	30.4	31.5	32.4	32.2	32.2
Klebsiella spp.	1,219	6.8	7.0	6.9	7.1	7.0	8.4	9.0	9.1	9.2	9.1
Enterobacter spp.	326	1.9	1.9	1.7	1.7	1.9	2.4	2.5	2.3	2.2	2.4
Proteus spp.	267	1.7	1.6	1.6	1.6	1.5	2.1	2.1	2.1	2.1	2.0
Other *Enterobacteriaceae*	401	2.3	2.2	1.8	1.8	2.3	2.9	2.9	2.3	2.3	3.0
Pseudomonas spp.	246	1.7	1.8	1.7	1.6	1.4	2.1	2.3	2.2	2.0	1.8
Other Gram-negative aerobic and facultative anaerobic bacteria	345	2.1	2.0	2.1	2.4	2.0	2.6	2.6	2.7	3.0	2.6
Bacteroides spp.	392	2.4	2.2	2.2	1.9	2.3	3.0	2.9	2.8	2.4	2.9
Other anaerobic bacteria	636	3.2	3.1	3.2	3.8	3.7	3.5	3.6	3.7	4.4	4.4
Yeasts	215	1.5	1.4	1.4	1.3	1.2	1.8	1.8	1.8	1.7	1.6
Total	**17,361**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 26 and Figure 60, aerobic and facultative Gram-positive and Gram-negative bacteria represented 51.8% and 41.0% of all isolates, respectively. The predominance of Gram-positives among all isolates was at the same level as in previous years. The most common Gram-positive species were coagulase negative staphylococci, which represented 20.9%. This is at the same level as 20.7% in 2016, 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 *Propionibacterium* spp.) were excluded with 38.0% aerobic Gram-positives and 53.1% aerobic Gram-negatives.

Among aerobic Gram-positives, the prevalence of *S. pneumoniae* has steadily declined from 12.1% in 2005 to 3.6% in 2017 (skin contaminants excluded), following the introduction of the conjugate pneumococcal vaccine in the national childhood immunisation programme in June 2006. The proportions of other aerobic Gram-positives have remained stable over many years.

E. coli (32.2%) and other *Enterobacteriaceae* (16.5%) accounted for the vast majority of aerobic Gram-negative isolates, but the proportions have remained relatively unchanged over the years. *Pseudomonas* spp. (1.8%) 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 6.0% (7.3% excluding skin flora). Yeasts accounted for 1.2% (1.6% excluding skin flora) which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (2.3%/2.9%) and among yeasts *Candida albicans* (0.7%/1.0%). However, a multitude of other species was 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 60. Distribution of all blood culture isolates (left, n=17,361) and blood culture isolates excluding common skin contaminants (right, n=13,378) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. Data for 2017 were retrieved from the information systems of all Norwegian laboratories.

Escherichia coli in blood cultures

TABLE 27. *Escherichia coli* blood culture isolates in 2017 (n=2,136). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	55.9	-	44.1
Amoxicillin-clavulanic acid	≤ 8	> 8	72.7	-	27.3
Piperacillin-tazobactam	≤ 8	> 16	94.6	3.9	1.5
Cefotaxime	≤ 1	> 2	93.0	0.3	6.7
Ceftazidime	≤ 1	> 4	92.6	1.1	6.3
Cefepime	≤ 1	> 4	92.1	2.0	5.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	92.9	0.1	7.0
Ciprofloxacin	≤ 0.25	> 0.5	82.0	2.8	15.2
Tigecycline	≤ 1	> 2	99.6	0.4	0.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	74.2	0.5	25.3
ESBL	Negative	Positive	93.4	-	6.6

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

NORM results are interpreted according to NordicAST/ EUCAST breakpoints at the time of analysis. The results are presented in Table 27. In addition, zone diameters for tetracycline are included in the text box on surgical prophylaxis on page 81. The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobial agents such as cefotaxime (93.0%), ceftazidime (92.6%), gentamicin (92.9%), cefepime (92.1%), piperacillin-tazobactam (94.6%), tigecycline (99.6%) and meropenem (100.0%) (Table 27). There were no significant changes in the prevalence of susceptibility for these agents from 2016. The prevalence of non-susceptibility (intermediate susceptibility and resistance) to gentamicin increased only slightly from 6.7% in 2016 to 7.1% in 2017 (Figure 61). However, the prevalence of gentamicin resistance is approximately eight times higher than at the turn of the century. A high proportion of gentamicin non-susceptible isolates (51/152, 33.6%) also produced ESBL enzymes. They were retrieved from 18 different laboratories across the country. The prevalence at individual laboratories varied due to relatively small numbers. When aggregated by region there were only minor geographical differences (South-East 7.9%, North 5.2%, Middle 7.2% and West 6.1%). Regional trends for gentamicin non-susceptibility over time are presented in detail on page 87.

The prevalence of non-suscpetibility to ciprofloxacin was 18.0% (2.8% I and 15.2% R). The breakpoints for ciprofloxacin were reduced from R > 1 mg/L to R > 0.5 mg/L and from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L in 2017, and the results from previous years have been updated according to the 2018 breakpoint table. The apparent increase from 11.9% non-susceptibility in 2015 is only a relatively minor change from 16.6% to 18.0% when adjusting for the new breakpoints. The temporal association between ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 62. A similar association between increasing quinolone use and resistance in systemic *E. coli* isolates is also reported internationally. Further surveillance is needed to ascertain whether reduced ciprofloxacin usage will lead to a reduction of quinolone resistance rates. The resistance rates for ampicillin (43.5% in 2016, 44.1% in 2017) and trimethoprim-sulfamethoxazole (25.8% in 2016, 25.3% in 2017) are relatively 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 140 isolates (6.6%) were reported as ESBL positive, which is at the same level as in 2015 (6.5%) and 2016 (5.5%) (Figure 64). The isolates originated from 20 participating laboratories across the country. Estimates at laboratory level are uncertain due to small numbers. When aggregated at regional level the prevalence of ESBL was higher in the South-East (7.9%) compared to the North (6.9%), Middle (4.3%) and West (4.6%) regions. Most of the ESBL isolates were non-susceptible to cefotaxime (n=138), ceftazidime (n=133) and cefepime (n=125). Many isolates were intermediately (n=27) or even fully susceptible (n=105) to piperacillin-tazobactam and also susceptible to amoxicillin-clavulanic acid (n=80). The isolates displayed high rates of co-resistance to ciprofloxacin (n=106), gentamicin (n=51) and/or trimethoprim-sulfamethoxazole (n=89). Only a single isolate was intermediately susceptible to meropenem due to a combination of ESBL and reduced permeability or efflux mechanisms, thus no carbapenease-producing isolates were detected. Twenty-six additional isolates were reported as non-susceptible to cefotaxime (n=11) and/or ceftazidime (n=25) without being confirmed as ESBL producers.

The 140 *E. coli* isolates with suspected ESBL production were molecularly characterised and revealed a predominance of CTX-M groups 1 (n=88) and 9 (n=40). The remaining 12 isolates harboured CMY (n=9) and DHA (n=2) beta-lactamases, whereas a single isolate only contained a wildtype AmpC genotype. No isolates with carbapenemase production were detected.

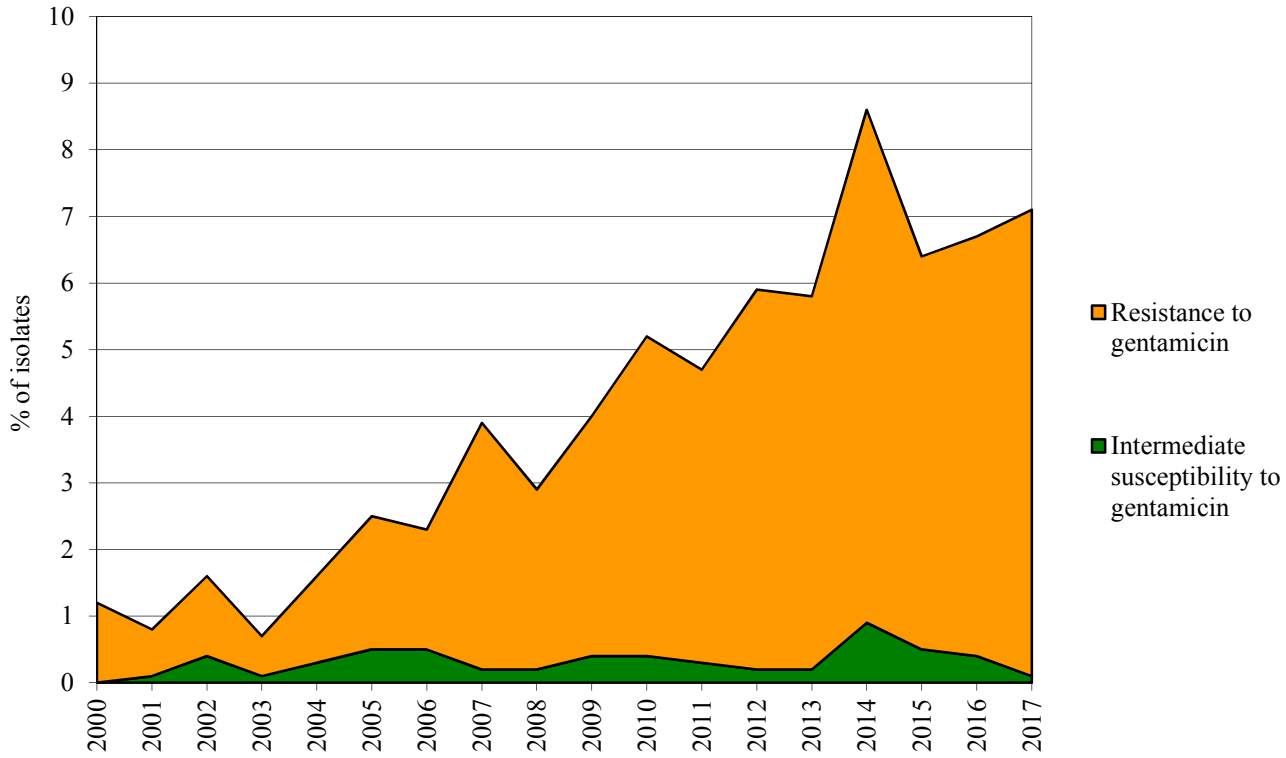


FIGURE 61. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2017.

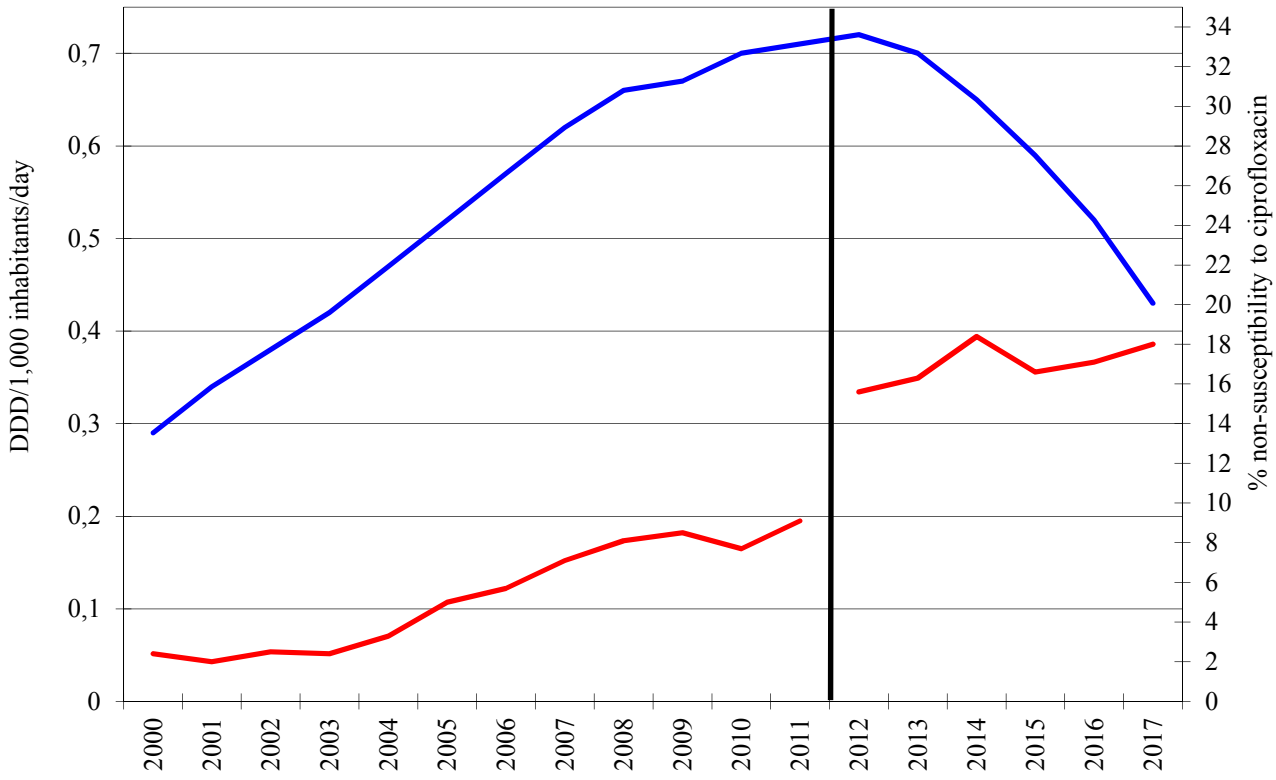


FIGURE 62. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates (red) as defined by MIC > 0.5 mg/L (2000-2011) and MIC > 0.25 mg/L (2012-2017). The breakpoint cannot be calibrated over the entire time period due to changes in susceptibility testing methodology in 2012.

Escherichia coli in urine

TABLE 28. *Escherichia coli* urinary tract isolates in 2017 (n=1,510). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	66.0	-	34.0
Mecillinam	≤ 8	> 8	94.0	-	6.0
Amoxicillin-clavulanic acid*	≤ 32	> 32	92.7	-	7.3
Cefotaxime	≤ 1	> 2	96.6	0.1	3.3
Ceftazidime	≤ 1	> 4	96.7	0.8	2.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	95.3	0.3	4.4
Ciprofloxacin	≤ 0.25	> 0.5	87.5	2.3	10.2
Nitrofurantoin	≤ 64	> 64	98.5	-	1.5
Fosfomycin	≤ 32	> 32	96.6	-	3.4
Trimethoprim	≤ 2	> 4	76.9	0.1	23.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	79.0	0.5	20.5
ESBL	Negative	Positive	97.0	-	3.0

*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 2017 is shown in Table 28 and the rates of resistance for 2000-2017 are shown in Figure 63.

The resistance rates among urinary tract isolates have remained relatively stable over the last ten years, but are slowly increasing for most antibiotics. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to 35%. Resistance to trimethoprim and trimethoprim-sulfamethoxazole has remained stable around 20-25%. The prevalence of resistance to mecillinam was 6.0% in 2017 compared to 5.1% in 2015 and 5.9% in 2016. Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. When adjusting for changes in breakpoint (see text Figure 62), the prevalence of resistance has remained stable around 8-9% over the last five years. In 2017, 10.2% of the isolates were resistant to ciprofloxacin in addition to 2.3% that were intermediately susceptibe. The corresponding rates for blood culture isolates were 2.8% intermediate susceptibility and 15.2% resistance. The persistent discrepancy between urinary tract isolates and isolates from bloodstream infections suggests that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and/or topoisomerase genes, whereas urinary tract isolates may be more representative of the wild-type normal flora.

The prevalence of resistance to amoxicillin-clavulanic acid was 7.3% in 2017 compared to 6.1% in 2015 and 7.4% in 2015. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (98.5%) remained fully susceptible to nitrofurantoin. Fosfomycin was included in NORM for the first time in 2017. The vast majority of isolates were categorised as susceptible (96.6%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Forty-six isolates (3.0%) were reported as ESBL producers, which is at the same level as in 2015 (3.1%) and 2016 (3.0%). As seen in Figure 64, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (6.6%). The ESBL positive strains were isolated at 16 different laboratories in all parts of the country. Thirty isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=8) or patients in nursing homes (n=4), outpatient clinics (n=3) or unknown location (n=1). The ESBL isolates were all resistant to ampicillin, as well as non-susceptible to cefotaxime (46/46) and ceftazidime (41/46). Most isolates were registered as *in vitro* susceptible to mecillinam (42/46). The clinical relevance of this finding is doubtful, since mecillinam is not stable for most beta-lactamases. Many of the ESBL isolates were non-susceptible to quinolones (34/46) and trimethoprim-sulfamethoxazole (30/46), but remained susceptible to nitrofurantoin (44/46) and gentamicin (32/46). All ESBL isolates were clinically susceptible to carbapenems.

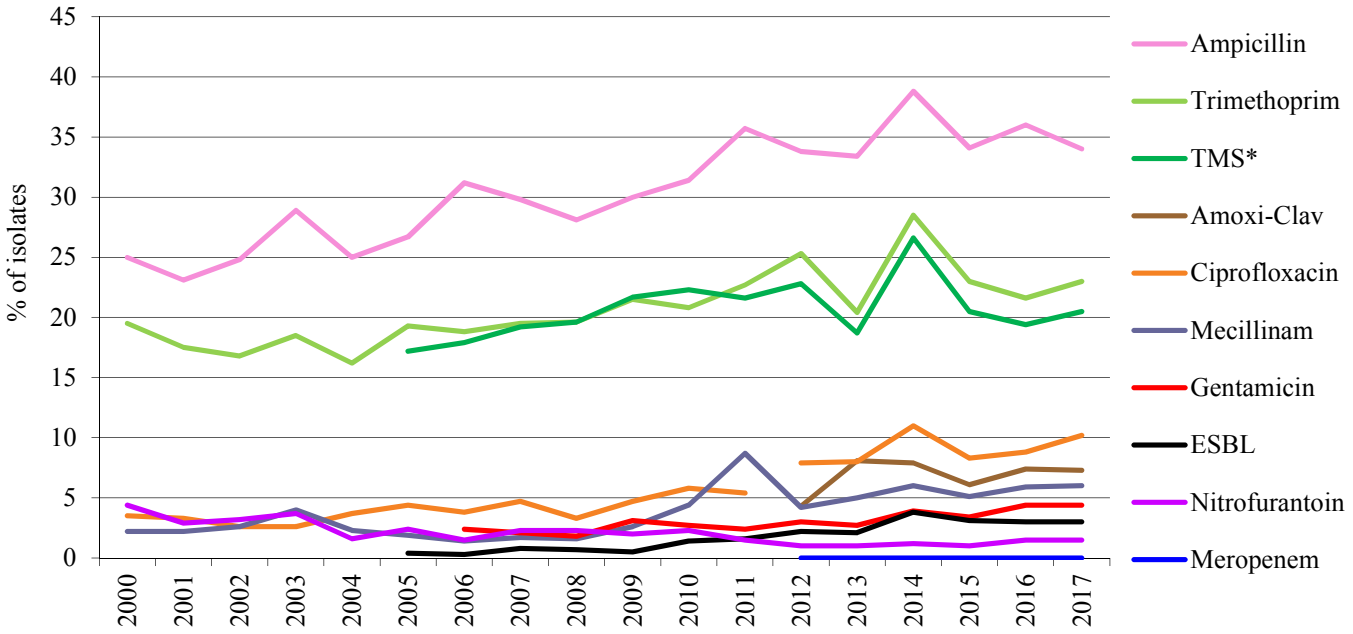


FIGURE 63. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2017 categorised according to the 2018 EUCAST guidelines. The breakpoint for ciprofloxacin resistance was changed from R > 1 mg/L to R > 0.5 mg/L in 2017. Data from 2012-2017 have been recategorised according to the new breakpoint, but earlier results (2000-2011) cannot be calibrated due to changes in susceptibility testing methodology in 2012. *TMS=Trimethoprim-sulfamethoxazole.

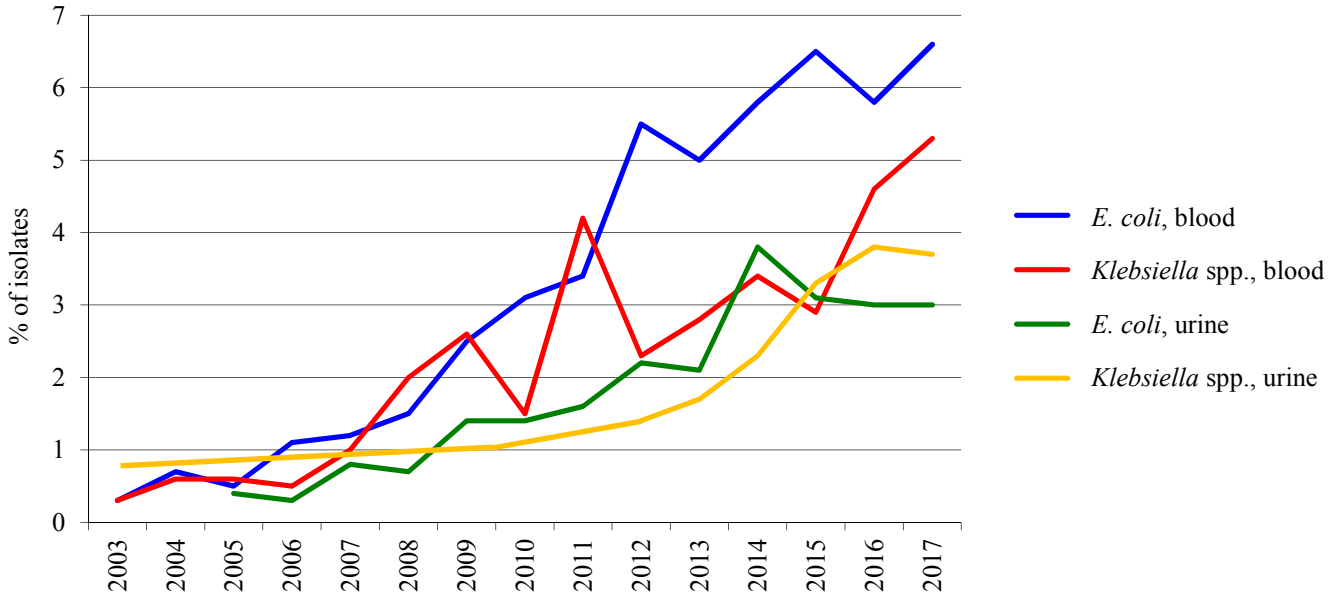


FIGURE 64. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2017.

Antibiotic prophylaxis against surgical site infections

The use of antibiotic prophylaxis to avoid infections is a prerequisite for most surgical procedures today although evidence is scarce. Importance has increased over time as more elderly and immunocompromised patients are undergoing more advanced surgical procedures. The aim of antibiotic prophylaxis is to achieve, during the entire operation, a bactericidal antibiotic concentration in the tissue that may be contaminated, targeting the most common pathogens unique for the surgical procedure, thereby preventing surgical site infections (SSI) and SSI-related morbidity and mortality. Preferably, the drug of choice should be of the narrowest spectrum, with a minimum of adverse effects and with no negative consequences for the microbial flora for the patient or the hospital.

Current best practice for antibiotic prophylactic regimens

For most clean and clean-contaminated surgical procedures, cefazolin, a 1st generation cephalosporine, is widely studied and the drug of choice for prophylaxis internationally. Cefazolin has a reasonable safety profile, low cost, proven efficacy, desirable duration of action and a broad spectrum of activity against organisms encountered in surgery.

The most common pathogens causing SSIs after clean procedures stem from the skin flora, mainly *Staphylococcus aureus* and coagulase-negative staphylococci. In clean-contaminated procedures, including abdominal procedures and heart, kidney, and liver transplantations, the predominant organisms are Gram-negative rods and enterococci in addition to skin flora, and anaerobes in colorectal procedures. For the latter, 2nd or 3rd generation cephalosporins together with metronidazole are recommended internationally.

For most procedures, one preoperative dose, usually given within 30-60 minutes of the incision, has been found equally effective as multiple-dose regimens. A strong recommendation for prophylaxis relates to clean-contaminated procedures. In clean procedures with low infection rates, prophylaxis is recommended for procedures where the consequences of an infection are particularly severe – e.g, in prosthetic implant surgery (1). Dosing must be repeated during surgery if the duration of the operation exceeds two half-lives of the antibiotic used or if excessive bleeding occurs (2).

Comparative studies of antimicrobial agents are in general hampered by small sample sizes, and significant differences between antimicrobial agents are difficult to detect. In most guidelines, the choice of antimicrobial agents is therefore based on cost, safety profile, ease of administration, pharmacokinetic profile and microbiological activity.

Importance of the increase in multiresistant bacteria

The microbial spectrum in SSIs and, more importantly, the susceptibility pattern of causative microorganisms has changed over the past two decades. Guidelines for antimicrobial prophylaxis against SSIs are partly based on older studies when multi-drug resistant organisms (MDRO) were less prevalent. Individual hospitals, especially large institutions performing specialised surgery on high-risk patients, need to develop local guidelines that reflect the local antimicrobial resistance pattern and their MDRO distribution (2).

This may be exemplified by the guidelines for SSI prophylaxis for transrectal prostate biopsies. European Association of Urology recommends on equal terms 2nd and 3rd generation cephalosporins, fluoroquinolones and trimethoprim-sulphamethoxazole (TMP-SMX) as prophylaxis, the drug of choice to be based on the local pathogen profile and antibiotic susceptibility patterns. *Escherichia coli* is most commonly isolated in blood cultures in urological postoperative infections. NORM-data from 2016 show resistance rates for cefuroxime 9.4%, cefotaxime 6%, ciprofloxacin 12.6% and TMP-SMX 25.8% for E. coli in blood cultures. At which point should TMP-SMX be reconsidered as the drug of choice in prostate biopsies in Norwegian guidelines?

Norwegian practice differs from international guidelines

Cefalotin dominates in Norwegian surgical prophylaxis probably because the internationally preferred 1st generation cephalosporin, cefazolin, was registered only recently for use in Norway. The Norwegian national antibiotic guideline from 2013 (3) is long overdue for a full revision to be initiated by the Norwegian Directorate of Health. One urgent task will be to change recommendations for SSI prophylactic regimens from cefalotin, which must be re-dosed every 90 minutes, to cefazolin which is longer-acting, cheaper, and has an identical spectrum of activity.

In Norway, doxycycline is the preferred regimen for many procedures involving the gastrointestinal tract instead of 2nd or 3rd generation cephalosporins. In addition, metronidazole is given for anaerobic coverage. This recommendation is based on a 35-year-old prospective, controlled Norwegian study (4). In a recent study from Tromsø adequate serum-levels of doxycycline above ECOFF were found for common *Enterobacteriaceae* species in only half of the patients receiving the regime (5). There are no established tetracycline susceptibility breakpoints in EUCAST or CLSI for *Enterobacteriaceae*. Unpublished data from NORM shows that in 22.7% of *E. coli* blood culture isolates from 2017, no zone diameter with disc testing is established for tetracycline. The official Norwegian regimen for intestinal SSI prophylaxis thus appears to target *Enterobacteriaceae* only incompletely. Further studies should be performed.

Are the adverse effects of prophylactic antibiotics for SSI underestimated?

For many clean and clean-contaminated procedures, antibiotic prophylaxis recommendations against SSIs are based on a low grade of evidence or expert opinion. Some guidelines put little emphasis on the potential harm of irrational antibiotic use, for example when "prolonged" prophylaxis is being administered – just in case.

Even short-term antibiotic prophylactic regimens may cause intestinal disturbances and allergic reactions. More serious is the patient`s risk of acquiring multiresistant bacteria or antibiotic-induced *Clostridium difficile* infections due to changes in the colon microbiome. A publication from 2015 showed that even a single antibiotic treatment in healthy individuals might contribute to resistance development and lead to long-lasting shifts in the intestinal flora (6).

Moreover, due to the large numbers of surgical procedures, a potential negative ecological impact of even single prophylactic antibiotic doses may be underestimated. Cefalotin is used almost exclusively for SSI prophylaxis in Norway – often dosed as 2 g qid. From Norwegian hospital antibiotic surveillance data 2012 – February 2018 (unpublished data), a ranking of antibiotic generic substances according to their total amount in defined daily doses (DDDs) shows that cefalotin ranks as number five. When adjusting DDDs for doses used in hospitals, where the penicillins are administered in much higher daily doses than defined by the WHO DDD system (7), cefalotin ranks as the third most commonly used antibiotic substance after benzylpenicillin and cefotaxime. Doxycycline, also little used in hospitals other than for SSI prophylaxis, ranks as the 11th and 9th most used antibiotic using WHO DDDs and hospital-adjusted DDDs, respectively. One aspect of this extensive use is that any change in recommendations toward more broad-spectrum antibiotics for SSI prophylaxis may constitute a substantial driver for increased antibiotic resistance.

Future challenges

Present guidelines are based on research that needs to be repeated and extended due to recent changes in microbial flora and susceptibility patterns, more elderly and multimorbid patients in our hospitals, and because risks and negative consequences of antibiotic SSI prophylaxis may have been underestimated. Closer collaboration between surgeons and microbiological and infectious disease clinical teams is desirable. Antibiotic stewardship teams active in all Norwegian Health Trusts should be attentive to SSI prophylaxis with respect to incorrect use, overuse, and sound indications for changes in regimens. Finally, the Norwegian antibiotic guideline should be updated on a regular basis, according to intentions stated in the first published version.

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Klebsiella spp. in blood cultures

TABLE 29. *Klebsiella* spp. blood culture isolates in 2017 (n=884). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amoxicillin-clavulanic acid	≤ 8	> 8	83.6	-	16.4
Piperacillin-tazobactam	≤ 8	> 16	87.1	8.8	4.1
Cefotaxime	≤ 1	> 2	94.0	0.6	5.4
Ceftazidime	≤ 1	> 4	93.0	1.9	5.1
Cefepime	≤ 1	> 4	91.1	2.9	6.0
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 4	96.7	0.1	3.2
Ciprofloxacin	≤ 0.25	> 0.5	82.5	5.2	12.3
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	85.7	0.3	14.0
Tigecycline	≤ 1	> 2	88.1	9.7	2.1
ESBL	Negative	Positive	94.7	-	5.3

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 30. *Klebsiella pneumoniae* blood culture isolates in 2017 (n=685). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amoxicillin-clavulanic acid	≤ 8	> 8	82.9	-	17.1
Piperacillin-tazobactam	≤ 8	> 16	87.0	10.1	2.9
Cefotaxime	≤ 1	> 2	93.6	0.1	6.3
Ceftazidime	≤ 1	> 4	91.8	1.9	6.3
Cefepime	≤ 1	> 4	90.8	2.9	6.3
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 4	95.9	0.0	4.1
Ciprofloxacin	≤ 0.25	> 0.5	79.4	6.0	14.6
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	83.1	0.4	16.5
Tigecycline	≤ 1	> 2	86.3	11.5	2.2
ESBL	Negative	Positive	93.4	-	6.6

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 31. *Klebsiella oxytoca* blood culture isolates in 2017 (n=156). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amoxicillin-clavulanic acid	≤ 8	> 8	84.6	-	15.4
Piperacillin-tazobactam	≤ 8	> 16	87.8	2.6	9.6
Cefotaxime	≤ 1	> 2	94.2	2.6	3.2
Ceftazidime	≤ 1	> 4	96.1	2.6	1.3
Cefepime	≤ 1	> 4	90.4	3.2	6.4
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	99.4	0.6	0.0
Ciprofloxacin	≤ 0.25	> 0.5	94.3	1.9	3.8
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	95.5	0.0	4.5
Tigecycline	≤ 1	> 2	96.8	2.6	0.6
ESBL	Negative	Positive	98.7	-	1.3

*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 685 *K. pneumoniae* (77.5%), 156 *K. oxytoca* (17.6%), and 43 (4.9%) isolates not identified to the species level, giving a total of 884 *Klebsiella* spp. isolates (Tables 29-31).

The majority of *Klebsiella* spp. isolates remains susceptible to aminoglycosides. The prevalence of non-susceptibility was 3.3% in 2017 compared to 3.5% in 2016. *K. oxytoca* isolates are more often susceptible to aminoglycosides (99.4%) than *K. pneumoniae* isolates (95.9%). Aminoglycoside resistance in common *Enterobacteriaceae* species is a cause for great concern as these antimicrobials have traditionally been used in the empirical regimen for treatment of septiceamia 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 data from previous years have been updated according to the 2018 protocol, but results earlier than 2012 cannot be recategorised due to changes in susceptibility testing methodology. The overall prevalence of non-susceptibility to ciprofloxacin has been stable at 13-16% when taking into account the changes in breakpoints and interpretive criteria. However, the 17.5% non-susceptibility (5.2% intermediate susceptibility and 12.3% resistance) observed in 2017 is a significant increase from 13.1% in 2015 and 15.5% in 2016. Non-susceptibility to ciprofloxacin is much more common in *K. pneumoniae* (20.6%) than in *K. oxytoca* (5.7%).

Non-susceptibility to trimethoprim-sulfamethoxazole increased to 14.3% compared to 10.4% in 2015 and 12.0% in 2016. As for ciprofloxacin, the prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (4.5%) than in *K. pneumoniae* (16.5%).

A comparison of non-susceptibility 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 to cefotaxime (94.0%), ceftazidime (93.0%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (87.1%), see Figure 65. The rates of non-susceptibility to 3rd generation cephalosporins were at the same level as in previous years.

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 2.9% in 2015 and 4.6% 2016, to 5.3% in 2017 (Figure 64). The 47 ESBL isolates originated from 17 different laboratories and were identified as *K. pneumoniae* (n=45, 6.6%) and *K. oxytoca* (n=2, 1.3%). The ESBL isolates were generally non-susceptible to ceftazidime (45/47), cefotaxime (45/47) and cefepime (45/47), and co-resistance was frequently seen for ciprofloxacin (38/45), trimethoprim-sulfamethoxazole (41/45) and gentamicin (26/47). Many isolates were intermediately (18/47) or even fully (20/47) susceptible to piperacillin-tazobactam, and most (34/47) were susceptible to tigecycline. A single isolate was resistant to meropenem and contained both NDM and OXA-48 like enzymes. In addition, a large number of isolates were positive by the EUCAST screening breakpoints but were not confirmed as carbapenemase producers.

Molecular characterisation of 42 *K. pneumoniae* isolates with a phenotypic ESBL profile at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-Res) confirmed the predominance of CTX-M groups 1 (n=34) and 9 (n=5). Single isolates contained non-CTX-M ESBL (n=1) or DHA (n=1) beta-lactamases, or displayed SHV hyperproduction. One *K. oxytoca* isolate harboured a CTX-M group 1 enzyme, whereas two additional isolates were K1 hyper-producers. No genetic determinants for carbapenemases were detected.

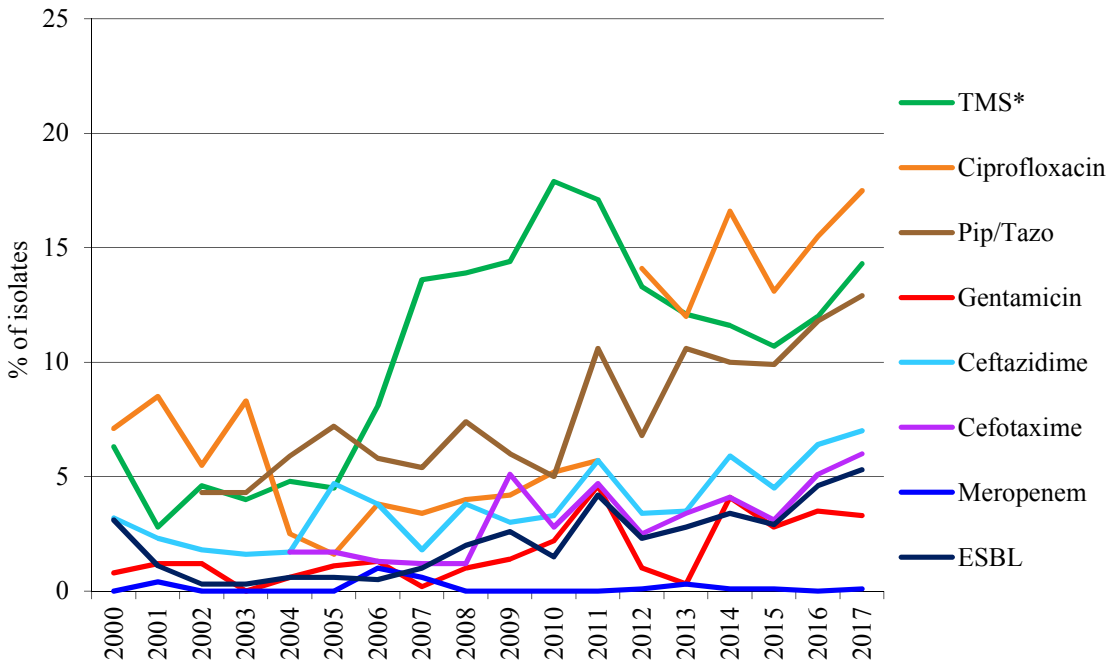

FIGURE 65. Prevalence of non-susceptibility to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2017. The breakpoint for ciprofloxacin resistance was changed from R > 1 mg/L to R > 0.5 mg/L in 2017. Data from 2012-2016 have been recategorised according to the new breakpoint, but earlier results (2000-2011) cannot be calibrated due to changes in methodology in 2012. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 32. *Klebsiella* spp. urinary tract isolates in 2017 (n=952). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	90.5	-	9.5
Amoxicillin-clavulanic acid*	≤ 32	> 32	91.5	-	8.5
Piperacillin-tazobactam	≤ 8	> 16	90.1	6.3	3.6
Cefotaxime	≤ 1	> 2	95.8	0.2	4.0
Ceftazidime	≤ 1	> 4	94.5	1.7	3.8
Cefepime	≤ 1	> 4	94.0	2.5	3.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.0	0.6	2.4
Ciprofloxacin	≤ 0.25	> 0.5	88.8	3.4	7.9
Trimethoprim	≤ 2	> 4	80.8	1.2	18.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	86.7	0.8	12.5
ESBL	Negative	Positive	96.3	-	3.7

*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 2012-2016. 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. breakpoints for nitrofurantoin. The rates of resistance to urinary tract antibiotics were slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Tables 32-34). The majority of isolates are still susceptible to gentamicin (97.0% compared to 97.1% in 2016). Among urinary tract *E. coli*, 95.3% were susceptible to gentamicin in 2017. When adjusting for changes in ciprofloxacin breakpoints, the rates of non-susceptibility in *Klebsiella* spp. have remained stable at 11.0% in 2015, 13.9% in 2016 and 11.3% in 2017 (3.4% intermediate susceptibility and 7.9% resistance). The comparable rate for urinary tract *E. coli* in

2017 was 12.5% (2.3% intermediate susceptibility and 10.2% resistance). Susceptibility to trimethoprim (80.8% in 2017 compared to 81.2% in 2016) and trimethoprim-sulfamethoxazole (86.7% in both 2016 and 2017) was higher than in *E. coli* (79.0% in 2017). There are no EUCAST breakpoints for fosfomycin in *Klebsiella*. Our data may indicate that the *E. coli* breakpoints are not suitable for *Klebsiella* (79.2% 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 non-susceptibility to cefotaxime and/or ceftazidime and subsequent confirmatory ESBL MIC gradient tests. Thiry-five isolates were reported as ESBL positive of which 34 were *K. pneumoniae* and one was *K. oxytoca*. The 35 ESBL isolates were retrieved from 15 different laboratories and originated from general practices (n=18), hospitals (n=13), outpatient clinics (n=1), nursing homes (n=2) and unknown location (n=1). The 3.7% ESBL rate (4.6% in *K. pneumoniae*) was at the same level as in 2016 (3.8% for all *Klebsiella*, 4.8% in *K. pneumoniae*). The 35 ESBL isolates were generally non-susceptible to trimethoprim (n=30), trimethoprim-sulfa-methoxazole (n=30) and ciprofloxacin (n=30), but many remained susceptible to gentamicin (n=16), mecillinam (n=32) and piperacillin-tazobactam (n=22).

All isolates were susceptible to meropenem according to the clinical breakpoints, and no carbapenemase-producing isolates were detected by the screening breakpoint.

TABLE 33. *Klebsiella pneumoniae* urinary tract isolates in 2017 (n=740). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	91.6	-	8.4
Amoxicillin-clavulanic acid*	≤ 32	> 32	94.2	-	5.8
Piperacillin-tazobactam	≤ 8	> 16	91.0	7.0	2.0
Cefotaxime	≤ 1	> 2	95.3	0.1	4.6
Ceftazidime	≤ 1	> 4	93.3	2.2	4.5
Cefepime	≤ 1	> 4	93.7	2.4	3.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.5	0.5	3.0
Ciprofloxacin	≤ 0.25	> 0.5	86.7	4.2	9.1
Trimethoprim	≤ 2	> 4	78.4	1.2	20.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.1	0.8	14.1
ESBL	Negative	Positive	95.4	-	4.6

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

TABLE 34. *Klebsiella oxytoca* urinary tract isolates in 2017 (n=133). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	88.7	-	11.3
Amoxicillin-clavulanic acid*	≤ 32	> 32	87.2	-	12.8
Piperacillin-tazobactam	≤ 8	> 16	85.0	1.5	13.5
Cefotaxime	≤ 1	> 2	96.2	0.8	3.0
Ceftazidime	≤ 1	> 4	98.5	0.0	1.5
Cefepime	≤ 1	> 4	94.0	3.0	3.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	99.2	0.8	0.0
Ciprofloxacin	≤ 0.25	> 0.5	98.5	0.0	1.5
Trimethoprim	≤ 2	> 4	94.0	0.0	6.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.5	0.0	4.5
ESBL	Negative	Positive	99.2	-	0.8

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

Temporal and regional trends in gentamicin resistance in *Enterobacteriaceae* in Norway

Aminoglycosides are part of the empirical treatment regimen against serious infections caused by aerobic Gram-negative bacilli in Norway. Thus, the increasing prevalence of gentamicin resistance in common *Enterobacteriaceae* reported by the NORM surveillance program is of great concern. Continuous development of epidemiological knowledge can improve our understanding and control of the resistance problem. This is the first report on temporal and regional trends in gentamicin resistance prevalence in *Enterobacteriaceae* in Norway.

Routine data on gentamicin non-susceptibility (intermediate susceptibility and resistance) among *Escherichia coli* and *Klebsiella pneumoniae* blood culture isolates from primary diagnostic laboratories in Norway in 2011-17 were collected as part of the EARS-Net (European Antimicrobial Resistance Surveillance Network) collaboration. Altogether 19 Norwegian laboratories reported data for at least one year within the time period. Total number of *E. coli* and *K. pneumoniae* blood culture isolates tested for gentamicin sensitivity and number of participating laboratories per year from each health region are presented in tables.

TABLE 35. Proportions of intermediate susceptibility and resistance to gentamicin among *Escherichia coli* blood culture isolates in Norway 2011-2017 by health region (South-East is shown as East and South, separately). Number of laboratories per region is given in brackets.

Region	2011	2012	2013	2014	2015	2016	2017	*P-trend**
East	53/1095 (5**)	74/1140 (5)	76/1112 (5)	89/1242 (5)	70/1067 (4)	68/1158 (4)	81/1042 (4)	*0.075*
South	20/399 (2)	24/436 (3)	29/477 (3)	44/471 (3)	40/498 (3)	39/605 (4)	67/720 (4)	*0.049*
West	14/204 (2)	33/541 (3)	34/556 (3)	39/711 (4)	46/706 (4)	47/806 (4)	50/880 (4)	*0.63*
Mid	10/417 (4)	18/397 (4)	32/478 (4)	24/507 (4)	28/500 (4)	29/575 (4)	40/608 (4)	*0.025*
North	3/168 (2)	15/312 (2)	13/332 (2)	15/349 (2)	18/322 (2)	11/312 (2)	21/358 (2)	*0.15*
Norway	100/2283	164/2826	184/2955	211/3280	202/3093	194/3456	259/3608	*0.001*

*Chi-square test for slope. East: *P trend 0.11* when limited to the four laboratories with consistent reporting in 2011-17. South: *P trend 0.007* when limited to the three laboratories with consistent reporting in 2012-17. West: *P trend 0.82* when limited to the three laboratories with consistent reporting in 2012-17. Norway: *P trend 0.12* when limited to laboratories with consistent reporting in 2012-17. **Data from Oslo University Hospital Aker and Ullevål were merged.

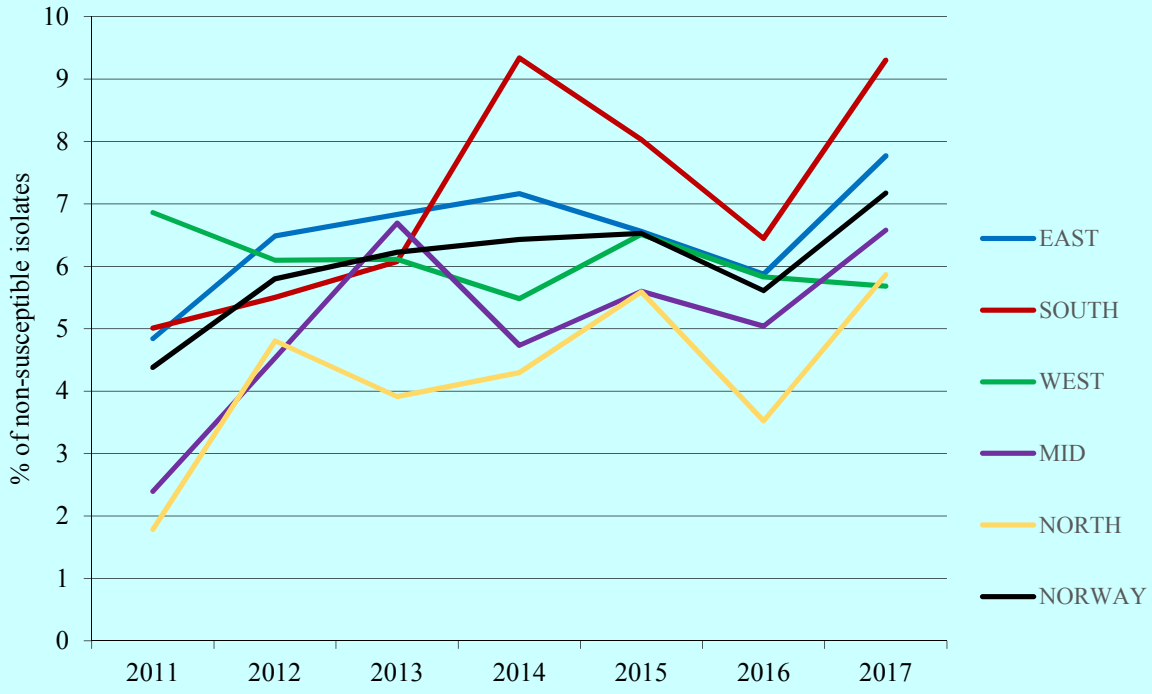

FIGURE 66. Proportion of *Escherichia coli* blood culture isolates reported as gentamicin non-susceptible (intermediate susceptibility and resistance) in Norway 2011-2017 by health region.

There was a statistically significant increase in the overall prevalence of gentamicin non-susceptibility in *E. coli* blood culture isolates in Norway from 4.4% in 2011 to 7.2% in 2017 (*P for trend* 0.001). This growing trend was seen for all health regions apart from West Norway, which had a stable and relatively high prevalence at about 6%. Health region South had the steepest increase in prevalence; from 5.0% in 2011 to 9.3% in 2017 (*P for trend* 0.049), followed by Mid and North (*P for trend* 0.025 and 0.15, respectively). There was a North-South gradient with gentamicin non-susceptibility in *E. coli* being less frequent in the northernmost regions for most of the years during 2011-2017.

For *K. pneumoniae* blood culture isolates, the overall national prevalence of gentamicin non-susceptibility was 3.1% in 2011 and 3.9% in 2017 (*P for trend* 0.26) with a maximum of 5.6% in 2014. The prevalence increased in health region South from 1.5% in 2011 to 4.1% in 2017 (*P for trend* 0.029) and North from 4.3% in 2011 to 7.9% in 2017 (*P for trend* 0.11). There was a fluctuating prevalence pattern for all health regions during 2011-2017. However, the prevalence curve for health region North was clearly on top for the last five years. Importantly, due to low number of observations per health region, careful interpretation of these data is required.

TABLE 36. Proportions of intermediate susceptibility and resistance to gentamicin among *Klebsiella pneumoniae* blood culture isolates in Norway 2011-2017 by health region (South-East is shown as East and South, separately). Number of laboratories per region is given in brackets.

Region	2011	2012	2013	2014	2015	2016	2017	*P-trend**
East	5/189 (5**)	11/237 (5)	7/240 (5)	20/281 (5)	7/196 (4)	4/239 (4)	8/218 (4)	*0.078*
South	1/66 (2)	0/97 (2)	2/90 (2)	3/105 (3)	2/110 (3)	8/169 (4)	7/172 (4)	*0.029*
West	3/38 (2)	2/133 (3)	0/118 (3)	8/167 (4)	9/174 (4)	3/172 (4)	3/162 (4)	*0.69*
Mid	2/67 (4)	0/65 (3)	2/82 (4)	2/88 (3)	3/95 (4)	1/129 (4)	6/140 (4)	*0.42*
North	1/23 (1)	0/60 (2)	6/82 (2)	8/92 (2)	4/80 (2)	8/80 (2)	6/76 (2)	*0.11*
Norway	12/383	13/592	17/612	41/733	25/655	24/789	30/768	*0.26*

*Chi-square test for slope. East: *P trend 0.41* when limited to the four laboratories with consistent reporting in 2011-17. South: *P trend 0.32* when limited to the two laboratories with consistent reporting in 2011-2017. West: *P trend 0.55* when limited to the three laboratories with consistent reporting in 2012-2017. Mid: *P trend 0.35* when limited to the three laboratories with consistent reporting in 2011-2017. North: *P trend 0.12* when limited to 2012-2017. Norway: *P trend 0.22* when limited to laboratories with consistent reporting in 2012-2017. **Data from Oslo University Hospital Aker and Ullevål were merged.

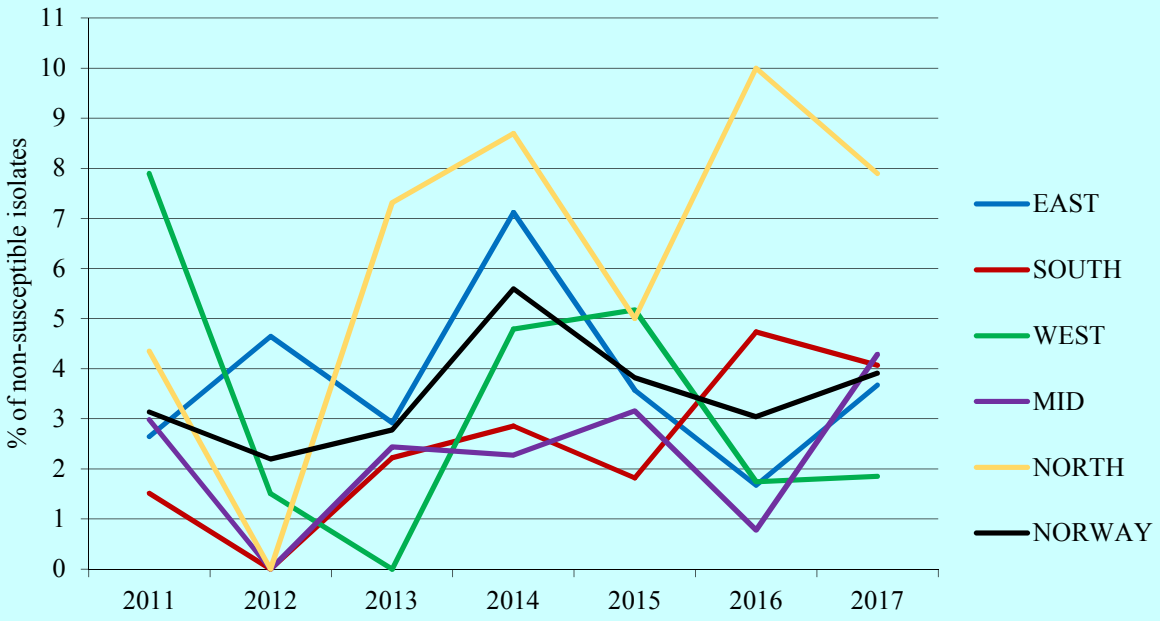

FIGURE 67. Proportion of *Klebsiella pneumoniae* blood culture isolates reported as gentamicin non-susceptible (intermediate susceptibility and resistance) in Norway 2011-2017 by health region.

In conclusion, blood culture surveillance data show an increase in the prevalence of gentamicin resistance in *E. coli* in Norway during 2011-2017 and regional differences in prevalence. Data on prevalence of gentamicin resistance in *K. pneumoniae* are more difficult to interpret due to low number of observations, although some regional differences were relatively consistently present during 2011-2017. Future studies should include more detailed data on the microbes and risk factors in order to understand potential drivers of these changes in gentamicin resistance in *Enterobacteriaceae* over time and across regions.

Anne-Sofie Furberg, NORM, University Hospital of North Norway and UiT – The Arctic University of Norway, Tromsø, and Frode Width Gran, St. Olav University Hospital, Trondheim, Norway.

Proteus spp. in blood cultures

TABLE 37. *Proteus* spp. blood culture isolates in 2017 (n=192). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	78.6	-	21.4
Amoxicillin-clavulanic acid	≤ 8	> 8	94.8	-	5.2
Piperacillin-tazobactam	≤ 8	> 16	99.5	0.5	0.0
Cefotaxime	≤ 1	> 2	99.0	0.0	1.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Cefepime	≤ 1	> 4	96.9	2.1	1.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	95.8	1.6	2.6
Ciprofloxacin	≤ 0.25	> 0.5	91.1	1.6	7.3
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	82.9	1.0	16.1
ESBL	Negative	Positive	99.5	-	0.5

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Proteus spp. blood culture isolates have previously not been included in the NORM surveillance programme. The present survey covered all consecutive blood culture isolates in Norway in the first nine months of 2017 identified as *Proteus mirabilis* (n=179), *Proteus vulgaris* (n=11) and *Proteus* spp. (n=2). Due to the predominance of *P. mirabilis*, all 192 isolates are analysed as a single group. The results are presented in Table 37.

The prevalence of resistance to ampicillin (21.4%) was significantly lower than in *E. coli* blood culture isolates (44.1%). Similarly, resistance to trimethoprim-sulfamethoxazole (16.1%) was lower than in *E. coli* (25.3%), but at the same level as in *Klebsiella* spp. (14.0%). The prevalence of non-susceptibility to ciprofloxacin was 8.9% (1.6% I and 7.3% R) compared to 18.0% in *E. coli* and 17.7% in *Klebsiella* spp.

The vast majority of isolates were susceptible to beta-lactam/beta-lactamase inhibitor combinations (amoxicillin-clavulanic acid (94.8%), piperacillin-tazobactam (99.5%) and broad-spectrum cefalosporins (cefepime (96.9%), cefotaxime (99.0%), and ceftazidime (100.0%)). A single isolate was confirmed as an ESBL producer. In total, eight isolates (4.2%) were intermediately susceptible (n=3) or resistant (n=5) to gentamicin. All isolates were fully susceptible to meropenem. *Proteus* spp. are inherently resistant to tigecycline.

Proteus spp. in urine

TABLE 38. *Proteus* spp. urinary tract isolates in 2017 (n=433). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	78.5	-	21.5
Mecillinam	≤ 8	> 8	88.7	-	11.3
Amoxicillin-clavulanic acid	≤ 32	> 32	96.1	-	3.9
Cefotaxime	≤ 1	> 2	99.8	0.0	0.2
Ceftazidime	≤ 1	> 4	99.8	0.0	0.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.3	0.9	2.8
Ciprofloxacin	≤ 0.25	> 0.5	94.5	0.7	4.8
Trimethoprim	≤ 2	> 4	62.6	5.3	32.1
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	83.8	1.4	14.8
ESBL	Negative	Positive	99.8	-	0.2

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 39. *Proteus mirabilis* urinary tract isolates in 2017 (n=357). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	85.2	-	14.8
Mecillinam	≤ 8	> 8	91.3	-	8.7
Amoxicillin-clavulanic acid	≤ 32	> 32	99.2	-	0.8
Cefotaxime	≤ 1	> 2	99.7	0.0	0.3
Ceftazidime	≤ 1	> 4	99.7	0.0	0.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.4	1.1	2.5
Ciprofloxacin	≤ 0.25	> 0.5	93.9	0.8	5.3
Trimethoprim	≤ 2	> 4	67.5	4.8	27.7
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	85.3	0.6	14.3
ESBL	Negative	Positive	99.7	-	0.3

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 40. *Proteus vulgaris* urinary tract isolates in 2017 (n=29). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
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
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Trimethoprim	≤ 2	> 4	55.2	0.0	44.8
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	89.7	3.4	6.9
ESBL	Negative	Positive	100.0	-	0.0

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

Urinary tract *Proteus mirabilis* isolates were previously surveyed by NORM in 2006, but due to changes in breakpoints and susceptibility test methodology, it is impossible to compare directly with the results from 2017. A total of 433 isolates consisting of 357 *Proteus mirabilis*, 29 *Proteus vulgaris*, and 47 isolates not identified to the species level, were included. Most of the isolates were recovered from samples submitted by general practitioners (n=253), hospital wards (n=93) or nursing homes (n=63).

Table 38 presents data for all *Proteus* isolates interpreted according to the *P. mirabilis* breakpoints. Most isolates are susceptible to ampicillin (78.5%) and mecillinam (88.7%), and this is even more pronounced at the species level for *P. mirabilis* as presented in Table 39 (85.2% and 91.3%, respectively). There are no breakpoints for these antibiotics in *P. vulgaris* (Table 40). Almost all *Proteus* isolates were susceptible to cefalosporins and only a single ESBL-producing *P. mirabilis* isolate was detected. All isolates were susceptible to meropenem.

The prevalence of resistance to trimethoprim was generally higher (32.1%) than in *E. coli* (23.0%) and *Klebsiella* spp. (18.1%) urinary tract isolates, but the difference was smaller for trimethoprim-sulfamethoxazole (14.8% versus 20.5% in *E. coli* and 12.5% in *Klebsiella* spp., respectively). Non-susceptibility to ciprofloxacin was lower in *Proteus* spp. (5.5%) than in *E. coli* (12.5%) and *Klebsiella* spp. (11.3%). All *P. vulgaris* isolates were fully susceptible to quinolones. There are no EUCAST breakpoints for nitrofurantoin and fosfomycin in *Proteus* spp.

The isolates from nursing homes were generally more resistant to ampicillin (28.6%) and ciprofloxacin (9.5%) than isolates submitted by general practicioners (ampicillin 20.6% and ciprofloxacin 4.0%) or hospital wards (ampicillin 21.5% and ciprofloxacin 3.2%). For the other antibiotics there were only minor differences.

The current situation of carbapenemase-producing Gram-negative bacteria in Norway

Carbapenem resistant *Enterobacterales*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are classified by The World Health Organization as "critical" in terms of research, discovery and the development of new antibiotics (1). Carbapenem resistance can be caused by a variety of mechanisms including reduced permeability (loss or changes in porins) and/or efflux mechanisms, frequently in combination with ESBL or AmpC beta-lactamases, and carbapenemases (2). Carbapenemases are of particular concern as the carbapenemase genes are located on mobile genetic elements (e.g. plasmids) that increase the potential for horizontal spread and rapid dissemination (2). Moreover, infections with carbapenemase-producing Gram-negative bacteria are associated with high mortality rates due to limited treatment options (3). Consequently, the rapid global dissemination of carbapenemase-producing organisms is considered a significant threat to patients and healthcare systems (4).

In Norway, carbapenemase-producing bacteria are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) after confirmation at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-res). Here we summarise the findings of carbapenemase-producing Gram-negative bacteria in 2017. Isolates from the same patient are included if they were of different species and/or harboured different carbapenemase variants.

In 2017, thirty-five patients were identified with carbapenemase-producing *Enterobacterales* which is similar to 2015 (n=30) and 2016 (n=33) (Figure 68). In total 42 isolates were identified, as seven patients harboured two isolates each, that where either of different species or the same species but with different carbapenemase gene content. As in 2016, equal number of carbapenemase-producing *Escherichia coli* (n=19) and *Klebsiella pneumoniae* (n=19) isolates were identified in 2017 (Figure 69). Two carbapenemase-producing *Enterobacter cloacae* complex and single isolates of carbapenemase-producing *Providencia stuartii* and *Citrobacter* spp. were also identified.

The trend for an increasing proportion of OXA-48-like carbapenemases continued in 2017, as 22 isolates were identified harbouring the OXA-48-like gene (Figure 70). Moreover, four isolates were identified harbouring both NDM and OXA-48-like carbapenemases. Nine, six and one isolate were identified harbouring NDM, KPC and VIM, respectively.

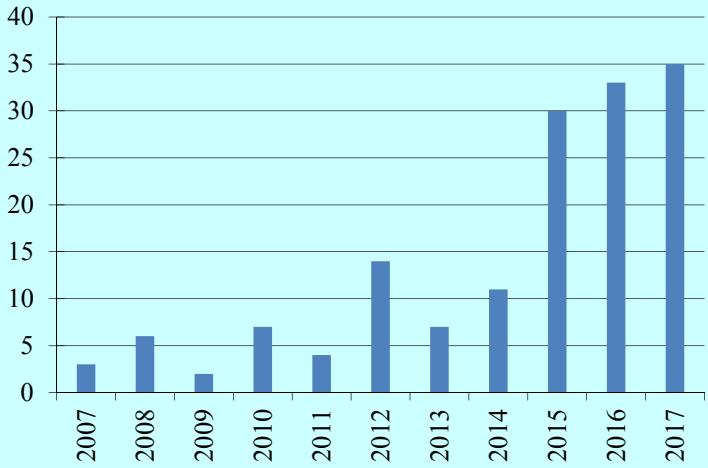

FIGURE 68. Number of patients identified with carbapenemase-producing *Enterobacterales* 2007-2017.

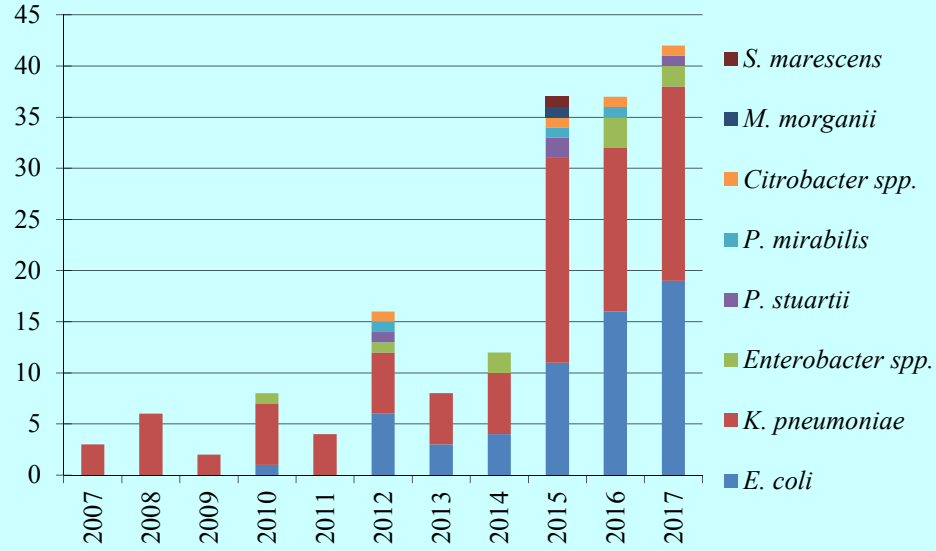

FIGURE 69. Number of carbapenemase-producing *Enterobacterales* isolates according to species.

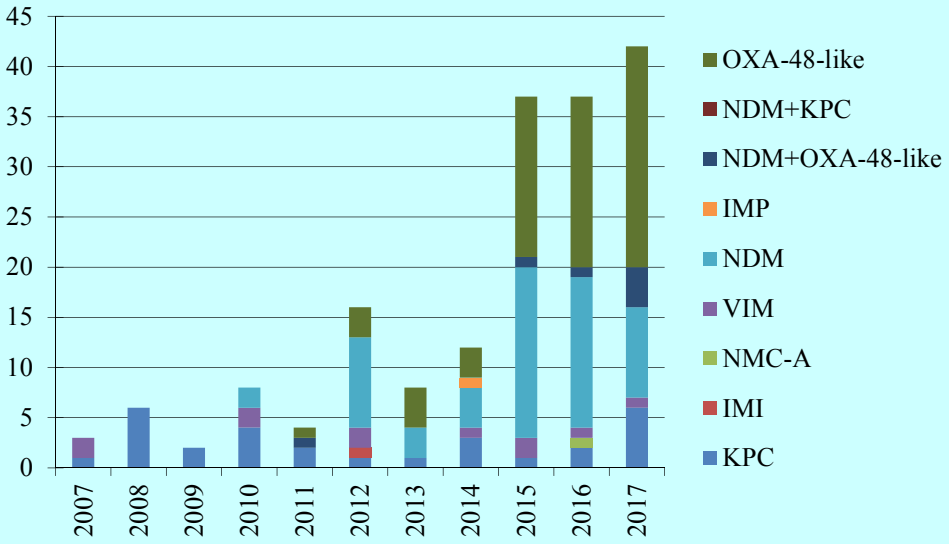

FIGURE 70. Number of carbapenemase-producing *Enterobacterales* isolates according to carbapenemase variant.

Analysis of data submitted to MSIS revealed that in 23 (66%) of the cases there was an association with cross-border infection (reported infected abroad/hospitalisation abroad within the last 12 months) (Figure 71). The imported cases were associated with a diversity of countries with India (n=5), Spain (n=3) and Thailand (n=2) as the only countries associated with more than one case. For five cases (14%), no association with travel abroad was identified and for seven cases (20%), travel history was unknown. Interestingly, all five cases associated with domestic acquisition were OXA-48-like-producing *E. coli*, from five different laboratories, different municipalities of residence and were identified in different months (January, May, June, July and September). Moreover, four of the cases with an unknown import status were also OXA-48-like-producing *E. coli*. This might indicate that OXA-48-like-producing *E. coli* are present in the community in Norway, but further investigations are required.

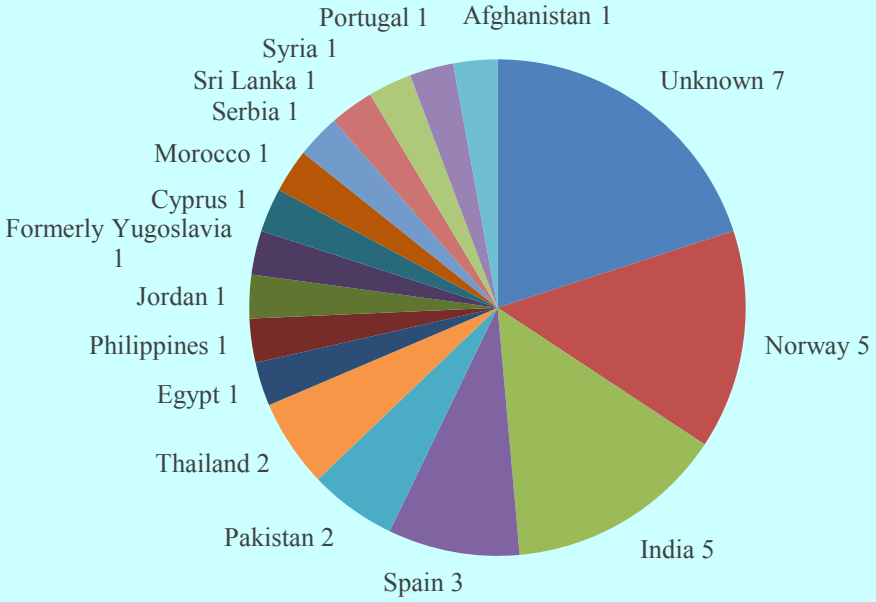

FIGURE 71. Association with infection abroad for cases (*n*) of carbapenemase-producing *Enterobacterales* in Norway 2017.

In 2017, ten cases of carbapenemase-producing *Acinetobacter* spp. (n=8) and *Pseudomonas* spp. (n=2) were identified, respectively (Figure 72). This is less than half the number of cases reported in 2016 (n=21). The reason for the lower number of cases in 2017 is unclear. Seven of the eight *Acinetobacter* cases were OXA-23-like-producing *A. baumannii* and five were associated with import from Thailand (n=3), Turkey (n=1) and Albania (n=1). For two isolates the import status was unknown. Interestingly, one NDM-producing *Acinetobacter* spp. non-*baumannii* was identified in 2017 with no travel history abroad. Both cases of carbapenemase-producing *Pseudomonas* spp. were associated with import (Syria and Spain) and harboured the carbapenemases VIM and IMP, respectively.

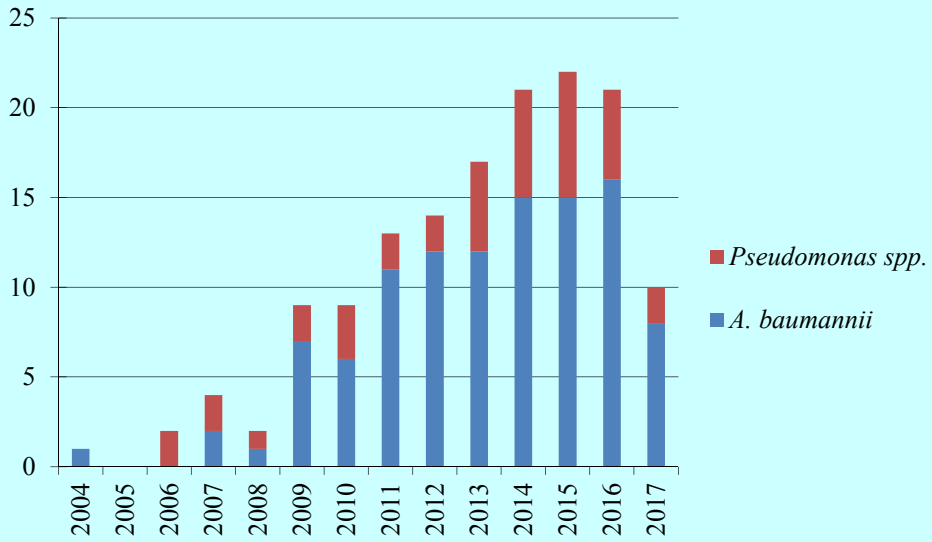

FIGURE 72. Identified carbapenemase-producing *Pseudomonas* spp. and *Acinetobacter* spp. in Norway 2004-2017.

In conclusion, the number of carbapenemase-producing Gram-negative bacteria in Norway is still low although there has been a clear increase observed in the last three years. However, the proportionally high number of OXA-48-producing *E. coli* without a travel history abroad in 2017 requires further investigation. Continued surveillance, antibiotic stewardship, strict infection control measures as well as high clinical and diagnostic awareness is important to prevent and control domestic spread.

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1. World Health Organization (WHO). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017; http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
2. Logan LK. and Weinstein RA. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. J. Infect. Dis. 2017;215(suppl_1):S28-S36
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4. European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenem-resistant *Enterobacteriaceae* – 8 April 2016. Stockholm:ECDC; 2016.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 41. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2017 (n=118). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 1	> 1	77.1	-	22.9
Amoxicillin-clavulanic acid	≤ 2	> 2	94.5	-	5.1
Cefuroxime	≤ 1	> 2	78.8	5.1	16.1
Cefotaxime	≤ 0.125	> 0.125	98.3	-	1.7
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Meropenem	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin	≤ 0.06	> 0.06	100.0	-	0.0
Chloramphenicol	≤ 2	> 2	98.3	-	1.7
Tetracycline	≤ 1	> 2	97.5	0.0	2.5
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 1	81.4	3.4	15.3
Beta-lactamase	Negative	Positive	82.2	-	17.8

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 42. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2017 (n=118). Distribution (%) of MICs (mg/L) and zone diameters for penicillin G and cefaclor (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Ampicillin							34.7	32.2	10.2	4.2	0.8	0.8	0.8	3.4		12.7
Amoxi-clav**							10.2	45.8	24.6	14.4	4.2	0.8				
Cefuroxime			0.8				0.8	31.4	45.8	5.1	4.2	8.5	1.7	1.7		
Cefotaxime		9.3	42.4	30.5	11.9	4.2		1.7								
Ceftriaxone	56.8	25.4	13.6	3.4		0.8										
Meropenem			0.8	19.5	39.0	32.2	6.8	1.7								
Ciprofloxacin	10.2	45.8	42.4	1.7												
Chloramph.							0.8	11.9	82.2	3.4		0.8	0.8			
Tetracycline						0.8	25.4	70.3	0.8		1.7		0.8			
TMS***	0.8	4.2	21.2	34.7	11.9	6.8		1.7	3.4	5.1		0.8		9.3		

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. **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 programme in 2013. Resistance data are provided by the Reference Laboratory at the Norwegian Institute of Public Health on a yearly basis.

In 2017, 118 *H. influenzae* isolates were recovered from blood cultures (n=115), a cerebrospinal fluid (n=1) and unspecified specimens (n=2). One of the latter was also isolated in a blood culture, but the rest all represented unique patients (Tables 41-42). Beta-lactamase production was detected in 21/118 isolates (17.8%), which is at the same level as in 2016 (17.3%).

Cefuroxime MIC > 2 mg/L has been suggested as the most precise indicator for alterations in the wild-type PBP3 sequence. Nineteen isolates (16.1%) displayed this phenotype compared to 8.3% in 2015 and 11.1% in 2016. Some of these isolates remained susceptible to ampicillin (7/19) and amoxicillin-clavulanic acid (13/9). Six isolates were concomitantly non-susceptible to cefuroxime and beta-lactamase positive, thus indicating a combination of resistance mechanisms.

Two isolates were resistant to cefotaxime, both with an MIC of 0.5 mg/L. All isolates were fully susceptible to ceftriaxone and meropenem.

Different substrates have been suggested for screening of beta-lactam resistance in *H. influenzae*. The penicillin G 1U disk (PCG1) successfully identified almost all ampicillin (26/27) and cefuroxime (19/19) resistant strains. Seventeen out of 97 (17.5%) beta-lactamase negative isolates were resistant to PCG1. Six of these isolates were resistant to ampicillin and 15 were non-susceptible to cefuroxime. Only two remained susceptible to both agents.

The breakpoint for the cefaclor disk test is calibrated for beta-lactamase positive isolates. Ten out of 21 (48%) beta-lactamase positive isolates were resistant to cefaclor, and cefaclor correctly identified all six cefuroxime non-susceptible isolates in addition to four cefaclor borderline

isolates (19-22 mm zone diameters) where cefuroxime resistance was not verified. The results illustrate the continuing challenges in defining the optimal algorithm for beta-lactam susceptibility testing in *H. influenzae*.

As seen in previous surveys of systemic *H. influenzae* isolates, resistance to ciprofloxacin (0.0%), tetracycline (2.5%) and chloramphenicol (1.7%) was at very low levels. The 15.3% resistance to trimethoprim-sulfamethoxazole was an increase compared to 11.5% in 2015 and 9.9% in 2016.

Haemophilus influenzae in respiratory tract specimens

TABLE 43. *Haemophilus influenzae* in respiratory tract specimens in 2017 (n=1,028). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 1	> 1	80.5	-	19.5
Amoxicillin-clavulanic acid	≤ 2	> 2	95.6	-	4.4
Cefuroxime	≤ 1	> 2	76.2	10.3	13.5
Cefotaxime	≤ 0.125	> 0.125	98.6	-	1.4
Ciprofloxacin	≤ 0.06	> 0.06	98.4	-	1.6
Chloramphenicol	≤ 2	> 2	98.7	-	1.3
Tetracycline	≤ 1	> 2	99.0	0.1	0.9
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 1	74.9	2.7	22.4
Beta-lactamase	Negative	Positive	84.8	-	15.2

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 44. *Haemophilus influenzae* in respiratory tract specimens in 2017 (n=1,028). Distribution (%) of MICs (mg/L) and zone diameters for penicillin G and cefaclor (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
Ampicillin					0.3	2.9	30.4	33.3	13.6	5.8	1.0	1.4	2.9	2.3	1.3	4.8
Amoxi-clav**			0.1		0.4	0.8	22.0	45.1	16.7	10.5	2.0	1.5	0.	0.1	0.1	0.1
Cefuroxime				0.2	0.1	1.0	4.9	32.3	37.7	10.3	5.2	3.7	2.6	1.7		0.4
Cefotaxime	0.9	7.4	43.6	26.8	13.8	6.2	0.3	0.2	0.3	0.5		0.1				
Ciprofloxacin	2.4	17.3	69.0	9.3	0.4	0.9	0.1	0.1	0.1				0.1	0.3		
Chloramph.							1.2	15.3	70.2	12.1		0.2	1.1			0.2
Tetracycline		0.1			0.4	10.7	68.7	18.4	0.8	0.1	0.6	0.3				
TMS***	0.6	2.0	7.1	21.1	26.0	11.1	4.1	2.9	2.7	3.5	2.4	1.9	0.9	13.6		

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

RESULTS AND COMMENTS

A total of 1,028 *H. influenzae* isolates were recovered from respiratory tract specimens including eye and middle ear samples during 2017 (Tables 43-44). Beta-lactamase production was detected in 15.2%, which is a slight decline from 17.3% in 2014 (Figure 73). The 19.5% ampicillin resistance rate was unchanged from 18.3% in 2011 and 19.7% in 2014, and beta-lactamase production was present in 129/200 (64.5%) of these isolates. Eleven of the 129 isolates were concomitantly resistant to cefuroxime, thus indicating a combination of beta-lactamase production and chromosomal resistance mechanisms.

Twenty-seven isolates were reported as ampicillin susceptible in spite of being beta-lactamase positive, and 14/27 were also susceptible to the penicillin G 1 IU screening disk. The results indicate problems with interpretation of the beta-lactamase test. It should be noted that EUCAST recommends all beta-lactamase positive isolates to be reported as resistant to ampicillin and amoxicillin.

The 71 beta-lactamase negative, ampicillin resistant strains were, with a single exception, non-susceptible to cefuroxime, suggesting a chromosomal basis for beta-lactam resistance. Twenty-two of them were also resistant to amoxicillin-clavulanic acid.

A total of 139 isolates (13.5%) displayed resistance to cefuroxime (MIC > 2 mg/L) compared to 17.0% in 2011 and 13.4% in 2014. The rate of both beta-lactamase production and PBP-mediated beta-lactam resistance may thus have stabilised over the last years. Many of the cefuroxime resistant isolates remained susceptible to ampicillin (68/139) and amoxicillin-clavulanic acid (106/139). Fourteen isolates (1.4%) were reported as resistant to cefotaxime (MIC 0.25 – 8 mg/L). Most of them were beta-lactamase negative (8/14) and susceptible to cefuroxime (5/14), ampicillin (8/14) and amoxicillin-clavulanic acid (8/14). The results may suggest technical difficulties with interpretation of the MIC gradient test. Respiratory tract isolates were not tested for ceftriaxone and meropenem susceptibility.

The penicillin G 1U disk (PCG1) successfully identified most isolates resistant to ampicillin (197/200), amoxicillin-clavulanic acid (43/45) and cefuroxime (132/139). Conversely, 191/872 (21.9%) beta-lactamase negative isolates were resistant to PCG1; 69 of these were resistant to ampicillin and 116 were resistant to cefuroxime. Cefaclor correctly identified all 16 beta-lactamase positive, cefuroxime resistant isolates in addition to 40 isolates where cefuroxime resistance was not confirmed.

As seen in blood culture isolates and previous surveys of respiratory tract isolates, resistance to ciprofloxacin (1.6%), chloramphenicol (1.3%) and tetracycline (0.9%) was at a very low level. The prevalence of resistance to trimethoprim-sulfamethoxazole was 22.4%. This is higher than in blood cultures (15.3%), but comparable to findings in respiratory tract isolates in 2011 (22.0%) and 2014 (19.0%). The prevalence of resistance to chloramphenicol and tetracycline was higher in beta-lactamase positive isolates (7.1% and 5.8%, respectively) than in beta-lactamase negative isolates (0.2% and 0.0%, respectively).

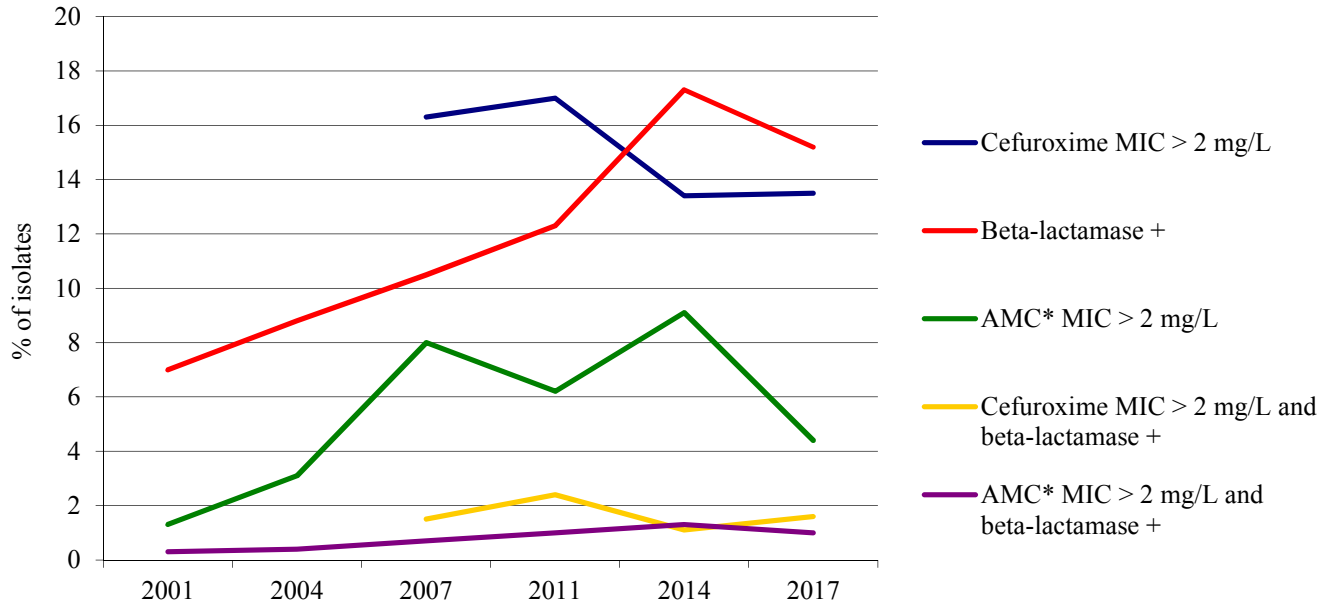


FIGURE 73. Prevalence of beta-lactamase production, chromosomally encoded beta-lactam resistance, and combination of both mechanisms in *Haemophilus influenzae* respiratory tract isolates 2001-2017. The time intervals on the x-axis are not identical. *AMC=Amoxicillin-clavulanic acid. Note irregular time intervals on the x-axis.

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 45. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2017 (n=17). 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	≤ 0.06	> 0.25	94.1	5.9	0.0
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Ciprofloxacin	≤ 0.03	> 0.03	100.0	-	0.0
Chloramphenicol	≤ 2	> 4	100.0	0.0	0.0
Rifampicin	≤ 0.25	> 0.25	100.0	-	0.0

TABLE 46. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2017 (n=17). Distribution (n) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G				4	12		1									
Ceftriaxone	17															
Ciprofloxacin	13	4														
Chloramph.								4	11	2						
Rifampicin	8	6	2	1												
Azithromycin							1	8	8							
Tetracycline						2	6	7	2							
Sulfonamide								1	3				4			9

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. Non-shaded rows indicate that breakpoints have not been defined.

RESULTS AND COMMENTS

N. meningitidis from blood cultures and cerebrospinal fluids were first included in NORM in 2013. As for systemic *H. influenzae* isolates, the Reference Laboratory at the Norwegian Institute of Public Health provides data on *N. meningitidis* on a yearly basis. The results are presented in Tables 45-46.

A total of 17 isolates were recovered from blood cultures (n=15), cerebrospinal fluid (n=1) and "other material" (n=1). All isolates were from unique patients and there were no known associations between the cases. The isolates belonged to serogroups B (n=3), C (n=2), Y (n=7) and W (n=5). Together, serogroups Y and W, belonging to the sequence type (ST) 11 and ST23 clonal complexes, respectively, accounted for 76% of the cases. The two serogroup C isolates were also ST-11. Serogroup W isolates belonging to ST-11 have recently been increasing elsewhere in Europe. One isolate displayed a penicillin G MICs of 0.25 mg/L and was thus intermediately susceptible to this agent. The genetic basis for non-susceptibility was not determined, but was most likely caused by alterations in the penicillin-binding protein 2 (PBP2) encoded by *penA*. All isolates were fully susceptible to ceftriaxone, ciprofloxacin, chloramphenicol and rifampicin. Sulfonamide resistance has been widespread in *N. meningitidis* since the 1960ies. EUCAST has not defined clinical breakpoints for this agent, but the MIC distribution clearly demonstrates a high prevalence of acquired resistance among Norwegian isolates.

Neisseria gonorrhoeae

TABLE 47. *Neisseria gonorrhoeae* from all specimen types in 2017 (n=681). 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	≤ 0.06	> 1	1.9	81.5	16.6
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	99.7	-	0.3
Azithromycin	≤ 0.25	> 0.5	54.6	36.4	9.0
Ciprofloxacin	≤ 0.03	> 0.06	59.9	0.0	40.1
Tetracycline	≤ 0.5	> 1	49.9	20.9	29.2
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	84.7	-	15.3

TABLE 48. *Neisseria gonorrhoeae* from all specimen types in 2017 (n=681). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G**		0.3	0.9	0.7	3.4	26.9	33.8	11.7	5.7	4.3	2.5	2.5	1.3	6.0		
Ceftriaxone	72.5	13.5	4.7	4.7	3.4	1.2										
Cefixime			86.3	5.4	5.9	2.1	0.3									
Azithromycin			0.1	1.3	5.3	17.0	30.8	36.4	4.1	3.2	0.6	0.1	0.1	0.3		0.4
Ciprofloxacin	48.6	9.4	1.5	0.4		0.3		0.3	3.5	9.7	8.2	6.5	5.4	6.2		
Tetracycline						3.7	18.9	27.3	20.9	8.5	0.4	1.2	7.3	9.5	2.1	0.1
Spectinomycin											0.4	27.3	72.0	0.1		

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

RESULTS AND COMMENTS

Neisseria gonorrhoeae was surveyed in NORM in 2003 and 2010. Oslo University Hospital analysed Norwegian gonococcal isolates 2013-2015, and from 2016, the Reference Laboratory at the Norwegian Institute of Public Health provides resistance data on *N. gonorrhoeae* on a yearly basis. All isolates from all specimen types were included in the survey, but only a single isolate was accepted from each patient. The microbiological data could not be linked to information from the Norwegian Surveillance System for Communicable Diseases (MSIS).

In 2017, a total of 681 isolates were available for analysis. The isolates were reported to originate from urethra (n=319), cervix uteri (n=55), anus (n=177), throat (n=78), eye (n=3) or "others/uknown" (n=49). A total of 587 (86.2%) isolates originated from men and 94 (13.8%) 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 within the NORM protocol.

The results from susceptibility testing are presented in Tables 47-48. A majority of the isolates were intermediately susceptible (66.1% in 2016, 81.5% in 2017) or resistant (31.0% in 2016, 16.6% in 2017) to penicillin G. 104 isolates (15.3%) produced beta-lactamase and were phenotypically non-susceptible to penicillin G. This is a further decrease from 28.2% in 2015 and 23.6% in 2016. Most beta-lactamase positive isolates (94/104, 90.4%) were also non-susceptible to ciprofloxacin. In addition, 11 isolates were resistant and 553 were intermediately susceptible to penicillin G in spite of being beta-lactamase negative, probably caused by alterations in penicillin binding proteins (PBPs) and/or reduced permeability through the outer cell membrane.

No isolates were categorised as resistant to ceftriaxone. Ceftriaxone resistant isolates from Norway have previously been linked to treatment failure. Two (0.3%) isolates were resistant to the oral cephalosporin cefixime compared to three isolates in 2015 and nine in 2016. Cefixime is no longer recommended for empirical treatment in Norway. The results confirm the emergence of cephalosporin resistant gonococci in Norway, which is of course extremely alarming from both a clinical and a public health perspective. The current European treatment guidelines consist of a combination of ceftriaxone and azithromycin. It should be noted that 45.4% of the isolates were categorised as non-susceptibilible to azithromycin. This is an increase from 35.9% in 2016.

Ciprofloxacin was previously used for empirical treatment of gonorrhoeae acquired outside South-East Asia. The prevalence of ciprofloxacin resistance persisted at a high level (40.1%) in spite of a significant reduction from 62.2% in 2015 and 48.6% in 2016. 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 49. *Staphylococcus aureus* blood culture isolates in 2017 (n=1,312). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	96.9	0.1	3.0
Clindamycin	≤ 0.25	> 0.5	98.9	0.4	0.7
Fusidic acid	≤ 1	> 1	95.9	-	4.1
Ciprofloxacin	≤ 1	> 1	96.4	-	3.6
Gentamicin	≤ 1	> 1	99.2	-	0.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	98.9	0.6	0.5
Tetracycline	≤ 1	> 2	96.7	0.4	2.9
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.6	0.2	0.2
Beta-lactamase	Negative	Positive	29.7	-	70.3
Cefoxitin screen	≥ 22	< 22	99.2	-	0.8
MRSA (*mecA*)	Negative	Positive	99.2	-	0.8

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Ten methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2017, corresponding to a prevalence of 0.8% (Table 49). This is at the same level as in 2015 (0.7%) and 2016 (1.0%). The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from five different hospitals.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. All MRSA isolates had cefoxitin zone diameters below the screening breakpoint. Some MRSA isolates were concomitantly resistant to erythromycin (1/10), fusidic acid (1/10) and/or ciprofloxacin (3/10). All MRSA isolates were susceptible to clindamycin, gentamicin, tetracycline, trimethoprim-sulfamethoxazole, linezolid and rifampicin. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 53 on page 104. No methicillin susceptible *S. aureus* (MSSA) isolates were reported with cefoxitin zone diameters below the screening breakpoint.

The NORM findings are at the same level as the reports from the databases of the participating laboratories where 18 out of 1,742 (1.0%) *S. aureus* blood culture isolates were MRSA. None of the 25 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 18/1,767 (1.0%). This is unchanged from 2016.

Fourty-one *S. aureus* isolates (3.1%) were non-susceptible to erythromycin. This is a decrease from 5.5% in 2015 and 5.2% in 2016. The macrolide resistance phenotypes of erythromycin non-susceptible isolates were determined by the double disk diffusion (DDD) test. Four isolates (10%) were constitutively MLS_B resistant, 31 (75%) were inducibly MLS_B resistant and six (15%) displayed efflux mediated M-type resistance. These figures represent 0.3%, 2.3% and 0.5% of all *S. aureus* isolates from blood cultures, respectively. The distribution of MLS phenotypes was essentially unchanged from 2016 to 2017.

The prevalence of resistance to fusidic acid at 4.1% was comparable to 4.8% in 2015 and 4.5% in 2016. The 3.6% prevalence of ciprofloxacin resistance is a decrease from 6.9% in 2016, but at the same level as 2.3% in 2015. There were no significant changes for gentamicin, rifampicin or trimethoprim-sulfamethoxazole. All isolates were linezolid susceptible. The general test panel for *S. aureus* did not include tigecycline or vancomycin in 2017.

Figure 74 shows the prevalence of non-susceptibility to various antimicrobials. A total of 70.3% of the isolates were beta-lactamase positive, which is a slight decrease from 72.7% in 2016. There were only minor differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

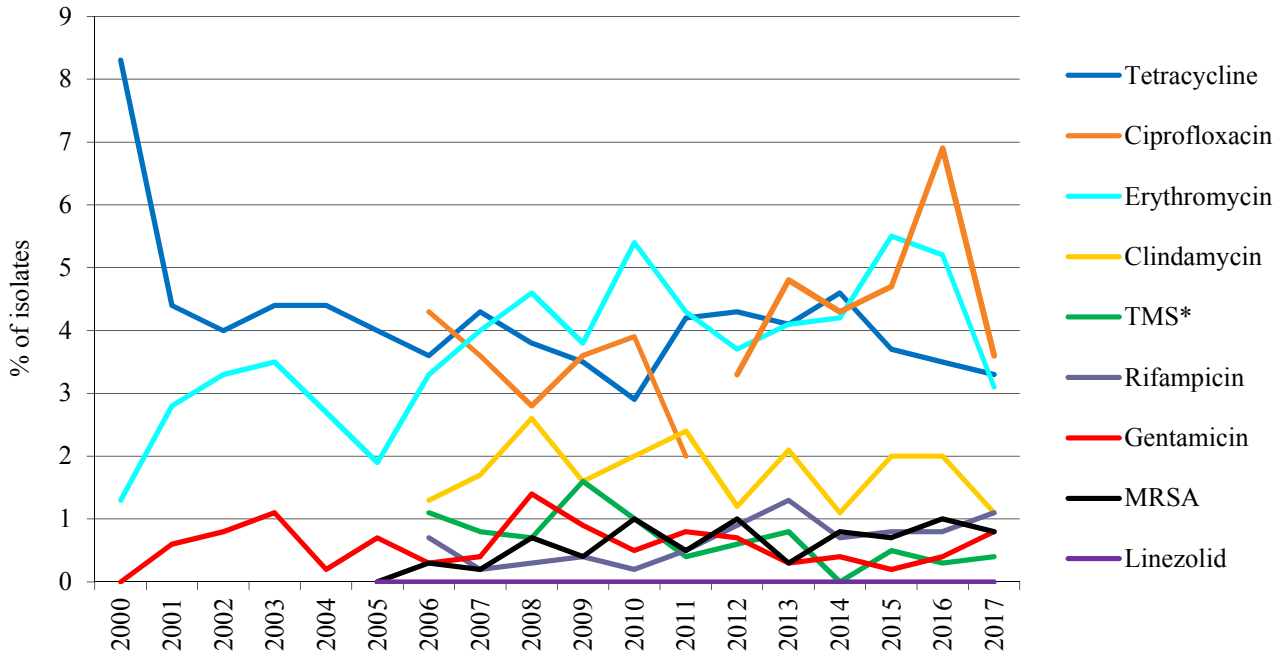


FIGURE 74. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* blood culture isolates 2000-2017. Doxycycline was replaced by tetracycline in 2006. The zone diameter of the breakpoint for ciprofloxacin resistance was adjusted in 2017. Data from 2012-2016 have been recategorised, but earlier results (2000-2011) cannot be calibrated due to changes in methodology in 2012. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 50. *Staphylococcus aureus* isolates from wound specimens in 2017 (n=1,098). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	94.4	0.3	5.3
Clindamycin	≤ 0.25	> 0.5	98.5	0.5	1.0
Fusidic acid	≤ 1	> 1	93.7	-	6.3
Ciprofloxacin	≤ 1	> 1	95.9	-	4.1
Gentamicin	≤ 1	> 1	99.4	-	0.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.064	> 0.5	98.4	1.4	0.2
Tetracycline	≤ 1	> 2	96.7	0.0	3.3
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.4	0.3	0.3
Beta-lactamase	Negative	Positive	25.4	-	74.6
Cefoxitin screen	≥ 22	< 22	98.8	-	1.2
MRSA (*mecA*)	Negative	Positive	98.8	-	1.2

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Thirteen out of 1,098 (1.2%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at the same level as in 2014 (1.3%), 2015 (1.2%), and 2016 (1.6%). The MRSA isolates originated from patients visiting general practitioners (n=10), hospital wards (n=2) and outpatient clinics (n=1) in different parts of the country. Most MRSA isolates displayed reduced susceptibility or co-resistance to erythromycin (n=4), tetracycline (n=2), ciprofloxacin (n=2) and/or clindamycin (n=2) in different combinations. All MRSA isolates were phenotypically susceptible to fusidic acid, gentamicin, rifampicin, linezolid and trimethoprim-sulfamethoxazole. 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 104).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates decreased from 7.3% in 2016 to 6.3% in 2017 (Table 50 and Figure 75). 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 significantly lower in blood culture isolates (4.1 %). For other antimicrobial agents such as trimethoprim-sulfamethoxazole, gentamicin, rifampicin, and tetracycline there were only minor changes from 2016 to 2017, and the prevalence of non-susceptibility was in general similar for blood culture isolates and isolates from wound specimens. Three isolates displayed disk diffusion diameters below the breakpoint for linezolid resistance, but they were all verified as susceptible by MIC testing (4 mg/L).

Sixty-one (5.8%) isolates were non-susceptible to erythromycin, which is a small decrease from 6.0% in 2016. Sixty of these isolates were further examined for determination of resistance phenotype and the majority were either inducibly (41/60, 69% of macrolide non-susceptible isolates) or constitutively (8/60, 13% of macrolide non-suscpetible isolates) resistant to clindamycin, thus representing the $iMLS_B$ and $cMLS_B$ phenotypes, respectively. A minor proportion of the isolates displayed low-level resistance to erythromycin only (11/60, 18% of macrolide non-susceptible isolates) compatible with efflux mediated M-type resistance. The findings are in accordance with the results from previous years.

A total of 74.6% of the isolates were beta-lactamase positive compared to 76.5% in 2016. Beta-lactamase positive isolates were more likely to be resistant to erythromycin (6.2%), clindamycin (1.2%) and ciprofloxacin (4.5%) compared to beta-lactamase negative isolates (2.5%, 0.4% and 2.9%, respectively). For the other antimicrobials there were only minor differences.

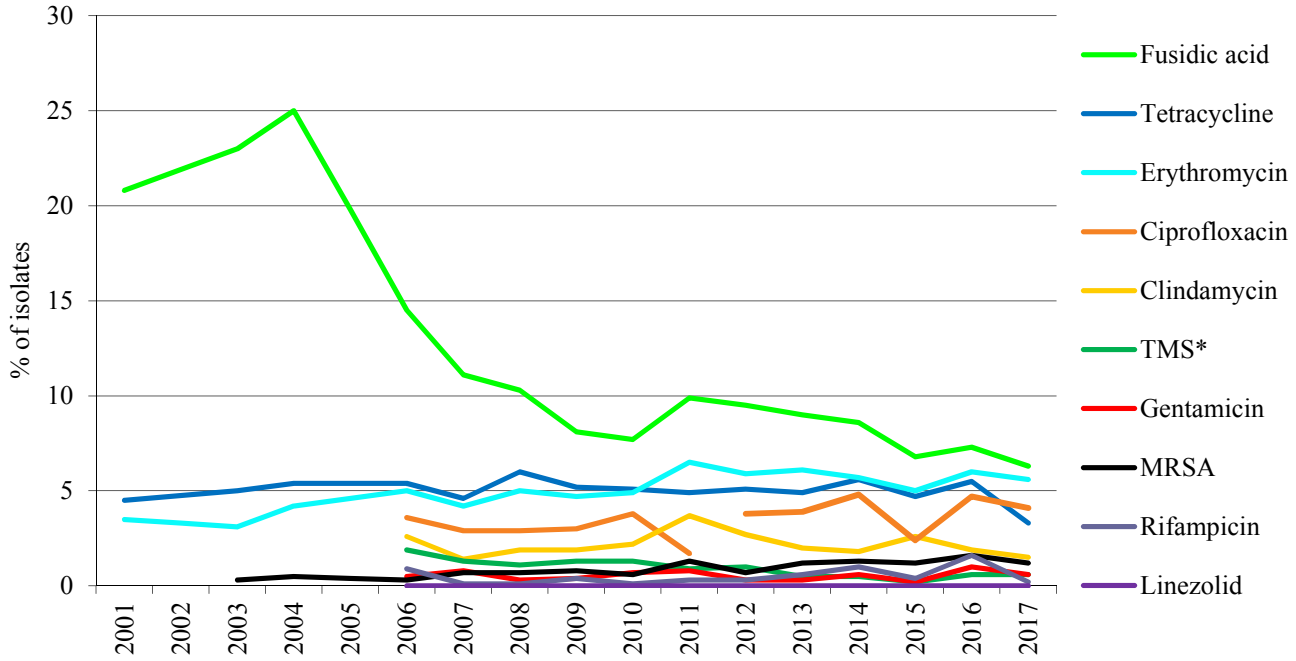


FIGURE 75. Prevalence of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* wound isolates 2001-2017. Doxycycline was replaced by tetracycline in 2006. The zone diameter of the breakpoint for ciprofloxacin resistance was adjusted in 2017. Data from 2012-2017 have been recategorised, but earlier results (2000-2011) cannot be calibrated due to changes in methodology in 2012. *TMS=Trimethoprim-sulfamethoxazole.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2017

For the first time in ten years, the total number of people notified to MSIS with MRSA in 2017 was lower than the preceding year (Figure 76). In all, 2,568 notifications from 2,292 persons were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2017, giving an incidence rate of 44 persons per 100,000 person-years. Of these, 763 (33%) persons were reported with clinical infections while 1,529 were registered as colonised (1,469) or with unknown status (60). The incidence rate of MRSA infections has plateaued in the last four years.

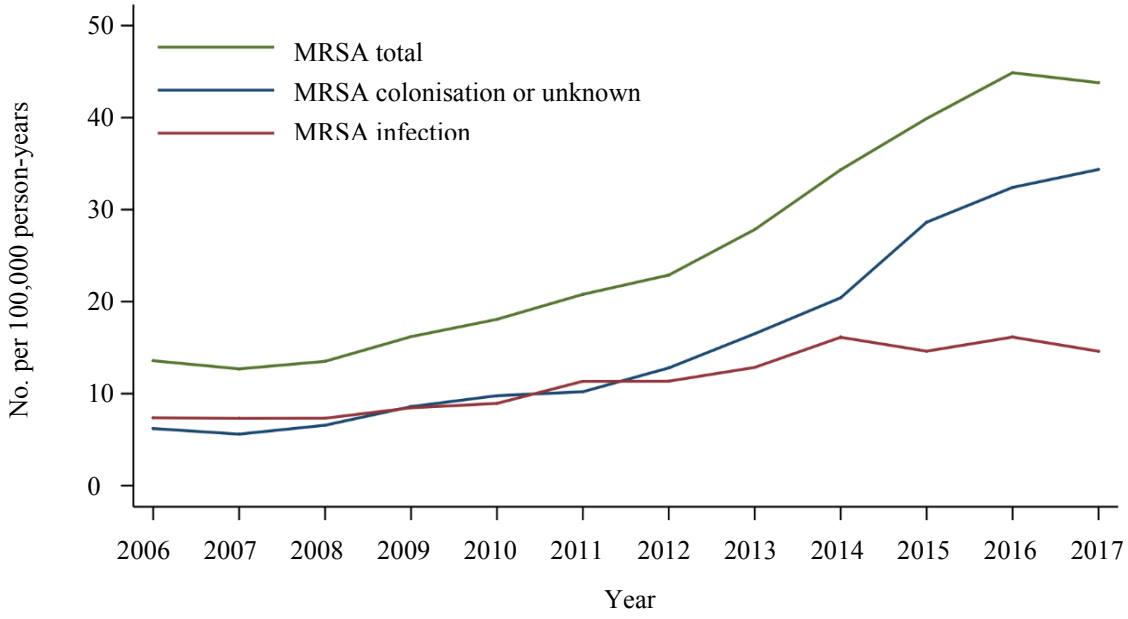


FIGURE 76. Number of persons notified with MRSA per 100,000 person-years in Norway 2006-2017, by infection and colonisation.

The main objective of the Norwegian MRSA infection control measures is to prevent MRSA from becoming endemic in healthcare institutions. As in previous years, persons were primarily diagnosed with MRSA by their general practitioners. In 2017, 425 (19%) of all persons notified with MRSA were inpatients at the time of diagnosis. Fifty-two (2%) were residents in nursing homes and 1,764 (78%) were diagnosed in general practice. In total, 132 were reported to be healthcare workers.

Norway has implemented surveillance of MRSA in swine farms. In 2017, only a few sporadic cases were notified with MRSA *spa*-types previously identified in livestock in Norway. So far, measures against LA-MRSA have effectively controlled the spread of MRSA in swineherds and prevented further dissemination of MRSA from farms to the community (1, 2).

Both imported and domestic MRSA cases have increased during the last ten years. Up to 2016 there was a steeper rise in the number of persons assessed to be infected in another country than persons reported infected in Norway (Figure 77). However, a pronounced decrease in imported cases was reported in 2017. This could reflect a change in migration or in screening routines. However, although notifications to MSIS should contain both a laboratory report and a clinical record from the treating physician, we have an increasing number of notifications where the treating physicians have not sent in the notification form. Although every MRSA case diagnosed in Norway is notified by the medical laboratories, missing information from medical practitioners for a proportion of the cases limits the possibility to use data in MSIS to follow trends regarding places of infection or clinical outcome of MRSA.

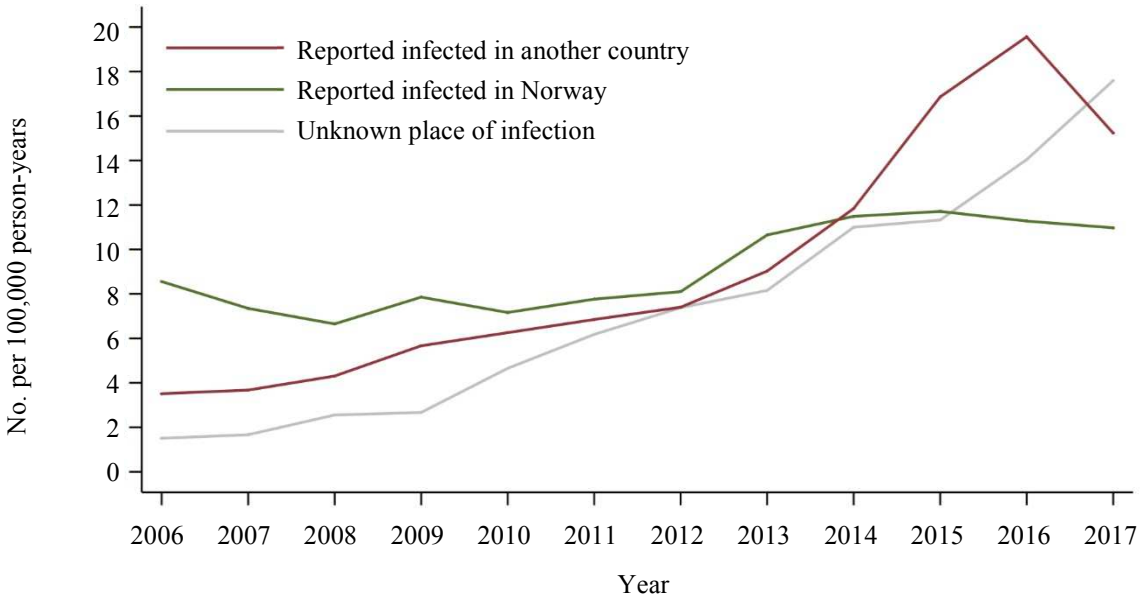


FIGURE 77. Incidence rate (number of persons notified per 100,000 person-years) of MRSA in Norway 2006-2017, by place of infection.

The Norwegian MRSA Reference Laboratory, St. Olavs Hospital, Trondheim University Hospital, received 2,587 methicillin resistant *Staphylococcus aureus* (MRSA) isolates in 2017. In total, 427 different *spa*-types were identified. 238 *spa*-types were reported as single events.

TABLE 51. The ten most common *spa*-types in Norway in 2017.

spa-type	CC	No. of isolates	% of total
t223	22	227	8.8
t002	5	188	7.3
t304	6	173	6.7
t127	1	144	5.6
t008	8	141	5.5
t019	30	117	4.5
t044	80	82	3.2
t437	59	73	2.8
t105	5	52	2.0
t688	5	42	1.6

Based on *spa*-type, the isolates were assigned to MLST clonal complexes (CC). 2,243 isolates (86.8 %) belonged to the ten most prevalent CC.

TABLE 52. The ten most common clonal complexes in Norway in 2017.

CC	*spa*-types grouped in CC*	No. of isolates	% of total
22	t223, t005, t5168, t790, t852	458	17.7
5	t002, t105, t688, t010, t067	443	17.1
1	t127, t657, t386, t5414, t321	252	9.7
8	t008, t1476, t024, t121, t190	237	9.2
30	t019, t021, t363, t665, t018	222	8.6
6	t304, t711, t12135, t121, t13429	202	7.8
45	t004, t026, t015, t1081, t630	138	5.3
88	t690, t1339, t786, t325, t1814	131	5.1
80	t044, t131, t376, t042, t1247	95	3.7
59	t437, t172, t216, t441, t163	94	3.6

* The five most common *spa*-types in each CC.

The Reference Laboratory identified 15 Livestock Associated MRSA (LA-MRSA) (CC398, PVL negative) in humans, of *spa*-type t034 (n=6), t011 (n=6), t571 (n=1), t899 (n=1) and t1606 (n=1). t034 was the 13th most common *spa*-type in Norway in 2017 (including PVL negative and positive strains).

Ten isolates were positive for *mecC* (*spa*-type t6292 and t843), all collected from Norwegian Veterinary Institute.

Susceptibility testing was performed with the EUCAST 2017 disc diffusion method and interpreted according to breakpoints from NordicAST 2017. The laboratory received 2,492 complete antibiograms and 1,025 (41.1 %) of strains were sensitive to all antibiotics tested except beta-lactams (cefoxitin). The highest proportion of resistance was found for erythromycin (32.4%) followed by tetracycline (25.1%) and clindamycin (21.9%). Of the 21.9% of strains resistant to clindamycin, 68.3% of strains had inducible resistance (indicated by D-test). The lowest rates of resistance among the antibiotics tested were found towards mupirocin (0.6%), rifampicin (0.6%) and trimethoprim-sulfamethoxazole (1.2%). No isolates were resistant to linezolid in 2017.

TABLE 53. MRSA isolates from human cases in 2017. Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	67.4	0.2	32.4
Clindamycin	≤ 0.25	> 0.5	76.6	1.4	21.8
Fusidic acid	≤ 1	> 1	88.4	-	11.6
Ciprofloxacin	≤ 1	> 1	78.9	-	21.1
Gentamicin	≤ 1	> 1	89.2	-	10.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.0	0.4	0.6
Tetracycline	≤ 1	> 2	74.5	0.4	25.1
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	97.4	1.4	1.2
Mupirocin	≤ 1	> 256	97.2	2.1	0.7
Vancomycin	≤ 4	> 4	100.0	-	0.0

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

References:

1. Elstrøm P, Grøntvedt CA, Gabrielsen C, Stegger M, Angen Ø, Åmdal S, et al. Livestock-associated MRSA CC1 in Norway; introduction to pig farms, zoonotic transmission and eradication. Front Microbiol. 2018;(submitted).
2. Grontvedt CA, Elstrom P, Stegger M, Skov RL, Skytt Andersen P, Larssen KW, et al. Methicillin-Resistant Staphylococcus aureus CC398 in Humans and Pigs in Norway: A "One Health" Perspective on Introduction and Transmission. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(11):1431-8.

Enterococcus spp. in blood cultures

TABLE 54. *Enterococcus* spp. blood culture isolates in 2017 (n=684). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	78.4	0.7	20.9
Imipenem	≤ 4	> 8	75.4	2.5	22.1
Gentamicin*	≤ 128	> 128	-	78.4	21.6
Linezolid	≤ 4	> 4	99.9	-	0.1
Tigecycline	≤ 0.25	> 0.5	99.7	0.3	0.0
Vancomycin (any genotype)	≤ 4	> 4	96.8	-	3.2
Vancomycin (Van A or VanB)	Negative	Positive	99.0	-	1.0

*The wild-type is defined as intermediately susceptible.

TABLE 55. *Enterococcus faecalis* blood culture isolates in 2017 (n=453). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	99.8	0.0	0.2
Imipenem	≤ 4	> 8	98.7	1.3	0.0
Gentamicin*	≤ 128	> 128	-	84.5	15.5
Linezolid	≤ 4	> 4	99.8	-	0.2
Tigecycline	≤ 0.25	> 0.5	99.6	0.4	0.0
Vancomycin (VanA or VanB)	Negative	Positive	100.0	-	0.0

*The wild-type is defined as intermediately susceptible.

TABLE 56. *Enterococcus faecium* blood culture isolates in 2017 (n=192). 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 (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	25.5	1.6	72.9
Imipenem	≤ 4	> 8	18.8	5.2	76.0
Gentamicin*	≤ 128	> 128	-	59.4	40.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.5	100.0	0.0	0.0
Vancomycin (VanA or VanB)	Negative	Positive	96.4	-	3.6

*The wild-type is defined as intermediately susceptible.

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 54. The surveillance in NORM 2017 included 453 (66.2%) *E. faecalis* isolates (68.3% in 2016), 192 (28.1%) *E. faecium* isolates (29.2% in 2016) and 39 (5.7%) unspeciated enterococcal isolates (5.4% in 2016). 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 was 2.6 in 2016 and 2.4 in 2017, which is comparable to previous years. The panel of antimicrobial agents examined and the breakpoints for interpretation remained unchanged from 2016 to 2017.

E. faecalis was universally susceptible to ampicillin with a single exception (MIC 6 mg/L) (Table 55). The prevalence of resistance to ampicillin in *E. faecium* decreased from

80.9% in 2016 to 72.9% in 2017 (Table 56). As expected, the results for imipenem closely mirrored those for ampicillin. The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 15.5%, which is a slight decrease from 18.1% in 2015 and 18.8% in 2016 (Figure 78). The prevalence of HLGR in *E. faecium* has been stable around 40% over the last years (38.3% in 2016 and 40.6% in 2017, respectively). All 78 HLGR *E. faecium* isolates were concomitantly resistant to ampicillin and imipenem. Conversely, 78 of 143 (54.5%) ampicillin non-susceptible *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.

Transferable 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. Twenty-two blood culture isolates were reported as vancomycin resistant in NORM 2017 (3.2%), but only seven of these were confirmed by PCR to harbour transferable vancomycin resistance (all VanB *E. faecium*). Five VanB *E. faecium* were isolated at a single hospital with persistent VRE transmission. The remaining fifteen vancomycin resistant isolates were either *E. gallinarum* (n=10) or *E. casseliflavus* (n=5), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. A single *E. faecalis* isolate was resistant to linezolid due to an *optr-A* encoded efflux mechanism.

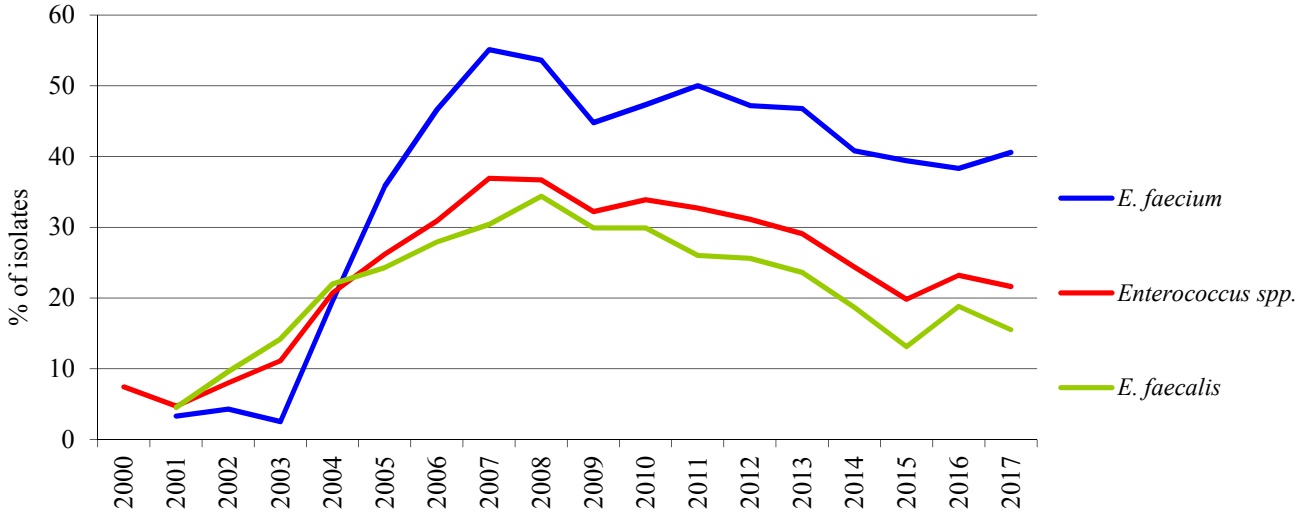


FIGURE 78. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2017. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 57. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2017 (n=536). 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	≤ 0.06	> 2	90.3	8.8	0.9
Cefotaxime	≤ 0.5	> 2	97.9	1.9	0.2
Ceftriaxone	≤ 0.5	> 2	98.5	1.5	0.0
Erythromycin	≤ 0.25	> 0.5	92.2	0.0	7.8
Clindamycin	≤ 0.5	> 0.5	93.8	-	6.2
Tetracycline	≤ 1	> 2	91.3	1.1	7.6
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	89.2	2.6	8.2
Chloramphenicol	≤ 8	> 8	99.4	-	0.6
Oxacillin screen (mm)	≥ 20	< 20	87.3	-	12.7

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 58. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2017 (n=536). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G		0.4	50.4	36.0	3.5	1.5	4.1	1.3	0.7	1.1	0.6	0.2		0.2		
Cefotaxime		4.7	75.2	7.6	3.5	3.5	2.4	0.9	1.9		0.2					
Ceftriaxone		12.5	71.6	4.1	4.3	3.2	1.5	1.3	1.1	0.4						
Erythromycin				0.6	23.5	67.2	0.9		0.2	0.4	0.6	0.6	0.4			5.8
Clindamycin				0.6	11.2	71.3	10.8							0.2		6.0
Tetracycline					4.1	77.1	10.1			1.1	0.7	0.6	2.6	3.7		
TMS**					0.2	29.1	54.7	2.8	2.4	2.6	1.7	1.7	1.1	3.7		
Chloramph.						0.2			0.2	45.3	53.0	0.7	0.6			
Norfloxacin										2.6	27.2	59.9	9.9	0.2		0.2

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	12.7	0.6	0.6	1.3	3.4	10.3	19.2	11.8	18.5	12.3	3.7	5.0	0.4	0.2		0.2

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

RESULTS AND COMMENTS

The results are summarised in Tables 57-58 and Figures 79-80. All systemic *S. pneumoniae* isolates submitted to the National Reference Laboratory for Pneumococci at the Norwegian Institute of Public Health during 2017 were included in the surveillance protocol. Thirteen strains were isolated from cerebrospinal fluids and 16 were isolated from other materials, and seven of these strains were retrieved from patients who concomitantly had positive blood cultures. Both blood culture isolates and isolates from other sterile sites were included from patients with positive cultures from more than one specimen type. Norwegian breakpoints for pneumococci are in accordance with EUCAST, and these remained unchanged in 2017. 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 8.8% (47/536) of *S. pneumoniae* isolates were intermediately susceptible to penicillin G (MIC 0.125-2 mg/L) and five isolates (0.9%) were classified as resistant (MIC 4-32 mg/L). The 9.7% prevalence of penicillin G non-susceptibility was an increase from 7.5% in 2015 and 5.4% in 2016. Two of the penicillin G intermediately susceptible strains were recovered from cerebrospinal fluids and were thus clinically resistant (MIC 0.125-0.5 mg/L). Eleven cefotaxime intermediate (n=10) or resistant (n=1) isolates from unique patients (three blood, eight unknown specimen) were either intermediate (n=6) or resistant (n=5) to penicillin G, and eight of them were also intermediately susceptible to ceftriaxone.

The oxacillin screening disk is often used to discriminate between penicillin susceptible and non-susceptible isolates. Among 52 penicillin G non-susceptible isolates, 51 were resistant to oxacillin. Conversely, 17/467 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 98.1% and 96.4%, respectively. Many of the penicillin non-susceptible *S. pneumoniae* isolates were also non-susceptible to erythromycin (26/52), clindamycin (22/52), tetracycline (25/52) and/or trimethoprim-sulfamethoxazole (22/52).

The prevalence of macrolide non-susceptibility increased from 5.6% in 2016 to 7.8% in 2017. Most of these isolates (33/42, 79% of macrolide non-susceptible isolates, 6.1% of all isolates) were concomitantly high-level resistant to erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining nine isolates (21% of macrolide non-suscpetible isolates, 1.7% of all isolates) were either low-level resistant to erythromycin and susceptible to clindamycin as seen in the efflux-based M-type resistance, or inducibly MLS_B resistant. The distribution of MLS phenotypes was not significantly altered from 2016 to 2017. The results may suggest a continuing predominance of *erm*-mediated macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 80).

The 10.8% non-susceptibility to trimethoprim-sulfamethoxazole was unchanged from 2016. The prevalence of non-susceptibility to tetracycline increased from 6.9% in 2016 to 8.7% in 2017 (Figure 79). The vast majority of isolates (99.4%) were susceptible to chloramphenicol, which was earlier used for empirical treatment of meningitis in Norway. The low prevalence of high-level norfloxacin resistance (Table 58) may reflect the very limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

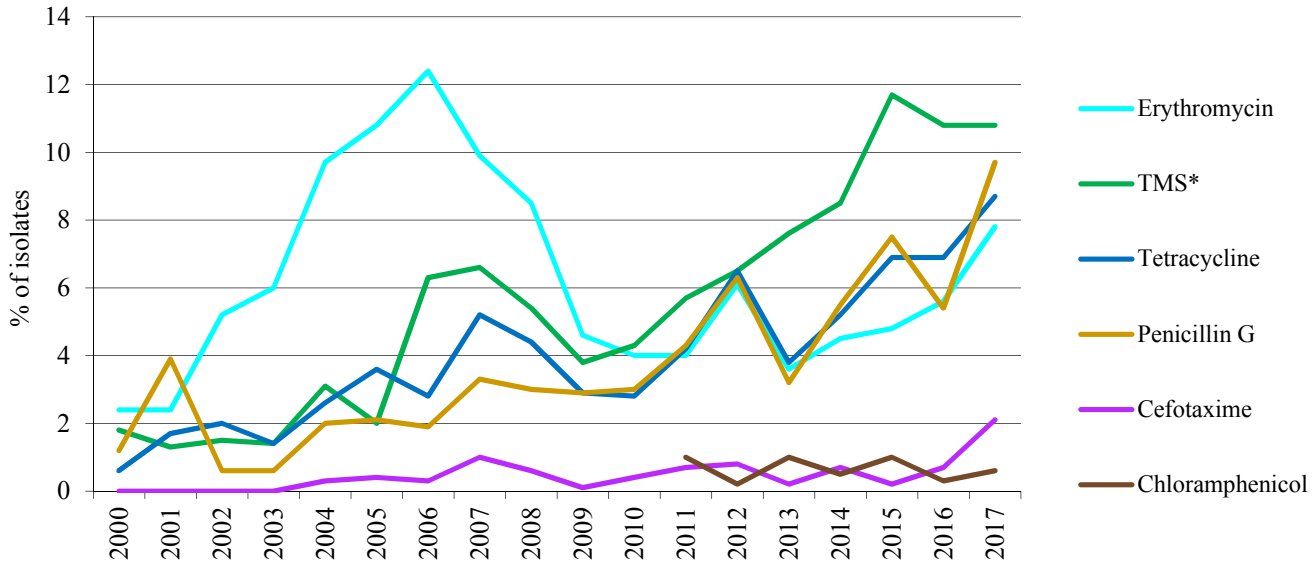


FIGURE 79. Prevalence (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2017. Doxycycline was substituted by tetracycline in 2005. All results are categorised according to the 2018 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

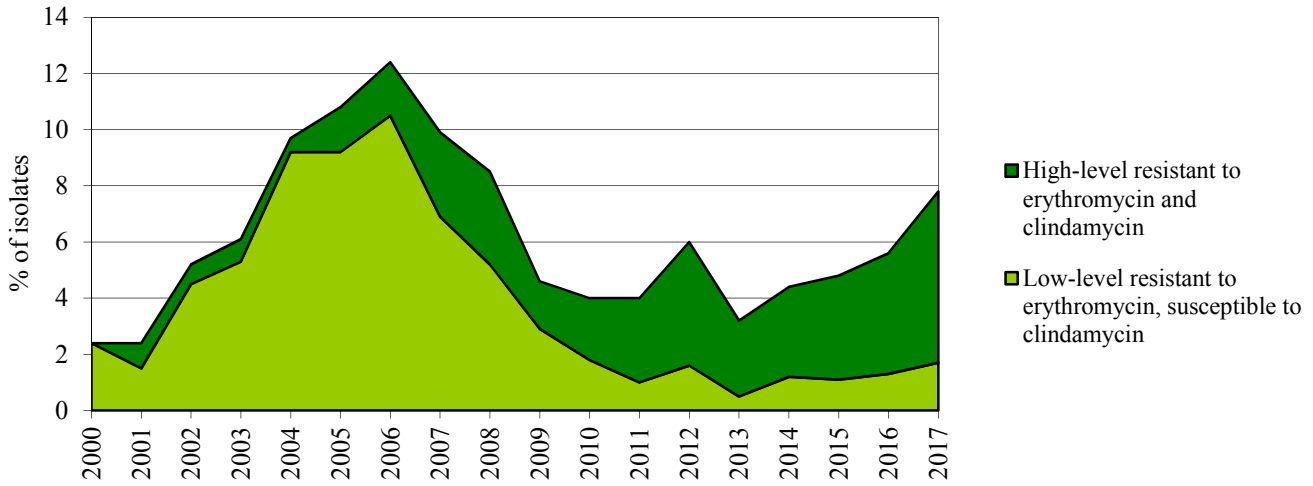


FIGURE 80. Prevalence (%) of non-susceptibility to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2017.

Streptococcus pyogenes in blood cultures

TABLE 59. *Streptococcus pyogenes* in blood cultures in 2017 (n=239). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	95.8	0.0	4.2
Clindamycin	≤ 0.5	> 0.5	97.5	-	2.5
Tetracycline	≤ 1	> 2	89.1	0.0	10.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	99.2	0.0	0.8

*Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 60. *Streptococcus pyogenes* in blood cultures in 2017 (n=239). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G		5.4	92.5	1.7	0.4											
Erythromycin				2.9	56.1	36.4	0.4			0.4			0.4		0.4	2.1
Clindamycin				2.5	61.9	32.6		0.4	0.4							2.1
Tetracycline					10.0	74.1	4.6		0.4		0.4	0.8	2.1	5.9	1.7	
TMS**				2.1	17.2	53.1	23.0	2.9	0.8		0.4			0.4		

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (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. The Norwegian breakpoints for haemolytic streptococci are in accordance with EUCAST. All comparisons in this report are based on the 2018 recommendations.

As expected, all isolates were fully susceptible to penicillin G (Tables 59-60). The prevalences of resistance to erythromycin (4.2%) and clindamycin (2.5%) increased slightly from 2016 (3.7% and 2.1%, respectively). Five of the ten macrolide resistant isolates were also high-level resistant to clindamycin. The prevalence of tetracycline resistance decreased from 16.0% in 2016 to 10.9% in 2017, whereas the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole decreased from 2.1% in 2016 to 0.8% in 2017.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 61. *Streptococcus agalactiae* isolates from sterile sites in 2017 (n=235). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	77.3	0.0	22.7
Clindamycin	≤ 0.5	> 0.5	84.9	-	15.1
Tetracycline	≤ 1	> 2	23.9	0.4	75.6
Vancomycin	≤ 2	> 2	100.0	-	0.0

TABLE 62. *Streptococcus agalactiae* isolates from sterile sites in 2017 (n=235). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G			1.3	49.2	48.7	0.8										
Erythromycin				0.8	16.4	51.3	8.8		1.3	3.8	5.0	5.4	1.7			5.5
Clindamycin					2.5	56.3	24.8	1.3	2.1	1.7	0.8	1.3				9.2
Tetracycline				2.1	20.2	1.3		0.4		0.4		9.2	43.7	20.6	2.1	
Vancomycin				0.4	1.7	44.1	52.9	0.8								
Gentamicin												2.1	9.7	56.3	29.0	2.9

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Calculation was performed on 235 of a total 238 strains isolated from unique patients. Three strains isolated from different specimens collected at the same time from the same patient were excluded.

RESULTS AND COMMENTS

Streptococcus agalactiae (beta-haemolytic group B streptococci) have previously been included in NORM in 2006, 2009, 2012 and 2016. All systemic isolates in Norway are referred to the National Reference Laboratory at St. Olavs Hospital, Trondheim University Hospital, where confirmatory identification and susceptibility testing are performed. Since 2014, the reference laboratory has provided resistance data for all invasive *S. agalactiae* isolates on a yearly basis.

Relevant breakpoints have remained unchanged since 2009. A total of 238 isolates were retrieved from invasive infections (bacteremia and cerebrospinal infections) in 2017, representing 235 unique patients. The analysis included only a single isolate per patient. Thirty-five isolates originated from neonates and small children < 1 year of age (10 EOD and 25 LOD). Most isolates (98.7%) were recovered from blood cultures, but there were also three isolates from cerebrospinal fluids.

As seen in Tables 61-62 there were no isolates with reduced susceptibility to penicillin G or vancomycin. Fifty-four isolates (22.7%) were resistant to erythromycin compared to 17.9% in 2015 and 17.1% in 2016. No isolates were reported as intermediately susceptible. All of the 54 erythromycin non-susceptible isolates were analysed for MLS_B resistance phenotype. This phenotype, indicating the presence of an *erm* determinant, was found in 48 isolates. A constitutive MLS_B phenotype was dominated in 37 isolates, while inducible MLS_B resistance was detected in 11 isolates. The remaining six isolates had a resistance pattern in accordance with an efflux-mediated M phenotype encoded by a *mef* gene. A single isolate was recorded as clindamycin resistant (MIC 1 mg/L) in spite of erythromycin susceptibility (MIC 0.064 mg/L).

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 2.9% of the isolates. The prevalence of resistance to tetracycline (75.6%) was at the same high level as in 2016 (73.0%) with the majority of isolates displaying MIC values of 16-32 mg/L (Table 62).

Mycobacterium tuberculosis

A total of 261 cases of tuberculosis disease (TB) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2017. Of these, 30 cases were born in Norway. Two hundred and twenty-one cases had TB for the first time, 20 cases had been treated with anti-TB drugs previously; 17 for active TB and three for latent TB infection (LTBI) in Norway. One of the latter was ethnically Norwegian. Seven cases had a prior history of TB, but had not been treated with chemotherapy. The rest, 13 cases, were categorised as uncertain.

Two hundred and fourteen cases were confirmed infections with *M. tuberculosis* complex by culture, and all isolates were susceptibility tested. The results are presented in Table 63. Cases are registered in MSIS the year in which the first culture positive test was taken. There were nine MDR-TB cases. Eight were co-resistant to pyrazinamide, four of them also ethambutol resistant, and two were co-resistant to prothionamid. None were resistant to amikacin or capreomycin, but two had low-level resistance to moxifloxacin. No XDR-TB cases were detected. All MDR-TB cases had TB for the first time. Eleven isolates were resistant to isoniazid, but were not MDR cases. Of these, eight were co-resistant to pyrazinamide.

TABLE 63. Antimicrobial susceptibility of 214 isolates of *Mycobacterium tuberculosis* complex (not *M. bovis* (BCG)) from human infections in 2017. Figures from 2016 in parentheses.

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents (No. of isolates)				
			Isoniazid	Rifampicin	Ethambutol	Pyrazinamid	MDR-TB
Norway	30 (33)	20 (22)	1 (2)	1 (2)	1 (0)	1 (0)	1 (2)
Europe excl. Norway	24 (39)	20 (34)	3 (3)	2 (2)	1 (2)	3 (7)	2 (2)
Asia	97 (104)	80 (80)	4 (4)	1 (3)	0 (0)	0 (2)	1 (3)
Africa	109 (120)	93 (90)	12 (10)	5 (4)	2 (0)	8 (6)	5 (4)
America	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oseania	0 (1)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	261 (298)	214 (228)	20 (19)	99 (11)	4 (2)	12* (15*)	9 (11)
Proportion resistant isolates (%)			9.2 (8.3)	4.2 (4.8)	1.8 (0.9)	5.6 (6.6)	4.2 (4.8)

*Of these three *M. bovis* isolates in 2017, (and in 2016) with inherent resistance to pyrazinamid.
MDR-TB: Multi-drug resistant tuberculosis, resistant to at least rifampicin and isoniazid.
XDR-TB: Extensively drug-resistant tuberculosis, resistant to at least rifampicin and isoniazid plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Candida spp. in blood cultures

TABLE 64. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=127). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	100.0	0.0	0.0
Voriconazole*	≤ 0.125	> 0.125	100.0	-	0.0
Anidulafungin*/**	≤ 0.03	> 0.03	100.0	-	0.0
Micafungin*/**	≤ 0.016	> 0.016	100.0	-	0.0

* Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2017. ** There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible.

TABLE 65. *Candida albicans* blood culture isolates (n=127). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B				0.8	0.8	3.9	46.5	45.6	2.4								
Fluconazole						3.1	48.0	46.5	1.6	0.8							
Voriconazole	13.4	78.0	7.9	0.7													
Anidulafungin	77.2	22.8															
Micafungin		24.4	75.6														
Caspofungin**			0.8	3.1	54.4	37.0	4.7										

* Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (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.

TABLE 66. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=36). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 0.002	> 32	0.0	61.1	38.9
Anidulafungin*/**	≤ 0.06	> 0.06	97.2	-	2.8
Micafungin*/**	≤ 0.03	> 0.03	94.4	-	5.6

* Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2017. There is insufficient evidence that *C. glabrata* is a good target for therapy with voriconazole and no clinical breakpoints are available. An MIC with comment without an accompanying S, I or R categorisation may be reported. ** There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible.

TABLE 67. *Candida glabrata* blood culture isolates (n=36). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B					2.8	8.3	11.1	50.0	27.8								
Fluconazole										2.8	2.8	30.6	13.9	11.1		2.8	36.1
Voriconazole**					8.3	8.3	27.8	16.7	8.3	5.6	8.3	2.8	2.8	11.1			
Anidulafungin	5.6	33.3	52.8	2.8	2.8	2.8											
Micafungin		13.9	66.7	13.9	5.6												
Caspofungin***					2.8	22.2	58.3	16.7									

* Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (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 breakpoints are available. An MIC with comment without an accompanying S, I or R categorisation may be reported. ***There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible.

TABLE 68. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates (n=15). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	93.7	6.7	0.0
Voriconazole*	≤ 0.125	> 0.125	100.0	-	0.0
Anidulafungin*/**	≤ 0.06	> 0.06	93.3	-	6.7

* Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2017. ** There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin are considered susceptible. There is insufficient evidence that the wild-type population of *C. tropicalis* is susceptible to micafungin.

TABLE 69. *Candida tropicalis* blood culture isolates (n=15). Distribution (n) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B								5	10								
Fluconazole						1	4	6	1	2	1						
Voriconazole			5	4	4	2											
Anidulafungin		1	13							1							
Micafungin**			5	9						1							
Caspofungin***						8	6							1			

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

TABLE 70. Antimicrobial susceptibility of *Candida parapsilosis*** blood culture isolates (n=10). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	90.0	-	10.0
Voriconazole*	≤ 0.125	> 0.125	90.0	-	10.0
Anidulafungin*/**	≤ 0.002	> 4	0.0	100.0	0.0
Micafungin*/**	≤ 0.002	> 2	0.0	100.0	0.0

* Recommended breakpoints by the European Committee on antimicrobial susceptibility testing - EUCAST. ** There are no European breakpoints for caspofungin. Strains intermediate to anidulafungin and micafungin can be considered intermediate to caspofungin. ***The fluconazole resistant isolate was identified as *Candida orthopsilosis*, a species belonging to the *C. parapsilosis* complex.

TABLE 71. *Candida parapsilosis*** blood culture isolates (n=10). Distribution (n) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B								6	4								
Fluconazole								5	3	1							1
Voriconazole			5	4					1								
Anidulafungin								1	5	3	1						
Micafungin								3	6	1							
Caspofungin***								7	3								

* Shaded areas in each row indicate susceptibility (light), intermediate susceptibility and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined. ** There are no European breakpoints for caspofungin. Strains intermediate to anidulafungin and micafungin can be considered intermediate to caspofungin. ***The fluconazole resistant isolate was identified as *Candida orthopsilosis*, a species belonging to the *C. parapsilosis* complex.

RESULTS AND COMMENTS

In 2017, 206 isolates of ten different *Candida* species were isolated from bloodstream infections in 191 patients and referred to the National Mycology Reference Laboratory. In 2016 the Reference Laboratory received 213 such isolates of ten different *Candida* species. Five mixed infections with two or more different *Candida* spp, and 11 persistent infections in four patients with the same species more than four weeks apart were observed in 2017.

Candida albicans is by far the most common species in candidemia in Norway (n=127, 61.7%). Internationally *C. albicans* is often seen in less than 50% of the candidemias, and over the last decade we observe a steady decrease from 74.9% in 2007. The number of *Candida glabrata* isolates is low but increasing (n=36, 17.5%) followed by small numbers of *Candida tropicalis* (n=15, 7.3%), *Candida parapsilosis* (n=10, 4.9%) *Candida dubliniensis* (n=7, 2.4%), *Candida krusei* (n=6, 2.9%) and five isolates of four other *Candida* spp.

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 are confirmed by the EUCAST standardised broth microdilution method at Statens Serum Institut in Copenhagen. The results are presented in Tables 64-71.

Acquired resistance is rare and species identification predicts the susceptibility pattern of the *Candida* species isolated in Norway, except in patient on long-term antifungal treatment. All *C. albicans* isolates were susceptible to all drugs tested. Aquired echinocandin resistance was found in two patients, in two *C. glabrata* isolates from one patient > four weeks apart and one *C. tropicalis*. All *C. parapsilosis* (n=9) and *C. orthopsilosis* (n=1), which belongs to the *C. parapsilosis* species complex, belonged to the wild-type, categorised as intermediately susceptible to echinocandins.

Intermediate susceptibility to fluconazole was found in one *C. tropicalis*-isolate from a patient on long-term treatment, with MICs of 4 mg/L. Breakpoints for fluconazole (S ≤ 0.002 and R > 32 mg/L) in *C. glabrata* categorise the wild-type as intermediate. This year 14 of the *C. glabrata* isolates were categorised as resistant (38.9%). Otherwise reduced susceptibility to fluconazole was due to intrinsic resistance in *C. krusei* (n=6) or found in species known to display high fluconazole MICs (*C. guilliermondii* (n=2), *C. nivariensis* (n=1) and *C. blankii* (n=1)).

There is still insufficient evidence that *C. glabrata* and *C. krusei* are good targets for therapy with voriconazole, and no breakpoints are set. EUCAST recommends reporting the MIC value without S, I and R categorisation. Except from the fluconazole resistant *C. orthopsilosis*, all isolates with defined breakpoints were found susceptible to voriconazole. In 2015 isavuconazole has been added to the EUCAST breakpoint table for *Candida* spp., but there is still insufficient evidence that *Candida* spp. is a good target for therapy with the drug and breakpoints have not been set.

All tested isolates were susceptible to amphotericin B. Amphotericin B is not recommended treatment of *C. lusitaniae* (n=1) infections as *C. lusitaniae* has high MICs or develop resistance during treatment. Decreased susceptibility to different antifungal classes is common in some of the species not shown in the figures like *C. guilliermondii* (n=2), a species without any breakpoints, but known to exhibit decreased susceptibility to amphotericin B, fluconazole and the echinocandins.

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.

Both VMPs and HMPs have to be dispensed through pharmacies that are supplied by wholesalers. Medicated feed (manufactured from premix VMPs) is supplied to the end user by feed mills and is currently only used for farmed fish; this is due to the small size of livestock herds in Norway. Group/flock treatment of livestock (terrestrial animals) with antibacterial agents is subjected to administration 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). The data on sales of each product presentation (name, form, strength and pack size) of the included VMPs were obtained from the NIPH. An exception is for antibacterials for farmed fish for the years 2013-2015 for which the data were obtained from the Veterinary Prescription Register (VetReg). Veterinarians are not allowed to dispense VMPs except in emergency situations in the field. 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 delivery of VMPs and HMPs to VetReg except for those to companion animals. Pharmacies and feed mills have to report all deliveries to veterinarians or animal owners, including medicines prescribed for companion animals.

For farmed fish the reporting of prescription of antibacterials has been shown to be complete for the years 2013-2017 and thus these data are used for farmed fish for these years (1). For 2012-2014 data from VetReg on antibacterials for terrestrial food-producing animals, the quality of the prescriptions were unsatisfactory (unpublished data). This was the case for oral paste and intramammaries for the entire period 2012-2017. However, the number of prescriptions could be used to obtain a picture of the prescribing per species for these formulations. In this analysis only 2015-2017 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 2015-2017. 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 thought to give a rough picture of the prescription of antibacterial classes by formulation and animal species. These 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).

Ionophore coccidiostat feed additives

Data on sales of coccidiostat feed additives have been collected from the Norwegian Food Safety Authority.

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 he ATCvet codes shown in the below table 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) (3). For the estimation of prescription of HMPs, antibacterials belonging to the ATC codes J01 and J04AB are included (extracted from VetReg data).

Antibacterial veterinary medicinal products included

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 sulphonamides.

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 (3).

Data sources animal population data
Data on animal population, including farmed fish, were obtained from Statistics Norway (https://www.ssb.no).

Indicators
The National Strategy against Antibiotic Resistance (2015-2020) 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 measure to reduce the consumption for food-producing animals, the proposed indicator is overall sales in mg/PCU (mg active substance/ population correction unit) (4). Therefore, the indicators used to report the usage of antibacterials are kg active substance and for food-producing animals also mg/PCU. The animal categories included in the PCU as well as the calculation are identical to ESVAC and is detailed in the ESVAC 2015 report (3).

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 - has been converted to the corresponding values for the active ingredient, here benzylpenicillin (3).

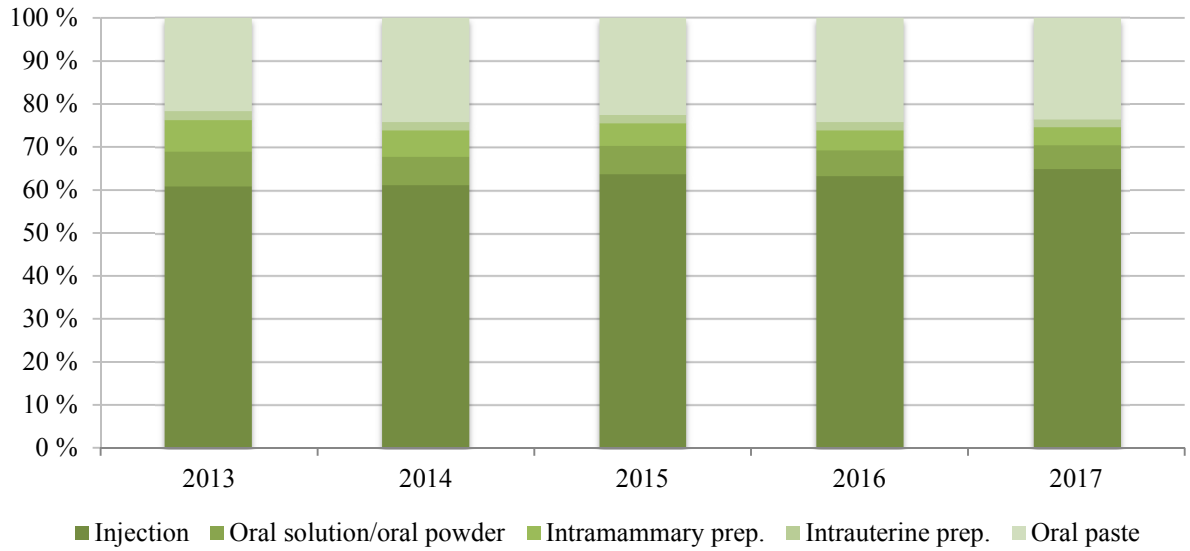
The sales data of antibacterial VMPs for terrestrial animals have been split into sales for food-producing animals (including horses) and companion animals. Sales of antibacterial VMPs for companion animals refer to sales of tablets, oral solution and oral paste that are approved solely for companion 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 to be sold for use only in food-producing animals (including horses). There is some use of injectable VMPs in companion animals thus the usage for this animal category is slightly underestimated and thus slightly overestimated for food-producing animals. Sales of VMPs for food-producing animals have been further stratified into VMPs for treatment of individual food-producing animals - bolus, oral paste injectables, intramammary preparations, intrauterine preparations and some tablets (dihydrostreptomycin pack size 20 and 100) and for group treatment (oral solution and oral powder).

Estimation of sales for cattle, pigs, sheep, goat and poultry
To evaluate the goals set down in the national strategy, the sales data for 2013-2017 have been further refined in order to obtain estimates on the usage in livestock animals that are more accurate in terms of identifying changes over time. Sales data show that oral paste approved for horses were accounting for 22% to 24% of the total annual sales of antibacterial VMPs for terrestrial food-producing animals during 2013-2017 (Figure). Data on prescribing per animal species obtained from the 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 2015-2017 around 4% of the prescribing (kg) for horse was injectables and oral powder/oral solution. Moreover, 97% of the number of prescriptions of antibacterial oral paste VMPs was for horses. Therefore, 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, goat and poultry. Intramammaries and oral paste have been excluded from the analysis of prescribed amounts (kg) of the VetReg data due to quality issues (2).

Changes in sales (wholesalers), in kg of active substance, of antibacterial veterinary medicinal products by major pharmaceutical forms approved for cattle, pigs, sheep, goat, poultry and/or horses in Norway 2007-2017, and proportion of prescription (data from the Veterinary Prescription Register) of such VMP formulations for the main animal species. Sales data were obtained from Norwegian Institute of Public Health.

Pharmaceutical form	% changes sales 2013-2017	Main animal species (VetReg) – total (kg) 2015-2017
Injection	-1%	Cattle (57%), pigs (30%), sheep (10%), horse (3%)
Oral solution/oral powder	-38%	Pigs (86%), sheep (11%), cattle (1%); horse (1%)
Intrauterine preparations	-27%	Cattle (93%), sheep (6%)



Proportion of sales (wholesalers) in Norway of antibacterial VMPs approved for one or more of the food-producing animal species, including horses, by pharmaceutical forms.

The usage of HMPs for cattle, pigs, sheep, goat 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 represent an underestimate.

Estimation of sales of HMPs for dogs and cats

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

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

References

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3. EMA, 2016. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). Web Based Sales Data and Animal Population Data Collection Protocol (version 2) (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/06/WC500188365.pdf).
4. 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 *Sykehusapotekenes Legemiddelstatistikk* (the hospital pharmacies drug statistics database) which is a cooperation of LIS (Legemiddel Innkjøp Samarbeid - Drug Purchasing Cooperation) and the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. *Sykehusapotekenes Legemiddelstatistikk* collects sales data from each pharmacy delivering drugs to hospitals. Data are collected as sales from the pharmacy to hospital wards. Data have been available since 2006. The National Centre for the use of antibiotics in hospitals (*Nasjonal kompetanse-tjeneste for antibiotikabruk i spesialisthelsetjenesten*) have 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 for out-patients in Norway. For analyses on prescriptions and DDDs, all prescriptions and DDDs to outpatients are included. For the results on annual prevalence (number of individuals per population group being prescribed antibiotics within a year), only prescriptions to individuals with national ID numbers are included. The data give us the exact population prevalence of antibacterial use in the total population in ambulatory care. More information is available at www.fhi.no. Data are available from 2004.

Drug Classification
The data are categorised according to the ATC classification system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2018 is used.

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 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), rifaximin (A07AA11) and oral and rectal metronidazole (P01AB01) are also included in some figures. For antifungals, only ATC-group J02 *antimycotics for systemic use* is included. Of the antimycobacterials (ATC J04), only rifampicin is included. The content of rifampicin has been calculated in plain products and in combinations and data is presented as total amount of rifampicin. 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 2018. WHO Collaborating Centre, Oslo
2. Definitions Norwegian Directorate of Health https://volven.helsedirektoratet.no/begrep.asp?id=452&catID=12

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

Sampling strategy

Caecal samples from cattle < one year of age and finishing swine were collected at slaughter throughout the year by The Norwegian Food Safety Authority (NFSA), following the specifications set by the European Food Safety Authority (EFSA; EFSA Journal 2014;12(5):3686). Between one and three individual caecal sample were included per herd, in total 303 and 306 samples from cattle and swine, respectively. The included indicator bacterium *Escherichia coli* was retrieved from these samples. The caecal samples were also used for selective isolation of *E. coli* resistant to 3rd generation cephalosporins, and for carbapenemase-producing *Enterobacteriaceae* (CPE). In addition, the caecal samples from swine were used for selective isolation of *Campylobacter coli*. Samples were also taken from poultry breeder flocks. See separate presentation page 50.

Faecal and nasal swab samples from a total of 246 horses were collected by local practicing veterinarians from May and throughout the year. The sampled horses were between 1 and 29 years of age and stabled all around the country. The included indicator bacterium *E. coli* was retrieved from the faecal swab samples. The same samples were also used for selective isolation of *E. coli* resistant to 3rd generation cephalosporins, quinolone resistant *E. coli* (QREC) and CPE. The nasal swabs were used for selective isolation of MRSA.

All food samples were collected by the NFSA. Beef and pork samples, 343 and 340, respectively, were collected at retail in all regions of Norway following the specifications set by EFSA (EFSA Journal 2014;12(5):3686). Samples were collected without taking place of origin into account. A total of 188 samples of leafy greens and leafy herbs were collected. The 139 leafy greens samples comprised both imported and domestically produced, washed and unwashed leafy salads and included a variety of salad types. The 49 leafy herbs were all imported and comprised a variety of washed and unwashed leafy herbs. Only one sample from each production batch was included.

All the food samples were analysed using selective isolation for *E. coli* resistant to 3rd generation cephalosporins and CPE. The leafy greens and leafy herbs samples were also subjected to selective isolation of QREC and colistin resistant *E. coli*. In addition, *E. coli* indicator bacteria were isolated from leafy greens and leafy herbs.

Indicator isolates of *E. coli*

Sample material, i.e. caecal content from one cattle and one finishing swine per herd and faecal material from horse, were plated directly onto MacConkey agar (Difco) and incubated at 41.5±0.5°C for 20±2h. From vegetable samples, 25±0.5 g sample material was homogenised in 225 mL buffered peptone water (BPW-ISO) and incubated at 37±1°C for 20±2h according to the protocol from the European Union Reference Laboratory for Antimicrobial Resistance (EURL-AR; https://www.eurl-ar.eu/protocols). From the overnight enrichment broth 10-20 µL were plated onto MacConkey agar and incubated at 44±1°C for 20±2h. From all sample types, typical colonies were subcultured on blood agar (Heart infusion agar, Difco) containing 5% bovine blood and incubated at 37±1°C for 20±2h. Colonies were identified as *E. coli* by typical colony appearance and a positive indole reaction.

Enrichment of samples

All samples were enriched prior to plating onto selective media. A total of 1±0.1 g caecal sample material was homogenised with 9 mL of BPW-ISO. Faecal swab samples were inoculated in 5 mL of BPW-ISO. A total of 25±0.5 g sample material of beef, pork, leafy greens and leafy herbs were 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). After incubation, 10-20 µL of the enrichment broth was plated onto selective media as described in the sections below.

***E. coli* resistant to 3rd generation cephalosporins**

Aliquots from the overnight BPW-ISO broth from all caecal, faecal, beef, pork, leafy green and leafy herbs samples were plated onto MacConkey agar (Difco) containing 1 mg/L cefotaxime and MacConkey agar (Difco) containing 2 mg/L ceftazidime. The agar plates were incubated at 41.5±0.5°C (caecal and faecal samples) or 44±1.0°C (food samples) for 20±2h. Presumptive cephalosporinase-producing *E. coli* were subcultured onto MacConkey agar (Difco) containing 1 mg/L cefotaxime and blood agar, and confirmed as *E. coli* using MALDI-TOF MS (Bruker Daltonics GmbH, Bremen, Germany) before further testing for cephalosporinase production.

Quinolone resistant *E. coli*

Aliquots from the overnight BPW-ISO broth from faecal, leafy greens and leafy herbs samples were plated onto MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin. Plates were incubated at 41.5±0.5°C (faecal samples) or 44±1.0°C (leafy greens and leafy herbs samples) for 20±2h. Presumptive QREC were subcultured onto MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin and blood agar and confirmed as *E. coli* using MALDI-TOF MS before further phenotypical testing.

Carbapenemase-producing *Enterobacteriaceae*

Aliquots from the overnight BPW-ISO broth from all caecal, faecal, beef, pork, leafy greens and leafy herbs samples were plated onto chromID™ CARBA and chromID™ OXA-48 agar (bioMérieux, Marcy l'Etoile, France). The plates were incubated at 37±1°C for 24-48 h. Presumptive carbapenemase-producing *Enterobacteriaceae* were subcultured on respective selective chromID™ agar and blood agar, and species were confirmed using MALDI-TOF MS.

Colistin resistant *E. coli*

Aliquots from the overnight BPW-ISO broth from leafy greens and leafy herbs were plated onto SuperPolymyxin agar (Oxoid) and incubated at 44±1.0°C for 20±2h (Nordmann *et al.* 2016). Presumptive positive colonies were selected, subcultured on blood agar and Super-Polymyxin agar, and confirmed as *E. coli* using MALDI-TOF MS before further phenotypical testing.

MRSA
Nasal swabs from horses were analysed for MRSA by incubation in Mueller-Hinton broth with 6.5% NaCl at 37±1.0°C for 18-24 hours. A loopful of the overnight broth (10 µL) was plated onto Brilliance™ MRSA2 agar plate (Oxoid, Oslo, Norway) (EFSA journal 2012: 10 (10):2897). Suspected colonies were subjected to species identification using the MALDI-TOF MS before further phenotypical testing.

Genotyping
For the presumptive cephalosporin resistant *E. coli*, PCR was performed for the identification of the genotypes $bla_{\text{CTX-M}}$, bla_{TEM}, bla_{SHV}, multiplex PCR for plasmid-mediated AmpC genes, or PCR for the $bla_{\text{CMY-2}}$ gene (Pérez-Pérez et al. 2002, Hasman et al. 2005, Briñas et al. 2002, Sundsfjord et al. 2004). For *E. coli* isolates with an AmpC beta-lactamase resistance profile where no plasmid-mediated AmpC genes were detected, amplification of the promoter and attenuator regions of the chromosomal *ampC* gene was performed (Agersø et al. 2012, Peter-Getzlaff et al. 2011, Tracz et al. 2007). For the presumptive colistin resistant *E. coli*, PCR was performed for the identification of the genotypes *mcr-1* and *mcr-2* according to the EURL-AR protocol (http://eurl-ar.eu/data/images/ protocols/mcr-multiplex_pcr_protocol_ v2_oct16.pdf). For presumptive MRSA isolates, realtime PCR for the detection of *mecA* and *nuc* genes together with a conventional PCR for the *mecC* gene was performed (Tunsjø et al. 2013, Stegger et al. 2012).

Susceptibility testing
Isolates were tested for antimicrobial susceptibility using a broth microdilution method at NVI, Oslo. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the tested bacteria. Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 13.05.2018) were used, except for tigecycline for *E. coli* for which cut-off values defined by EFSA was used, and for azithromycin for *E. coli* for which cut-off values are not defined. See Appendix 6 for definitions of cut-off values.

Quality assurance systems
The following susceptible bacterium was included as quality control on a regular basis: *E. coli* ATCC 25922. The following resistant bacteria were tested on a regular basis: *E. coli* CCUG 37382, *E. coli* K8-1 (ESBL), *E. coli* K5-20 (AmpC), *E. coli* 2012-60-1176-27 (*mcr-1*) and *E. coli* KP37 (*mcr-2*). 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).

Data processing
Susceptibility data were recorded and stored in the sample registration system at NVI as discrete values (MIC). Data management was performed both in SAS-PC System® v 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and in R version 3.5.0 Copyright (C) 2017 (The R Foundation for Statistical Computing Platform), while the statistical analysis was performed in R. The significance tests for differences between proportions of resistant isolates were calculated using Pearson's Chi-squared Test or Fisher's Exact Test for Count Data as appropriate. 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.

Overview of antimicrobial groups and agents tested for in NORM-VET 2017.

Antimicrobial group	Antimicrobial agents	*E. coli**	*Salmonella* spp.	*Campylobacter coli*
Tetracyclines	Tetracycline	X	X	X
	Tigecycline	X	X	
Amphenicols	Chloramphenicol	X	X	
Penicillins with extended spectrum	Ampicillin	X	X	
2nd generation cephalosporins	Cefoxitin	(X)		
3rd generation cephalosporins	Cefotaxime	X	X	
	Ceftazidime	X	X	
4th generation cephalosporins	Cefepime	(X)		
Carbapenems	Meropenem	X	X	
	Ertapenem	(X)		
	Imipenem and enzyme inhibitor	(X)		
Trimethoprim and derivatives	Trimethoprim	X	X	
Sulfonamides	Sulfamethoxazole	X	X	
Macrolides	Erythromycin			X
	Azithromycin	X	X	
Streptogramins	Quinupristin and dalfopristin			
Streptomycins	Streptomycin			X
Other aminoglycosides	Gentamicin	X	X	X
Fluoroquinolones	Ciprofloxacin	X	X	X
Other quinolones	Nalidixic acid	X	X	X
Polymyxins	Colistin	X	X	

*(X) = 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.

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

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
Sample material, i.e. caecal content from one finishing swine per herd were plated directly onto mCCDA agar and incubated under microaerobic conditions at 41.5±0.5°C for 48h. Typical colonies were subcultured on blood agar and confirmed as *Campylobacter coli* using MALDI-TOF MS.

Susceptibility testing animal isolates
Isolates were tested for antimicrobial susceptibility at NVI, Oslo. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacteria to be tested. For animal isolates, epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 13.05.2018) were used, except for tigecycline for *Salmonella* spp. where EFSA recommended cut-off was used, and for azithromycin and colistin for *Salmonella* spp. for which cut-off values are not defined. 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 (Appendix 6).

Quality assurance systems NORM-VET
The following susceptible bacteria were included as quality controls on a regular basis: *E. coli* ATCC 25922 and *C. jejuni* ATCC 33560. NVI and the Reference Laboratory for Enteropathogenic Bacteria/NIPH have a quality assurance system according to the requirements of NS-EN ISO/IEC 17025. The participating laboratories at NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in external quality assurance programmes for veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit Loughborough. UK) and for resistance monitoring (EURL for Antimicrobial Resistance in Denmark).

Data processing animal isolates
Susceptibility data were recorded and stored in the sample registration system at NVI as discrete values (MIC). Data management was performed both in SAS-PC System® v 9.4 for Windows (SAS Institute Inc. Cary. NC. USA) and in R version 3.5.0 Copyright (C) 2017 (The R Foundation for Statistical Computing Platform), while the statistical analysis was performed in R. The significance tests for differences between proportions of resistant isolates were calculated using Pearson's Chi-squared Test or Fisher's Exact Test for Count Data as appropriate. 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 specimens. 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 human campylobacteriosis cases registered were submitted in the following way: Five regional laboratories submitted the first five independent isolates each month to the NRL for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

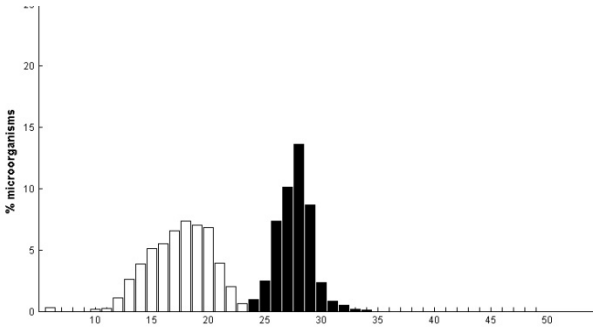
Identification of bacteria – human isolates
The reference analyses on human clinical isolates of enteropathogenic bacteria were performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th edition ASM-Press, Washington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

Susceptibility testing human isolates
Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the NRL for Enteropathogenic Bacteria at the NIPH by agar disk diffusion tests according to the EUCAST standardised method for AMR testing of non-fastidious bacteria. *Campylobacter* isolates from humans were tested for antimicrobial susceptibility using MIC Test Strips (Liofilchem).
For human isolates EUCAST clinical or epidemiological breakpoints for *Enterobacteriaceae*, version 8.1 2018 were used if defined. In the absence of clinical breakpoints, ECOFFs were used as determined by EUCAST or breakpoints were based on national zone distribution evaluations (e.g. nalidixic acid, azithromycin and tetracycline). Pefloxacin was used for inferred ciprofloxacin resistance in *Salmonella*, EUCAST breakpoints were adjusted in accordance with local epidemiological cut-off value.
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.

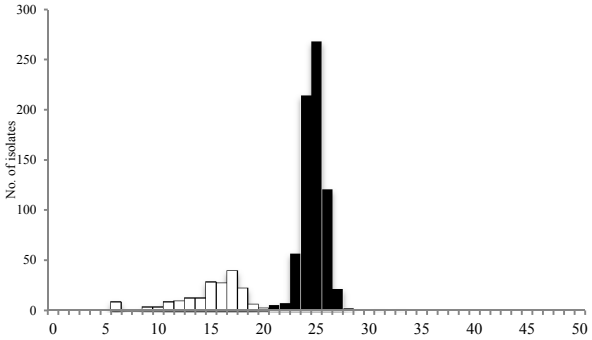
Quality assurance systems human isolates
The NRL for Enteropathogenic Bacteria at the NIPH is accredited according to the requirements of NS-EN ISO/IEC 17025. *E. coli* ATCC 25922 was used as quality control strain for AMR testing of non-fastidious *Enterobacteriaceae.* The NRL participated in the external 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.



EUCAST, zone distribution pefloxacin/*Salmonella* spp. based on 1,257 observation; ECOFF at 24 mm (accessed June 2017).



NIPH zone distribution pefloxacin/*Salmonella* spp. based on 895 tested isolates; epidemiological cut-off set at 21 mm.

Appendix 5: Sampling, microbiological methods and data processing in NORM

General considerations

NORM is based on a combination of periodic sampling and testing in primary diagnostic laboratories and annual results from national reference laboratories for specific micro-oganisms. Isolates are included from defined clinical conditions such as respiratory tract infections, wound infections, urinary tract infections, and septicaemiae. For enteric infections see Appendix 4. 2017 was the eighteenth year of surveillance, and 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 2017 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus, Enterococcus* spp. and *Proteus* spp. in blood cultures (9 months); *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Haemophilus influenzae*, *Neisseria meningitidis* and *Candida* spp. from blood cultures and cerebrospinal fluids (12 months); *S. aureus* from wound specimens (1 week); *H. influenzae* from respiratory tract samples (3 week); *E. coli* from urinary tract infections (3 days); *Klebsiella* spp. and *Proteus* spp. from urinary tract infections (3 weeks); *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, as well as *N. gonorrhoeae* from all clinical samples, were analysed at the the Norwegian Institute of Public Health in Oslo. *Candida* spp. isolates from blood cultures were analysed at Oslo University Hospital, Rikshospitalet. MRSA and *S. agalactiae* isolates were analysed at St. Olav University Hospital in Trondheim. ESBL-producing *Enterobacteriaceae* were genetically characterised at University Hospital of North Norway in Tromsø. *M. tuberculosis* isolates were analysed at the Norwegian Institute of Public Health and Oslo University Hospital (Ullevål and Rikshospitalet).

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp., *S. aureus* and *Proteus* spp. isolates were examined according to the EUCAST disk diffusion standard 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 of NordicAST, which are harmonised with EUCAST. Beta-lactamase production in *S. aureus*, *H. influenzae* 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. *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *H. influenzae*, *N. meningitides,* and *N. gonorrhoeae* were susceptibility tested using MIC gradient tests (bioMerieux or Liofilchem) on MH II agar supplemented with 5% lysed horse blood or GC agar with 1% haemoglobin and Isovitalex (*N. gonorrhoeae*). 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 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 according to the instructions of the manufacturer (Liofilchem). ESBL positive strains from blood cultures were subjected to PCR and DNA sequencing for determination of ESBL genotype. *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. Erythromycin non-susceptible *S. pneumoniae*, *S. aureus, S. pyogenes* and *S. agalactiae* isolates were analysed for determination of MLS phenotype 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, *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 49247, *H. influenzae* NCTC 8468, *N. gonorrhoeae* CCUG 26213/ATCC 49266, *N. gonorrhoeae* WHO L, *P. aeruginosa* ATCC 27853, *C. albicans* ATCC 90028, *C. krusei* ATCC 6258 and *C. parapsillosis* ATCC 22019.

Data processing

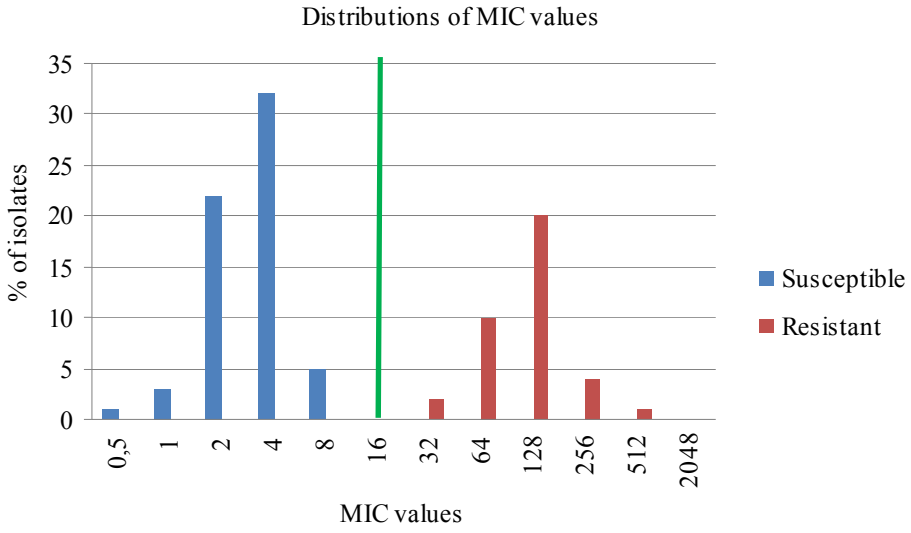
The specially designed web-based eNORM computer programme was used for registration and storage of patient data, sample data and resistance data. The results were further analysed by WHONET 5.6 with the aid of the BacLink programme, both developed by Dr. John Stelling. The distribution of microbial species 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.

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. EUCAST definitions of clinical breakpoints and ECOFFs are presented at http://www.srga.org/Eucastwt/eucastdefinitions.htm.

The terms and usage of these two ways of classification of resistance are further explained below. The epidemiological breakpoint would normally be lower for MIC values and higher for disk diameters than the clinical breakpoints. However this is not always the case.



Epidemiological cut-off values

The epidemiological cut-off values may indicate emerging resistance in the bacterial populations. Based on the distribution of the minimum inhibitory concentration (MIC) or the inhibition zone diameter distribution, each bacterial population could (in an ideal case) be divided into two populations by a biphasic curve as shown in the example above. The curve to the left (blue) shows the susceptible or wild-type distribution whereas the curve to the right (red) shows the resistant or non wild-type distribution. The green line indicates a possible ECOFF value applicable to the distributions in the example.

However, for several bacterial populations and corresponding tested antimicrobial substances these distributions may be overlapping. A part of the population within the overlapping area may carry resistance mechanisms and others not. In the area with the non wild-type distribution, new resistance mechanisms are responsible for the resistance either alone or in addition to the resistance mechanisms present at lower MIC values. In order to establish MIC values for each specific bacterial population and antimicrobial agent, large amounts of data are collected and assessed. In the NORM-VET part of this report, we have mainly used the ECOFF values recommended by EUCAST. However, for some combinations of bacteria and antimicrobial agents these were not applicable to our data. In these cases ECOFF values defined on the basis of the actual MIC distributions obtained in the NORM-VET programme were used.

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 predetermined 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 on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2017 by EFSA (EFSA Journal 2017; 15(2):4694) 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%

Appendix 7:
Cut-off values NORM-VET

Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 13.05.2018) 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.

Antimicrobial agents	Resistant MIC (mg/L)	*Salmonella* spp.	*Escherichia coli*	*Campylobacter coli*
Ampicillin	> 8	■	■	
Azithromycin*	ND	X	X	
Cefotaxime	> 0.25		■	
	> 0.5	■		
Ceftazidime	> 0.5		■	
	> 2	■		
Chloramphenicol	> 16	■	■	
Ciprofloxacin	> 0.064	■	■	
	> 0.5			■
Colistin	> 2		■	
	ND	X		

Antimicrobial agents	Resistant MIC (mg/L)	*Salmonella* spp.	*Escherichia coli*	*Campylobacter coli*
Erythromycin	> 8			■
Gentamicin	> 2	■	■	■
Meropenem	> 0.125	■	■	
Nalidixic acid	> 16	■	■	■
Streptomycin	> 4			■
Sulfamethoxazole	> 64		■	
	> 256	●		
Tetracycline	> 2			■
	> 8	■	■	
Tigecycline	> 0.5	#	#	
Trimethoprim	> 2	■	■	

■ Cut-off values recommended by EUCAST. *Cut-off not defined (ND). ● Cut-off defined by the MIC distributions obtained in NORM-VET.
Cut-off defined by EFSA

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)		*Escherichia coli*	*Klebsiella* spp.	*Proteus* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
	S	R																			
Amphotericin B	≤ 1	> 1																■	■	■	■
Ampicillin	≤ 1	> 1								■											
	≤ 4	> 8												■							
	≤ 8	> 8	■		■	■	■	■													
Amoxi-Clav*	≤ 2	> 2								■											
	≤ 8	> 8	■	■	■																
	≤ 32	> 32	■	■	■																
Anidulafungin	≤ 0.002	> 4																			■
	≤ 0.03	> 0.03																■			
	≤ 0.06	> 0.06																	■	■	
Azithromycin	≤ 0.25	> 0.5										■									
						■[2]	■[2]	■[2]													
Cefaclor										■[1]											
Cefepime	≤ 1	> 4	■	■	■																
Cefixime	≤ 0.125	> 0.125										■									
Cefoxitin													■[1]								
Cefotaxime	≤ 0.125	> 0.125								■											
	≤ 0.5	> 2													■						
	≤ 1	> 2	■	■	■	■	■	■													
Ceftazidime	≤ 1	> 4	■	■	■	■	■	■													
Ceftriaxone	≤ 0.125	> 0.125								■	■	■									
	≤ 0.5	> 2													■						
Cefuroxime	≤ 1	> 2								■											
Chloramphenicol	≤ 2	> 2								■											
	≤ 2	> 4									■										
	≤ 8	> 8				■	■	■							■						
Ciprofloxacin	≤ 0.03	> 0.03									■										
	≤ 0.03	> 0.06										■									
	≤ 0.06	> 0.06								■											
	≤ 0.25	> 0.5	■	■	■		■	■													
	≤ 0.5	> 0.5							■												
	≤ 1	> 1											■								
						■[3]															
Clindamycin	≤ 0.25	> 0.5											■								
	≤ 0.5	> 0.5													■	■	■				
Erythromycin	≤ 0.25	> 0.5													■	■	■				
	≤ 1	> 2											■								
	≤ 4	> 4							■												

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Proteus* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
Fluconazole	≤ 0.002	> 32																	■		
	≤ 2	> 4																■		■	■
Fosfomycin	≤ 32	> 32	■																		
Fusidic acid	≤ 1	> 1											■								
Gentamicin	≤ 1	> 1											■								
	≤ 2	> 2							■[1]												
	≤ 2	> 4	■	■	■	■	■	■													
	≤ 128	> 128												■							
Imipenem	≤ 4	> 8												■							
Linezolid	≤ 4	> 4											■	■							
Mecillinam	≤ 8	> 8	■	■	■																
Meropenem	≤ 2	> 2								■											
	≤ 2	> 8	■	■	■	■	■	■													
Micafungin	≤ 0.002	> 2																			■
	≤ 0.016	> 0.016																■			
	≤ 0.03	> 0.03																	■		
Mupirocin	≤ 1	> 256											■								
Nalidixic acid						■[1]	■[1]	■[1]	■[1]												
Nitrofurantoin	≤ 64	> 64	■																		
Oxacillin															■[1]						
Penicillin G	≤ 0.06	> 0.25									■										
	≤ 0.06	> 1										■									
	≤ 0.06	> 2													■						
	≤ 0.25	> 0.25														■	■				
										■[1]											
Pip-Tazo**	≤ 8	> 16	■	■	■																
Rifampicin	≤ 0.06	> 0.5											■								
	≤ 0.25	> 0.25									■										
Spectinomycin	≤ 64	> 64										■									
Tetracycline	≤ 0.5	> 1										■									
	≤ 1	> 2								■			■		■	■	■				
	≤ 2	> 2							■												
						■[2]	■[2]	■[2]													
Tigecycline	≤ 0.25	> 0.5												■							
	≤ 1	> 2	■	■																	
Trimethoprim	≤ 2	> 4	■	■	■																

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Proteus* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
TMS***	≤ 0.5	> 1								■											
	≤ 1	> 2													■	■					
	≤ 2	> 4	■	■	■	■	■	■					■								
Vancomycin	≤ 2	> 2															■				
	≤ 4	> 4											■	■							
Voriconazole	≤ 0.125	> 0.125																■		■	■

[1] Epidemiological cut-off value based on the wild-type distribution by EUCAST. [2] Epidemiological cut-off values based on national zone distribution evaluations. [3] Low-level resistance against ciprofloxacin is underestimated using breakpoints based on ciprofloxacin disk diffusion. EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. Susceptibility to ciprofloxacin is therefore inferred from pefloxacin disk diffusion susceptibility with breakpoints based on epidemiological cut-off values on national zone distribution evaluations in line with EUCAST recommendation. * Amoxi-Clav= Amoxicillin-Clavulanic acid. ** Pip-Tazo=Piperacillin-Tazobactam. *** TMS Trimethoprim-sulfamethoxazole. Breakpoints for the combination are given for the trimethoprim component only.

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