2018

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 the food production chain.

In response to the growing concern about antimicrobial resistance, the Norwegian Ministry of Health and Social Affairs issued a national action plan against antimicrobial resistance in March 2000. The importance of monitoring the human and animal health sectors as well as food production, was emphasised. The action plan recognised the need for ongoing surveillance as a fundamental component of the strategy. The NORM and NORM-VET programmes were consequently established in order to provide and present data on the occurrence and distribution of antimicrobial resistance over time. The national action plan formally expired by the end of 2004. However, the need for continued surveillance of both resistance and antimicrobial usage was emphasised at subsequent consultations and an integrated national strategy for prevention of infections in the health service and antibiotic resistance (2008-2012) was issued in the summer of 2008. Following the renewed effort of the WHO in recent years, the Norwegian government launched a new national strategy (2015-2020) in June 2015 including an explicit target of 30% reduction in antibiotic consumption in human medicine by 2020 compared to 2012. For food-producing terrestrial animals and companion animals the target is 10% and 30% reduction in the usage, respectively, by 2020, with 2013 as reference year. Additional specific targets in the food production chain is that livestock associated MRSA will not be established in the Norwegian pig population, and that ESBL in the poultry production will be reduced to a minimum. Mapping of reservoirs of antimicrobial resistant bacteria will also be carried out in the most relevant animal populations and plants important to food safety.

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 nineteenth annual joint report from NORM and NORM-VET, presents data on resistance and usage for 2018. 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 2019

SAMMENDRAG

Dette er den nittende 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 2018. 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 2018 utgjorde salget av antibakterielle veterinærpreparater til landdyr 5167 kg aktivt stoff som er en nedgang på 7,5 % sammenlignet med 2017.

Salget av antibakterielle veterinærpreparater til matproduserende landdyr, inkludert hest, var på 4821 kg. Til gris, storfe, sau, geit og fjørfe ble det i all hovedsak brukt penicilliner og av disse var det nesten utelukkende benzylpenicillin som ble benyttet. Fra 2013 til 2018 var det en nedgang i forbruket av antibakterielle veterinærpreparater til de viktigste matproduserende artene (storfe, gris, sau, geit og fjørfe) på 17 % målt i kg aktivt stoff. Også når salget relateres til dyrepopulasjonen, var nedgangen i forbruket 17 %. Det er fortsatt lavt forbruk av de antibakterielle midlene som er høyest prioritert av Verdens helseorganisasjon (blant de kritisk viktige antibakterielle midlene for humanmedisinen). Salget av antibakterielle veterinærpreparater som kan benyttes til flokkbehandling, er fortsatt lavt; i 2018 utgjorde salg av slike preparater 4 % av totalsalget. Til hest ble det i hovedsak brukt trimetoprim-sulfa (oralpasta).

Forbruket av veterinære antibakterielle midler til oppdrettsfisk som går til matproduksjon (forbruk til rensefisk utelatt), var fortsatt svært lavt i 2018 og utgjorde 871 kg. Dette representerer en nedgang på over 99 % sammenlignet med toppåret 1987. I 2018 ble det foretatt behandling med anti-biotika av laks og regnbueørret i 1,6 % av sjølokalitetene.

Til kjæledyr (hund og katt) ble det i 2018 solgt 347 kg veterinære antibakterielle midler. Dette er en nedgang på 34 % sammenlignet med 2013. Når bruken av humane antibakterielle midler til hund og katt inkluderes, estimert ved bruk av data fra Veterinært legemiddelregister, er nedgangen fra 2013 til 2018 på 24 %.

Narasin ble faset ut som fôrtilsetningsmiddel til slaktekylling sommeren 2016. Bruken av antibiotika til behandling av slaktekylling er fortsatt svært lavt; i 2018 ble det foretatt behandling i 0,1 % av slaktekylling-flokkene og det ble kun brukt smalspekterede penicilliner.

Forbruk av antibiotika hos mennesker

Den totale antibiotikabruken er kontinuerlig redusert siden 2012. Bruken har gått ned med 24 % siden 2012. Med totalt antibiotikabruk mener vi her alt salg i Norge av antibakterielle midler til systemisk bruk hos mennesker (J01 ekskl. metenamin) dvs. i primærhelsetjenesten og til institusjoner. Også i 2018 fortsatte reduksjonen, med 3 % sammenliknet med 2017. Det totale salget gikk ned fra 13,3 DDD/1000 innbyggere/døgn i 2017 til 12,9 DDD/1000 innbyggere/døgn i 2018. Andelen smalspektrede penicilliner (J01CE) var stabil med 27 % av totalt salg (J01, ekskl. metenamin), men redusert i forhold til tidligere år. I 1997 (20 år siden) var andelen 35 % av det totale salget.

Rundt 84 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. I 2018 var penicilliner (J01C) mest brukt i primærhelsetjenesten; 53 % av alle DDD for antibakterielle midler til systemisk bruk (J01, ekskl. metenamin), etterfulgt av tetracykliner (J01A; 26 %). De tre hyppigst brukte antibiotika i 2018 var fenoksymetylpenicillin, doksycyklin og pivmecillinam. Disse tre representerte 50 % av alle forskrevne resepter og 54 % 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 2018. I norske sykehus ble det gjennomsnittlig brukt 74 DDD/100 liggedøgn i 2018, dette er en økning på 10 % siden 2012. DDD/sykehusinnleggelse (i 2018; 3,1 DDD/innleggelse) økte med 2 % i samme periode. Terapimønster av antibakterielle midler i sykehus endres ikke mye fra ett år til et annet. Bruken av bredspektrede antibiotika er redusert fra 26 % av totalt antall DDD i 2012 til 21 % i 2018. I sykehus, ble penicilliner (J01C) mest brukt (ca halvparten av bruken målt i DDD) mens cefalosporiner er den neststørste antibiotikagruppen (18 % av alle DDD). Det er store variasjoner mellom sykehus, både målt i volum av antibiotika (DDD/100 liggedøgn) som brukes og i terapiprofil. Variasjonene kan ikke forklares med forskjeller i aktivitet eller pasientsammensetning alene.

Resistens hos kliniske isolater fra dyr

I 2018 ble det undersøkt kliniske isolater fra infeksjoner med *Escherichia coli* hos fjørfe (kylling, kalkun og vaktel) og *Staphylococcus aureus* fra mastitt hos sau. De aller fleste isolatene av både *E. coli* og *S. aureus* var fullt følsomme for de antibiotika det ble testet for. For *E. coli* var det vanligst å finne resistens mot kinoloner, tetracyklin og ampicillin. Resistens mot sulfamethoxazol og trimetoprim var vanligst hos *S. aureus* isolatene.

Resistens hos indikatorbakterier fra dyr og mat

Dataene fra NORM-VET 2018 bekrefter at forekomsten av antimikrobiell resistens hos bakterier fra dyr og mat i Norge er lav sammenliknet med andre land.

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* som er resistente mot tredje generasjons cefalosporiner eller karbapenemer, og kinolonresistente *E. coli*.

I 2018 ble det undersøkt avføringsprøver fra sau, samt blindtarm fra kylling- og kalkunflokker. I tillegg ble blindtarmsprøver fra kylling som slaktes etter 50 dagers levetid, undersøkt. Nesesvabre og miljøprøver fra sauebesetninger ble undersøkt for MRSA. I tillegg presenteres 2018-resultatene fra overvåkingsprogrammet for MRSA hos svin i rapporten. Av prøver fra mat ble det undersøkt kylling- og kalkunkjøtt, samt meieriprodukter, bladsalat og krydder-urter.

Analysene viser at majoriteten av *E. coli* isolatene fra sau, kylling og kalkun var fullt følsomme for alle de antibiotika det ble testet for. Blant isolatene som viste nedsatt følsomhet, var det resistens mot kinoloner og ampicillin som var mest vanlig fra kylling, mens resistens mot ampicillin, sulfamethoxazol, tetracyklin og trimetoprim var mest vanlig fra kalkun og sau. Dette er i samsvar med resultater fra tidligere år.

I den selektive screeningen for *E. coli* som er resistent mot tredje generasjons cefalosporiner, ble det kun påvist noen svært få isolater med plasmidmediert resistens fra kylling og kalkun, samt kylling- og kalkunkjøtt. Dette viser at forekomsten av disse overførbare resistensformene hos kylling og kalkun nå er sjelden i Norge sammenliknet med tidligere år. Det har vært en betydelig reduksjon av slik plasmidmediert resistens hos fjørfe og i fjørfekjøtt de siste årene. Dette har vært mulig takket være innsats gjort av fjørfenæringen. Resistens mot tredje generasjons cefalosporiner kan også være forårsaket av mutasjoner i bakterienes kromosom, og fra sau, kalkun, og kalkunkjøtt ble det påvist slike *E. coli* isolater. Det ble ikke påvist *E. coli* som er resistent mot tredje generasjons cefalosporiner, i den selektive screeningen av meieriprodukter. Fra bladsalat og krydderurter ble det imidlertid påvist noen isolater, og disse var forårsaket av gener som ikke er vanlige funn fra norske produksjonsdyr eller fra norskprodusert mat.

Karbapenemaseproduserende *Enterobacteriaceae* har aldri blitt påvist i prøver fra dyr eller mat fra Norge. Den selektive screeningen for karbapenemaseproduserende enterobakterier ble utført på alle de undersøkte kategorier av dyr og mat i 2018, uten at slike bakterier ble påvist. Det ble heller ikke påvist kolistinresistente *E. coli* i den selektive screeningen som ble utført på prøvene fra bladsalat og krydderurter, men ett av isolatene fra den selektive screeningen for *E. coli* med resistens mot tredje generasjons cefalosporiner hadde også et plasmidmediert kolistinresistensgen.

Selektive metoder for isolering av kinolonresistente *E. coli* ble utført på prøver fra sau og kylling som slaktes etter 50 dagers levetid, samt fra meieriprodukter, bladsalat og krydderurter. Resultatene viser at forekomsten for sau er tilsvarende som for storfe, og at forekomsten for kyllingflokkene som slaktes etter 50 dagers levetid tilsvarer forekomsten tidligere observert for ordinær kyllingproduksjon. Ingen av meieriproduktprøvene var positive, mens det ble påvist isolater fra noen av prøvene av bladsalat og krydderurter. Av disse isolatene var det noen som i tillegg var resistente mot tredje generasjons cefalosporiner og kolistin.

En høyere andel av *Enterococcus* spp. isolater fra kalkun enn fra kylling viste nedsatt følsomhet for flere av de antibiotika det ble testet for. Blant de *E. faecalis* isolatene som viste nedsatt følsomhet, var det resistens mot tetracyklin som var vanligst, fulgt av resistens mot erytromycin (og narasin for kalkunisolatene). Blant *E. faecium* var det resistens mot narasin som var vanligst, fulgt av resistens mot tetracyklin og erytromycin hos kyllingisolatene og resistens mot erytromycin, tetracyklin og ampicillin hos kalkunisolatene. Ingen av isolatene var resistente mot vankomycin. Det har vært en nedgang i forekomsten av vankomycinresistente *Enterococcus* spp. (VRE) de siste årene. I 2018, ble det ikke påvist VRE i noen av prøvene fra kylling og kalkun i de selektive undersøkelsene.

Det er begrensede funn av MRSA i den norske dyrepopulasjonen. Årlig gjennomføres det et omfattende overvåkingsprogram for MRSA i svinepopulasjonen. I 2018 ble det ikke påvist MRSA i noen svinebestninger. Prøver fra sau ble også undersøkt for MRSA i 2018, og MRSA ble påvist fra en miljøprøve i én besetning (0,4 %). Isolatet inneholdt *mecC* genet og tilhørte MRSA CC130, *spa*-type t843.

Resistens hos zoonotiske bakterier og andre enteropatogene bakterier

Zoonosebakterier isolert fra dyr

Den norske husdyrpopulasjonen er regnet som fri for *Salmonella*. I 2018 ble det sensitivitetstestet 18 *Salmonella* isolater fra dyr, hhv. fra fem katter, fire hunder, tre storfe, tre griser, et villsvin, et pinnsvin og en gås. Ni av isolatene var fullt følsomme, mens tre av de ni andre var resistent mot totalt seks av de undersøkte antibiotika. Alle disse tre var isolert i forbindelse med et *Salmonella* utbrudd på hest.

Campylobacter jejuni fra kylling og kalkun ble inkludert i overvåkingen i 2018. Resultatene viser at det er en lav forekomst av antibiotikaresistens blant *C. jejuni* fra både kylling (også hos de slaktet etter 50 dagers levetid) og kalkun.

Kliniske isolater av tarmpatogene bakterier fra mennesker

Kliniske isolater av *Salmonella, Campylobacter*, *Yersinia* og *Shigella* fra mennesker ble ikke inkludert i overvåkingen i 2018 på grunn av omorganisering av referanselaboratoriet ved Folkehelseinstituttet.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2018. Det ble påvist 11 tilfeller av methicillinresistente *Staphylococcus aureus* (MRSA) blant de 1445 blodkulturisolatene (0,8 %) som ble inkludert i NORM-protokollen. Dette samsvarer godt med tall fra laboratorienes datasystemer som rapporterte 17 MRSA-isolater blant 2055 *S. aureus* (0,8 %) fra blodkultur og spinalvæske i 2018. Andelen er på samme nivå som i 2016 (1,0 %) og 2017 (0,8 %). Meldesystemet for infeksjonssykdommer (MSIS) registrerte 905 tilfeller av MRSA-infeksjon i 2018 mot 887 i 2016 og 763 i 2017. De fleste tilfellene var fra pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (17 av 992; 1.7 %) slik de har gjort i tidligere år (1,6 % i 2016, 1,2 % i 2017). MSIS

registrerte videre 1631 tilfeller av MRSA-kolonisering i 2018 mot 1651 i 2016 og 1529 i 2017. I alt ble det meldt funn av MRSA hos 2301 personer i 2018, svarende til en insidensrate på 48/100 000 innbyggere. Overvåkingen viser at det totale antallet MRSA-registreringer er stabilt. Det påvises fortsatt svært få alvorlige MRSA-infeksjoner. Den økte insidensen av MRSA-kolonisering over de siste årene kan utgjøre en reell økning av MRSA-forekomsten, men kan også skyldes høyere testaktivitet.

Blodkulturisolater av *E. coli* viste en svakt synkende forekomst av resistens mot bredspektrede antibiotika i 2018. Forekomsten av gentamicinresistens var 5,4 % i 2018 sammenliknet med 6,3 % i 2016 og 7,0 % i 2017, mens forekomsten av resistens mot ciprofloxacin ble redusert fra 12,6 % i 2016 og 15,2 % i 2017, til 11,7 % i 2018. *Klebsiella* spp. har fortsatt lavere forekomst av resistens mot gentamicin (5,2 %) og ciprofloxacin (8,1 %) enn *E. coli*, men forskjellen er mindre enn tidligere.

Produksjon av bredspektrede beta-laktamaser (ESBL) er blitt et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 142/2184 *E. coli* (6,5 %) og 59/888 *Klebsiella* spp. (6,6 %) fra blodkultur ble rapportert som ESBL-positive i 2018. Forekomsten er stabil for *E. coli* (5,8 % i 2016; 6,6 % i 2017) men økende for *Klebsiella* spp. (4,6 % i 2016; 5,3 % i 2017). Andelen av ESBL-positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (6,5 %) enn fra urinprøver (3,7 %).

Karbapenemaseproduserende *Enterobacterales* (CPE), *Pseudomonas aeruginosa* og *Acinetobacter* spp. har vært meldepliktige til MSIS siden juli 2012. Antallet pasienter meldt med CPE økte fra 35 i 2017 til 54 i 2018, mens antallet pasienter meldt med karbapenemaseproduserende *P. aeruginosa* (n=3) og *Acinetobacter* spp. (n=19) var på samme nivå som i 2014-2016.

Overvåkingen av resistens hos *Haemophilus influenzae* og *Neisseria meningitidis* fra systemiske infeksjoner var meget begrenset i 2018 på grunn av omorganisering av referanselaboratoriene ved Folkehelseinstituttet. Et begrenset utvalg av *Neisseria gonorrhoeae* (n=315) viste utbredt resistens mot penicillin G (10,7 %), og bare 1,0 % var følsomme for standard dosering svarende til villtypepopulasjonen. Hele 68,9 % var resistente mot ciprofloxacin. Fire isolater var resistente mot cefixim (1,3 %), men alle var følsomme for ceftriaxon.

Det ble påvist tre enterokokkisolater fra blodkultur med klinisk signifikant vankomycinresistens i 2018 (alle VanB *E. faecium*). Forekomsten av resistens mot ampicillin i *E. faecium* ligger stabilt rundt 70-80 %. Høygradig gentamicinresistens ble påvist i 14,1 % av *E. faecalis* og 32,0 % av *E. faecium*. Dette er en reduksjon fra henholdsvis 15,5 % og 40,6 % i 2017, og dermed fortsatte den fallende tendensen for aminoglykosidresistens hos enterokokker. Alle *E. faecium* med høygradig gentamicinresistens var også resistente mot ampicillin. Det ble ikke funnet linezolidresistente enterokokker i NORM-overvåkingen i 2018, men referanselaboratoriet ved K-res på UNN påviste i alt ni slike tilfeller (*E. faecalis* n=6; *E. faecium* n=3).

Det ble påvist resistens mot penicillin G hos 0,6 % av *Streptococcus pneumoniae* fra blodkultur/spinalvæske og 0,2 % fra luftveisprøver, men henholdsvis 8,3 % og 6,9 % av isolatene var kun følsomme ved forhøyet dosering. Dette er på samme nivå som i 2017. Det ble ikke påvist resistens mot cefalosporiner. Forekomsten av makrolidresistens ved systemiske infeksjoner var 6,0 % i 2018 sammenliknet med 5,6 % i 2016 og 7,8 % i 2017.

Alle isolater av betahemolytiske streptokokker gruppe A (*Streptococcus pyogenes*), B (*S. agalactiae*), C og G (*S. dysgalactiae*) var følsomme for penicilin G. Det ble påvist resistens mot makrolider hos 22,6 % av betahemolytiske streptokokker gruppe B (22,7 % i 2017) og 10,2 % av gruppe C og G (ikke tidligere undersøkt) fra systemiske infeksjoner.

I alt 209 tilfeller av tuberkulose ble meldt til MSIS i 2018. Det ble utført resistensbestemmelse av 167 *Mycobacterium tuberculosis* isolater. Fire isolater (2,4 %) fra pasienter smittet i henholdsvis Afrika (n=2) og Europa utenom Norge (n=2) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 178 *Candida* blodkulturisolater av ti ulike species. De vanligste artene var *C. albicans* (n=117), *C. glabrata* (n=33), *C. tropicalis* (n=8), *C. parapsilosis* (n=7) og *C. dubliniensis* (n=7). Alle *C. albicans* var følsomme for de undersøkte midlene bortsett fra et enkelt echinokandinresistent isolat. Det ble kun påvist enkelte non-albicans isolater med ervervet resistens mot anytimykotika, 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 nineteenth 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 2018. 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 5,167 kg active substance in 2018.

Sales of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,821 kg in 2018. Penicillins continued to be the most-selling antibacterial class for the major species – i.e. cattle, pigs, goat, sheep and poultry – and were almost exclusively accounted for by benzylpenicillin. From 2013 to 2018 the estimated sales of antibacterial VMPs for cattle, pigs, poultry, sheep and goat declined by 17% both when measured in kg and in mg/PCU (population correction unit). The sales of the antibacterial VMPs containing substances defined by the World Health Organization as highest priority critically important antimicrobials (CIA) for human medicine remained very low. The sales (kg) of antibacterial VMPs for group treatment of terrestrial food-producing animals in Norway continued to be very low; in 2018 such products accounted for only 4% of the total sales. For horses, the usage was mainly accounted for by trimethoprim-sulfa (oral paste).

In 2018, the sales (kg) of antibacterial VMPs for farmed fish for consumption (i.e. cleaner fish excluded) were 871 kg. This is a reduction of more than 99% compared to 1987, when the sales were at its highest. For Atlantic salmon and rainbow trout, fish in only 1.6% of the on-grower locations were subjected to antibacterial treatment in 2018.

The sales (kg) of antibacterial VMPs marketed for companion animals were 347 kg in 2018. From 2013 to 2018 the sales of such VMPs for use in companion animals have been reduced by 34%. When including prescription of antibacterial human medicinal products (estimated from Veterinary Prescription Register) the estimated reduction was 24%.

In February 2015, the Norwegian poultry industry launched a project aiming at phasing out use of narasin as coccidiostat feed additive in broilers, a goal that was reached in June 2016. The usage of therapeutic antibiotics for broilers continues to be very low; in 2018, 0.1% of the broiler flocks were subjected to such treatment and only narrow-spectrum 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 24% since 2012. With total antibiotic use we mean all sales of antibacterial agents for systemic use in humans (J01, excl. methenamine) i.e. in primary care and to institutions. Also in 2018 the decrease continued, by 3% compared with last year. Total sales declined from 13.3 DDD/1,000 inhabitants/day in 2017 to 12.9 DDD/1,000 inhabitants/day in 2018. The proportion of narrow-spectrum penicillins (J01CE) was stable at 27% 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 84% of the total human sales of antibacterials are used in primary care, i.e. outside health institutions. For ambulatory care, the most important antibiotic group in 2018 were penicillins (J01C) with 53% of all DDDs for systemic antibacterials (J01, excl. methenamine), followed by tetracyclines (J01A) at 26%. The three most commonly prescribed antibiotics for outpatients in 2018 were phenoxymethylpenicillin, doxycycline and pivmecillinam. These three substances represented 50% of all prescriptions and 54% of all DDDs sold. Dentists prescribe around 5% of all DDDs in primary care.

In 2018, the antibacterial sales (in DDDs) to hospitals represented 8% of total sales of antibacterials for human use in the country. In 2018, a mean use of 74 DDD/100 bed days was observed, an increase by 10% since 2012. The amount measured in DDD/admission (3.1 in 2018) increased by 2 % in the same period. The therapy pattern of antibacterials in hospitals does not change much from one year to another. The use of broad-spectrum antibiotics is reduced and accounted for 21% of total DDDs for hospitals in 2018 compared to 26% in 2012. Around half of the hospital use is penicillins (J01C) when measured in DDDs. The second largest group is the cephalosporins; 18% of all DDDs. There are large variations between the hospitals in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile. The variations cannot be accounted for by differences in activity or patient composition alone.

Resistance in animal clinical isolates

The clinical isolates included in NORM-VET 2018 were from *Escherichia coli* infections in poultry (broiler, turkey and quail) and *Staphylococcus aureus* from mastitis (milk) in sheep. The majority of both *E. coli* and *S. aureus* isolates were susceptible to all antimicrobial agents included in the susceptibility testing. The most common resistances among *E. coli* isolates were to quinolones, tetracycline, and ampicillin. Resistance to sulfamethoxazole and trimethoprim was most common for the *S. aureus* isolates.

Resistance in indicator bacteria from animals and food

The 2018 data confirm that the prevalence of antimicrobial resistance in bacteria from animals and food in Norway is low compared to other countries. 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 in animals and food (2013/652/EU). In addition, antimicrobial testing of bacteria from other sources than those included in this decision, or investigation of the presence of specific antimicrobial resistant bacteria by selective methods, are included. The use of selective methods is especially relevant for low-prevalence sources, as it enables early detection of important resistance mechanisms; thereby enabling these to be monitored and characterised.

In 2018, sheep, and broiler and turkey flocks were sampled at slaughter to obtain bacteria from the intestinal flora. An additional survey of bacteria from the intestinal flora of broilers over 50 days of age at slaughter were also performed. From sheep herds, nasal swabs and sterile moistened cloths for environmental samples were also included for methicillin resistant *Staphylococcus aureus* (MRSA) detection. In addition, the results from the surveillance programme for MRSA in swine are described in the report. Food samples included broiler and turkey meat, as well as dairy products, and leafy greens and leafy herbs.

The majority of *E. coli* isolates from broilers, turkey and sheep were fully susceptible to the antimicrobial agents in the test panel. Among the isolates showing decreased susceptibility, resistance to quinolones (ciprofloxacin and nalidixic acid) and ampicillin was most common in broilers, while resistance to ampicillin, sulfamethoxazole, tetracycline and trimethoprim was most common in turkey and sheep. These results are in concordance with previous results.

Only a few isolates resistant to third generation cephalosporins due to plasmid encoded resistance genes were detected in the selective screening of samples from broilers and turkey, and meat thereof, indicating that such plasmids are rare. There has been a substantial decrease of *E. coli* resistant to third generation cephalosporins in broiler flocks and meat thereof compared to previous years. This decrease has been possible due to measures taken by the industry. A few isolates resistant to third generation cephalosporins due to chromosomal mutations were detected, and these were from turkey and turkey meat, and from sheep. None of the samples from dairy products were positive in the screening for third generation cephalosporin resistant *E. coli*. A few isolates were detected from leafy greens and leafy herbs, and these isolates harboured plasmid-mediated genes not commonly found in samples from domestic production animals or food.

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 2018. No colistin resistant *E. coli* were detected by selective screening of samples from leafy greens and leafy herbs. However, one isolate detected in the selective screening for *E. coli* resistant to third generation cephalosporins from leafy herbs was in addition resistant to colistin and harboured a plasmid-encoded colistin resistance gene.

A selective method for isolation of quinolone resistant *E. coli* was performed on samples from sheep, broilers over 50 days of age at slaughter, dairy products and leafy greens and leafy herbs. The results from sheep are consistent with previous results from cattle, with 7.3% positive samples. Similarly, the results for broilers over 50 days of age at slaughter are consistent with previous results from ordinary broiler flocks. Quinolone resistant *E. coli* was detected in 80.8% of the flock samples. None of the dairy product samples were positive. Among the isolates detected from leafy greens and leafy herbs (6.2%), a few showed additional resistance to third generation cephalosporins due to presence of plasmid encoded genes. Additional resistance to colistin was also detected in one quinolone resistant isolate, and this was encoded by a plasmid-mediated gene as well.

Enterococcus spp. isolates from turkey were less susceptible than broiler isolates. Among the *E. faecalis* isolates showing decreased susceptibility, resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to erythromycin (and narasin for the turkey isolates). Among *E. faecium* isolates, resistance to narasin was the most frequently identified resistance determinant, followed by resistance to tetracycline and erythromycin for broiler isolates and resistance to erythromycin, tetracycline and ampicillin in turkey isolates. None of the isolates displayed resistance to vancomycin.

There has been a significant decrease in the occurrence of vancomycin resistant *Enterococcus* spp. (VRE) the last years. In 2018, no VRE were detected from any of the broiler or turkey flock samples in the selective screening.

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 MRSA in 2018. In addition, samples from sheep herds were investigated for MRSA, which was detected in one environmental sample from one of the herds (0.4%). The isolate carried the *mecC* gene and belonged to CC130, *spa*-type t843.

Resistance in zoonotic bacteria and non-zoonotic enteropathogenic bacteria

Animal isolates

The Norwegian animal production population is considered virtually free from *Salmonella* spp. In 2018, 18 *Salmonella* spp. isolates from animals were susceptibility tested. These included five cats, four dogs, three cattle, three pigs, one wild hog, one hedgehog and one goose, respectively. Nine of the isolates were fully susceptible to all substances tested for. Three of the nine remaining isolates were resistant to a total of six of the tested antimicrobials. These three were obtained in connection to a *Salmonella* outbreak in horses.

Campylobacter jejuni from broilers (including broilers slaughtered after 50 days of age) and turkey were included in 2018. The results indicate a low occurrence of resistance among the *C. jejuni* isolates from both broilers and turkey.

Human clinical enteropathogenic isolates

Clinical isolates of *Salmonella, Campylobacter*, *Yersinia* and *Shigella* from humans were not included in the surveillance programme in 2018 due to reorganisation of the reference laboratory at the Norwegian Institute of Public Health.

Resistance in human clinical isolates

The prevalence of antimicrobial resistance in human clinical isolates was still low in Norway in 2018. Only eleven methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 1,445 strains included in the NORM protocol (0.8%). During 2018, the total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 2,055 including 17 MRSA strains (0.8%). This is at the same level as in 2016 (1.0%) and 2017 (0.8%). The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 905 cases of MRSA infections in 2018 compared to 887 in 2016 and 763 in 2017. The majority of MRSA cases were reported as wound infections and/or abscesses. The proportion of MRSA among non-invasive *S. aureus* isolates is still very low at 1.7% (17/992), as it was in 2016 (1.6%) and 2017 (1.2%). Furthermore, MSIS registered 1,631 MRSA colonisations compared to 1,651 in 2016 and 1,529 in 2017. A total of 2,301 persons were reported with MRSA in 2018, corresponding to an incidence rate of 48/100,000 inhabitants. The results indicate a relatively stable rate of MRSA notifications. The incidence of invasive disease has remained stable at a low level. The increased rate of reported colonisation in recent years may reflect spread of MRSA in the population and/or increased test activity.

The rate of resistance to broad-spectrum antimicrobials in *E. coli* blood culture isolates decreased slightly in 2018. The prevalence of gentamicin resistance was 5.4% in 2018 compared to 6.3% in 2016 and 7.0% in 2017, while the prevalence of ciprofloxacin resistance decreased from 12.6% in 2016 and 15.2% in 2017, to 11.7% in 2018. *Klebsiella* spp. still demonstrates lower rates of resistance to gentamicin (5.2%) and ciprofloxacin (8.1%) than *E. coli*, but the difference is reduced compared to previous years.

Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 142/2,184 (6.5%) *E. coli* and 59/888 (6.6%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2018. The prevalence was stable for *E. coli* (5.8% in 2016; 6.6% in 2017) but increasing for *Klebsiella* spp. (4.6% in 2016; 5.3% in 2017). The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (6.5%) than in urinary tract isolates (3.7%). Carbapenemase-producing *Enterobacterales* (CPE), *Pseudomonas aeruginosa* and *Acinetobacter* spp. have been notifiable to MSIS since July 2012. The number of patients reported with CPE increased from 35 in 2017 to 54 in 2018, while the number of patients with carbapenemase-producing *P. aeruginosa* (n=3) and *Acinetobacter* spp. (n=19) was stable 2014-2016.

The surveillance of resistance in systemic isolates of *Haemophilus influenzae* and *Neisseria meningitidis* was very limited in 2018 due to reorganisation of the reference laboratories at the Norwegian Institute of Public Health. A limited number of *Neisseria gonorrhoeae* isolates (n=315) displayed resistance to penicillin G (10.7%), and only 1.0% were susceptible to standard dosage corresponding to the wildtype population. Ciprofloxacin resistance was detected in 68.9% of the isolates. Four isolates were resistant to cefixime (1.2%), but all remained susceptible to ceftriaxone and spectinomycin.

Three enterococcal blood culture isolates (0.5%) with clinically significant vancomycin resistance were detected in 2018 (all VanB *E. faecium*). The prevalence of ampicillin resistance in *E. faecium* has stabilised around 70-80%. High-level gentamicin resistance (HLGR) was detected in 14.1% of *E. faecalis* and 32.0% of *E. faecium* isolates. This is a decrease from 15.5% and 40.6% in 2017, respectively, thus continuing the downward trend for aminoglycoside resistance in enterococci. All HLGR *E. faecium* isolates were also resistant to ampicillin. There were no linezolid resistant isolates in the NORM surveillance program in 2018, but the reference laboratory at K-res/UNN detected a total of nine such isolates (*E. faecalis* n=6 and *E. faecium* n=3).

Penicillin G resistance was detected in 0.6% of *Streptococcus pneumoniae* isolates from blood cultures and cerebrospinal fluids and in 0.2% from respiratory tract samples, but 8.3% and 6.9% of the isolates were only susceptible to increased dosage, respectively. This is at the same level as in 2017. Resistance to cephalosporins was not detected. The prevalence of macrolide resistance in systemic infections was 6.0% in 2018 compared to 5.6% in 2016 and 7.8% in 2017.

All isolates of beta-haemolytic streptococci group A (*Streptococcus pyogenes*), B (*S. agalactiae*), C and G (*S. dysgalactiae*) were susceptible to penicillin G. Macrolide resistance was detected in 22.6% of streptococci group B (22.7% in 2017) and in 10.2% of streptococci group C and G (not previously surveyed) from systemic infections.

A total of 209 cases of tuberculosis were reported to MSIS in 2018. Susceptibility testing was performed on 167 *Mycobacterium tuberculosis* isolates. Four isolates (2.4%) originating from Africa (n=2) and Europe excluding Norway (n=2) were classified as multi-drug resistant (MDR).

Susceptibility testing was performed on 178 *Candida* spp. blood culture isolates of ten different species. The most common species were *C. albicans* (n=117), *C. glabrata* (n=33), *C. tropicals* (n=8), *C. parapsilosis* (n=7) and *C. dubliniensis* (n=7). All *C. albicans* isolates were fully susceptible to the substances examined with the exceptipon of a single echinocandin resistant isolate. Only single non-albicans isolates with acquired fluconazole resistance were detected, but as expected there was a high prevalence of resistance to azoles among *C. glabrata*. 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. Continuous efforts and awareness rising are needed to preserve the favourable situation and ensure that antibacterials are effective when needed. The NORM/ NORM-VET report is vital in order to document the trends in antibiotic usage and occurrence of resistance in humans and animals, and to evaluate the effectiveness of interventions.

POPULATION STATISTICS

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

TABLE 1. Human population in Norway as of 01.01.2019.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	294 863	151 852	143 011
5 to 14 years	640 095	328 144	311 951
15 to 24 years	661 730	341 501	320 229
25 to 44 years	1 438 768	737 090	701 678
45 to 64 years	1 373 915	700 751	673 164
65 years and older	918 841	425 735	493 106
All age groups	5 328 212	2 685 073	2 643 139

TABLE 2. Livestock population in Norway in 2018.
Data provided by the Register of Production Subsidies as of 1.03.2018.

	Number* of	
Animal category	Herds	Animals
Cattle	13,700	992,000
Dairy cows only**	6,800	182,000
Suckling cow only**	4,400	77,800
Combined production (cow)**	750	39,000
Goat	1,200	69,600
Dairy goat**	340	35,500
Sheep	14,300	1,006,000
Breeding sheep > 1 year**	14,300	1,006,000
Swine	2,000	800,000
Breeding animal > 6 months**	1,100	49,500
Fattening pigs for slaughter**	1900	443,000
Laying hen flocks > 250 birds	590	4,338,000
Broilers	660[1]	62,739,000[2]
Turkey, ducks, geese for slaughter (flock > 250 birds)	38	406,000

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

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2018. Data provided by the Norwegian Directorate of Fisheries updated by 19.06.2019.

Year	Atlantic salmon (tonnes)	Rainbow trout (tonnes)	Cod (tonnes)	Arctic char (tonnes[2])	Halibut (tonnes[2])	Blue mussels (tonnes)	Scallops[1] (tonnes)	Oysters (tonnes)
1992	141,000	-	-	-	-	-	-	-
1993	170,000	-	-	-	-	-	-	-
1994	204,686	14,571	569	262	63	542	-	-
1995	261,522	14,704	284	273	134	388	-	-
1996	297,557	22,966	191	221	138	184	-	-
1997	332,581	33,295	304	350	113	502	-	-
1998	361,879	48,431	203	200	291	309	-	-
1999	425,154	48,692	147	498	451	662	67	41
2000	440,061	48,778	169	129	548	851	38	8
2001	435,119	71,764	864	318	377	920	22	3
2002	462,495	83,560	1,258	319	424	2,557	5	2
2003	509,544	68,931	2,185	272	426	1,829	1	2
2004	563,915	63,401	3,165	365	648	3,747	46	3
2005	586,512	58,875	7,409	352	1,197	4,885	3	2
2006	629,888	62,702	11,087	897	1,185	3,714	4	1
2007	744,222	77,381	11,104	394	2,308	3,165	6	4
2008	737,694	85,176	18,052	468	1,587	2,035	4	3
2009	862,908	73,990	20,924	421	1,568	1,649	7.7	3.8
2010	939,575	54,451	21,240	492	1,610	1,930	10.3	2.1
2011	1,064,868	58,472	15,273	276	2,767	1,743	13	2
2012	1,241,482	70,364	10,033	309	1,741	1,967	21	2
2013	1,168,324	71,449	3,770	281	1,385	2,328	23	5
2014	1,258,356	68,910	1,213	285	1,257	1,983	13	4
2015	1,303,346	72,921	5	257	1,243	2,731	21	10
2016	1,233,619	87,446	0	330	1,461	2,231	12	11
2017	1,236,353	66,902	117	339	1,623	2,383	29	17
2018[3]	1,281,872	67,886	495	285	1,843	1,649	28	18

[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 2018 was 21 camelids, 16 sheep and 29,561 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 1993-2018 of antibacterial veterinary medicinal products (VMP) for terrestrial animal species, obtained at wholesaler's level, have been stratified into sales of antibacterial VMPs approved for terrestrial food-producing animals, including horses, and approved for companion animals, respectively (Appendix 1). The data are based on sales to Norwegian pharmacies from medicine wholesalers of VMPs for therapeutic use. This includes all pharmaceutical formulations approved for food-producing terrestrial animals, including horses, and for companion animals sold in Norway (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 2018 were 5,167 kg. A decline of the annual sales of such VMPs of 44% in the period 1993-2018 is observed (Figure 1).

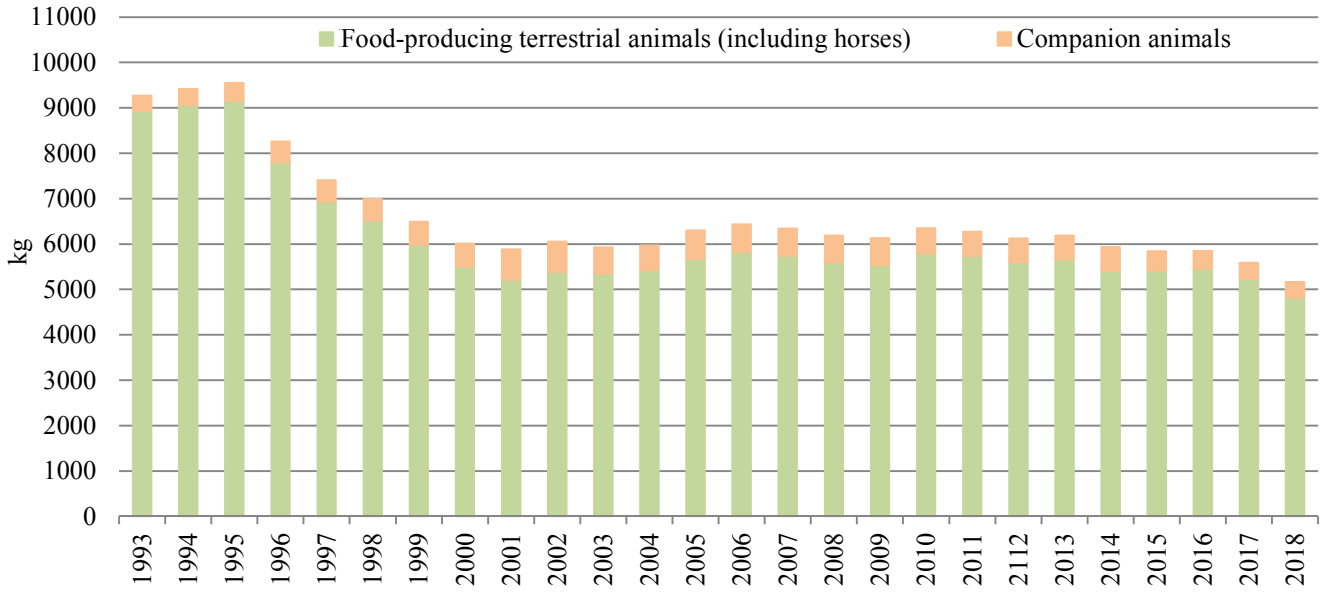

FIGURE 1. Total sales, in kg active substance, for food-producing terrestrial animals (including horses) and companion animals, of antibacterial veterinary medicinal products for therapeutic use in Norway in 1993-2018.

Food-producing terrestrial animals, including horses

In 2018 the sales, in kg active substance, of antibacterial VMPs for use in terrestrial food-producing animals, including horses, were 4,821 kg. Compared to 1993, a decrease in the sales of such VMPs of 46% is observed (Figures 1 and 2).

In total, 58% of the sales (kg) of antibacterial VMPs for this animal category contained penicillins only; 28% was accounted for by combination VMPs with trimethoprim-sulfa; of this combination 83% was sold as orale paste for horses.

The proportion of sales of VMPs containing only penicillins for this animal category increased from 19% to 58% during the period 1993-2018. This is almost solely due to reduced sales of injectable and intramammary combination VMPs of penicillins and aminoglycosides (dihydrostreptomycin) that have been gradually replaced by products containing penicillin as the sole antibacterial agent.

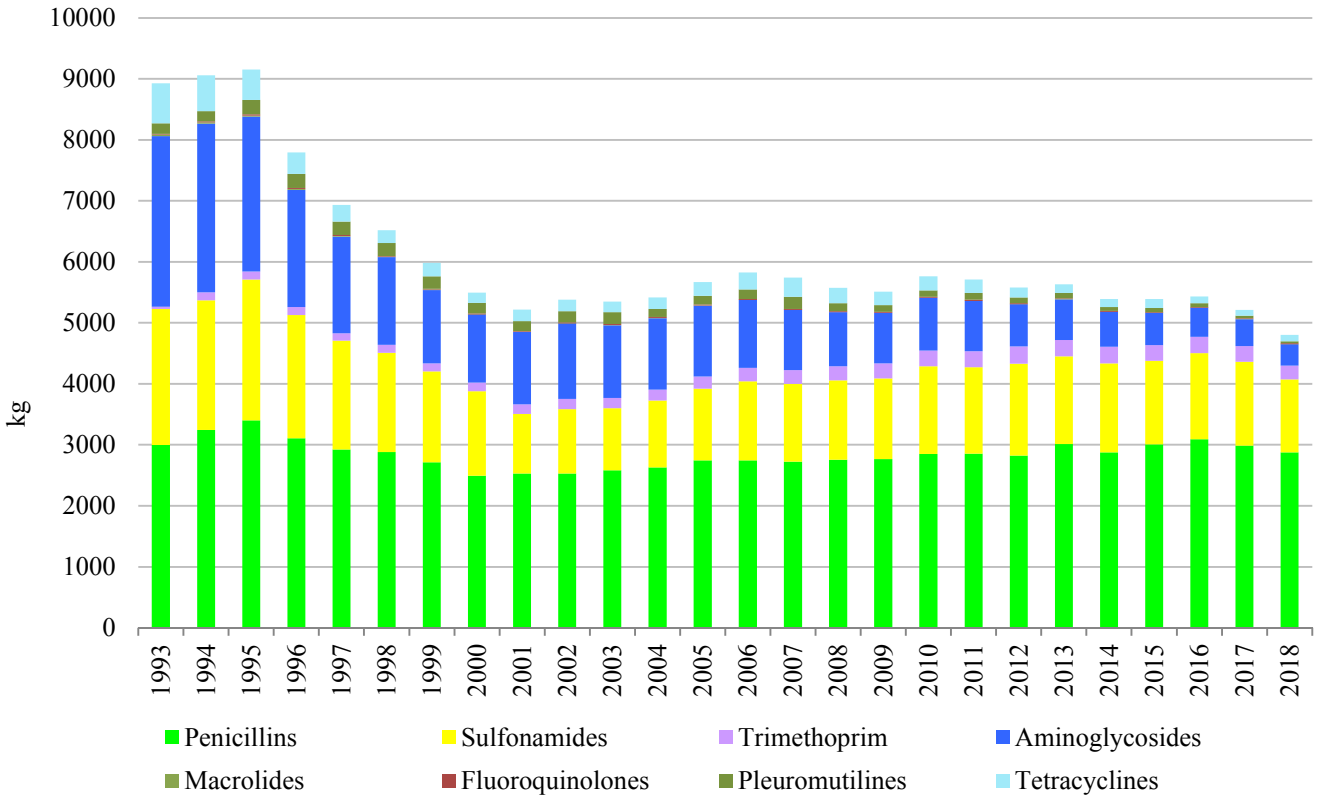

FIGURE 2. Sales, in kg active substance, of antibacterial veterinary medicinal products (VMPs) for therapeutic use in food-producing terrestrial animals, including horses, in Norway in 1993-2018. In addition, minor amounts of amphenicols VMPs were sold in 2008-2018 (range 16-27 kg). Minor amounts of baquiloprim sold annually 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 (https://www.who.int/foodsafety/cia/en/) have decreased substantially (59%) from 1993 to 2018 (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 1993-2018 accounting for between 0.2% and 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 HP CIA should be the last choice antibiotic. During 1993-2018 no VMPs containing third and higher generations of cephalosporins have been approved for food-producing animals in Norway via national procedures. Two third generation products have been approved via community procedures, but these are not marketed in Norway. Applications for special permits to use such VMPs marketed in other EEA countries for food-producing animals are normally not approved. An approval would only be given for specific animals if sensitivity testing precludes all other options. This is the case also for polymyxins (colistin) VMPs (Tonje Høy, Norwegian Medicines Authority, personal communication). Glyco-peptides are not allowed for food-producing animals in EU/EEA countries.

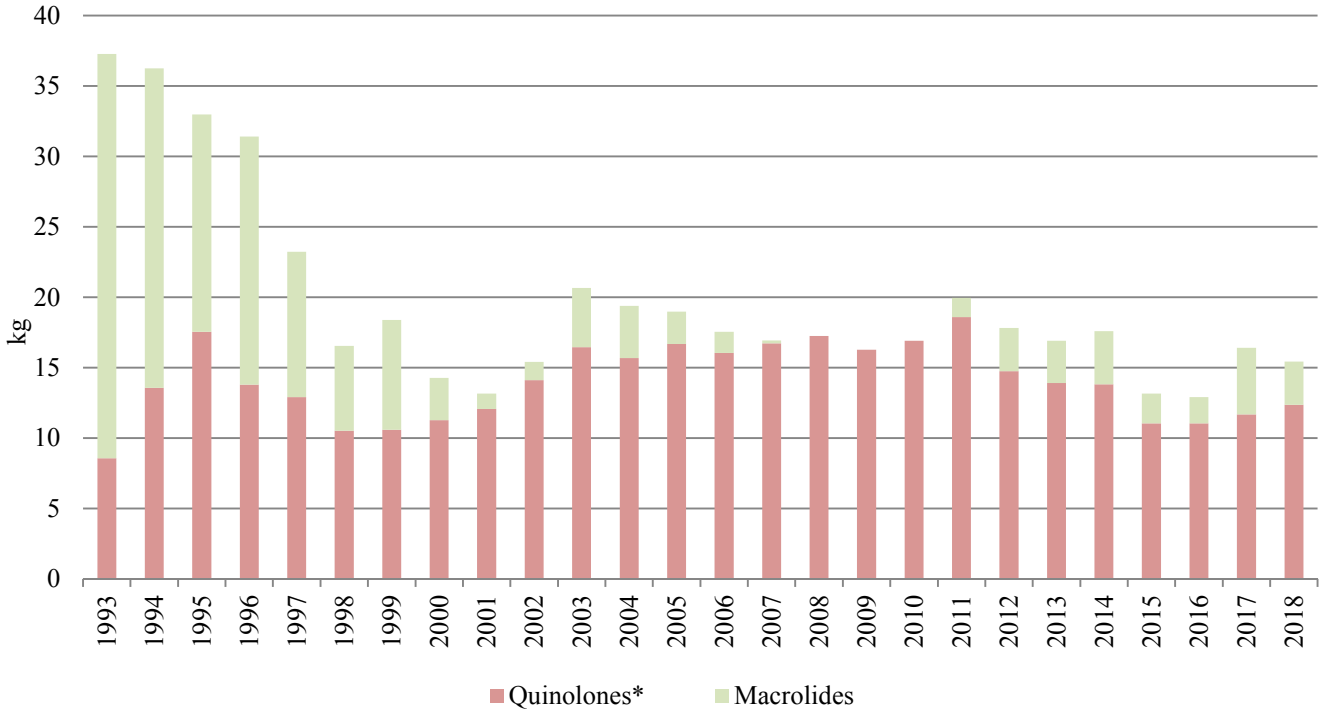

FIGURE 3. Overall sales, in kg of active substance, of antibacterial veterinary medicinal products (VMPs) containing the highest priority critically important antimicrobials for human medicine (categorised by WHO), i.e. quinolones (*fluoroquinolones only) and macrolides, for therapeutic use in terrestrial food-producing animals (including horses) in Norway in 1993-2018.

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 primarily by injectables. This reflects that the livestock is characterised by small herds, but it can also partly be explained by therapeutic traditions. In 2018, only 4% of the sales of antibiotic VMPs for food-producing terrestrial animals were for VMPs for group treatment (oral treatment).

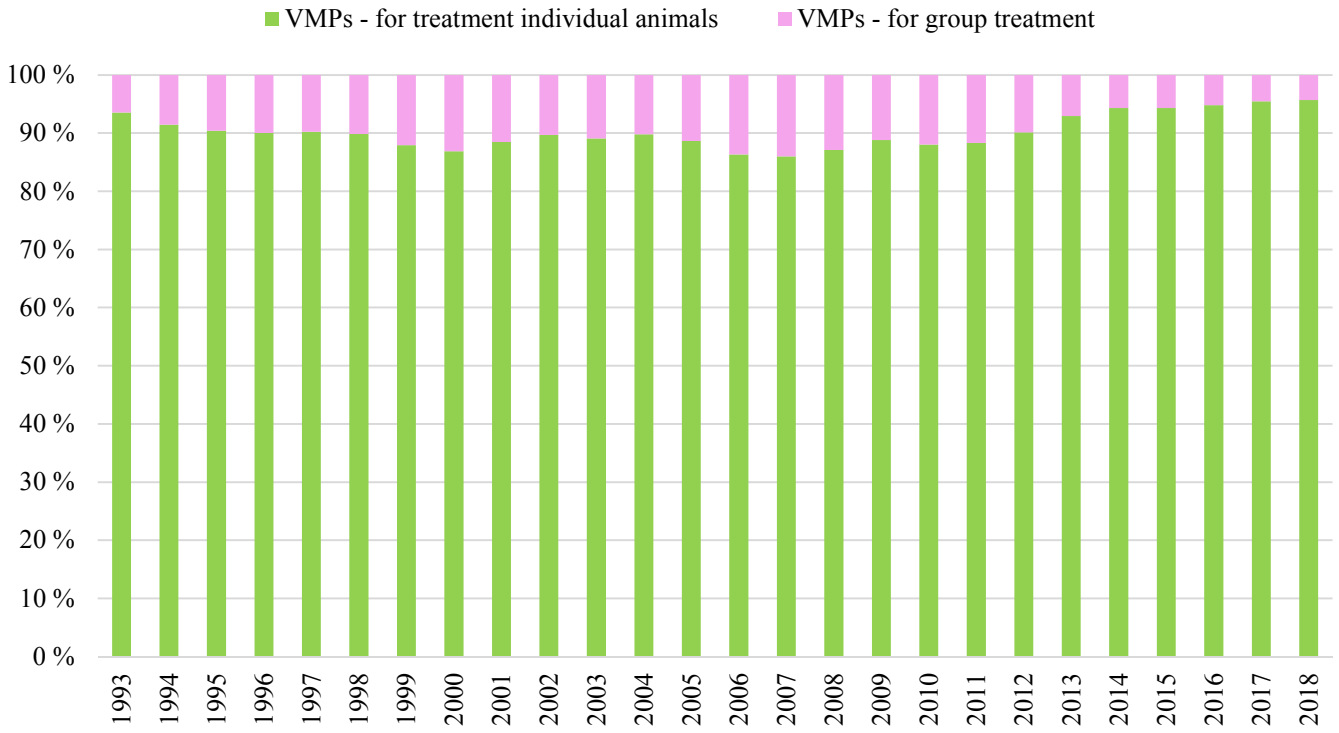

FIGURE 4. Proportion of sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for treatment of individual food-producing terrestrial animals (bolus, injectables, intramammary preparations, intrauterine preparations, oral paste and some tablet VMP presentations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

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 in 2018, 85.8% were penicillins, 5.7% trimethoprim-sulfa, 4.2% aminoglycosides, 1.4 % tetracyclines and 2.9% others. Of the penicillins 98% was accounted for by benzylpenicillin (as prodrugs). Note that intramammaries were not included in this analysis (see Appendix 1).

Of prescriptions (VetReg data) of VMPs for cattle in 2018, 89.2% (kg active substance) were for penicillins (intra-mammaries not included); of these 99% was accounted for by benzylpenicillin (as prodrugs) (Figure 5). These figures were in the same order for 2015, 2016 and 2017.

For intrammaries the sales data are used to document the prescribing patterns; the sales of intramammaries containing penicillins only accounted for 30% in 2018 and for combinations of penicillins and aminoglycosides (dihydrostreptomycin) this figure was 70%. Of the penicillins VMPs reported to VetReg as prescribed for treatment of pigs (Figure 6), 86.8% was accounted for by penicillins; of this 96% was accounted for by benzylpenicillin (as prodrugs).

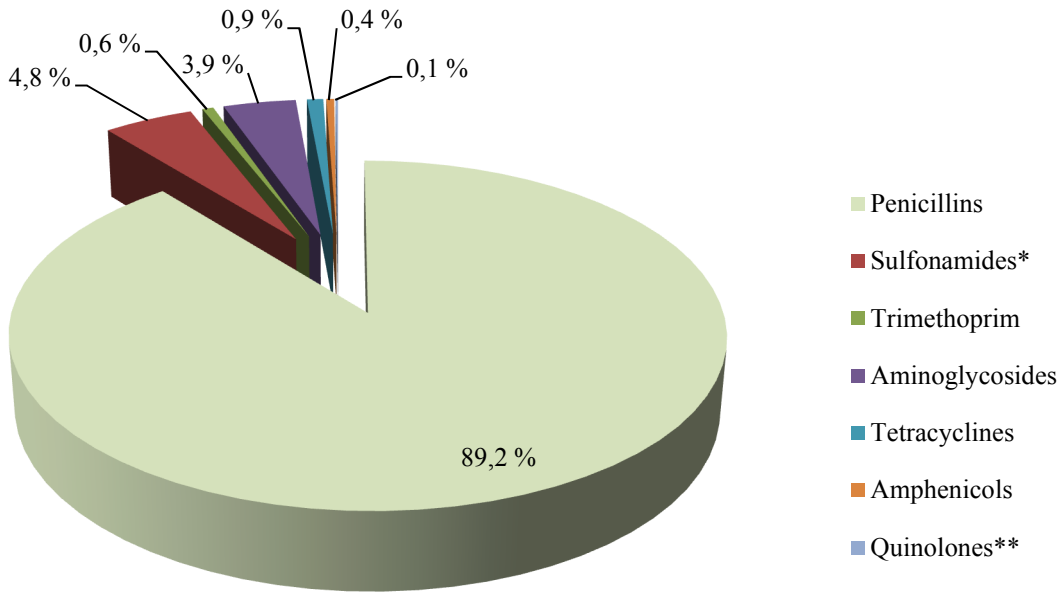

FIGURE 5. Prescribing patterns, in kg active substance, of antibacterial veterinary medicinal products for cattle in Norway in 2018. Data were obtained from the Veterinary Prescription Register (intramammaries not included); *In combination with trimethoprim only. **Fluoroquinolones only. In addition < 0.05% of the prescribed amounts were macrolides.

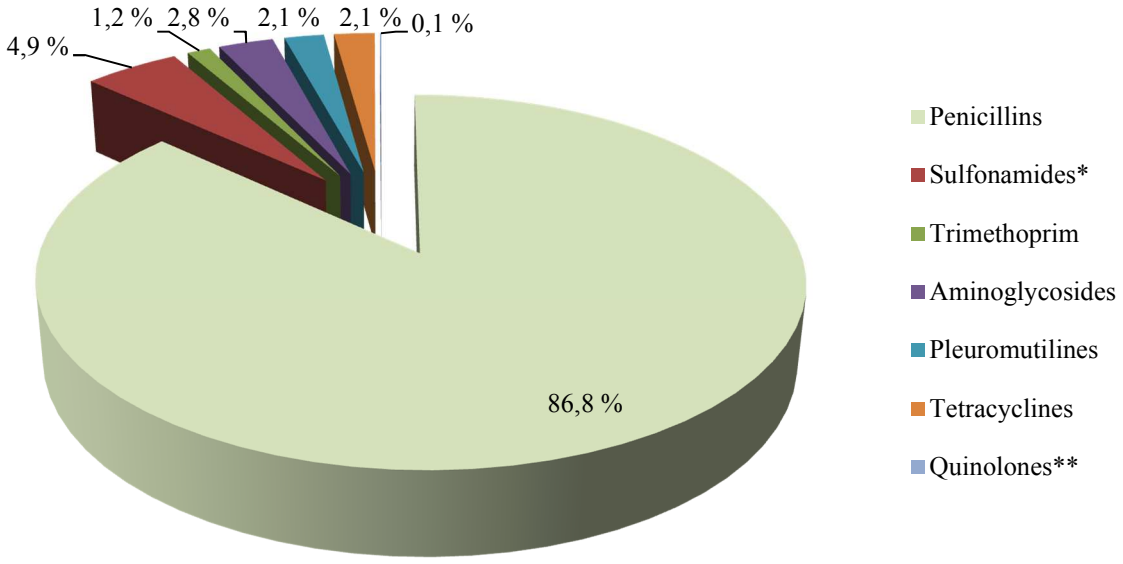

FIGURE 6. Prescribing patterns, in kg active substance, of antibacterial veterinary medicinal products for pigs in Norway in 2018. Data were obtained from the Veterinary Prescription Register. *In combination with trimethoprim only. **Fluoroquinolones only.

Farmed fish

In 2018, the total amount of antibiotics prescribed for use in aquaculture in Norway was 931 kg (Table 4); of this 871 kg were prescribed for farmed fish for human consumption (cleaner fish excluded). Compared to 2015 and 2016, there was an increase in the amounts (kg) of antibacterials prescribed for farmed fish in 2017 and 2018. This was not due to an increase in the number of treatments of farmed fish with antibacterials as the number of prescriptions for these four years was 61, 63, 63 and 43, respectively (Figure 7). The reason for the observed increase is that both in 2017 and 2018 a few sea-site locations with Atlantic salmon with high weight were subjected to treatment with antibiotics, while in 2015 and 2016 such cases were not reported.

TABLE 4. Usage, in kg of active substance, of antibacterial veterinary medicinal products for farmed fish in Norway in 2009-2018. For 2009-2012 the data represent sales data from feed mills and wholesalers collected by the Norwegian Institute of Public Health; for 2013-2018 data represent prescription data obtained from the Veterinary Prescription Register (See Appendix 1). Note that data include antibacterials for use in cleaner fish.

Active substance	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018[1]
Tetracyclines										
Oxytetracycline	40	10	1	1	0	0	0	0	0	20
Amphenicols										
Florfenicol	303	275	336	191	236	399	189	135	269	858
Quinolones										
Flumequine	1	0	0	0	0	25	< 0.05	< 0.05	< 0.05	0
Oxolinic acid	926	308	212	1,399	599	99	84	66	343	54
Combinations										
Spectinomycin + lincomycin (2+1)	43	57	0	0	0	0	0	0	0	0
Total	**1,313**	**650**	**549**	**1,591**	**860**	**523**	**273**	**201**	**612**	**931**

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

For the years 2013 to 2018, the major proportion of prescriptions was for farmed fish in the pre-ongrower phase (Figure 7). The number of prescriptions of antibacterial VMPs for Atlantic salmon ongrowers was negligible during the period 2013-2018, despite that Atlantic salmon represents more than 95% of the biomass farmed fish produced in Norway. This is a strong indication that the vaccines used are efficient and that the coverage of vaccination of fingerlings is complete.

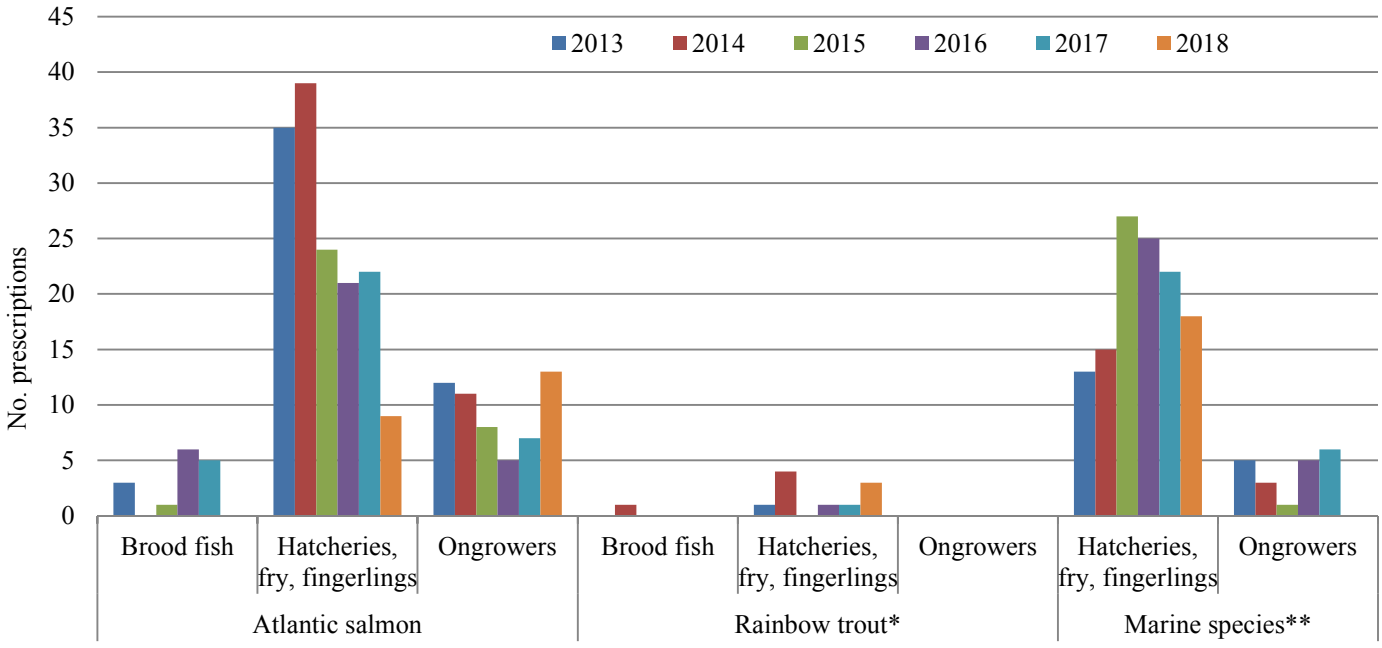

FIGURE 7. Number of prescriptions of antibiotics by fish species, split into production stages/types, in Norway in 2013-2018. Data were obtained from the Veterinary Prescription Register. *Includes two prescriptions for trout (*Salmo tutta*) fingelings. **Cod, halibut, pollack, turbot and wolffish. Note that cleaner fish are not included.

The annual sales of antibacterial VMPs for use in aquaculture peaked in 1987 when it amounted to 48 tonnes (Figure 8) – i.e. 876 mg/PCU; the corresponding figure in 2018 was 0.7 mg/PCU. Thus the sales in mg/PCU have declined by 99.9% (Table 4). The significant decrease in the usage of antibacterial agents in Norwegian aquaculture from 1987 is mainly attributed to the introduction of effective vaccines against bacterial diseases in Atlantic salmon and rainbow trout but also prevention of bacterial diseases and their spread.

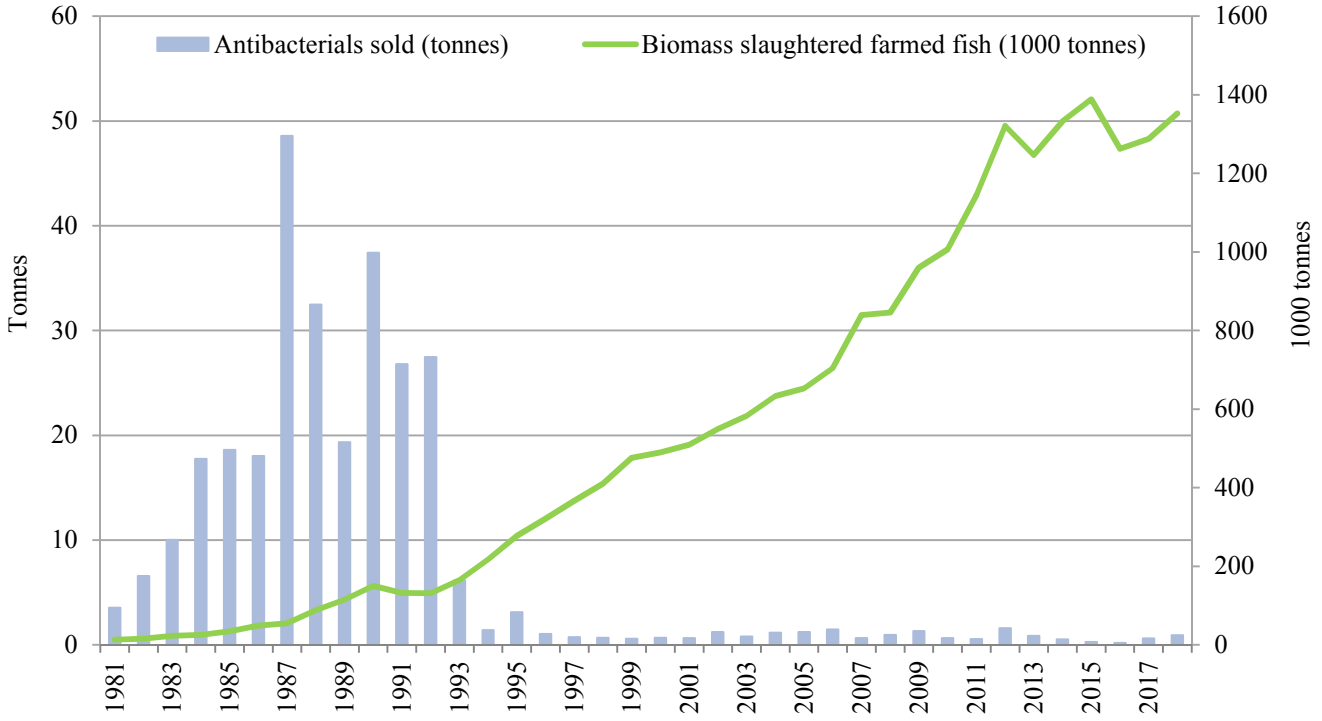

FIGURE 8. Sales, in tonnes of active substance, of antibacterial veterinary medicinal products for therapeutic use in farmed fish (including cleaner fish) in Norway in 1981-2018 versus produced biomass (slaughtered) farmed fish. For 1981-2014 the data represent sales data provided by the Norwegian Institute of Public Health; for 2013-2018 data represent prescription data obtained form the Veterinary Prescription Register. Data on slaughtered biomass farmed fish were obtained from Statistics Norway.

In a report from 2018 it was shown that for Atlatic salmon and rainbow trout, fish in only 1.5%, 1.4%, 1.0%, 0.6% and 0.8% of the ongrowers locations were subjected to treatment in the years 2013-2017, respectively (1). For 2018 this figure was 1.6%.

Companion animals (dogs and cats)

The sales in 2018 of antibacterial VMPs approved solely for companion animals (includes VMPs formulated as tablets, oral solution, injectable and oral paste) were 347 kg: in 2017 this figure was 359 kg (Figures 1 and 9). As shown in Figure 9, a steady increase in the sales from 1993 to 2001 was observed. This can in part be explained by changes in the number of antibacterial VMPs marketed for dogs and cats during that period. When the availability of VMPs for dogs and cats was lower, antibacterial human medicinal products (HMPs) were likely prescribed for dogs and cats.

In 1993, only eight antibacterial VMP presentations (name, form, strength and pack size) were authorised in Norway for dogs and cats, while in 2001 the corresponding number was 36. The number of VMP presentations for dogs and cats amounted to 49 in 2015; in 2018 this figure had decreased to 34. Since the sales of human antibacterials are not included in the sales statistics (Figure 9) the observed changes across the period 1993 to 2018 should be interpreted with caution (see chaper on National Strategy).

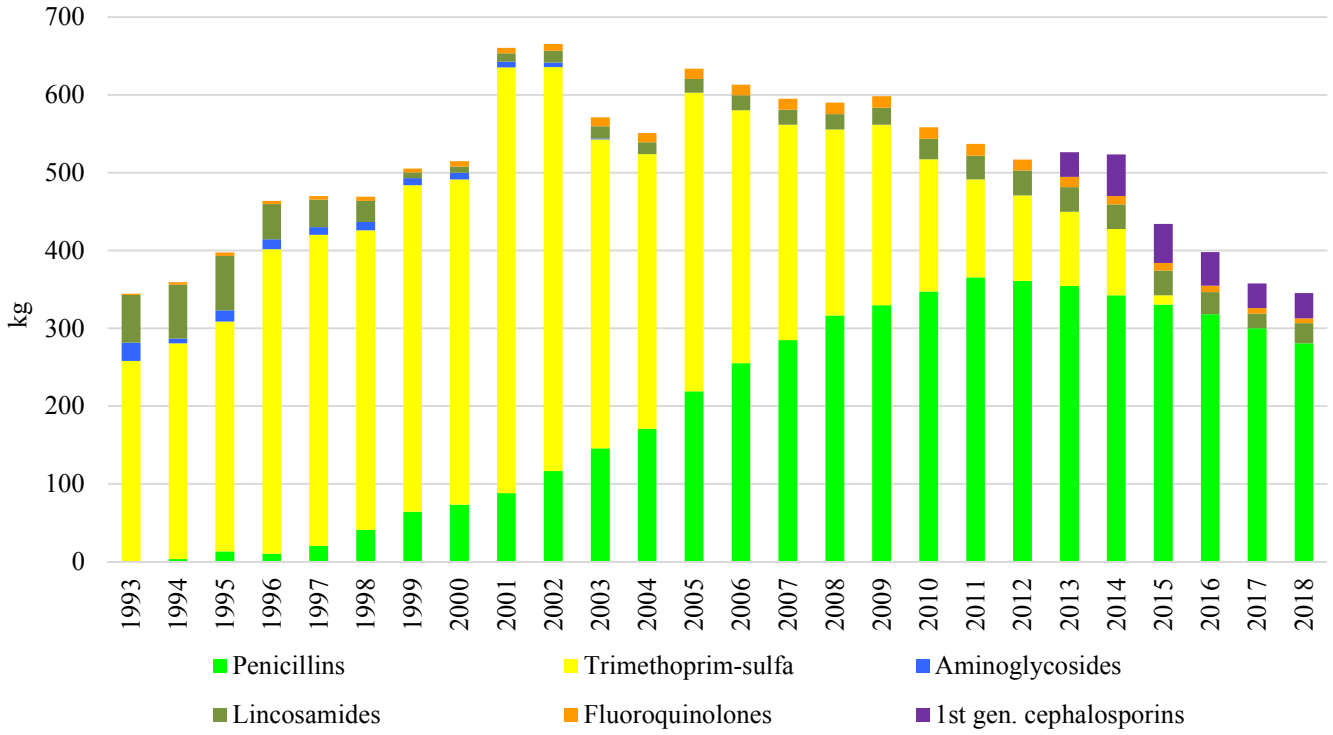

FIGURE 9. Sales, in kg active substance, of antibacterial veterinary medicinal products marketed solely for use in companion animals (injectables, oral paste, oral solution and tablets; note the exceptions for tablets: see Appendix 1) in Norway for the period 1993-2018. Minor sales of a third generation cephalosporin injectable VMP (range 0.5-1.1 kg) in 2008-2018 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 1993-2018 (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 81% (Figure 9). Of the sales of penicillin VMPs in 2018, approximately 81% of the sales were for the combination amoxicillin and clavulanic acid (Figure 10).

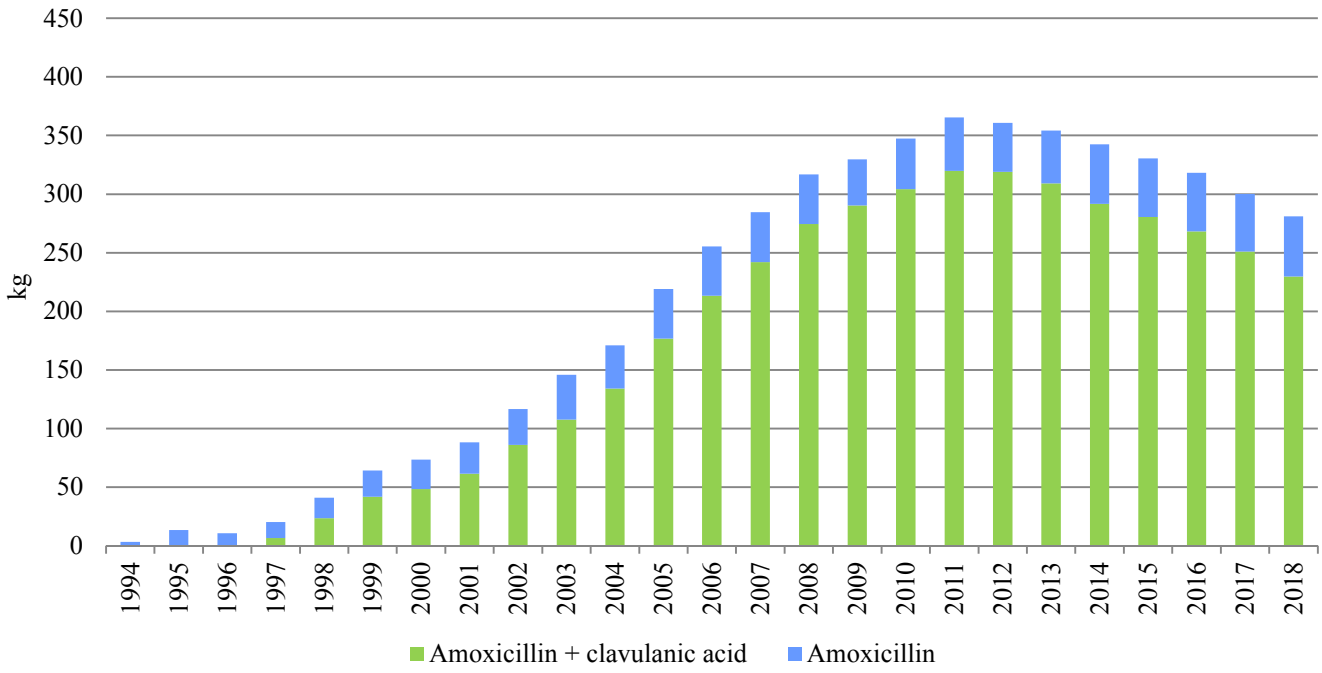

FIGURE 10. Sales, in kg active substance, of penicillin veterinary medicinal products for companion animals (dogs and cats), in Norway in 1994-2018.

The sales for companion aimals of VMPs belonging to the highest priority CIA for human medicine increased during 1993-2011 (Figure 11) when sales of such antimicrobial VMPs were peaking; since then a gradual decline is observed. The proportions of the total sales of antibacterial VMPs for companion animals accounted for by such CIAs were however low during this period (range 0.5% to 3.0%).

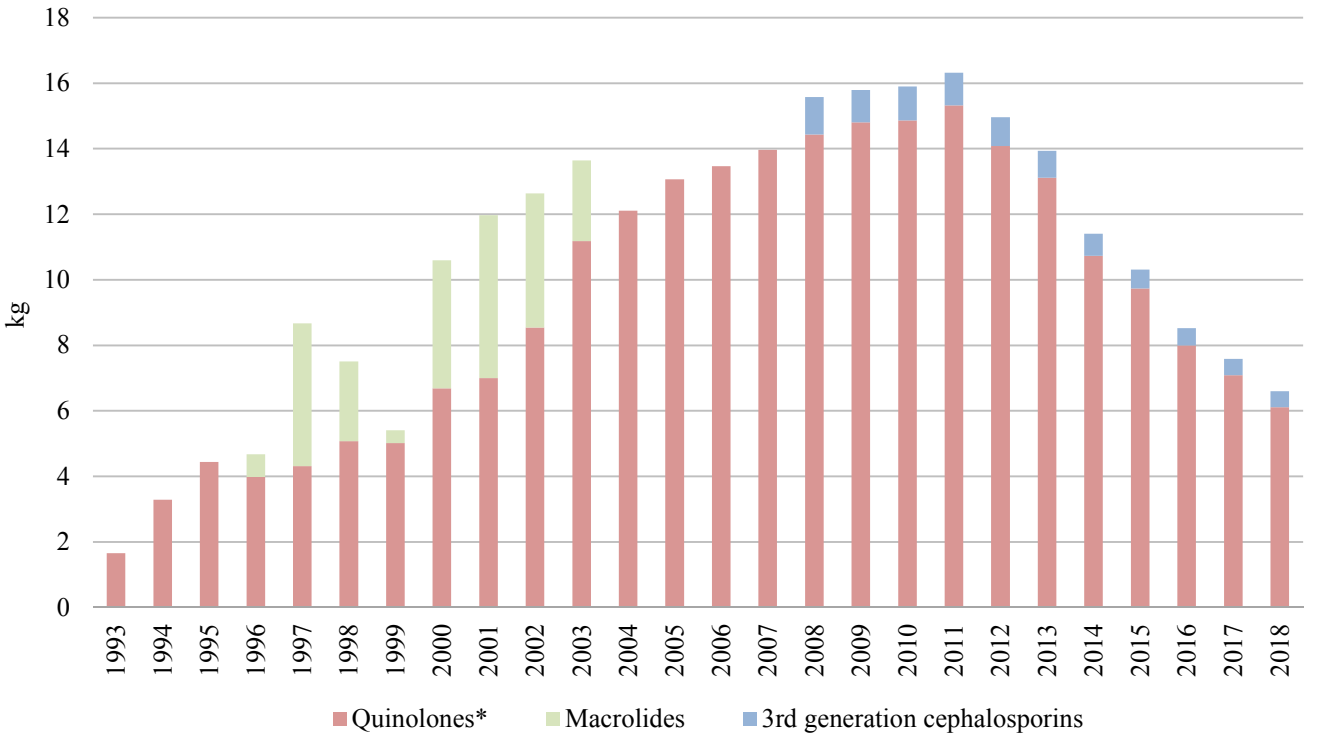

FIGURE 11. Sales, in kg active substance, of antibacterial veterinary medicinal products containing the highest priority critically important antimicrobials for human medicine (categorised by WHO) – i.e. quinolones (*fluoroquinolones only), macrolides and third generation cephalosporins – for therapeutic use in companion animals (dogs and cats) in Norway in 1993-2018.

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 phasing 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 as historical reference.

TABLE 5. Sales, in kg of active substance, of ionophore coccidiostat feed additives in Norway in 2008-2018; 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	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
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	**549**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Lasalocid	996	16	63	0	0	0	0	0	164	0	0	0
Monensin	3,422	896	885	805	1,060	1,080	1,174	1,313	1,081	874	875	820
Salinomycin	214	0	0	0	0	0	0	0	0	0	0	0
Narasin	24	9,212	8,621	9,080	9,394	10,378	12,345	12,409	9,126	562	92**	52**
Total ionophore coccidiostats	**4,656**	**10,124**	**9,569**	**9,885**	**10,454**	**11,458**	**13,519**	**13,722**	**10,371**	**1,436**	**967**	**872**

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

References

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

Previous targets for food-producing terrestrial animals

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

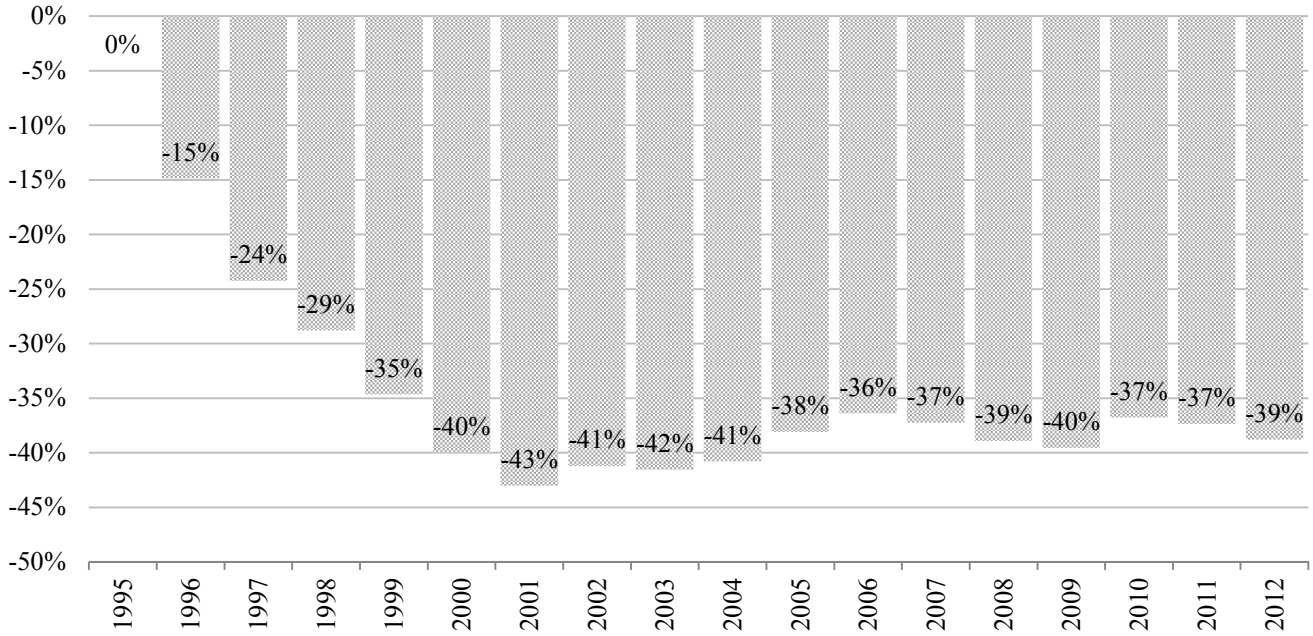

FIGURE 12. Changes in sales (kg active substance) in Norway of antibacterial veterinary medicinal products (VMPs) approved for use in food-producing terrestrial animals, including horses, 1995 being the reference year.

Targets 2015 – 2020

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

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

Approach – assessment of changes

To evaluate progress in terms of reaching the goals set down in the national strategy, sales data for 2013-2018 have been further refined in order to obtain estimates on the usage that are more accurate in terms of identifying changes over time. Data on prescription per animal species obtained from the Veterinary Prescription Register (VetReg) has been used as supportive information for this refinement (see Appendix 1).

Food-producing terrestrial animals

In order to achieve Target 1 of the national strategy Animalia, whose role is to provide Norwegian farmers with knowledge and expertise (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 (active substance)/PCU (population correction unit) (see Appendix 1).

The result of this analysis shows that both when measured in kg and in mg/PCU the reduction in the usage of antibacterial VMPs for cattle, pigs, sheep, goat and poultry from 2013 to 2018 was 17% (Figure 13). The sales patterns (data from wholesalers) have been stable across the period 2013 to 2018, both in terms of proportion by antibacterial substances and by pharmaeutical forms. The figures are therefore assumed not to be biased by changes towards products/antibacterial classes with higher or lower dosing per treatment. The sales of injectable antibacterial VMP are included in sales for food-producing terrestrial animals (horses excluded), but as the prescription of such products for horses and companion animals (VetReg data) was relatively stable across 2015-2018, 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, a HMP is allowed to be used. For food-producing species it requires that a maximum residue level (MRL) has been established for the active substance in question or that it is shown that MRL is not nessecary. VetReg data show that usage of HMPs for cattle, pig, sheep and goat was low for the years 2015-2018 (68 kg, 38 kg, 32 kg and 36 kg, respectively) and was primarily accounted for by benzylpenicillin for injection that was almost exclusively prescribed for sheep (see Appendix 1 for estimation methodology; Table 6 on treatment of broilers). The impact on the trends by excluding HMPs from the material is thought to be minimal.

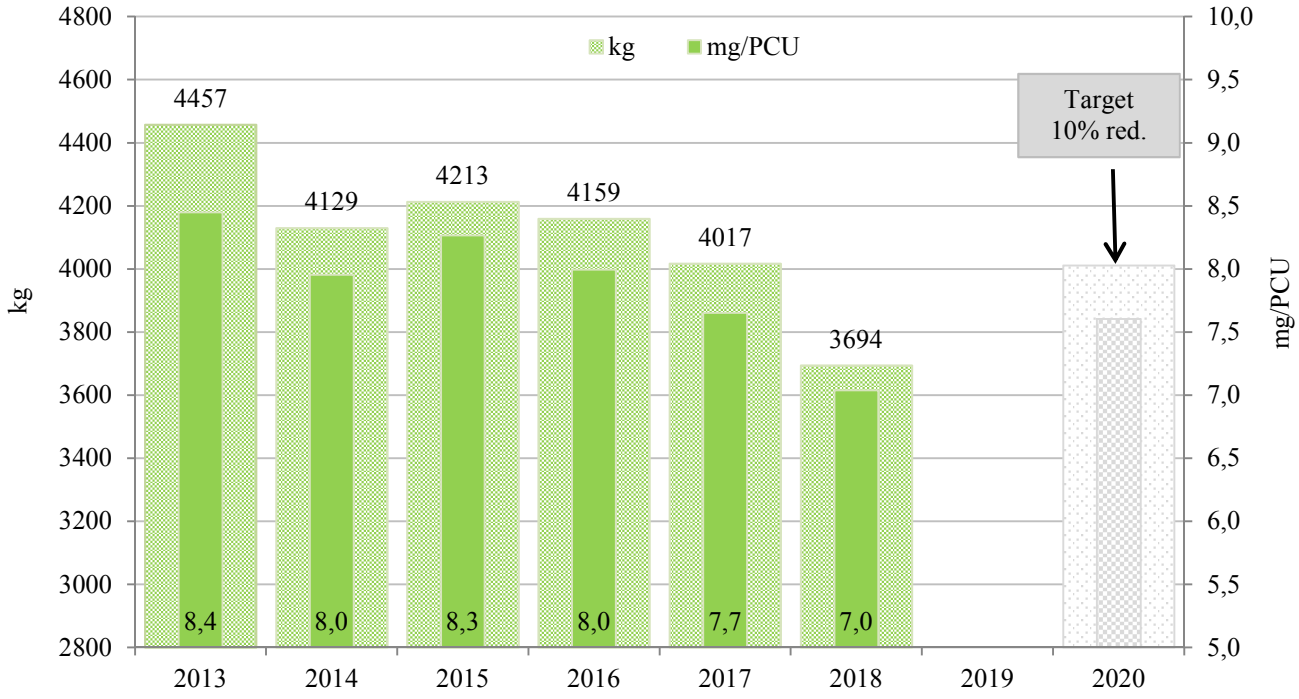

FIGURE 13. Estimated sales, in kg active substance and in mg active substance/PCU (population correction unit), of antibacterial veterinary medicinal products for cattle, pigs, sheep, goat and poultry in Norway in 2013-2018 and the target according to the National Strategy. Sales data were obtained from the Norwegian Institute of Public Health. Note that antibacterial human medicinal products are not included. Note the differences in starting points and scales of the Y-axes.

Farmed fish

For farmed fish the goal is that the usage of antibacterials should be at the same level or lower in 2020 than the average for the period 2004-2014 – i.e. the usage should not be above 1,003 kg or 1.14 mg/PCU (maximum values). Note that the maximum values have been corrected compared to the values presented in NORM/NORM-VET 2017 (then given as 971 kg and 1.43 mg/PCU, respectively). Figure 14 shows that sales of antibacterial VMPs for farmed fish in 2018 were lower than the maxium level set.

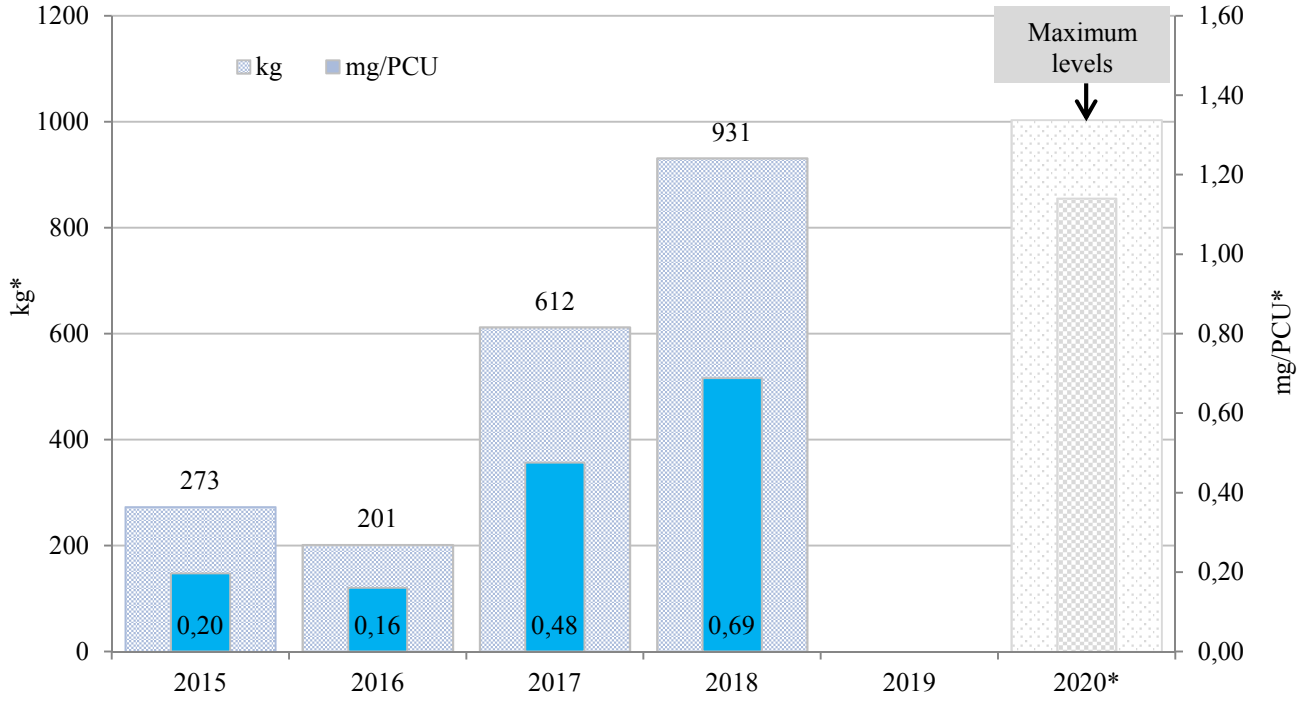

FIGURE 14. Prescription, in kg active substance and in mg active substance/PCU (population correction unit), of antibacterial VMPs for farmed fish, in Norway in the periode 2015-2018 and the target according to the National Strategy. Maximum levels are based on average for the period 2004-2014. Prescription data were obtained from the Veterinary Prescription Register and includes prescription for cleaner fish. Note the differences in the scales of the Y-axes. *The maximum levels given in this report are slighly higher compared to those presented in the the NORM-VET 2017 report for which there was an error in the calculation of the maximum values given.

Companion animals (dogs and cats)

Sales of antibacterial VMPs for companion animals include tablets, oral solution, injectables and oral paste approved for dogs and cats only (see Appendix 1 for exception for tablets). From 2013 to 2018 a reduction in the sales of such antibacterial VMPs for companion animals of 34% is observed (Figure 15). The usage of antibacterial HMPs for dogs and cats for 2015, 2016, 2017 and 2018, estimated by use of VetReg data, was realtively stable; the average annual usage of HMPs was 265 kg (see Appendix I for estimation methodology). This indicates that the decline in the sales of antibacterial VMPs for companion animals has not been substituted by prescribing of antibacterial 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) for companion animals is 24% from 2013 to 2018.

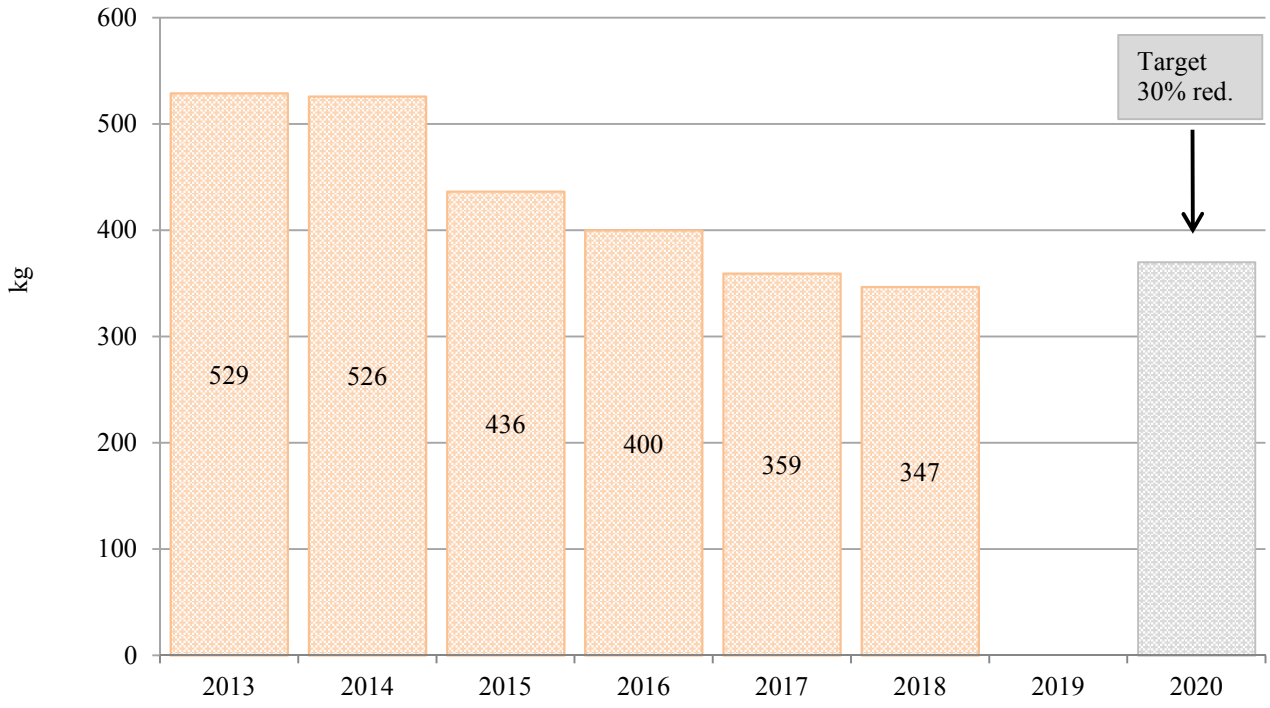

FIGURE 15. Sales in Norway, in kg active substance, of antibacterial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals only (oral paste, injectables, oral solution and tablets; exceptions for tablets - see Appendix 1) in the period 2013-2018 and the target according 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 6, Figure 16). One of the targets stated in the National Strategy against Antibiotic Resistance is phasing out the 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 for broilers), data on 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 the years 2013 to 2018.

TABLE 6. Number and percentages of broiler flocks, by production stage, treated with antibacterial veterinary medicinal products (VMPs) in Norway in the period 2013-2018[1]. Data were obtained from HelseFjørfe, Animalia.

	2013	2014	2015[2]	2016[3]	2017	2018
Broiler production	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)	No of flocks treated (%)
Breeders P[4] (Rearing)	1 (1.1)	2 (2.2)	1 (1)	0 (-)	0 (-)	0 (-)
Breeders P[4] (Layers)	1 (1.1)	0 (-)	1 (1)	2 (2.1)	0 (-)	1 (1.4)
Broiler	8 (0.16)	2 (0.04)	1 (0.02)	3 (0.07)	7 (0.18)	4 (0.10)
No. flocks treated	10	4	3	5	7	5

[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 and 2018, 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 2 days was applied (Bruce David, Nortura, personal communication).

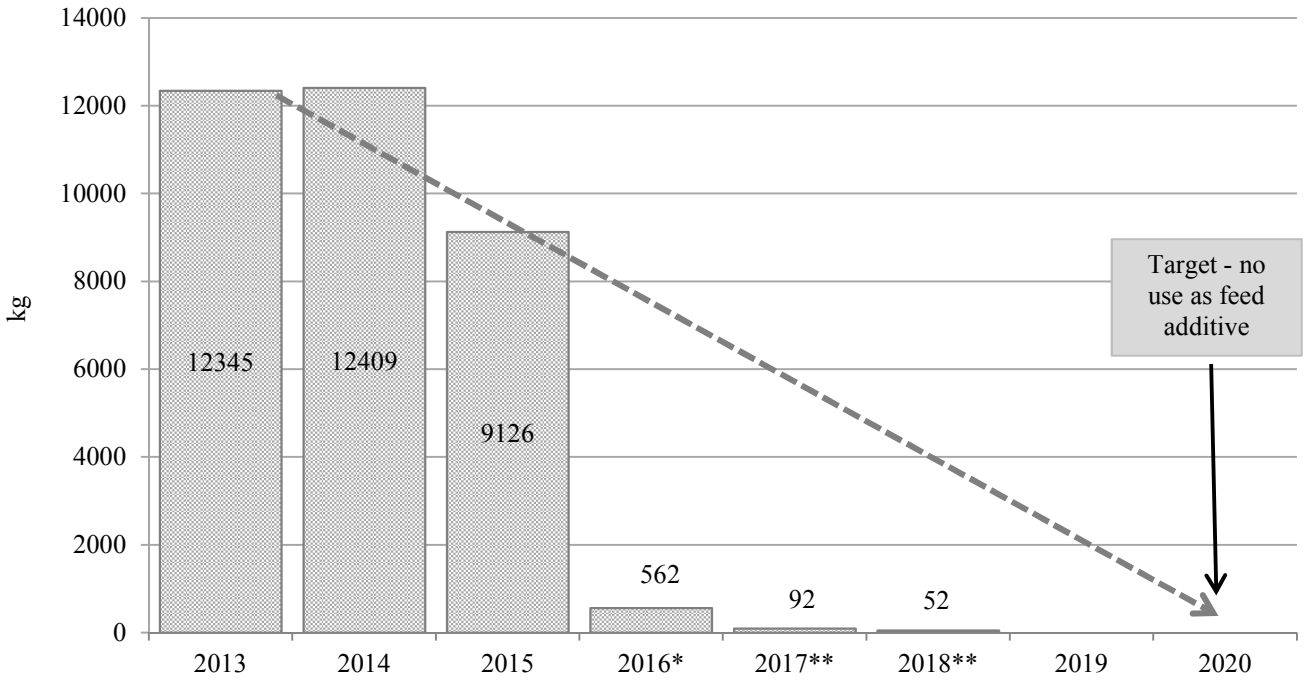

FIGURE 16. Sales of narasin as coccidiostat feed additive for use in broilers in Norway during the period 2013-2017. The statistics is obtained from Norwegian Food Safety Authority. *Sold until June 2016. **Used to control some cases of necrotic enteritis (*Clostridium perfringens*) (Bruce David, Nortura,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

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USAGE IN HUMANS

Hege Salvesen Blix, Marion Neteland, Per Espen Akselsen, Morten Lindbæk

Overall antibiotic sales

In 2018, the total sales of antibacterials for systemic use in humans (J01, excl. methenamine) decreased by 3% compared to 2017; from 13.3 to 12.9 DDD/1,000 inhabitants/day (Table 7). In January 2019, the values of DDDs changed for several important antibiotics, this resulted in changed statistics, i.e. lower numbers of DDD/1,000 inhabitants/day, but patterns over time are the same, see separate chapter for explanation.

Antibiotics are prescription-only drugs in Norway. Overall antibiotic comsumption includes all sales of antibiotics to humans in Norway i.e. in primary care, in hospitals and in long-term care institutions. Around 84% of the human use of antibacterials are used by patients in primary care, i. e. outside health institutions. Hospitals cover 8% of total DDDs and long-term care institutions also around 8%.

The overall consumption (J01, excluding methenamine) has decreased by 24% since 2012, when a *Mycoplasma pneumoniae* epidemic caused a high prescription rate of macrolides and tetracyclins. In recent years, decreased sales are observed for all main antibiotic subgroups (Figure 17).

The proportion of narrow-spectrum penicillins (J01CE) of total sales (J01, excl. methenamine) is stable around 26%, but it was higher 20 years ago. In 1997 the proportion was 35% and in 2018 27%. The proportion of prescriptions with guideline-recommended antibiotics has increased from 48% of prescriptions in 2012 to 52% in 2018.

TABLE 7. Human usage of antibacterial agents in Norway 2011-2018 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2017-2018. Methods for collection of data on human usage of antimicrobial agents are presented in Appendix 2.

ATC	Groups of substances	2011	2012	2013	2014	2015	2016	2017	2018	Change (%) 2017-8017
J01A	Tetracyclines	3.47	3.87	3.54	3.46	3.38	3.16	3.01	2.86	- 5
J01B	Amphenicols	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
J01CA	Penicillins with extended spectrum	2.69	2.79	2.82	2.90	2.73	2.62	2.47	2.46	-
J01CE	Beta-lactamase sensitive penicillins	4.47	4.30	4.09	3.88	3.88	3.73	3.61	3.43	- 5
J01CF	Beta-lactamase resistant penicillins	0.88	0.90	0.79	0.91	0.89	0.90	0.84	0.90	+ 7
J01CR	Combination of penicillins	0.03	0.04	0.05	0.07	0.08	0.10	0.07	0.08	-
J01D	Cephalosporins, monobactams, carbapenems	0.54	0.53	0.50	0.46	0.43	0.42	0.38	0.39	+ 3
J01E	Sulfonamides and trimethoprim	0.87	0.87	0.86	0.88	0.88	0.85	0.84	0.88	+ 5
J01F	Macrolides, lincosamides and streptogramins	2.31	2.26	1.94	1.68	1.51	1.33	1.18	1.05	- 11
J01G	Aminoglycosides	0.07	0.08	0.07	0.08	0.08	0.08	0.09	0.09	-
J01M	Quinolones	0.74	0.74	0.71	0.67	0.69	0.53	0.45	0.42	- 7
J01X*	Other antibacterials	0.49	0.47	0.45	0.43	0.41	0.38	0.36	0.32	- 11
J01	**Total excluding methenamine**	**16.6**	**16.9**	**15.8**	**15.4**	**14.9**	**14.1**	**13.3**	**12.9**	**- 3**
J01XX05	Methenamine	3.44	3.57	3.70	3.86	3.99	4.09	4.11	4.08	- 1
J01	**Total all antimicrobial agents**	**20.0**	**20.4**	**19.5**	**19.3**	**18.9**	**18.2**	**17.4**	**16.9**	**- 3**

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

The beta-lactamase sensitive penicillin group (J01CE), the tetracyclines (J01A) and the penicillins with extended spectrum (J01CA) were the three most used antibacterial groups in Norway in 2018 (Table 7 and Figure 18).

Use of the urinary prophylactic agent methenamine seems to have reached a stable level (Figure 17, Table 8). Methenamine has the largest amounts of DDDs of all antibiotics and accounts for 93% of subgroup J01X and 24% of total antibacterial use.

Among the tetracyclines (J01A), doxycycline is most frequently used, followed by lymecycline, a drug mainly indicated for acne (Table 8).

In 2018, the penicillins (ATC group J01C) accounted for 41% of the total antibacterial use in Norway (Figure 18). Over the years there has been a shift towards use of more broad-spectrum penicillins. Beta-lactamase sensitive penicillins accounted for half of the penicillin group (50% share) measured in DDDs and this picture has been stable since 2012. Penicillins with extended spectrum (J01CA) represent 36% of the J01C group compared to 23% in 1999 (Figure 18 and Figure 20). This is mainly due to increasing use of amoxicillin and pivmecillinam. An increased use of penicillins with beta-lactamase inhibitors has been observed in the latest years, however due to global shortage of piperacillin/tazobactam there was decreased use in 2017.

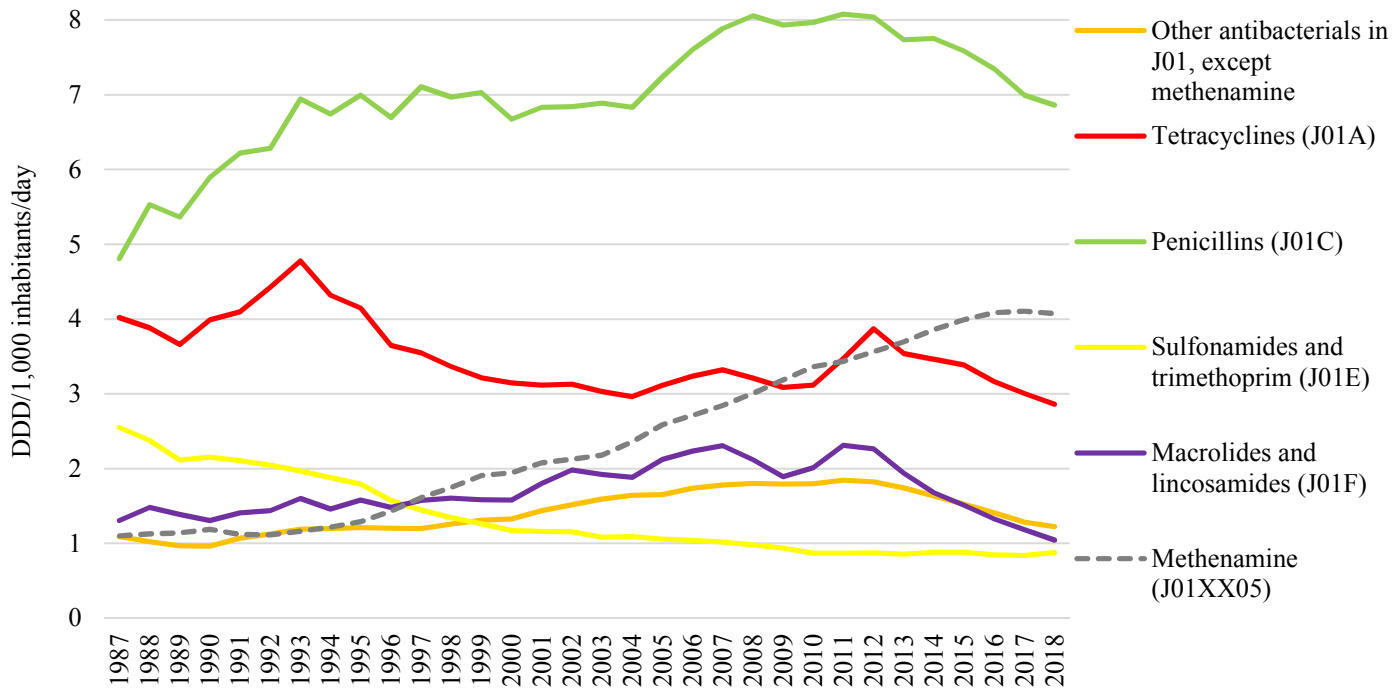

FIGURE 17. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine and other antibacterials in Norway 1987-2018. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05).

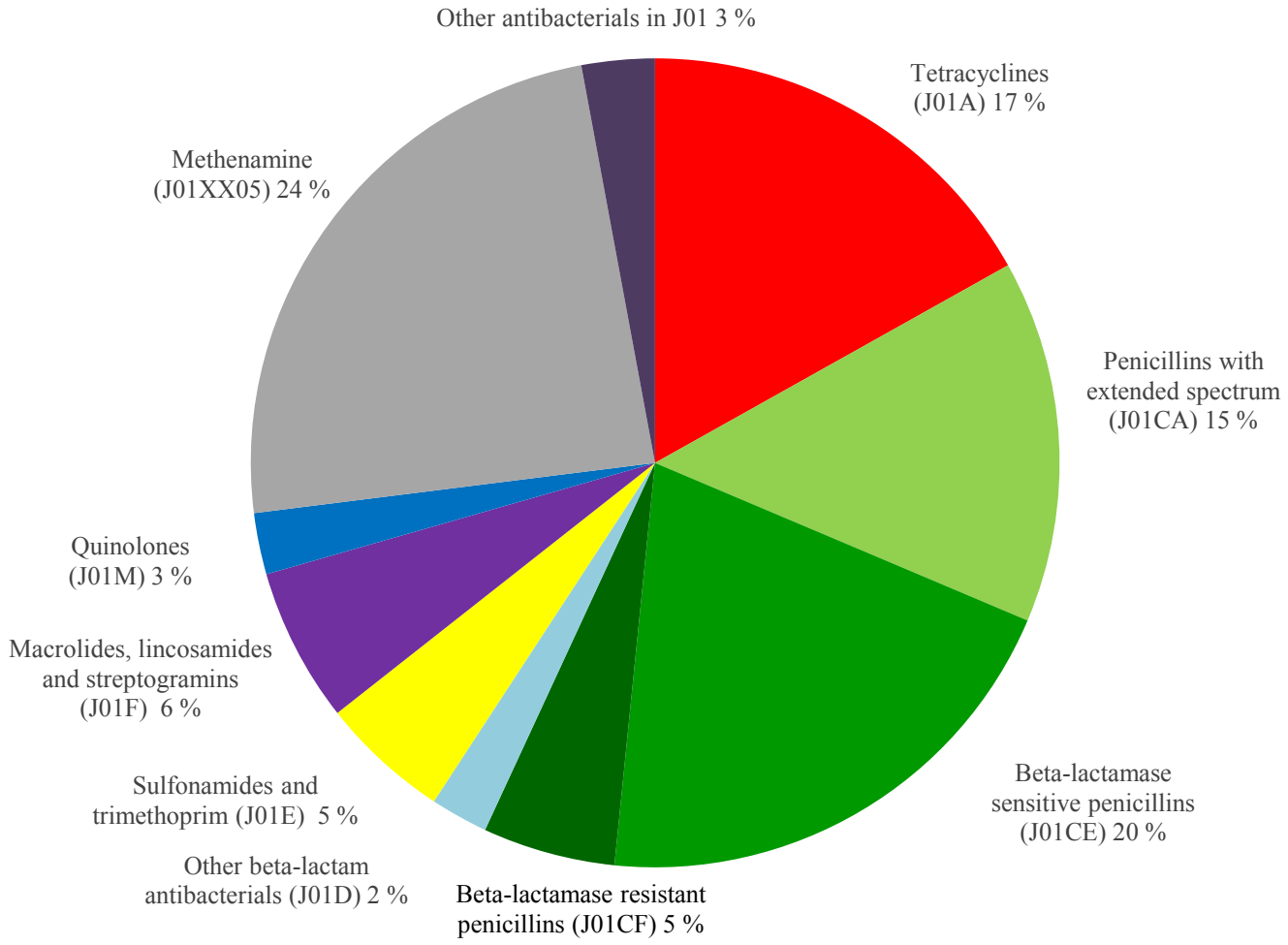

FIGURE 18. Relative amount of antibacterial agents for systemic use in 2018 in Defined Daily Doses (DDD) (total sales in the country).

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

In 2018, the overall sales in Norway of antibacterials for use in humans, terrestrial animals and farmed fish measured in weight of active substance were 56.3 tonnes (Figure 19). Total sales data are captured from the Norwegian drug wholesales statistics, supplemented with data on medicated feed from feed mills. Of the total sales of antibacterials in Norway, sales for human use accounted for 89%, use for terrestrial animals 9% and for use in fish only for 2% of the total use. Methenamine accounted for almost 16 tonnes (28% of total weight). Since 2012, a decreased use of 6% has been observed in all the three settings. Penicillins are highly utilised in humans and animals (green colour), accounting for nearly half of the total weight in tonnes.

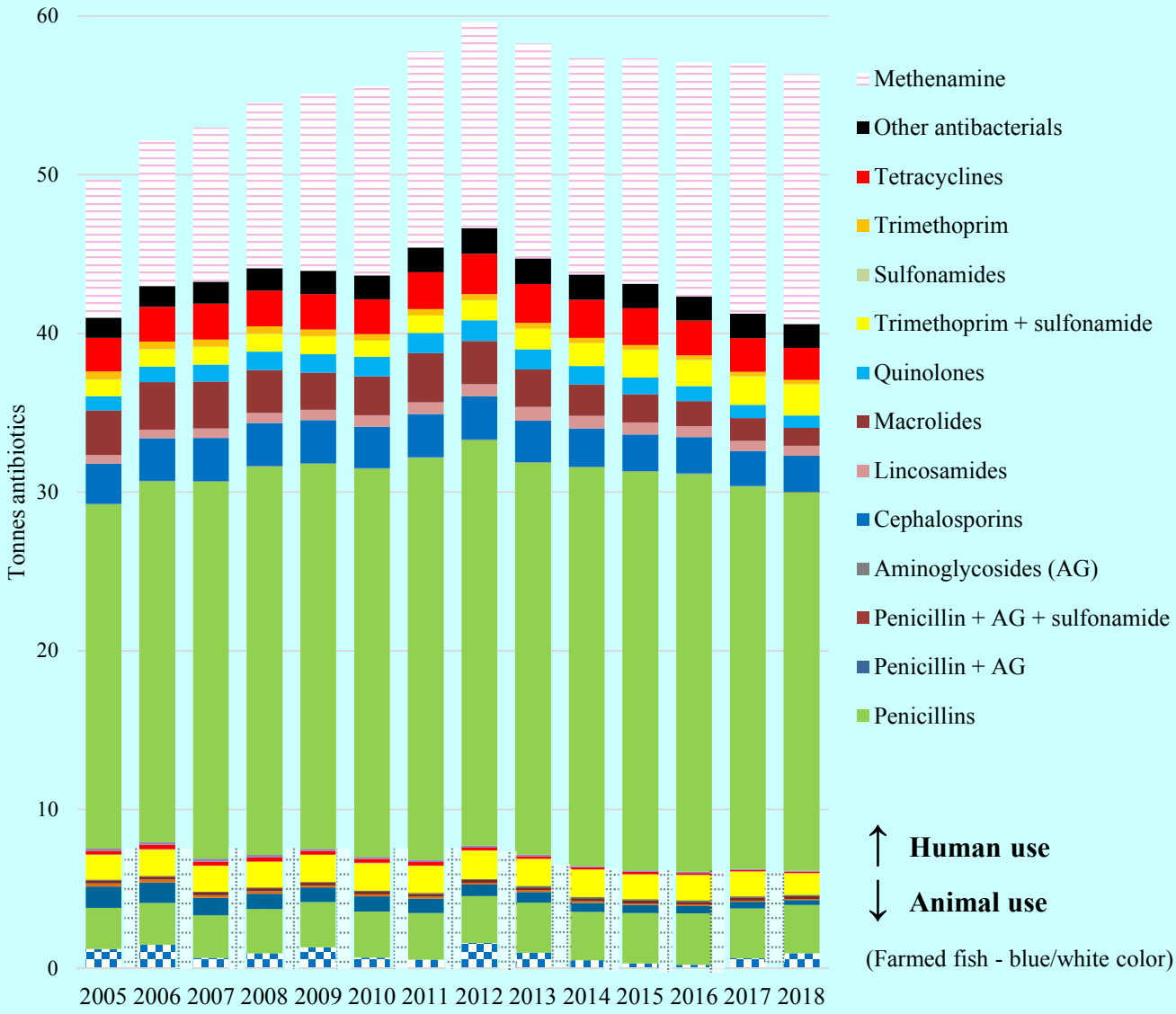

FIGURE 19. Sales, in tonnes of active substance, of antibacterials for humans, animals and fish, for the years 2005-2018. The use in farmed fish is shown at the bottom in blue/white texture.

Oral formulations are dominating in human medicine. In 2018, 86% of human antibacterial weight was oral forms followed by parenteral formulations (13.5%). Sales of other formulations for eye, ear and skin, is limited. In humans, sales for dermatological forms constituted 91 kg active substance, vagitories or rectal forms 34 kg, eye and ear formulations 27 kg and inhalations 22 kg.
In veterinary medicine the dominating formulations are the parenteral ones (60%), followed by oral forms (34%) and intramammary treatment (4%).

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The use in 2018 was at the same level as in 2017 (Table 8). In May 2017, oral amoxicillin/clavulanic acid was approved in Norway and since then a significant increase has been observed (Table 8, Figure 20). Pivmecillinam is used for urinary tract infections at the expense of trimethoprim. Although the subgroup of sulfonamides and trimethoprim has decreased over the years, trimethoprim-sulfamethoxazole is increasing; since 2012 by 49% (Figures 17-18, Table 8).

Since 2012 the use of macrolides has dropped markedly, (Tables 7-8, Figures 17-18 and 21). Use of the group J01F macrolides, lincosamides and streptogramins has followed a wavy pattern over the years. The shifts in use could be explained to some degree by the recurrent epidemics of *M. pneumoniae* in Norway, occurring with four- to six-year intervals. Furthermore, the decreased use since 2012 can partly be explained by a change in treatment guidelines for sexually transmitted diseases as azithromycin is no longer first-line treatment.

In the latest years, sales of ATC group J01D (cephalosporins, monobactams and carbapenems) have decreased, mainly due to decreased use of first and second generation cephalosporins (Tables 7-8, Figures 18 and 22). The quinolones represent only a small fraction (3%) of total antibacterial sales (Table 7 and 8, Figure 18) and the use has decreased steadily since 2012. Ciprofloxacin is the main substance accounting for 94% of the quinolone group in 2018.

TABLE 8. Total human usage of single antibacterial agents for systemic use in Norway 2012-2018. Sales for overall use are given in DDD/1,000 inhabitants/day and in number of prescriptions/1,000 inhabitants/year (prescriptions account for primary care only). The methodology for collection of data on human usage of antibacterial agents is presented in Appendix 2.

ATC group	ATC code	Substance	2012	2014	2016	2018	No Rx/1,000 inhabitants in primary care[1]
J01A - Tetracyclines	J01A A02	Doxycycline	2.36	1.99	1.82	1.60	27
	J01A A04	Lymecycline	0.90	0.96	0.94	0.93	7
	J01A A06*	Oxytetracycline	-	<0.001	<0.001	<0.001	
	J01A A07	Tetracycline	0.62	0.50	0.40	0.32	5
	J01A A08*	Minocycline	0.006	0.003	0.002	0.001	5
	J01A A12	Tigecycline	<0.001	<0.001	<0.001	<0.001	5
J01B - Amphenicols	J01B A01	Chloramphenicol	<0.001	<0.001	<0.001	<0.001	
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.03	0.04	0.04	0.05	
	J01C A04	Amoxicillin	0.97	0.97	0.88	0.84	28
	J01C A08	Pivmecillinam	1.78	1.87	1.69	1.57	
	J01C A11	Mecillinam	0.008	0.008	0.005	0.002	
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.24	0.24	0.23	0.24	
	J01C E02	Phenoxymethyl-penicillin	4.07	3.64	3.50	3.18	85
	J01C E08*	Benzathine benzylpenicillin	<0.001	<0.001	<0.001	<0.001	
J01CF - Beta-lactamase resistant penicillins	J01C F01	Dicloxacillin	0.76	0.72	0.74	0.74	25
	J01C F02	Cloxacillin	0.14	0.19	0.17	0.16	
	J01C F05*	Flucloxacillin	<0.001	<0.001	<0.001	<0.001	
J01CR - Combination of penicillins, incl. beta-lactamase inhibitors	J01C R02	Amoxicillin and enzyme inhibitor	0.002	0.008	0.011	0.028	1
	J01C R05	Piperacillin and enzyme inhibitor	0.03	0.07	0.09	0.05	
J01DB – first gen. cephalosporins	J01D B01	Cefalexin	0.18	0.14	0.10	0.09	3
	J01D B03	Cefalotin	0.08	0.09	0.09	0.07	
	J01D B04	Cefazolin				0.03	
J01DC – second gen. cephalosporins	J01D C02	Cefuroxime	0.08	0.06	0.04	0.03	
J01DD – third gen. cephalosporins	J01D D01	Cefotaxime	0.12	0.12	0.12	0.12	
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.01	
	J01D D04	Ceftriaxone	0.03	0.02	0.02	0.02	
	J01D D08*	Cefixime			<0.001	<0.001	
	J01D D52	Ceftazidime and avibactam				<0.001	

ATC group	ATC code	Substance	2012	2014	2016	2018	No Rx/1,000 inhabitants in primary care[1]
J01DF - Monobactams	J01D F01	Aztreonam	<0.001	0.001	0.001	<0.001	
J01DH - Carbapenems	J01D H02	Meropenem	0.03	0.03	0.03	0.02	
	J01D H03	Ertapenem	0.002	0.002	0.002	0.002	
	J01D H51	Imipenem and enzyme inhibitor	0.002	0.002	0.002	0.002	
J01DI – Other cephalo-sporins and penems	J01D I02	Ceftaroline fosamil		<0.001	<0.001	<0.001	
	J01DI54	Ceftolozane and enzyme inhibitor			<0.001	<0.001	
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.51	0.46	0.38	0.34	18
	J01E C02*	Sulfadiazine			0.001	<0.001	
	J01E E01	Sulfamethoxazole and trimethoprim	0.36	0.40	0.44	0.53	18
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	1.06	0.75	0.60	0.44	15
	J01F A02	Spiramycin	0.01	0.005	0.003	0.002	
	J01F A06*	Roxithromycin		<0.001	<0.001	<0.001	
	J01F A09	Clarithromycin	0.39	0.23	0.14	0.11	3
	J01F A10	Azithromycin	0.48	0.35	0.30	0.24	10
	J01FS15	Telithromycin	<0.001	<0.001	<0.001		
	J01F F01	Clindamycin	0.33	0.34	0.28	0.25	11
J01G - Aminoglycosides	J01GA01*	Streptomycin	<0.001	<0.001	<0.001	<0.001	
	J01G B01	Tobramycin	0.03	0.02	0.02	0.01	
	J01G B03	Gentamicin	0.05	0.05	0.06	0.08	
	J01G B06*	Amikacin	0.001	0.001	0.001	0.001	
J01M - Quinolones	J01M A01	Ofloxacin	0.02	0.01	0.01	0.01	
	J01M A02	Ciprofloxacin	0.71	0.64	0.51	0.39	10
	J01MA12	Levofloxacin	0.002	0.002	0.003	0.004	
	J01MA14*	Moxifloxacin	0.004	0.007	0.009	0.011	
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.02	0.02	0.02	
	J01X A02	Teicoplanin	0.001	<0.001	<0.001	<0.001	
	J01X B01	Colistin	0.004	0.005	0.006	0.006	
	J01X C01	Fusidic acid	0.005	0.004	0.003	0.003	
	J01X D01	Metronidazole	0.07	0.05	0.03	0.04	
	J01X E01	Nitrofurantoin	0.37	0.35	0.31	0.25	9
	J01XX01	Fosfomycin	<0.001	<0.001	<0.001	<0.001	
	J01X X05	Methenamine	3.57	3.86	4.09	4.08	34
	J01XX08	Linezolid	0.01	0.007	0.01	0.009	
	J01XX09	Daptomycin	0.001	<0.001	0.001	<0.001	
	J01X X11	Tedizolid			<0.001	<0.001	
Antibiotics in other ATC groups	A07A A09	Vancomycin	0.002	0.002	0.002	0.002	
	A07A A11	Rifaximin	0.004	0.012	0.043	0.076	
	A07A A12	Fidaxomicin	<0.001	<0.001	<0.001	<0.001	
	P01A B01	Metronidazole	0.23	0.24	0.23	0.21	
	D06A X09/ R01A X06*	Mupirocin (grams)[2]	145	174	185	2	

*Drugs not licensed at the Norwegian marked in 2018. [1]Number of prescriptions (Rx)/1,000 inhabitants in primary care given in whole numbers, only substances with more than 0.5 Rx/1000 inhabitants is included in the table. [2]Given as the total amount grams (g) mupirocin per year.

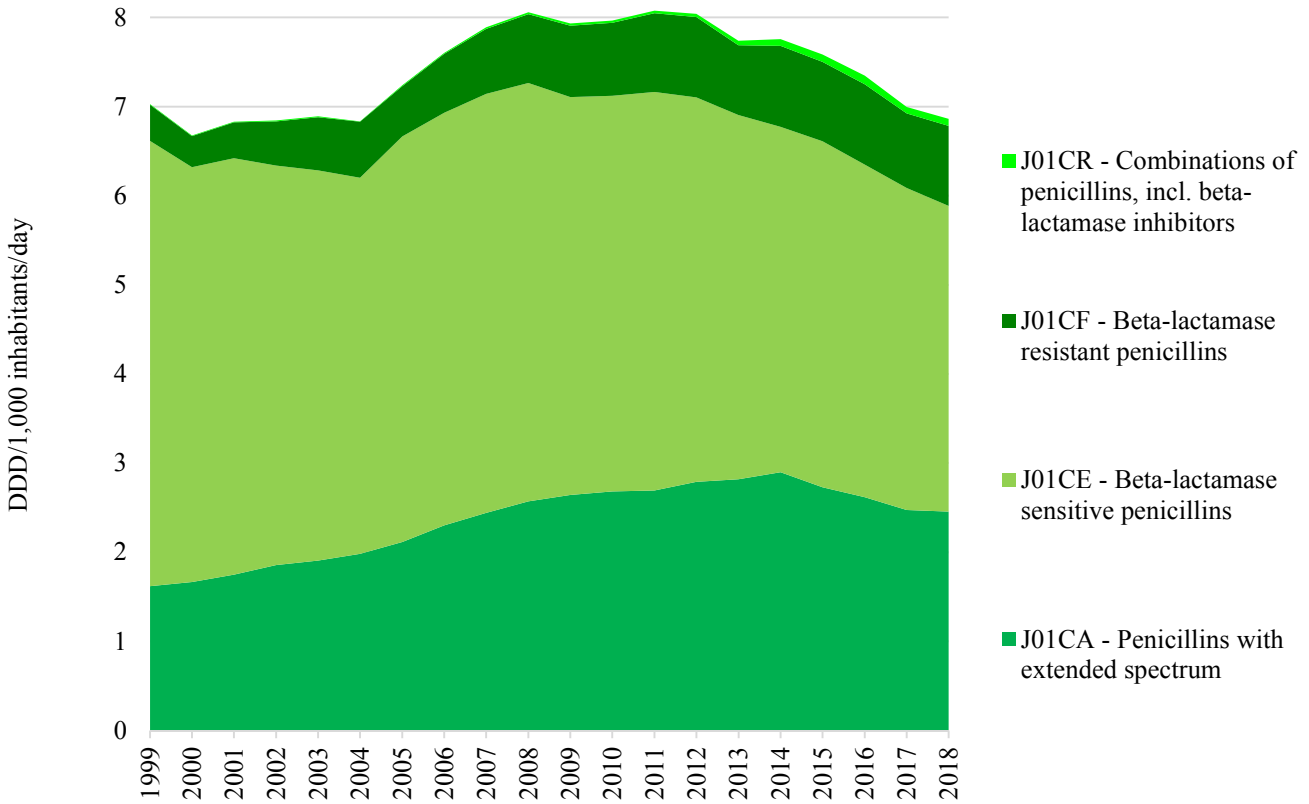

FIGURE 20. Total sales of penicillins (J01C) in Norway 1999-2018 and changes between groups of penicillins.

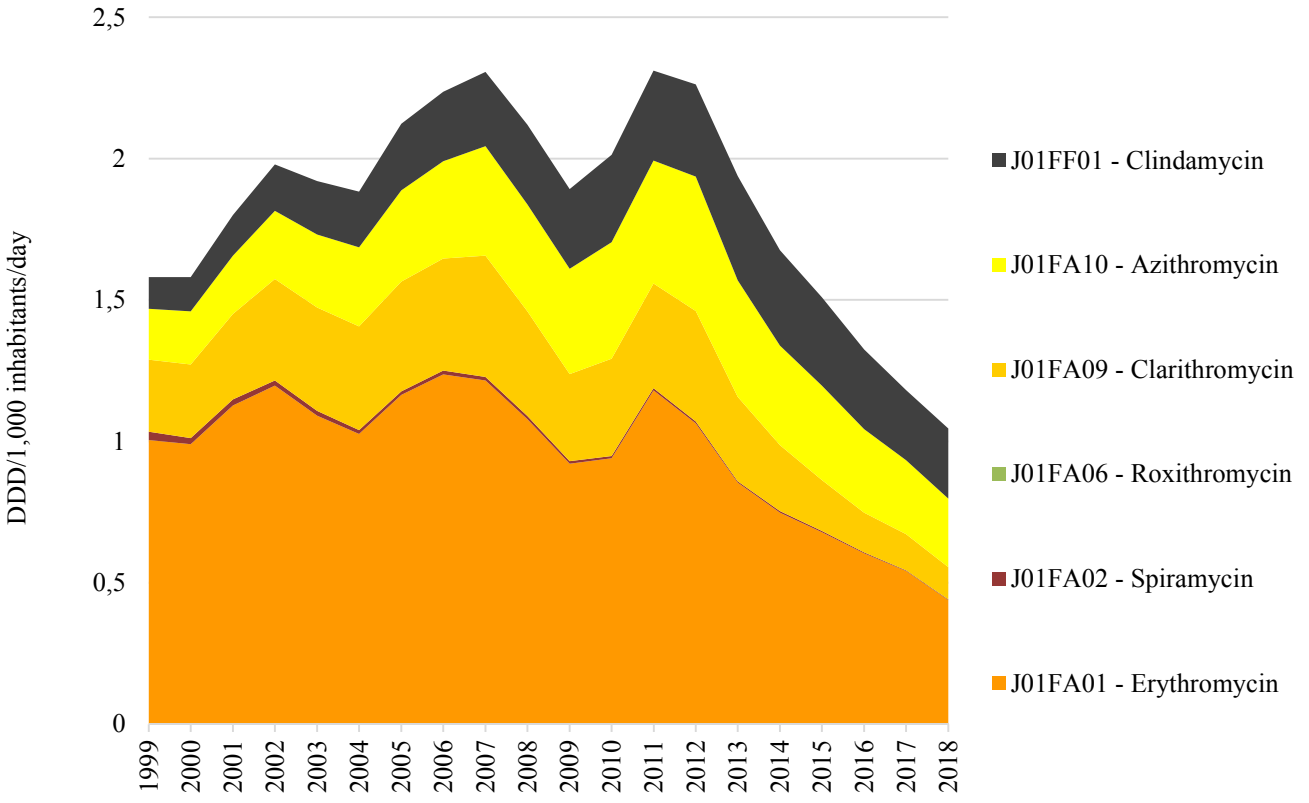

FIGURE 21. Total sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1999-2018.

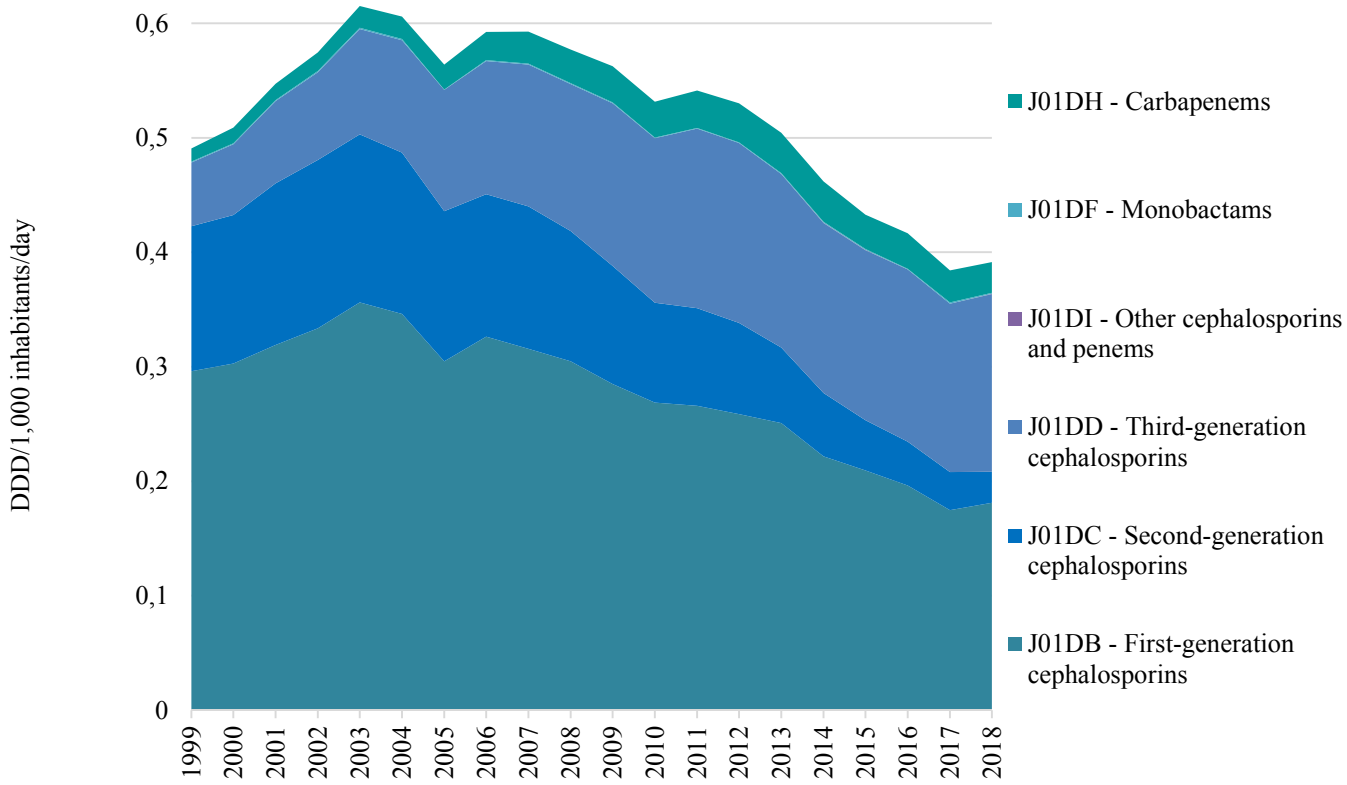

FIGURE 22. Total sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1999-2018 and changes between generations of cephalosporins and monobactams/carbapenems.

Antibiotic usage in primary care

Around 84% of the total human sales of antibacterials are used by persons living at home, i.e. primary care. The data include all prescriptions of antibacterials dispensed to persons living in Norway (including those antibiotics prescribed from hospitals to discharged patients and out-patients), i.e. all antibiotic use in primary care is captured in these figures.

For primary care, the most important antibiotic group in 2018 was the penicillins, J01C (53% of DDDs in ATC group J01, excl.methenamine). Tetracyclines (J01A) was the second most commonly used group (26%) followed by macrolides and lincosamides (J01F) at 9%. The three antibiotic substances most often prescribed for outpatients in 2018 were phenoxymethylpenicillin, doxycycline and pivmecillinam (Table 8). These three antibiotics represented 50% of all prescriptions and 54% of all DDDs of the antibacterial group J01, excluding methenamine. Of the whole ATC group J01 antibacterials for systemic use in primary care, the urinary antiseptic methenamine represented 27% of the DDDs and 10% of the prescriptions. Sales of antibiotics to outpatients have decreased since 2012.

Geographical variation

The usage of antibacterials varies among the 18 Norwegian counties. The county using the least is using around 72% in DDDs and 74% in prescriptions compared to the county using the most (Figures 25-26). Over the years, and measured in DDDs, the same counties seem to be high-use counties and low-use counties, respectively. However, the decrease in total volume over the latest years, is larger in some counties, Oslo being the county with the largest decrease in use of antibiotics with a 30% reduction since 2012 (blue dots in Figure 28).

Females use more antibiotics than males; 23% of females purchased at least one antibiotic prescription (methenamine excluded) in 2018 compared to 15% of males. The prevalence of use has decreased over the years, more so in the young children than in the elderly. The gender pattern is similar in all regions of the country. Young children, young women and the elderly are high users of antibiotics (Figures 29-30). Among those who use antibacterials, the elderly population use more. 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 30). The number of prescriptions per user is the same as in 2017, while the number of DDDs/user has decreased by around 0.7 DDDs. Mean number of DDDs/prescription is around 11 DDDs, wich indicates a mean treatment length of 11 days.

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. Moreover, they prescribe 17% of all DDDs of metronidazole oral forms. In 2018, dentists most often prescribed phenoxymethyl-penicillin (75% of all antibiotic DDDs prescribed by dentists) followed by amoxicillin (9%), clindamycin (5%) and oral metronidazole (4%).

Urinary tract infections in men

Urinary tract infection (UTI) in men is by definition complicated, and must be investigated, treated and monitored differently than uncomplicated UTIs (uUTI). Complicated UTIs (cUTI) are classified as a cystitis in which anatomical, structural or other conditions of the patient may affect the course of the disease, as well as all cystitis in pregnant women, men and children, and often in elderly patients (1). According to a study based on numbers from Norwegian general practitioners in 2010, men account for approximately 14% of the overall occurrences of UTIs (2). Predisposing and/or complicating factors in men are often found in the distal urinary tract. This applies in particular to conditions that can cause residual urine such as prostate hyperplasia, strictures, other obstruction or neurogenic bladder disorders including diabetes mellitus. Conditions in the bladder that promote bacterial growth such as catheters, calculi and cancer are also important factors (2). Increasing age is another major risk factor for developing UTI, as such functional and anatomical abnormalities of the urinary tract system occur more frequently in elderly men. The incidence of UTI in men are highest in those living in long-term care facilities, and it rarely develops in men under the age of 50 years (3).

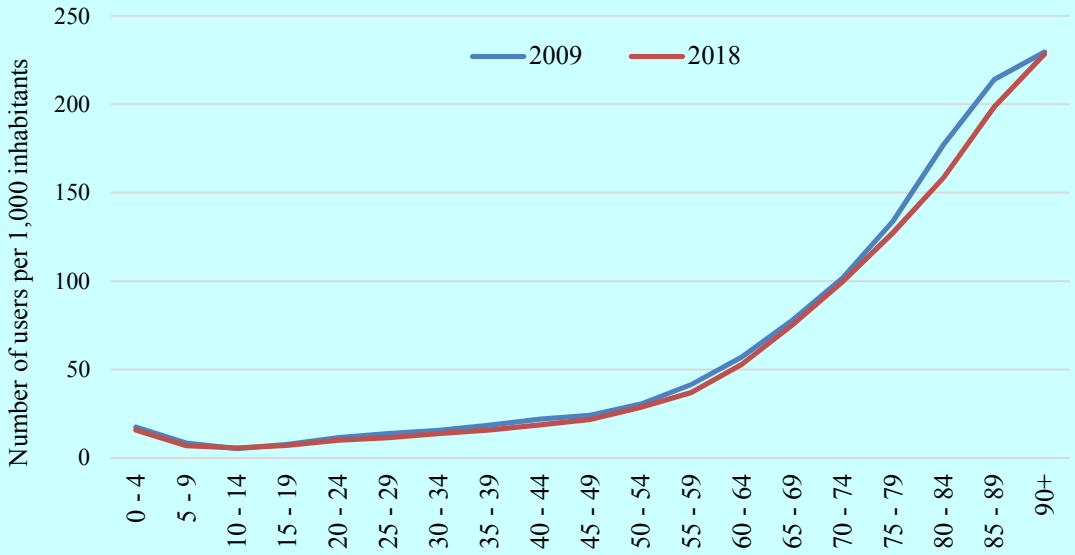

FIGURE 23. Proportion (No/1,000 inhabitants/year) of men by age groups having prescribed a typical UTI-antibiotic (nitrofurantoin, trimethoprim, pivmecillinam, trimethoprim-sulfa and ciprofloxacin) at least once, numbers from 2009 and 2018. Data from the Norwegian Prescription Database (NorPD).

The diagnostic criteria for a UTI are typical symptoms and the findings of leukocytes and growth of uropathogen bacteria. The initial test is a urine dipstick, followed by a urine culture from a midstream sample if positive. The criteria for significant bacteriuria vary depending on the type of sample, and the category and number of isolated species (4). The urine culture is important both for confirming the diagnosis, and for adjusting the therapy according to the susceptibility results. The spectrum of bacteria causing cUTIs are much broader than in uUTIs, and the bacteria are more likely to be resistant (5).
The symptoms include frequency, urgency, dysuria and suprapubic pain. Children and elderly patients may be asymptomatic, or only present with a reduced general condition (6). The history and examination should aim to exclude differentials, most importantly a more serious condition requiring hospitalisation. Relevant differentials are pyelonephritis, urethritis and bacterial prostatitis. The history should include systemic signs as fever, chills and rigors, and symptoms suggesting a different diagnosis such as urinary discharge, perineal/rectal or flank/costovertebral angle pain. The physical examination should include the abdomen, genitalia and a digital rectal examination (3).

National guidelines for primary health-care recommend nitrofurantoin 50 mg x 3, pivmecillinam 200-400 mg x 3 or trimethoprim 160 mg x 2 / 300 mg for 5-7 days if the patient has mild to moderate symptoms and no fever as treatment for complicated UTI in men. In case of a febrile UTI and/or marked symptoms, trimethoprim-sulfa 160/800 x 2 for 5-7 days is recommended, or alternatively ciprofloxacin 500 mg x 2 for 5-7 days in the case of sulpha allergy or resistance to the first-line choice (1). Both the European Association of Urology (EAU) and the national guidelines on antibiotic use for hospitals recommend treatment with an antibiotic penetrating into prostate tissue, since uUTI in men without prostate involvement is uncommon. They both recommend trimethoprim-sulfa 160/800 x 2 or alternatively ciprofloxacin 500 mg x 2 for 7-10 days (5, 7).

Men should have a clinical follow-up a few weeks after completing a UTI, seeking to identify underlying and/or complicating factors. A urological investigation is recommended if a recurrent infection occurs, or in some cases after the first infection depending on the findings regarding complicating factors, the age of the patient and the severity of the infection (3, 6, 7).

While the overall usage of typical UTI-antibiotics amongst men (nitrofurantoin, trimethoprim, pivmecillinam, trimethoprim-sulfa and ciprofloxacin) has been rather stable over the last ten years, there have been major changes in the usage of the individual antibiotics (8). For ciprofloxacin, the number of male users per 1,000 inhabitants is reduced by 41% from 2012 to 2018 (8), and the total amount of defined daily doses (DDD) has been reduced by 40% from 2012 to 2017 (9). Despite this reduction in usage, the prevalence of *E. coli* non-susceptibility to fluoroquinolones collected from human blood culture isolates continues to increase, from 11.7% in 2012 to 18% in 2017 (9, 10). In line with this reduction, we see an increase in the usage of trimethoprim-sulfa amongst men. This is in accordance with the national guidelines, where trimethoprim-sulfa is the preferred choice at the treatment level suggesting the alternative use of ciprofloxacin. From 2012 to 2018 there has been a 77% increase in male users of trimethoprim-sulfa per 1,000 inhabitants (8). The data concerning the number of users does not include the usage in hospitals and nursing homes.

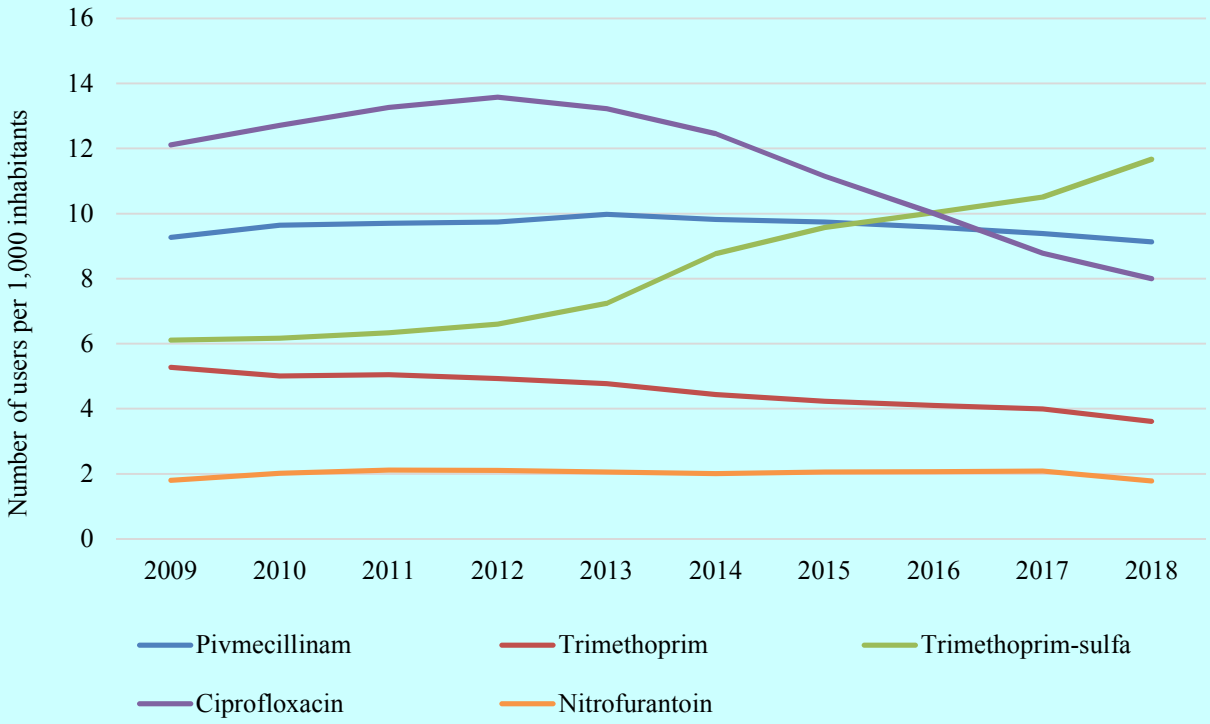

FIGURE 24. Proportion (No/1,000 inhabitants/year) of men (all age groups) having prescribed a typical UTI-antibiotic at least once. Data from the Norwegian Prescription Database (NorPD).

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Antibiotic treatment of Lyme borreliosis in Norway

Lyme borreliosis (LB), caused by the spirochete bacteria genocomplex *Borrelia burgdorferi sensu lato*, is the most common tick-borne infection in Norway, as it is worldwide. LB can cause several different disease manifestations, from the localised skin infection erythema migrans (EM), to systemic infections like Lyme neuroborreliosis (LNB), Lyme arthritis or musculoskeletal borreliosis. A persistent skin infection, called acrodermatitis chronicum atroficans (ACA), can occur if an EM is left untreated, and is suspected to be underdiagnosed. Carditis and other organ affections are also seen, but more seldomly (1).

Although as many as 20-25% of ticks in some areas of Norway carry *Borrelia* (2), it is estimated that only about 1-2% of tick bites lead to infection (3).

In Norway, systemic LB infection is mandatory reportable to the Surveillance System for Communicable Diseases (MSIS) (4). About 450 cases are reported annually. The cases are unevenly distributed through the country, with most cases along the shoreline. Earlier, most cases were seen along the southern coast, but now LB is commonly seen from the Oslofjord and all the way up to the North-Western part of the country (Møre og Romsdal). The 450 annual cases give an incidence of approximately 8.5 LB/100,000 inhabitants/year. The incidence of EM has been calculated in a Norwegian study from 2017 to a national average of 148 EM/100,000 inhabitants/year, showing that EM is almost twenty times more common than systemic LB (5).

As the *Borrelia* bacterium does not spread further after infecting humans (humans work as "dead-end hosts" in the life cycle of the bacterium, normally spreading from their reservoir in small rodents and birds, to larger host animals like roe deer, using the ticks as vectors), antibiotic resistance in *Borrelia* is not a threat in the same way as it is for most other infections (1). Assessing the susceptibility of *Borrelia* to antibiotics is complicated for several reasons. The bacteria are difficult to culture, and studies of susceptibility have shown large differences between *in vitro* and *in vivo* results (6). There are no known antibiotic resistance mechanisms in *Borrelia*, but there are some innate and some acquired hyposensibilities (7). *In vivo*, several antibiotics have proven to be effective; penicillins, tetracyclines and cephalosporins among others, while both macrolides and quinolones seem to be slightly less effective (6, 8). When it comes to *Borrelia,* the question of antimicrobial resistance is therefore more about how abundant use of antibiotics can lead to resistance of *other* bacteria in and around the patients.

As the species of the *Borrelia* bacteria are unevenly distributed in the USA and in Europe (9), it is important to be aware of the local epidemiology, and not uncritically import research results and guidelines from abroad. For other infectious diseases, this usually has to do with antibiotic resistance patterns. For *Borrelia,* however, this has more to do with the distribution of species. In Norway, *B. afzelii* accounts for more than 60% of *Borrelia* found in ticks (2). Although all species of the *B. burgdorferi* genocomplex can cause all manifestations of LB, *B. afzelii* is more likely to cause EM than is *B. burgdorferi sensu strictu*, the predominant species in North America, known to mainly cause Lyme arthritis. There are two main reasons for treating LB. One is to resolve the manifestation in question and the other is to lower the risk for recurrent or disseminated infection (10).

Norwegian guidelines for antibiotic use in primary care and in hospitals also have recommendations for LB (11,12). For EM the drug of choice is phenoxymethylpenicillin (PcV) p.o. for 14 days. In the EM incidence study mentioned above, it was shown that Norwegian general practitioners used PcV in about 60% of EM cases, doxycycline in 26% and amoxicillin in 2%. There was a higher prescribing rate for both macrolides (5%) and amoxicillin (6%) for the youngest children. Few other antibiotics were prescribed (5).

It has been questioned whether PcV is sufficient for EM treatment as it does not pass the blood-brain-barrier and does not work intracellularly. In another Norwegian trial from 2018, PcV, amoxicillin and doxycycline were compared in a randomised, controlled trial (RCT) in Norwegian general practice, and the treatments came out equally efficient regarding EM duration, concomitant symptoms and side effects (13). In this trial with 188 patients, there were no treatment failures, i.e. none of the patients developed a systemic LB infection during the 1 year follow up. The trial is included in a recent meta-analysis from the Cochrane Germany Foundation (14), concluding that PcV, amoxicillin, doxycycline, together with cefuroxime axetil, ceftriaxone, azithromycin and minocycline is equally effective for EM treatment. In all Nordic countries, PcV is the drug of choice, however, doxycycline is recommended for those with penicillin allergy or symptoms like fever. Doxycycline may be used from 8 years of age (with azithromycin as an alternative for the youngest) (11).

For Lyme arthritis and ACA doxycycline p.o. for 3 weeks is recommended. Amoxicillin is an alternative (11,12).

For LNB the recommended treatment until 2008 used to be ceftriaxone i.v.. In 2008, Norwegian neurologist Unn Ljøstad et al. showed in an RCT that doxycycline p.o. for 14 days was as effective (15), and this has since then been the drug of choice in both Norwegian and European guidelines (16). Nevertheless, a recent Norwegian study showed that the actual treatment differs from hospital to hospital in Norway, both regarding the choice of antibiotics and duration of treatment (17).

Some alternative clinics in both Norway and abroad state that prolonged and combined antibiotic treatment is necessary for the treatment of persistent symptoms after an LB infection (18). This group of patients is difficult to define, and studies to approve or debunk this theory are therefore rare. In 2016, an RCT reported in New England Journal of Medicine, although criticised, could not show any significant effect of prolonged or combined antibiotic therapy (19). Still, some people with persistent symptoms believed to be caused by a tick-borne disease seek "alternative" treatment, and in 2018 the Norwegian Directorate of Health initiated a process for a Nordic consensus for diagnostics, treatment and rehabilitation of these patients. The consensus is expected to be ready in 2020 (20).

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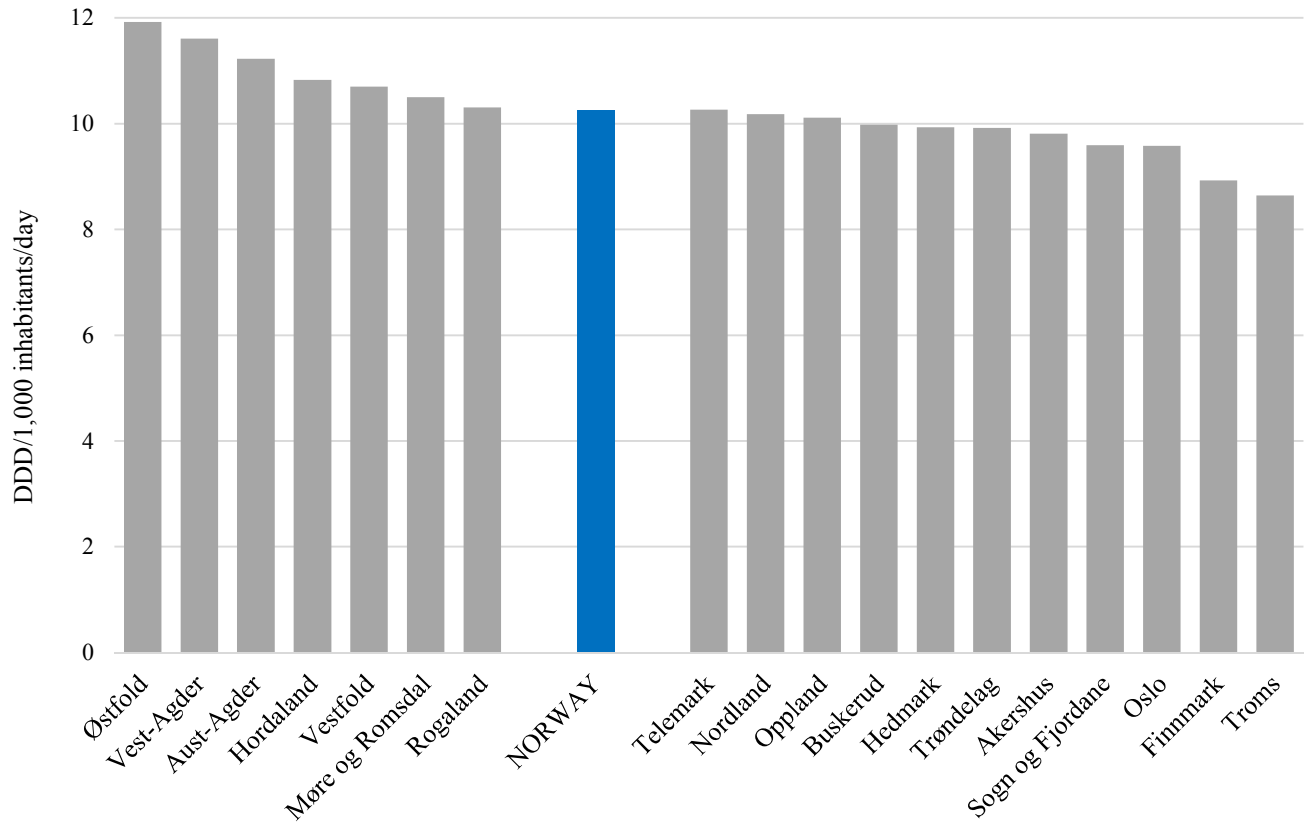

FIGURE 25. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2018 measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers own practice not included).

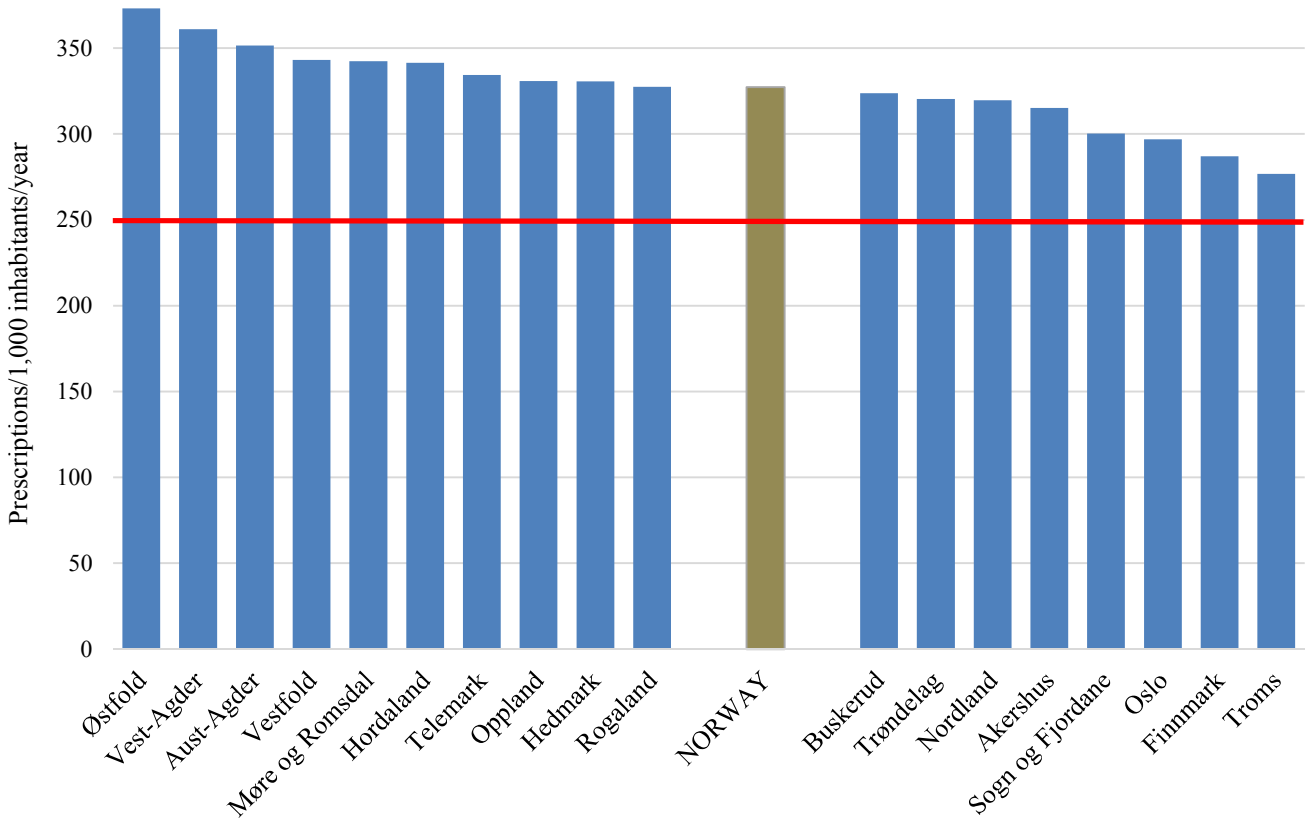

FIGURE 26. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2018 measured as number of prescriptions/1,000 inhabitants. Data from NorPD (excl. health institutions). Red line; goal set by the National Strategy against Antibiotic Resistance 2015-2020.

Changes in Defined Daily Doses and consequences for antibiotic statistics

ATC/DDD makes it possible to look at aggregated drug use data in a simplified manner. We can compare different drug groups with each other and we can do studies over time, despite the fact that the drug dosages may vary between countries and change over time. In addition, we can compare local use with regional, national and international use. The statistics make it possible to compare actual use to the recommendations in the therapy guidelines and to identify possible irrational antibiotic use. The defined daily dose (DDD) is a theoretical unit of measurement for drug use, and the recommended dosages do not always correspond to the DDD. This is sometimes difficult to explain to clinicians. The WHO Global Action Plan on antimicrobial resistance encourages countries to strengthen knowledge through surveillance and research, and WHO recommends countries to use the ATC/DDD methodology for antibiotic surveillance. To facilitate better match between DDDs and actual daily doses, a global WHO expert meeting was set up in 2017, hosted by the ECDC (European Centre for Disease Prevention and Control). The experts proposed changes to DDDs for several antibiotics that are widely used in many countries. It was finally decided to change nine DDDs for antibiotics that are considered important internationally, see Table 9. When presenting drug consumption statistics the ability to compare is important - with others and/or over time. Then we must use the same method, in this sense - the same values for the DDD. The national statistics are always made with the latest updated version of ATC/DDD, i.e. for the current NORM/NORM-VET data, ATC/DDD index 2019 is used. If you want to show historical data, the statistics for all the years must be made with the same version of the ATC/DDD index. All the changed DDD values have increased compared to previous ones. When a DDD value increases, the number value of DDD/1,000 inhabitant/day is reduced. Hence, earlier NORM/ NORM-VET reports present different (i.e. higher) values for DDD/1,000 inhabitants/day than the current report. The trend over the years will always be the same, see Figure 27. Because not all DDDs for antibiotics are changed, the change will affect countries differently, e.g. the DDD for phenoxymethylpenicillin is not changed (DDD=2g). In Scandinavia, where we use a lot of phenoxymethylpenicillin for respiratory tract infections (RTIs), the decrease in DDD/1,000 inhabitants/day for the antibiotics will be less than in countries where they use amoxicillin (for which the DDD is increased) as a first choice for RTIs. This implies that the ranking of countries in Europe may change according to the antibiotics used in each country. One of the goals in the Norwegian Strategy was that Norway should be one of the three European countries with the lowest use of antibiotics in humans, measured in DDD/1,000 inhabitants/day. Since Norway recommends and uses a lot of the narrow spectrum penicillin phenoxymethylpenicillin for the same indications where other countries in Europe use amoxicillin (a penicillin with extended spectrum), we will probably never reach that specific goal.

TABLE 9. DDD changes for antibacterials, valid from January 2019.

ATC code	Active ingredient	Form	Old DDD	New DDD (2019)	Note
J01CA01	Ampicillin	P	2 g	6 g	
J01CA04	Amoxicillin	O	1 g	1.5 g	
J01CA04	Amoxicillin	P	1 g	3 g	Not available in Norway
J01CA17	Temocillin	P	2 g	4 g	Not available in Norway
J01CR02	Amoxicillin/beta-lactamase inhibitor	O	1 g	1.5 g	
J01DE01	Cefepime	P	2 g	4 g	Not available in Norway
J01DH02	Meropenem	P	2 g	3 g	
J01MA02	Ciprofloxacin	P	0.5 g	0.8 g	
J01XB01	Colistin	P	3 MU	9 MU	

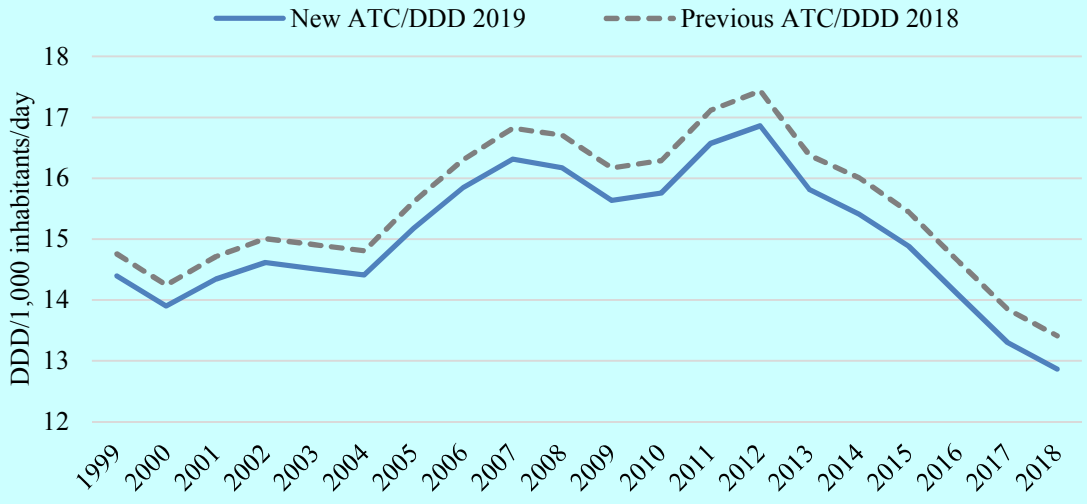

FIGURE 27. Effect of changes in DDDs. The blue line shows antibacterial use (J01, excl. methenamine) in Norway 1999-2018 by the ATC/DDD 2019 version. In 2018, the consumption was 4% lower than if the ATC/DDD-index 2018 had been used (grey dotted line). Note that the y-axis begins at 12.

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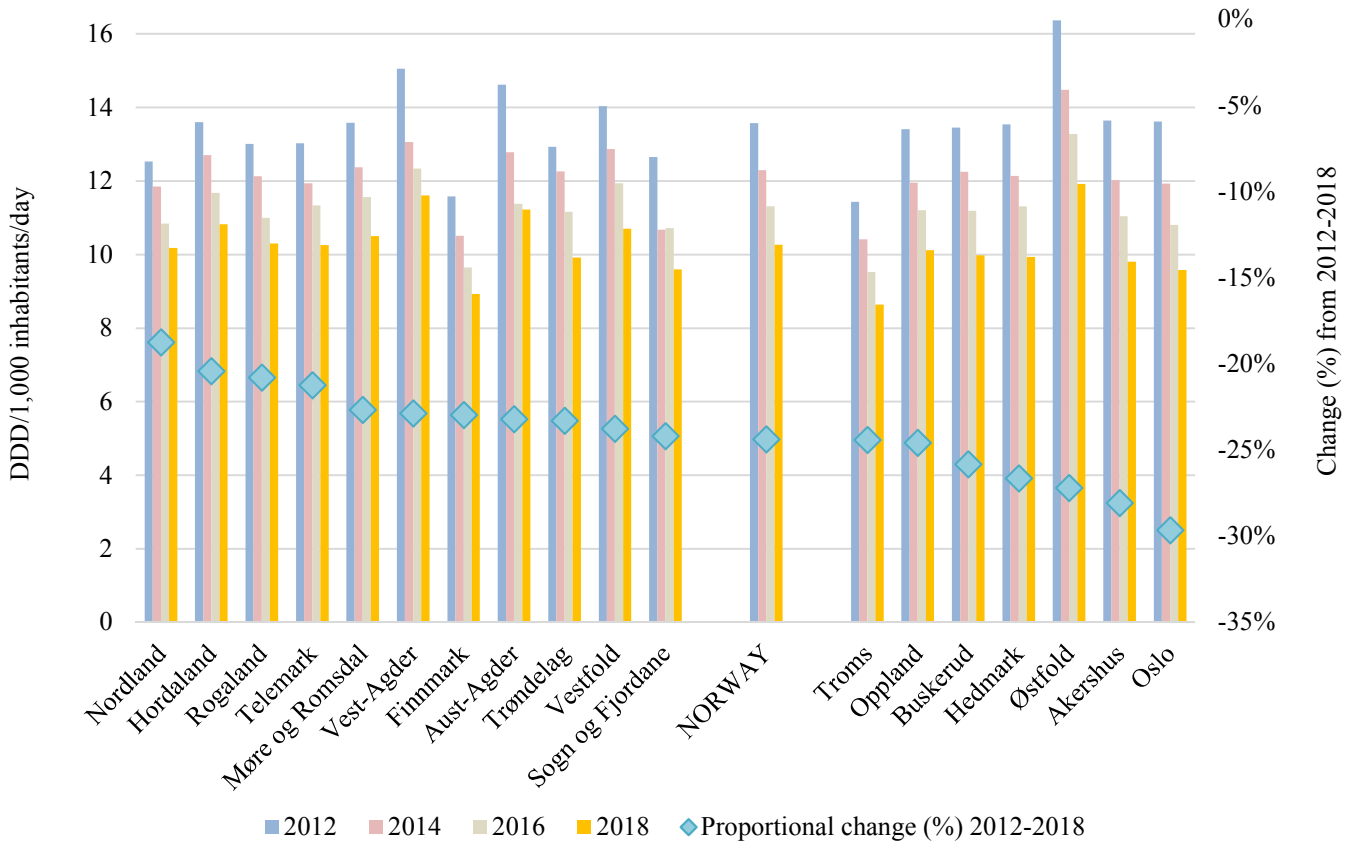

FIGURE 28. Consumption of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2012, 2014, 2016 and 2018; and proportional change (reduction in %) measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers own practice not included).

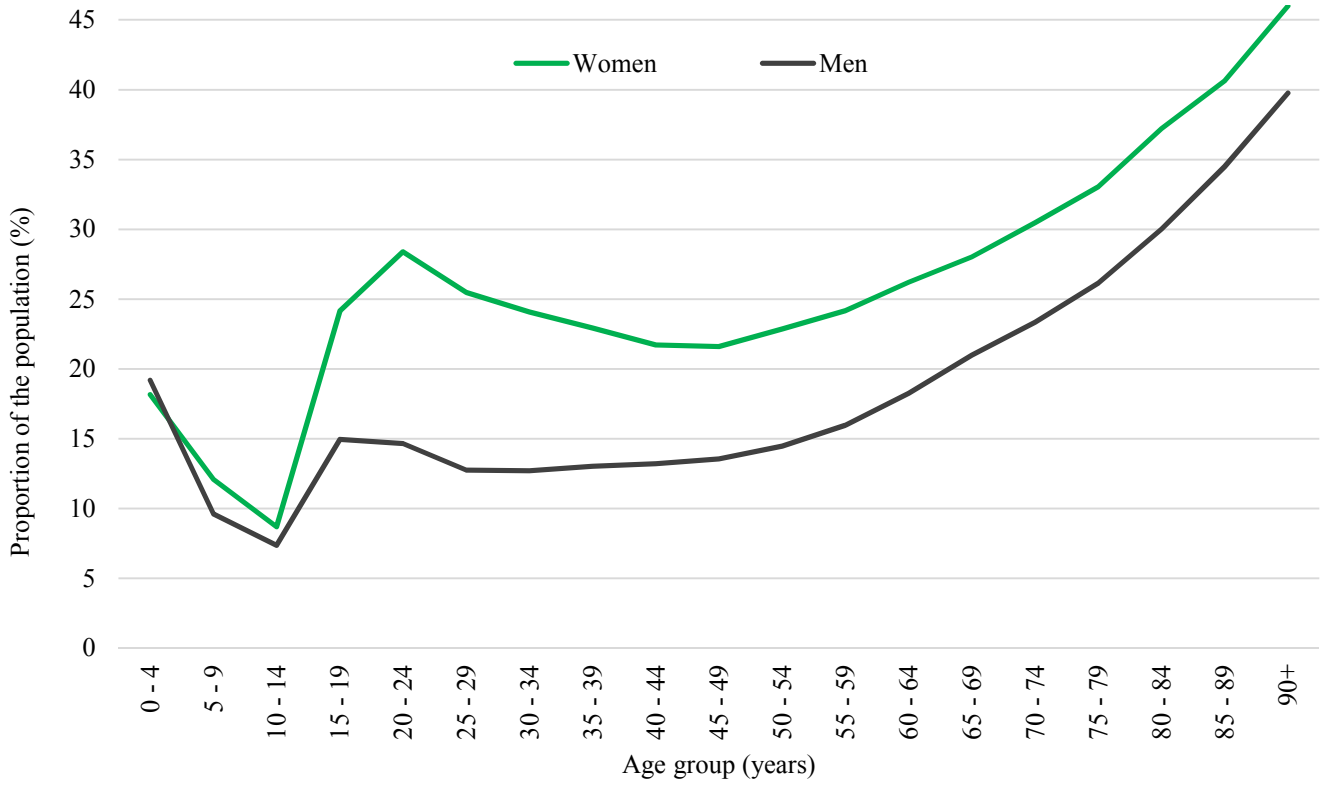

FIGURE 29. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one year prevalence) in primary care by gender and age in Norway, 2018. Antibacterials included are antibacterials for systemic use (ATC group J01), vancomycin (A07AA09), fidaxomicin (A07AA12) and metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions.

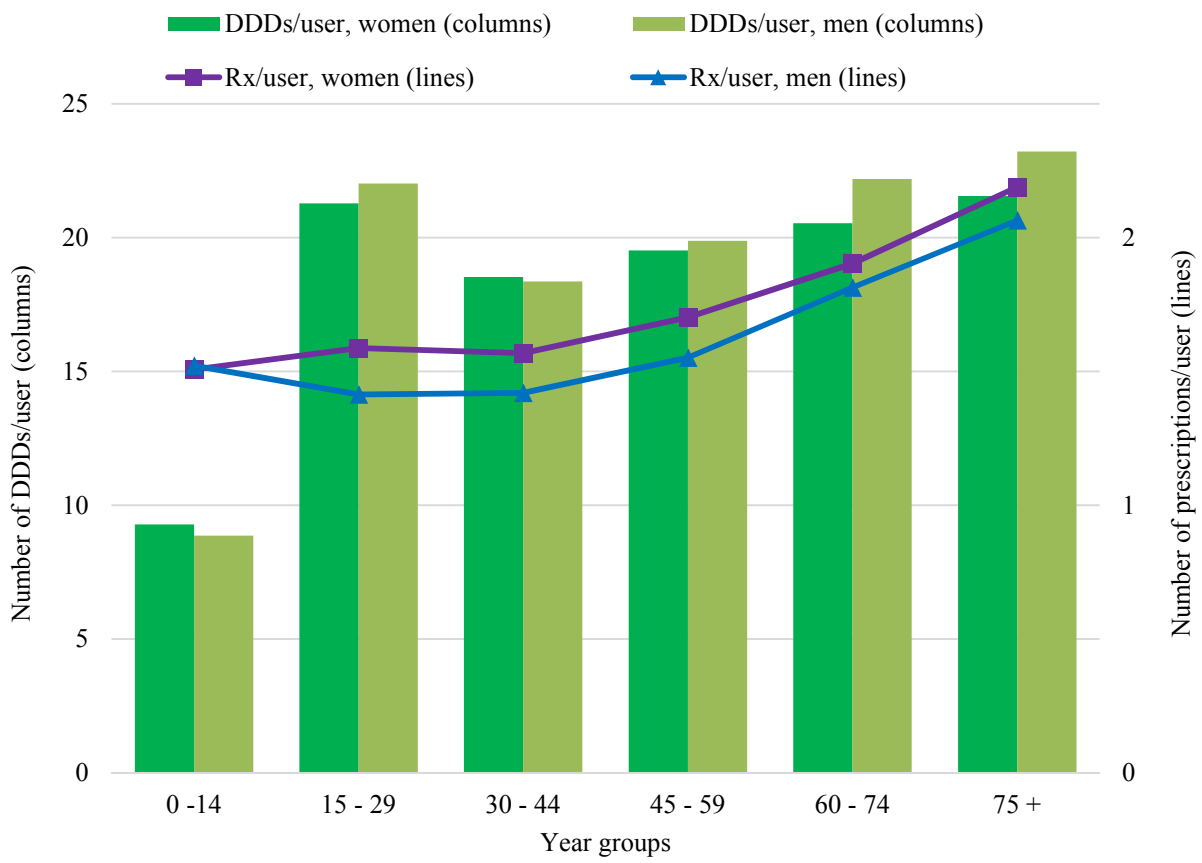

FIGURE 30. Mean number of prescriptions (Rx) per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway, 2018. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

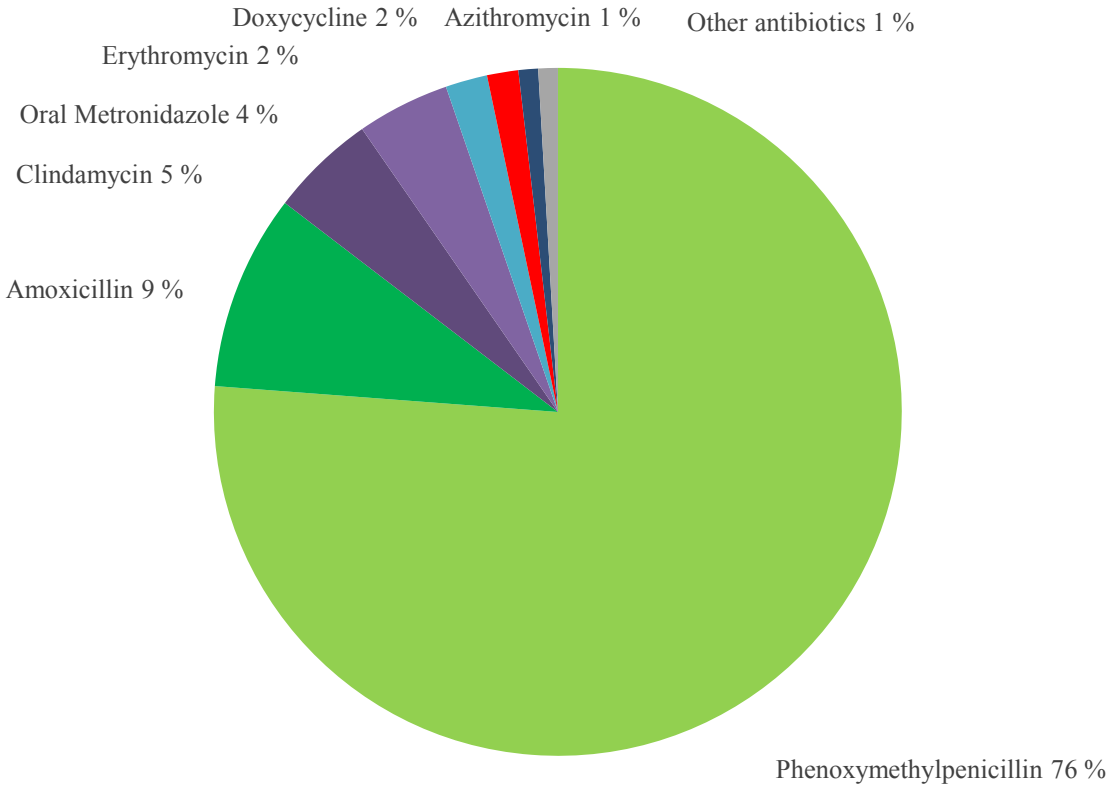

FIGURE 31. Relative amount of antibacterial agents for systemic use prescribed by dentists in Norway in 2018, as measured in Defined Daily Doses (DDD).

Antibiotic usage in hospital care

In 2018, the antibacterial sales (in DDDs) to hospitals represented around 8% of total sales of antibacterials for human use in the country. This is a slight decrease of 4% in DDD/1,000 inhibitants/day compared to 2012, but an increase of 3% since 2016 (Figure 32). The recent increase is due to several factors and is partially explained by increased use of narrow-spectrum antibiotics including combination regimens with an aminoglycoside. The DDDs are lower than the doses most commonly used, and this will give artificially higher values for volume. Moreover, combination regimens with a penicillin plus an aminoglycoside account for more DDDs than if monotherapy with a cephalosporin or carbapenem is used.

The therapy pattern of antibacterials in hospitals does not change much from one year to another, however a decrease in use of broad-spectrum antibiotics has been observed since 2012. Five selected groups of broad-spectrum antibiotics accounted for 21% of total DDDs for hospitals in 2018 compared to 26% in 2012. This is due to increased use of narrow-spectrum antibiotics. The share of beta-lactamase sensitive penicillins is 20% of totals (Figure 32). Penicillins (J01C) represent 47% of the use measured in DDDs in hospitals (J01CE 20%, J01CA 10%, J01CF 13% and J01CR 4%). The second largest group is the cephalosporins with 18% of all DDDs, the dominant subgroup being third generation cephalosporins (J01DD). In 2018, six substances accounted for 50% of all DDDs used in hospitals. These are benzylpenicillin, cloxacillin, cefotaxime, gentamicin, doxycycline and cefalotin. Three single substances accounted for 35% of all antibacterial DDDs in hospitals; benzylpenicillin (16%), cloxacillin (11%) and cefotaxime (8%).

Figure 34 shows annual trends in national antibiotic use in hospitals by 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. The length of stay (LOS) in Norwegian hospitals in the latest years is relatively stable according to national statistics, but the number of admissions and bed days are going down.

Seven selected groups that mainly are used in hospitals are shown in Figure 35. The use of piperacillin/tazobactam has been increasing over many years, but was markedly reduced in 2017 and 2018 due to a nationwide shortage. There was increased use of third generation cephalosporins, aminoglycosides and metronidazole (not shown). This is partly a result of the piperacillin/tazobactam shortage, as these drugs may be components of alternative regimens to piperacillin/tazobactam, but is probably also a result of the implementation of antibiotic stewardship programmes in Norwegian hospitals from 2016. The use of aminoglycosides increased by 33% from 2016 to 2018, whereas the use of quinolones has decreased by 41% from 2012 to 2018. The use of carbapenems peaked in 2014 after many years of increasing use, and seems to have reached a stable level. The use of second generation cephalosporins has decreased over many years. It should be noted that only parenteral formulations of second and third generation cephalosporins as well as carbapenems are licensed in Norway. Figure 36 shows that the distribution between "preferred antibiotics" (which largely reflects standard treatment regimens in national guidelines) and "resistance driving antibiotics" was 68.3% vs 31.7%, respectively.

There are large variations in volume of antibiotics used, measured in DDD/100 bed days, and in therapy profile between the hospitals. Figure 37 shows the use of the five selected groups of broad-spectrum antibiotics targeted in the National Action Plan in all Norwegian hospitals/health trusts. The large variations cannot be accounted for by differences in activity or patient composition alone.

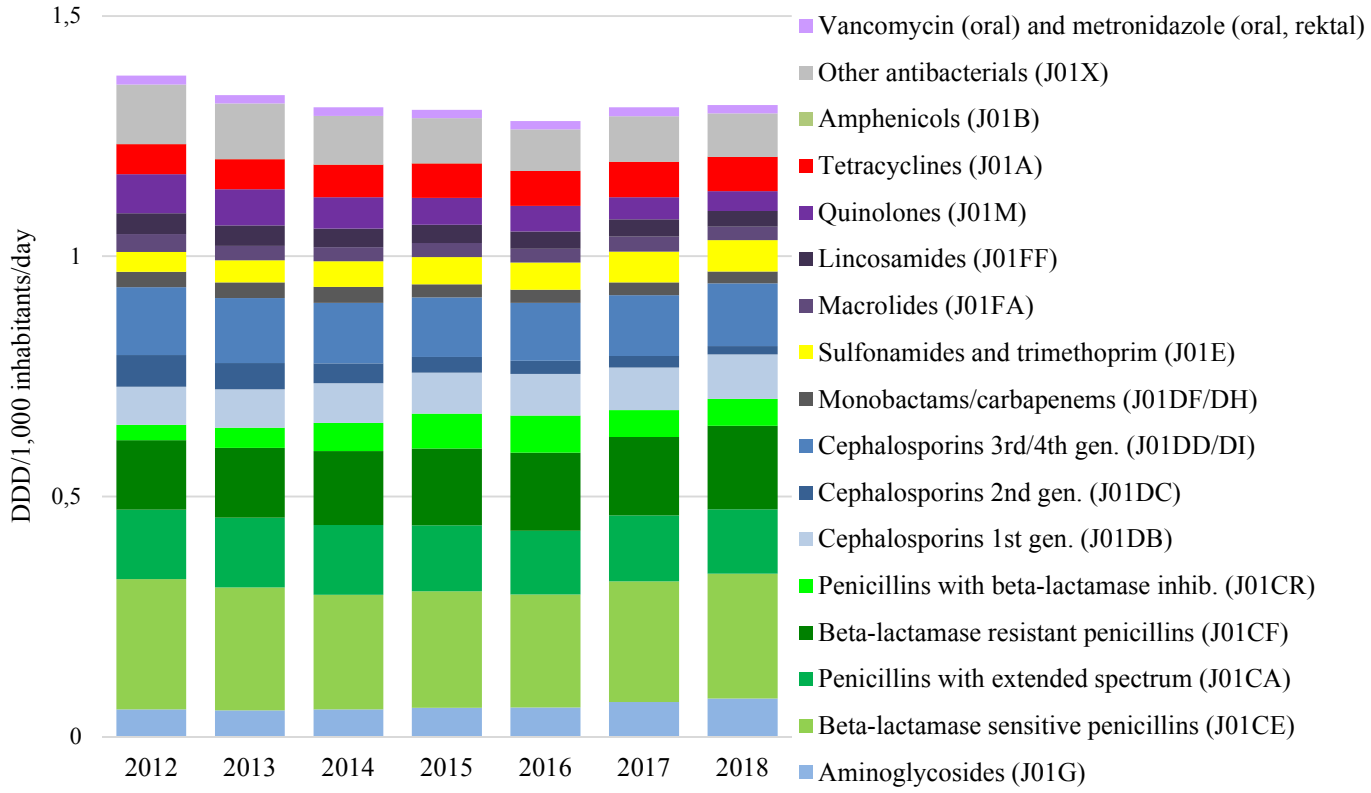

FIGURE 32. Antibacterial agents for systemic use (J01) in Norwegian hospitals 2012-2018, in DDD/1,000 inhabitants/day.

New evidence supports shorter antibiotic treatment courses in Norwegian healthcare

In order to reduce the risk of antimicrobial resistance, prescribers are encouraged to choose the narrowest possible spectrum of antibiotics in doses that ensure an effective concentration at the site of infection. A treatment regimen should be as short as necessary to cure, or in most cases help the patient cure the infection, and long enough to avoid therapeutic failure and infection recurrence. An extensive knowledge-base exists regarding the resistance-driving properties of antibiotic agents and the pharmacological basis for their correct dosing. However, the recommended length of antibiotic treatment has been arbitrary for most infectious diseases and based mainly on conventions and expert opinions rather than well-designed studies. In recent years, the duration of antibiotic treatment for common infections has achieved increased attention both in the primary and hospital care settings. Current national antibiotic guidelines for both care levels recommend spans of treatment days (e.g. 5-7 days, 7-10 days) rather than a specific number of days for several conditions. As supported by a European survey of specialists in infectious diseases (1), upcoming revisions of guidelines will replace such duration spans with an exact and lowest number of days (e.g. seven days rather than 7-10 days).

In primary care, the long-standing belief that it is essential to finish a course of antibiotics to prevent the development of antimicrobial resistance has been rejected, based as it is on myths rather than evidence (2). It is not feasible to monitor the treatment effect from day to day in general practice. The most appropriate treatment advice must consequently be given to the patient at the time of antibiotics prescription. Even though more than half of primary care patients receiving antibiotics for a lower respiratory tract infection fail to complete the course (3), there is reason to believe that general practitioners will find it unsafe to recommend patients to discontinue the course once they feel better. A more feasible strategy will be to revise the guidelines' recommended treatment duration based on existing and upcoming evidence, and advice patients to reconsult if their condition deteriorates.

A recent review of systematic reviews concluded that short courses of antibiotics are as effective as longer courses for most common infections treated in primary care (4). However, there is still a shortage of high-quality studies on the topic, and few apply to the narrow-spectrum antibiotics commonly recommended in Norway. The process of implementing new findings has already started. In the UK, The National Institute for Health and Care Excellence (NICE) now recommends five days of antibiotic treatment when antibiotics are warranted for acute sinusitis and 5-10 days for sore throat. Corresponding Norwegian recommendations for antibiotic use in primary care still are 7-10 days and 10 days, respectively. Streptococcal tonsillitis has traditionally been treated for 10 days, mainly to prevent complications of acute rheumatic fever. As the prevalence of acute rheumatic fever has declined in high-income countries, a shortening of the course from 10 to five days could be appropriate. A Swedish study comparing five and 10 days treatment for streptococcal tonsillitis is about to be published (5), and may influence the recommendations in the Norwegian guidelines.

There is a small trend towards lower relative use of large packages (40 tablets, equals 13.3 days of treatment based on the WHO/DDD definition) and higher use of small packages (20 tablets, equals 6.7 days of treatment) of amoxicillin 500 mg and phenoxymethylpenicillin 660mg in data from NorPD 2008-2017 (Figure 33). If this trend is to continue, further clinical research in primary care and continuous revisions of the guidelines is needed.

In hospitalised patients, randomised-controlled and non-inferiority studies have demonstrated that:

- in Gram-negative sepsis, one week is non-inferior to 14 days of antibiotic therapy if the patient is clinically stable before day seven and the primary focus was controlled (6),
- for community-acquired and hospital-acquired/ventilator-associated pneumonia antibiotic therapy may be as short as five days (7) and seven days (8), respectively,
- for acute pyelonephritis, seven days of treatment is as effective at 14 days or more even if the patient is bacteremic (more prolonged treatment is probably needed in patients with urogenital abnormalities) (9),
- for complicated intraabdominal infections after adequate source control, four days of antibiotic therapy is non-inferior to 10 days (10),
- for uncomplicated cellulitis, five days of antibiotic therapy appears as effective as 10 days (11),
- for typhoid fever, abbreviated courses of antibiotic therapy (2–3 days) are probably safe, provided azithromycin is used in case of fluoroquinolone-resistant strains (12).

The list is even longer, and more quality studies are underway. The concept of antibiotic stewardship programs (ABS) (13) has evolved together with the increased research efforts to determine the optimal duration of antibiotic treatment. A point of interest is the somewhat controversial role of the inflammatory marker procalcitonin (PCT). Numerous studies have proven its usefulness to help decide early termination of antibiotic use for sepsis and pneumonia in hospitalised patients; however, explicit algorithms for PCT have been lacking or seem challenging to implement. A recently published consensus for PCT use incorporates the physician's assessment of the probability and seriousness of infections into the proposed algorithms (14). PCT is officially recommended for use as a decision aid in ABS in the South-East Regional Health Trust of Norway.

Most international studies on therapy duration have investigated broader-spectrum antibiotics than those of first or even second choice in Norwegian guidelines, reflecting our present fortunate situation of low antibiotic resistance rates. However, serious concerns about the applicability of study results are probably unwarranted, at least in hospitals, given the higher efficacy of the penicillins compared to most broad-spectrum antibiotics. More worrying is the ever-decreasing length of hospital stays, now on average 3-4 days in many Norwegian acute-care hospitals (15). A high patient volume renders healthcare workers increasingly more focused on rapid discharge rather than on expectant clinical observations and proper microbiologic sampling of the patient. The turn-over pressure tends to result in unnecessary use of broad-spectrum agents,

and furthermore to encourage extended post-discharge treatment prescriptions far beyond what is necessary – "just to be sure". This "real world" situation bears little similarity to the predefined conditions required e.g. in research protocols for duration of antibiotic treatments, and the discrepancies are probably increasing proportionally with a higher quality-rating of studies. Finally, a lack of national guidelines for OPAT (Outpatient Parenteral Antibiotic Therapy) should be addressed in a situation where advanced intravenous antibiotic regimens are regularly prescribed at the discharge of patients, often for treatment at home to an extent which is mostly unknown.

Half a decade of new research results on the subject of antibiotic treatment duration is available for the planned update of our national antibiotic guideline for antibiotic use in hospitals over the next two-year period. Implementation-modifying factors, as discussed above, are essential to keep in mind in this process.

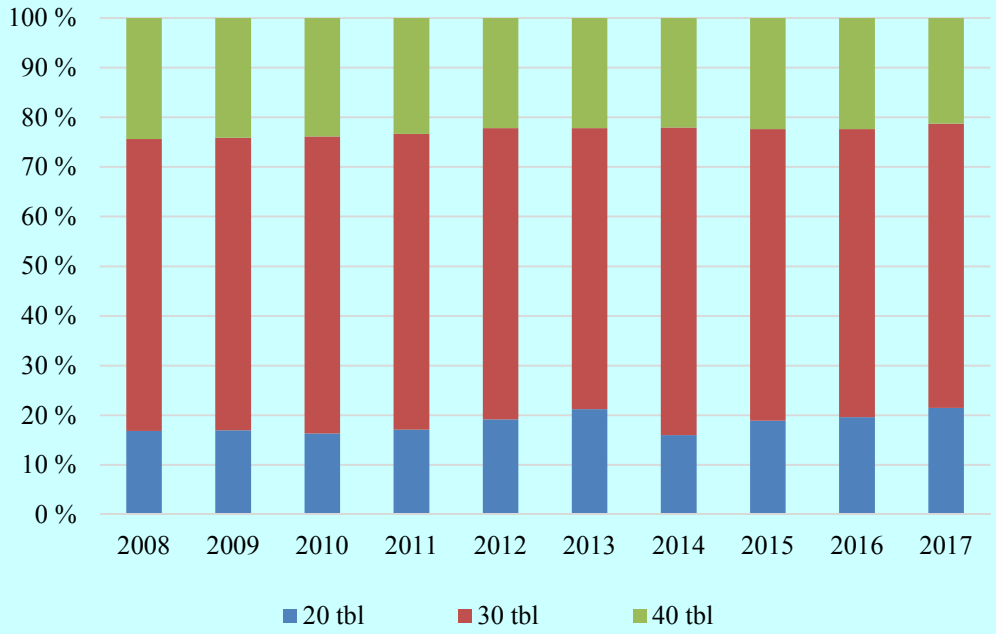

FIGURE 33. Relative use of different package sizes of amoxicillin 500mg and phenoxymethylpenicillin 660mg 2008-2017. 20 tablets equal 5-7 days treatment dependent of dosage.

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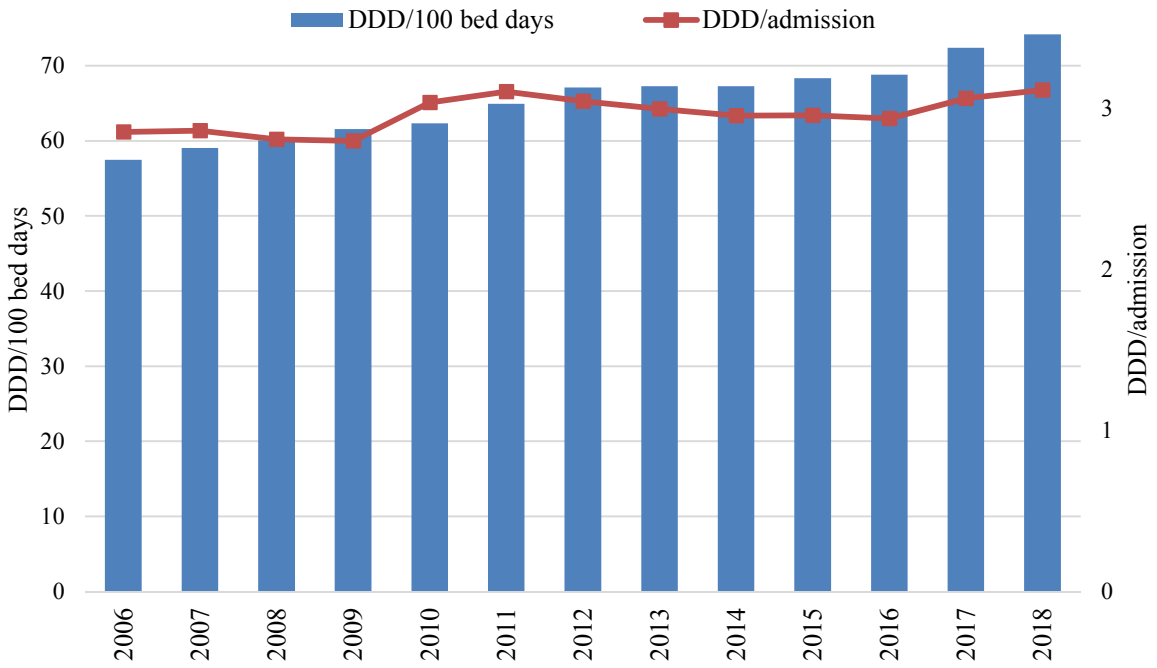

FIGURE 34. Total use of antibiotics in Norwegian hospitals (somatic) 2006-2018, measured in DDD/100 bed days (blue bars) and DDD/admission (red line). Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

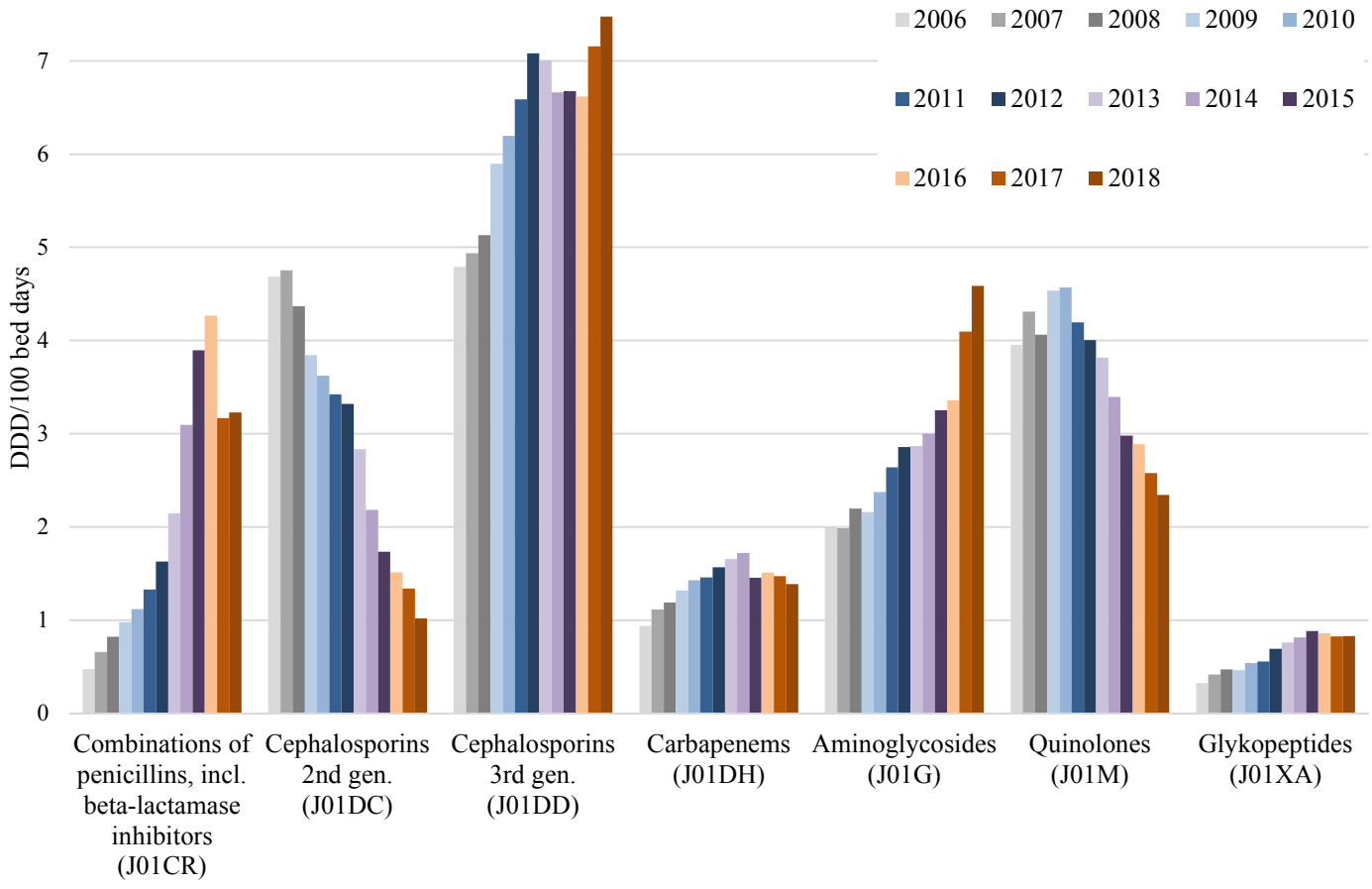

FIGURE 35. Usage of selected antibacterial agents for systemic use (ATC J01CR, J01DC, J01DD, J01DH, J01G, J01M and J01XA) in Norwegian hospitals 2006-2018, measured in DDD/100 bed days.

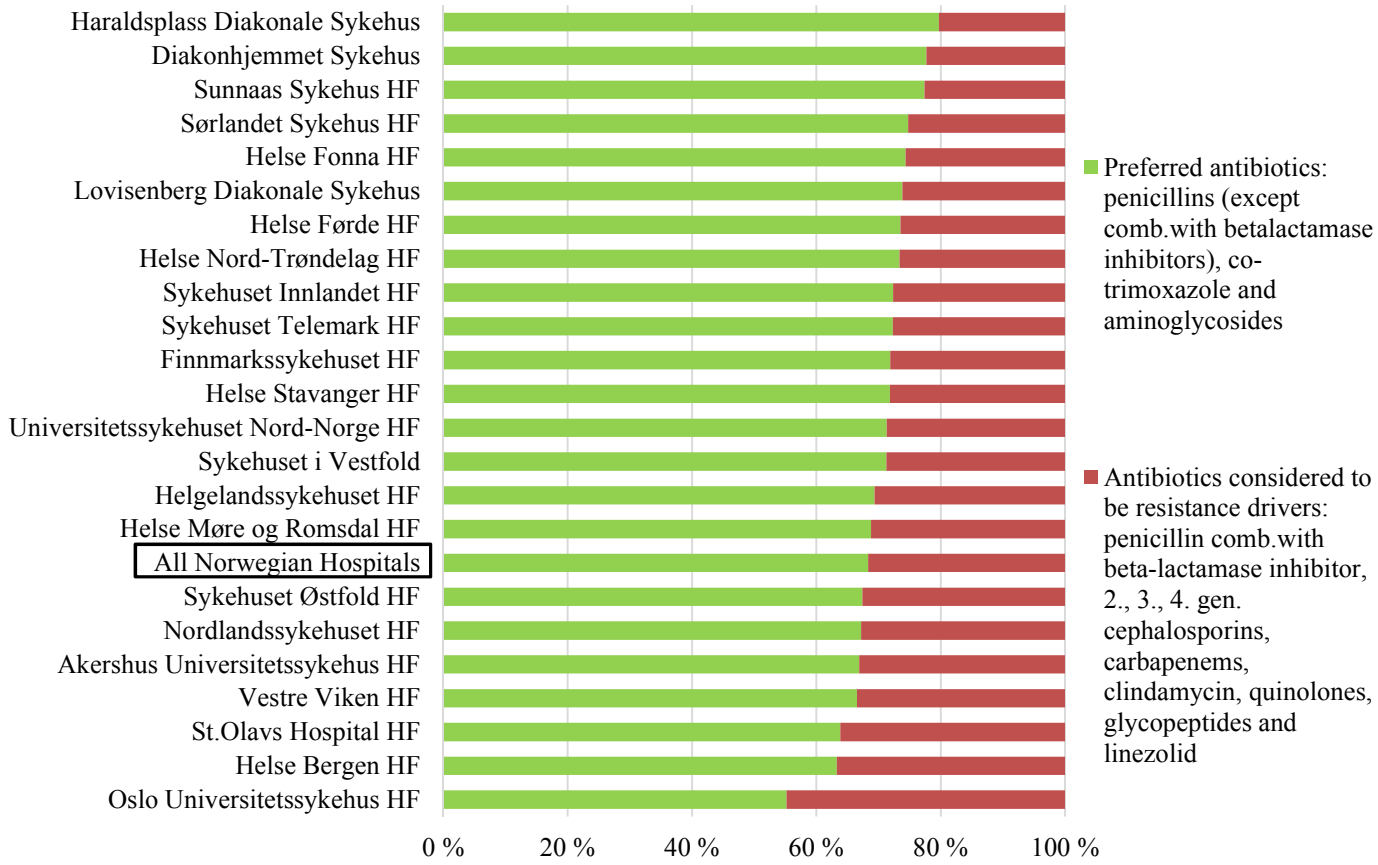

FIGURE 36. Proportions (% of DDDs) of preferred antibiotics (green) and antibiotics that are considered to be drives of antibiotic resistance (J01CR, J01DC, J01DD, J01DH, J01M, J01XA and J01XX08) (red) in Norway, presented per hospital/health trust in 2018. First generation cephalosporins and tetracyclines are not included as they in hospitals mainly are used for surgical prophylaxis. Metronidazole is also excluded from the figure because it does not readily fit either of the descriptions "preferred" or "resistance driver", and there are no alternative drugs mainly targeting anaerobic bacteria.

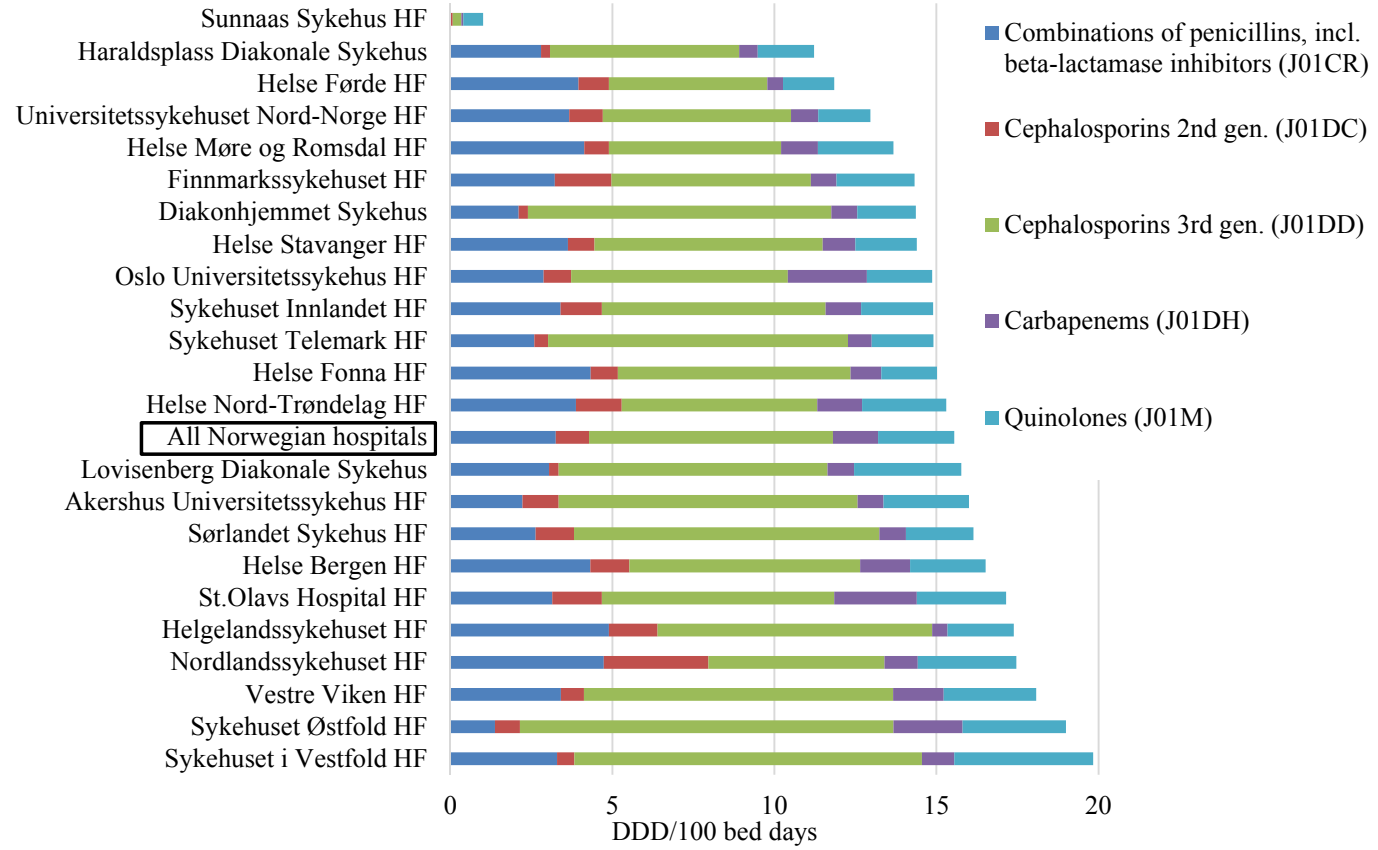

FIGURE 37. Usage of selected antibacterial agents for systemic use (ATC J01CR, ATC group J01DC, J01DD, J01DH and J01M) in Norway, 2018, presented per hospital/health trust and measured in DDD/100 bed days.

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

In 2015, a National Strategy against Antibiotic Resistance was agreed upon, aiming to reduce the total volume of antibiotics by 30%, as compared to 2012, by the end of 2020. The Strategy was followed by a National Action Plan, issued January 2016, with suggested ways to reach the targets within 2020. The overall goal for total human consumption was reduction of DDDs by 30%. In addition, two sector specific goals in ambulatory care were introduced; reduction of average number of prescriptions (target; 250 precriptions per 1,000 inhabitants per year) and the reduction of antibiotics for respiratory tract infections by 20% (in DDD/1,000 inhabitants/day). Figure 38 shows total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to National targets. DDD/1,000 inhabitants/day for J01, excluding methenamine is reduced by 24% since 2012. There are county differences; some counties use more "guidelines recommended antibiotics" (i.e. narrow spectrum antibiotics), indicating a higher adherence rate to the national guidelines, see Figure 39. The county differences in proportional use of "Guidelines recommended antibiotics" were smaller in 2018 compared to 2012 (range 44-52% of total use in 2012 and 50-54% in 2018). This indicates that awareness of AMR as well as adherence to guidelines have increased in all counties in the period. Prescriptions per 1,000 inhabitants per year (J01, excluding methenamine) is reduced by 27% since 2012, from 444 to 324.

Since 2012, there has been a reduced prevalence of use in all age groups. The largest reduction is seen in small children (0-9 years) by more than 30%, whereas the reduction among elderly above 70 years is only 15%. Moreover, the use in men is reduced more than in women (27% reduction in prescriptions pr 1,000 in men vs. 22% in women). The largets reduction in prescriptions per 1,000 is observed in children 0-9 years old (approx. 37% fewer prescriptions pr 1,000 in 2018 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 programmes mandatory in Norwegian hospitals. Figure 40 shows the annual variation of total hospital use of these groups in the years 2006-2018 according to the national target. Figure 41 shows how the use of these five groups has changed in the different Norwegian hospitals/health trusts in relation to the national target; a reduction by 30% (marked by a grey line in the figure). For all hospitals in Norway together there was 12% reduction in use of the five selected groups of broad-spectrum antibiotics 2012-2018 when adjusted for activity (bed days). The number of bed days is going down every year and there is a large increase in outpatient consultation, therefore it is probably necessary to use more than one indicator of clinical activity in hospitals when assessing drug use data. Unadjusted sales data shows a reduction of 19% for the same period.

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

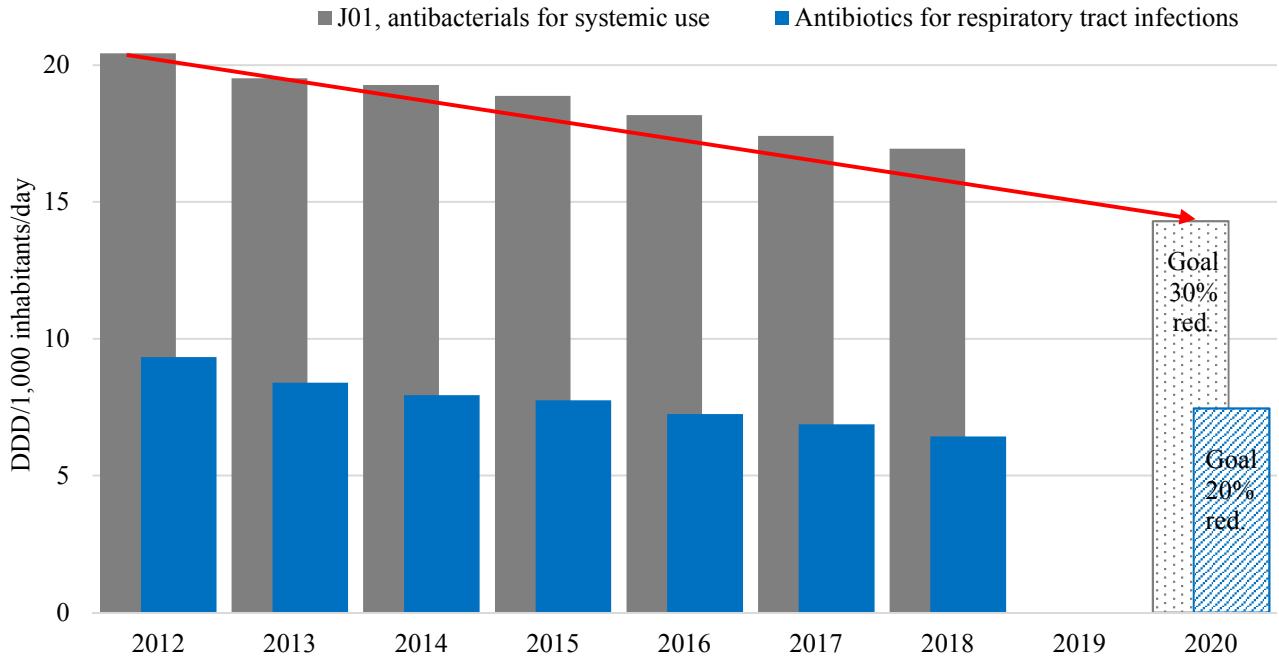

FIGURE 38. Total human sales of antibacterial agents for systemic use (ATC group J01) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2018 measured in DDD/1,000 inhabitants/day. According to the National Action Plan, the target for 2020 is 30% reduction, measured in DDDs. Bars show measured use 2012-2018 (grey; J01, blue; antibiotics for respiratory tract infections), red line and bars with pattern; targets set in the National Strategy against Antibiotic Resistance 2015-2020.

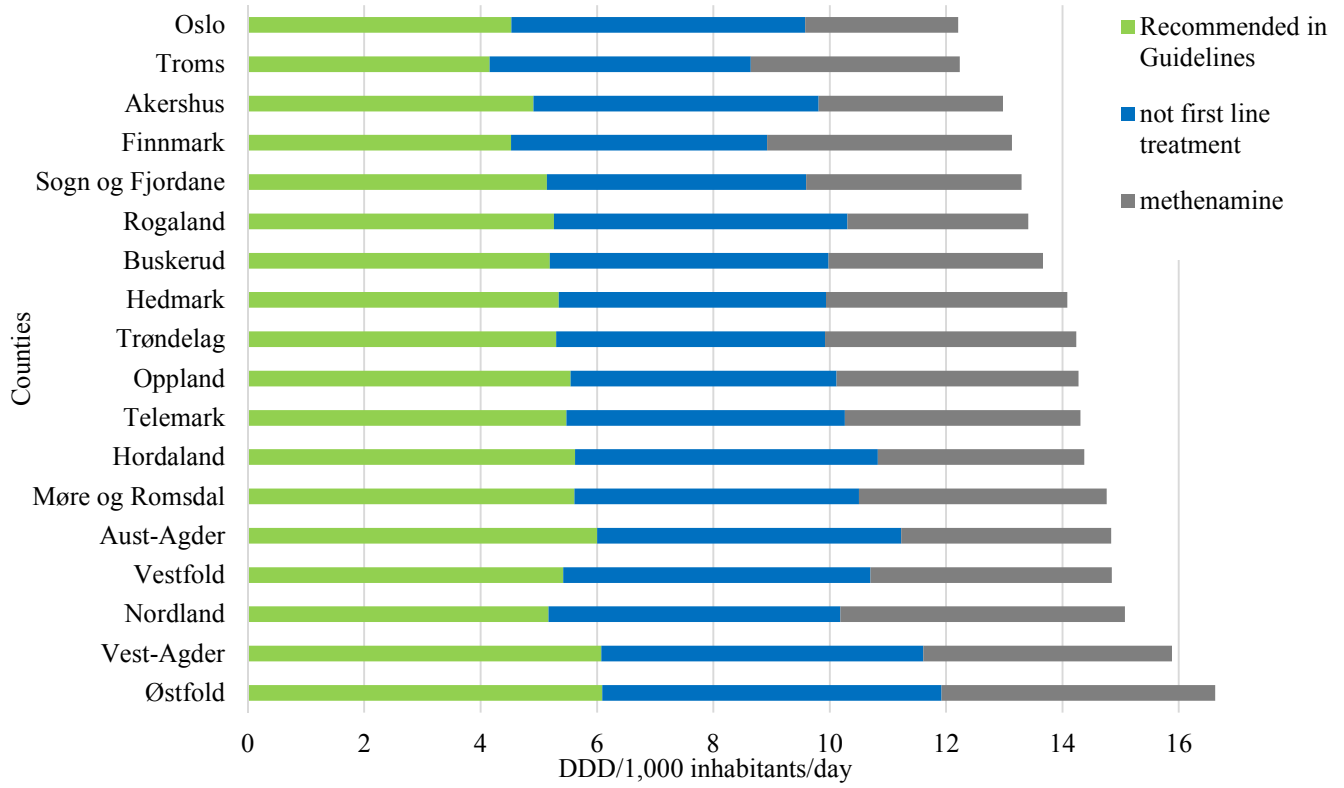

FIGURE 39. Consumption of antibacterial agents for systemic use (ATC group J01) in outpatients in the different counties of Norway, 2018. The data are aggregated into three groups; a) methenamine, b) antibiotics recommended as first-line treatment in the Guidelines for Primary care (phenoxymethylpenicillin for respiratory tract infections, pivmecillinam, trimethoprim and nitrofurantoin for urinary tract infections, and dicloxacillin for skin infections), c) not first-line treatment includes all other antibiotics in J01. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions and sales to prescribers own practice not included).

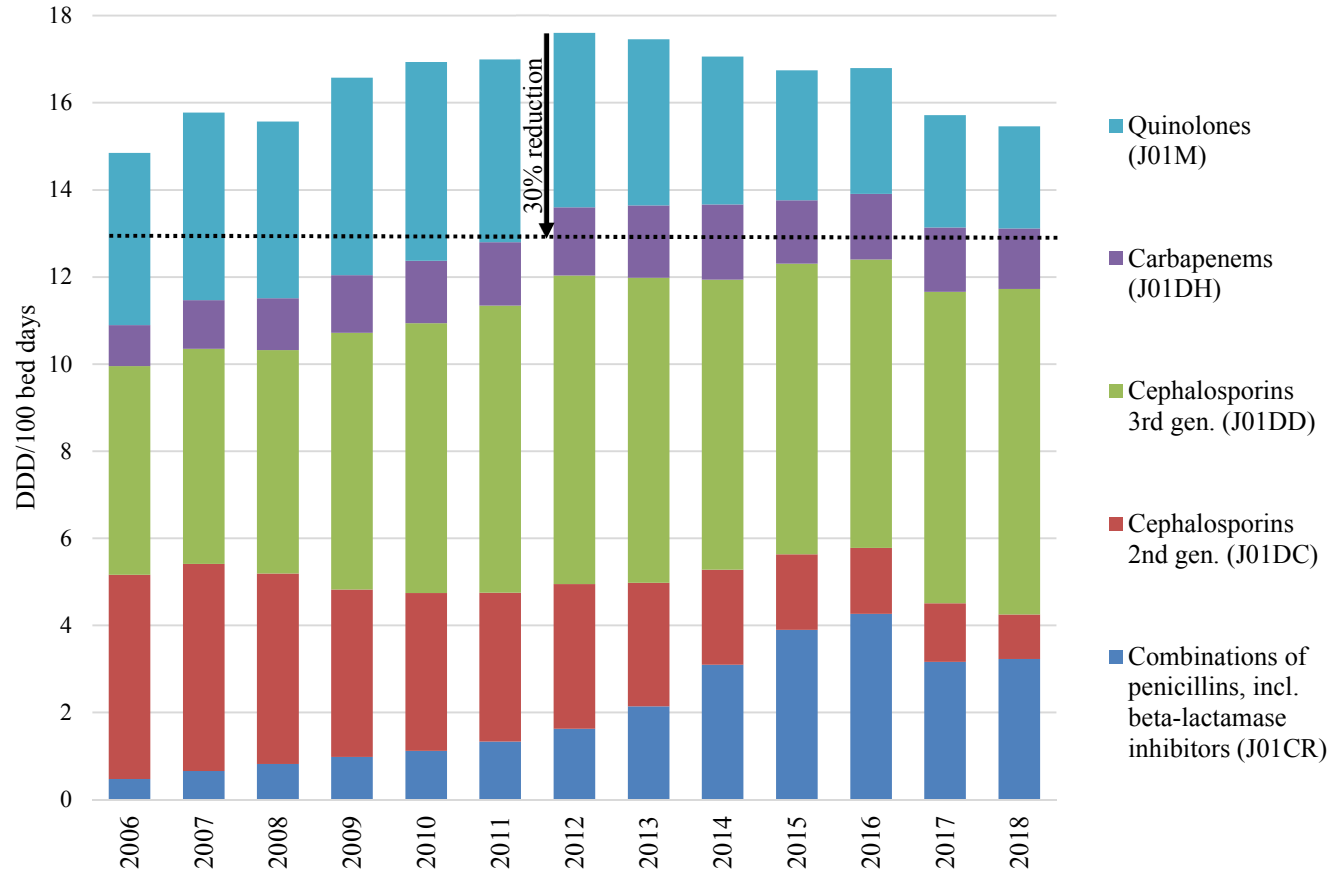

FIGURE 40. Consumption of selected antibacterial agents for systemic use (ATC J01CR, J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2018, measured in DDD/100 bed days.

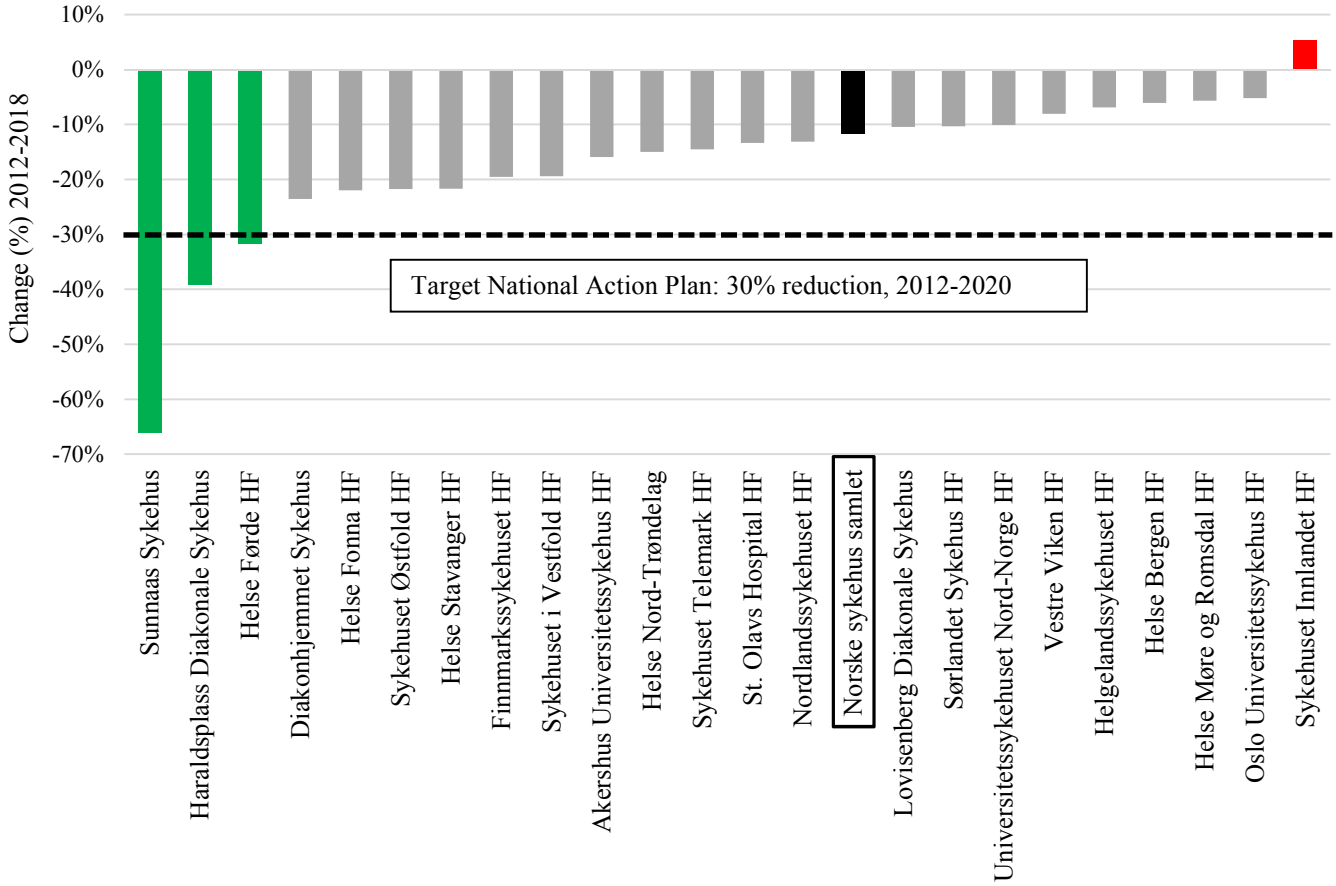

FIGURE 41. Change in consumption of selected antibacterials for systemic use (ATC group J01CR, J01DC, J01DD, J01DH and J01M) in Norway, 2012-2018. The data are presented per hospital/heath trust as measured in DDD/100 bed days.

OCCURRENCE OF ANTIMICROBIAL RESISTANCE

ANIMAL CLINICAL ISOLATES

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

The clinical isolates included in NORM-VET 2018 were from *Escherichia coli* infections in poultry and *Staphylococcus aureus* mastitis (milk) in sheep. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from poultry

A total of 209 isolates of *Escherichia coli* from clinical submissions in poultry (broiler: n=175; turkey: n=33; quail: n=1) were collected between 2015 and 2018. One isolate per submission was susceptibility tested. The results are presented in Table 10 and in the text.

TABLE 10. Antimicrobial resistance in clinical isolates of *Escherichia coli* from poultry (n=209) 2015-2018.

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	8.6	[5.2-13.3]								88.5	2.9			0.5	7.2	1.0		
Tigecycline	1.0	[0.1-3.4]					91.4	7.7	1.0									
Chloramphenicol	0.5	[0.0-2.6]										99.0	0.5				0.5	
Ampicillin	5.7	[3.0-9.8]							1.4	45.5	45.5	1.9				5.7		
Cefotaxime	0.0	[0.0-1.7]					100											
Ceftazidime	0.0	[0.0-1.7]						100										
Meropenem	0.0	[0.0-1.7]		100														
Sulfamethoxazole	4.8	[2.3-8.6]										70.3	16.8	7.7	0.5			4.8
Trimethoprim	1.9	[0.5-4.8]					85.2	11.0	1.9						1.9			
Azithromycin	ND	ND								6.7	72.7	20.6						
Gentamicin	3.3	[1.4-6.8]						48.3	38.8	9.6	2.4	0.5	0.5					
Ciprofloxacin	8.6	[5.2-13.3]	72.3	18.7	0.5		3.8	4.8										
Nalidixic acid	8.6	[5.2-13.3]									90.4	0.5	0.5		1.4	5.3	1.9	
Colistin	0.0	[0.0-1.7]							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.

RESULTS AND COMMENTS

In total, 73.2% of the isolates were susceptible to all antimicrobial agents included in the susceptibility testing. The following proportions of isolates were resistant to one or more antimicrobial agents: 15.3% were resistant to one (mainly tetracycline or ampicillin), 8.1% to two (mainly to quinolones) and 3.4% to three or more antimicrobial agents, respectively. Resistance towards quinolones, tetracycline, and ampicillin was most common. None of the *E. coli* isolates displayed resistance to the third generation cephalosporins cefotaxime or ceftazidime, nor to the carbapenem meropenem. In total, 26.8% of the isolates were resistant to at least one of the tested antimicrobial agents, indicating a high occurrence of resistance among these clinical isolates according to the EFSA classification described in Appendix 6. This is similar to the results for indicator *E. coli* from broilers and turkey.

E. coli isolates from clinical submissions of poultry have been sensitivity tested previously, in 2004 and in 2011. However, the number of isolates tested was limited and changes have been made in the panel of antimicrobial agents tested for, making comparisons difficult.

Staphylococcus aureus from mastitis in sheep

A total of 142 isolates of *Staphylococcus aureus* from mastitis milk of sheep were susceptibility tested. The results are presented in Table 11 and in the text.

TABLE 11. Antimicrobial resistance in clinical *Staphylococcus aureus* from mastitis in sheep (n=142) in 2018.

	Resistance (%)		Distribution (%) of MIC values (mg/L)*															
Substance	[95% CI]		0.015	0.032	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	0.0	[0.0-2.6]						76.7	23.2									
Chloramphenicol	0.0	[0.0-2.6]									93.7	6.3						
Benzylpenicillin	8.5	[4.4-14.3]				91.6	0.7		0.7	4.2	2.8							
Cefoxitin	2.1	[0.4-6.0]								6.3	91.6	2.1						
Trimethoprim	24.6	[17.8-32.6]								75.4	21.8	2.1		0.7				
Sulfamethoxazole	75.4	[67.4-82.2]													11.3	13.4	19.7	55.6
Erythromycin	1.4	[0.2-5.0]					1.4	96.5	0.7	0.7		0.7						
Clindamycin	0.0	[0.0-2.6]				97.2	2.8											
Quinupristin/ dalfopristin	0.0	[0.0-2.6]						95.8	4.2									
Streptomycin	1.4	[0.2-5.0]									19.7	71.1	7.8	1.4				
Gentamicin	0.0	[0.0-2.6]							100									
Kanamycin	0.0	[0.0-2.6]										100						
Ciprofloxacin	0.0	[0.0-2.6]					80.3	19.7										
Vancomycin	0.0	[0.0-2.6]							99.3	0.7								
Fusidic acid	3.5	[1.2-8.0]						96.5	2.1	1.4								
Tiamulin	2.1	[0.4-6.0]							7.0	90.9	0.7	1.4						
Linezolid	0.0	[0.0-2.6]							2.8	66.9	30.3							
Mupirocin	0.0	[0.0-2.6]						100										
Rifampicin	0.7	[0.0-3.9]	99.3		0.7													

*Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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 total, 19% of the isolates were susceptible to all antimicrobial agents included. 45.1% of the isolates from sheep were resistant to one antimicrobial agent (mainly to sulfamethoxazole), 33.8% to two (mainly to sulfamethoxazole and trimethoprim), and 2.1% to three antimicrobial agents, respectively.

S. aureus isolates from mastitis milk of sheep have previously been sensitivity tested in NORM-VET in 2003 and 2005. Due to changes made in the test panel, comparison to previous years is difficult.

The occurrence of resistance to the various antimicrobial agents detected in 2018 reflects their usage. Penicillin is the most commonly used antimicrobial agent for clinical purposes in sheep, but sulphonamides are also commonly used.

INDICATOR BACTERIA FROM ANIMALS

Madelaine Norström, Jannice Schau Slettemeås 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 third generation cephalosporins 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 have an impact on resistance development in human bacterial populations.

NORM-VET is following the requirements set in Commission implementing decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU). In addition, 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 is especially relevant for low prevalence sources, as it enables early detection of important resistance mechanisms; thereby enabling these to be monitored and characterised.

In NORM-VET, *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria. Selective methods for detection of *E. coli* resistant to third 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* were implemented as well.

In 2018, animal samples included caecal samples from broiler and turkey flocks, as well as faecal samples from sheep. These samples were analysed for *E. coli* and for *Enterococcus* spp. In addition, the results from screening of methicillin resistant *Staphylococcus aureus* in sheep and swine are described (separate textbox).

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 2018. Sampling, laboratory methods and data processing are described in Appendix 3.

PRODUCTION ANIMALS

Escherichia coli from broiler, turkey and sheep

Caecal samples from a total of 280 broiler flocks and 157 turkey flocks were examined and *E. coli* isolates were obtained from 278 (99.3%) and 156 (99.4%) samples, respectively. From sheep, a total of 302 faecal samples were examined and *E. coli* isolates were obtained from 295 (97.7%) of the samples. One isolate per positive sample was susceptibility tested. The results are presented in the text, in Tables 12-13 and Figures 42-46.

TABLE 12. Antimicrobial resistance in isolates of *Escherichia coli* from caecal samples from broiler and turkey flocks (n=278 and n=156, respectively) in 2018.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample	[95% CI]		0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Broiler	2.2	[0.8-4.6]								95.3	2.5				1.8	0.4		
	Turkey	10.3	[6.0–16.1]								84.6	5.1				5.1	5.1		
Tigecycline	Broiler	1.4	[0.4-3.6]					95.0	3.6	1.4									
	Turkey	0.6	[0.0-3.5]					94.2	5.1	0.6									
Chloramphenicol	Broiler	0.4	[0.0-2.0]										97.1	2.5				0.4	
	Turkey	1.3	[0.2-4.6]										98.1	0.6				1.3	
Ampicillin	Broiler	4.0	[2.0-7.0]							4.0	38.8	51.4	1.8				4.0		
	Turkey	16	[10.6-22.7]							3.2	21.2	55.8	3.8				16.0		
Cefotaxime	Broiler	0.0	[0.0-1.3]					100											
	Turkey	0.0	[0.0-2.3]					100											
Ceftazidime	Broiler	0.0	[0.0-1.3]						100										
	Turkey	0.0	[0.0-2.3]						100										
Meropenem	Broiler	0.0	[0.0-1.3]		100														
	Turkey	0.0	[0.0-2.3]		100														
Sulfamethoxazole	Broiler	1.4	[0.4-3.6]										90.3	6.8	1.4				1.4
	Turkey	10.3	[6.0-16.1]										81.4	5.8	2.6				10.3
Trimethoprim	Broiler	1.1	[0.2 - 3.1]					90.3	8.3	0.4						1.1			
	Turkey	6.4	[3.1-11.5]					87.2	6.4					0.6		5.8			
Azithromycin	Broiler	ND	ND								3.6	47.8	46.8	1.8					
	Turkey	ND	ND								9.0	55.8	34.6	0.6					
Gentamicin	Broiler	1.1	[0.2-3.1]						62.9	30.9	5.0	1.1							
	Turkey	2.6	[0.7-6.4]						55.8	34.6	7.1	0.6	0.6	1.3					
Ciprofloxacin	Broiler	10.8	[7.4-15.0]	71.9	17.3			0.4	0.7	7.6	0.4	0.4	1.1	0.4					
	Turkey	0.6	[0.0-3.5]	82.7	16.7			0.6											
Nalidixic acid	Broiler	10.8	[7.4-15]									88.5	0.7				1.1	9.7	
	Turkey	0.6	[0.0-3.5]									98.7		0.6			0.6		
Colistin	Broiler	0.0	[0.0-1.3]							99.3	0.7								
	Turkey	0.6	[0.0-3.5]							99.4		0.6							

*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.

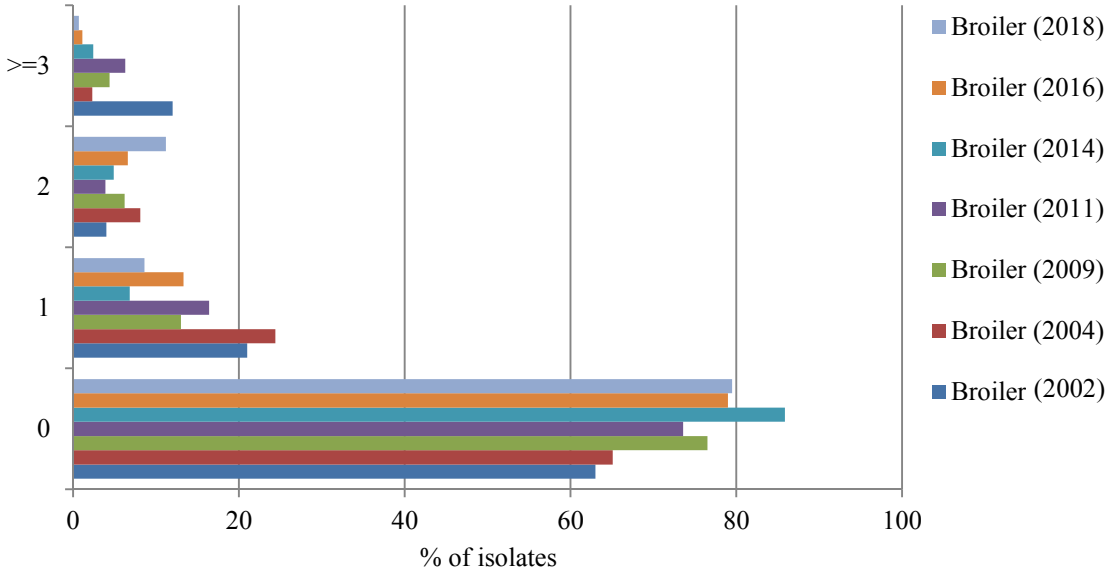

FIGURE 42. Antimicrobial resistance profile for *Escherichia coli* faecal isolates from broiler in 2002-2018. Proportions of isolates susceptible to all or resistant to one, two, and three or more antimicrobial agents are illustrated. The antimicrobial agents tested for vary between the years and this probably has an effect on the results.

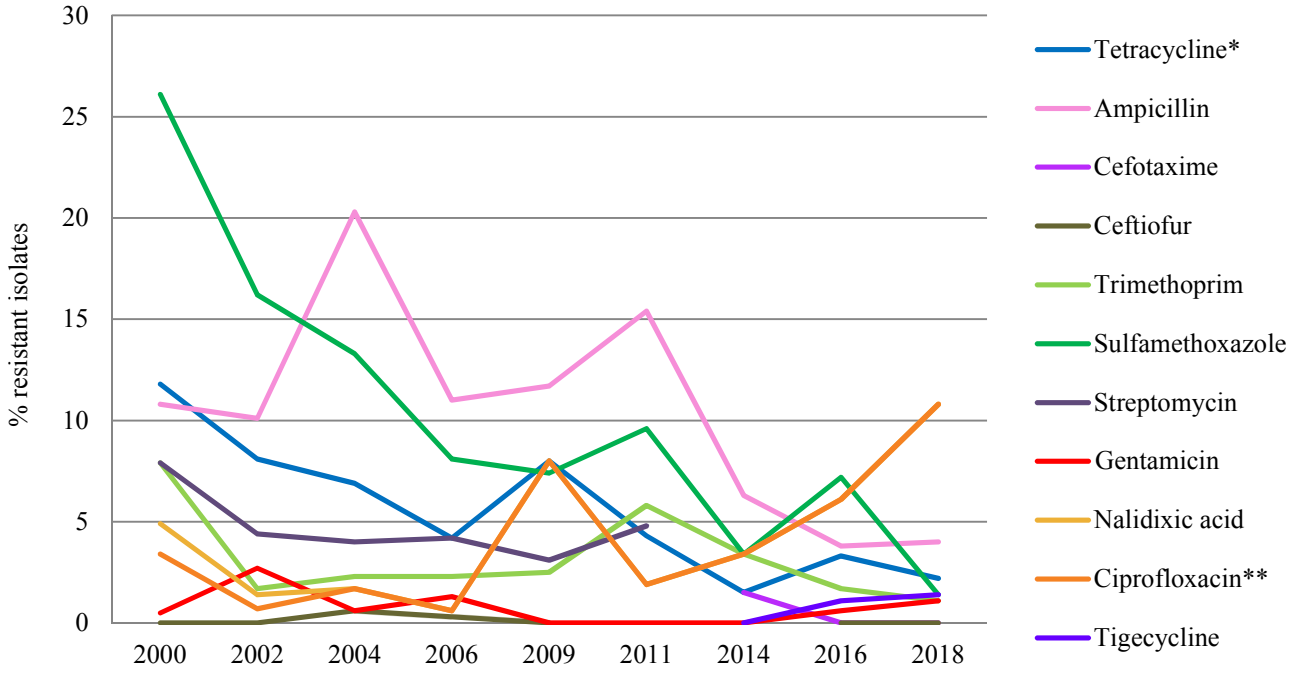

FIGURE 43. Prevalence of resistance to various antimicrobials in *Escherichia coli* faecal isolates from broiler in 2000-2018. The cut-off values used in NORM-VET 2018 were applied. *Oxytetracycline in 2002 and 2004. **Enrofloxacin before 2006.

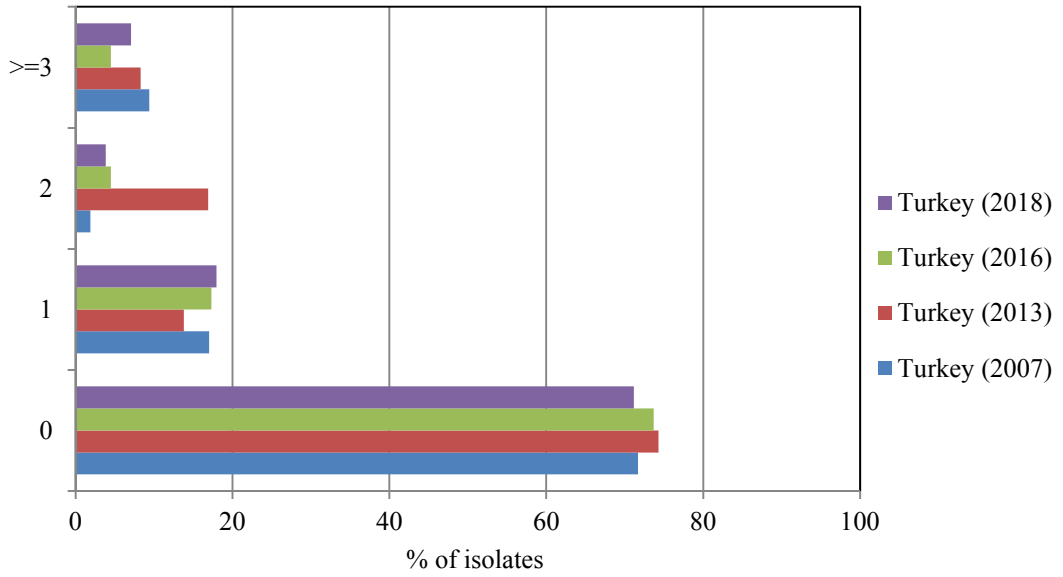

FIGURE 44. Antimicrobial resistance profile for *Escherichia coli* faecal isolates from turkey in 2007-2018. Proportions of isolates susceptible to all or resistant to one, two, and three or more antimicrobial agents are illustrated. The antimicrobial agents tested for vary between the years and this probably has an effect on the results.

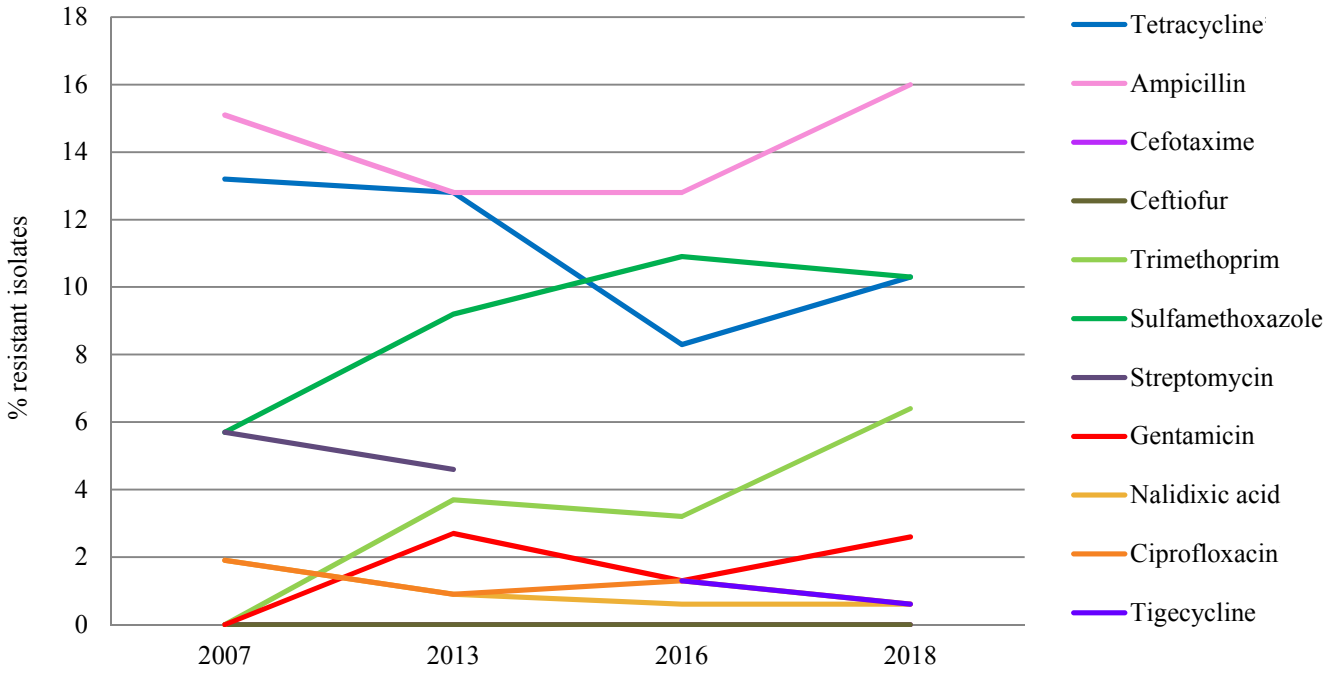

FIGURE 45. Prevalence of resistance to various antimicrobials in *Escherichia coli* faecal isolates from turkey in 2007-2018. The cut-off values used in NORM-VET 2018 were applied.

TABLE 13. Antimicrobial resistance in *Escherichia coli* isolates (n=295) from faceal samples from sheep in 2018.

	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	1.7	[0.5-3.9]								95.6	2.7				0.3	1.4		
Tigecycline	0.0	[0.0-1.2]					95.9	4.1										
Chloramphenicol	0.0	[0.0-1.2]										99.3	0.7					
Ampicillin	2.7	[1.2-5.3]							0.7	26.4	65.8	4.4	0.3			2.4		
Cefotaxime	0.7	[0.1-2.4]					99.3		0.7									
Ceftazidime	0.7	[0.1-2.4]						99.3			0.7							
Meropenem	0.0	[0.0-1.2]		100														
Sulfamethoxazole	1.7	[0.6-3.9]										96.6	1.4	0.3				1.7
Trimethoprim	1.0	[0.2-2.9]					94.6	4.4					0.3		0.7			
Azithromycin	ND	ND								31.5	48.1	20.3						
Gentamicin	0.0	[0.0-1.2]						77.3	19.7	3.1								
Ciprofloxacin	0.3	[0.0-1.9]	76.3	23.4		0.3												
Nalidixic acid	0.3	[0.0-1.9]									98.6	1.0					0.3	
Colistin	0.3	[0.0 -1.9]							97.6	2.0		0.3						

*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.

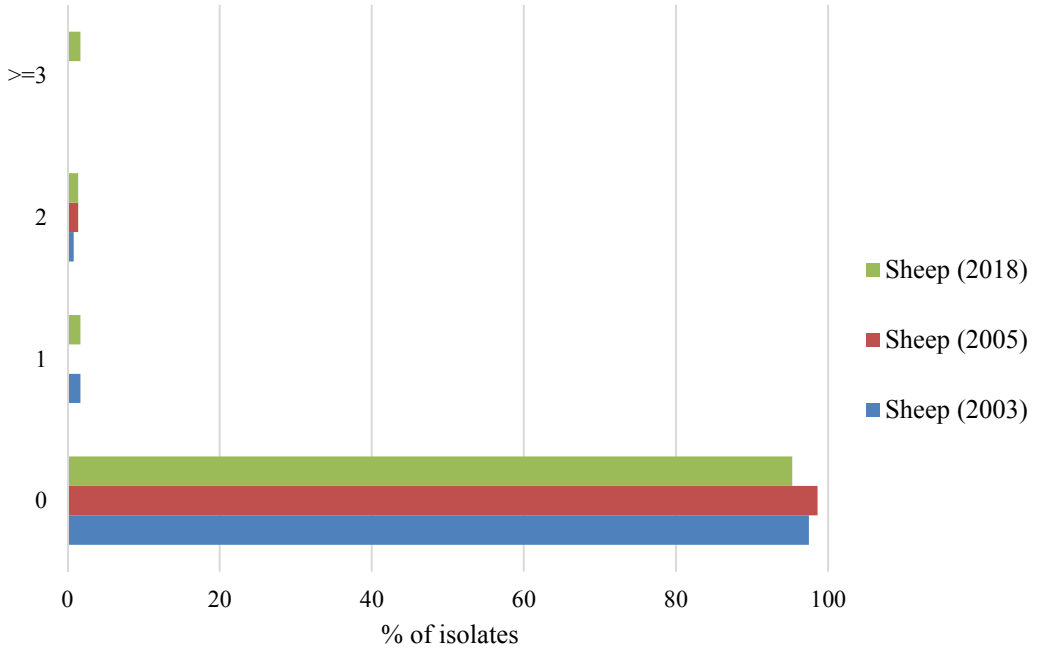

FIGURE 46. Antimicrobial resistance profile for *Escherichia coli* faecal isolates from sheep in 2003-2018. Proportions of isolates susceptible to all or resistant to one, two, and three or more antimicrobial agents are illustrated. The antimicrobial agents tested for vary between the years and this probably has an effect on the results.

RESULTS AND COMMENTS

BROILER

The 2018 data showed that 79.5% of the *E. coli* isolates from broiler caecal samples were susceptible to all antimicrobial agents included. Altogether, 8.6% of the isolates were resistant to one antimicrobial agent (predominantly ampicillin), 11.2% to two (nalidixic acid and ciprofloxacin), and 0.7% to three antimicrobial agents (Figure 42). In total, 20.5% of the isolates were resistant to at least one antimicrobial agent, indicating a high occurrence of resistance in broilers according to the EFSA classification described in Appendix 6. Resistance to ciprofloxacin and nalidixic acid were the most frequently identified resistance determinants, followed by resistance to ampicillin.

When comparing to data pre-2014, the proportion of isolates being fully susceptible seems to have increased. However, there has been a change in the panel of antimicrobial agents tested for and this may have an effect

on the comparison result. Compared to the 2016 data, the results indicate that the proportion of isolates being resistant to two antimicrobial agents has increased and the proportion being resistant to one antimicrobial agent has decreased. The observed change is, however, not statistically significant and further monitoring is necessary to see if this is a true increasing trend. Nevertheless, since the start of NORM-VET in 2000, the prevalence of resistance to some antimicrobial agents in *E. coli* from broilers has indeed decreased as illustrated in Figure 43, especially resistance to sulfamethoxazole, tetracycline and ampicillin. In contrast, the resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) has increased over the years ($p<0.0001$), and was identified in 10.8% [95% CI: 7.4 – 15.0] of the isolates in 2018. In 2016, 6.1% of the isolates displayed resistance to quinolones, while 3.4% and 2.0% of the indicator *E. coli* displayed resistance to quinolones in 2014 and 2011, respectively.

None of the *E. coli* isolates from broilers displayed resistance to the third generation cephalosporins cefotaxime or ceftazidime indicating a prevalence below 1.3%. This is in concordance with the results from 2016. In addition, a selective method was used to investigate the occurrence of *E. coli* resistant to third generation cephalosporins in the same broiler caecal sample material (page 61).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian broiler is low, though the occurrence varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance levels (EFSA and ECDC Summary report 2016). This favorable situation is probably due to the very limited use of antibiotics in the Norwegian broiler production.

TURKEY

The 2018 data showed that 71.2% of the *E. coli* isolates were susceptible to all antimicrobial agents included. Altogether, 17.9% of the isolates were resistant to one antimicrobial agent (predominantly ampicillin or tetracycline), 4.0% to two and 7.0% to three or more antimicrobial agents (Figure 44). In total, 28.9% of the isolates were resistant to at least one antimicrobial agent, indicating a high occurrence of resistance in turkey according to the EFSA classification described in Appendix 6. Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to sulfamethoxazole, tetracycline and trimethoprim.

Overall comparison to pre-2016 results is difficult as there has been a change in the susceptibility panel of antimicrobial agents. Nevertheless, the results as shown in Figure 45 indicate that there has been an increase in resistance to sulfamethoxazole and trimethoprim from 5.7% and 0%, respectively, in 2007 to 10.3% and 6.4% in 2018. The observed changes are, however, not statistically significant and further monitoring is needed to assess whether this is a true increasing trend. Moreover, the sampling procedure has changed from boot swabs monitoring occurrence of resistance in the turkey house in 2007 and 2013 to pooled caecal samples monitoring occurrence of resistance in the animals in 2016 and 2018, and this may have had an impact on the result.

Resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) was identified in 0.6% [95% CI: 0.0 - 3.5] of the isolates. These results are in concordance with the results from previous years. One isolate showed decreased sensitivity to colistin, and was investigated by whole genome sequencing to determine the resistance mechanism. No acquired colistin resistance genes were detected. None of the isolates displayed any resistance to the third generation cephalosporins cefotaxime or ceftazidime. In addition, a selective method was used to investigate the occurrence of *E. coli* resistant to third generation cephalosporins in the same turkey caecal sample material (page 61).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian turkey is low, though the occurrence varies markedly between countries reporting to EFSA with the Nordic countries having the lowest resistance levels (EFSA and ECDC Summary report 2016). This favorable situation is probably due to the limited use of antibiotics in the Norwegian turkey production.

SHEEP

The 2018 data showed that 95.2% of the *E. coli* isolates from sheep faecal samples were susceptible to all antimicrobial agents included. Altogether, 1.7% of the isolates were resistant to one antimicrobial agent, 1.4% to two and 1.7% to three or more antimicrobial agents (Figure 46). In total, 4.8% of the isolates were resistant to at least one antimicrobial agent, indicating a low occurrence of resistance in sheep according to the EFSA classification described in Appendix 6. Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to tetracycline and sulfamethoxazole.

Two of the *E. coli* sheep isolates displayed resistance to the third generation cephalosporins cefotaxime and ceftazidime (0.7% [95% CI: 0.1 - 2.4]). These isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype. Genotyping showed that they had mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. In addition, a selective method was used to investigate the occurrence of *E. coli* resistant to third generation cephalosporins in the same sheep faecal sample material (page 61). One of the *E. coli* sheep isolates displayed resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) (0.7% [95% CI: 0.1 - 2.4]), and one displayed reduced susceptibility to colistin. This isolate was further investigated by whole genome sequencing to determine the resistance mechanism. No acquired genes were detected that would cause reduced susceptibility to colistin.

E. coli isolates from sheep have previously been susceptibility tested in 2003, 2005, 2007 and 2009. However, the 2007 and 2009 isolates were Shiga toxin producing *E. coli* isolates of specific serotypes, and this may have had an effect on the results. In addition, there has been a change in the panel of antimicrobial agents tested for during these years, making some comparisons difficult. For instance, 14% of the *E. coli* (mainly belonging to serogroups O26 and O103) in 2009 displayed resistance to streptomycin, an increase from previous years where the resistance had been ≤ 2%. Since streptomycin is no longer part of the standard antimicrobial agents being tested for, this possible change in resistance was not followed up in the 2018 testing. Nevertheless, the other results from these years indicate that there has been no change in the overall level of resistance in *E. coli* from sheep.

Cephalosporin resistant *Escherichia coli* from broiler, turkey and sheep

In 2018, selective screening for *E. coli* resistant to third generation cephalosporins was performed on caecal samples from broiler and turkey flocks, and faecal samples from sheep herds. A total of 280 broiler and 157 turkey flocks, and 302 sheep herds were investigated. The results are presented in the text and in textbox page 62.

RESULTS AND COMMENTS

BROILER

By use of the selective method, *E. coli* resistant to third generation cephalosporins were found in 0.4% [95% CI: 0.0-2.0] of the 280 broiler caecal samples. As described above, no cephalosporin resistant isolates were found by using the standard non-selective procedure, indicating that the within-flock prevalence is very low.

The identified isolate was resistant to sulfamethoxazole in addition to the beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime. The isolate had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and PCR and sequencing showed that it contained the $bla_{\text{CMY-2}}$ gene. The current findings by the selective method show that there has been a substantial reduction of *E. coli* resistant to third generation cephalosporins in broiler flocks compared to previous years ($p<0.0001$). This is further described in the textbox page 62.

In a European perspective, the prevalence of *E. coli* resistant to third generation cephalosporins in broilers in Norway 2018 is very low though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary report 2016). The South-Eastern, South-Central and South-Western countries tended to report a higher prevalence than the Nordic countries and, to a lesser extent, than countries from Western Europe. There is also variations in prevalence between the Nordic countries, with Norway having the lowest reported prevalence.

TURKEY

By use of the selective method, *E. coli* resistant to third generation cephalosporins were found in 9.6% [95% CI: 5.4 - 15.3] of the 157 turkey caecal samples. As described above, no cephalosporin resistant isolates were found by using the non-selective procedure, indicating that the within-flock prevalence is low.

Most of the isolates were only resistant to beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime. Two isolates were in addition resistant to the quinolones ciprofloxacin and nalidixic acid. None of the isolates showed decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance.

Thirteen isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and genotyping showed that the resistance was due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. Two isolates had a cephalosporin resistance profile corresponding to an extended spectrum beta-lactamase (ESBL) phenotype, and genotyping showed that resistance was due to the $bla_{\text{SHV-12}}$ gene. The $bla_{\text{SHV-12}}$ gene has not been detected from turkey isolates previously, nor from any other production animals investigated in NORM-VET. In 2018, it was detected from both turkey caecal samples and from turkey meat samples.

Compared to previous results, it seems to have been a decrease in *E. coli* resistant to third generation cephalosporins due to presence of the plasmid mediated $bla_{\text{CMY-2}}$ gene from 5.1% [95% CI: 2.2-9.9] in 2016 to 0% [95% CI: 0-2.3] in 2018. There was an unexplained peak in third generation cephalosporin resistance due to chromosomal mutations in 2013 with 12.9% [95% CI: 7.7-20.0] positive flocks. Since then the occurrence has decreased to 5.1% [95% CI: 2.2-9.9] and 5.7% [95% CI: 2.7-10.6] in 2016 and 2018, respectively. All these observed differences are, however, non-significant and further monitoring is necessary to see if these are true trend changes. In addition, there has been a change in sampling procedure from boot swabs in 2013 that mirrors the prevalence in the turkey house, to caecal material in 2016 and 2018 that mirrors the prevalence in the animals, and this may have had an effect on the observed changes.

In an international perspective, the occurrence of *E. coli* resistant to third generation cephalosporins in Norwegian turkey is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary report 2016).

SHEEP

By use of the selective method, *E. coli* resistant to third generation cephalosporins were found in 2.6% [95% CI: 1.5-5.2] of the 302 sheep faecal samples. As described above, two cephalosporin resistant isolates were found by using the standard non-selective procedure, indicating that the within-herd prevalence is low.

All, but one, of the isolates were only resistant to beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime. The last isolate was in addition resistant to tigecycline.

All eight isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and genotyping showed that the resistance was due to mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* over-expression.

Selective methods for isolation of *E. coli* resistant to third generation cephalosporins have not been performed on sheep samples previously, and comparisons to previous years is therefore not possible.

A success story of the Norwegian broiler production industry – reservoir of *Escherichia coli* displaying resistance towards extended-spectrum cephalosporins (ESC) virtually eliminated

Escherichia coli displaying resistance towards extended-spectrum cephalosporins (ESC) has been widely disseminated in the broiler production worldwide. In Norway, the first ESC-resistant *E. coli* was detected from broilers in NORM-VET in 2006 (1). A selective method was implemented for detection of ESC-resistant *E. coli* in NORM-VET in 2011. The method was conducted on boot swab samples from broiler flocks, and a total of 43% of the flocks were positive for ESC-resistant *E. coli* carrying the plasmid-borne bla_{CMY-2} gene (2). This high prevalence of ESC-resistant *E. coli* raised concern, and the poultry industry introduced measures to limit the occurrence. This work has since 2014 been formalised in the Poultry industry's action plan on antimicrobial resistant bacteria (3,4). The National Strategy against antimicrobial resistance 2015-2020 has also included the target to reduce the ESC-resistant *E. coli* reservoir in the Norwegian poultry production to a minimum (5).

There is no selection pressure from cephalosporin usage in Norway, but the poultry production is dependent on import of breeding animals. These animals were shown to be the source of introduction, and the industry therefore took measures to limit the number of imported breeding animals carrying ESC-resistant *E. coli.* In addition to the measures on the breeding animal level, the measures included improved routines for cleaning and disinfection between poultry flocks to limit any vertical transmission between flocks.

Since the first screening in 2011, broiler flocks and broiler meat have regularly been investigated by the selective method (Figure 47). In 2014, 35.7% of the broiler caecal samples and 28.9% of the meat samples were found positive for ESC-resistant *E. coli* (6). This was a small decrease at broiler flock level compared to the 2011 results, but could be due to change in sampling; from boot swabs mirroring the occurrence in the broiler house to caecal samples mirroring the presence in the animals. However, in 2016, there was a significant observed decrease with 10.8% positive flocks and 9.7% meat samples positive (7). In 2018, only a single flock and one single meat sample was positive for ESC-resistant *E. coli* due to presence of bla_{CMY-2}. This is a remarkable result, showing that the measures taken by the industry have been successful.

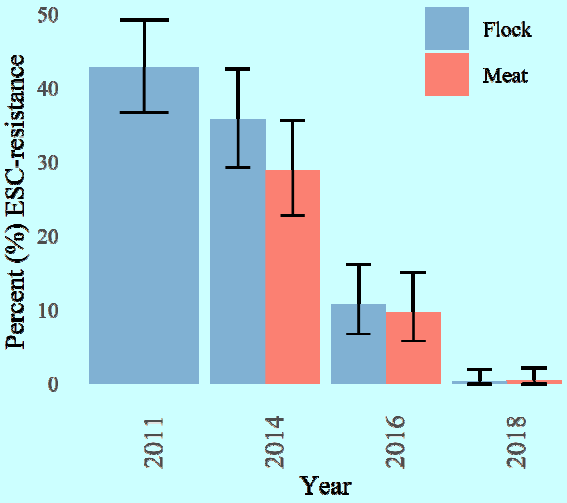

FIGURE 47. Occurrence (%) of extended-spectrum cephalosporin (ESC)-resistant *E. coli* in broiler flock samples and in meat samples in 2011 - 2018. The 2011 flock samples were boot swab samples, while the flock samples from 2014 have been pooled caecal samples. All isolates were carrying the plasmid-borne bla_{CMY-2} gene.

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Quinolone resistant *Escherichia coli* from sheep

In 2018, selective screening for quinolone resistant *E. coli* was performed on caecal samples from sheep herds. A total of 302 sheep herds were investigated, and presumptive quinolone resistant *E. coli* was detected from 29 of these (9.6%). The results are presented in the text and in Table 14.

TABLE 14. Antimicrobial resistance in quinolone resistant *Escherichia coli* isolates (n=22) from faceal samples from sheep in 2018.

		Distribution (n) of MIC values (mg/L)*															
Substance	n resistant	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	10								12					3	7		
Tigecycline	0					19	3										
Chloramphenicol	4										18			1	3		
Ampicillin	6								6	9	1			1	5		
Cefotaxime	0					22											
Ceftazidime	0						22										
Meropenem	0		22														
Sulfamethoxazole	7										13	2					7
Trimethoprim	6					16							1	5			
Azithromycin	ND								1	5	14	1	1				
Gentamicin	3						13	6					2	1			
Ciprofloxacin	22				6	10	2	1			3						
Nalidixic acid	19										3		2	6	3	8	
Colistin	0							22									

*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

Of the presumptive quinolone resistant *E. coli*, 22 isolates isolates were confirmed displaying resistance to quinolones in the sensitivity testing (7.3% of samples [95% CI: 4.6 - 10.8]). The most common resistance was to tetracycline, followed by sulfamethoxazole, trimethoprim and ampicillin. None of the quinolone resistant *E. coli* isolates displayed resistance to the third generation cephalosporins cefotaxime or ceftazidime.

Selective methods for isolation of quinolone resistant *E. coli* have not been performed on samples from sheep previously, and comparison to previous years is therefore not possible. The results from sheep are similar to the prevalence found in cattle caecal samples in NORM-VET 2015.

Carbapenemase-producing *Enterobacteriaceae* from broiler, turkey and sheep

Selective screening for carbapenemase-producing *Enterobacteriaceae* was performed on caecal samples from a total of 280 broiler and 157 turkey flocks, and faecal samples from 302 sheep herds. 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.

Enterococcus spp. from broiler and turkey

Caecal samples from a total of 280 broiler flocks and 157 turkey flocks were collected. *E. faecalis* was obtained from 144 (51.4%) and *E. faecium* from 261 (93.2%) of the broiler samples. From turkey, *E. faecalis* was obtained from 68 (43.3%) of the samples and *E. faecium* from 145 (92.4%) of the samples. Of these, 139 and 66 *E. faecalis* from broiler and turkey, respectively, were susceptibility tested. Of the *E. faecium* isolates that were subjected to susceptibility testing, 251 were from broiler and 142 from turkey. The results are presented in Tables 15-16, Figures 48-49, and in the text.

TABLE 15. Antimicrobial resistance in *Enterococcus faecalis* from caecal samples from broiler (n=139) and turkey (n=66) flocks in 2018.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Broiler	36.7	[28.7-45.3]						62.6	0.7		0.7	2.9	11.5	18.7	2.9		
	Turkey	69.7	[57.1-80.4]						27.3	3.0				34.8	25.8	7.6	1.5	
Tigecycline	Broiler	0.0	[0.0-2.6]	0.7	12.2	35.3	49.6	2.2										
	Turkey	0.0	[0.0-5.4]		10.6	60.6	27.3	1.5										
Chloramphenicol	Broiler	0.0	[0.0-2.6]								6.5	86.3	6.5	0.7				
	Turkey	0.0	[0.0-5.4]								22.7	74.2	1.5	1.5				
Ampicillin	Broiler	0.0	[0.0-2.6]					3.6	71.2	24.5	0.7							
	Turkey	0.0	[0.0-5.4]					15.2	69.7	15.2								
Erythromycin	Broiler	20.9	[14.4-28.6]						48.2	29.5	1.4	5.0	10.1	3.6	0.7		1.4	
	Turkey	12.1	[5.4-22,5]						60.6	25.8	1.5	1.5	1.5	1.5	1.5		6.1	
Quinupristin -	Broiler	0.0	[0.0-2.6]					0.7	2.2	0.7	0.7	91.4	4.3					
Dalfopristin	Turkey	0.0	[0.0-5.4]								3.0	97						
Gentamicin	Broiler	0.0	[0.0-2.6]									52.5	44.6	2.9				
	Turkey	0.0	[0.0-5.4]									63.6	33.3	3.0				
Ciprofloxacin	Broiler	0.7	[0.0-3.9]					9.4	66.9	20.9	2.2	0.7						
	Turkey	0.0	[0.0-5.4]				1.5	15.2	75.8	7.6								
Vancomycin	Broiler	0.0	[0.0-2.6]						46.0	38.8	15.1							
	Turkey	0.0	[0.0-5.4]						36.4	60.6	3.0							
Teicoplanin	Broiler	0.0	[0.0-2.6]					99.3	0.7									
	Turkey	0.0	[0.0-5.4]					100										
Linezolid	Broiler	0.0	[0.0-2.6]						7.9	87.1	5.0							
	Turkey	0.0	[0.0-5.4]					1.5	19.7	77.3	1.5							
Daptomycin	Broiler	0.7	[0.0-3.9]						12.2	76.3	10.8	0.7						
	Turkey	1.5	[0.0-8.2]				1.5	3.0	31.8	57.6	4.5	1.5						
Narasin	Broiler	3.6	[1.2-8.2]			3.6	41.7	46.8	2.9	1.4	2.2	1.4						
	Turkey	18.2	[9.8-29.6]			4.5	25.8	18.2	9.1	24.2	18.2							

*Bold vertical lines denote microbiological 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.

TABLE 16. Antimicrobial resistance in *Enterococcus faecium* from caecal samples from broiler (n=251) and turkey (n=142) flocks in 2018.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*													
Substance	Sample	[95% CI]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥512
Tetracycline	Broiler	8.0	[4.9-12]						91.2	0.4	0.4		0.4	0.8	6.0	0.4	0.4	
	Turkey	12.0	[7.1-18.5]						86.6		1.4		1.4		7.0	3.5		
Tigecycline	Broiler	0.4	[0.0-2.2]	8.0	19.5	63.3	8.8	0.4										
	Turkey	0.7	[0.0-3.9]	9.2	21.8	58.5	9.9	0.7										
Chloramphenicol	Broiler	0.0	[0.0-1.5]								10.8	78.9	8.8	1.6				
	Turkey	0.0	[0.0-2.6]								14.1	78.9	7.0					
Ampicillin	Broiler	2.4	[0.9-5.1]				0.4	36.3	32.3	21.1	7.6	2.4						
	Turkey	11.3	[6.6-17.7]					26.8	27.5	17.6	16.9	10.6				0.7		
Erythromycin	Broiler	7.6	[4.6-11.6]						67.7	19.5	5.2		3.2	0.8			3.6	
	Turkey	17.6	[11.7-24.9]						61.3	16.9	4.2	11.3	3.5	1.4			1.4	
Quinupristin –	Broiler	ND	ND					13.9	34.7	15.9	34.3	0.8	0.4					
Dalfopristin	Turkey	ND	ND					16.2	16.2	17.6	50.0							
Gentamicin	Broiler	0.4	[0.0-2.2]									82.1	16.7	0.8	0.4			
	Turkey	0.7	[0.0-3.9]									76.8	20.4	2.1	0.7			
Ciprofloxacin	Broiler	7.2	[4.3-11.1]				0.4	1.6	13.1	28.3	49.4	4.4	0.8	2.0				
	Turkey	7.0	[3.4-12.6]				0.7	3.5	18.3	23.2	47.2	7.0						
Vancomycin	Broiler	0.0	[0.0-1.5]						86.9	12.4	0.8							
	Turkey	0.0	[0.0-2.6]						85.2	14.1	0.7							
Teicoplanin	Broiler	0.4	[0.0-2.2]					99.2	0.4			0.4						
	Turkey	0.0	[0.0-2.6]					98.6	1.4									
Linezolid	Broiler	0.0	[0.0-1.5]						0.4	64.5	35.1							
	Turkey	0.0	[0.0-2.6]							66.2	33.8							
Daptomycin	Broiler	0.0	[0.0-1.5]					0.8	5.2	31.5	55.4	7.2						
	Turkey	0.0	[0.0-2.6]				0.7	0.7	2.8	25.4	59.9	10.6						
Narasin	Broiler	24.7	[5.6–13.0]			0.4	7.2	42.6	24.7	0.4	15.9	8.4	0.4					
	Turkey	81.0	[20.3-35.6]					7.7	6.3	4.9	53.5	27.5						

*Bold vertical lines denote microbiological 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.

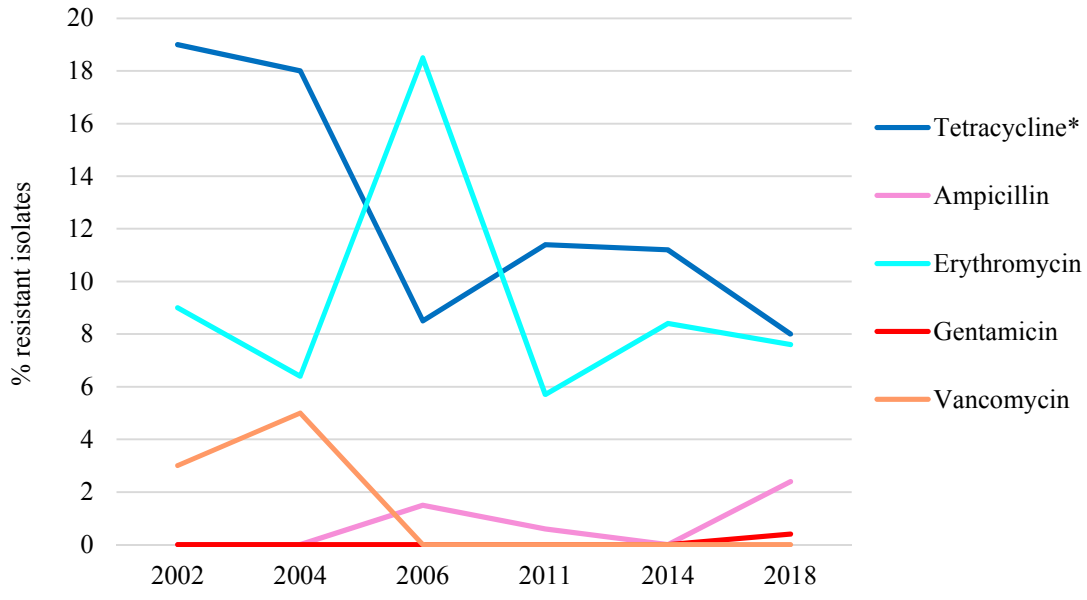

FIGURE 48. Prevalence of resistance to various antimicrobial agents in *Enterococcus faecium* isolates from caecal samples from broiler 2002-2018. The epidemiological cut-offs used in NORM-VET 2018 were applied. * Oxytetracycline in 2002 and 2004.

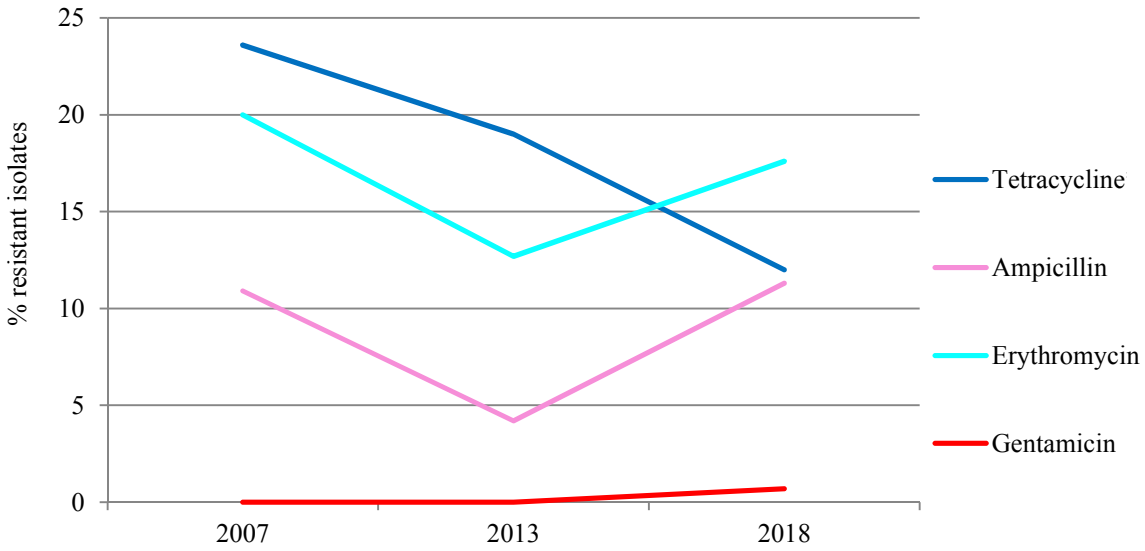

FIGURE 49. Prevalence of resistance to various antimicrobial agents in *Enterococcus faecium* isolates from caecal samples from turkey 2007-2018. The epidemiological cut-offs used in NORM-VET 2018 were applied.

RESULTS AND COMMENTS

BROILER

The 2018 data showed that 45.3% of the *E. faecalis* and 59.8% of the *E. faecium* isolates from broiler caecal samples were susceptible to all antimicrobial agents included in the test panel.

E. faecalis: Altogether, 44.6% of the isolates were resistant to one antimicrobial agent (mainly tetracycline or erythromycin) and 10.1% to two (mainly tetracycline and erythromycin. Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to erythromycin.

E. faecium: Altogether, 31.5% of the isolates were resistant to one antimicrobial agent (mainly narasin), 6.8% to two (mainly narasin and erythromycin), and 2.0% to three antimicrobial agents. Resistance to narasin was the most frequently identified resistance determinant, followed by resistance to tetracycline and erythromycin.

In total, 54.7% of the *E. faecalis* isolates and 40.2% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a high and very high occurrence of resistance, respectively, according to the EFSA classification described in Appendix 6.

Compared to the data from 2014, there seems to have been a decrease in occurrence of tetracycline resistance among *E. faecalis* from 52.3% to 36.7%. This is, however, a non-significant decrease (p=0.05) and further monitoring is necessary to see if this is a true trend. The prevalence of tetracycline resistance among *E. faecalis* is surprising, as there is insignificant use of oxytetracycline for clinical purposes in Norwegian broiler production. Resistance to narasin has decreased compared to previous investigations, for further description see textbox page 67.

None of the *E. faecium* or *E. faecalis* isolates displayed resistance to vancomycin. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. Studies have shown that this use has selected for an extensive reservoir of vancomycin resistant enterococci (VRE) in Norwegian broiler production. The reservoir persisted for many years after the ban was implemented (see selective VRE screening and textbox page 67).

TURKEY

The 2018 data showed that 22.7% of the *E. faecalis* and 12.7% of the *E. faecium* isolates from turkey caecal samples were susceptible to all antimicrobial agents included in the test panel.

E. faecalis: Altogether, 56.1% of the isolates were resistant to one antimicrobial agent (mainly tetracycline), 18.2% to two (mainly narasin and tetracycline), and 3.0% to three antimicrobial agents. Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to narasin and erythromycin.

E. faecium: Altogether, 50.7% of the isolates were resistant to one antimicrobial agent (mainly narasin), 31.0% to two (mainly narasin and erythromycin), and 5.6% to three or more antimicrobial agents. Resistance to narasin was the most frequently identified resistance determinant, followed by resistance to erythromycin, tetracycline and ampicillin.

In total, 77.3% of the *E. faecalis* isolates and 87.3% of the *E. faecium* isolates were resistant to at least one antimicrobial agent, indicating a very high to extremely high occurrence of resistance, respectively, according to the EFSA classification described in Appendix 6.

None of the *E. faecium* or *E. faecalis* isolates displayed resistance to vancomycin. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. Studies have shown that this use has selected for an extensive reservoir of vancomycin resistant enterococci (VRE) in Norwegian poultry production. The reservoir persisted for many years after the ban was implemented (see selective VRE screening described below and textbox page 67).

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

A total of 280 caecal samples from broiler flocks and 157 caecal samples from turkey flocks were screened for the presence of vancomycin resistant *Enterococcus* spp. (VRE).

No VRE were detected. The occurrence of VRE has decreased significantly since 2002 ($p<0.0001$). See textbox below.

No vancomycin resistant enterococci (VRE) detected in the Norwegian poultry production for the first time since the monitoring started

The glycopeptide avoparcin was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. The use selected for a reservoir of vancomycin resistant enterococci (VRE) in both broilers and turkeys. This reservoir persisted without known selective pressure for many years after the ban was implemented (documented in previous NORM-VET reports). However, as shown in Figure 50, the occurrence of VRE in broilers has decreased significantly the last years, i.e. from 7.5% in 2009, 15.9% in 2011, 6.7% in 2014 to 0% in 2018 ($p<0.0001$). There has also been a decrease in the occurrence of VRE in turkey from 12.2% in 2013 to 0% in 2018 ($p<0.0001$). Although comparison of the 2018 results with results before 2014 should be made with caution due to changes made in sampling procedure from boot swabs mirroring the prevalence in the broiler house to caecal samples mirroring the prevalence in the animals, this is a remarkable decline.

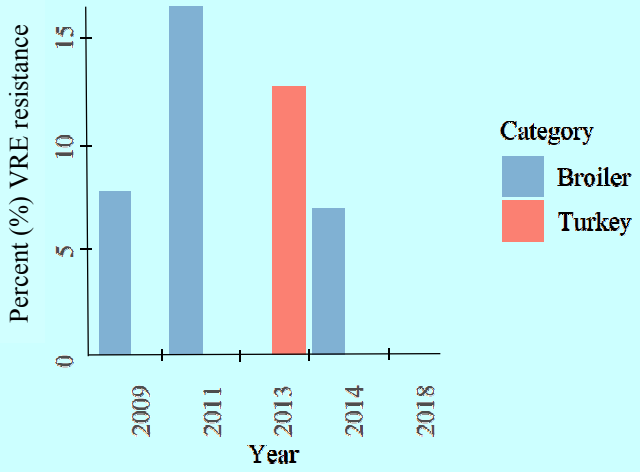

FIGURE 50. Prevalence of vancomycin resistant enterococci (VRE) in Norwegian poultry production from 2009-2018. In 2018, samples from both broilers and turkey were examined. All analyses were performed by selective methods for isolation of VRE.

The observed decline in VRE coincides in time with two interventions initiated by the poultry industry in an attempt to reduce the occurrence of antimicrobial resistant bacteria in the Norwegian poultry population. The first intervention introduced improved routines for cleaning and disinfection between poultry flocks with the intention to decrease the occurrence of *Escherichia coli* resistant to third generation cephalosporins (1, 2). The second intervention addressed a general concern regarding development of antimicrobial resistance due to use of narasin in the broiler production. Narasin is a coccidiostat that was introduced as a feed additive in broilers to avoid the broilers developing coccidiosis after the ban of avoparcin in 1995. In addition to the anticoccidial effect of narasin, it also possesses antibacterial activity. Therefore, a discontinuation of the use of narasin as a coccidiostat feed additive was one of the targets for 2015-2020 stated in the National Strategy against antimicrobial resistance (3). Narasin was gradually phased out from 2015, and from June 2016 broilers in Norway have been raised without the use of coccidiostats. This has been possible due to implementation of a coccidia vaccine for all broilers.

Narasin resistance has been frequently observed among indicator enterococci from broilers and turkeys, especially among *E. faecium*. As shown in this report, 24.7% of the *E. faecium* isolates from broilers showed reduced susceptibility to narasin in 2018, whereas 81.0% of the *E. faecium* isolates from turkeys showed reduced susceptibility. For broilers, this is a significant reduction in narasin resistance compared to 2011 ($p<0.01$) (Figure 51), but there has been no change in occurrence of narasin resistance in turkeys.

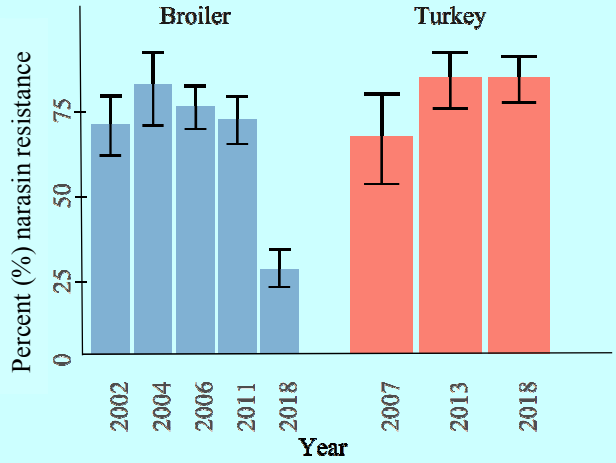

FIGURE 51. Prevalence of narasin resistance among *Enterococcus faecium* from Norwegian broiler and turkey flocks from 2002-2018. 95% CI shown as bars.

VRE isolated from broilers and turkeys through the years in NORM-VET has solely belonged to *E. faecium*. All, but one VRE isolate, have shown additional resistance to narasin. A Swedish study from 2012 reported co-transfer of vancomycin and narasin resistance (4), and in a follow-up study, they suggest that ABC transporter genes can be responsible for the transferable narasin resistance (5). It is possible that the discontinuation of narasin as a feed additive in broiler production may have contributed to the absence of VRE in broilers. However, due to high toxicity in turkeys, narasin has never been used in the turkey production. Instead, the coccidiostat monensin with similar anticoccidial and antibacterial effects, has been used. Monensin is still being used in Norwegian turkey production today. There is no indication of cross-resistance between narasin and monensin (6, 7), and monensin resistance has not been associated with vancomycin resistance in bacteria. It is therefore not obvious why a large proportion of the *E. faecium* population of turkeys is narasin resistant, nor does it explain why VRE were absent from turkey samples in 2018.

Although a clear-cut conclusion cannot be drawn, it is possible that one or both of the interventions initiated by the poultry industry in 2015 – 2016 has contributed to the observed reduction in VRE in the Norwegian poultry population.

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Antimicrobial resistant bacteria in broilers over 50 days of age at slaughter

Broilers older than 50 days when slaughtered consist of a mixed group of different niche productions such as slow-growing broilers, ecologically-bred broilers, and free-ranging broilers. These niches of the broiler production have not been included in the ordinary surveillance of *Campylobacter* spp. in Norwegian broilers that has been running since spring 2001.

It is suspected that some of these niches of the broiler production could have a higher occurrence of *Campylobacter* spp. due to a longer life span, and for some niches also due to more contact with the environment, than the conventional broiler production. These aspects are also of interest with regard to antimicrobial resistance (AMR); is there any observed difference in occurrence of AMR bacteria between ordinary broiler production and broilers slaughtered older than 50 days of age? A study was therefore conducted in 2018 investigating broiler flocks older than 50 days when slaughtered for the occurrence of both *Campylobacter* spp. and selected AMR bacteria.

Material and methods

All broiler flocks older than 50 days of age at slaughter were sampled by the Norwegian Food Safety Authority at the slaughterhouse during the period May through October 2018, which is the same time period as the surveillance programme of the action plan regarding *Campylobacter* spp. in Norwegian broilers. Caecal material from 10 broilers per flock were sent to the Norwegian Veterinary Institute for cultivation of thermotolerant *Campylobacter* spp., as well as the AMR indicators *E. coli*, *Enterococcus faecalis* and *Enterococcus faecium*. In addition, selective methods for detection of *E. coli* resistant to third generation cephalosporins, quinolone resistant *E. coli*, carbapenemase-producing *Enterobacteriaceae*, and vancomycin resistant *E. faecalis*/*E. faecium* (VRE) were used as described in Appendix 3. Further susceptibility testing, data managing and statistical analyses were performed as described in Appendix 3.

Results and discussion

Escherichia coli

Caecal samples from a total of 104 flocks of broilers over 50 days of age at slaughter were examined, and *E. coli* isolates were obtained from 100 (96.2%) of the flocks. No *E. coli* resistant to third generation cephalosporins, nor any carbapenemase-producing *Enterobacteriaceae* were detected in the selective screenings. Quinolone resistant *E. coli* was detected in 86 (83.5% [95% CI: 74.9-90.1]) samples from the 103 flocks tested in the selective screening.

The results showed that 81% of the 100 *E. coli* isolates were susceptible to all antimicrobial agents included. Altogether, 11% of the isolates were resistant to one antimicrobial agent (predominantly ampicillin), 6% to two (predominantly to nalidixic acid and ciprofloxacin), and 2% to three antimicrobial agents. In total, 19% of the isolates were resistant, indicating a moderate occurrence of resistance in *E. coli* from broilers over 50 days of age at slaughter according to the EFSA classification described in Appendix 6. Resistance to ampicillin, ciprofloxacin and nalidixic acid were the most frequently identified resistance determinants, followed by resistance to tigecycline and sulfamethoxazole. None of the isolates displayed any resistance to the third generation cephalosporins cefotaxime and ceftazidime, indicating a prevalence below 3.5%.

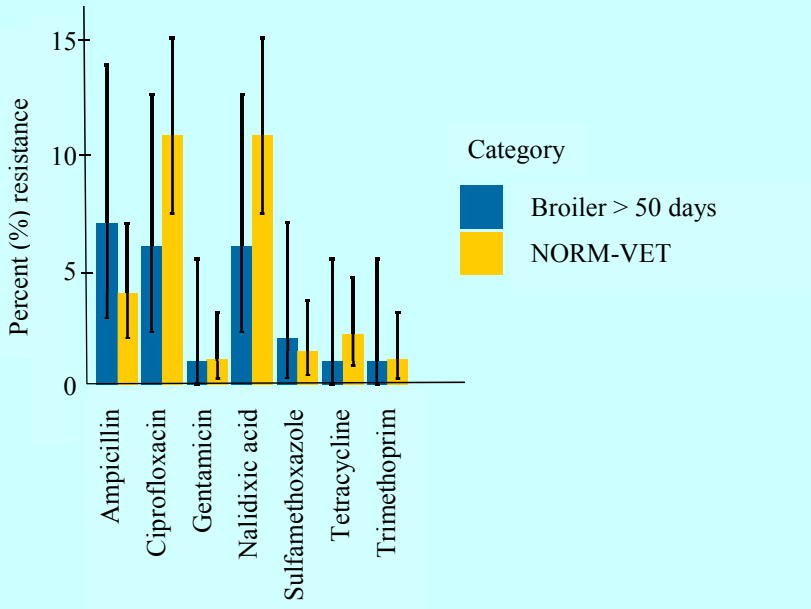

FIGURE 52. Percent resistance to some of the antimicrobial agents included in the test panel, among *E. coli* isolates from broiler flocks over 50 days of age at slaughter and from broiler flocks in the ordinary NORM-VET surveillance in 2018. 95% CI shown as bars.

As shown in Figure 52, the resistance in *E. coli* from flocks of broilers over 50 days of age at slaughter is similar to *E. coli* from broilers included in the standard NORM-VET surveillance. The flocks included in the standard surveillance consist mostly of samples from broilers slaughtered at the age of 30-31 days, but more slow-growing broilers being slaughtered at

45 days of age have become more common the last few years. However, it cannot be excluded that a few samples from broilers over 50 days of age at slaughter may also have been sampled in the standard NORM-VET surveillance. Although it may seem like the occurrence of resistance to the quinolones ciprofloxacin and nalidixic acid is lower in the flocks of broilers over 50 days at slaughter, these results are non-significant. Moreover, the 83.5% occurrence of quinolone resistant *E. coli* in broiler flocks over 50 days at slaughter as investigated by the selective method, is in concordance with previous results from the ordinary NORM-VET surveillance in 2014 (89.5%). In addition, there were no significant differences with regard to resistance among the quinolone resistant isolates from these two categories.

Enterococcus spp.

Caecal samples from a total of 104 broiler flocks over 50 days of age at slaughter were examined. *E. faecalis* was obtained from 55 (52.9%) of the samples and *E. faecium* from 96 (92.3%) of the samples. No vancomycin resistant *Enterococcus* spp. (VRE) was detected from the samples. This is in concordance with the results from broiler samples included in the standard NORM-VET surveillance.

The 2018 data showed that 27.3% of the *E. faecalis* and 76.0% of the *E. faecium* isolates were susceptible to all antimicrobial agents included in the test panel. *E. faecalis*: Altogether, 49.1% of the isolates were resistant to one antimicrobial agent (mainly tetracycline), 21.8% to two (mainly tetracycline and erythromycin), and 1.8% to three antimicrobial agents. Resistance to tetracycline was the most frequently identified resistance determinant, followed by resistance to erythromycin. *E. faecium:* Altogether, 40.0% of the isolates were resistant to one antimicrobial agent (mainly erythromycin) and 1.8% to two antimicrobial agents. In total, 70.9% of the *E. faecalis* and 41.8% of the *E. faecium* isolates were resistant, indicating a very high and high occurrence of resistance, respectively, according to the EFSA classification described in Appendix 6.

The results indicate that the prevalence of *E. faecalis* isolates displaying resistance to tetracycline and erythromycin was higher for broilers over 50 days of age at slaughter than for the broilers included in the standard NORM-VET surveillance (Figure 53A). However, this is opposite for the *E. faecium* isolates where the resistance to tetracycline is lower for broilers over 50 days of age at slaughter than for the others (Figure 53B), but these observed differences are non-significant. The only significant difference was for occurrence of narasin resistance in *E. faecium* as shown in Figure 53B, with an 8.3% occurrence among the 96 isolates from broilers over 50 days of age at slaughter and 24.7% among the isolates from the broilers included in the standard NORM-VET surveillance ($p<0.01$).

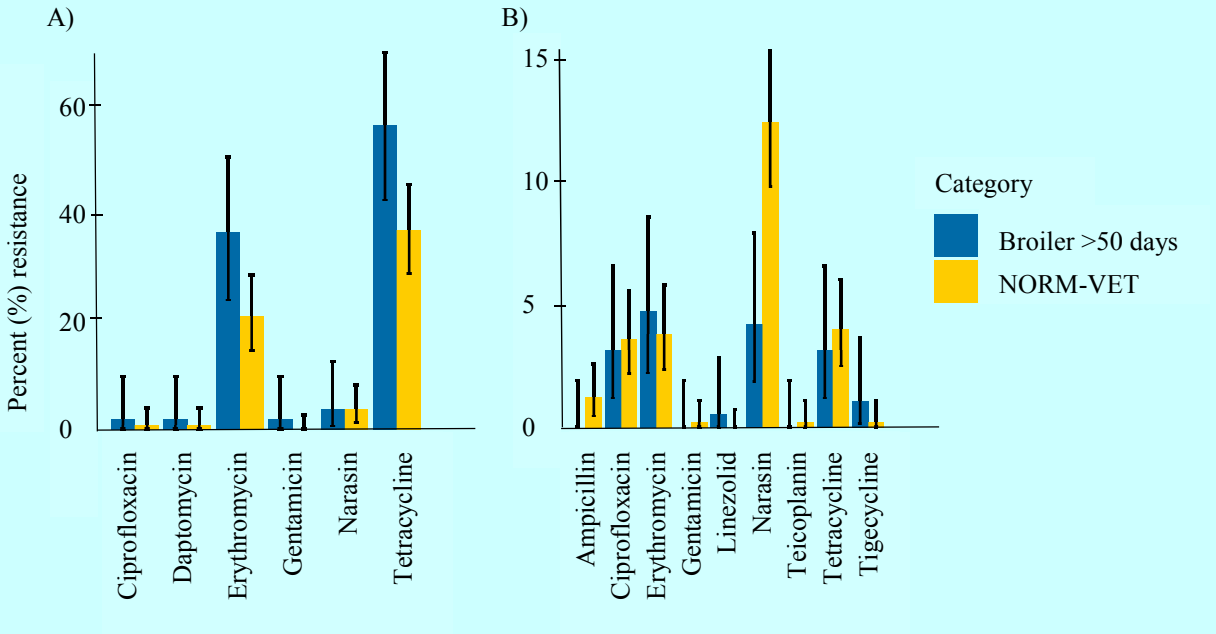

FIGURE 53. Antimicrobial resistance in A) *Enterococcus faecalis* and B) *Enterococcus faecium* from caecal samples from broiler flocks over 50 days of age at slaughter and from flocks included in the ordinary NORM-VET surveillance in 2018, respectively. 95% CI shown as bars.

Campylobacter jejuni

Caecal samples from a total of 104 broiler flocks over 50 days of age at slaughter were examined, and *Campylobacter jejuni* was obtained from 45 (43.3%) of the samples. In total, 39 isolates were susceptibility tested. 97.5% of the 39 isolates were susceptible to all antimicrobial agents included in the susceptibility test panel. Resistance to three antimicrobial agents (quinolones and tetracycline) was detected in only one of the isolates.

The prevalence of AMR among *C. jejuni* isolates from Norwegian broilers over 50 days of age at slaughter is low according to the EFSA classification described in Appendix 6. As shown in Figure 54, there is no significant difference in the prevalence of AMR in *C. jejuni* obtained from broilers over 50 days of age at slaughter compared to those obtained from broilers included in the standard NORM-VET surveillance.

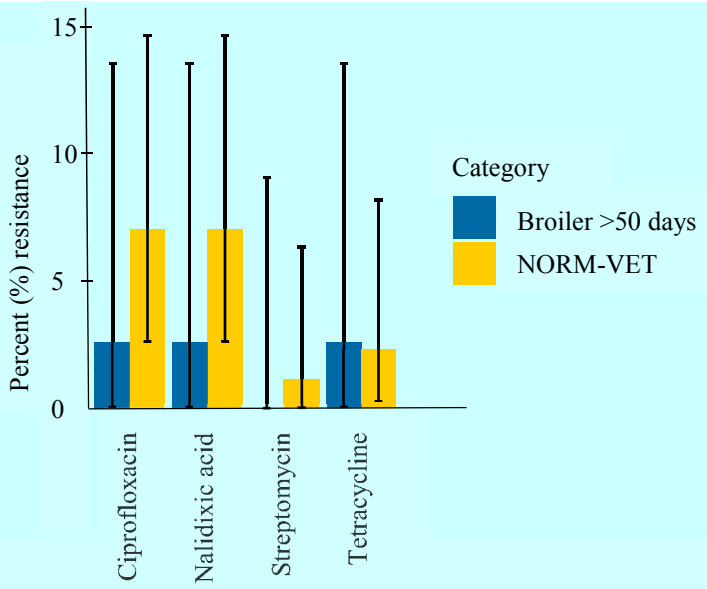

FIGURE 54. Antimicrobial resistance in *Campylobacter jejuni* (n=39) from broiler flocks over 50 days of age at slaughter and from flocks included in the ordinary NORM-VET surveillance in 2018. 95% CI shown as bars.

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Surveillance of methicillin resistant *Staphylococcus aureus* (MRSA) in swine in Norway in 2018

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-MRSAs have 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 Grøntvedt *et al.* 2016 (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. This strategy is also a specific target in the National Strategy against antimicrobial resistance 2015-2020.

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 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 other herds positive for the same CC and *spa*-type, and eradication was initiated. No MRSA CC398 was detected among the 85 genetic nucleus or multiplier herds, 12 sow pool herds, or the 729 herds with more than 10 sows included in the 2017 surveillance programme. However, MRSA CC7, and CC130 and CC425 were detected in one multiplier herd and in two farrow to finish herds, respectively (5).

The surveillance programme in 2018 did not detect any pig herds with MRSA. In total, 716 herds were included in the survey, of which 86 were genetic nucleus or multiplier herds, 12 herds were central units of the sow pool herds, 19 were of the largest farrow to grower or farrow to finish herds, and 599 were finishing pig herds. Further details of the surveillance can be found in the report "The surveillance programme for methicillin resistant *Staphylococcus aureus* in swine in Norway 2018" (6).

TABLE 17. Summary of surveillanve and surveys of MRSA in the Norwegian swine population 2008-2018.

Year	Survey / material	No. herds tested	MRSA positive herds	Type of MRSA
2008	EU baseline / dust	252	1	
2008	National study / abbatoir	200	1	CC398
2011	National study / nasal swabs, abbatoir	207	6 (from 1 abbatoir)	CC398
2012	National study/10 skin swabs at farm	175	1	CC398
2014	MRSA surveillance / sow farms	986	1	CC398
2015	MRSA surveillance / breeder and finisher farms	821	4	CC398 (2), CC1 (2)
2016	MRSA surveillance / sow farms	872	1	CC398
2017	MRSA surveillance / sow farms	826	3	CC7, CC130, CC425
2018	MRSA surveillance / breeder and finisher farms	716	0	

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Survey of methicillin resistant *Staphylococcus aureus* (MRSA) in sheep

In total 306 sheep herds were to be sampled by the Norwegian Food Safety Authorities at the farm. The sheep herds were randomly selected from the Norwegian Register of Production Subsidies (Norwegian Agricultural Authorities, Oslo, Norway), which includes more than 95% of all commercial sheep herds in Norway.

Samples from a total of 276 sheep herds were screened for the presence of methicillin resistant *Staphylococcus aureus* (MRSA). From each herd, nasal swabs were collected from ten sheep and analysed as two sets of pooled samples each containing five swabs. The swabs were enriched in 8 mL Mueller Hinton broth with 6.5% NaCl at 37±1°C for 18-24 h. After incubation, 10 µL were inoculated on Brilliance™ MRSA2 Agar (Oxoid, Thermo Fisher Scientific Inc., Waltham, Massachusetts, USA) and incubated at 37±1°C for 24±2 h. In addition to the nasal swabs, sterile SodiBox™ cloths (Sodibox™, Pont C'hoat 29920 Nevez, France) moistened with sterile saline water were used for environmental samples from each herd. Each 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 cloths were analysed by enrichment in 450 mL Mueller Hinton broth with 6.5% NaCl at 37ºC for 18-24 h. From the culture obtained in the Mueller Hinton Broth, 10 µL were streaked on Brilliance™ MRSA2 Agar (Oxoid) and incubated at 37±1ºC for 24±2 h. For presumptive MRSA isolates, real-time PCR for the detection of *mecA* and *nuc* genes was performed in addition to a conventional PCR for the *mecC* gene (1, 2). The 95% confidence interval (CI) was calculated based on a binomial distribution.

MRSA was detected in an environmental sample from one of the herds (0.4%) [95% CI: 0.01-2.0]). The MRSA isolate harboured the methicillin resistance gene *mecC*, a homologue to the more common *mecA* gene, first described in 2011 (3). Susceptibility testing revealed susceptibility to all tested antimicrobials except the beta-lactam antibiotics. The isolate belonged to clonal complex (CC) 130, *spa*-type t843, which is the most commonly described clonal lineage and *spa* type in *mecC* MRSA in Europe (2,3). *mecC* MRSA has been associated with carriage and clinical infections in both humans and a variety of animal species including livestock and wildlife. There is good evidence to regard *mecC* MRSA as an LA-MRSA with zoonotic potential (3,4). *mecC* MRSA has previously been detected from pigs in Norway as part of the national surveillance programme for MRSA in swine (5).

Follow-up sampling on the MRSA positive farm included new samples from the sheep flock, and from other animal species and their respective environments. *mecC* MRSA isolates of the same CC and *spa*-type as initially isolated were obtained from other sheep at the farm, in one pig sample (pooled cloth sample), and from sheep and dog environmental samples. Samples from cattle and horses were all negative. This is the first screening for MRSA in the Norwegian sheep population, and comparison to previous years is therefore not possible.

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INDICATOR BACTERIA FROM FOOD

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NORM-VET is following the requirements set in Commission implementing decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistant bacteria in food (2013/652/EU). In addition, antimicrobial testing of bacteria from other food 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 is especially relevant for low prevalence sources, as it enables early detection of important resistance mechanisms; thereby enabling these to be monitored and characterised.

Bacterial resistance to critically important antimicrobials, such as third generation cephalosporins 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 occurrence of bacteria resistant to these substances in different food is therefore of special interest. A reservoir of such resistant bacteria in the food chain is of concern as they may have an impact on resistance development in human bacterial populations.

In NORM-VET, *Escherichia coli* are used as indicator bacteria from food sources. Selective methods for detection of *E. coli* resistant to third 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 *Entero-bacteriaceae*, and from 2016 a selective method for colistin resistant *E. coli* were implemented as well. In 2018, food samples included broiler and turkey meat, leafy greens and leafy herbs, and dairy products.

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 2018. Sampling, laboratory methods and data processing are described in Appendix 3.

Cephalosporin resistant *Escherichia coli* from broiler and turkey meat

In 2018, selective screening for *E. coli* resistant to third generation cephalosporins was performed on samples from broiler and turkey meat. A total of 254 broiler and 192 turkey meat samples were analysed. Results are presented in the text below.

RESULTS AND COMMENTS

BROILER MEAT

E. coli resistant to third generation cephalosporins, i.e. cefotaxime and/or ceftazidime, were found in one (0.4%) [95% CI: 0.0-2.2] out of 254 meat samples. The isolate was only resistant to beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime.

The isolate had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype, and PCR and sequencing showed that the isolate contained the $bla_{\text{CMY-2}}$ gene. The isolate did not show decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance. The current findings by the selective method show that there has been a substantial reduction of *E. coli* resistant to third generation cephalosporins in broiler meat compared to previous years ($p<0.001$). This is further described in textbox page 62.

In a European perspective, the occurrence of 0.4% of *E. coli* resistant to third generation cephalosporins in broiler meat in Norway is very low, although the occurrence varied markedly between countries reporting to EFSA in 2016 (EFSA and ECDC Summary report 2016). The South-Eastern, South-Central and South-Western countries tended to report a higher prevalence than the Nordic countries and, to a lesser extent, than countries from Western Europe. There is also variations in prevalence between the Nordic countries, with Norway having the lowest prevalence.

TURKEY MEAT

E. coli resistant to third generation cephalosporins, i.e. cefotaxime and/or ceftazidime, were found in seven (3.6%) [95% CI: 1.5-7.4] out of 192 turkey meat samples. The seven isolates were resistant to beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime. Two of the seven were additionally resistant to the quinolones ciprofloxacin and nalidixic acid. None of the isolates showed decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenem resistance. Five of the isolates had a cephalosporin resistance profile corresponding to an AmpC beta-lactamase phenotype. Genotyping showed that one isolate contained the $bla_{\text{CMY-2}}$ gene and four had mutations in the promoter and attenuator regions of the chromosomally located *ampC* gene resulting in *ampC* overexpression. Two isolates had a cephalosporin resistance profile corresponding to an ESBL phenotype. Genotyping showed that both isolates contained the $bla_{\text{SHV-12}}$ gene.

The present results on cephalosporin resistance that correspond to an AmpC phenotype are in concordance with the 2016 results from selective screening for cephalosporin resistant *E. coli* in turkey meat samples. In 2013, 35.3% of the isolates were resistant to third generation cephalosporins due to upregulation of the chromosomally located AmpC gene. This was not the case in 2016 or 2018 when only a few isolates with this mechanism were detected. The reason for this decrease is unknown. The $bla_{\text{SHV-12}}$ gene has not been detected among turkey meat isolates previously, nor from any other meat samples investigated in NORM-VET. It has, however, been isolated from a leafy green sample (NORM-VET 2017). In 2018, it was detected from both turkey meat samples and from turkey caecal samples.

In a European perspective, the occurrence of cephalosporin resistant *E. coli* in Norwegian turkey meat is low; although the occurrence varied markedly between countries reporting to EFSA in 2016 (EFSA and ECDC Summary report 2016).

Carbapenemase-producing *Enterobacteriaceae* from broiler and turkey meat

A total of 251 broiler and 191 turkey meat 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 194 samples; i.e. 141 samples of leafy greens of which 60 were of domestic and 81 were of imported origin, and 53 samples of leafy herbs (all imported) were screened for the presence of indicator *E. coli* after enrichment. *E. coli* was detected from a total of 33 of the leafy green and leafy herb samples, and one isolate per sample was susceptibility tested. The results are presented in Table 18 and in the text.

TABLE 18. Antimicrobial resistance in *Escherichia coli* isolates (n=33) from leafy greens and leafy herbs in 2018.

		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	5								27	1				3	2		
Tigecycline	0					22	11										
Chloramphenicol	2										31			1		1	
Ampicillin	5								4	22	2			1	4		
Cefotaxime	0					33											
Ceftazidime	0						33										
Meropenem	0		33														
Sulfamethoxazole	4										21		8				4
Trimethoprim	2					26	5							2			
Azithromycin	ND								3	9	20	1					
Gentamicin	0						17	14	2								
Ciprofloxacin	3	18	12			1	2										
Nalidixic acid	2									30	1				1	1	
Colistin	0							33									

*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, 78.8% of the 33 isolates were susceptible to all antimicrobial agents included in the test panel. Altogether, 9.1% of the isolates were resistant to one antimicrobial agent, 3.0% to three and 9.1% to four or more antimicrobial agents. None of the isolates displayed any resistance to the third generation cephalosporins cefotaxime or ceftazidime, nor to carbapenems or colistin. Selective methods were also used on the same sample material to investigate the occurrence of these substances with more sensitive methods (page 75).

Leafy herbs were investigated in NORM-VET for the first time in 2017, while leafy greens were investigated in 2015 and 2017. Comparisons are however, difficult due to the limited number of isolates and variety of sampled products. Sampling of leafy greens and leafy herbs continues in 2019. 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 third generation cephalosporins was performed on a total of 194 samples. *E. coli* resistant to third generation cephalosporins was detected in one of the 141 leafy green samples (0.7%) [95% CI: 0-3.9] and in three of the 53 leafy herb samples (5.7%) [95% CI: 1.2-15.7]. In addition to being resistant to beta-lactams, i.e. ampicillin and the third generation cephalosporins cefotaxime and ceftazidime, between two and four of the isolates showed decreased susceptibility to tetracycline, chloramphenicol, sulfamethoxazole, trimethoprim, gentamicin, ciprofloxacin and nalidixic acid. One isolate was also resistant to colistin. All four isolates displayed an ESBL phenotype. The resistance in the three isolates from leafy herbs was encoded by $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-55}}$, and $bla_{\text{CTX-M-65}}$, respectively. In the isolate from leafy greens the resistance mechanism was encoded by $bla_{\text{CTX-M-15}}$.

These four isolates were all subjected to whole genome sequencing (WGS). In the $bla_{\text{CTX-M-15}}$ positive isolate from leafy greens, the *qnrS1* gene encoding fluroroquinolone resistance was one of the other resistance genes detected. All three isolates from leafy herbs were multi-drug resistant. The leafy herb isolate encoding the $bla_{\text{CTX-M-14}}$ gene also harboured genes like $bla_{\text{TEM-1C}}$ (beta-lactam) and *qnrB19* (fluoroquinolone), while the leafy herb isolate encoding the $bla_{\text{CTX-M-55}}$ gene also harboured genes like $bla_{\text{TEM-1B}}$ (beta-lactam), *oqxA/oqxB* and *qnrS1* (fluoroquinolone). The isolate from leafy herbs encoding the $bla_{\text{CTX-M-65}}$ gene was also resistant to colistin and the *mcr-1* gene was detected by WGS.

E. coli carrying the plasmid-mediated colistin resistance gene *mcr-1* has not been detected in animals, food or feed originating from Norway. It has, however, previously been reported from seafood and dog food imported to Norway.

The screening in 2015 did not detect any *E. coli* resistant to third generation cephalosporins in leafy greens, while in 2017 it was detected in one sample. Comparison to the 2015 survey should be done with caution due to sample variability. Results from 2017 and 2018 are further summarised in textbox page 76.

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

Selective screening for quinolone resistant *E. coli* was performed on a total of 194 samples. Quinolone resistant *E. coli* was detected in a total of 12 (6.2% [95% CI: 3.2-10.6]) of the samples, where five (9.4% [95% CI: 3.1 - 20.7]) were detected from leafy herbs and seven (4.9% [95% CI: 2.0 - 10.0]) were from leafy greens. In addition to being resistant to quinolones, resistance to ampicillin and tetracycline was common.

Two isolates, one from leafy herbs and one from leafy greens, were additionally resistant to cephalosporins (see also the selective screening for *E. coli* resistant to third generation cephalosporins) and they both displayed an ESBL phenotype. In one of the isolates, the resistance mechanism encoding the cephalosporin resistance was the $bla_{\text{CTX-M-65}}$ gene. This isolate was also resistant to colistin and the plasmid-encoded *mcr-1* gene was deteted by WGS. In the other isolate the resistance mechanism encoding the cephalosporin resistance was the $bla_{\text{CTX-M-15}}$ gene.

The survey performed in 2015 detected quinolone resistant *E. coli* in two of the investigated 243 samples of leafy greens. In 2017, quinolone resistant *E. coli* was detected in three samples, with one of the isolates also displaying an ESBL phenotype. Comparison to the 2015 survey should be done with caution due to sample variability. Results from 2017 and 2018 are further summarised in textbox page 76.

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

A total of 194 samples were screened for the presence of colistin resistant *E. coli*. None of the samples were positive. However, we detected an *E. coli* isolate resistant to colistin from the selective screening for quinolone resistant *E. coli* from one sample, this isolate was not detected in the selective screening for colistin resistant *E. coli*. This indicates that the selective method in use could have been more sensitive. Several methods/protocols for detecting colistin resistant *E. coli* have been developed during the last years, and will be considered for use in the future.

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

A total of 194 samples were screened for the presence of carbapenemase-producing *Enterobacteriaceae*. None of the samples were positive.

Antimicrobial resistance in bacteria from leafy greens and leafy herbs – a summary of the 2017 and 2018 surveys

There is a lack of knowledge of antimicrobial resistant bacteria in fresh produce. Samples of leafy greens and leafy herbs have therefore been included in NORM-VET the last two years. The samples have been made available through a surveillance programme investigating *Escherichia coli* and *Salmonella* in leafy greens and leafy herbs. A total of 150 samples of leafy greens of both imported and domestic origin and 50 samples of imported leafy herbs were to be collected annually. The sampling continues in 2019, and will thus give data from three consecutive years. The samples were collected by the Norwegian Food Safety Authority and sent overnight to the Norwegian Veterinary Institute. The samples were analysed for indicator *E. coli*, and by selective methods for *E. coli* resistant to third generation cephalosporins, quinolone resistant *E. coli*, colistin resistant *E. coli*, and carbapenemase-producing *Enterobacteriaceae* as described in Appendix 3.

In total, 382 samples of domestic and imported leafy greens and imported herbs were analysed in the period 2017 and 2018, with 116, 164 and 102 samples in each category, respectively. Indicator *E. coli* was isolated from a total of 60 samples over the period (Figure 55). The majority (81.7%) of the isolates were susceptible to all antimicrobial agent included. Altogether, 8.3% of the isolates were resistant to one antimicrobial agent, 1.7% to two, 3.3% to three and four antimicrobial agents, respectively, and 1.7% of the isolates were resistant to five antimicrobial agents.

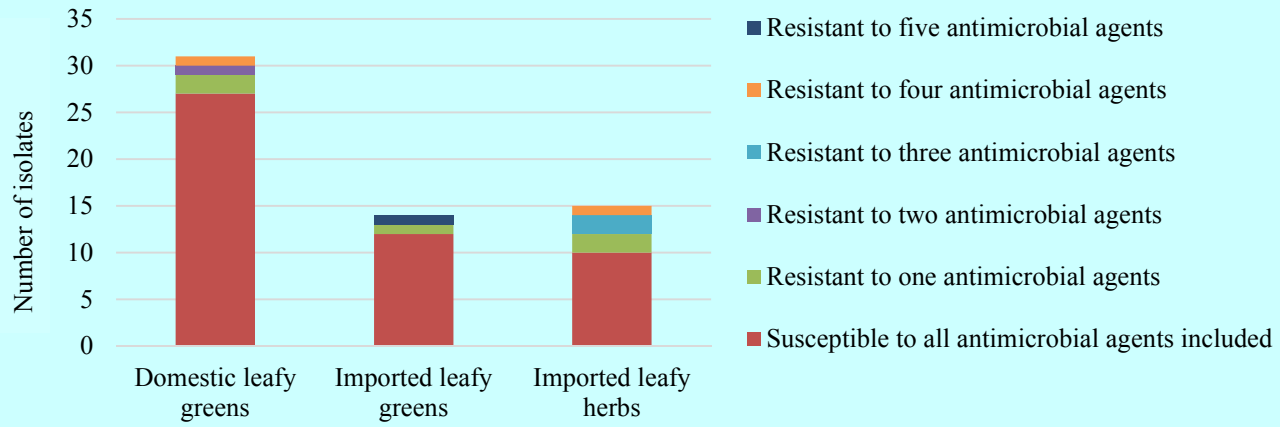

FIGURE 55. Antimicrobial resistance profile in *E. coli* isolates from domestic and imported leafy greens and imported leafy herbs 2017-2018. Proportions of isolates susceptible to all or resistant to one, two, and three or more antimicrobial agents.

The results from the selective methods for the two years 2017 and 2018 are summarised in Table 19. Altogether five *E. coli* isolates resistant to third generation cephalosporins were obtained, all displaying an extended spectrum beta-lactamase (ESBL) phenotype. The resistance in the three isolates from leafy herbs was encoded by $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-55}}$, and $bla_{\text{CTX-M-65}}$, respectively. For the two isolates from leafy greens the resistance mechanism was encoded by $bla_{\text{CTX-M-15}}$ and $bla_{\text{SHV-12}}$, respectively. Some of these isolates contained plasmid-encoded quinolone resistance and one isolate harboured plasmid-encoded colistin resistance (*mcr-1*). By the use of selective screening, *E. coli* resistant to quinolones were isolated from a total of 15 samples as shown in Table 19. However, as mentioned above, one of the quinolone resistant isolates that displayed an ESBL phenotype, also harboured the *mcr-1* gene as identified by whole genome sequencing. Colistin resistant *E. coli* and carbapenemase-producing *Enterobacteriaceae* were not isolated from any of the samples by selective methods.

TABLE 19. A summary of the results from selective screening of the samples from domestic and imported leafy greens and imported leafy herbs for the years 2017 - 2018.

			Selective method			
No. samples	Sample type	No. samples	No. cephalosporin resistant *E. coli*	No. quinolone resistant *E. coli*	No. colistin resistant *E. coli*	No. carbapenemase-producing *Enterobacteriaceae*
382	Domestic leafy greens	116	0	3	0	0
	Imported leafy greens	164	2	7	0	0
	Imported leafy herbs	102	3	5	0	0

Comparisons between the different categories of leafy greens and leafy herbs are difficult due to the low number of samples and isolates retrieved. Caution should therefore be used when interpreting the results. Although there are few isolates retrieved, the results indicate that imported leafy greens and leafy herbs may have bacteria present carrying plasmids encoding resistance towards antimicrobials considered critically important antimicrobials, such as third generation cephalosporins, fluoroquinolones and colistin, which are not commonly identified among production animals in Norway nor from domestically produced food.

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Escherichia coli from dairy products

A total of 189 samples of a variety of dairy products, which comprised 146 domestically produced and 43 imported products, where approximately half of the samples were from unpasteurised milk (see Appendix 3), were screened for the presence of indicator *E. coli*. The majority of the samples were cheese products. *E. coli* was detected from 60 of these, and one isolate per sample was susceptibility tested. The results are presented in Table 20 and in the text.

TABLE 20. Antimicrobial resistance in *Escherichia coli* isolates (n=60) from a variety of dairy products in 2018.

		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								53	5	1			1			
Tigecycline	5					48	7	5									
Chloramphenicol	0										58	2					
Ampicillin	8							2	13	34	3		1		7		
Cefotaxime	0					60											
Ceftazidime	0						60										
Meropenem	0		60														
Sulfamethoxazole	6										54						6
Trimethoprim	1					57	2							1			
Azithromycin	ND								2	18	36	4					
Gentamicin	0						35	21	4								
Ciprofloxacin	0	49	11														
Nalidixic acid	0									60							
Colistin	0							60									

*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, 83.3% of the 60 isolates were susceptible to all antimicrobial agents included. Decreased susceptibility to ampicillin, followed by sulfamethoxazole and tigecycline were the most commonly detected resistance. None of the isolates displayed any resistance to the third 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.

Although the samples included in 2018 were of a variety of dairy products, the majority from which *E. coli* were isolated from, were cheese products (n=40). Cheese was also investigated in NORM-VET in 2016. Comparison to the 2016 survey should, however, be done with caution due to sample variability and small sample sizes. Further monitoring is recommended to aquire more knowledge of antimicrobial resistance in such products, particularly since these are typical products consumed without any heat treatment.

Cephalosporin resistant *Escherichia coli* from dairy products

Selective screening for *E. coli* resistant to third generation cephalosporins was performed on a total of 189 samples. *E. coli* resistant to third generation cephalosporins was not detected in any of the samples. These results are in agreement with the results from 2016 when cheese products were investigated. Comparison to the 2016 survey should, however, be done with caution due to sample variability and small sample sizes.

Quinolone resistant *Escherichia coli* from dairy products

Selective screening for quinolone resistant *E. coli* was performed on a total of 189 samples. Quinolone resistant *E. coli* was not detected in any of the samples. In 2016, quinolone resistant *E. coli* was detected in six cheese samples. However, comparisons should be done with caution due to sample variabilitiy and and small sample sizes.

Colistin resistant *Escherichia coli* from dairy products

A total of 189 samples were screened for the presence of colistin resistant *E. coli*. None of the samples were positive.

Carbapenemase-producing *Enterobacteriaceae* from dairy products

A total of 189 samples were screened for the presence of carbapenemase-producing *Enterobacteriaceae.* None of the samples were positive, which is in concordance with the results from 2016 when cheese products were investigated. Comparison to the 2016 survey should, however, be done with caution due to sample variability and small sample sizes.

ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

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Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum. In NORM-VET, *Salmonella* and *Campylobacter* isolates are monitored for antimicrobial resistance. In NORM, *Salmonella*, *Campylobacter*, *Yersinia* and *Shigella* clinical isolates from human clinical cases are monitored for antimicrobial resistance. Sampling, laboratory methods and data processing are described in Appendix 4.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food production animals in Norway is very favourable as such animal populations are considered virtually free from *Salmonella* spp. To document and maintain this favourable situation, Norway runs an extensive surveillance programme that covers both live animals (cattle, pigs and poultry) and meat samples. The *Salmonella* isolates examined in NORM-VET include those that are detected in this programme, as well as isolates detected by clinical submissions to the Norwegian Veterinary Institute. The data are presented in Table 21 and in the text.

TABLE 21. Antimicrobial resistance in *Salmonella* spp. (n=18) from animals (cat=5, dog=4, wild hog=1, swine=3, cattle=3, geese=1, and hedgehog=1); *S.* Typhimurium (n=13) and other *Salmonella* spp. (n=5) in 2018.

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	3								15						3			
Tigecycline	0					15	3											
Chloramphenicol	3										14	1				3		
Ampicillin	3							11	4						3			
Cefotaxime	0					15	3											
Ceftazidime	0						18											
Meropenem	0		11		7													
Sulfamethoxazole	3											2	1	2	10			3
Trimethoprim	3					6	9							3				
Azithromycin	ND									9	9							
Gentamicin	3						13	1	1			1	2					
Ciprofloxacin	0	1		17														
Nalidixic acid	0									18								
Colistin	2							6	10	1	1							

*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 2018, a total of 18 *Salmonella* spp. isolates from animals were susceptibility tested. The 13 isolates of *S.* Typhimurium included one each from five cats, three dogs, three cattle, one wild hog and one goose, respectively. The remaining five isolates belonged to three different serovars; *S.* Kedougu from three pigs, *S.* Agona from a dog and *S. Enteritidis* from a hedgehog. Nine of the isolates were fully susceptible to all substances tested for. Four of the isolates were resistant to sulfamethoxazole and two were resistant to both sulfamethoxazole and colistin. The colistin resistant isolates will be subjected to whole genome sequencing for further characterisation of the responsible resistance mechanisms.

Three of the isolates were resistant to a total of six of the tested antimicrobials. These isolates were obtained in connection to a *Salmonella* outbreak in horses, and are probably the same strain of *S.* Typhimurium, monophasic (4,[5],12 : i : -).

Salmonella from human clinical specimens

There were no resistance data for human *Salmonella* isolates in 2018 due to reorganisation of the reference laboratory at the Norwegian Institute of Public Health.

CAMPYLOBACTER SPP.

Campylobacter jejuni from broilers and turkey

Caecal samples from a total of 138 broiler flocks were examined. These were flocks identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks in Norway in 2018, or flocks that for some reasons had not been tested in the *Campylobacter* surveillance programme. In total the *Campylobacter* surveillance programme examined 1,986 flocks from 515 producers. *C. jejuni* isolates were obtained from 86 of the 138 flocks (62.3%) previously identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks in Norway in 2018. The isolates were further susceptibility tested. In addition, caecal samples from 152 turkey flocks were examined and *C. jejuni* isolates were obtained from 22 of these samples (14.5%), and subjected to susceptibility testing. The results are presented in Tables 22-23, Figure 56 and in the text.

TABLE 22. Antimicrobial resistance in *Campylobacter jejuni* from broiler (n=86) in 2018.

	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	2.3	[0.3-8.1]				96.5	1.2				1.2			1.2	
Erythromycin	0.0	[0.0-4.2]					100								
Streptomycin	1.2	[0.0-6.3				2.3	12.8	76.7	7.0			1.2			
Gentamicin	0.0	[0.0-4.2]		1.2	3.5	53.5	41.9								
Ciprofloxacin	7.0	[2.6-14.6]		93.0							7.0				
Nalidixic acid	7.0	[2.6-14.6]						1.2	81.4	9.3	1.2		1.2	5.8	

*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.

TABLE 23. Antimicrobial resistance in *Campylobacter jejuni* from turkey (n=22) in 2018.

		Distribution (n) of MIC values (mg/L)*												
Substance	n resistant	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Tetracycline	0				22									
Erythromycin	0					22								
Streptomycin	2					5	13	2	1		1			
Gentamicin	0		2	2	17	1								
Ciprofloxacin	2		20								2			
Nalidixic acid	2						2	14	4				2	

*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.

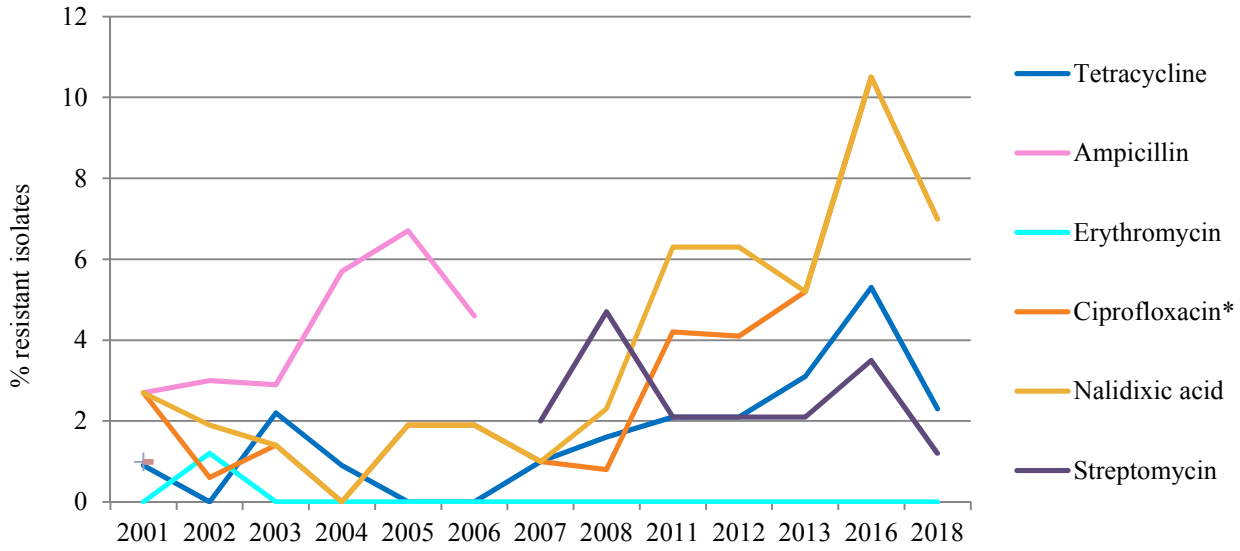

FIGURE 56. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers 2001-2018. The cut-off values used in NORM-VET 2018 were applied.

RESULTS AND COMMENTS

BROILER

The prevalence of antimicrobial resistance among *C. jejuni* isolates from Norwegian broilers is low. In total, 93.0% of the 86 isolates were susceptible to all antimicrobial agents included in the test panel.

Resistance to two antimicrobial agents (quinolones) was detected in 3.5%, and resistance to three antimicrobial agents (quinolones and tetracycline or streptomycin) was detected in 3.5% of the isolates. Resistance to the quinolones ciprofloxacin and nalidixic acid were the most frequently identified resistance determinants, followed by resistance to tetracycline and streptomycin.

The 2016 results indicated an increasing trend in prevalence of resistance to ciprofloxacin and nalidixic acid among *C. jejuni* (Figure 56). The 2018 results are, however, similar to the results from 2013. An increase in quinolone resistance in *C. jejuni* from broilers has been shown in several of the countries reporting to EFSA (EFSA and ECDC Summary Report 2016). Further monitoring is needed to see whether such an increase will take place in Norway as well. In a European perspective, the occurrence of quinolone resistance in *C. jejuni* from Norwegian broilers is quite low, although the occurrence varies between countries reporting to EFSA with the Nordic countries having the lowest resistance levels.

TURKEY

In total, 18 of the 22 isolates were susceptible to all antimicrobial agents included in the test panel. Two isolates displayed resistance to streptomycin and two isolates to the quinolones ciprofloxacin and nalidixic acid.

C. jejuni from turkey caecal samples have only been susceptibility tested once before. In 2007, only 14 isolates were tested. Although a limited number of isolates have been tested both these years, the results indicate that the occurrence of resistance in *C. jejuni* isolated from Norwegian turkey flocks is low.

In a European perspective, the overall prevalences of resistance to ciprofloxacin, nalidixic acid and tetracycline in *C. jejuni* are very high, while resistance to erythromycin, streptomycin and gentamicin are low to very low according to the EFSA classification described in Appendix 6. Complete susceptibility was observed for only 17.2% of the isolates reported by European countries in 2016 (EFSA and ECDC Summary Report 2016). Compared to these European data, the occurrence of resistance in *C. jejuni* from turkey flocks in Norway is among the lowest.

Campylobacter spp. from human clinical cases

There were no resistance data for human *Campylobacter* isolates in 2018 due to reorganisation of the reference laboratory at the Norwegian Institute of Public Health.

Yersinia enterocolitica from human clinical cases

There were no resistance data for human *Yersinia* isolates in 2018 due to reorganisation of the reference laboratory at the Norwegian Institute of Public Health.

Shigella spp. from human clinical cases

There were no resistance data for human *Shigella* isolates in 2018 due to reorganisation of the reference laboratory at the Norwegian Institute of Public Health.

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 24, proportions are therefore estimated for all isolates and for all isolates excluding species considered to be common skin contaminants such as coagulase negative staphylococci, *Micrococcus* spp., *Corynebacterium* spp., *Bacillus* spp. and *Cutibacterium* spp. This does not imply that such isolates cannot cause infections, but only that it was not possible to enforce a standardised protocol for inclusion of the clinically significant isolates. Similarly, all isolates were registered as individual findings although polymicrobial bloodstream infections are regularly detected in some patients. Limitations in the data extraction procedure prohibited in-depth analysis of these parameters.

TABLE 24. Number of blood culture isolates in 2018, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) 2014-2018. The table is based on data from the information systems of all laboratories in Norway.

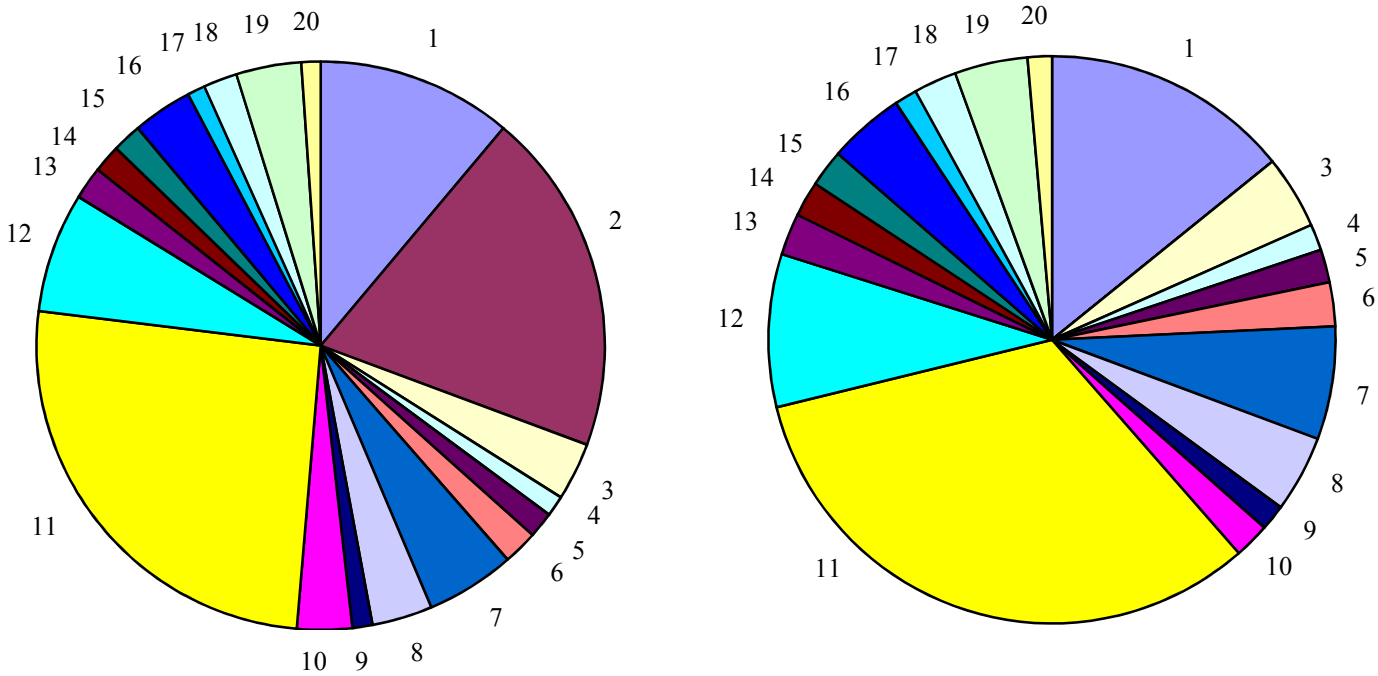
Species	No. of isolates 2018	% of all isolates					% of all isolates excluding skin flora				
		2014	2015	2016	2017	2018	2014	2015	2016	2017	2018
Staphylococcus aureus	2,040	11.0	11.1	10.5	10.1	11.1	14.2	14.4	13.6	13.1	14.2
Coagulase negative staphylococci	3,586	20.4	21.1	20.7	20.9	19.5	-	-	-	-	-
Streptococcus pneumoniae	604	3.6	3.2	3.4	2.7	3.3	4.6	4.2	4.4	3.6	4.2
Streptococcus pyogenes	215	1.1	1.3	1.1	1.2	1.2	1.4	1.7	1.4	1.5	1.5
Streptococcus agalactiae	271	1.6	1.7	1.6	1.4	1.5	2.0	2.2	2.1	1.8	1.9
Beta-haemolytic streptococci group C and G	360	1.2	1.5	1.3	1.5	2.0	1.6	2.0	1.7	2.0	2.5
Viridans- and non-haemolytic streptococci	927	4.6	4.6	5.0	5.5	5.1	5.9	6.0	6.5	7.2	6.4
Enterococcus faecalis	631	3.8	3.1	3.6	3.6	3.4	5.0	4.0	4.6	4.7	4.4
Enterococcus faecium	212	1.6	1.4	1.4	1.4	1.2	2.1	1.8	1.9	1.9	1.5
Other Gram-positive aerobic and facultative anaerobic bacteria	570	3.5	3.6	3.3	3.5	3.1	2.0	2.3	2.3	2.2	2.0
Escherichia coli	4,697	24.4	24.8	24.9	24.9	25.5	31.5	32.4	32.2	32.2	32.6
Klebsiella spp.	1,253	7.0	6.9	7.1	7.0	6.8	9.0	9.1	9.2	9.1	8.7
Enterobacter spp.	342	1.9	1.7	1.7	1.9	1.9	2.5	2.3	2.2	2.4	2.4
Proteus spp.	290	1.6	1.6	1.6	1.5	1.6	2.1	2.1	2.1	2.0	2.0
Other *Enterobacteriaceae*	625	2.2	1.8	1.8	2.3	3.4	2.9	2.3	2.3	3.0	4.3
Pseudomonas spp.	304	1.8	1.7	1.6	1.4	1.7	2.3	2.2	2.0	1.8	2.1
Other Gram-negative aerobic and facultative anaerobic bacteria	185	2.0	2.1	2.4	2.0	1.0	2.6	2.7	3.0	2.6	1.3
Bacteroides spp.	352	2.2	2.2	1.9	2.3	1.9	2.9	2.8	2.4	2.9	2.4
Other anaerobic bacteria	679	3.1	3.2	3.8	3.7	3.7	3.6	3.7	4.4	4.4	4.2
Yeasts	200	1.4	1.4	1.3	1.2	1.1	1.8	1.8	1.7	1.6	1.4
Total	**18,343**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 24 and Figure 57, aerobic and facultative Gram-positive and Gram-negative bacteria represented 51.4% and 41.9% of all isolates, respectively. The predominance of Gram-positives among all isolates was at the same level as in previous years. The most common Gram-positive species were coagulase negative staphylococci, which represented 19.5%. This is a decrease from 20.9% in 2017, but minor fluctuations may result from inconsistent reporting from the laboratories. The difference between aerobic Gram-positives and Gram-negatives was reversed when species of the skin flora (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp.) were excluded with 38.6% aerobic Gram-positives and 53.4% 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. However, the proportion was 4.2% in 2018 corresponding to an increase from 477 cases in 2017 to 604 in 2018. The proportions of other aerobic Gram-positives have remained stable over many years.

E. coli (32.6%) and other *Enterobacteriaceae* (17.4%) accounted for the vast majority of aerobic Gram-negative isolates, but the proportions have remained relatively unchanged over the years. *Pseudomonas* spp. (2.1%) 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 5.6% (6.6% excluding skin flora). Yeasts accounted for 1.1% (1.4% excluding skin flora) which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (1.9%/2.4%) and among yeasts *Candida albicans* (0.7%/0.9%). 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 57. Distribution of all blood culture isolates (left, n=18,343) and blood culture isolates excluding common skin contaminants (right, n=14,397) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Cutibacterium* spp. Data for 2018 were retrieved from the information systems of all Norwegian laboratories.

Escherichia coli in blood cultures

TABLE 25. *Escherichia coli* blood culture isolates in 2018 (n=2,184). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	56.8	-	43.2
Amoxicillin-clavulanic acid*	≤ 8	> 8	75.5	-	24.5
Piperacillin-tazobactam	≤ 8	> 16	95.2	2.8	2.0
Cefuroxime	≤ 8	> 8	90.4	-	9.6
Cefotaxime	≤ 1	> 2	93.2	0.2	6.6
Ceftazidime	≤ 1	> 4	93.3	1.5	5.2
Cefepime	≤ 1	> 4	92.6	1.7	5.7
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	93.5	1.1	5.4
Ciprofloxacin	≤ 0.25	> 0.5	84.9	3.4	11.7
Tigecycline	≤ 0.5	> 0.5	99.7	-	0.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	74.4	0.5	25.1
ESBL	Negative	Positive	93.5	-	6.5

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

RESULTS AND COMMENTS

NORM results are interpreted according to NordicAST/ EUCAST clinical breakpoints at the time of analysis. The isolates are categorised as susceptible with standard exposure (S), susceptible with increased exposure (I), or resistant (R). The vast majority of isolates were susceptible (S or I) to broad-spectrum antimicrobial agents such as cefotaxime (93.4%), ceftazidime (94.8%), gentamicin (94.6%), cefepime (94.3%), piperacillin-tazobactam (98.0%), tigecycline (99.7%) and meropenem (100.0%) (Table 25). There were no significant changes in the prevalence of resistance to these agents from 2017.

The prevalence of resistance to gentamicin decreased from 7.0% in 2017 to 5.4% in 2018 (Figure 58). However, the prevalence of gentamicin resistance is approximately six times higher than at the turn of the century. A high proportion of gentamicin resistant isolates (41/117, 35.0%) 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 6.0%, West 6.2%, Middle 5.8% and North 2.4%).

The prevalence of resistance to ciprofloxacin was 11.7%, compared to 12.6% in 2016 and 15.2% in 2017. The breakpoint for ciprofloxacin resistance has been changed many times over the years, most recently in 2017 with a reduction from R > 1 mg/L to R > 0.5 mg/L and from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L. The long-term trend for ciprofloxacin resistance cannot be precisely determined due to changes in susceptibility test methodology, but it appears that the increase seen 2006-2015 has now stabilised when using the present breakpoint 2016-2018. The temporal association between ciprofloxacin resistance and ciprofloxacin usage is depicted in Figure 59. A similar association between 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 (44.1% in 2017, 43.2% in 2018) and trimethoprim-sulfamethoxazole (25.3% in 2017, 25.1% in 2018) 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 142 isolates (6.5%) were reported as ESBL positive, which is at the same level as in 2017 (6.6%) (Figure 61). 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 there were no significant differences in ESBL prevalence; South-East (7.1%), North (6.0%), Middle (5.2%) and West (5.1%). Most of the ESBL isolates were resistant to cefuroxime (n=140), cefotaxime (n=139), cefepime (n=112) and ceftazidime (n=104). Many isolates were susceptible to piperacillin-tazobactam at standard (n=124) or increased (n=11) exposure. Ninety-eight isolates were susceptible to amoxicillin-clavulanic acid using breakpoints for non-urinary tract infections, whereas 44 were resistant. The ESBL isolates displayed high rates of co-resistance to ciprofloxacin (n=94), gentamicin (n=41) and/or trimethoprim-sulfamethoxazole (n=95). All isolates were fully susceptible to meropenem according to both clinical and screening breakpoints, thus no carbapenemase-producing isolates were detected.

E. coli isolates with suspected ESBL production were not molecularly characterised in 2018. CTX-M groups 1 and 9 have traditionally dominated in Norway. From 2019 onwards, periodic whole genome sequencing will probably be used to characterise selected ESBL isolates as part of the routine surveillance programme.

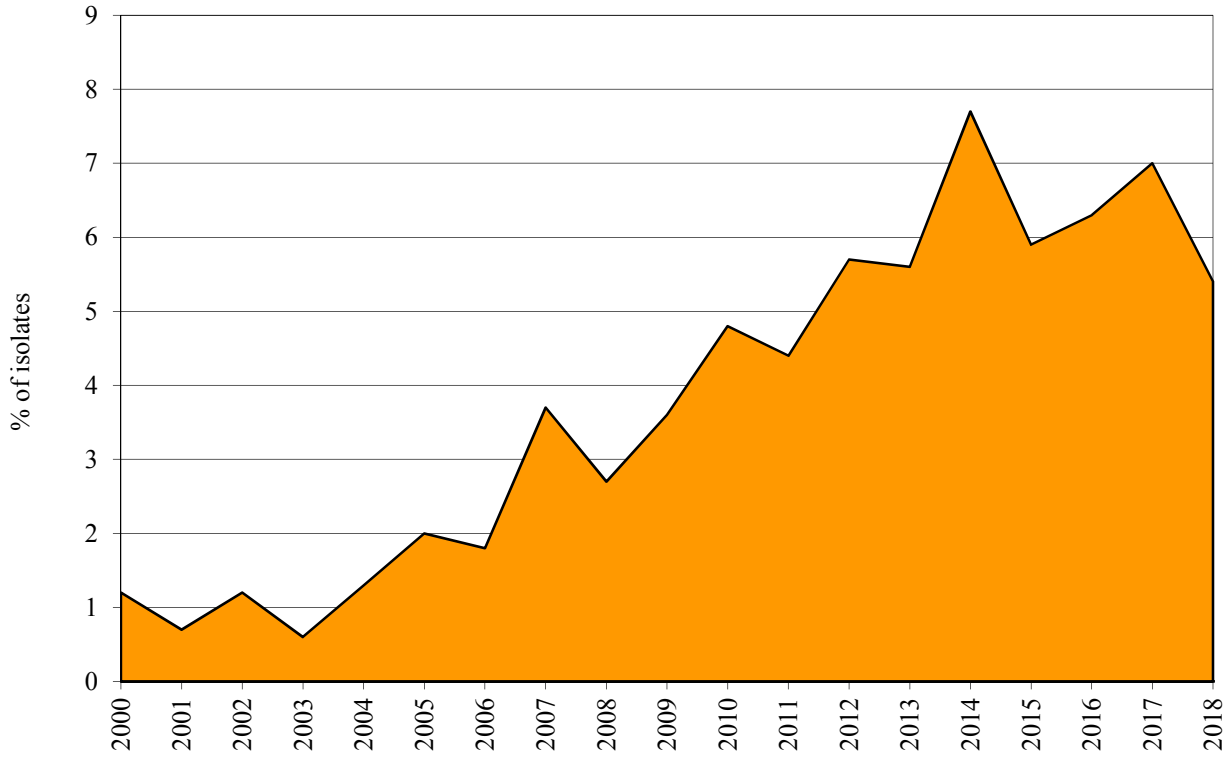


FIGURE 58. Prevalence of resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2018.

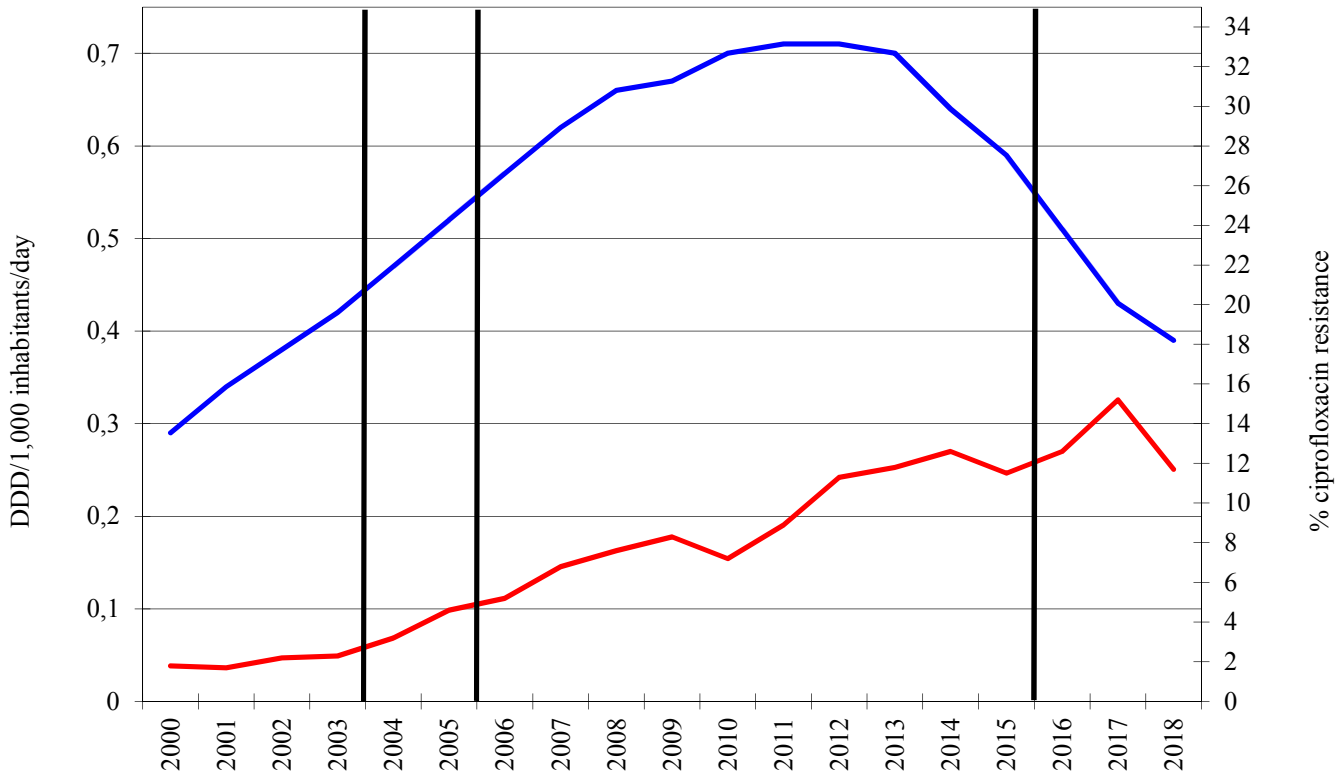


FIGURE 59. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin resistance in *Escherichia coli* blood culture isolates (red) as defined by MIC > 4 mg/L (2000-2003), MIC > 2 mg/L (2004-2005), MIC > 1 mg/L (2006-2015), and MIC > 0.5 mg/L (2016-2018). The breakpoint cannot be calibrated over the entire time period due to changes in susceptibility test methodology.

Escherichia coli in urine

TABLE 26. *Escherichia coli* urinary tract isolates in 2018 (n=1,423). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 8	> 8	65.6	-	34.4
Mecillinam	≤ 8	> 8	95.6	-	4.4
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.3	-	6.7
Cefotaxime	≤ 1	> 2	96.5	0.1	3.4
Ceftazidime	≤ 1	> 4	96.7	0.6	2.7
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	94.9	0.8	4.3
Ciprofloxacin	≤ 0.25	> 0.5	88.5	2.2	9.3
Nitrofurantoin	≤ 64	> 64	99.0	-	1.0
Fosfomycin	≤ 32	> 32	97.2	-	2.8
Trimethoprim	≤ 2	> 4	77.1	0.3	22.6
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	79.7	0.8	19.5
ESBL	Negative	Positive	96.3	-	3.7

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *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 2018 is shown in Table 26 and the rates of resistance for 2000-2018 are shown in Figure 60.

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 4.4% in 2018 compared to 5.9% in 2016 and 6.0% in 2017.

Ciprofloxacin is used as a second line agent for urinary tract infections in Norway. When adjusting for changes in breakpoint (see text Figure 59), the prevalence of resistance has remained stable around 8-9% over the last five years. In 2018, 9.3% of the isolates were resistant to ciprofloxacin in addition to 2.2% that were only susceptible to increased exposure through adjustment of dosage or higher concentration at the site of infection. The corresponding rates for blood culture isolates were 11.7% resistance and 3.4% susceptibility to increased exposure. The persistent discrepancy between urinary tract isolates and isolates from bloodstream infections suggests that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and/or topoisomerase genes, whereas urinary tract isolates may be more representative of the wild-type normal flora.

The prevalence of resistance to amoxicillin-clavulanic acid was 4.4% in 2018 compared to 7.4% in 2016 and 7.3% in 2017. The breakpoint used (R > 32 mg/L) is only valid for uncomplicated urinary tract infections. Almost all isolates (99.0%) remained susceptible to nitrofurantoin. Fosfomycin was included in NORM for the first time in 2017. The vast majority of isolates were categorised as susceptible (97.2%), but the analysis may be technically challenging for inexperienced personnel and the results should be interpreted with caution.

Fifty-two isolates (3.7%) were reported as ESBL producers, which is at small increase from 2016 (3.0%) and 2017 (3.0%). As seen in Figure 61, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (6.5%). The ESBL positive strains were isolated at 18 different laboratories in all parts of the country. Thirty-five isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=9) or patients in nursing homes (n=4) or outpatient clinics (n=4). The ESBL isolates were all resistant to ampicillin, and the majority were also resistant to cefotaxime (49/52) and ceftazidime (37/52). Most isolates were registered as *in vitro* susceptible to mecillinam (49/52), and recent data suggest that this may be a viable treatment option provided a dosage of 400 mg x 3. Many of the ESBL isolates were resistant to ciprofloxacin (29/52) and trimethoprim-sulfamethoxazole (27/52), but remained susceptible to nitrofurantoin (49/52) and gentamicin (37/52). All ESBL isolates were clinically susceptible to carbapenems, and no carbapenemase producers were detected by phenotypical screening.

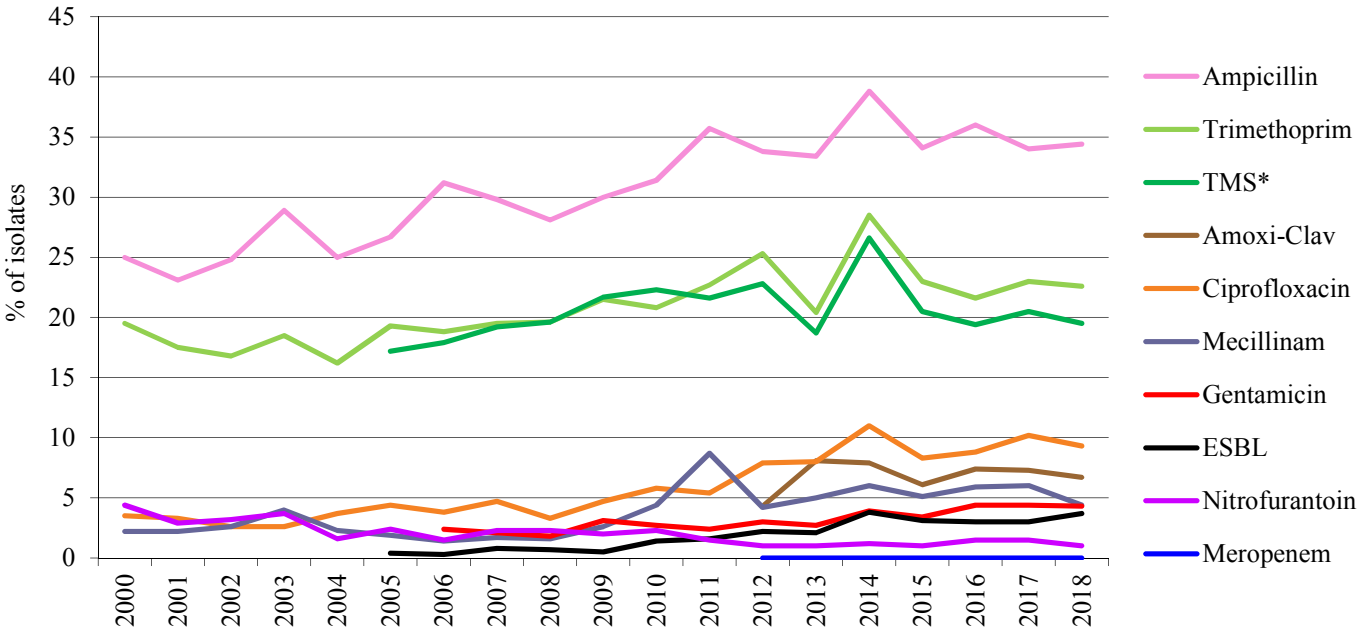


FIGURE 60. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2018. Isolates are categorised according to the breakpoints at the time of analysis for each year.
*TMS=Trimethoprim-sulfamethoxazole.

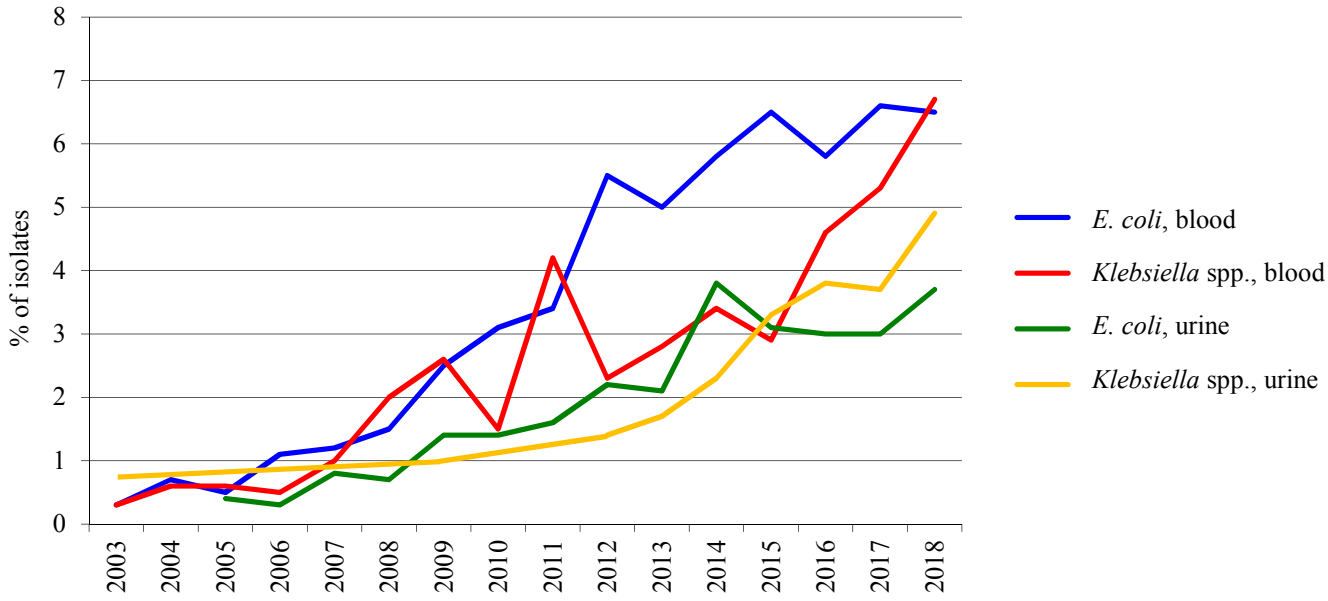


FIGURE 61. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2018.

The clinical sample report from the microbiologist - new definitions of S, I and R

With effect from 1 January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has changed the classification of bacteria's susceptibility to antibiotics (1,2). The categories (SIR-system) now take more account of and emphasise the importance of how antibiotics are dosed and administered. The new categories are:

- Susceptible, standard dosing regimen (S); A microorganism is categorised as "Susceptible, standard dosing regimen" when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- Susceptible, increased exposure (I); A microorganism is categorised as "susceptible, increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting dosing regimen or by its concentration at the site of infection.
- Resistant (R); A microorganism is categorised as "Resistant" when there is a high probability of therapeutic failure even when there is increased exposure.

The significance of S and R is virtually unchanged. The new definition of the I-category (formerly "intermediately sensitive"), however, will have clinical consequences. Thus, when a microbe is classified as susceptible, increased exposure (I) to an antimicrobial agent, one may still use the appropriate agent if adequate exposure can be achieved.

Exposure
Exposure is a term that states something about the availability of an antibiotic at the site of infection based on dose, dosing interval, and route of administration, distribution, metabolism and excretion. You can achieve adequate exposure in several ways. Often, increased dosage, by either increased single doses or more frequent dosing, will be sufficient (see Table 27). It will also be possible in some cases to increase the exposure by changing from oral to intravenous administration. At certain infection sites, the pharmacokinetic properties of an antibiotic can result in increased exposure. This applies, for example, to urinary tract infections, where excretion through the kidneys leads to a high concentration in the urine that enables the treatment of less susceptible microbes.

SIR and dosage
The SIR-system for susceptibility categorisation of bacteria has been in use in Norway for around 20 years with unchanged definitions. It is especially the definition and use of the old I-category ("intermediate") that has been associated with great uncertainty. In many cases, this uncertainty has probably led to the use of other antibiotics. "I" may have been interpreted as "I don't know / I won't use". This is unfortunate at a time of ever-increasing incidence of resistance, and contributes to the unnecessary use of broad-spectrum antibiotics with an enhanced selection for resistant microbes.

The microbiological laboratories use clinical breakpoints (thresholds) to categorise microbes according to S, I, and R. The breakpoints are thus the key that allows the determination of susceptibility to predict the likelihood of therapeutic success in a patient with an infection. All clinical breakpoints require a standardised minimum dose. In Norway, the standard doses that form the basis of the S category largely correspond to the dosage recommendations found in the national guidelines for the use of antibiotics (3,4). However, there are some discrepancies, and the dosage regimens underlying the I category are often omitted. Based on this, the Norwegian Working Group on Antibiotics (AFA) recommends that the microbiological laboratories provide a dosage recommendation for the I-category within their clinical sample report.

In the summer of 2019, the Norwegian Directorate of Health begins work on the revision of the National Guidelines for the use of antibiotics in hospitals. The work will extend over approximately two years. It is envisaged that revised therapy chapters will be published continuously with updated recommendations for dosing in accordance with those that form the basis of the SIR system.

Area of Technical Uncertainty (ATU)
The old definition of intermediate was comprised of four different definitions, including the possible use of intermediate as a buffer zone to prevent technical errors. Ideally, antimicrobial susceptibility testing (AST) should clearly separate susceptible from resistant isolates. This would assure the test's ability to predict the likelihood of therapeutic outcome. However, there are situations where interpretation of AST results is uncertain due to poor reproducibility or poor correlation between methods. For these instances, EUCAST has introduced ATU to be used as a warning to the laboratory. It is the responsibility of the laboratory to react to and to deal with this warning. Alternative actions have been suggested by EUCAST, however, the appropriate action may vary with circumstances.

Rational use of antibiotics
Rational use of antibiotics assumes that prescribers of antibiotics understand the significance of the susceptibility categories reported by the microbiological laboratories. When a relevant antibiotic is reported as "I", prescribers must consider whether increased exposure is possible. If needed, contact a more experienced colleague, clinical microbiologist or infectious disease specialist for advice.
Implementation of the new definitions will probably vary somewhat between the microbiological laboratories. AFA has recommended that all Norwegian laboratories communicate this change to their users and convey the importance of the new definitions. We believe it will be an important contribution to the work on the rational use of antibiotics.

TABLE 27. Three different antibiotics and the dosage regimens that underlie the susceptibility catagorisation (S-I-R). Increased dose and/or altered administration results in increased exposure that is highly likely to support efficient treatment.

Antibiotic	Minimum inhibitory concentration (MIC)	Susceptibility category	Dosing for adults
Amoxicillin	≤ 0.5 mg/L	S – susceptibile, standard dose	500 mg x 3 (oral)
	1 mg/L	I – susceptible, increased exposure	750-1000 mg x 3 (oral)
	> 1 mg/L	R – resistant	Should not be used
Erytromycin (Enterocapsules)	≤ 1 mg/L	S – susceptible, standard dose	500 mg x 2-4 (oral)*
	2 mg/L	I – susceptible, increased exposure	1 g x 4 (oral)*
	> 2 mg/L	R – resistant	Should not be used
**NB! Own dosage regimens for oral suspension due to different bioavailablity.*			
Meropenem	≤ 2 mg/L	S – susceptible, standard dose	1 g x 3 (30 min iv. infusion)
	4-8 mg/L	I – susceptible, increased exposure	2 g x 3 (3hour iv. infusion)
	> 8 mg/L	R – resistant	Should not be used

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On behalf of the Norwegian Working Group on Antibiotics (NWGA): Paul Christoffer Lindemann, Karianne Wiger Gammelsrud, Iren Høyland Löhr, Per Espen Akselsen and Arnfinn Sundsfjord.

Antimicrobial susceptibility testing of *Legionella pneumophila*

The genus *Legionella* consists of 61 species and about 30 of these may cause a severe pneumonia in humans called Legionnaires' disease with an overall case-fatality rate of about 8% (1). *Legionella pneumophila* serogroup 1 is responsible for 70-92% of the infections, while *L. pneumophila* serogroup 2-16 and other species such as *L. micdadei, L. longbeachae, L. bozemanae and L. dumoffii* are less common.

Legionella species are responsible for 1-5% of community-acquired pneumonia. The bacteria live naturally in freshwater and soil and infections occur after inhalation of contaminated aerosols or aspiration of *Legionella*-containing water. Most cases are sporadic, but large outbreaks may occur. France, Germany, Italy and Spain account for about 70% of legionellosis cases diagnosed in Europe (1). In Norway, 40-70 cases have been diagnosed annually the last 5 years and 60-65% of the patients are infected abroad, most commonly when travelling to Spain, Italy, Turkey, Greece and Thailand.

Legionella species are Gram-negative, slow-growing fastidious bacteria. Culture is the gold standard for detecting Legionnaires' disease, but expertise is needed to get a high sensitivity. A selective medium is needed and colonies usually appear within 3-5 days. Culture enables antimicrobial susceptibility testing and genotyping (sequence based typing, SBT) of isolates, which is important in outbreak investigation. Urinary antigen test is the fastest and most easy test to perform, but is limited to *L. pneumophila* serogroup 1. A first void urine specimen is needed and it takes about 15 minutes to perform the test in the laboratory. PCR is increasingly introduced in diagnostic laboratories. The test is sensitive and specific and is especially useful in diagnosing other species/serogroups than *L. pneumophila* serogroup 1. The test detects all *Legionella* species, although a specific test for *L. pneumophila* serogroup 1 also exists. Serology has a limited clinical utility and is mainly useful as an epidemiological tool. It takes several weeks for antibodies to appear and some patients do not produce antibodies at all.

TABLE 28. Diagnostic tests for *Legionella**.

Test or diagnostic method	Specimen	Information by positive test	Sensitivity (%)/ Specificity (%)
Urinary antigen test	Urine	*L. pneumophila* serogroup 1 only	70-90/95-100
PCR	Sputum or respiratory secretion	All *Legionella* species and *L. pneumophila* serogroup 1	30-100/95-100
Culture	Sputum or respiratory secretion	All *Legionella* species	<10-80/~100

*Modified from reference (2).

Recommended antimicrobial treatment for Legionnaires' disease is the newer macrolide azithromycin or a fluoroquinolone, which both give a high intracellular concentration in infected cells. No standard test for antimicrobial susceptibility testing exists and it has not been customary to test for antimicrobial susceptibility of *Legionella* isolates in the routine microbiology laboratory. EUCAST recommends the use of a gradient diffusion test on buffered charcoal yeast extract agar medium supplemented with α-ketoglutarate (BCYE-α) in routine laboratories for the purpose of detecting strains with MICs above the wild-type distribution [3]. Tentative ECOFFs are for azithromycin 0.5 mg/L, clarithromycin 0.5 mg/L, ciprofloxacin 2 mg/L, levofloxacin 1 mg/L, rifampicin 0.032 mg/L and doxycycline 8 mg/L. There are no established clinical breakpoints (3,4).

Strains resistant to antimicrobial agents can easily be induced *in vitro* by growing *L. pneumophila* in increasing concentration of antibiotics (5,6) but only a few clinical strains have been found resistant to antibiotics. A strain of *L. pneumophila* serogroup 1 potentially resistant to ciprofloxacin (MIC 2 mg/L) and azithromycin (MIC 8 mg/L) has been isolated from a patient with Legionnaires' disease in The Netherlands after ciprofloxacin treatment for 4 days (7). A point mutation in the *gyrA* gene was identified (8). *L. pneumophila gyrA* mutants responsible for fluoroquinolone resistance were also detected in two patients in France during fluoroquinolone treatment (9). Since few strains have been tested, the frequency of resistance to antimicrobial agents is uncertain.

Reduced susceptibility to azithromycin was demonstrated in clinical isolates *of L. pneumophila* serogroup 1 in Canada in 2014, where 30 (96.7%) of the isolates belonging to sequence type (ST)1 and one ST52 isolate showed MICs above the wild-type distribution with MICs 0.5-2 mg/L (10). An efflux pump (lpeAB) was later found responsible for the reduced susceptibility to azithromycin (6). Studies by Vandewalle-Capo *et al*. of *L. pneumophila* clinical strains and our studies of *L. pneumophila* clinical and environmental strains have showed that all ST1 strains, which is the most common ST worldwide, and some related STs have reduced susceptibility to azithromycin with MICs 0.5-2 mg/L, but the clinical significance is unclear (4,6). So far, clinical studies have found azithromycin and fluoroquinolones to be comparable in the treatment of Legionnaires' disease (11). More data are needed to establish clinical breakpoints and definition of resistance for these and other relevant antimicrobial agents.

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Klebsiella spp. in blood cultures

TABLE 29. *Klebsiella* spp. blood culture isolates in 2018 (n=888). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	84.8	-	15.2
Piperacillin-tazobactam	≤ 8	> 16	89.3	7.2	3.5
Cefuroxime	≤ 8	> 8	86.5	-	13.5
Cefotaxime	≤ 1	> 2	92.9	0.6	6.5
Ceftazidime	≤ 1	> 4	92.3	1.6	6.1
Cefepime	≤ 1	> 4	90.4	3.3	6.3
Meropenem	≤ 2	> 8	99.9	0.1	0.0
Gentamicin	≤ 2	> 4	94.1	0.7	5.2
Ciprofloxacin	≤ 0.25	> 0.5	86.6	5.3	8.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.3	0.8	13.9
ESBL	Negative	Positive	93.4	-	6.6

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

TABLE 30. *Klebsiella pneumoniae* blood culture isolates in 2018 (n=659). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	82.2	-	17.8
Piperacillin-tazobactam	≤ 8	> 16	87.9	9.1	3.0
Cefuroxime	≤ 8	> 8	84.1	-	15.9
Cefotaxime	≤ 1	> 2	91.4	0.3	8.3
Ceftazidime	≤ 1	> 4	90.2	2.1	7.7
Cefepime	≤ 1	> 4	88.4	3.6	8.0
Meropenem	≤ 2	> 8	99.8	0.2	0.0
Gentamicin	≤ 2	> 4	92.6	0.8	6.7
Ciprofloxacin	≤ 0.25	> 0.5	83.0	6.5	10.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	81.3	1.1	17.6
ESBL	Negative	Positive	91.5	-	8.5

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

TABLE 31. *Klebsiella oxytoca* blood culture isolates in 2018 (n=151). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amoxicillin-clavulanic acid*	≤ 8	> 8	90.7	-	9.3
Piperacillin-tazobactam	≤ 8	> 16	90.8	2.6	6.6
Cefuroxime	≤ 8	> 8	92.1	-	7.9
Cefotaxime	≤ 1	> 2	96.7	1.3	2.0
Ceftazidime	≤ 1	> 4	98.0	0.0	2.0
Cefepime	≤ 1	> 4	97.4	1.3	1.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	98.7	0.0	1.3
Ciprofloxacin	≤ 0.25	> 0.5	97.4	0.7	2.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	96.7	0.0	3.3
ESBL	Negative	Positive	98.0	-	2.0

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

RESULTS AND COMMENTS

The surveillance of *Klebsiella* spp. in blood cultures included 659 *K. pneumoniae* (74.2%), 151 *K. oxytoca* (17.0%), and 78 (8.8%) isolates not identified to the species level, giving a total of 888 *Klebsiella* spp. isolates (Tables 29-31).

The majority of *Klebsiella* spp. isolates remained susceptible to aminoglycosides, but the prevalence of gentamicin resistance increased from 3.2% in 2017 to 5.2% in 2018. *K. pneumoniae* isolates were more often resistant to aminoglycosides (6.7%) than *K. oxytoca* isolates (1.3%). 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 septicemia in Norway.

As for *E. coli*, the breakpoints for ciprofloxacin were reduced from R > 1 mg/L to R > 0.5 mg/L and from S ≤ 0.5 to S ≤ 0.25 in 2017. The prevalence of resistance to ciprofloxacin peaked at 11-12% in 2016-2017, but decreased again to 8.1% in 2018. The results should be interpreted with caution due to the repeated changes in breakpoints and test methodology over the last decade. Suscpetibility testing for quinolones may be technically challenging, and further surveillance is needed to determine the long-term trend for ciprofloxacin resistance in *Klebsiella* spp. Resistance to ciprofloxacin is much more common in *K. pneumoniae* (10.5%) than in *K. oxytoca* (2.0%). Resistance to trimethoprim-sulfamethoxazole remained stable at 13.9% in 2018 compared to 14.0% in 2017. As for ciprofloxacin, the prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (3.3%) than in *K. pneumoniae* (17.6%).

A comparison of resistance to beta-lactam antibiotics between *Klebsiella* species is complicated by the diagnostic challenges of the chromosomal K1 beta-lactamase in *K. oxytoca*. Most *Klebsiella* spp. isolates were susceptible (defined as S+I) to cefotaxime (93.5%), ceftazidime (93.9%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (96.5%), see Figure 62. The rates of resistance to third generation cephalosporins increased slightly from 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 4.6% in 2016 and 5.3% in 2017, to 6.6% in 2018 (Figure 61). The 59 ESBL isolates originated from 18 different laboratories and were identified as *K. pneumoniae* (n=56, 8.5%) and *K. oxytoca* (n=3, 2.0%). The ESBL isolates were generally resistant to ceftazidime (52/59), cefotaxime (58/59) and cefepime (51/59), and co-resistance was frequently seen for ciprofloxacin (44/59), trimethoprim-sulfamethoxazole (49/59) and gentamicin (38/59). Many isolates were susceptible to piperacillin-tazobactam at standard (33/59) or increased (20/59) exposure. A single isolate displayed a zone diameter below the meropenem screening breakpoint and was categorised as I by the clinical breakpoints. The isolate contained a gene encoding an OXA-48-like enzyme. Several other isolates were positive by the EUCAST screening breakpoints but were not confirmed as carbapenemase producers.

Klebsiella spp. isolates with suspected ESBL production were not molecularly characterised in 2018. CTX-M groups 1 and 9 have traditionally dominated in Norway. From 2019 onwards, periodic whole genome sequencing will probably be used to characterise selected ESBL isolates as part of the routine surveillance programme.

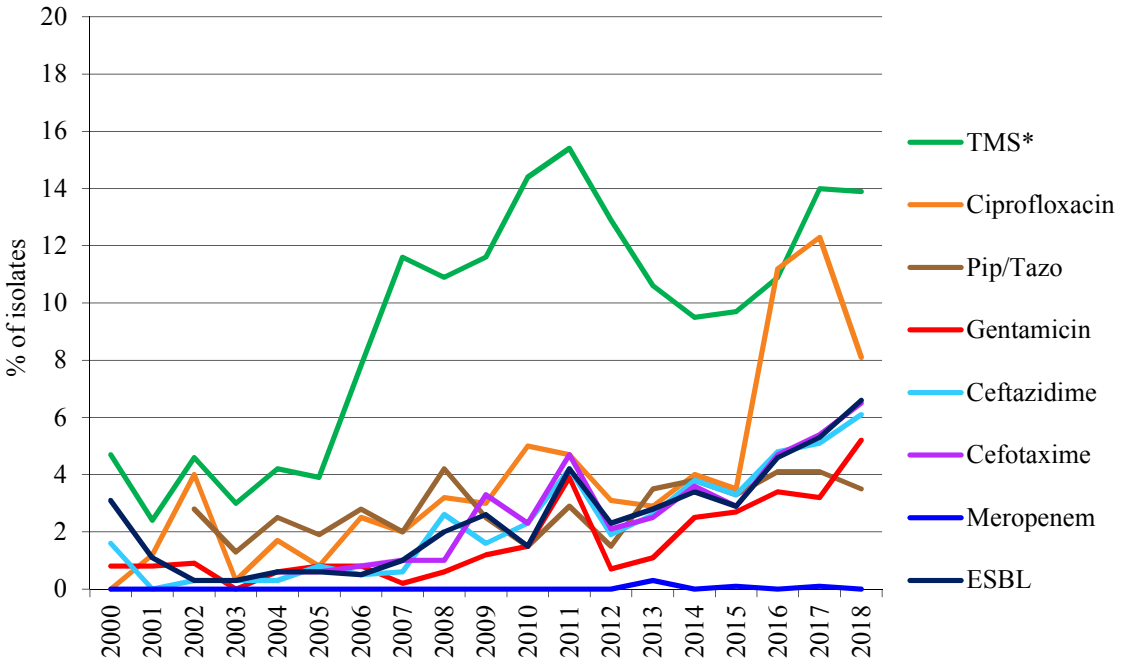

FIGURE 62. Prevalence of resistance to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2018. Isolates are categorised according to the breakpoints at the time of analysis for each year.
*TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 32. *Klebsiella* spp. urinary tract isolates in 2018 (n=922). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	89.8	-	10.2
Amoxicillin-clavulanic acid*	≤ 32	> 32	94.4	-	5.6
Piperacillin-tazobactam	≤ 8	> 16	92.0	4.4	3.6
Cefotaxime	≤ 1	> 2	95.3	0.4	4.3
Ceftazidime	≤ 1	> 4	94.5	0.9	4.6
Cefepime	≤ 1	> 4	93.7	2.8	3.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.1	0.9	3.0
Ciprofloxacin	≤ 0.25	> 0.5	90.6	3.1	6.3
Trimethoprim	≤ 2	> 4	81.7	1.1	17.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.7	0.9	13.4
ESBL	Negative	Positive	95.1	-	4.9

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *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 2012-2017. 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 were susceptible (S+I) to gentamicin at 97.0% compared to 97.6% in 2017. Among urinary tract *E. coli*, 95.7% were susceptible to gentamicin in 2018. The rates of resistance to ciprofloxacin in *Klebsiella* spp. decreased from 9.1% in 2016 and 7.9% in 2017, to 6.3% in 2018. The comparable rate for urinary tract *E. coli* in 2018 was 9.3%. Susceptibility (S+I) to trimethoprim (82.8% in 2018, 82.0% in 2017) and trimethoprim-sulfamethoxazole

(86.6% in 2018, 87.5% in 2017) was higher than in *E. coli* (77.4% and 80.5%, respectively, in 2018). There are no EUCAST disk diffusion breakpoints for fosfomycin in *Klebsiella*. Our data may indicate that the *E. coli* breakpoints are not suitable for *Klebsiella* (72.1% resistance).

All *Klebsiella* isolates are inherently resistant to ampicillin due to the chromosomal SHV beta-lactamase. As for *Klebsiella* spp. blood culture isolates, ESBL detection in urinary tract isolates was based on resistance to cefotaxime and/or ceftazidime and subsequent confirmatory ESBL MIC gradient tests. Fourty-five isolates were reported as ESBL positive of which 41 were *K. pneumoniae*, one was *K. oxytoca* and three were not identified to the species level.

The 45 ESBL isolates were retrieved from 16 different laboratories and originated from general practices (n=24), hospitals (n=15) or outpatient clinics (n=6). The 4.9% ESBL rate (5.9% in *K. pneumoniae*) was an increase from 2017 (3.7% for all *Klebsiella*, 4.6% in *K. pneumoniae*). The 45 ESBL isolates were often resistant to trimethoprim (n=39), trimethoprim-sulfamethoxazole (n=39), ciprofloxacin (n=26) and gentamicin (n=25), but many remained susceptible to mecillinam (n=33) and piperacillin-tazobactam (n=32).

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 2018 (n=694). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	89.3	-	10.7
Amoxicillin-clavulanic acid*	≤ 32	> 32	94.4	-	5.6
Piperacillin-tazobactam	≤ 8	> 16	91.6	4.9	3.5
Cefotaxime	≤ 1	> 2	94.4	0.3	5.3
Ceftazidime	≤ 1	> 4	93.4	1.0	5.6
Cefepime	≤ 1	> 4	93.1	2.7	4.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	95.7	0.7	3.6
Ciprofloxacin	≤ 0.25	> 0.5	88.3	3.9	7.8
Trimethoprim	≤ 2	> 4	79.1	0.7	20.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	82.4	1.0	16.6
ESBL	Negative	Positive	94.1	-	5.9

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

TABLE 34. *Klebsiella oxytoca* urinary tract isolates in 2018 (n=117). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Mecillinam	≤ 8	> 8	93.2	-	6.8
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.2	-	6.8
Piperacillin-tazobactam	≤ 8	> 16	93.1	0.9	6.0
Cefotaxime	≤ 1	> 2	98.2	0.9	0.9
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Cefepime	≤ 1	> 4	96.6	3.4	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	99.1	0.0	0.9
Ciprofloxacin	≤ 0.25	> 0.5	100.0	0.0	0.0
Trimethoprim	≤ 2	> 4	95.7	0.9	3.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	99.1	0.0	0.9
ESBL	Negative	Positive	99.1	-	0.9

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

Update on carbapenemase-producing Gram-negative bacteria in Norway 2018

Colonisation or infections with carbapenemase-producing Gram-negative bacteria (*Enterobacterales*, *Pseudomonas* and *Acinetobacter*) 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 2018. Isolates from the same patient are included if they were of different species and/or harboured different carbapenemase variants.

In 2018, 54 patients were identified with carbapenemase-producing *Enterobacterales* (CPE), an increase from 35 cases in 2017 (Figure 63). Forty-four cases were associated with import while five cases had no link to import. No information where reported to MSIS for the remaining five cases. According to the information in MSIS, twelve cases were diagnosed with infection. The other cases were linked to screening samples.

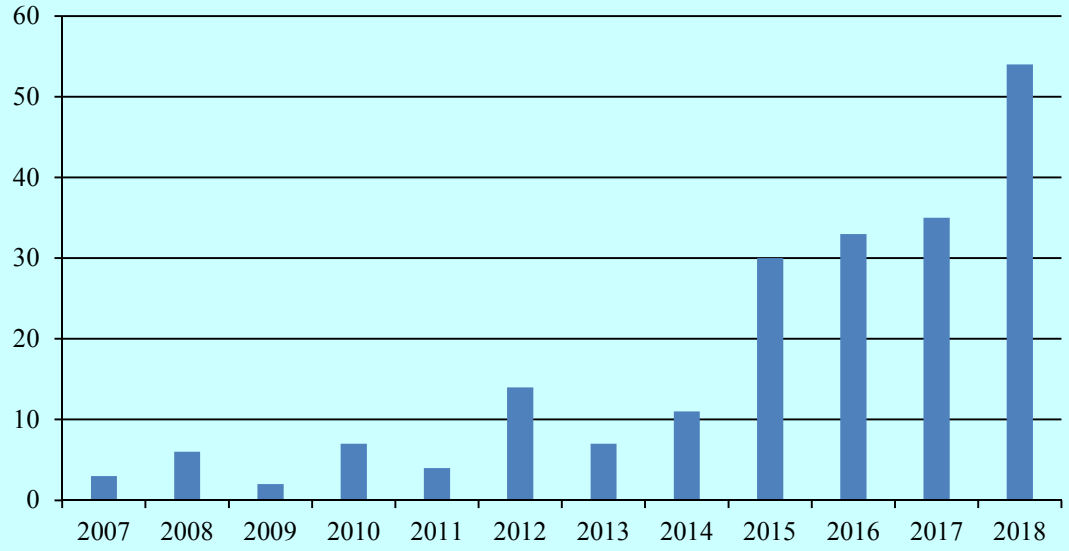

FIGURE 63. Number of cases with carbapenemase-producing *Enterobacterales* in Norway 2007-2018.

In total, 59 CPE isolates were identified in 2018. In three patients, two different carbapenemase-producing species were identified and in one patient three different species of CPE were identified. *Escherichia coli* (n=26) and *Klebsiella pneumoniae* (n=26) were the dominant species. Four, two and one carbapenemase-producing *Enterobacter* spp., *Citrobacter* spp. and *Klebsiella oxytoca* were identified, respectively (Figure 64).

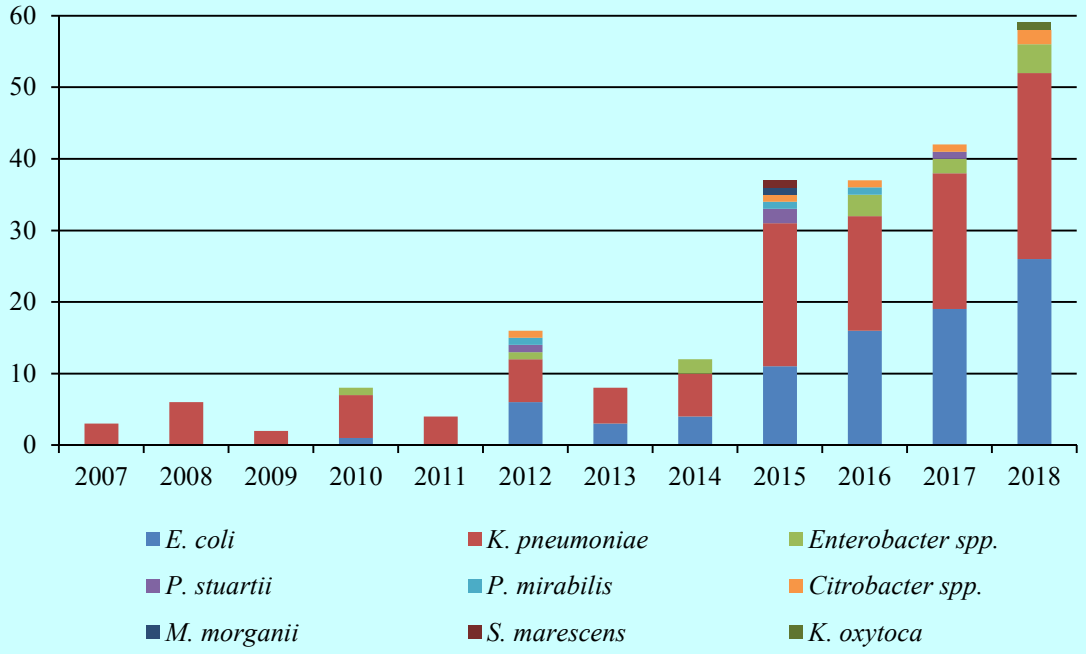

FIGURE 64. Number of carbapenemase-producing *Enterobacterales* isolates according to species.

OXA-48-like enzymes were identified in 39 isolates (Figure 65), including four isolates with both OXA-48-like and NDM. NDM was also identified in 15 additional isolates including one isolate also positive for KPC. Four additional cases were identified with KPC only. VIM was identified in a single isolate.

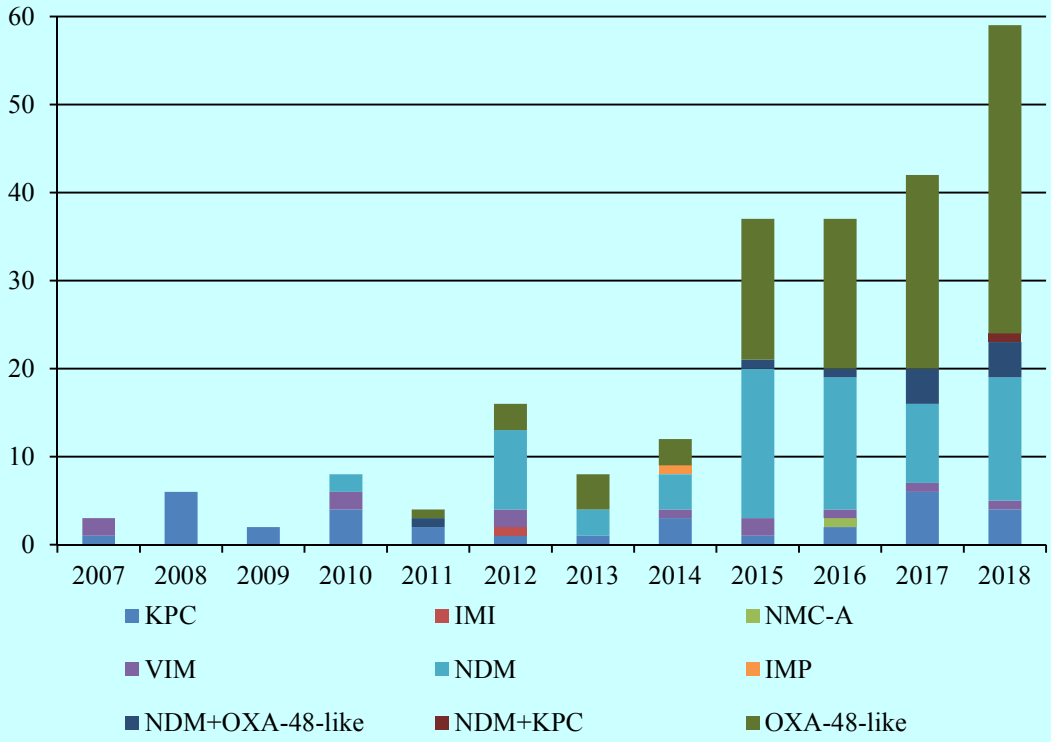

FIGURE 65. Number of carbapenemase-producing *Enterobacterales* isolates according to carbapenemase variant.

For one *E. coli* isolate, discrepancy between the phenotypic and genotypic profile was observed. The isolate was molecularly positive for both OXA-48-like and NDM. However, the phenotypic profile was characteristic of OXA-48-like production only with susceptibility to third and fourth generation cephalosporins. Immunochromatography tests showed that the NDM protein was not expressed.

Whole genome sequencing showed a large genetic diversity of the CPE isolates with 15 and 16 different sequence types among the *E. coli* (n=26) and *K. pneumoniae* (n=26) isolates, respectively. Along with the strong association with import this indicates limited transmission within Norway. A cluster (n=10) of OXA-48-producing *K. pneumoniae* ST392 was identified, where all cases were associated with import including seven associated with hospitalisation in Gran Canaria. Acquisition of OXA-48-producing *K. pneumoniae* ST392 associated to hospital admission in Gran Canaria was also observed in Sweden in 2018 (1).

Three cases of carbapenemase-producing *P. aeruginosa* were identified in 2018 compared to two cases in 2017 (Figure 66). All three cases were associated with infections caused by NDM-producing *P. aeruginosa*. Two of the cases were associated with import.

Carbapenemase-producing *Acinetobacter* spp. were identified in 19 patients in 2018 compared to eight in 2017. In total, 21 isolates were identified (Figure 66). In 12 cases the identification was linked to an infection. In two patients carbapenemase-producing *Acinetobacter* spp. of different species or the same species but different carbapenemase genes were identified. Thirteen isolates were carbapenemase-producing *Acinetobacter baumannii* including eleven harbouring OXA-23. With the exception of one isolate, all OXA-23 positive isolates were associated with import. Single isolates of *A. baumannii* harbouring OXA-72 (OXA-24 variant) or OXA-58 plus NDM were identified. The isolate with OXA-72 was associated with import.

In addition, eight isolates of NDM positive *Acinetobacter* non-*A. baumannii* were identified from seven patients. This included six *Acinetobacter lwoffii* and single isolates of *Acinetobacter pittii* and *Acinetobacter johnsonii*. For all cases no clear link to import was reported to MSIS and all cases were reported from two laboratories in the same regional health authority. Detailed investigation into these cases is ongoing.

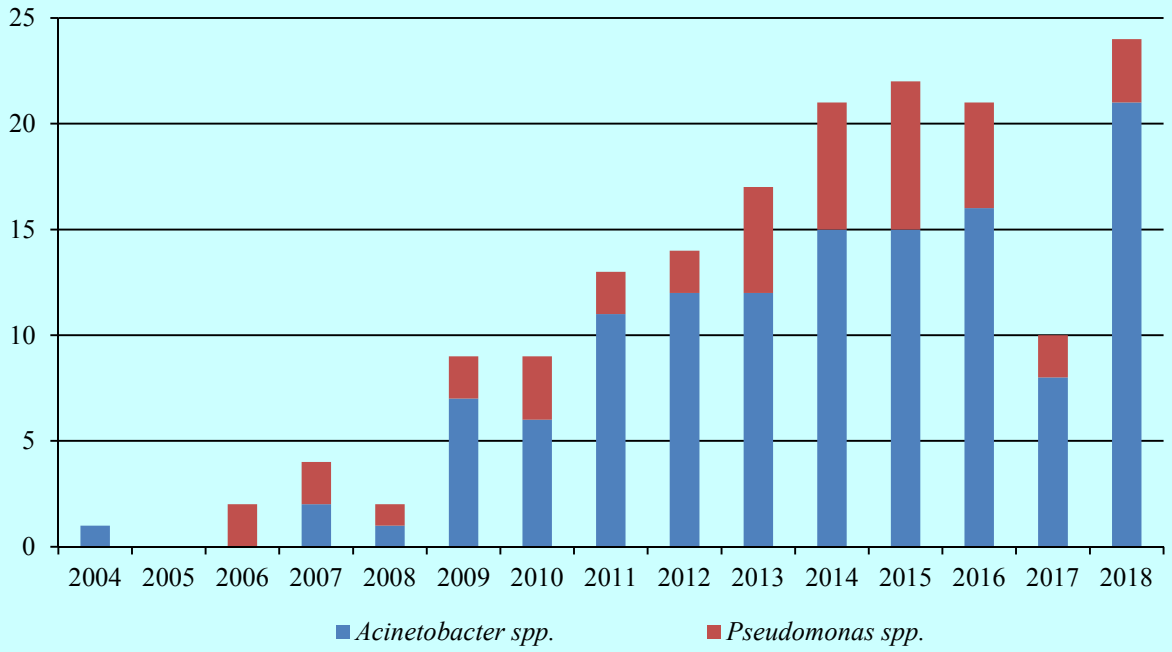

FIGURE 66. Identified carbapenemase-producing *Pseudomonas* spp. and *Acinetobacter* spp. in Norway 2004-2018.

In conclusion, an increase of carbapenemase-producing Gram-negative bacteria was observed in 2018 compared to 2017, but the overall number of cases is still low compared to other European countries (2). For CPE and *Pseudomonas* spp. there is no clear evidence of domestic spread. The observation of NDM positive *Acinetobacter* non-*A. baumannii* with no clear link to import is a concern and under investigation. A high level of continued surveillance, antibiotic stewardship, strict infection control measures as well as clinical and diagnostic awareness is important to prevent and control domestic spread.

References

1. World European Centre for Disease Prevention and Control. Rapid risk assessment: Carbapenemase-producing (OXA-48) *Klebsiella pneumoniae* ST392 in travellers previously hospitalised in Gran Canaria, Spain. – 10 July 2018, Stockholm. https://ecdc.europa.eu/sites/portal/files/documents/28-06-2018-RRA-Klebsiella-pneumoniae-Spain-Sweden-Finland-Norway.pdf
2. Brolund A, Lagerqvist N, Byfors S, Struelens MJ, Monnet DL, Albiger B, Kohlenberg A; European Antimicrobial Resistance Genes Surveillance Network EURGen-Net Capacity Survey Group. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. Euro Surveill. 2019; Feb:24(9). doi: 10.2807/1560-7917.ES.2019.24.9.1900123.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 35. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2018 (n=14). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 1	> 1	85.7	-	14.3
Amoxicillin-clavulanic acid	≤ 2	> 2	92.9	-	7.1
Cefuroxime	≤ 1	> 2	85.8	7.1	7.1
Cefotaxime	≤ 0.125	> 0.125	100.0	-	0.0
Ceftriaxone	≤ 0.125	> 0.125	92.9	-	7.1
Meropenem*	≤ 2	> 2	100.0	-	0.0
Ciprofloxacin	≤ 0.06	> 0.06	100.0	-	0.0
Chloramphenicol	≤ 2	> 2	100.0	-	0.0
Tetracycline	≤ 1	> 2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 1	78.6	7.1	14.3
Beta-lactamase	Negative	Positive	85.7	-	14.3

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

TABLE 36. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2018 (n=14). 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
Ampicillin						1	3	7	1				2			
Amoxi-clav*					1			5	6	1		1				
Cefuroxime			1					1	10	1		1				
Cefotaxime		1	7	5	1											
Ceftriaxone	8	4		1					1							
Meropenem			1		7	5	1									
Ciprofloxacin		8	6													
Chloramph.				1				2	7	4						
Tetracycline							1	13								
TMS**			2	5	4				1	1				1		

Shaded areas in each row indicate susceptibility with standard exposure (light), susceptibility with increased exposure (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. *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, but the sample for 2018 was limited to only 14 isolates due to reorganisation of the laboratory. The results are presented for SIR categorisation (%) and MIC distribution (n) in Tables 35-36, but the very low number of isolates does not warrant any further analyses or comparisons with previous years.

Neisseria gonorrhoeae

TABLE 37. *Neisseria gonorrhoeae* from all specimen types in 2018 (n=315). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.06	> 1	1.0	88.3	10.7
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	98.7	-	1.3
Ciprofloxacin	≤ 0.03	> 0.06	31.1	0.0	68.9
Tetracycline	≤ 0.5	> 1	44.4	35.9	19.7
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	91.4	-	8.6

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

TABLE 38. *Neisseria gonorrhoeae* from all specimen types in 2018 (n=315). 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*			0.6	0.3	1.6	12.4	23.2	39.0	12.1	2.9	0.6	0.3	0.6	6.3		
Ceftriaxone	42.5	12.4	17.1	24.1	2.9	1.0										
Cefixime			50.5	16.2	20.6	11.4	1.3									
Ciprofloxacin	27.0	2.5	1.6				0.3	2.5	21.6	26.3	8.3	5.7	0.6	3.5		
Tetracycline					1.0	4.1	10.8	28.6	35.9	8.6	0.3	1.0	3.5	4.8	1.6	
Spectinomycin											0.3	16.2	80.6	2.9		
Azithromycin			0.3	0.6	3.2	7.6	45.7	28.9	7.9	3.5	1.9					0.3

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

RESULTS AND COMMENTS

Neisseria gonorrhoeae was surveyed in NORM in 2003 and 2010, and then yearly since 2013. In 2018, only samples submitted to Oslo University Hospital were analysed and included in the statistics. This may introduce a bias as the results are limited to the South-Eastern part of Norway. The data were submitted to NORM by the reference laboratory at the Norwegian Institute of Public Health. Only a single isolate was included from each patient. The microbiological data could not be linked to information in the Norwegian Surveillance System for Communicable Diseases (MSIS).

In 2018, a total of 315 isolates were available for analysis. The isolates were reported to originate from urethra (n=130), cervix uteri (n=20), anus (n=108), throat (n=44), eye (n=1) or "others/uknown" (n=12). A total of 248 (78.7%) isolates originated from men, 24 (7.6%) from women and 43 (13.7%) from unknown gender. The geographical location where the infection was acquired was in most cases unknown to the laboratory. From MSIS it is reported that gonococcal infections frequently are acquired abroad with secondary transmission in sexual networks within Norway. There is an ongoing outbreak among men who have sex with men, but the strains linked to this outbreak could not be identified in the NORM protocol.

The results from susceptibility testing are presented in Tables 37-38. A majority of isolates were either susceptible to increased exposure (88.3%) or resistant (10.7%) to penicillin G. The corresponding figures for 2017 were 81.5% and 16.6%, respectively. Twenty-seven isolates (8.6%) produced beta-lactamase and were phenotypically resistant to penicillin G. This is a decrease from 23.6% in 2016 and 15.3% in 2017, but the findings should be interpreted with caution due to the limited number of isolates from one region of the country. Most beta-lactamase positive isolates (25/27) were also resistant to ciprofloxacin. Seven isolates were resistant and 278 were only susceptible to increased exposure to penicillin G in spite of being beta-lactamase negative. This illustrates the alternative mechanisms for penicillin resistance, such as alterations in penicillin binding proteins (PBPs) and/or reduced permeability through the outer cell membrane.

No isolates were categorised as resistant to ceftriaxone. Ceftriaxone resistant isolates from Norway have previously been linked to treatment failure. Four isolates (1.3%) were resistant to the oral cephalosporin cefixime compared to two isolates in 2017. Cefixime is no longer recommended for empirical treatment in Norway. The results confirm the emergence of cephalosporin resistant gonococci in Norway, which is extremely alarming from both a clinical and a public health perspective.

The current European treatment guidelines recommend empirical combination treatment with ceftriaxone and azithromycin. It should be noted that 5.7% of the isolates displayed azithromycin MIC values above the EUCAST screening breakpoint for acquired resistance at 1 mg/L. The corresponding figure for 2017 was 4.7%.

Ciprofloxacin was previously used for empirical treatment of gonorrhoeae acquired outside South-East Asia. The prevalence of ciprofloxacin resistance persisted at a high level (68.9%) in 2018. 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 39. *Staphylococcus aureus* blood culture isolates in 2018 (n=1,445). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 2	94.4	0.3	5.3
Clindamycin	≤ 0.25	> 0.5	98.4	0.6	1.0
Fusidic acid	≤ 1	> 1	97.0	-	3.0
Ciprofloxacin	≤ 1	> 1	95.6	-	4.4
Gentamicin	≤ 1	> 1	99.4	-	0.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	98.9	0.8	0.3
Tetracycline	≤ 1	> 2	95.9	0.4	3.7
Tigecycline	≤ 0.5	> 0.5	99.3	-	0.7
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.5	0.2	0.3
Beta-lactamase	Negative	Positive	30.2	-	69.8
Cefoxitin screen	≥ 22	< 22	99.2	-	0.8
MRSA (*mecA*)	Negative	Positive	99.2	-	0.8

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

RESULTS AND COMMENTS

Eleven methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2018, corresponding to a prevalence of 0.8% (Table 39). This is at the same level as in 2016 (1.0%) and 2017 (0.8%). The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from seven 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 (7/11), clindamycin (3/11), ciprofloxacin (3/11), gentamicin (2/11) and/or tetracycline (1/11). All MRSA isolates were susceptible to fusidic acid, tigecycline, trimethoprim-sulfamethoxazole, linezolid and rifampicin. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 43 on page 106. 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 17 out of 2,044 (0.8%) *S. aureus* blood culture isolates were MRSA. None of the 11 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 17/2,055 (0.8%). This is at the same level as in 2017 (1.0%).

Seventy-seven *S. aureus* isolates (5.3%) were resistant to erythromycin. This is an increase from 3.0% in 2017, but at the same level as 5.5% in 2015 and 5.2% in 2016. The macrolide resistance phenotypes of erythromycin resistant isolates were determined by the double disk diffusion (DDD) test. Five isolates (6%) were constitutively MLS_B resistant, 59 (77%) were inducibly MLS_B resistant and 13 (17%) displayed efflux mediated M-type resistance. These figures represent 0.3%, 4.1% and 0.9% of all *S. aureus* isolates from blood cultures, respectively. The distribution of MLS phenotypes was essentially unchanged from 2017 to 2018.

The prevalence of resistance to fusidic acid at 3.0% was a further decrease from 4.5% in 2016 and 4.1% in 2017. The 4.4% prevalence of ciprofloxacin resistance was a slight increase from 3.6% in 2017, but below 6.9% in 2016. There were no significant changes for gentamicin, rifampicin, tigecycline or trimethoprim-sulfamethoxazole. All isolates were linezolid susceptible. The general test panel for *S. aureus* did not include vancomycin in 2018.

Figure 67 shows the prevalence of resistance to various antimicrobials. A total of 69.8% of the isolates were beta-lactamase positive, which is at the same level as 70.3% in 2017. There were only minor differences in the prevalence of resistance to non-beta-lactam antibiotics between beta-lactamase positive and negative isolates.

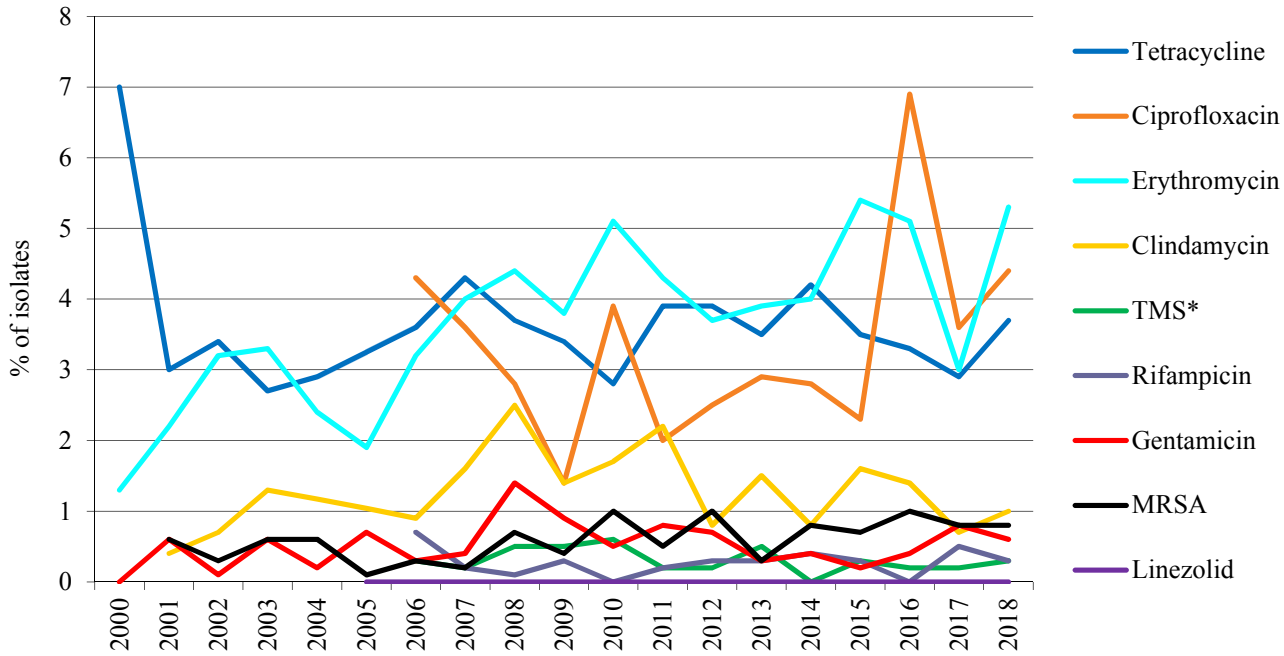

FIGURE 67. Prevalences of antimicrobial resistance among *Staphylococcus aureus* blood culture isolates 2000-2018. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 40. *Staphylococcus aureus* isolates from wound specimens in 2018 (n=992). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 2	94.4	0.1	5.5
Clindamycin	≤ 0.25	> 0.5	98.2	0.6	1.2
Fusidic acid	≤ 1	> 1	94.1	-	5.9
Ciprofloxacin	≤ 1	> 1	97.3	-	2.7
Gentamicin	≤ 1	> 1	99.4	-	0.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.5	0.4	0.1
Tetracycline	≤ 1	> 2	96.3	0.1	3.6
Tigecycline	≤ 0.5	> 0.5	99.8	-	0.2
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.5	0.2	0.3
Beta-lactamase	Negative	Positive	27.4	-	72.6
Cefoxitin screen	≥ 22	< 22	98.3	-	1.7
MRSA (*mecA*)	Negative	Positive	98.3	-	1.7

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

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. Seventeen out of 992 (1.7%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at the same level as in 2016 (1.6%) and 2017 (1.2%). The MRSA isolates originated from patients visiting general practitioners (n=11), hospital wards (n=4), an outpatient clinic (n=1), and an unknown location (n=1) in different parts of the country. Most MRSA isolates were co-resistant to tetracycline (7/17), erythromycin (6/17), ciprofloxacin (5/17), fusidic acid (2/17) and/or clindamycin (1/17) in different combinations. All MRSA isolates were susceptible to 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 106).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates decreased from 6.3% in 2017 to 5.9% in 2018 (Table 40 and Figure 68). 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 (3.0 %). For other antimicrobial agents such as trimethoprim-sulfamethoxazole, gentamicin, rifampicin, and tetracycline there were only minor changes from 2017 to 2018, and the prevalence of resistance was in general similar for blood culture isolates and isolates from wound specimens. A single isolate displayed a disk diffusion diameter below the breakpoint for linezolid resistance, but it was verified as susceptible by MIC testing (1 mg/L).

Fifty-five (5.5%) isolates were resistant to erythromycin, which is unchanged from 5.3% in 2017. They were all further examined for determination of resistance phenotype and the majority were either inducibly (38/55, 69% of erythromycin resistant isolates) or constitutively (5/55, 9% of erythromycin resistant isolates) resistant to clindamycin, thus representing the $iMLS_B$ and $cMLS_B$ phenotypes, respectively. A minor proportion of the isolates displayed low-level resistance to erythromycin only (12/55, 22% of erythromycin resistant isolates) compatible with efflux mediated M-type resistance. The findings are in accordance with the results from previous years.

A total of 72.6% of the isolates were beta-lactamase positive compared to 74.6% in 2017. Beta-lactamase positive isolates were more likely to be resistant to tetracycline (4.3%) and ciprofloxacin (3.2%) compared to beta-lactamase negative isolates (1.8% and 1.5%, respectively). For the other antimicrobials there were only minor differences.

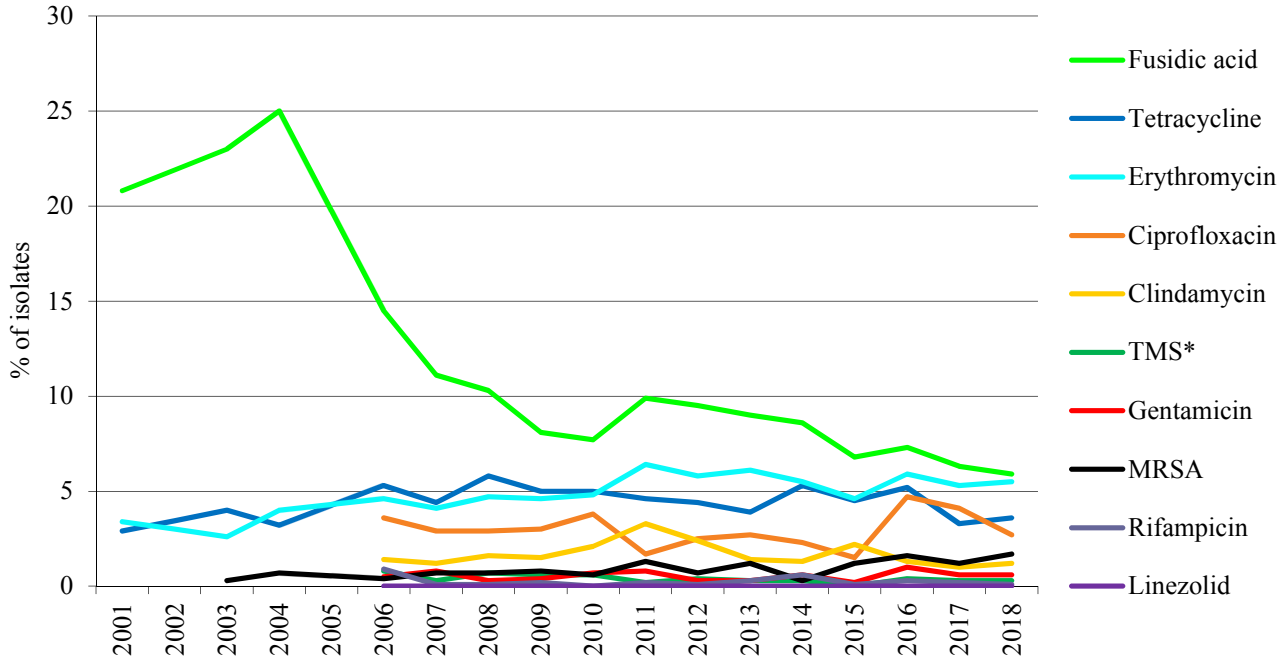

FIGURE 68. Prevalence of antimicrobial resistance among *Staphylococcus aureus* wound isolates 2001-2018. Doxycycline was replaced by tetracycline in 2006. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2018

The total number of people notified to MSIS with MRSA in 2018 was the same as in the last two years (Figure 69). In all, 2,567 notifications from 2,301 persons were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2018, an incidence rate of 48 persons per 100,000 person years. Of these, 905 (36%) patients were notified with clinical infections while 1,631 were colonised. The incidence rate of MRSA infections (not including colonisation) has plateaued in the last four years.

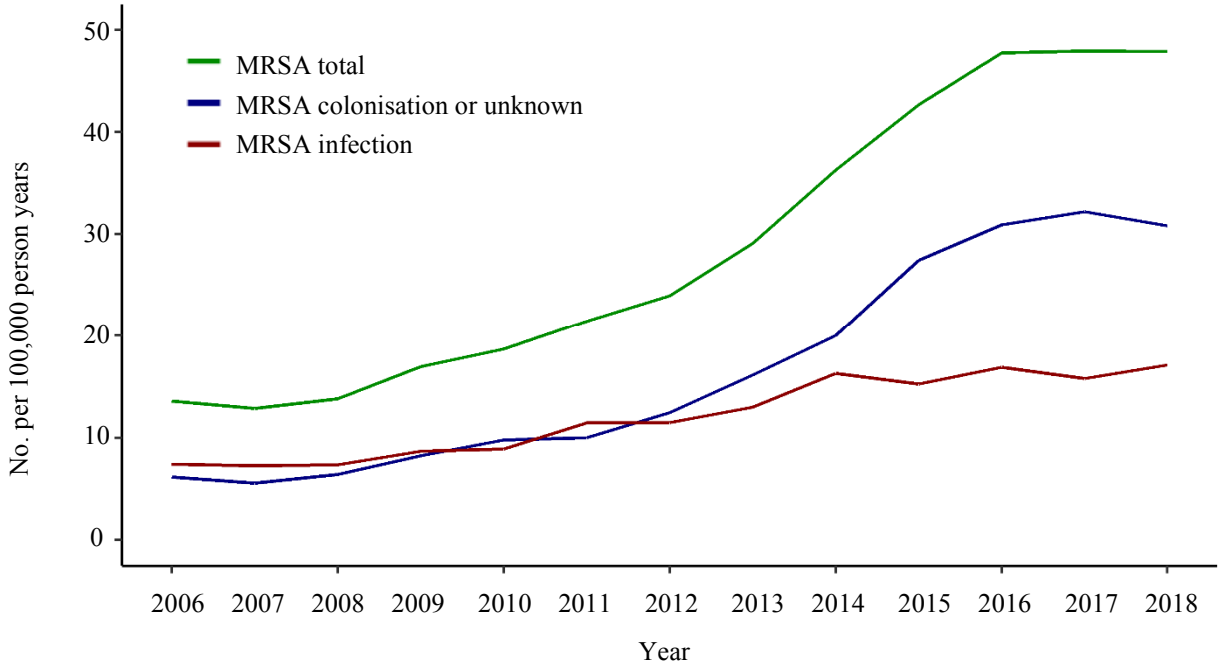

FIGURE 69. Number of persons notified with MRSA per 100,000 person years in Norway 2006-2018, by infection and colonisation.

The main objective of the Norwegian MRSA infection control measures is to prevent MRSA from becoming endemic in healthcare institutions. As in previous years, most people were diagnosed by their general practitioners. In 2018, 479 (19%) of all persons notified with MRSA were inpatients at the time of diagnosis. Forty-seven (2%) were residents in nursing homes and 2,010 (79%) were diagnosed in general practice. In total, 87 were reported to be healthcare workers.

Norway has implemented surveillance of MRSA in swine farms. In 2018, 20 persons were diagnosed with MRSA strains associated with livestock (PVL-negative MRSA CC398, or spa-types within CC1 previously identified in Norwegian livestock). Of these, 15 were reported as either infected in Norway or it was not known where they had been infected. No persons identified with possible livestock associated MRSA were notified with a severe infection.

During the last ten years an increasing number of people identified with MRSA in Norway are assessed to be infected in other countries. The incidence rate of persons infected with MRSA in Norway has not increased over the last four years (Figure 70). 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 microbiology laboratories, missing information from medical practitioners for a large part of the cases limits the possibility to use data in MSIS to follow trends regarding places of infection or clinical outcome of MRSA.

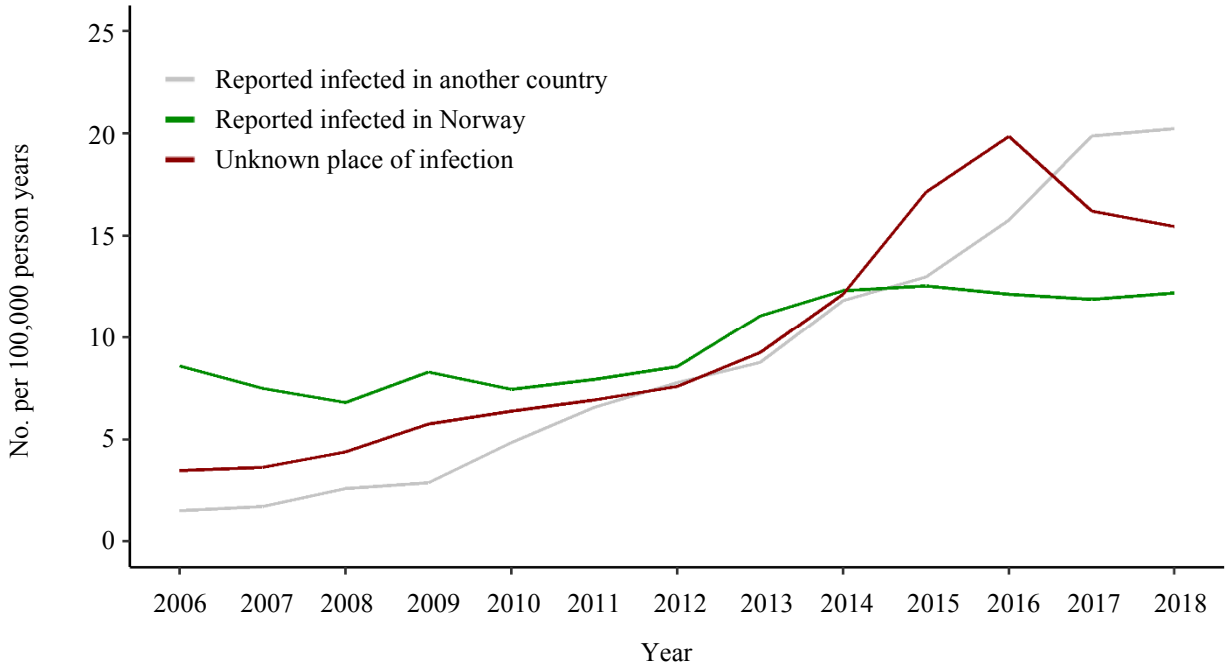

FIGURE 70. Incidence rate (number of persons notified per 100,000 person years) of MRSA in Norway 2006-2018, by place of infection.

The Norwegian Reference Laboratory for Methicillin Resistant *Staphylococcus aureus* (MRSA) at St. Olavs Hospital, Trondheim University Hospital, received 2,725 MRSA isolates in 2018. Genotyping was performed on selected isolates. In total, 1,382 isolates were prioritised for genotyping (*spa*-typing), and the main part of these were isolates from infections. Additionally, 329 isolates were randomly selected for genotyping and 24 isolates were genotyped by request from local microbiology laboratories. Among the genotyped isolates, 344 different *spa*-types were identified. One-hundred ninety-three *spa*-types were reported as single events, and 121 *spa*-types were reported from two to ten times. Only 30 *spa*-types were reported more than 10 times (Table 41).

TABLE 41. The 10 most common *spa*-types in Norway in 2018.

spa-type	CC	No. of isolates	% of total*
t002	5	150	8.7 %
t304	6	124	7.2 %
t008	8	120	6.9 %
t127	1	110	6.3 %
t223	22	109	6.3 %
t019	30	67	3.9 %
t437	59	46	2.7 %
t034	398	44	2.5 %
t044	80	30	1.7 %
t105	5	30	1.7 %

* % of isolates genotyped.

Based on *spa*-type, the isolates were assigned to multilocus sequence type (MLST) and clonal complex (CC) (Table 42). The 10 most prevalent CCs comprised 1,526 isolates (88.0%).

TABLE 42. The 10 most common clonal complexes (CC) in Norway in 2018.

CC	*spa*-types grouped in CC*	No. of isolates	% of total
5	t002 (150), t105 (30), t688 (19), t442 (10), t010 (8)	293	16.9
22	t223 (108), t005 (25), t852 (16), t4450 (16), t309 (8)	231	13.3
8	t008 (120), t024 (20), t1476 (9), t4549 (6), t068 (4)	208	12.0
1	t127 (110), t657 (29), t386 (11), t345 (8), t5414 (7)	201	11.6
30	t019 (67), t021 (25), t363 (13), t665 (13), t1752 (7)	154	8.9
6	t304 (124), t711 (6), t4562 (3), t11475 (3), t13429 (2)	143	8.2
88	t690 (21), t786 (10), t186 (9), t1339 (6), t692 (5)	87	5.0
45	t1081 (14), t015 (13), t004 (9), t026 (8), t2275 (6)	86	4.9
59	t437 (46), t172 (4), t18180 (3), t441 (2), t1151 (2)	64	3.7
398**	t034 (44), t011 (11), t571 (2), t2876 (1), t18284 (1)	59	3.4

* The five most common *spa*-types in each CC (n). **All isolates from pasients with association to livestock are genotyped.

The MRSA reference laboratory identified 26 Livestock Associated MRSA (LA-MRSA) (CC398, PVL (Panton-Valentine leucocidin) negative) in humans, of *spa*-type t034 (n=14), t011 (n=10), t2876 (n=1) and t18484 (n=1). Three isolates were positive for *mecC* (*spa*-type t6292 and t843), two were human isolates, and one was received from the Norwegian Veterinary Institute.

Antimicrobial susceptibility testing was performed by the local laboratories according to the EUCAST 2018 disk diffusion method and the NordicAST 2018 breakpoints.

The MRSA reference laboratory received 2,556 complete antibiograms. Among these strains, 1,092 (41.5%) were sensitive to all antibiotics tested except beta-lactams (cefoxitin). The highest proportion of resistance was found for erythromycin (32.3%), followed by tetracycline (24.5%) and ciprofloxacin (21.5%). The lowest rate of resistance was found for rifampicin (0.5%), mupirocin (0.7%) and trimethoprim-sulfamethoxazole (1.3%). No isolates showed decreased susceptibility to linezolid or vancomycin in 2018.

TABLE 43. MRSA isolates from human cases in 2018 (n=2,617). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Erythromycin	≤ 1	> 2	67.5	0.2	32.3
Clindamycin	≤ 0.25	> 0.5	89.9	2.0	8.1*
Fusidic acid	≤ 1	> 1	88.9	-	11.1
Ciprofloxacin	≤ 1	> 1	78.5	-	21.5
Gentamicin	≤ 1	> 1	88.8	-	11.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.0	0.5	0.5
Tetracycline	≤ 1	> 2	75.2	0.3	24.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	97.4	1.3	1.3
Mupirocin	≤ 1	> 256	96.8	2.5	0.7
Vancomycin	≤ 4	> 4	100.0	-	0.0

S=Susceptible with standard exposure, I=Susceptible with increased exposure, R=Resistant. *Due to an error, the proportion of clindamycin resistant strains was reported to be 21.9% in 2017. The correct number should have been 9.6%. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

Enterococcus spp. in blood cultures

TABLE 44. *Enterococcus* spp. blood culture isolates in 2018 (n=638). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	81.7	0.2	18.2
Imipenem	≤ 4	> 8	79.8	0.9	19.3
Gentamicin HLR*	≤ 128	> 128	82.4	-	17.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	99.5	-	0.5
Vancomycin (any genotype)	≤ 4	> 4	97.5	-	2.5
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.5	-	0.5

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

TABLE 45. *Enterococcus faecalis* blood culture isolates in 2018 (n=454). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Imipenem	≤ 4	> 8	99.3	0.0	0.7
Gentamicin HLR*	≤ 128	> 128	85.9	-	14.1
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	99.6	-	0.4
Vancomycin (*vanA* or *vanB*)	Negative	Positive	100.0	-	0.0

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

TABLE 46. *Enterococcus faecium* blood culture isolates in 2018 (n=150). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	24.0	0.7	75.3
Imipenem	≤ 4	> 8	19.3	2.0	78.7
Gentamicin HLR*	≤ 128	> 128	68.0	-	32.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.25	99.3	-	0.7
Vancomycin (*vanA* or *vanB*)	Negative	Positive	98.0	-	2.0

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

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a genus and separately for *E. faecalis* and *E. faecium*. The results for each species are microbiologically more valid as resistance rates differ significantly between *E. faecalis* and *E. faecium*. However, overall rates of resistance are of interest when formulating empirical treatment strategies because they include the probability of systemic infections with each enterococcal species. The overall results for enterococci are presented in Table 44. The surveillance in NORM 2018 included 454 (71.2%) *E. faecalis* isolates (66.2% in 2017), 150 (23.5%) *E. faecium* isolates (28.1% in 2017) and 34 (5.3%) unspeciated enterococcal isolates (5.7% in 2017). 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, 2.4 in 2017 and 3.0 in 2018. This is within the variation seen in previous years. The panel of antimicrobial agents examined and the breakpoints for interpretation remained unchanged from 2017 to 2018.

E. faecalis was universally susceptible to ampicillin (Table 45). The prevalence of resistance to ampicillin in *E. faecium* was 75.3% in 2018 compared to 80.9% in 2016 and 72.9% in 2017 (Table 46). As expected, the results for imipenem closely mirrored those for ampicillin. The prevalence of

high-level gentamicin resistance (HLGR) in *E. faecalis* was 14.1%, which is a slight decrease from 18.8% in 2016 and 15.5% in 2017 (Figure 71). The prevalence of HLGR in *E. faecium* has also slowly declined over the last years and dropped to 32.0% in 2018. All 48 HLGR *E. faecium* isolates were concomitantly resistant to ampicillin and imipenem. Conversely, 48 of 113 (42.5%) ampicillin resistant *E. faecium* also displayed HLGR. High-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and beta-lactams often used for treatment of severe entero-coccal 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. Sixteen blood culture isolates were reported as vancomycin resistant in NORM 2018 (2.5%), but only three of these were confirmed by PCR to harbour transferable vancomycin resistance (all *vanB E. faecium*). The three *vanB* isolates were isolated at separate hospitals. The remaining thirteen vancomycin resistant isolates were either *E. gallinarum* (n=9) or *E. casseliflavus* (n=4), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All enterococcal isolates were susceptible to linezolid.

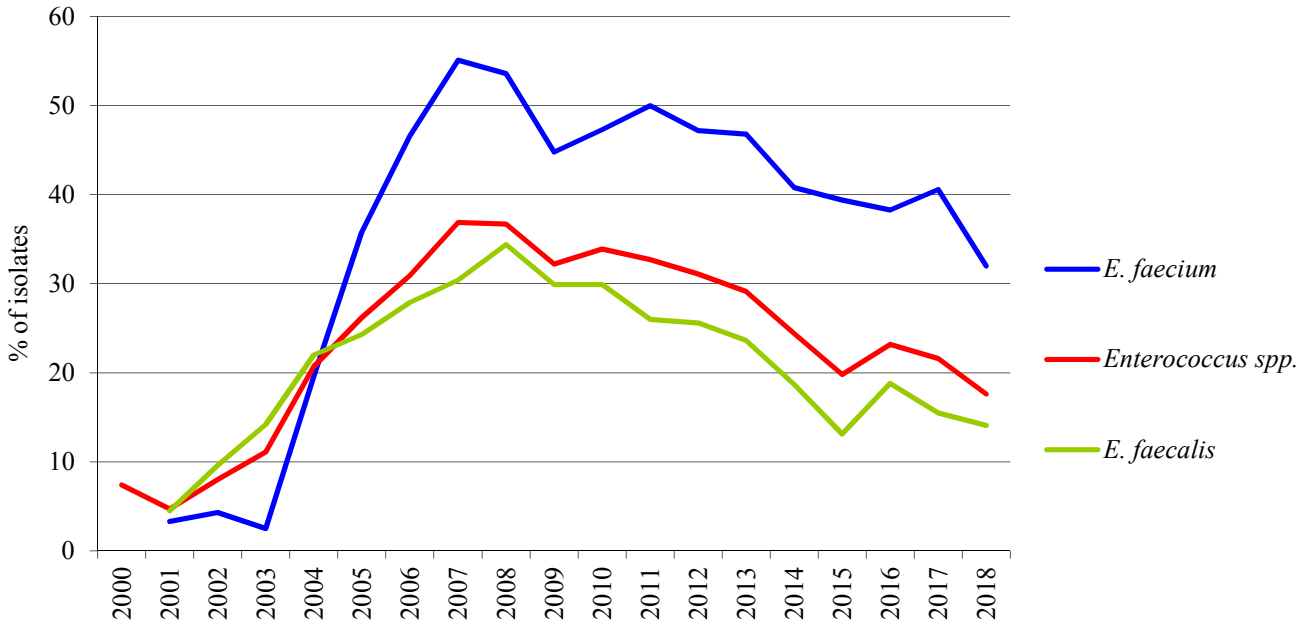

FIGURE 71. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2018. The breakpoint was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Enterococcus spp. in urine

TABLE 47. *Enterococcus* spp. urinary tract isolates in 2018 (n=1,024). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	95.9	0.0	4.1
Gentamicin HLR*	≤ 128	> 128	86.3	-	13.7
Ciprofloxacin	≤ 4	> 4	88.5	-	11.5
Trimethoprim	≤ 1	> 1	78.5	-	21.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin (any genotype)	≤ 4	> 4	99.9	-	0.1
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.9	-	0.1

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

TABLE 48. *Enterococcus faecalis* urinary tract isolates in 2018 (n=967). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Gentamicin HLR*	≤ 128	> 128	86.0	-	14.0
Ciprofloxacin	≤ 4	> 4	91.6	-	8.4
Trimethoprim	≤ 1	> 1	80.9	-	19.1
Nitrofurantoin	≤ 64	> 64	99.7	-	0.3
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin (*vanA* or *vanB*)	Negative	Positive	99.9	-	0.1

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

TABLE 49. *Enterococcus faecium* urinary tract isolates in 2018 (n=51). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Ampicillin	≤ 4	> 8	19.2	0.0	80.8
Gentamicin HLR*	≤ 128	> 128	90.4	-	9.6
Ciprofloxacin	≤ 4	> 4	27.5	-	72.5
Trimethoprim	≤ 1	> 1	35.3	-	64.7
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin (*vanA* or *vanB*)	Negative	Positive	100.0	-	0.0

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

RESULTS AND COMMENTS

Enterococcal urinary tract isolates have previously been surveyed in NORM in 2001, 2010 and 2015. The results from 2001 were not stratified by species, and the breakpoints have also changed considerably over the years. Comparisons over time are therefore of limited value.

The proportion of *E. faecalis* was significantly higher (94.5%) among urinary tract isolates than in blood cultures (71.2%). The proportion of *E. faecium* was correspondingly lower (5.0% in urine versus 23.5% in blood cultures), and there were very few enterococcal isolates from urine that were either unspeciated or belonged to species other than *E. faecalis* and *E. faecium* (0.5%).

E. faecalis isolates from urine were uniformly susceptible to ampicillin, and the prevalence of high-level gentamicin resistance (HLGR) (14.0%) was at the same level as in blood cultures (14.1%). The prevalence of HLGR has not changed since 2015 (14.0%). The rates of ampicillin resistance were also similar in *E. faecium* urinary tract and blood culture isolates (approximately 80%). There were too few isolates to conclude about the difference in *E. faecium* high-level gentamicin resistance (32.0% in blood cultures, 9.6% in urine).

The clinical benefit of trimethoprim and trimethoprim-sulfamethoxazole in the treatment of enterococcal urinary tract infections is uncertain. According to the ecological cut-off value (ECOFF) issued by EUCAST, 19.1% of *E. faecalis* and 64.7% of *E. faecium* isolates displayed zone diameters above the ECOFF. Ciprofloxacin breakpoints are only valid for uncomplicated urinary tract infections. Most *E. faecalis* isolates (91.6%) appeared susceptible by this definition, whereas *E. faecium* isolates were generally resistant (72.5%). There are no previous ciprofloxacin results for comparison in NORM. Almost all *E. faecalis* isolates (99.7%) were susceptible to nitrofurantoin, but this agent is not suitable for treatment of *E. faecium* infections. All enterococcal isolates remained susceptible to linezolid, and only a single *vanB E. faecalis* displayed transferable vancomycin resistance.

Linezolid resistant enterococci in Norway 2018

Enterococci are the third most common bacterial cause of hospital associated infections in Europe (1). They are intrinsically resistant to many antimicrobial agents and readily acquire resistance towards new clinically important antimicrobials (2). Linezolid is considered a last resort treatment in infections caused by multi-resistant enterococci, in particular vancomycin resistant enterococci. The prevalence of linezolid resistant enterococci is still low (<1%) worldwide (3), but is increasing in many countries (4,5).

Linezolid binds to the ribosome and inhibits bacterial protein synthesis. Acquired resistance to linezolid may be due to structural changes in the ribosome based on mutations in the ribosomal RNA and/or ribosomal proteins as well as through gene products that chemically modify (methylate) the ribosome (*cfr*). Another type of resistance mechanism is due to proteins (encoded by *optrA* and *poxtA*) that protect the ribosome against binding of linezolid. The *cfr*, *optrA* and *poxtA* genes can all be localised on mobile genetic elements (4,6,7).

In Norway, linezolid resistant enterococci (LRE) 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).

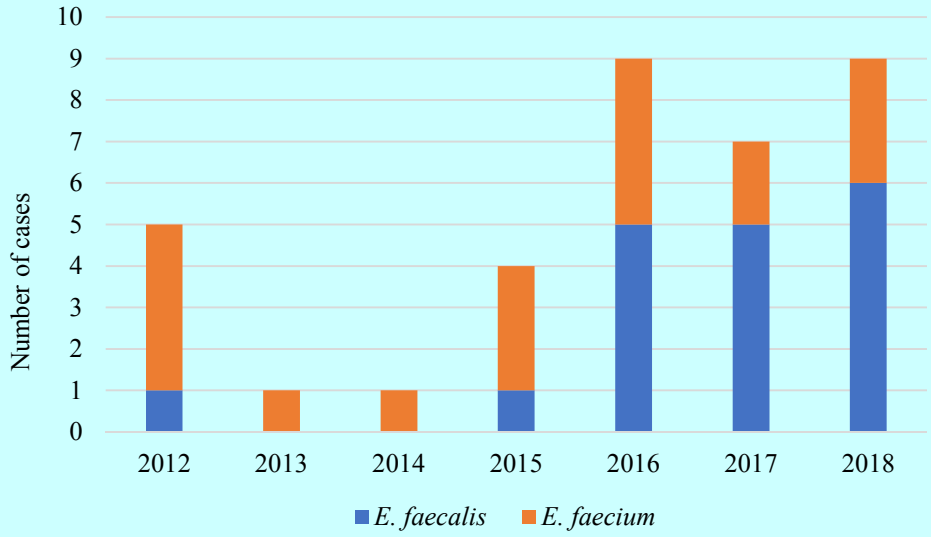

FIGURE 72. Number of linezolid resistant enterococci (LRE), by species, in Norway 2012-2018. This overview also includes LRE that are vancomycin resistant.

In 2018 nine cases of LRE were detected in Norway (Figure 72). Phylogenetic analyses revealed isolates with the same sequence type (ST), but not closely related to each other. There has been an increase in LRE per year as of 2016 and simultaneously the species distribution changed from predominantly *E. faecium* towards *E. faecalis*. The increase in *E. faecalis* LRE in Norway as of 2016 (n=15) is due to non-clonal spread of isolates with *optrA* (n=14) (Figure 73).

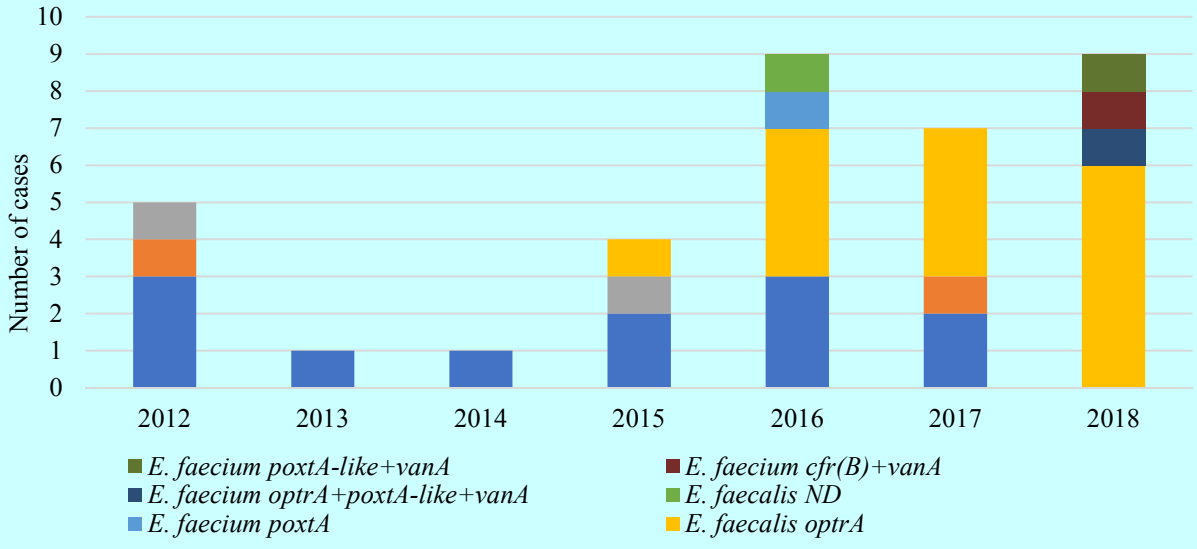

FIGURE 73. Number of linezolid resistant enterococci (LRE) according to resistance mechanisms per year. ND = Not determined genotype. This isolate was not sent to K-res or archived at the primary laboratory.

Linezolid resistance in enterococci has traditionally mostly been mediated by point mutations in the 23S rRNA region, mainly the G2576U mutation. Mutations are known to occur after long-term exposure to linezolid (8). Isolates with mutational linezolid resistance were not reported in 2018. In the 2018 isolates (n=9) linezolid resistance was due to *optrA*, *cfr(B)* and an unknown probably transferable mechanism (*poxtA*-like) that we are investigating further (Figure 73). Three of these isolates (all *optrA*) were from infections whereas the rest were carrier isolates. Five isolates were found in patients who were probably infected abroad. The *E. faecium* isolates (n=3) belonged to the same hospital associated sequence type (ST80). All *E. faecalis* isolates reported in 2018 (n=6) had *optrA*, but belonged to four different ST types with ST16 (n=3) being most common (Table 50). Internationally, *E. faecalis* ST16 has been reported to be the most prevalent ST type associated with *optrA* (9).

TABLE 50. Species, resistance mechanism and sequence type among LRE in Norway 2018.

Species	Resistance mechanism	ST
E. faecalis (*n*=6)	*optrA* (*n*=6)	ST16 (*n*=3); ST314 (*n*=1); ST480 (*n*=1); ST631(*n*=1)
E. faecium (*n*=3)	*optrA*+*poxtA*-like (*n*=1); *cfr(B)* (*n*=1); *poxtA*-like (*n*=1)	ST80 (*n*=3)

In conclusion, the number of LRE reported in Norway per year is still low. Since 2016 there has been a change from *E. faecium* with mutation-based linezolid resistance to finding of LRE with transferable resistance mechanisms dominated by *E. faecalis* with *optrA*. The change towards LRE with transferable resistance mechanisms is not due to domestic spread.

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Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 51. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2018 (n=168). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.06	> 2	91.1	8.3	0.6
Cefotaxime	≤ 0.5	> 2	98.2	1.8	0.0
Ceftriaxone	≤ 0.5	> 2	99.4	0.6	0.0
Erythromycin	≤ 0.25	> 0.5	94.0	0.0	6.0
Clindamycin	≤ 0.5	> 0.5	95.2	-	4.8
Tetracycline	≤ 1	> 2	93.4	0.6	6.0
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	93.4	1.2	5.4
Chloramphenicol	≤ 8	> 8	99.4	-	0.6
Oxacillin screen (mm)	≥ 20	< 20	88.1	-	11.9

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

TABLE 52. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2018 (n=168). 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			55.4	32.7	3.0	1.8	4.2	0.6	1.2	0.6	0.6					
Cefotaxime		1.2	76.8	11.3	3.0	3.0	2.4	0.6	1.8							
Ceftriaxone		4.2	83.9	1.8	3.0	3.6	1.2	1.8	0.6							
Erythromycin					11.9	78.6	3.6				0.6	0.6				4.8
Clindamycin				0.6	4.2	69.6	20.8									4.8
Tetracycline				0.6	5.4	86.3	1.2			0.6		1.2	2.4	2.4		
TMS*					0.6	44.0	45.2	1.8	1.8	1.2	1.8	0.6	0.6	2.4		
Chloramph.									0.6	20.8	78.0		0.6			
Norfloxacin										1.2	25.0	62.5	10.1	1.2		

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	11.9				4.2	15.5	22.6	11.3	19.0	11.3	1.8	1.8	0.6			

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

RESULTS AND COMMENTS

All systemic *S. pneumoniae* isolates in Norway are submitted to the National Reference Laboratory for Pneumococci at the Norwegian Institute of Public Health, but the 2018 sample only included the first three months of the year due to reorganisation of the laboratory. The results should therefore be interpreted with caution.

The results are summarised in Tables 51-52 and Figures 74-75. Seven strains were isolated from cerebrospinal fluids and three were isolated from other materials. Three of these ten 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 2018. 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 8.3% (14/168) of *S. pneumoniae* isolates were only susceptible to penicillin G with increased exposure (MIC 0.125-2 mg/L), and a single isolate was classified as resistant (MIC 4 mg/L). These rates are at the same level as in 2017 (combined 9.7% and 8.9% in 2017 and 2018, respectively). The penicillin G resistant isolate was also categorised as I for cefotaxime and ceftriaxone (MIC 1 mg/L for both substances). One isolate recovered from a cerebrospinal fluid had penicillin G MIC 0.25 mg/L and was thus clinically resistant according to the menigitis breakpoint, but it was susceptible to third generation cephalosporins. Two additional blood culture isolates were only susceptible to increased exposure to cefotaxime.

The oxacillin screening disk is often used to differentiate isolates susceptible to standard penicillin G doses from isolates that are resistant or require increased exposure. All the 15 penicillin G I + R isolates were resistant to oxacillin. Conversely, 5/153 penicillin G S isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 100% and 96.7%, respectively. Many of the *S. pneumoniae* isolates with reduced susceptibility to

penicillin G were also resistant to erythromycin (7/15), tetracycline (7/15), clindamycin (6/15) and/or trimethoprim-sulfamethoxazole (6/15).

The prevalence of erythromycin resistance was relatively stable at 6.0% in 2018 compared to 7.8% in 2017. Most of these isolates (8/10) were high-level resistant to both erythromycin and clindamycin, which is compatible with a constitutive MLS_B phenotype. The remaining two isolates displayed low-level resistance to erythromycin and were susceptible to clindamycin, as seen in efflux-mediated M-type resistance. Double disk diffusion tests were not performed. The distribution of MLS phenotypes was not significantly altered from 2017 to 2018. The results may suggest a continuing predominance of *erm*-encoded macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 75).

The 5.4% resistance to trimethoprim-sulfamethoxazole was a decrease from 8.2% in 2017. The prevalence of tetracycline resistance decreased from 7.6% in 2017 to 6.0% in 2018 (Figure 74). 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 52) may reflect the very limited use of levofloxacin and moxifloxacin for respiratory tract infections in Norway.

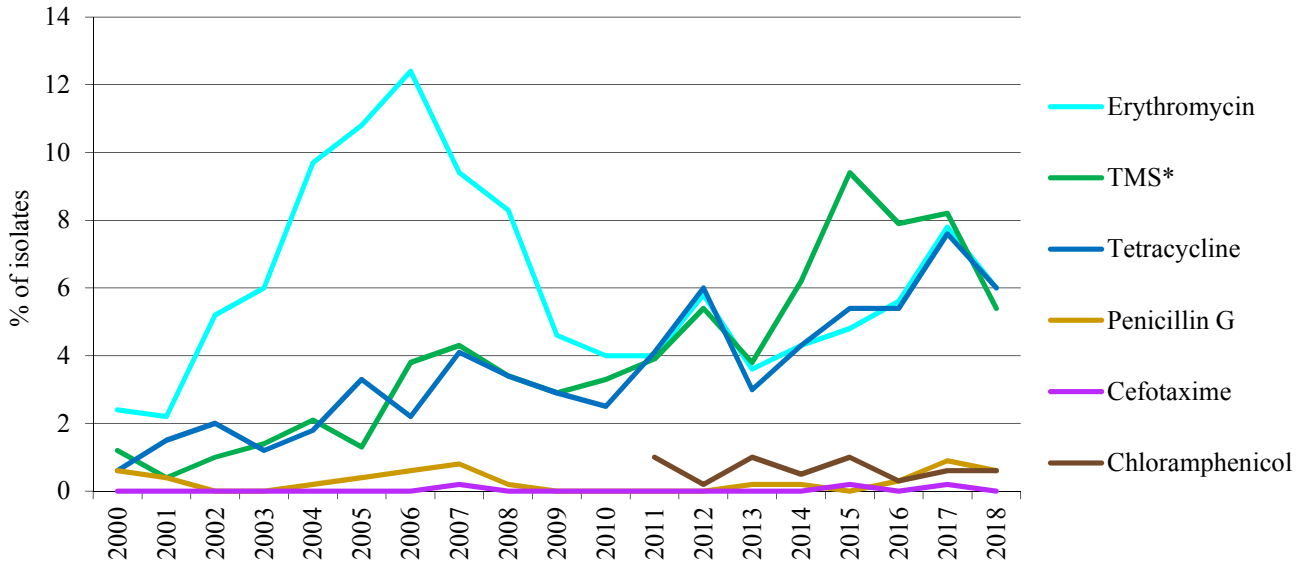

FIGURE 74. Prevalence (%) of resistance to antimicrobial agents in *Streptococcus pneumoniae* blood culture and cerebrospinal fluid isolates during 2000-2018. Doxycycline was substituted by tetracycline in 2005. Isolates are categorised according to the breakpoints at the time of analysis for each year. *TMS=Trimethoprim-sulfamethoxazole.

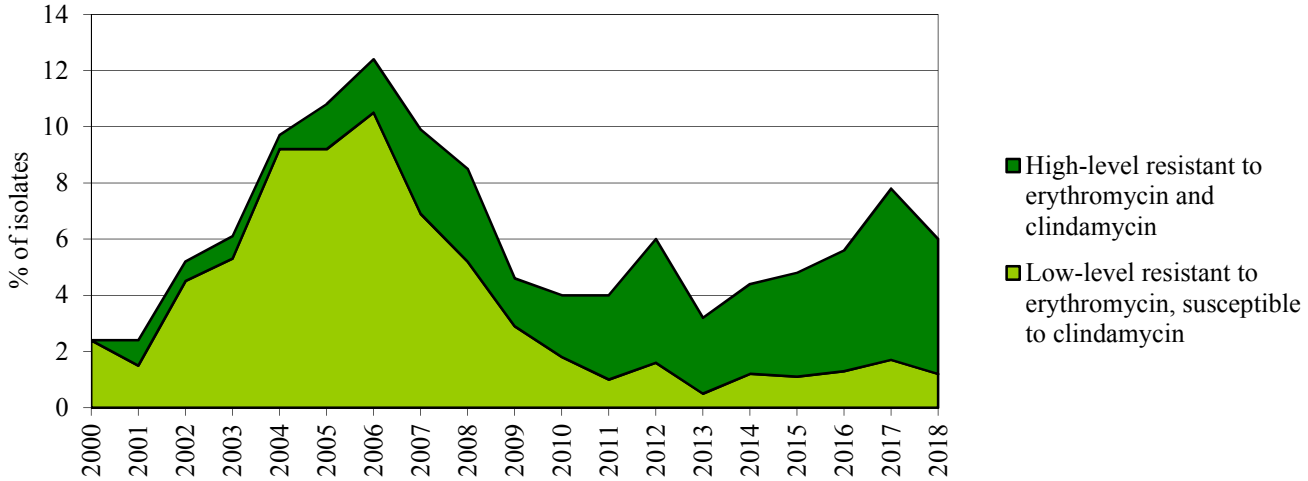

FIGURE 75. Prevalence of resistance (%) to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2018.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 53. *Streptococcus pneumoniae* in respiratory tract specimens in 2018 (n=476). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.06	> 2	92.9	6.9	0.2
Cefotaxime	≤ 0.5	> 2	99.2	0.8	0.0
Ceftriaxone	≤ 0.5	> 2	99.6	0.4	0.0
Erythromycin	≤ 0.25	> 0.5	87.8	4.0	8.2
Clindamycin	≤ 0.5	> 0.5	95.2	-	4.8
Tetracycline	≤ 1	> 2	92.5	0.6	6.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	89.1	2.7	8.2
Chloramphenicol	≤ 8	> 8	98.5	-	1.5
Oxacillin screen (mm)	≥ 20	< 20	91.4	-	8.6

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

TABLE 54. *Streptococcus pneumoniae* in respiratory tract specimens in 2018 (n=476). 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	1.7	33.8	48.9	6.9	1.5	2.9	1.7	1.1	0.8	0.4	0.2					
Cefotaxime	1.9	18.7	59.0	9.9	2.5	3.4	2.5	1.3	0.4	0.4						
Ceftriaxone	12.6	50.8	26.5	2.3	2.5	2.7	1.3	0.8	0.5							
Erythromycin			0.2	0.2	2.7	32.6	52.1	4.0			0.6	0.6	0.8	1.1	0.6	4.4
Clindamycin				0.4	7.8	37.6	35.7	13.7					0.2			4.6
Tetracycline				0.2	25.4	61.8	4.6	0.2	0.2	0.6	0.4	0.8	3.4	2.1	0.2	
TMS*					0.8	9.7	42.6	30.9	5.0	2.7	1.7	1.1	0.6	4.8		
Chloramph.									0.4	12.4	66.6	19.1	0.4	0.6	0.2	0.2
Norfloxacin										5.7	28.8	48.7	15.3	0.8	0.2	0.4

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	8.6	1.3	0.6	0.6	6.5	5.7	9.0	9.7	11.1	12.8	9.5	9.7	2.9	4.0	1.9	6.1

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

RESULTS AND COMMENTS

S. pneumoniae isolates from respiratory tract specimens were last surveyed in NORM in 2016. The rates of resistance to various antimicrobials are shown in Tables 53-54 and Figure 76.

The prevalence of resistance to penicillin G was still very low (0.2%) according to the non-meningitis breakpoint of R > 2 mg/L. A single isolate with a penicillin G MIC of 4 mg/L concomitantly had MICs of 2 mg/L and 1 mg/L for cefotaxime and ceftriaxone, respectively. A considerable proportion of isolates (8.2% in 2016, 6.9% in 2018) would require increased exposure for treatment with penicillin G as they had MICs in the 0.125-2 mg/L range. These isolates should be categorised as penicillin G resistant in the context of clinical meningitis, and three of them would have required increased exposure to cefotaxime and/or ceftriaxone.

Thirty-two of the 34 isolates with penicillin G MIC > 0.06 mg/L were detected by the oxacillin screening test (sensitivity 94.1%), whereas nine fully penicillin susceptible isolates were classified as oxacillin resistant (specificity 98.0%). Isolates with elevated penicillin G MICs were commonly cross-resistant to other antimicrobial agents such as erythromycin (18/34), tetracycline (16/34) and trimethoprim-sulfamethoxazole (14/34).

The rate of resistance to erythromycin was 8.2% in 2018 compared to 9.0% in 2016. Macrolide resistance was thus more common in respiratory tract isolates than in isolates from blood and sterile sites (6.0%). The MLS fenotype of 38/39 erythromycin resistant isolates was determined by double disk diffusion. Twenty-three isolates (61% of erythromycin resistant isolates, 5.0% of all isolates) displayed constitutive MLS_B resistance to erythromycin and clindamycin, whereas only a single isolate (3%) was inducibly resistant to clindamycin. Low-level M-type resistance was detected in 14 isolates (37% of erythromycin resistant isolates, 3.0% of all isolates). Additional isolates with M-type resistance were detected in the group categorised as erythromycin I.

Tetracycline resistance decreased from 9.0% in 2016 to 6.9% in 2018, whereas trimethoprim-sulfamethoxazole resistance increased from 6.1% in 2016 to 8.2% in 2018. The norfloxacin MIC distribution did not change significantly in the period 2016-2018.

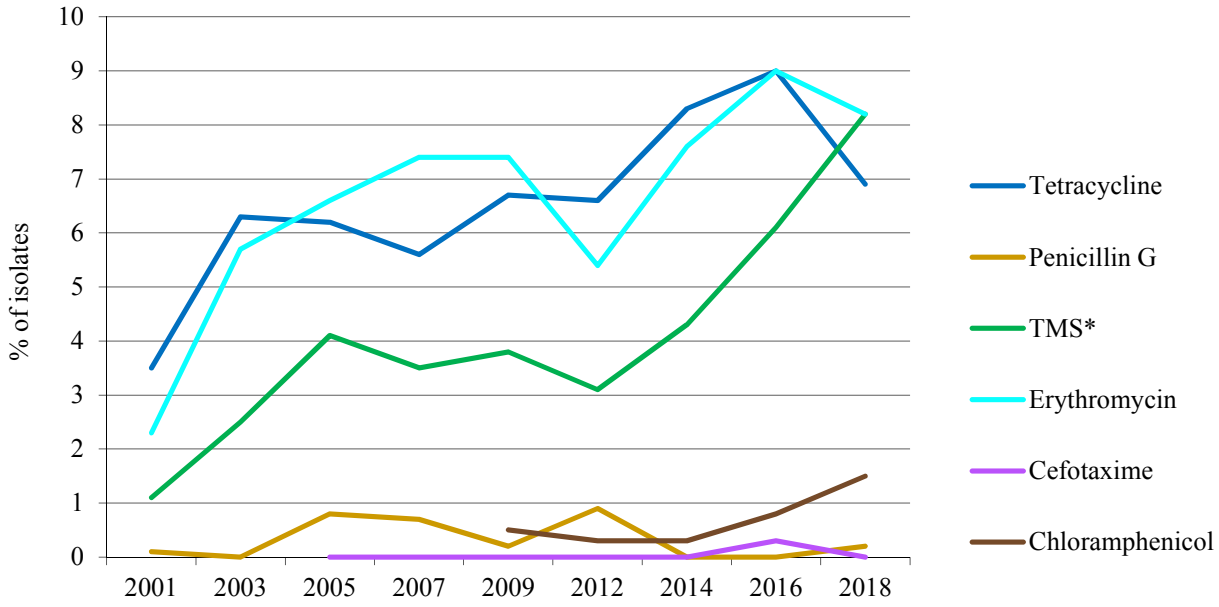

FIGURE 76. Prevalence of antimicrobial resistance in *Streptococcus pneumoniae* from respiratory tract samples 2001-2018. Isolates are categorised according to the breakpoints at the time of analysis for each year. Doxycycline was replaced by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole. Please note that the x-axis is not to scale.

Streptococcus pyogenes in blood cultures

TABLE 55. *Streptococcus pyogenes* in blood cultures in 2018 (n=57). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	100.0	0.0	0.0
Clindamycin	≤ 0.5	> 0.5	100.0	-	0.0
Tetracycline	≤ 1	> 2	98.2	0.0	1.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	96.4	1.8	1.8

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

TABLE 56. *Streptococcus pyogenes* in blood cultures in 2018 (n=57). 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		1.8	98.2													
Erythromycin					45.6	54.4										
Clindamycin				1.8	75.4	22.8										
Tetracycline					17.5	77.2	3.5							1.8		
TMS**					3.5	45.6	40.4	5.3	1.8	1.8				1.8		

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

RESULTS AND COMMENTS

The reference laboratory at the Norwegian Institute of Public Health provides resistance data for systemic *S. pyogenes* isolates on a yearly basis, but the 2018 sample only included the first three months of the year due to reorganisation of the laboratory. The results should therefore be interpreted with caution.

As expected, all isolates were fully susceptible to penicillin G (Tables 55-56). There were no isolates resistant to erythromycin or clindamycin in 2018 compared to 4.2% and 2.5% resistance in 2017, respectively. The prevalence of tetracycline resistance decreased from 10.9% in 2017 to 1.9% in 2018, whereas the prevalence of resistance to trimethoprim-sulfamethoxazole was 1.8% in 2018 and 0.8% in 2017.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 57. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2018 (n=265). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	77.4	0.0	22.6
Clindamycin	≤ 0.5	> 0.5	87.5	-	12.5
Tetracycline	≤ 1	> 2	24.2	0.4	75.4
Vancomycin	≤ 2	> 2	100.0	-	0.0

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

TABLE 58. *Streptococcus agalactiae* isolates in blood cultures and cerebrospinal fluids in 2018 (n=265). 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			1.5	52.5	44.5	1.5										
Erythromycin				2.6	33.2	39.6	1.9		4.5	5.7	3.8	1.1	0.4		0.4	6.8
Clindamycin				1.1	21.1	37.0	25.3	3.0	3.0	1.5			0.4			7.5
Tetracycline				0.4	19.6	3.4	0.4	0.4		0.4	2.3	9.8	44.5	17.4	0.8	0.8
Vancomycin				0.8	2.3	50.6	43.8	2.6								
Gentamicin												2.3	13.6	58.9	23.8	1.5

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

RESULTS AND COMMENTS

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

A total of 265 isolates were retrieved from invasive infections (bacteremia and cerebrospinal infections) in 2018. The analysis included only a single isolate per patient. Twenty-nine isolates originated from neonates and small children < 1 year of age. Most isolates (98.9%) were recovered from blood cultures, but there were also three isolates from cerebrospinal fluids.

Relevant breakpoints have remained unchanged since 2009. As seen in Tables 57-58 there were no isolates with reduced susceptibility to penicillin G or vancomycin. Sixty isolates (22.6%) were resistant to erythromycin compared to 22.7% in 2017. Fifty-six erythromycin resistant isolates were analysed by double disk diffusion for MLS_B resistance phenotype. Constitutive MLS_B resistance was found in 35 isolates (63%), while inducible MLS_B resistance was detected in 13 isolates (23%). The remaining eight isolates (14%) had results in accordance with the efflux-mediated M phenotype encoded by *mef* genes. Two isolates were recorded as clindamycin resistant (MIC 1-2 mg/L) in spite of being susceptible to erythromycin (MIC 0.032-0.064 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 1.5% of the isolates. The prevalence of resistance to tetracycline (75.4%) was at the same level as in 2017 (75.6%) with the majority of isolates displaying MIC values of 16-32 mg/L (Table 58).

Streptococcus dysgalactiae in blood cultures

TABLE 59. *Streptococcus dysgalactiae* in blood cultures in 2018 (n=274). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	89.1	0.7	10.2
Clindamycin	≤ 0.5	> 0.5	96.7	-	3.3
Tetracycline	≤ 1	> 2	65.7	12.4	21.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	100.0	0.0	0.0

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

TABLE 60. *Streptococcus dysgalactiae* in blood cultures in 2018 (n=274). 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		10.9	84.3	4.4		0.4										
Erythromycin					0.7	19.3	69.0	0.7			2.9	1.8	2.9			2.6
Clindamycin				0.4	0.7	24.8	69.0	1.8	0.4	0.4						2.6
Tetracycline					10.0	74.1	4.6		0.4		0.4	0.8	2.1	5.9	1.7	
TMS*				21.5	67.2	10.2	1.1									

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

RESULTS AND COMMENTS

Streptococcus dysgalactiae (group C and G streptococci) have never previously been included in the NORM surveillance programme. The isolates were identified on the basis of colony morphology, group antigens, biochemical tests and MALDI-TOF analysis. Further details are given in appendix 5.

All isolates were susceptible to penicillin G and trimethoprim-sulfamethoxazole. As for *S. pyogenes* and *S. agalactiae*, a considerable proportion of isolates were resistant (21.9%) or would require increased exposure (12.4%) to treatment with tetracycline. Erythromycin resistance was detected in 28 isolates (10.2%) and these were further analysed by double disk diffusion. Eight isolates (29%) displayed constitutive MLS_B resistance, whereas the remaining 20 (71%) were inducibly resistant to clindamycin. No isolates were categorised as M-type resistant. A single isolate was clindamycin resistant (MIC 2 mg/L) in spite of being erythromycin susceptible (MIC 0.125 mg/L). One may speculate that such a phenotype is caused by ribosomal mutations, but this was not further investigated.

Streptococcus dysgalactiae in wound specimens

TABLE 61. *Streptococcus dysgalactiae* in wound specimens in 2018 (n=235). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	91.4	0.9	7.7
Clindamycin	≤ 0.5	> 0.5	97.9	-	2.1
Tetracycline	≤ 1	> 2	73.1	6.0	20.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	100.0	0.0	0.0

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

TABLE 62. *Streptococcus dysgalactiae* in wound specimens in 2018 (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		12.8	85.1	2.1												
Erythromycin					1.7	30.2	59.6	0.9			1.7	1.7	1.3			3.0
Clindamycin				0.4		31.5	65.1	0.9								2.1
Tetracycline			0.4		18.7	34.0	12.8	3.4	3.8	6.0	1.7	2.6	4.3	10.6	1.7	
TMS*				36.6	51.5	11.9										

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

RESULTS AND COMMENTS

Streptococcus dysgalactiae (group C and G streptococci) were also surveyed in samples from wounds and abscesses. As for blood cultures, the isolates were identified on the basis of colony morphology, group antigens, biochemical tests and MALDI-TOF analysis. Further details are given in appendix 5.

All isolates were susceptible to penicillin G and trimethoprim-sulfamethoxazole. The rate of tetracycline resistance (20.9%) was at the same level as in blood culture isolates (21.9%). The eighteen erythromycin resistant isolates (7.7%) were most often constitutively (n=5, 28%) or inducibly (n=11, 61%) resistant to clindamycin. In addition, two isolates displayed low-level erythromycin resistance compatible with *mef*-encoded M-type resistance. The genetic basis for macrolide resistance was not further explored.

One Health Resistome Surveillance

Antimicrobial resistance (AMR) is one of the biggest global health challenges of our time (1). In 2015, the World Health Organisation (WHO) adopted a global action plan to address AMR, highlighting the need for an effective One Health (OH) strategy to combat AMR (2). The European Commission's One Health Action Plan against AMR of 2016 highlighted the development and spread of AMR in the environment and the need for improved AMR surveillance as key areas for research and development (3).

National AMR surveillance data show that the prevalence of resistant bacteria is low in both animals and humans, and that the use of antimicrobials is low and decreasing in both domains in Norway (4). Yet, resistance to broad-spectrum antimicrobials in *Escherichia coli* and *Klebsiella* spp., tetracycline resistance in *Salmonella* Typhimurium and ciprofloxacin resistance in *Campylobacter jejuni* are increasing and have been increasing over the last decade. Extended spectrum beta-lactamases (ESBL) are now considered a significant clinical problem, and a worrying proportion of carbapenemase-producing Enterobacteriaceae (CPE), in particular the OXA-48-like-producing *E. coli,* persists as a potential threat for future healthcare in Norway (4).

The resistome

The fast pace of AMR influx, dissemination and persistence in the clinical environment suggest that a pre-existing pool of "AMR genes" is present in natural environmental reservoirs. In this context, one of the major challenges for microbiologists is to track these reservoirs of "AMR genes" and prevent their dissemination to pathogens where their expression becomes problematic. The bacterial resistome encompasses the collection of all the antibiotic resistance genes and their precursors including: i) resistance genes found in pathogenic bacteria, ii) resistance genes found in non-pathogenic antibiotic producers such as soil-dwelling bacteria, iii) cryptic resistance genes embedded in the bacterial chromosomes that do not obviously confer resistance, and iv) precursor genes that do not encode resistance, but encode proteins that have affinity to antibiotic molecules that may evolve to a full resistance gene given the appropriate selection pressure (5) (Figure 77). Local reservoirs of resistance genes in the environment include the Arctic ecosystem, the soil, wastewaters and the animal- and human microbiomes. These reservoirs are assumed to be principal in the development and dissemination of AMR genes, most critically at the interfaces where the different OH domains meet and interact (6).

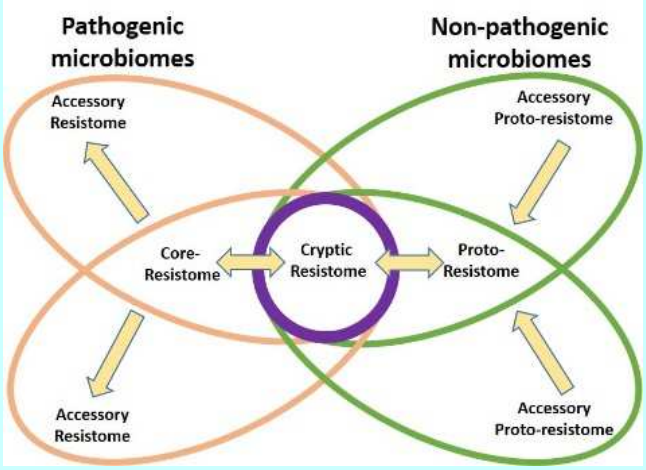

FIGURE 77. The Core Resistome is the antibiotic resistance genes shared by pathogenic bacteria (red), whereas the Proto-Resistome is the antibiotic resistance genes shared by non-pathogenic bacteria (green). The intersection of these genes is the Cryptic Resistome (purple). Resistance genes can be transferred reversibly from the Proto-Resistome to the Cryptic Resistome and then to the Core-Resistome. When they are no longer needed, genes can be transferred from the core to the accessory resistome (7).

Bacteria have evolved a wide spectrum of mechanisms to exchange genes, remodel their genomes and ultimately adapt to changing environmental conditions. Mobile genetic elements (MGE) circulate within and between different species, genera and families of bacteria (8). Conventional surveillance of resistance phenotypes or genotypes in selected pathogenic bacteria is therefore inadequate and needs to be complemented by a comprehensive approach to surveillance, which also includes systematic data collection of resistant bacteria and MGEs in non-pathogenic bacteria from all OH domains, in order to understand how and where these genes develop, accumulate and disseminate.

In microbial ecology, we still have to elucidate the origins and selection processes that are involved in the dissemination of the diverse mechanisms of antibiotic resistance that we are currently observing in clinical settings. Studies have shown that the antibiotic selective pressure is not the sole driver of these chains of events. Use of biocides and heavy metals, as well as urbanisation factors such as population density and building density are among others shown to be positively correlated with the transfer of antibiotic resistance genes (9). It has also been shown that all environments contain genes with significant similarities to antibiotic resistance genes we observe in clinic settings (10). When studying resistant bacteria from the environment with functional metagenomics, it has been demonstrated that a significant amount of resistance genes are shared between the soil and the gut microbiota of both animals and humans and can confer resistance to previously sensitive bacteria (11-13).

A metagenomics approach

Metagenomics is a critical tool to study conversion of what Baquero termed "pieces" into "patterns" i.e. from independent genetic determinants to the configuration of a resistant host (12) (Figure 78). A metagenomic approach to AMR surveillance has the potential to disentangle complex interactions between the pathogen and: i) the abundant taxa and species present in the microbiota, ii) the species that form genetic exchange communities, iii) the subcellular mobilome and iv) the AMR gene pool. At all levels from clones to MGE or genes, the ecology and evolution of AMR depends on the ability of a genetic element from one system to enter and be present in another system, the ability to exchange genetic sequences between members of these systems, the ability to withstand variability in the genetic sequence, and the ability to establish permanent links with their surrounding environment.

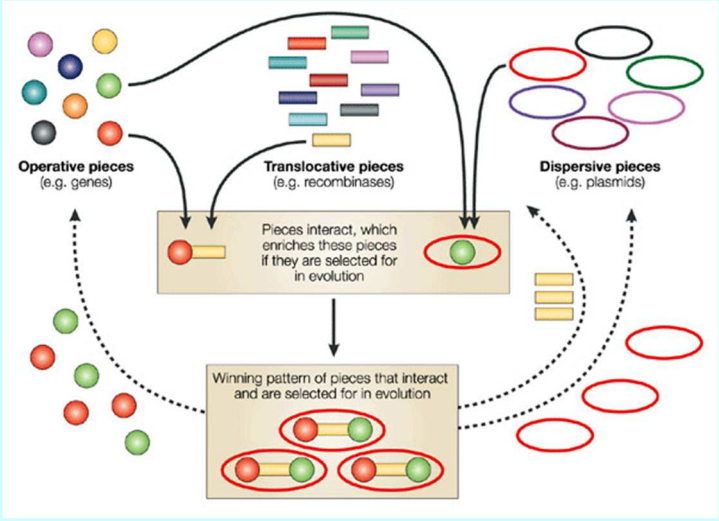

FIGURE 78. In any specific environment, there are ensembles of operative pieces, such as determinants of resistance or pathogenicity (shown here as filled circles), translocative pieces, such as recombinases (shown here as filled boxes), and dispersive pieces, such as plasmids, phages or clones (shown here as ovals). Combinations that are formed between pieces (shown here by arrows) might produce a winning combination or pattern that is enriched through selection. The success of winning patterns also enriches the available pool of pieces for those pieces that interact successfully (shown here by dashed arrows). This landscape of pieces is a local evolutionary unit. (Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, Nature Reviews Microbiology. From pieces to patterns: evolutionary engineering in bacterial pathogens, Fernando Baquero (14)).

Future strategies

Combatting AMR will require substantial changes to antibiotic development pipelines, antibiotic stewardship practices, and also to the antibiotic resistance surveillance systems. The changes in the surveillance system must embrace the resistome at its core and be used to monitor changes in the frequency of the evolutionary units or "pieces" at all levels of biological complexity. To establish a resistome-based surveillance system would require: i) international agreement of where to collect samples, ii) harmonising of sample extraction procedures, sequencing, management of sequenced data and which bioinformatic tools and platforms to use, and iii) description of existing surveillance systems and programs and how to identify undescribed resistance genes. Implementation of a resistome base surveillance system might reveal evolutionary paths to the development of high-risk pathogenic clones, against which targeted interventions could be designed, implemented and monitored.

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Mycobacterium tuberculosis

In 2018, 209 persons were reported with tuberculosis disease (TB) to the Norwegian Surveillance System for Communicable Diseases (MSIS). Of these, 29 were born in Norway. One hundred seventy-five had TB for the first time, of which three had received preventive treatment. Twenty had previously had TB, of which 16 had been treated with anti-TB drugs. The remaining 14 cases were categorised as uncertain.

One hundred sixty-seven cases were confirmed infections with *M. tuberculosis* complex by culture, and all isolates were susceptibility tested. The results are presented in Table 63. There were four MDR-TB cases. All four were co-resistant to pyrazinamide, two of them also to ethambutol and prothionamide, and one of the latter also resistant to para-aminosalicylic acid (PAS). One of the four had low-level resistance to moxifloxacin, but none were resistant to amikacin or capreomycin. There were consequently no XDR-TB cases. All MDR-TB cases had TB for the first time. In addition to the four MDR cases, two isolates were mono-resistant to rifampicin and eleven isolates were resistant to isoniazid.

TABLE 63. Antimicrobial susceptibility of 167 isolates of *Mycobacterium tuberculosis* complex (not *M. bovis* (BCG)) from human infections in 2018. Figures from 2017 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	29 (30)	21 (20)	2 (1)	0 (1)	0 (1)	1 (1)	0 (1)
Europe excl. Norway	25 (24)	22 (20)	3 (3)	3 (2)	2 (1)	2 (3)	2 (2)
Asia	79 (97)	69 (80)	5 (4)	2 (1)	1 (0)	3 (0)	2 (1)
Africa	76 (109)	55 (93)	5 (12)	1 (5)	0 (2)	0 (8)	0 (5)
America	0 (1)	0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Oseania	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	209 (261)	167 (214)	15 (20)	6 (9)	3 (4)	6 (12*)	4 (9)
Proportion resistant isolates (%)			9.0 (9.3)	3.6 (4.2)	1.8 (1.9)	3.6 (5.6)	2.4 (4.2)

*Of these three *M. bovis* isolates in 2017 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 in 2018 (n=117). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	100.0	0.0	0.0
Voriconazole*	≤ 0.064	> 0.25	100.0	0.0	0.0
Anidulafungin*/**	≤ 0.032	> 0.032	99.1	-	0.9
Micafungin*/**	≤ 0.016	> 0.016	99.1	-	0.9

S=Susceptible, I=Intermediately susceptible, R=Resistant. *Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2018. The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin and micafungin are considered susceptible.

TABLE 65. *Candida albicans* blood culture isolates in 2018 (n=117). 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					0.9	6.8	41.0	49.6	1.7								
Fluconazole						4.3	59.8	33.3	2.6								
Voriconazole	18.0	65.8	14.5	1.7													
Anidulafungin	80.3	17.1	1.7					0.9									
Micafungin	2.6	51.3	45.3						0.9								
Caspofungin*		0.9	3.4	25.6	39.3	25.6	4.3				0.9						

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Non-shaded cells represent MIC values that are not covered by the standard test method. *There 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 in 2018 (n=33). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 0.002	> 32	0.0	78.8	21.2
Anidulafungin*/**	≤ 0.064	> 0.064	100.0	-	0.0
Micafungin*/**	≤ 0.032	> 0.032	100.0	-	0.0

S=Susceptible, I=Intermediately susceptible, R=Resistant. *Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2018. The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. 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 in 2018 (n=33). 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					9.1	9.1	3.0	63.6	15.2								
Fluconazole										6.1	27.3	33.3	9.1	3.0	3.0		18.2
Voriconazole*				3.0	15.2	18.2	24.2	12.1	3.0		6.1	3.0		15.2			
Anidulafungin	3.0	54.5	36.4		6.1												
Micafungin		39.4	54.5	6.1													
Caspofungin**				3.0	9.1	27.3	51.5	9.1									

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Non-shaded cells represent MIC values that are not covered by the standard test method. *There is insufficient evidence 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 in 2018 (n=8). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	100.0	0.0	0.0
Voriconazole*	≤ 0.125	> 0.25	100.0	0.0	0.0
Anidulafungin*/**	≤ 0.064	> 0.064	100.0	-	0.0

S=Susceptible, I=Intermediately susceptible, R=Resistant. *Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2018. The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. **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 in 2018 (n=8). 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							25.0	25.0	50.0								
Fluconazole							25.0	50.0	12.5	12.5							
Voriconazole		12.5	25.0	25.0	25.0	12.5											
Anidulafungin		12.5	87.5														
Micafungin*			62.5	37.5													
Caspofungin***				12.5	12.5	62.5	12.5										

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Non-shaded cells represent MIC values that are not covered by the standard test method. *There is insufficient evidence that the wild-type population of *C. tropicalis* can be considered susceptible to micafungin. **There are no European breakpoints for caspofungin. Strains susceptible to anidulafungin are considered susceptible to caspofungin.

TABLE 70. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates in 2018 (n=7). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	S	R	S	I	R
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	85.7	14.3	0.0
Voriconazole*	≤ 0.125	> 0.25	100.0	0.0	0.0
Anidulafungin*/**	≤ 0.002	> 4	0.0	100.0	0.0
Micafungin*/**	≤ 0.002	> 2	0.0	100.0	0.0

S=Susceptible, I=Intermediately susceptible, R=Resistant. *Recommended breakpoints by the European Committee on Antimicrobial Susceptibility Testing – EUCAST 2018. The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. **There are no European breakpoints for caspofungin. Strains categorised as I to anidulafungin and micafungin can be considered I to caspofungin.

TABLE 71. *Candida parapsilosis* blood culture isolates in 2018 (n=7). 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							14.3	42.9	42.9								
Fluconazole								85.7			14.3						
Voriconazole		42.9	14.3	28.6	14.3												
Anidulafungin								28.6	42.9	14.3	14.3						
Micafungin								57.1	28.6	14.3							
Caspofungin*				14.3				71.4	14.3								

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Non-shaded cells represent MIC values that are not covered by the standard test method. *There are no European breakpoints for caspofungin. Strains categorised as I to anidulafungin and micafungin can be considered I to caspofungin.

RESULTS AND COMMENTS

The number of isolates from unique candidemias referred to the National Mycology Reference Laboratory declined from 206 in 2017 to 178 isolates in 2018. The laboratory received ten different *Candida* species from 168 patients. Two patients had mixed infections with two different *Candida* spp. Six patients had persistent infections with the same species in samples taken more than four weeks apart. In one patient, three episodes of candidemia with different species occurred during a three months period.

Candida albicans is still the most common species in candidemias in Norway (n=117, 65.7%). The number of *Candida glabrata* isolates is low (n=33, 18.5%) followed by small numbers of other species; *Candida tropicalis* (n= 8, 4.5%), *Candida parapsilosis* (n=7, 3.9%) *Candida dubliniensis* (n=7, 3.9%), and six isolates of four other *Candida* species.

All isolates were susceptibility tested for amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin by E-test according to the manufacturer's instructions (AB bioMérieux). Unexpected susceptibility patterns were confirmed by the EUCAST standardised broth microdilution method at Statens Serum Institut in Copenhagen. The results are presented in Tables 64-71.

The EUCAST AFST subcommittee is currently reviewing breakpoint tables to introduce necessary changes to match the new EUCAST definitions of S, I and R. Acquired resistance is rare and species identification predicts the susceptibility pattern of *Candida* species isolated in Norway, except in patients on long-term antifungal treatment. All but one *C. albicans* isolate were susceptible to all drugs tested. Acquired echinocandin- resistance was found in one *C.albicans.* The isolate was from a mixed infection with *C. parapsilosis* in a patient on long-term echinocandin therapy. FKS sequencing performed at Statens Serum Institutt in Copenhagen showed mutation in S645P.

All *C. parapsilosis* (n=7) belonged to the wild type and were still categorised as intermediately susceptible to echinocandins, but changes are likely as the new I category (susceptibility with increased exposure) is not an option with *C. parapsilosis* and echinocandin therapy. Reduced susceptibility to fluconazole (MIC 2 mg/L) was observed in one *C. parapsilosis* isolate, otherwise no acquired fluconazole resistance was found. Breakpoints for fluconazole ($S \leq 0.002$ and $R > 32$) in *C. glabrata* are expected to be changed, but the wild type is still supposed to be categorised as I. In 2018, 21% of the *C. glabrata* isolates were categorised as resistant. Otherwise reduced susceptibility to fluconazole was due to intrinsic resistance in *C. krusei* (n=2) or found in species known to display high fluconazole MICs (*C. guilliermondii* (n=1) and *C. nivariensis* (n=1)). Breakpoints for *C. dubliniensis* were established in 2018 but are not listed in the report due to the small number of isolates.

The wild-type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible and all isolates with defined breakpoints were found susceptible to voriconazole in 2018. The I category was introduced for *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* in 2018 to acknowledge that increased exposure can be obtained by intravenous dosing, which should be confirmed by TDM. There is not enough information available on the response to voriconazole in infections caused by *Candida* isolates with higher MICs, and there is insufficient evidence that *C. glabrata* and *C. krusei* are good targets for therapy with voriconazole. No breakpoints have therefore been set. 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 for treatment of infections with *C. lusitaniae* (n=1) as this species 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 tables. This applies to *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 or that it is shown that MRL is not nessecary.

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

Wholesalers and feed mills in Norway are mandated to provide sales statistics for veterinary medicinal products, including when supplied as medicated feed, to the Norwegian Institute of Public Health (NIPH). Data on sales of each product presentation (name, form, strength and pack size) of the included VMPs were obtained from the NIPH with one exeption; antibacterials for farmed fish for the years 2013-2018 were obtained from Veterinary Prescription Register (VetReg). Veterinarians in Norway are not allowed to dispense VMPs, except for treatments until a pharmacy can provide the VMPs. In such cases the medicinal products has to be sold at cost price.

Prescription data

The Norwegian Food Safety Authority established the Veterinary Prescription Register (VetReg) for farmed fish 1 January 2011 and for terrestrial animals 1 January 2012. The veterinarians are mandated to report any administration and deliveries of VMPs and HMPs to VetReg for all terrestrial food-producing animals and horses while it is voluntary for all other animal species such as companion animals. Pharmacies and feed mills have to report all deliveries, i.e. for all terrestrial animals and farmed fish, to veterinarians or animal owners, including medicines prescribed for companion animals and HMPs.

For farmed fish the reporting of prescription of antibacterials has been shown to be complete for the years 2013-2017 (1) and this was the case also for 2018 data; VetReg data are used for farmed fish for these years. For 2012-2014 data from VetReg on antibacterials for terrestrial food-producing animals, the quality of the prescription data were unsatisfactory (unpublished data) for oral paste and intramammaries for the entire period 2012-2018 resulting in that amounts used could not be calculated. The number of prescriptions was used to obtain a picture of the prescribing per species for these formulations. In this analysis only 2015-2018 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 2015-2018. The results show that the VetReg data cover around two thirds of the sales data for VMP injectables**,** oral powders and oral solution. It could not be identified whether the data are represenative for the prescribing of VMPs by animal species, but the VetReg data are nevertheless believed to give a rough picture of of the prescription of antibacterial classes by formulation and animal species. VetReg data have therefore been used as an additional souce in order to assess changes according to targets set in the National Strategy against Antibiotic Resistance (2015-2020) (3).

Ionophore coccidiostat feed additives

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

Antibacterial agents included in the data set

The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to identify the VMPs to be included in the data. Sales of VMPs belonging to the ATCvet codes shown in the table below were collected from the NIPH for terrestrial animals, for farmed fish data QJ01 was collected from VetReg. This is identical to the inclusion criteria by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (4). For the estimation of prescription of HMP, antibacterials belonging to the ATC codes J01 and J04AB are included (extracted from VetReg data).

Antibacterial veterinary medicinal products included in the data

Categories	ATCvet codes
Intestinal use	QA07AA;QA07AB
Intrauterine use	QG01AA; QG01AE, G01BA; QG01BE; QG51AA; QG51AG
Systemic use	QJ01
Intramammary use	QJ51
Antiparasitic agents[1]	QP51AG

[1] Only sulfonamides

Antibacterial veterinary medicinal products sold on special exemption from market authorisation are included in the sales data and prescription data. Dermatological preparations (QD) and preparations for sensory organs (QS) are not included in the data which is in accordance with the ESVAC protocol (4).

Data source animal population data. Denominator.
A population correction unit (PCU) has been established as a denominator for the reporting of ESVAC sales data. In this report, PCU has been used as denominator for sales of antibacterial VMPs. It is emphasised that the PCU is purely a surrogate for the animal population at risk.

The animal categories included in the PCU as well as the calculation methodology are identical to ESVAC and is detailed in the ESVAC 2016 report (3). The PCU for each terrestrial animal category is calculated by multiplying numbers of livestock animals (dairy cows, sheep, sows and horses) and slaughtered animals (cattle, goat, pigs, sheep, poultry, rabbits and turkeys) by the theoretical weight at the most likely time for treatment.

The PCU is calculated for each species, weight class and/or production type, as follows:

- Number of animals slaughtered × estimated weight at treatment
- Number of livestock × estimated weight at treatment

The total PCU is calculated according to the above data.

1 PCU = 1 kg of animal biomass.

For farmed fish, fish biomass live-weight slaughtered is used as PCU in ESVAC reports.

Data on animal population, including farmed fish, used to calculate PCU were obtained from Statistics Norway (https://www.ssb.no).

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

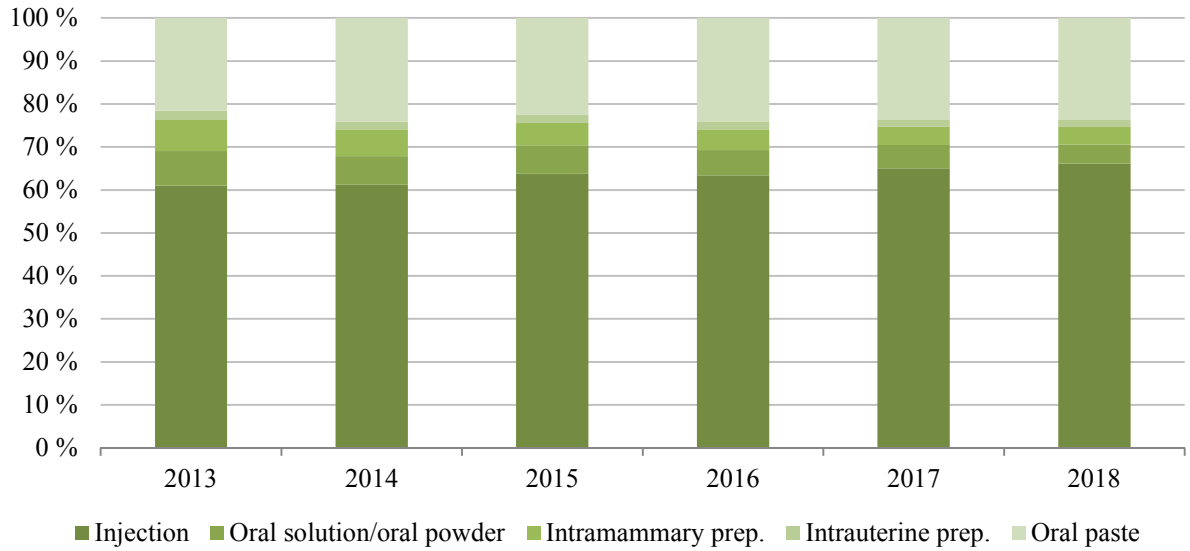
Analysis of the overall sales data
The sales data for each VMP presentation were calculated to express weight of active substance. In order to comply with the ESVAC standards, sales of prodrugs - e.g. procaine benzylpenicillin and penethamate hydriodide - has been converted to the corresponding values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

The sales data of antibacterial VMPs for terrestrial animals have been split into sales for food-producing animals, includs horses, and companion animals. Sales of anti-bacterial VMPs for companion animals refer to sales of tablets, oral solution and oral paste that are approved solely for companion animals; in addition dihydrostreptomycin tablets of pack size 10 pieces have been included in the data on sales for companion animals (no sales after 2004). The other antibacterial VMPs are assumed sold for use only in food-producing animals, including horses. There is some use of injectable VMPs in companion animals, thus the usage is slightly underestimated for this animal category and 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
The national strategy does not specify for which food-producing terrestrial animal species the reduction should cover. Because cattle, pigs, sheep, and poultry accounted for 99.9% of the Norwegian meat production in 2018 (https://www.ssb.no/slakt) these species, as well as goat, were selected to evaluate the goals set down in the national strategy (3).

The sales data for 2013-2018 have been further refined in order to obtain estimates on the usage in cattle, pigs, sheep, goat and poultry that are more accurate in terms of identifying changes across time. Sales data show that oral paste approved for horses accounted for 23- 24% of the total annual sales of antibacterial VMPs for terrestrial food-producing animals during 2013-2018, see Figure below. Data on prescribtions per animal species obtained from the Veterinary Prescription Register (VetReg) have been used as supportive information to the sales data for this refinement.

VetReg data show that for the years 2015-2018, 97% of the number of prescriptions of antibacterial oral paste VMPs was for horses. Off-lable use for other animal species of oral paste approved for horses was negligible. Oral paste (numerator) and PCU for horses (denominator) has been excluded from the analysis of data for the estimation of usage of antibacterial VMPs for cattle, pigs, sheep, goat and poultry. Intramammaries and oral paste have been excluded from the analysis of the VetReg data regarding prescribed amounts (kg) due to data quality issues (2).



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 in the period 2013-2018.

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 represents an underestimate

Estimation of sales of HMPs for dogs and cats

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

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

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5. EMA, 2017. Joint ECDC, EFSA and EMA scientific opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption in humans and food-producing animals (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* (Hospital Pharmacies´ Drug Statistics Database) which is a collaboration between *Legemiddelinnkjøpssamarbeid – LIS* (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 Norwegian Advisory Unit for Antibiotic Use in Hospitals (*Nasjonal kompetansetjeneste for antibiotikabruk i spesialisthelsetjenesten*) has analysed the data according to activity (admission and bed days).

Population statistics per 1 January 2019 are collected from Statistics Norway. Information on bed days and admissions are collected from the Norwegian Patient Register at the Norwegian Directorate of Health. The definition of bed days is "*the number of whole days an admitted patient disposes a bed*". An admission is defined as "*admission of patient where the medical interventions usually are complex and requires hospitalisation for one or more days*" (2).

Data on the use in ambulatory care are retrieved from NorPD, a nation-wide prescription database situated at the Norwegian Institute of Public Health. This database includes all prescriptions being prescribed to out-patients in Norway. For analyses on prescriptions and DDDs, all prescriptions and DDDs to outpatients are included. For the results on annual prevalence (number of individuals per population group being prescribed antibiotics within a year) only prescriptions to individuals with national ID numbers are included. The data give us the exact population prevalence of antibacterial use in the total population in ambulatory care. More information is available at www.fhi.no. Data are available from 2004.

Drug Classification
The data are categorised according to the ATC classification system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2019 is used for all years.

Unit of measurement
The ATC/DDD system is recommended by the WHO to serve as a tool for drug utilisation research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels.
The use of defined daily dose (DDD) as a unit of measurement, simplifies and improves the evaluation of drug consumption over time, nationally and internationally. The DDD is a theoretical unit of measurement, and does not necessarily reflect the recommended or Prescribed Daily Dose.

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

The DDDs for 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. 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
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Appendix 3:
Sampling, microbiological methods and data processing in NORM-VET

Sampling strategy

Escherichia coli was collected from clinical submissions of diverse infectious conditions/septiceamia in poultry (175 broiler isolates, 33 turkey isolates and one isolate from quail) submitted to the Norwegian Veterinary Institute (NVI) between 2015-2018. Altogether, 209 *E. coli* isolates were included for susceptibility testing. *Staphylococcus aureus* isolates were collected from a survey on mastitis in sheep taking part spring/summer 2018. Clinical examination and collection of udder secretions were carried out by veterinary practitioners, and the samples were sent to NVI in Oslo. In total, 142 isolates were included, i.e. from one or both mammary glands per animal.

The rest of the samples included in 2018 were collected by the Norwegian Food Safety Authority (NFSA). The indicator bacteria *Escherichia coli* were isolated from caecal samples of broiler and turkey flocks, and from faecal samples of sheep. The samples were collected at slaughter. From each poultry flock 10 caecal samples were collected, while from sheep herds a single faecal sample was collected. A total of 280 pooled samples from broiler and 157 pooled samples from turkeys, and 302 samples from sheep, were included. Only one sample from each poultry flock and sheep herd was included. The samples were also used for selective isolation of *E. coli* resistant to third generation cephalo-sporins, quinolone resistant *E. coli* (QREC, sheep), and carbapenemase-producing *Enterobacteriaceae* (CPE). From broiler and turkey flocks, caecal samples were also used for isolation of *Enterococcus faecalis*, *Enterococcus faecium* and vancomycin resistant *Enterococcus* spp. (VRE). Altogether, 254 broiler and 192 turkey meat samples were collected at retail in all regions of Norway following the specifications set by the European Food Safety Authorities (EFSA journal 2014;12(5):3686). Samples were to be taken without taking place of origin into consideration. A total of 194 samples of leafy greens and leafy herbs were collected which included 60 and 81 samples of domestic and imported leafy greens, respectively, as well as 53 imported leafy herbs. The samples comprised both washed and unwashed products and a variety of different salad and herb types. Samples of cheese and dairy products were also analysed and included a total of 189 samples, comprising 168 cheese samples and 21 samples of other dairy products (sour cream (13), icecream (2), butter (3) and yoghurt (3).The samples were of both Norwegian (146) and imported origin (43), with 93 products made from pasteurized and 96 of unpasteurized milk. One of the products included in unpasteurized products had undergone a mild heattreatment ("termisering"). Only one sample from each production batch of meat or leafy greens, leafy herbs, cheese and other dairy products was included. All the food samples were analysed using selective isolation for *E. coli* resistant to third generation cephalosporins and CPE. The leafy greens, leafy herbs, cheese and other dairy products samples were also subjected to analyses for *E. coli* indicator bacteria and selective isolation of QREC and colistin resistant *E. coli*.

Isolation and identification of bacteria

Clinical isolates of *Escherichia coli*

Swab or organ samples submitted to the NVI were plated directly onto blood agar (Blood Agar Base No.2 (Oxoid, Thermo Fisher Inc., Waltham, Massachusetts, USA) with 5% bovine blood) and lactose-saccarose-bromthymol blue agar. After incubation of the agar plates in 5% CO_2 atmosphere at 37±1°C for 18-24 hrs, suspected colonies were identified as *E. coli* by typical appearance, lactose and/or saccarose fermentation and a positive indole reaction, or by matrix-assisted laser desorption/ionisation time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany).

Clinical isolates of *Staphylococcus aureus*

Mastitis milk samples submitted to the NVI were plated on blood agar (Blood Agar Base No.2 (Oxoid) with 5% washed bovine blood). The plates were incubated in 5% CO_2 atmosphere at 37±1°C for 18-24 hrs and for 42-48 hrs. Staphylococcal isolates were selected based on the occurrence of hemolytic zones: greyish white typical colonies with a beta-toxic zone on blood agar were isolated and species identification was performed using MALDI-TOF MS (Bruker Daltonik GmbH).

Indicator isolates of *E. coli*

Sample material, i.e. caecal content from 10 broilers or turkeys per flock were pooled, and one faecal sample per sheep herd was plated directly onto MacConkey agar and incubated at 41.5±1°C for 24h. From vegetable and dairy 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 a loopful (10-20 µL) was 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 before further phenotypical testing.

Indicator isolates of *Enterococcus faecalis* and *Enterococcus faecium*

Sample material, i.e. caecal content from 10 broilers or turkeys per flock, were mixed and plated directly onto Slanetz and Bartley agar (Oxoid) and incubated at 41.5±1°C for 48h. 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 *Enterococcus faecalis* or *Enterococcus faecium* by typical colony appearance and verified using MALDI-TOF MS (Bruker Daltonik GmbH) before further phenotypical testing.

Vancymycin resistant *Entercococcus* spp.
Sample material, i.e. caecal content from 10 broilers or turkeys per flock, were mixed and plated directly onto Slanetz and Bartley agar containing 4 mg/L vancomycin (Oxoid) and incubated at 41.5±1°C for 48h. Typical colonies were subcultured on Slanetz and Bartley agar containing 4 mg/L vancomycin and blood agar (Heart infusion agar, Difco) containing 5% bovine blood and incubated at 37±1°C for 20±2h. Presumptive colonies were identified as *E. faecalis* or *E. faecium* by typical colony appearance and verified using MALDI-TOF MS (Bruker Daltonik GmbH) before further phenotypical testing.

Enrichment of samples
All samples were enriched prior to plating onto selective media. A total of 1±0.1 g caecal or faecal sample material was homogenised with 9 mL of BPW-ISO. A total of 25±0.5 g sample material of meat, vegetables and dairy products, 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 a loopful (10 µL) of enrichment broth was plated on selective media as described in the sections below.

***E. coli* resistant to third generation cephalosporins**
Aliquots from the overnight BPW-ISO broth from all caecal, faecal, meat, leafy greens, leafy herbs and dairy 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±1°C (caecal and faecal samples) or 44±1°C (leafy greens, leafy herbs and dairy samples) for 24-48h. Presumptive cephalosporinase-producing *E. coli* were subcultured on MacConkey agar (Difco) containing 1 mg/L cefotaxime and blood agar, and confirmed as *E. coli* using MALDI-TOF MS (Bruker Daltonik GmbH) before further tested for cephalosporinase production.

Quinolone resistant *E. coli*
Aliquots from the overnight BPW-ISO broth from sheep faecal, leafy greens, leafy herbs and dairy samples were plated onto MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin. Plates were incubated at 41.5±1°C (faecal samples) or 44±1°C (leafy greens, leafy herbs and dairy samples) for 20±2h. Presumptive QREC were subcultured on MacConkey agar (Difco) containing 0.06 mg/L ciprofloxacin and blood agar, and confirmed as *E. coli* using MALDI-TOF MS (Bruker Daltonik GmbH) before further phenotypical testing.

Carbapenemase-producing *Enterobacteriaceae*
Aliquots from the overnight BPW-ISO broth from all caecal, faecal, meat, leafy greens, leafy herbs and dairy samples were plated onto chromID™ CARBA and chromID™ OXA-48 agar (bioMérieux, Marcy l'Etoile, France). 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 (Bruker Daltonik GmbH) before further phenotypical testing.

Colistin resistant *E. coli*
Aliquots from the overnight BPW-ISO broth from leafy greens, leafy herbs and dairy products were plated onto SuperPolymyxin agar (Oxoid) and incubated at 44±1°C for 20±2h (Nordmann *et al.* 2016). Presumptive positive colonies were selected, subcultured on blood agar and SuperPolymyxin agar, and confirmed as *E. coli* using MALDI-TOF MS (Bruker Daltonik GmbH) 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 (Hasman *et al*. 2005, Briñas *et al.* 2002, Pérez-Pérez *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 presumptive carbapenemase-producing *Enterobacteriaceae*, PCR was performed for the identification of the genotypes NDM, KPC, VIM, IMP and OXA-48 according to published protocols (Mushtaq *et al*. 2011, Schechner *et al*. 2009, Ellington *et al*. 2007, Poirel *et al*. 2004).
For the presumptive colistin resistant *E. coli*, PCR was performed for the identification of the genotypes *mcr-1, mcr-2, mcr-3, mcr-4* and *mcr-5* according to the EURL-AR protocol (Rebelo *et al.* 2018).
Whole genome sequencing (WGS) was performed on isolates exhibiting phenotypic resistance where the genotypic identification procedures mentioned above were negative or inconclusive. DNA was extracted using QIAamp® DNA Mini Kit (QIAGEN, Hilden, Germany) and sequencing was performed at Eurofins GATC Biotech GmbH (Constance, Germany) on an Illumina HiSeq. The WGS data were quality controlled by adapter and quality trimming using Trimmomatic (Bolger *et al.* 2014), and assembled using SPAdes v3.11.0 using the "--careful" parameter (Bankevich *et al.* 2012). Genetic characterisation of the isolates was performed using the online tools with default settings from the Center for Genomic Epidemiology (http://www.genomicepidemiology.org) searching for both acquired and intrinsic antimicrobial resistance genes.

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 25.03.2019) were used, except for azithromycin for *E. coli* for which cut-off values are not defined. See Appendix 6 for definitions of cut-off values.

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

Antimicrobial group	Antimicrobial agents	*E. coli**	*Salmonella* spp.	*Enterococcus* spp.	*Campylobacter jejuni*	*Staphylococcus aureus*
Tetracyclines	Tetracycline	X	X	X	X	X
	Tigecycline	X	X	X		
Amphenicols	Chloramphenicol	X	X	X		X
Beta-lactamase sensitive penicillins	Benzylpenicillin					X
Penicillins with extended spectrum	Ampicillin	X	X	X		
Second generation cephalosporins	Cefoxitin	(X)				X
Third generation cephalosporins	Cefotaxime	X	X			
	Ceftazidime	X	X			
Fourth generation cephalosporins	Cefepime	(X)				
Carbapenems	Meropenem	X	X			
	Ertapenem	(X)				
	Imipenem	(X)				
Trimethoprim and derivatives	Trimethoprim	X	X			X
Sulfonamides	Sulfamethoxazole	X	X			X
Macrolides	Erythromycin			X	X	X
	Azithromycin	X	X			
Lincosamides	Clindamycin					X
Streptogramins	Quinupristin and dalfopristin			X		X
Streptomycins	Streptomycin				X	X
Other aminoglycosides	Gentamicin	X	X	X	X	X
	Kanamycin					X
Fluoroquinolones	Ciprofloxacin	X	X	X	X	X
Other quinolones	Nalidixic acid	X	X		X	
Glycopeptides	Vancomycin			X		X
	Teicoplanin			X		
Steroid antibacterials	Fusidic acid					X
Pleuromutilins	Tiamulin					X
Polymyxins	Colistin	X	X			
Other antibacterials	Linezolid			X		X
	Daptomycin			X		
	Mupirocin					X
	Rifampicin					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.

Quality assurance systems

The following susceptible bacteria were included as quality control on a regular basis: *E. coli* ATCC 25922, *E. faecalis* ATCC 25922 and *S. aureus* ATCC 29213. 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. The susceptibility data were stored as discrete values (MIC). Data management and analysis was performed in SAS-PC System® v 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and in R version 3.5.2 Copyright (C) 2016 The R Foundation for Statistical Computing Platform. The 95% confidence intervals were calculated by the exact binomial test using R v 3.5.2 for Windows (R Development Core Team, 2019).

Appendix 4:
Sampling, microbiological methods and data processing of zoonotic and non-zoonotic enteropathogenic bacteria in 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 jejuni
Caecal samples were collected by the Norwegian Food Safety Authority at slaughter. Samples from flocks identified as *Campylobacter* positive in the surveillance programme for *Campylobacter* spp. in broiler flocks and flocks with unknown *Campylobacter* status were included. Caecal content from one broiler flock were plated directly onto mCCDA agar (Oxoid) and incubated under microaerobic conditions at 41.5±1°C for 48h. Typical colonies were subcultured on blood agar and confirmed as *Campylobacter jejuni* using MALDI-TOF MS.

Susceptibility testing animal isolates
Isolates were tested for antimicrobial susceptibility using broth microdilution. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacteria to be tested. For animal isolates, epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 25.03.2019) were used, except for colistin for *Salmonella* spp. where EFSA recommended cut-off was used, and for azithromycin 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 (see also Appendix 6).

Quality assurance systems NORM-VET
The following susceptible bacteria were included as quality control on a regular basis: *E. coli* ATCC 25922, *C. coli* 2012-70-443-2 and *C. jejuni* ATCC 33560. NVI has a quality assurance system according to the requirements of NS-EN ISO/IEC 17025. The participating laboratories at NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in external quality assurance programmes for veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit Loughborough, UK), and for resistance monitoring (EURL for Antimicrobial Resistance in Denmark).

Data processing animal isolates
Susceptibility data were recorded and stored in the sample registration system at NVI. The susceptibility data were stored as discrete values (MIC). Data management and analysis was performed in SAS-PC System® v 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and in R version 3.5.2 Copyright (C) 2016 The R Foundation for Statistical Computing Platform. 95% confidence intervals were calculated by the exact binomial test using R version 3.5.2 for Windows (R Development Core Team, 2019).

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. 2018 was the nineteenth 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 2018 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. in blood cultures (9 months); *Streptococcus agalactiae*, *Streptococcus dysgalactiae* and *Candida* spp. from blood cultures (12 months); *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenza* spp. from blood cultures and cerebrospinal fluids were only included from January and February 2018 due to reorganisation of the reference laboratories at the Norwegian Institute of Public Health; *S. aureus* from wound specimens (1 week); *S. dysgalactiae* from wound specimens (4 weeks); *S. pneumoniae* from respiratory tract samples (3 weeks); *E. coli* from urinary tract infections (3 days); *Klebsiella* spp. and *Enterococcus* spp. from urinary tract infections (3 weeks); *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* from all samples (12 months). *S. pneumoniae, S. pyogenes,* and *H. influenzae* from blood cultures and cerebrospinal fluids were analysed at the the Norwegian Institute of Public Health in Oslo. *N. gonorrhoeae* and *Candida* spp. isolates were analysed at Oslo University Hospital (Ullevål and Rikshospitalet, respectively). MRSA and *S. agalactiae* isolates were analysed at St. Olav University Hospital in Trondheim. *S. dysgalactiae* isolates were analysed at Haukeland Univerity Hospital and Østfold Hospital Trust. *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., and *S. aureus* 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 from 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*, *S. dysgalactiae, H. influenzae* 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 were also tested for mutations in the *rpoB* gene to detect rifampicin resistance.

Confirmation of resistance phenotypes

E. coli and *Klebsiella* spp. with reduced susceptibility to third generation cephalosporins were examined for ESBL production using ESBL combination MIC gradient tests according to the instructions of the manufacturer (Liofilchem). *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 resistant *S. pneumoniae*, *S. aureus, S. pyogenes, S. agalactiae* and *S. dysgalactiae* isolates were analysed for determination of MLS phenotype using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

Quality control

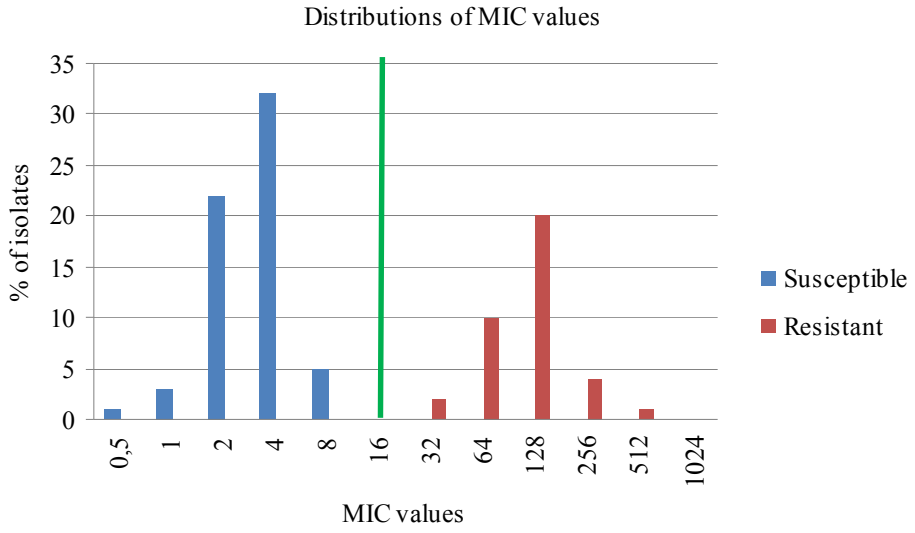
The following strains were used for quality control: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 (ESBL positive), *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. pneumoniae* ATCC 49619, *S. pneumoniae* TIGR4, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. aureus* ATCC 43300 (heterogeneous 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, *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 ECOFF values are presented at http://www.eucast.org/.
The terms and usage of these two ways of classification of resistance are further explained below. The ECOFF would normally be lower for minimum inhibitory concentration (MIC) values and higher for disk diameters than the clinical breakpoints. However this is not always the case.



Epidemiological cut-off values
The ECOFF may indicate emerging resistance in the bacterial populations. Based on the distribution of the MIC values or the inhibition zone diameter distribution, each bacterial population could (in an ideal case) be divided into two 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 level 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 Journal 2019; 17(2):5598 as follows:

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

Appendix 7: Cut-off values NORM-VET

Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 25.03.2019) 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.

Antimicrobials	Resistant MIC (mg/L)	*Salmonella* spp.	*Escherichia coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Campylobacter coli*	*Campylobacter jejuni*	*Staphylococcus aureus*
Ampicillin	> 4			■	■			
	> 8	■	■					
Benzylpenicillin	>0.125							■
Azithromycin*	ND	ND	ND					
Cefotaxime	> 0.25		■					
	> 0.5	■						
Cefoxitin	>4							■
Ceftazidime	> 0.5		■					
	> 2	■						
Chloramphenicol	> 16	■	■					■
	> 32			■	■			
Ciprofloxacin	> 0.064	■	■					
	> 0.5					■	■	
	> 1							■
	> 4			■	■			
Clindamycin	> 0.25							■
Colistin	> 2	#	■					
Daptomycin	> 4			■				
	> 8							
Erythromycin	> 1							■
	> 4			■			■	
	> 8				■	■		
Fusidic acid	> 0.5							■
Gentamicin	> 2	■	■			■	■	■
	> 32			■	■			
Kanamycin	> 8							■
Linezolid	> 4			■	■			■
Meropenem	> 0.125	■	■					
Mupirocin	> 1							■
Nalidixic acid	> 16	■	■			■	■	
Narasin	> 2			■	●			
Quinupristin- dalfopristin*	ND			ND	ND			
	> 1							■
Rifampicin	> 0.032							■
Streptomycin	> 4					■	■	
	> 16							■
Sulfamethoxazole	> 64		■					
	> 128							■
	> 256	●						
Teicoplanin	> 2			■	■			
Tetracycline	> 1						■	■
	> 2					■		
	> 4			■	■			
	> 8	■	■					
Tiamulin	> 2							■
Tigecycline	> 0.25				■			
	> 0.5		■	■				
	> 1	#						
Trimethoprim	> 2	■	■					■
Vanomycin	> 2							■
	> 4			■	■			

■ Cut-off values recommended by EUCAST. *Cut-off not defined (ND) by EUCAST.

● 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.	*Haemophilus influenzae*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Streptococcus dysgalactiae*	*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																
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			■											
	≤ 8	> 8	■	■												
Chloramphenicol	≤ 2	> 2			■											
	≤ 8	> 8							■							
Ciprofloxacin	≤ 0.03	> 0.06				■										
	≤ 0.06	> 0.06			■											
	≤ 0.25	> 0.5	■	■												
	≤ 0.5	> 0.5														
	≤ 1	> 1					■									
	≤ 4	> 4						■								
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.	*Haemophilus influenzae*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Streptococcus dysgalactiae*	*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														
	≤ 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																
Nitrofurantoin	≤ 64	> 64	■													
Oxacillin									■[1]							
Penicillin G	≤ 0.06	> 1				■										
	≤ 0.06	> 2							■							
	≤ 0.25	> 0.25								■	■	■				
					■[1]											
Pip-Tazo**	≤ 8	> 16	■	■												
Rifampicin	≤ 0.06	> 0.5					■									
Spectinomycin	≤ 64	> 64				■										
Tetracycline	≤ 0.5	> 1				■										
	≤ 1	> 2			■		■		■	■	■	■				
	≤ 2	> 2														
Tigecycline	≤ 0.25	> 0.25						■								
	≤ 0.5	> 0.5	■				■									
Trimethoprim	≤ 1	> 1						■								
	≤ 2	> 4	■	■												

Antimicrobials	MIC (mg/L) S	MIC (mg/L) R	*Escherichia coli*	*Klebsiella* spp.	*Haemophilus influenzae*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Streptococcus dysgalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
TMS***	≤ 0.5	> 1			■											
	≤ 1	> 2							■	■		■				
	≤ 2	> 4	■	■			■									
Vancomycin	≤ 2	> 2									■					
	≤ 4	> 4					■	■								
Voriconazole	≤ 0.06	> 0.25											■			
	≤ 0.125	> 0.25													■	■

[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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