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NORM
NORM-VET

Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM)

Veterinærinstituttet
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INTRODUCTION

Antimicrobial resistance is an emerging problem worldwide. It reduces the effectiveness of antimicrobial treatment of infectious diseases in humans and animals thereby leading to increased morbidity and mortality, as well as higher costs. It is well established that there is a strong association between the usage of antimicrobial agents and the occurrence of resistance. The selective pressure exerted following use of antimicrobial agents is a key issue in the epidemiology of resistance. Moreover, resistance can be disseminated through the spread of resistant pathogenic bacteria themselves or by horizontal transfer of resistance genes from one type of bacteria to another. Such transfer is not limited to closely related bacteria; it can also take place between bacteria of different evolutionary origins and/or ecological niches. Thus, antimicrobial drug usage and resistance in one ecological compartment can have consequences for the occurrence of resistance in another compartment. When addressing antimicrobial resistance – the occurrences, causes, consequences and preventive measures – a holistic approach is needed, encompassing both data on usage and resistance in human and veterinary medicine, as well as microbes in food production.

Several countries have implemented monitoring programmes for antimicrobial resistance and usage of antimicrobial agents in recent years. Some programmes focus primarily on human usage and resistance in human pathogens, whereas others also include data concerning veterinary medicine and food production. The EU supported this broad approach in 1998 through the Copenhagen recommendations and at later follow-up conferences. The World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Animal Health Organization (OIE) have through several expert consultations emphasised the importance of a One Health approach to monitoring of antimicrobial drug usage and resistance in both human and veterinary medicine. Several reports and recommendations have been published in this regard including the WHO Global Action Plan adopted at the World Health Assembly in May 2015.

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. Again, the importance of monitoring both the human and veterinary sectors, including food production, was emphasised. The action plan recognised the need for ongoing surveillance as a fundamental component of the strategy for containment of antimicrobial resistance. The NORM and NORM-VET programmes were consequently established in order to provide and present microbiologically and epidemiologically valid 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 drug 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 by 2020 compared to 2012.

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 the veterinary and food production sectors was established in 2000 and is coordinated by the Norwegian Veterinary Institute. The usage of antimicrobial agents is based on reporting of wholesalers' data for humans and animals, which was made mandatory from January 1st 2002, as well as human prescription data reported to the Norwegian Institute of Public Health. Data on the usage of feed additives, i.e. coccidiostat growth promoters, are collated at the Norwegian Food Safety Authority that is also responsible for the Veterinary Prescription Register; data from this register have been applied to present data by fish species.

This report, which is the sixteenth annual joint report from NORM and NORM-VET, presents data for 2015. In addition to resistance data, the NORM/NORM-VET reports present data on the usage of antimicrobial agents in humans and animals in Norway. The present report, together with earlier reports and reports from the years to come, form a basis for the detection, interpretation and evaluation of trends regarding usage of antimicrobial agents and occurrence of resistance in Norway. The NORM and NORM-VET programmes are valuable tools for setting policies, assessing risks and evaluating interventions.

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 2016

SAMMENDRAG

Dette er den sekstende 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 2015. Data fra relevante prosjekter som ikke er med i de kontinuerlige overvåkingsprogrammene, presenteres også.
Både NORM og NORM-VET programmene 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

Forbruket av antibiotika i norsk husdyrproduksjon og akvakultur er lavt. Totalsalget av veterinære antibiotika til terapeutisk bruk på landdyr i 2015 var 5850 kg. Fra 1993 til 2015 er salget av veterinære antibiotika til landdyr redusert med 37 %. For preparater som nesten utelukkende benyttes til produksjonsdyr (landdyr) er reduksjonen i denne perioden på 39 %. Salget av veterinære antibakterielle preparater som kun brukes til kjæledyr, har økt med 27 % (fra 398 til 436 kg) noe som delvis kan forklares ved at antallet vetrinærpreparater til kjæledyr har økt og at det derved brukes mindre av antibakterielle midler godkjent til humanmedisinen.
Forbruksmønsteret til produksjonsdyr har utviklet seg i gunstig retning siden 1993 idet andelen av rene penicillinpreparater har økt fra 19 % i 1993 til 59 % i 2015. Årsaken til dette er redusert forbruk av kombinasjonspreparater med penicillin og dihydrostreptomycin – fra 31 % i 1993 til 10 % i 2015. Siden det første penicillinpreparatet til smådyr kom på markedet i Norge i 1994 har bruk av veterinære penicillinpreparater, i kg, til smådyr økt fra 1 % til 76 % av totalsalget av antibakterielle midler markedsført kun til kjæledyr. Salget av antibakterielle VMPs for bruk til matproduserende landdyr og som er listet av WHO som kritisk viktige midler med høyest prioritet for humanmedisinen, dvs. 3. og 4. generasjons cefalosporiner, makrolider og kinoloner, er svært lavt i Norge. Salget av legemiddelformer beregnet til flokkbehandling av slike dyr er også svært lavt. Nedgangen i antibiotikaforbruket til produksjonsdyr (landdyr) og endringene i forskrivningsmønsteret skyldes først og fremst at husdyrnæringen i andre halvdel av 1990-tallet gjennomførte systematiske kampanjer for å redusere forbruket av antibiotika til dyr, samt for riktig bruk av antibiotika.
Landbruks- og matdepartementet har i sin handlingsplan mot antibiotikaresistens (2015-2020) satt som målsetning at forbruket av antibiotika til matproduserende landdyr skal reduseres med minst 10 % og til kjæledyr med minst 30 % sammenlignet med 2013. Sammenlignet med 2013 var forbruket til matproduserende landdyr, korrigert for biomasse, 2 % lavere i 2015 mens til kjæledyr var salget, i kg, 17 % lavere i 2015. Dette må imidlertid tolkes med stor forsiktighet siden trimetoprim+sulfa tabletter til hund ble avregistrert i denne perioden og ser ut til å ha blitt delvis erstattet av et 3. generasjons cefalosporin som doseres mange ganger lavere.
Totalsalget av veterinære antibiotika til terapeutisk bruk hos oppdrettsfisk i Norge var i 2015 på 273 kg aktiv substans, hvorav 69 % var amfenikoler mens tallet i 2014 var 79 %. I 2013 var andre kinoloner den mest solgte antibakterielle klassen til bruk på oppdrettsfisk (76 % av totalsalget). Forbruket av antibiotika i oppdrettsnæringen er redusert med 99 % siden 1987. Denne betydelige reduksjonen kan tilskrives innføringen av effektive vaksiner til laks og ørret samt andre infeksjonsforebyggende tiltak, herunder bedrede miljøforhold.
Avoparcin ble brukt som antibakteriell vekstfremmer i norsk broiler- og kalkunproduksjon fra 1986 inntil det ble forbudt i 1995. Samme år innførte husdyrnæringene et selvpålagt forbud mot bruk av alle antibakterielle vekstfremmere. Koksidiostatika som fôrtilsetningsstoff brukes fremdeles i norsk fjørfeproduksjon. Narasin ble introdusert i 1995, og siden 1996 har forbruket av koksidiostatika til fjørfe vært dominert av narasin. I desember 2014 vedtok fjørfenæringen å fase ut all bruk av narasin til slaktekylling i løpet av 2016. Utfasingen begynte i februar 2015 og fra 2014-2015 ble salget, i kg narasin, redusert med ca 14 %. Videre sier Landbruks- og matdepartementet i sin handlingsplan mot antibiotikaresistens (2015-2020) at «Narasin og andre koksidiostatika med antibakteriell virkning er faset ut av kyllingproduksjonen forutsatt at dette ikke går utover dyrehelse og dyrevelferd eller øker bruken av antibiotika til behandling.».

Forbruk av antibiotika hos mennesker

Totalt antibiotikasalg inkluderer alt forbruk hos mennesker i Norge til primærhelsetjenesten og institusjoner. I 2015 gikk det totale salget av antibakterielle midler til systemisk bruk hos mennesker (J01 unntatt methenamine) ned 4% sammenlignet med 2014; fra 15,7 til 15,1 DDD/1000 innbyggere/døgn. Forbruket er redusert med 13 % siden 2012. Andelen smalspektrede penicilliner (J01CE) av totalt salg (J01 unntatt metenamin) er redusert; i år 2000 var andelen 32 % av det totale salget og i 2015 25 %.
Rundt 85 % av totalt antall DDD av antibakterielle midler brukes i primærhelsetjenesten, dvs. utenfor helseinstitusjoner. Bruken av antibiotika i primærhelsetjenesten har gått ned siden 2012. I primærhelsetjenesten i 2015 var penicilliner (J01C) mest brukt (41% av DDD) etterfulgt av tetracykliner (J01A, 19%). De fire hyppigst brukte antibiotika i 2015 var fenoksymetylpenicillin, pivmecillinam, doksycyklin, og amoxicillin. Disse fire representerte ca. halvparten av alle forskrevne resepter og ca halvparten av alle solgte DDD.
Antibiotikasalg (i DDD) til sykehus utgjorde 7,4 % av totalt salg av antibakterielle midler til mennesker i 2015. I norske sykehus ble det gjennomsnittlig brukt 74 DDD/100 liggedøgn i 2015. Dette er en økning på 21 % siden 2006. Antall DDD/sykehusinnleggelse (3,2 i 2015) økte med 6 % i samme periode. Terapimønster av antibakterielle midler i sykehus endres ikke mye fra ett år til et annet. I sykehus ble penicilliner (J01C) mest brukt (ca 50 % målt i DDD). Cefalosporiner er den nest største antibiotikagruppen med 17 % av alle DDD. Det er store variasjoner mellom sykehus, både målt i total antibiotikamengde (DDD/100 liggedøgn) og i terapeutisk profil. Variasjonene kan ikke forklares bare med forskjeller i aktivitet eller sammensetning av pasientpopulasjon.

Resistens hos indikatorbakterier fra dyr

Forekomsten av ervervet antibiotikaresistens blant bakterier som er en del av den normale tarmfloraen, kan være indikator på selektivt antibiotikapress i ulike populasjoner.

I 2015 ble det fra storfe og svin undersøkt over 250 *Escherichia coli* fra blindtarmsprøver fra hver dyreart. Forekomsten av resistens hos storfeisolatene var lav med 95,4 % av isolatene fullt følsomme og kun 0,8 % multiresistente isolater. Blant svineisolatene var 78,9 % av isolatene fullt følsomme, mens 10,8 % av isolatene var multiresistente. Sammenliknet med tidligere år kan det se ut som om andelen *E. coli* som er fullt følsomme, har økt, men det er sannsynlig at nedgangen i resistens skyldes endringer i hvilke antibiotika det testes for. Forekomsten av resistente *E. coli* hos norske storfe og svin er lav i et internasjonalt perspektiv.

For å skaffe mer kunnskap om resistens mot kritisk viktige antibiotika, ble det brukt selektive metoder for påvisning av hhv. *E. coli* resistente mot tredjegenerasjons cefalosporiner, karbapenemaseproduserende *E. coli* og kinolonresistente *E. coli* på det samme prøvematerialet fra storfe og svin, samt fra kjøttprøver fra disse (~245 fra hver kategori av kjøtt). Isolater resistente mot cefotaksim og/eller ceftazidim ble påvist i én blindtarmsprøve (0,4 %) og tre kjøttprøver (1,2 %) fra storfe, og i 29 blindtarmsprøver (11,2 %) og to kjøttprøver (0,8 %) fra svin. Majoriteten av isolatene var resistente pga. kromosomale mutasjoner i promotorregionen til AmpC genet. Det ble imidlertid funnet plasmidbårne gener som årsak til resistensen hos to isolater fra storfekjøtt ($bla_{CTX-M-1}$) og tre fra svin (bla_{CMY-2} og $bla_{CTX-M-27}$). Ingen karbapenemaseproduserende *E. coli* ble påvist i noen av prøvene. Kinolonresistente *E. coli* ble påvist i 7,2 % av blindtarmsprøvene og 0,8 % av kjøttprøvene fra storfe. Fra svin ble kinolonresistente *E. coli* påvist i 54,3 % av blindtarmsprøvene, og i 6,2 % av kjøttprøvene. Dette indikerer at hygienetiltak forhindrer omfattende kontaminering av kjøttet under slakteprosessen. Med tanke på spredningspotensiale, er det viktig å videreføre overvåkningen av forekomst av resistens overfor kritisk viktige antibiotika hos bakterier i matproduserende dyr og i mat.

Totalt 243 prøver av salat ble undersøkt for indikator *E. coli*, samt selektivt for *E. coli* resistente mot tredjegenerasjons cefalosporiner, kinolonresistente *E. coli* og karbapenemaseproduserende *E. coli*. *E. coli* ble påvist fra 30,0 % av salatprøvene, og av disse var 82,2 % fullt følsomme. Det ble påvist *E. coli* resistente mot 3. og 4. generasjons cefalosporiner fra én prøve (bla_{OXA-1}), og kinolonresistente *E. coli* fra to prøver (0,8 %). Ingen karbapenemaseproduserende *E. coli* ble påvist. Salat kan bli forurenset av antibiotikaresistente bakterier fra dyr og mennesker. Siden salat er et produkt som spises uten videre varmebehandling er forekomst av resistente bakterier bekymringsfullt med tanke på spredningspotensiale, og videre overvåkning av salat og andre grønnsaker er viktig for å skaffe mer kunnskap og følge eventuelle trender.

Prøver fra 179 melkekubesetninger ble undersøkt for forekomst av meticillinresistente *Staphylococcus aureus* (MRSA). Det ble påvist MRSA (CC1, *spa*-type t127) fra én besetning (0,6 %).

Resistens hos zoonotiske bakterier og andre enteropatogene bakterier

Zoonosebakterier isolert fra dyr

I 2015 ble det undersøkt totalt 15 *Salmonella* spp. isolater fra dyr. Av disse var 12 isolater fullt følsomme, mens tre *S.* Typhimurium isolater var resistent mot henholdsvis tre, fire og fem antibiotika. Disse tre isolatene var opprinnelig isolert fra en hund og fra to storfe.

Av 217 *Campylobacter coli* isolater fra svin var 63,6 % fullt følsomme mens 5,5 % var multiresistente. *C. coli* har tidligere kun vært undersøkt i 2009. Resultatene fra 2015 viser en økning av de tre vanligst identifiserte resistensformene. Økningen er imidlertid ikke statistisk signifikant og det er behov for ytterligere overvåkning for å se om økningen er reell eller kun en tilfeldig variasjon. I et internasjonalt perspektiv er forekomsten av resistens hos *C. coli* fra norske svin lav.

Kliniske isolater av tarmpatogene bakterier fra mennesker

For kliniske *Salmonella* isolater fra mennesker sett under ett var forekomsten av multiresistens (MDR) litt under 7 %, mens forekomsten av bredspektrede beta-laktamaser (ESBL) holdt seg under 2 %. Når det gjelder blodkulturisolater (n=46), var forekomsten av MDR høyest for *Salmonella* spp. (alle serovarer unntatt *S.* Typhi, Paratyphi, Typhimurium og Enteritidis). Forekomsten av resistens var høyere for flere antibiotika i *S.* Typhimurium-gruppen (inkludert *S. enterica* serovar 4,[5],12:i:-) enn hos andre *Salmonella* serovarer. Forekomsten av resistens mot tetracyklin og ampicillin er også økende i denne bakteriegruppen hos pasienter smittet i utlandet.

Når det gjelder *Campylobacter*, er det økende resistens mot tetracyklin og kinoloner hos isolater ervervet ved innenlandssmitte, men forekomsten er fortsatt betydelig lavere enn for utenlandssmittede isolater.

De fleste tilfeller av *Shigella* infeksjoner i Norge kan knyttes til smittekilder i utlandet. Antibiotikaresistens var følgelig utbredt hos *Shigella* isolater, spesielt hos *S. flexneri,* i likhet med det som rapporteres fra andre land. ESBL hos *Shigella* er økende med en forekomst på 7 % i 2014 og vel 20 % i 2015. Det er også en tendens til økende resistens mot kinoloner hos *Shigella.*

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

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var fortsatt lav i 2015. Det ble påvist ni tilfeller av meticillinresistente *Staphylococcus aureus* (MRSA) blant de 1277 blodkulturisolatene (0,7 %) som ble inkludert i NORM-protokollen. Dette samsvarer godt med tall fra laboratorienes datasystemer som rapporterte 19 av 1801 (1,1 %) *S. aureus* fra blodkultur og spinalvæske som MRSA. Andelen er på samme nivå som i 2013 (1,0 %) og 2014 (0,8 %). Meldesystemet for infeksjonssykdommer (MSIS) registrerte 785 tilfeller av MRSA infeksjon i 2015 mot 659 i 2013 og 832 i 2014. De fleste tilfellene var pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (14 av 1125, 1,2 %) hvilket er på samme nivå som i 2013 (1,2 %) og 2014 (1,3 %). MSIS registrerte videre 1448 tilfeller av MRSA kolonisering i 2014 mot 1035 i

2014. Det totale antallet MRSA meldinger økte dermed fra 1867 i 2014 til 2233 i 2015 (+ 20 %). Overvåkingen viser at det totale antallet MRSA registreringer fortsetter å øke, men at antallet infeksjoner for første gang er redusert. Det påvises fortsatt svært få alvorlige infeksjoner. Økningen i antall meldte koloniseringer sammenfaller i tid med økt migrasjon fra land med høy forekomst av MRSA, men kan også skyldes høyere testaktivitet.

Blodkulturisolater av *E. coli* og *Klebsiella* spp. viste stabil forekomst av resistens mot bredspektrede antibiotika i 2015. Forekomsten av resistens og nedsatt følsomhet for gentamicin hos *E. coli* var 6,4 % i 2015 sammenliknet med 8,6 % i 2014. Forekomsten av resistens og nedsatt følsomhet for ciprofloxacin i *E. coli* ble redusert fra 13,6 % i 2014 til 11,9 % i 2015. Det er en klar samvariasjon mellom forbruket av fluorokinoloner og nedsatt følsomhet for denne antibiotikagruppen. *Klebsiella* spp. hadde lavere forekomst av resistens mot aminoglykosider og fluorokinoloner enn *E. coli*.

Produksjon av bredspektrede betalaktamaser (ESBL) er blitt et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 127/1952 *E. coli* (6,5 %) og 24/823 *Klebsiella* spp. (2,9 %) fra blodkultur ble rapportert som ESBL positive i 2015. Forekomsten er svakt økende for *E. coli* (5,0 % i 2013; 5,8 % i 2014) og stabil for *Klebsiella* spp. (2,8 % i 2013; 3,4 % i 2014). Andelen av ESBL positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (6,5 %) enn fra urinprøver (3,1 %). Karbapenemaseproduserende Enterobacteriaceae (CRE), *Pseudomonas aeruginosa* og *Acinetobacter* spp. har vært meldepliktige til MSIS siden juli 2012. Antallet pasienter meldt med CRE økte fra 11 i 2014 til 30 i 2015, mens antallet karbapenemaseproduserende *P. aeruginosa* (n=7) og *Acinetobacter* spp. (n=15) var uendret fra 2014.

Blant *Haemophilus influenzae* isolater fra systemiske infeksjoner (n=96) var 11,5 % betalaktamase positive og 8,3 % resistente mot cefuroxim som uttrykk for kromosomal betalaktamresistens. Åtte av ti *Neisseria meningitidis* isolater fra systemiske infeksjoner hadde nedsatt følsomhet for penicillin G, men de var fortsatt følsomme for andre relevante antibiotika. *Neisseria gonorrhoeae* (n=259) viste nedsatt følsomhet for penicillin G (96,9 %) og azitromycin (33,6 %). Hele 62,2 % var resistente mot ciprofloxacin. Tre isolater (1,2 %) var også resistente mot cefixim, men alle var følsomme for ceftriaxon.

Det ble bare påvist et enkelt enterokokkisolat fra blodkultur med klinisk signifikant vankomycinresistens i 2015 (VanB *E. faecium*). Forekomsten av nedsatt følsomhet for ampicillin i *E. faecium* ligger fortsatt på 80-90 %. Høygradig gentamicinresistens ble påvist i 13,1 % av *E. faecalis* og 39,4 % av *E. faecium*, dette er en svak nedgang fra henholdsvis 18,7 % og 40,8 % i 2014. Alle *E. faecium* isolater med høygradig gentamicinresistens hadde samtidig nedsatt følsomhet for ampicillin. Det ble ikke påvist linezolidresistente enterokokker i 2015.

Det ble påvist nedsatt følsomhet for penicillin G hos 7,5 % av *Streptococcus pneumoniae* fra blodkultur/spinalvæske. Dette er en økning fra 2013 (3,0 %) og 2014 (5,5 %). Ett enkelt blodkulturisolatisolat var penicillinresistent og hadde samtidig nedsatt følsomhet for cefalosporiner. Forekomsten av makrolidresistens var 4,8 % blant systemiske pneumokokkisolater.

Streptococcus pyogenes (betahemolytiske streptokokker gruppe A) fra blodkultur hadde stabil forekomst av erytromycinresistens (3,5 %) sammenliknet med 2013 (3,7 %). Forekomsten av resistens og nedsatt følsomhet for erytromycin blant *Streptococcus agalactiae* (betahemolytiske streptokokker gruppe B) økte fra 21,0 % i 2014 til 26,9 % i 2015. Alle isolatene var penicillin G følsomme.

I alt 318 tilfeller av tuberkulose ble meldt til MSIS i 2015. Det ble utført resistensbestemmelse av 245 *Mycobacterium tuberculosis* isolater. Fem isolater (2,0 %) fra pasienter smittet i henholdsvis Afrika (n=4) og Asia (n=1) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 210 *Candida* blodkulturisolater av elleve ulike species. De vanligste artene var *C. albicans* (n=139), *C. glabrata* (n=35), *C. tropicalis* (n=9) og *C. parapsilosis* (n=8). Bare ett isolat (*C. lipolytica*) hadde nedsatt følsomhet for amfotericin B. Det ble kun påvist enkelte non-albicans isolater med ervervet resistens mot fluconazol, men som forventet var det høy forekomst av resistens mot azoler hos *C. glabrata*. To *C. albicans* hadde nedsatt følsomhet for echinocandiner. Nøyaktig speciesbestemmelse er avgjørende for å forutsi iboende resistens og velge effektiv behandling. Resultatene er i samsvar med tidligere studier fra Norge.

Konklusjon

Antibiotikaresistens er fortsatt et begrenset problem i Norge når det gjelder bakterier fra både mennesker og dyr. Det lave forbruket av antibiotika og det fordelaktige forbruksmønsteret må opprettholdes for å bevare den gunstige situasjonen. Resultatene som presenteres i denne rapporten, viser at norske strategier for antibiotikabruk og antibiotikaresistens hittil har vært vellykkede både i husdyrholdet og i helsevesenet. Faren for økende resistensproblemer er imidlertid til stede i form av økt antibiotikaforbruk i Norge og import av resistente bakterier fra andre land. Det er derfor nødvendig med fortsatt aktiv innsats for å sikre at vi også i fremtiden kan gi effektiv antibiotikabehandling til dem som trenger det. NORM/NORM-VET-rapporten er et viktig bidrag til arbeidet med å forebygge utvikling og spredning av antibiotikaresistens.

SUMMARY

This is the 16th 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 2015. 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 usage of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in food producing animals in Norway is low. In 2015, the total sales of antimicrobial VMPs for terrestrial animals were 5,850 kg. The annual sales, in kg active substance, of antimicrobial VMPs approved for use in terrestrial animals decreased by approximately 37% from 1993 to 2015. The reduction in use is solely accounted for by a reduction in the use in food producing animals (39% reduction). For antimicrobial VMPs marketed for companion animals only an increase of 27% in the sales is observed for this periode; this increase can in part be explained by increased number of product presentations (name, form, strength and pack size) of antimicrobial VMPs marketed for companion animals and thus reduced prescribing of products marketed for humans.
The sales patterns of antimicrobial VMPs for terrestrial food producing animals have gradually become more favourable as the proportion of penicillin use has increased; the proportion accounted for by pure penicillin preparations rose gradually from 19% of total sales in 1995 to 59% in 2015. In this period, the sales of aminoglycosides decreased from 31% to 10% of total sales; this is due to a reduction in the use of combination preparations of penicillin and dihydrostreptomycin in food producing animals. Sales of the antimicrobial VMPs defined by the World Health Organization (WHO) with highest priority for human medicine i.e. 3rd and 4th generation cephalosporins, fluoroquinolones and macrolides for terrestrial food producing animals are very low. The sales of antimicrobial VMPs applicable for group treatment in food producing animals (farmed fish excluded) have been low during the years 1993-2015. The antimicrobial VMPs sold are predominantly for treatment of individual animals, and injectable VMPs account for the major propotion.
The reduced sales of antimicrobial VMPs in terrestrial animals as well as the favourable prescribing patterns are mainly explained by a campaign on prudent use of antimicrobials conducted by the Norwegian husbandry organisations and the Norwegian Medicine Authority during the second part of the 1990s. Furthermore, a target set by the Norwegian husbandry organisations to reduce the sales by 25% with 1995 as the reference year is thought to have had a major impact on this decrease. The Ministry of Agriculture and Food has in its action plan against anti-bacterial resistance set a target of reducing the consumption of veterinary antimicrobial medicinal products in terrestrial and companion animals by at least 10% and 30%, respectively, with 2013 as reference year.
From 2013, the consumption for food producing terrestrial animals corrected for biomass has been stable, as a reduction of 2% is observed. The sales, in kg active substance, for use in companion animals declined by 17% from 2013 to 2015. This figure should be interpreted with great caution as trimethoprim+sulfa tablets for dogs have been removed from the market during this period and seem to have been replaced by 3rd generation cephalosporin products for which the dosing is several orders lower than of trimethoprim+sulfa.
In 2015, the total sales of antimicrobial agents for therapeutic use in farmed fish were 273 kg of active substance. Amphenicols accounted for 67%. The sales of antimicrobial VMPs in Norwegian aquaculture declined by approximately 99% from 1987 to 1996 and have thereafter remained relatively constant. The reduction is mainly attributed to the introduction of effective vaccines and full-scale vaccination of salmonids. Following the ban of avoparcin as antimicrobial growth promoter in EU in 1995, narasin was introduced as coccidiostat feed additive in the Norwegian broiler production due to its effect on *Clostridium perfringens*. Since 1996 the sales of coccidiostat feed additives for use in Norwegian broiler production has been dominated by narasin. In February 2015, the poultry industry launched a project with the aim to phase out narasin by the end of 2016; as a consequence the sales of narasin, in kg active substance, declined by 14% from 2014 to 2015.

Usage of antimicrobial agents in humans

Antibiotics are prescription-only drugs in Norway, and overall antibiotic sales therefore include all consumption in humans in Norway i.e. primary care and institutions. The overall sales of antibacterials for systemic use in humans (J01 excl. methenamine) decreased by 4% from 15.7 DDD/1,000 inhabitants/day in 2014 to 15.1 in 2015. The overall consumption has decreased by 13% since 2012. The proportion of narrow-spectrum penicillins (J01CE) of total sales (J01, excl methenamine) was 32% in 2000 and has decreased to 25% in 2015.
Around 85% of total human sales of antibacterials are used in primary care, and sales to outpatients have decreased since 2012. The most important antibiotic groups in 2015 were penicillins (J01C, 41% of DDDs) and tetracyclins (J01A, 19%). The four most commonly prescribed antibiotics for outpatients were phenoxymethylpenicillin, pivmecillinam, doxycycline, and amoxicillin. These four represented approximately half of all prescriptions and DDDs.
In 2015, antibacterial sales to hospitals represented 7.4% (in DDDs) of total sales in the country. A mean use of 74 DDD/100 bed days was observed, which is an increase of 21% over the last 10 years. The number of DDDs/admission (3.2 in 2015) increased by 6% in the same period. The prescription pattern in hospitals does not change much from one year to another. Half of the hospital use, measured in DDDs, is penicillins (J01C). The second largest group (17%) is cephalosporins. There are large variations between hospitals in total antibiotic use and therapy profile which cannot be accounted for solely by differences in activity or patient populations.

Resistance in indicator bacteria from animals

The prevalence of antimicrobial resistance among bacteria of the normal enteric microflora can serve as an indicator for the selective antimicrobial pressure in various populations.

More than 250 *Escherichia coli* isolates from each of cattle and swine caecal samples were included in the surveillance in 2015. The prevalence of resistance among the bovine isolates was low with 95.4% of the isolates being susceptible to all antimicrobial agents tested and only 0.8% being multiresistant. Among the swine isolates, 78.9% were susceptible to all antimicrobial agents tested, and multi-resistance was detected in 10.8% of the isolates. Compared to previous years, the proportion of *E. coli* isolates being fully susceptible seems to have increased. However, the observed changes are probably due to changes made in the panel of antimicrobial agents tested for. In an international perspective, the occurrence of resistant *E. coli* in Norwegian cattle and swine is low.

To obtain more knowledge on the reservoirs of resistance to critically important antimicrobials, selective methods were included for detection of *E. coli* resistant to third generation cephalosporins, carbapenemase producing *E. coli* and quinolone resistant *E. coli* in the same cattle and swine caeacal samples and in meat thereof (~245 samples from each meat category). Isolates resistant to cefotaxime and/or ceftazidime were found in one caecal (0.4%) and three meat (1.2%) samples from cattle, and 29 caecal (11.2%) and two meat (0.8%) samples from swine. The majority of the isolates showed decreased susceptibility due to mutations in the promoter region of the chromosomally encoded AmpC gene, although two of beef isolates ($bla_{CTX-M-1}$) and three of the swine caecal isolates (bla_{CMY-2} and $bla_{CTX-M-27}$) showed decreased susceptibility due to plasmid encoded resistance genes. No carbapenemase producing *E. coli* were detected. Quinolone resistant *E. coli* were detected in 7.2% and 0.8% of the cattle caecal and beef samples, respectively. From swine, quinolone resistant *E. coli* were detected in 54.3% of the caecal, and in 6.2% of the pork samples. These results indicate that the hygienic measures taken during slaughter prevent extensive contamination to meat through the slaughtering process. Occurrence of resistance to critically important antimicrobial agents in food producing animals is of concern with regard to humans, and further monitoring is appropriate in the years to come.

A total of 243 samples of leafy salad were screened for the presence of indicator *E. coli*, *E. coli* resistant to third generation cephalosporins, quinolone resistant *E. coli* and for the presence of carbapenemase producing *E. coli*. *E. coli* were detected in 30.0% of the leafy salad samples, and 82.2% of the isolates were susceptible to all antimicrobial agents tested. Among the *E. coli*, one isolate was resistant to the 3. and 4. generation cephalosporins, cefotaxime and cefepime. The isolate carried the bla_{OXA-1} gene. Selective screening for *E. coli* resistant to third generation cephalosporins did, however, not reveal any isolates, indicating that the finding was a random finding and present at very low levels. No carbapenemase producing *E. coli* were detected. Quinolone resistant *E. coli* were detected from two samples (0.8%) by selective screening. Leafy salad has not previously been investigated in NORM-VET. During agricultural production and harvesting, leafy salad can become contaminated with antimicrobial resistant bacteria from animal and human sources. As salad is typically consumed raw and without any heat treatment, the presence of antimicrobial resistant bacteria is of concern, especially plasmid encoded resistance due to its dissemination potential. Further monitoring of vegetables is recommended, especially for those that are consumed raw.

Samples from a total of 179 cattle dairy herds were screened for the presence of MRSA. One positive sample was identified, giving a prevalence of MRSA in Norwegian dairy herds of 0.6%. The isolate belonged to clonal complex 1 (CC1), *spa*-type t127.

Resistance in zoonotic bacteria and non-zoonotic enteropathogenic bacteria

Animal isolates

In 2015, a total of 15 *Salmonella* spp. isolates from animals were susceptibility tested. Twelve isolates were fully susceptible, while three were resistant to three, four and five antimicrobial agents, respectively. These three isolates were all *S.* Typhimurium, and were recovered from one dog (monophasic isolate) and two cattle.

A total of 217 *Campylobacter coli* from swine caecal samples were included in the surveillance. 63.6% of the isolates were susceptible to all antimicrobial agents tested and 5.5% were multiresistant. *C. coli* has previously only been investigated in 2009, and an increase in resistance was observed for the three most frequently identified antimicrobial agents. However, these are non-significant results and further monitoring is needed to follow the situation in *C. coli* from swine. In an international perspective, the occurrence of resistance among *C. coli* from Norwegian swine is low.

Human clinical enteropathogenic isolates

The frequency of multidrug resistance (MDR) in human clinical isolates of all *Salmonella* serovars was just below 7%, and the frequency of ESBL stayed below 2%. Among the 46 *Salmonella* blood culture isolates, the highest frequency of MDR was found in *Salmonella* serovars other than *S.* Typhi, *S.* Paratyphi and the *S.* Typhimurium-group. Antimicrobial resistance in general is more prevalent in the *S.* Typhimurium-group (including *S. enterica* serovar 4,[5],12:i-) than in other serovars, and resistance to ampicillin and tetracycline is still increasing in this group. This applies to strains acquired abroad.

For *Campylobacter*, domestically acquired isolates are increasingly resistant to quinolones and tetracycline. However, resistance has not yet reached the same level as seen in isolates acquired abroad.

Most cases of shigellosis are acquired abroad, and there is widespread resistance, especially in *S. flexneri*, as reported from other countries. There may be a trend of increasing resistance to quinolones. The ESBL prevalence in *Shigella* was 20% in 2015. Antimicrobial resistance in *Yersinia enterocolitica* remains low, except for intrinsic resistance to ampicillin.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still low in Norway in 2015. Only nine methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among the 1,277 strains included in the NORM protocol (0.7%). During 2015 the total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 1,801, including 19 MRSA strains (1.1%). This prevalence is at the same level as in 2013 (1.0%) and 2014 (0.8%). The Norwegian Surveillance System for

Communicable Diseases (MSIS) registered 785 cases of MRSA infections in 2015 compared to 659 in 2013 and 832 in 2014. The majority of MRSA cases were reported to be wound infections and/or abscesses. The prevalence of MRSA among non-invasive *S. aureus* isolates is still very low at 1.2% (14/1,125) which is at the same level as 1.2% in 2013 and 1.3% in 2014. Furthermore, MSIS registered 1,448 cases of MRSA colonisation in 2015 compared to 1,035 in 2014. The total number of MRSA notifications thus increased from 1,867 in 2014 to 2,233 in 2015 (+ 20%). The results indicate an increasing number of MRSA notifications, but the number of infections decreased for the first time in 2015. The prevalence of invasive disease has remained stable at a low level. The increased number of colonisations coincides in time with increased migration from countries with a high MRSA prevalence, but may also be a consequence of increased test activity.

Antimicrobial resistance to broad-spectrum antimicrobials in *E. coli* and *Klebsiella* spp. blood culture isolates remained stable in 2015. The prevalence of gentamicin non-susceptibility in *E. coli* was 6.4% in 2015 compared to 8.6% in 2014. The prevalence of *E. coli* non-susceptibility to fluoroquinolones decreased from 13.6% in 2014 to 11.9% in 2015. There is a clear correlation between the total usage of fluoroquinolones and non-susceptibility to these agents. The prevalence of resistance to aminoglycosides and fluoroquinolones is lower in *Klebsiella* spp. isolates than in *E. coli*.

Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, including Norway. A total of 127/1,952 (6.5%) *E. coli* and 24/823 (2.9%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2015. The prevalence is slightly increasing for *E. coli* (5.0% in 2013; 5.8% in 2014) and stable for *Klebsiella* spp. (2.8% in 2013; 3.4% in 2014). The proportion of ESBL positive isolates is higher among *E. coli* from blood cultures (6.5%) than among urinary tract isolates (3.1%). Carbapenemase producing Enterobacteriaceae (CRE), *Pseudomonas aeruginosa* and *Acinetobacter* spp. have been notifiable to MSIS since July 2012. The number of patients reported with CRE increased from 11 in 2014 to 30 in 2015, whereas the numbers of carbapenemase producing *P. aeruginosa* (n=7) and *Acinetobacter* spp. (n=15) were unchanged from 2014.

Among *Haemophilus influenzae* isolates from systemic infections (n=96), 11.5% displayed beta-lactamase production and 8.6% were resistant to cefuroxime, thus indicating chromosomal resistance to beta-lactam antibiotics. Eight of ten *Neisseria meningitidis* isolates from systemic infections displayed reduced susceptibility to penicillin G, but all remained susceptible to other relevant antibiotics. *Neisseria gonorrhoeae* isolates (n=259) demonstrated non-susceptibility to penicillin G (96.9%) and azithromycin (33.6%), as well as resistance to ciprofloxacin (62.2%). Three isolates (1.2%) were resistant to cefixime but remained susceptible to ceftriaxone.

Only a single enterococcal blood culture isolate with clinically significant vancomycin resistance was detected in 2015 (VanB *E. faecium*). The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilised around 80-90%. High-level gentamicin resistance (HLGR) was detected in 13.1% of *E. faecalis* and 39.4% of *E. faecium*, which is a decline from 18.7% and 40.8% in 2014, respectively. All HLGR *E. faecium* isolates were also non-susceptible to ampicillin. Enterococcal resistance to linezolid was not detected in 2015.

Non-susceptibility to penicillin G was detected in 7.5% of *Streptococcus pneumoniae* isolates from blood cultures and cerebrospinal fluids. This is an increase from 3.0% in 2013 and 5.5% in 2014. A single blood culture isolate was resistant to penicillin G and at the same time showed reduced susceptibility to cephalosporins. The prevalence of macrolide resistance was 4.8% among pneumococcal blood culture isolates.

Streptococcus pyogenes (group A streptococcus) isolates from blood cultures had a stable prevalence of erythromycin resistance (3.5%) compared to 2014 (3.7%). The prevalence of macrolide non-susceptibility in *Streptococcus agalactiae* (group B streptococci) increased from 21.0% in 2014 to 26.9% in 2015. All isolates were susceptible to penicillin G.

A total of 318 cases of tuberculosis were reported to MSIS in 2015. Susceptibility testing was performed on 245 *Mycobacterium tuberculosis* isolates. Five isolates (2.0%) originating from Africa (n=4) and Asia (n=1) were classified as multidrug resistant (MDR).

Susceptibility testing was performed on 210 *Candida* spp. blood culture isolates of eleven different species. The most common species were *C. albicans* (n=139), *C. glabrata* (n=35), *C. tropicals* (n=9) and *C. parapsilosis* (n=8). Only one yeast isolate (*C. lipolytica*) was non-susceptible to amphotericin B. Single non-albicans isolates with acquired fluconazole resistance were detected, and as expected there was a high prevalence of resistance to azoles among *C. glabrata*. Two *C. albicans* were non-susceptible to echinocandines. 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 clinically important microbes in Norway. The relatively low usage of antimicrobial agents as well as appropriate patterns of use must be maintained to preserve this rather favourable situation. The data presented in this report show that Norwegian antimicrobial policies in food production and healthcare have been successful. However, the situation may rapidly change if the use of antimicrobial agents in Norway increases or resistant clones are imported from abroad. A continued effort is needed to prevent the development and spread of antimicrobial resistance and thereby ensure the effectiveness of antimicrobials when such treatment is needed. The NORM/NORM-VET report is a vital component in the work aimed at preventing the development and spread of antimicrobial resistance in Norway.

POPULATION STATISTICS

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

TABLE 1. Human population in Norway as of January 1st, 2016.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	305,395	156,720	148,675
5 to 14 years	628,560	321,629	306,931
15 to 24 years	669,658	345,180	324,478
25 to 44 years	1,426,190	732,932	693,258
45 to 64 years	1,329,082	678,645	650,437
65 years and older	855,100	390,005	465,095
All age groups	5,213,985	2,625,111	2,588,874

TABLE 2. Livestock population in Norway in 2015.
Data provided by the Register of Production Subsidies as of 31.07.2016.

	Number* of	
Animal category	Herds	Animals
Cattle	14,200	854,000
Dairy cows only**	8,000	201,000
Suckling cow only**	4,100	70,000
Combined production (cow)**	740	31,800
Goat	1,300	66,900
Dairy goat**	300	33,700
Sheep	14,300	2,400,000
Breeding sheep > 1 year**	14,200	912,000
Swine	2,100	818,000
Breeding animal > 6 months**	1,100	51,000
Fattening pigs for slaughter**	1,900	449,000
Laying hen flocks > 250 birds	580	4,266,000
Broilers	640[1]	65,289,300[1]
Turkey, ducks, geese for slaughter (flock > 250 birds)	170	509,600

* Numbers > 100 rounded to the nearest ten, numbers > 1000 rounded to the nearest hundred. ** Included in above total.
[1]Number from Landbruksdirektoratet (based on deliveries to slaughter).

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2015. *Data provided by the Norwegian Directorate of Fisheries updated by 23.06.2016.*

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[3]	1,314,584	71,905	5	256	1,277	2,545	21	10

[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 2015 was 13 cattle (yaks), 28 camelides and 25,311 day old chicks.

USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

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Therapeutic usage of veterinary antimicrobial agents

Total sales in Norway of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in terrestrial food producing animals and companion animals in 2015 were 5,850 kg. Annual sales for use for these animal categories in the period 1993-2015 are shown in Figure 1. The data are based on sales from drug wholesalers (see Appendix 1) of veterinary antimicrobial agents for therapeutic use to Norwegian pharmacies and include pharmaceutical formulations approved for food animals, including horses, and companion animals. Thus, the figures represent national sales data for veterinary antimicrobial agents (see Appendix 1 for inclusion criteria).

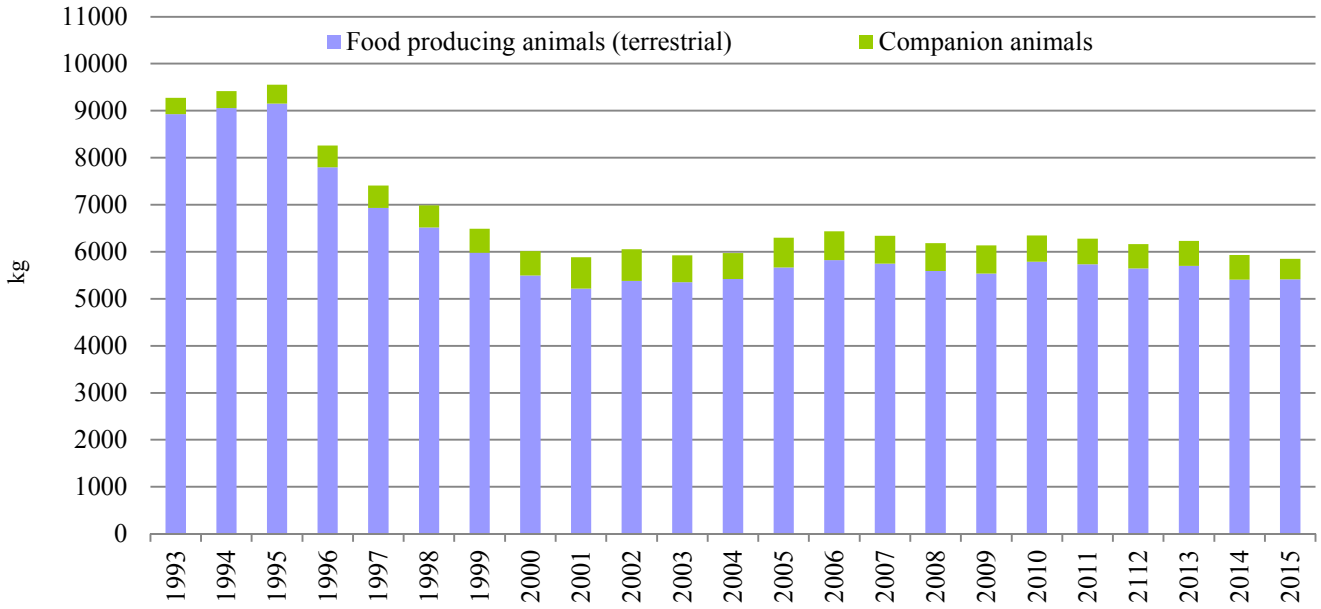

FIGURE 1. Total sales, in kg active substance, and sales for food producing animals (terrestrial animals) and companion animals of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in Norway in 1993-2015.

In 1996, the husbandry organisations in Norway set a target for reducing the amounts sold of antimicrobial VMPs, in weight of active substance, by 25% in five years; 1995 was indicated as the reference year. That target was reached already after three years; in 1998 the sales of antimicrobial VMPs for use in terrestrial food producing animals had been reduced by 29%. From 1995 to 2015 the sales, in kg active substance, of antimicrobial VMPs for use in terrestrial food producing animals have decreased by 41%. In the same periode, the proportion of sales of VMPs containing penicillins only increased from 25% to 59% (Figure 2), while the sales of aminoglycoside VMPs to food producing terrestrial animals decreased from 28% to 10% of the total sales. This change is mainly due to a reduction in the use of combination preparations of penicillin and dihydrostreptomycin (Figure 2).

For products approved for companion animals only (tablets and oral paste), an increase of 27% in the sales of antimicrobial VMPs is observed from 1993 to 2015 (Figures 1 and 5).

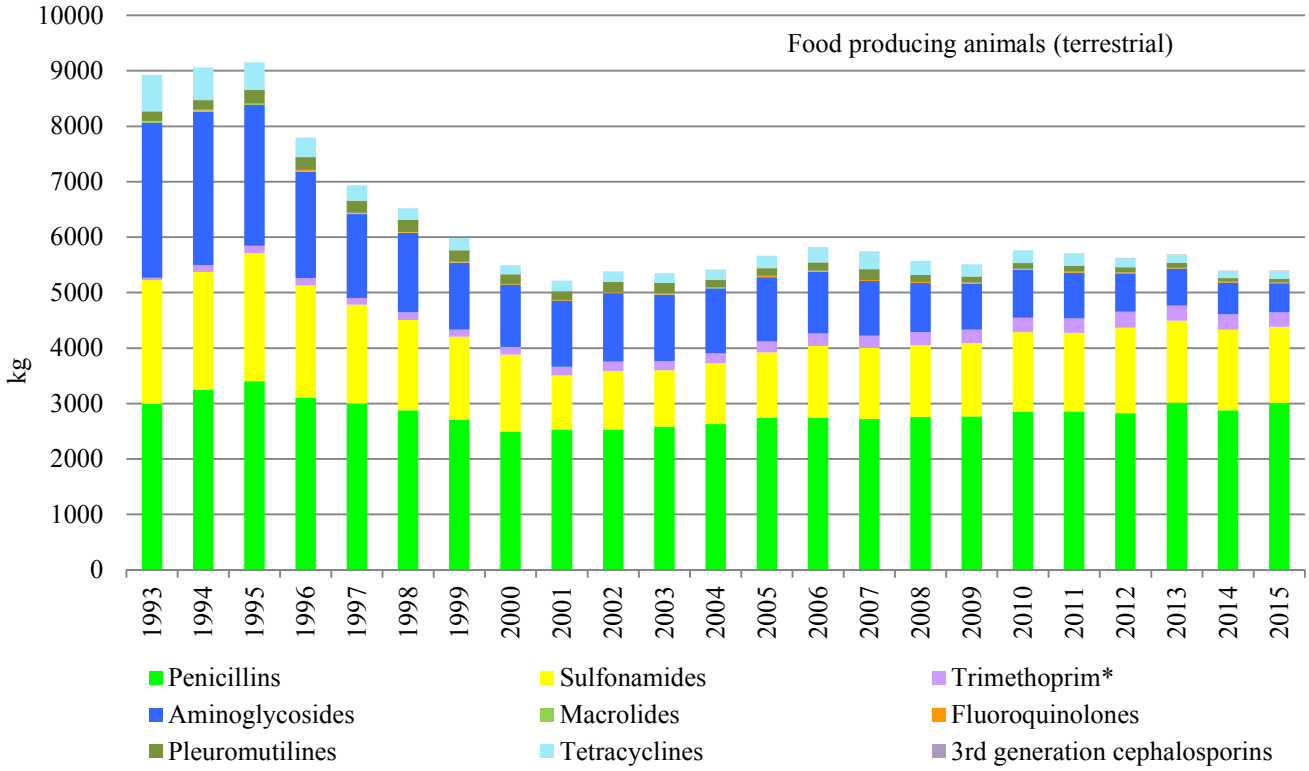

FIGURE 2. Sales in Norway, kg active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in terrestrial food producing animals (including horses) for the years 1993-2015. In addition, minor amounts of amphenicols (range 17-27 kg) were sold in 2008-2015. *Includes minor amounts of baquiloprim 1994-2000.

Figure 3 reports the sales, in kg active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in terrestrial food producing animals (including horses) normalised for the biomass "at risk" (population correction unit - PCU). The observed decrease in the sales – in mg/PCU - from 2010 to 2015 is 7.4% (see information about calculation of PCU in Appendix 1). The reduction is 6.2% when measured as kg active substance. Across the periode 2013-2015 the sales – measured in mg/PCU have been stable as only a 2% reduction is observed.

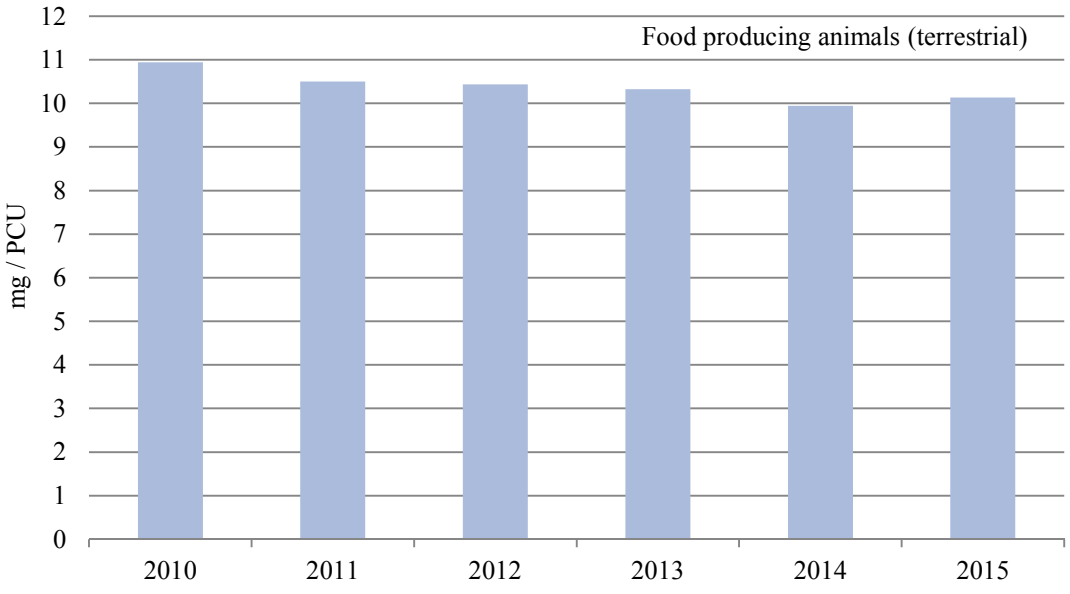

FIGURE 3. Sales (mg/PCU) in Norway, in mg active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in terrestrial food producing animals (including horses) normalised for population biomass (population correction unit - PCU) for the years 2010-2015.

The sales of the antimicrobial VMPs defined by the World Health Organization (WHO) as Critically Important Antimicrobials (CIA) with highest priority for human medicine (3rd and 4th generation cephalosporins, fluoroquinolones and macrolides) are low in Norway (Figure 4). The sales have been dominated by fluoroquinolones since the late 1990ies, which is mainly accounted for by VMPs for treatment of individual animals (injectables). The sales of CIA constituted only 0.3%-0.7% of the total annual sales of antimicrobial VMPs during the years 1993-2015.

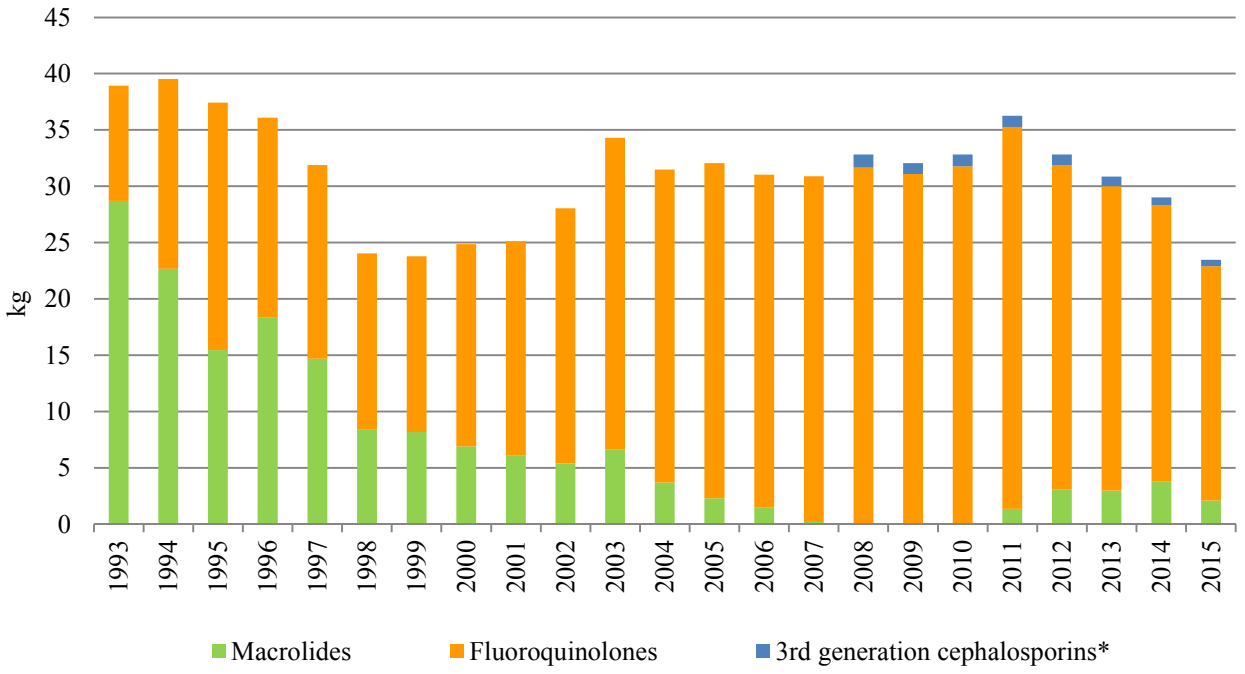

FIGURE 4. Sales in Norway, in kg active substance, of antimicrobial veterinary medicinal products (VMPs) containing macrolides, fluoroquinolones and 3rd generation cephalosporins for therapeutic use in animals (horses included) in 1993-2015. *Only for companion animals; sold only in 2012-2015 (range: 0.008-0.05 kg). No sales of 4th generation cephalosporins.

In Norway, treatment of food producing terrestrial animals (including horses), except for broilers, is dominated by treatment of individual animals (Figure 5). This reflects that the production is characterised by small herds, but also therapeutic traditions. In 2015, only 6% of the sales were for VMPs for group treatment.

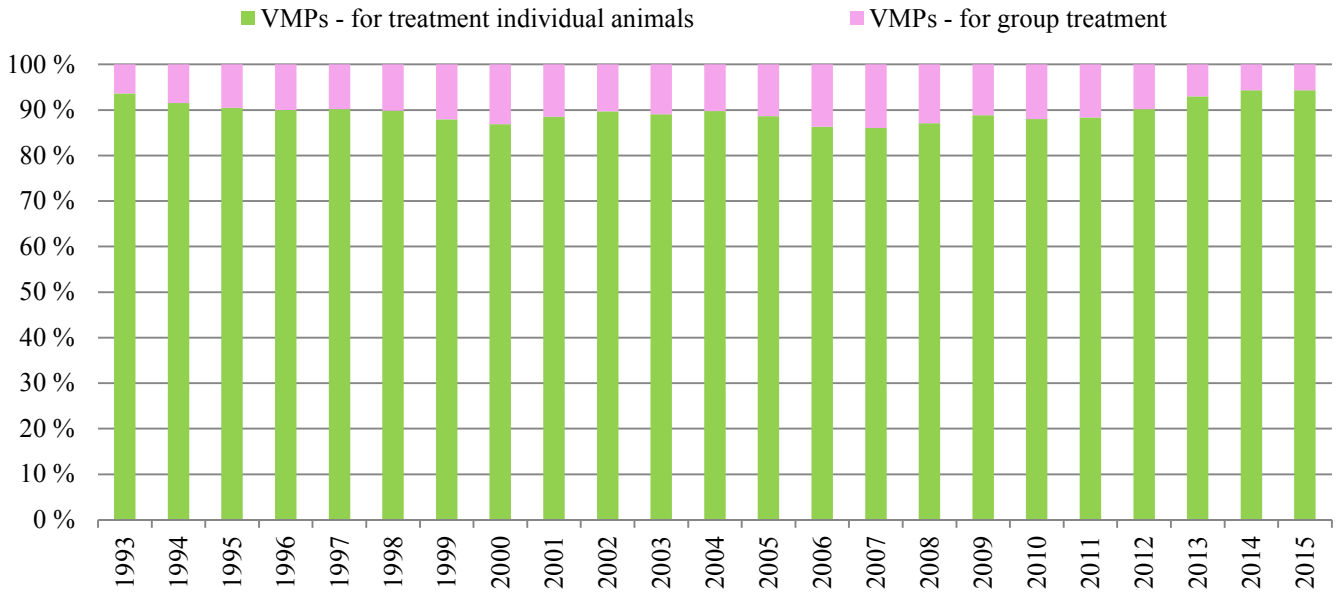

FIGURE 5. Sales in Norway, in kg active substance, of antimicrobial veterinary medicinal products (VMPs) marketed for treatment of individual food producing terrestrial animals (bolus, injectables, intramammary preparations, intrauterine preparations, paste and some tablet VMPs – see Appendix 1) and for group treatment through feed or drinking water (oral solution and oral powder; premix is not used for terrestrial animals in Norway).

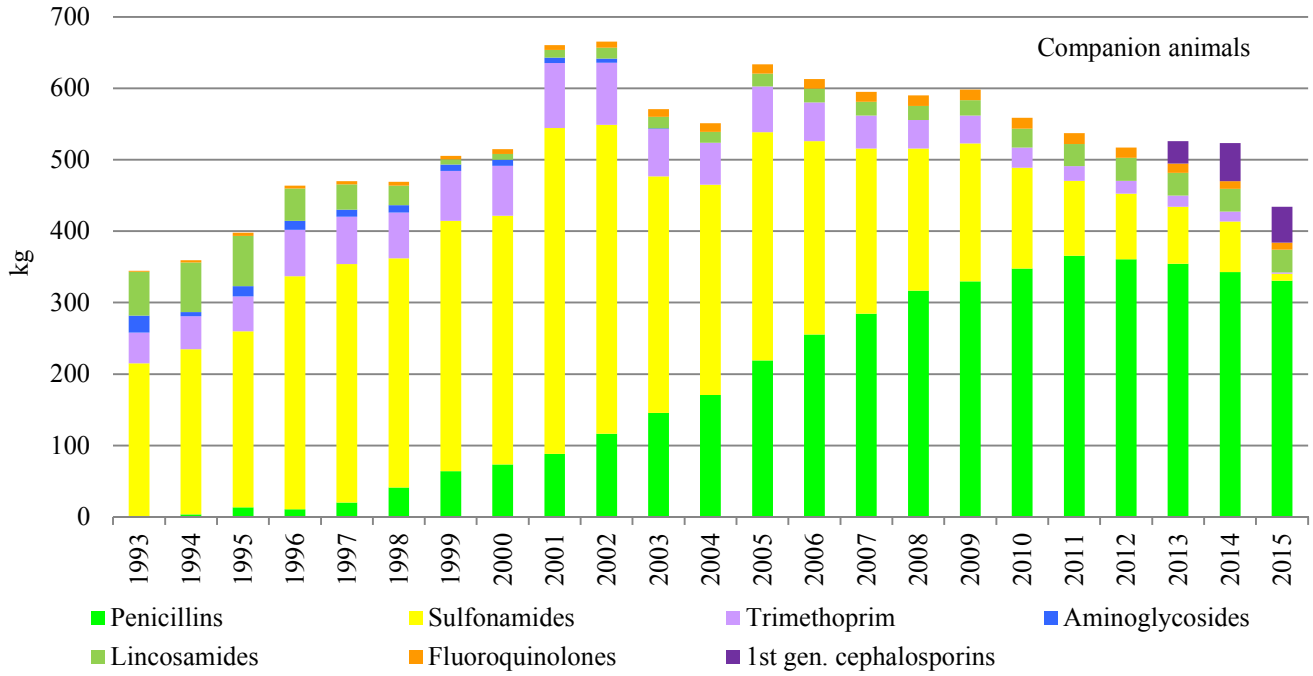

FIGURE 6. Sales in Norway, in kg active substance, of antimicrobial veterinary medicinal products (VMPs) marketed for therapeutic use in companion animals (tablets and oral paste) for the years 1993-2015. In addition, minor amounts of a 3. generation cephalosporin VMP (0.6-1.1 kg) were sold annually in 2008-2015 and of a macrolide VMP (0.4-5 kg) in 1998-2005.

Sales of antimicrobial VMPs marketed for companion animals fluctuated during the period 1993-2015; an increase of 27% in the sales, in kg active substance, from 345 to 436 kg is observed during the period as a whole (Figure 6). The observed increase is partly artificial. Only 12 antimicrobial VMP presentations (name, form, strength and pack size) authorised for companion animals were marketed in 1993. In 2015, the corresponding number was 51, and human antimicrobial medicinal products were thus earlier used for animals, in particular penicillins. The observed peak in the sales of sulfonamides in companion animals in 2001-2002 is probably due to use in sheep of a trimethoprim-sulfonamide VMP marketed for companion animals because of a withdrawal in 2001 of a product used for mastitis in sheep (Figure 6). The sales, in kg active substance, of VMPs for companion animals declined by 17% from 2013 to 2015. This figure should be interpreted with great caution as trimethoprim+sulfa tablets for dogs have been removed from the market during this period and seem to have been replaced by a 3rd generation cephalosporin product for which the dosing is several orders lower than of trimethoprim+sulfa (Figure 6).

Since the first penicillin VMP as tablets was marketed for companion animals in 1994 the proportion of penicillin sales of total antimicrobial VMPs for companion animals has increased from 1% to 76% of total sales. In 2015, approximately 85% of the sales of penicillin products marketed solely for companion animals was for the combination amoxicillin and clavulanic acid (Figure 7).

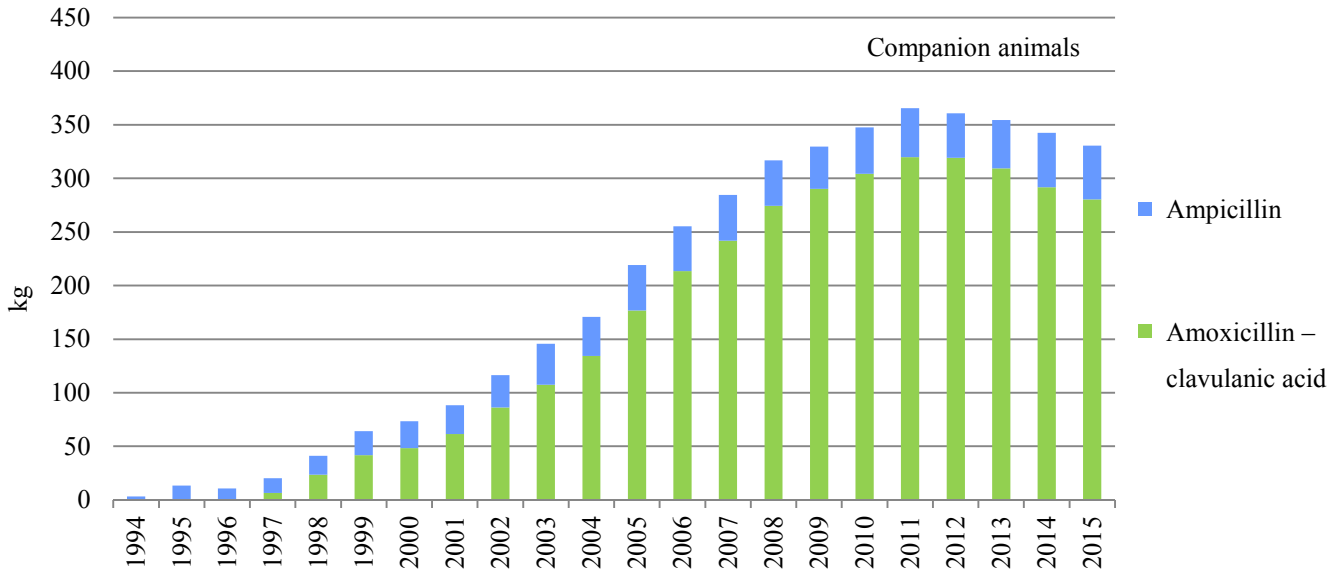

FIGURE 7. Sales, in kg active substance, of penicillin veterinary medicinal products for companion animals 1994-2015.

The annual sales of antimicrobial VMPs for use in farmed fish peaked in 1987 when the sales amounted to 48 tonnes (Figure 8). In 2015, the sales of antimicrobial VMPs for use in farmed fish were 273 kg active substance, of which 67% were amphenicols (Table 4). This implies that the sales have declined by approximately 99% from 1987. Note that for the last couple of years, the sales of antimicrobial VMPs for use in farmed fish have shifted from quinolones to amphenicols.

The significant decrease in the usage of antimicrobial agents in Norwegian aquaculture from 1987 is mainly attributed to the introduction of effective vaccines against bacterial diseases in Atlantic salmon and rainbow trout and to some extent also to improved health management.

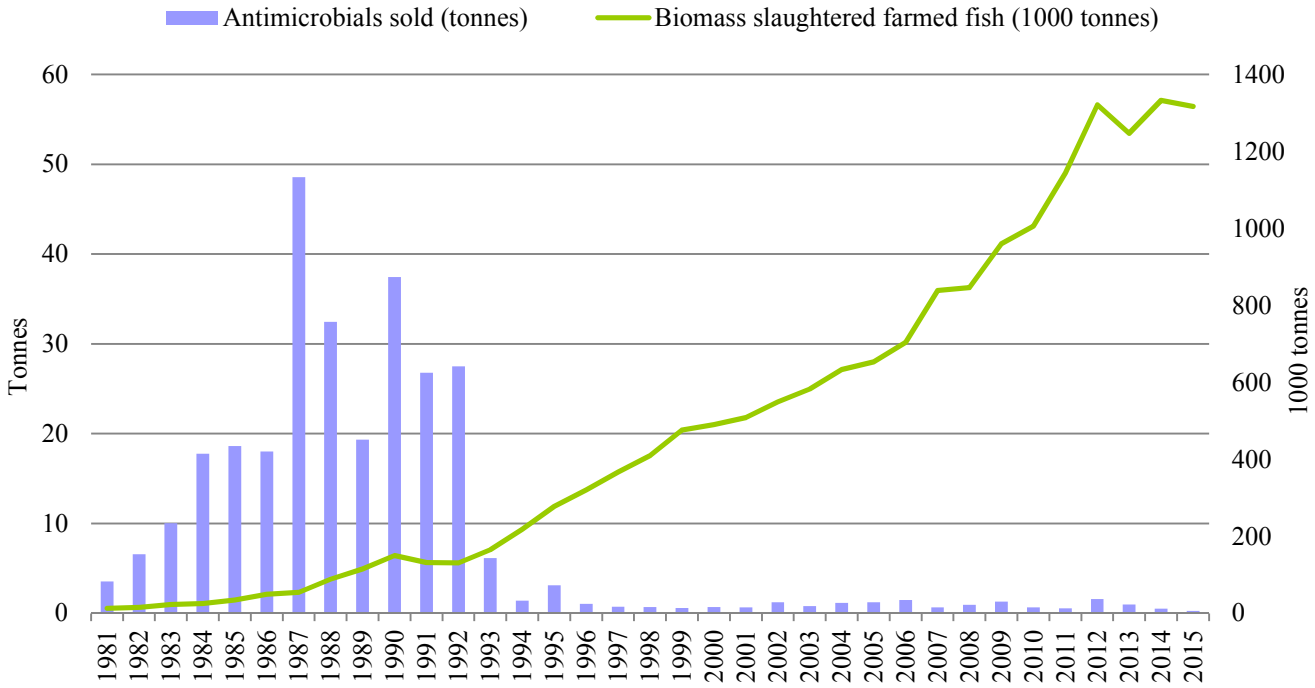

FIGURE 8. Total sales, in tonnes of active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 1981-2015 versus produced biomass (slaughtered) farmed fish. Note that for 2015 data represent prescription data.

TABLE 4. Sales, in kg of active substance, of antimicrobials for therapeutic use in farmed fish in Norway in the period 2005-2015. The data 2005-2014 represent sales data provided by the Norwegian Institute of Public Health (FHI). The 2015 data represent prescription data obtained from the Veterinary Prescription Register (See Appendix 1).

Group of substances/ active substance		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015[1]
Tetracyclines:	Oxytetracycline	8	0	19	23	40	10	1	1	0	0	0
Amphenicols:	Florfenicol	202	302	139	166	303	275	336	191	300	403	188
Quinolones:	Flumequine	28	7	18	1	1	0	0	0	0	0	0
	Oxolinic acid	977	1,119	406	681	926	308	212	1,399	672	108	85
Combinations:	Spectinomycin + lincomycin (2+1)	0	50	66	70	43	57	0	0	0	0	0
Total		**1,215**	**1,478**	**648**	**941**	**1,313**	**649**	**549**	**1,591**	**972**	**511**	**273**

[1] In addition, 25 kg oxytetracyclines were reported sold by FHI; however, this was used for cleaner fish that help control salmon lice in salmonid aquaculture.

Prescription of antimicrobials for farmed fish - by species and production stage

From January 2011, it became mandatory to report all prescriptions of medicines for use in farmed fish to the Veterinary Prescription Register (VetReg), a continuous electronic reporting system owned by the Norwegian Food Safety Authority (NFSA). For each prescription, information on fish species, production phase, diagnosis, prescribed antibacterial agent, and amount (kg active substance) are to be reported.

Material

Prescription data on antimicrobials for farmed fish were retrieved from VetReg for the years 2011 to 2015. In order to assess the reliability of the prescription data, these were compared to sales data on antimicrobials for use in fish, published by the Norwegian Institute of Public Health. The prescription data corresponded to the sales data for 2013, 2014 and 2015; for these years outliers were identified and corrected. These outliers were due to mistakes in calculation of the amount prescribed by the reporting feed mills. The prescription data for 2011 and 2012 were not checked for outliers due to time constraints. Data on biomass farmed fish produced was obtained from the Norwegian Directorate of Fisheries; for the seawater locations for farmed finfish the numbers of locations were 1,153; 1,085; 1,069; 1,078 and 1,053 in the years 2011 to 2015, respectively.

Results and discussion

The major proportion of antibacterials prescribed for all the study years is for Atlantic salmon (Figure 9) that accounted for between 93% and 95% of the total annual production of farmed fish in Norway during 2011-2015. A few prescriptions reported for ballan wrasse and other species used as salmon-louse cleaner fish were identified as incorrect in terms of fish species given for 2011 and 2012; these should have been for treatment of Atlantic salmon. For 2011 and 2012 the number of prescriptions for ”other species” is therefore overestimated, as well as underestimated for Atlantic salmon.

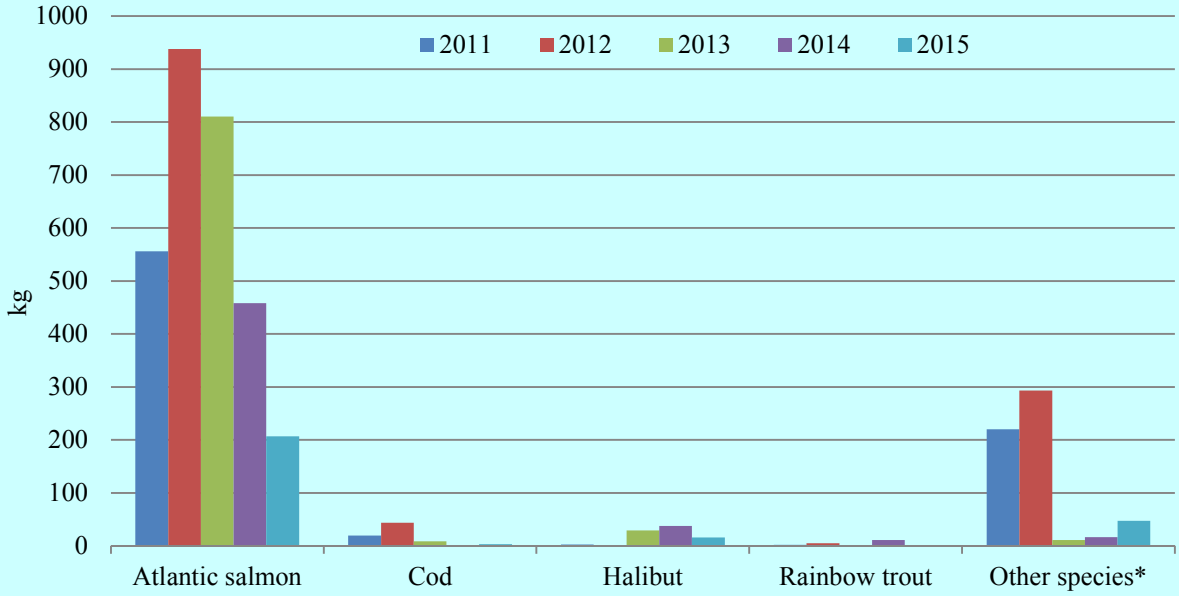

FIGURE 9. Prescribing, in kg active substance, of antimicrobial agents for the various fish species in Norwegian aquaculture.

When the annual amount of antimicrobials prescribed for Atlantic salmon was normalised by biomass produced, i.e. population correction unit (see Appendix 1), the prescription was in the range of 0.2-0.8 mg/PCU. The prescribing pattern for Atlantic salmon ongrowers changed from quinolones to amphenicols in 2014 and 2015 (Figure 10). Prescription of quinolones for ongrowers of Atlantic salmon was only 0.1 kg in 2015 (not visible in the graph).

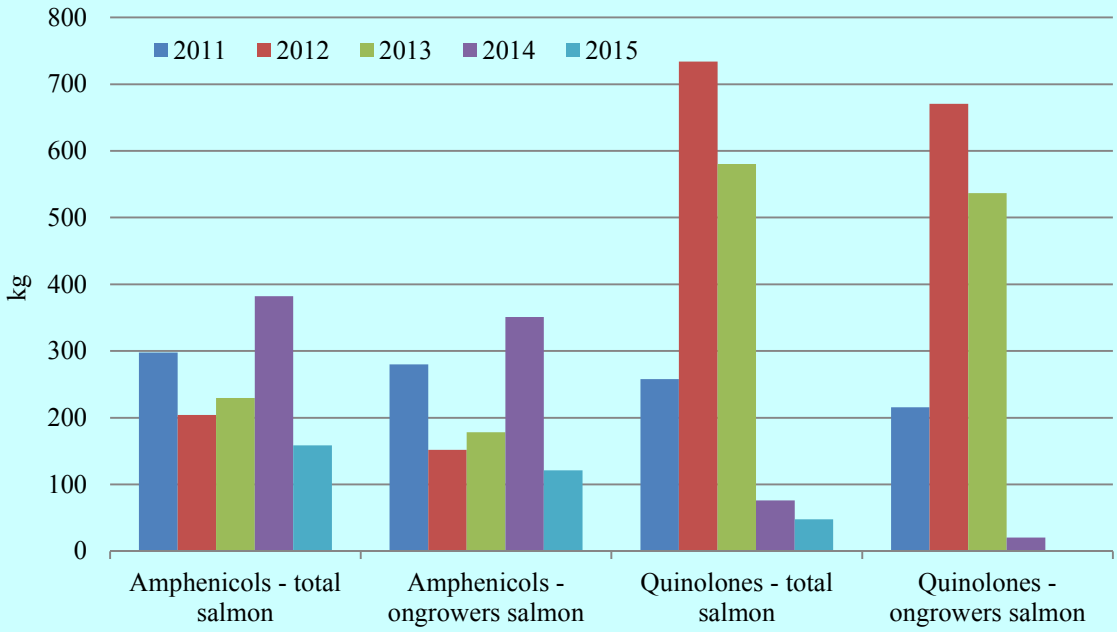

FIGURE 10. Prescribing, in kg active substance, by antimicrobial class for Atlantic salmon – total and for ongrowers.

The major proportion of the prescriptions was for treatment of farmed fish prior to the ongrowing phase (Figure 11). For the years 2011 to 2015, the numbers of prescriptions (treatments) for ongrowers per 100 seawater locations were approximately 1, 3, 2, 1 and 1, respectively. This is a valid indicator for the success of vaccination in terms of avoiding use of antimicrobials in Norwegian marine aquaculture.

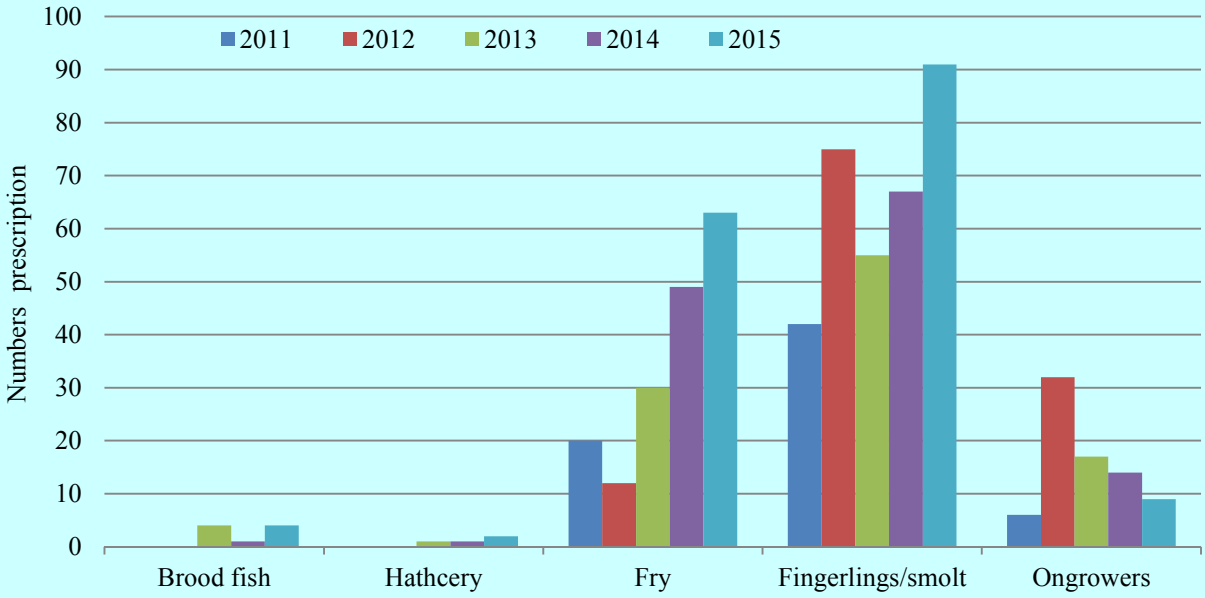

FIGURE 11. Numbers of prescriptions of antimicrobial agents for use in Norwegian fish farming during the years 2011-2015 distributed by production phase. Note that vaccination takes place in fingerlings and smolt during the fresh-water production phase.

Conclusions

Since full-scale systematic vaccination was implemented in salmonid aquaculture in Norway more than 25 years ago, prescribing of antimicrobial agents has continued to be on a very low level. Most prescriptions are for fish in early production stages, long before they reach market size.

References:

1. Norwegian Institute of Public Health (www.fhi.no/artikler/?id=117980).
2. Norwegian Directorate of Fisheries (http://www.fiskeridir.no/English/Aquaculture/Statistics).

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Antimicrobial and coccidiostat feed additives

Data on the sales of various substances and categories of feed additives (Table 5) were obtained through annual reports from the Norwegian Food Safety Authority.
The glycopeptide avoparcin was licensed in Norway as growth promoter in broilers and turkeys in 1986. In 1995 the food animal production industry voluntarily abandoned the use of all antimicrobial growth promoters (AGPs), including avoparcin. These measures resulted in an immediate decline in the use of AGPs (Figur 12). No antimicrobial growth promoters have been used in animals in Norway since 1997.

Following the ban of avoparcin as antimicrobial growth promoter in EU in 1995, narasin was introduced as coccidiostat feed additive in the Norwegian broiler production due to its effect on *Clostridium perfringens*. Since 1996 the sales of coccidiostat feed additives for use in Norwegian broiler production has been dominated by narasin. In February 2015, the Norwegian poultry industry launched a project with the aim to phase out narasin by the end of 2016; as a consequence the sales of narasin, in kg active substance, declined by 14% from 2014 to 2015 (Table 5).

TABLE 5. Total sales, in kg of active substance, of coccidiostat feed additives in Norway 2005-2014. Data were obtained through annual reports from the Norwegian Food Safety Authority.

Active substance	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Lasalocid	37	13	17	16	63	0	0	0	0	0	164
Monensin	852	889	919	897	885	805	1,060	1,080	1,174	1,313	1,081
Salinomycin	0	0	0	0	0	0	0	0	0	0	0
Narasin	5,318	5,615	7,065	9,212	8,621	9,080	9,394	10,378	12,345	12,409	9,126
Total ionophore coccidiostats	**6,207**	**6,517**	**8,001**	**10,125**	**9,569**	**9,885**	**10,454**	**11,458**	**13,519**	**13,722**	**10,371**

The sales, in kg active substance, of ionophore coccidiostat feed additives have increased steadily since the late 1990ies (Figure 12). This reflects the increased production of slaughter chicken (Figure 13). The apparent increase in the sales (mg/kg poultry produced) of iono-phores from 2006-2007 (Figure 13) is explained by a change in the withdrawal times for narasin from five to two days implying that the slaughter chicken were given feed with narasin three more days than previously.

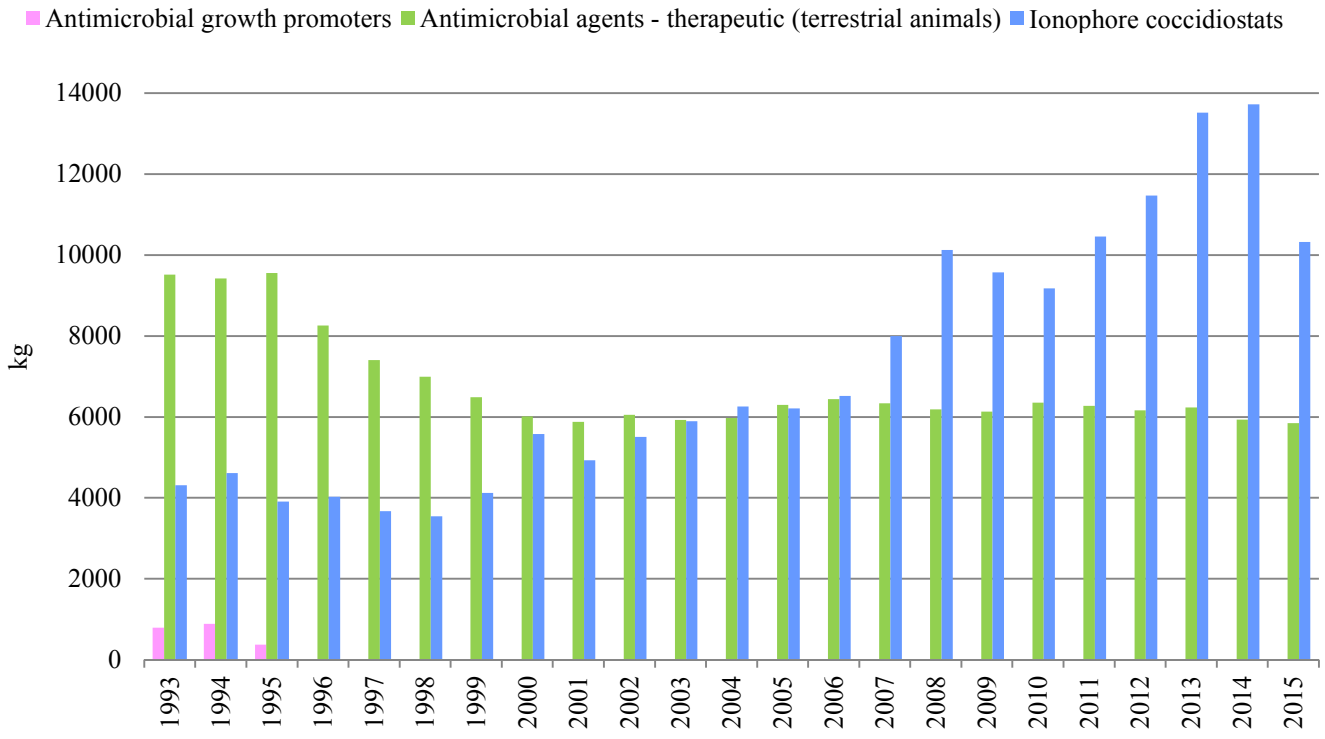

FIGURE 12. Sales, in kg active substance, of antimicrobial veterinary medicinal products (VMPs) for food producing animals (terrestrial) and of antimicrobial growth promoters and ionophore coccidiostats in Norway during 1993-2015.

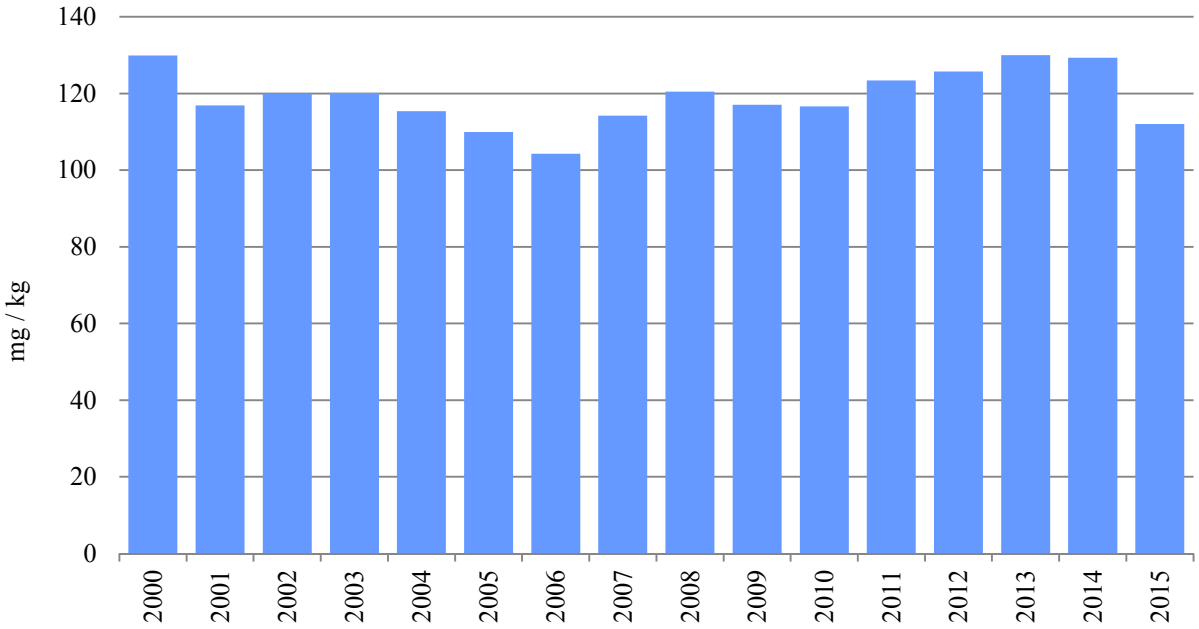

FIGURE 13. Sales, in mg active substance, of ionophore coccidiostats per kg poultry slaugthered in Norway during 2000-2015.

Usage of "Highest Priority Critically Important Antimicrobials for Human Medicine" in animals, fish industry and humans

The World Health Organization has classified certain antimicrobial classes as "Highest Priority Critically Important Antimicrobials" for human medicine in the so-called CIA list[1]. The CIA list is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that critically important antimicrobials are used prudently both in human and veterinary medicine. It is intended as a reference to help formulate and prioritise risk assessment and risk management strategies for containing antimicrobial resistance due to human and non-human antimicrobial use.

The justification for the classification is summarised as follows[1]:

Quinolones are known to select for quinolone resistant *Salmonella* and *E. coli* in animals. At the same time, quinolones are one of few available therapies for serious *Salmonella* and *E. coli* infections. Given the high incidence of human disease due to *Salmonella* and *E. coli*, the absolute number of serious cases is substantial.

Third and fourth generation cephalosporins are known to select for cephalosporin resistant *Salmonella* and *E. coli* in animals. At the same time, third and fourth generation cephalosporins are one of few available therapies for serious *Salmonella* and *E. coli* infections in humans, particularly in children. Given the high incidence of human disease due to *Salmonella* and *E. coli*, the absolute number of serious cases is substantial.

Macrolides and ketolides are known to select for macrolide resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. At the same time, macrolides are one of few available therapies for serious *Campylobacter* infections, particularly in children, for whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., especially *Campylobacter jejuni*, the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptide resistant *Enterococcus* spp. in food animals (e.g. when avoparcin was used as a growth promoter, vancomycin resistant enterococci (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals, and the very serious consequences of treatment failures in such cases, glycopeptides are classified as being of the highest priority.

In Norway, only a small proportion of all antibiotics classified as Highest Priority Critically Important Antimicrobials for Human Medicine are used in animals and in farmed fish (Figure 14). In 2015, 0.6% of total sales of CIAs in Norway were used in terrestrial animals. The proportion CIAs sold for use in farmed fish has varied over the years, but in 2015, 2.1% of all sales of CIA were for farmed fish. In total, 97.3% of the sales of CIAs in Norway were for use in human medicine.

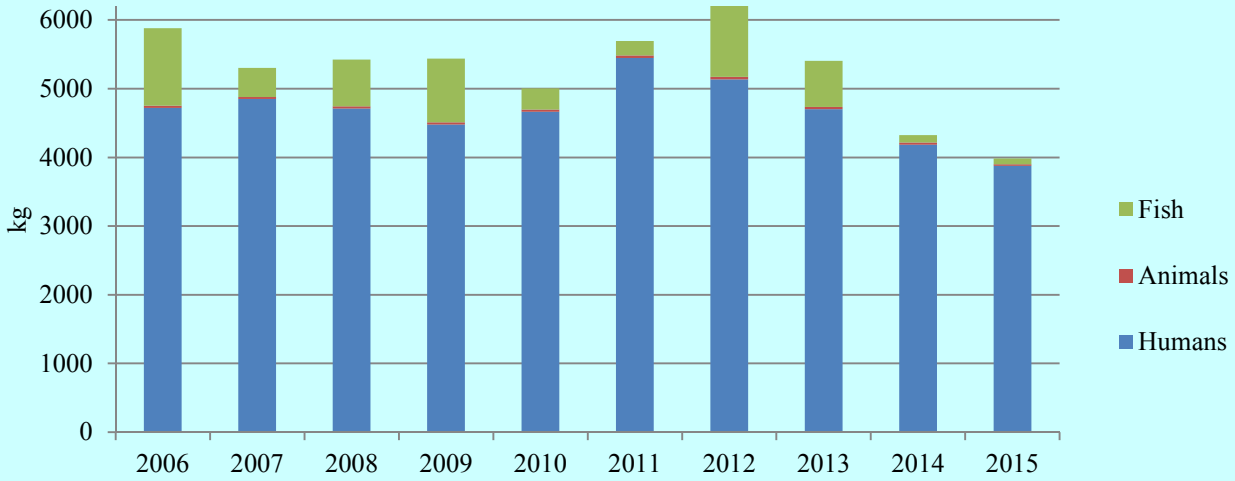

FIGURE 14. Trends in the sales of the WHO CIAs with highest priority for human medicine since the first list was published in 2005[2]. Data for 2006-2015 are separated into sales for use in humans, terrestrial animals and farmed fish.

References:

1. World Health Organization 2013. http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/Exe_summ_Report_AGISAR_5.pdf?ua=1.
2. World Health Organization 2005. http://apps.who.int/iris/bitstream/10665/43330/1/9241593601_eng.pdf?ua=1&ua=1.

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USAGE IN HUMANS

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Overall antibiotic sales

In 2015, the total sales of antibacterials for systemic use in humans (J01 excl. methenamine) decreased by 4% compared to 2014, from 15.7 to 15.1 DDD/1,000 inhabitants/day. Antibiotics are prescription-only drugs in Norway, and overall antibiotic sales include all consumption in humans in Norway i.e. primary care and institutions. The overall consumption has decreased by 13% since 2012, when a *Mycoplasma pneumonia* epidemic caused increased prescription rates for macrolides and tetracyclines. Increased sales of ATC group J01 antibacterials in the first decades of this century are mainly caused by increased use of penicillins and the urinary antiseptic methenamine (Table 6, Figure 15). In the same period the proportion of narrow-spectrum penicillins (J01CE) of total sales (J01, excl. methenamine) has decreased from 32% in year 2000 to 25% in 2015.

TABLE 6. Human usage of antibacterial agents in Norway 2008-2015 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2014-2015. Methodology for collection of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2008	2009	2010	2011	2012	2013	2014	2015	Change (%) 2014-2015
J01A	Tetracyclines	3.22	3.09	3.12	3.47	3.87	3.53	3.44	3.34	- 2
J01B	Amphenicols	0.001	0.002	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-
J01CA	Penicillins with extended spectrum	3.09	3.15	3.19	3.21	3.34	3.34	3.34	3.14	- 6
J01CE	Beta-lactamase sensitive penicillins	4.71	4.47	4.44	4.47	4.30	4.10	3.8	3.8	-
J01CF	Beta-lactamase resistant penicillins	0.77	0.80	0.82	0.88	0.90	0.78	0.89	0.86	- 3
J01CR	Combination of penicillins	0.02	0.02	0.03	0.03	0.04	0.05	0.08	0.09	+ 14
J01D	Cephalosporins, monobactams, carbapenems	0.60	0.58	0.55	0.56	0.55	0.52	0.47	0.43	- 8
J01E	Sulfonamides and trimethoprim	0.98	0.94	0.87	0.87	0.87	0.85	0.84	0.84	-
J01F	Macrolides, lincosamides and streptogramins	2.13	1.89	2.01	2.31	2.26	1.93	1.66	1.49	- 10
J01G	Aminoglycosides	0.07	0.07	0.07	0.07	0.08	0.07	0.08	0.08	-
J01M	Quinolones	0.70	0.71	0.73	0.75	0.75	0.72	0.65	0.58	- 11
J01X*	Other antibacterials	0.46	0.46	0.47	0.49	0.47	0.45	0.41	0.40	-
J01	**Total exclusive of methenamine**	**16.7**	**16.2**	**16.3**	**17.1**	**17.4**	**16.3**	**15.7**	**15.1**	**- 4**
J01XX05	Methenamine	3.01	3.19	3.37	3.44	3.57	3.67	3.65	3.76	+ 3
J01	**Total all antimicrobial agents**	**19.8**	**19.4**	**19.7**	**20.6**	**21.0**	**20.0**	**19.3**	**18.8**	**- 2.6**

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

The beta-lactamase sensitive penicillins (J01CE) and the tetracyclines (J01A) were the two most commonly used antibacterial groups in Norway in 2015, as they have been since the 1980ies. Among the tetracyclines (J01A), doxycycline is most frequently used, but lymecycline, mainly indicated for acne, is increasingly utilised (Figure 15 and Table 8). In 2015, the penicillins (J01C) accounted for 42% of the total antibacterial use in Norway (Figure 16). Over the years there has been a shift towards use of more broadspectered penicillins. Penicillins with extended spectrum (J01CA) now represent 40% of the penicillin group compared to 25% in 1996 (Figures 16 and 18). This is mainly due to increasing use of amoxicillin and pivmecillinam. Pivmecillinam is used for urinary tract infections, at the expense of the subgroup of sulfonamides and trimethoprim, which has decreased over the years (Figure 15).

The use of macrolides, lincosamides and streptogramins (J01F) has followed a wavy pattern over the years, but the internal pattern within the group has remained relatively unchanged (Figures 16 and 19). The shifts in use could be explained to some degree by the recurrent epidemics of *M. pneumoniae* in Norway, occurring at four- to six-year intervals. Since 2012, the use has decreased.

In the latest years, sales of cephalosporins, monobactams and carbapenems (J01D) have decreased, mainly due to decreased use of 1st and 2nd generation cephalosporins (Tables 6 and 8, Figure 20). The quinolones represent only a small fraction (3%) of total antibacterial sales (Figure 16) and the use has decreased over the last two years. Ciprofloxacin is the main substance accounting for 96% of the quinolone group in 2015. The use of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, accounting for 90% of subgroup J01X and 20% of total antibacterial use (Figure 16).

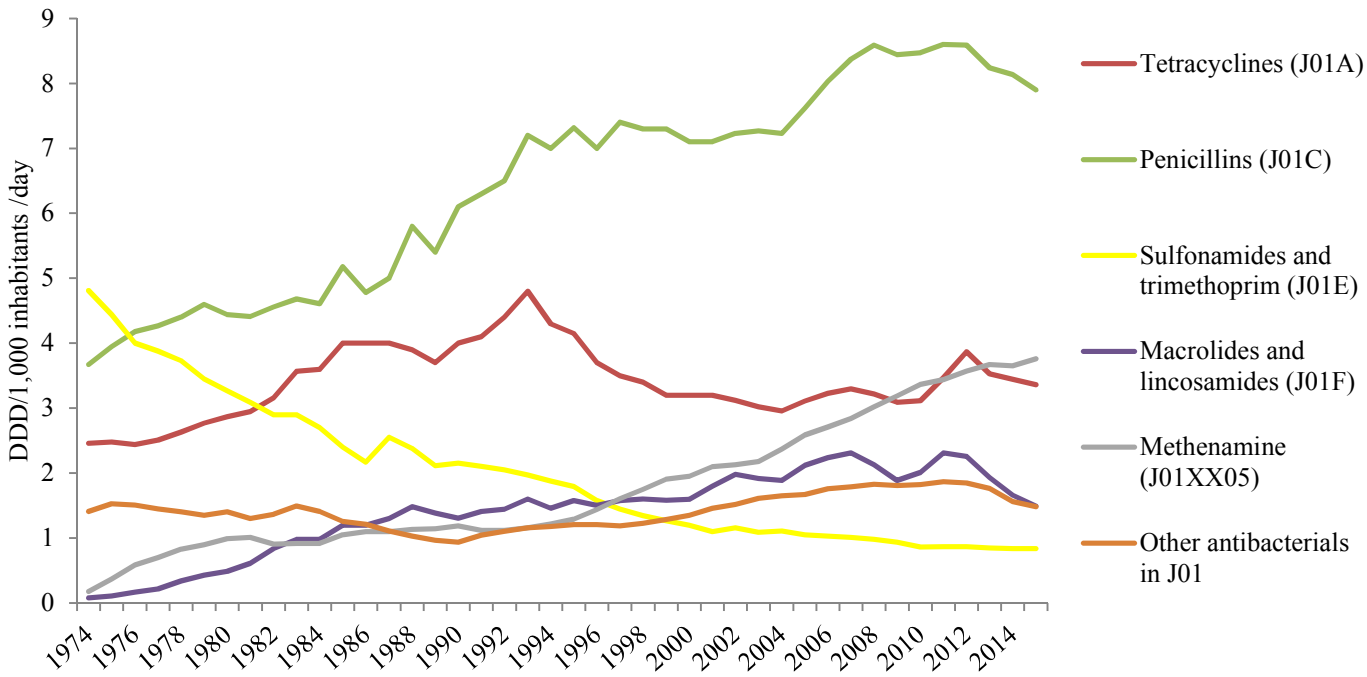

FIGURE 15. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), methenamine (J01XX05), and other antibacterials in Norway 1974-2015. Other types of antibacterials include all other antibacterials in ATC group J01.

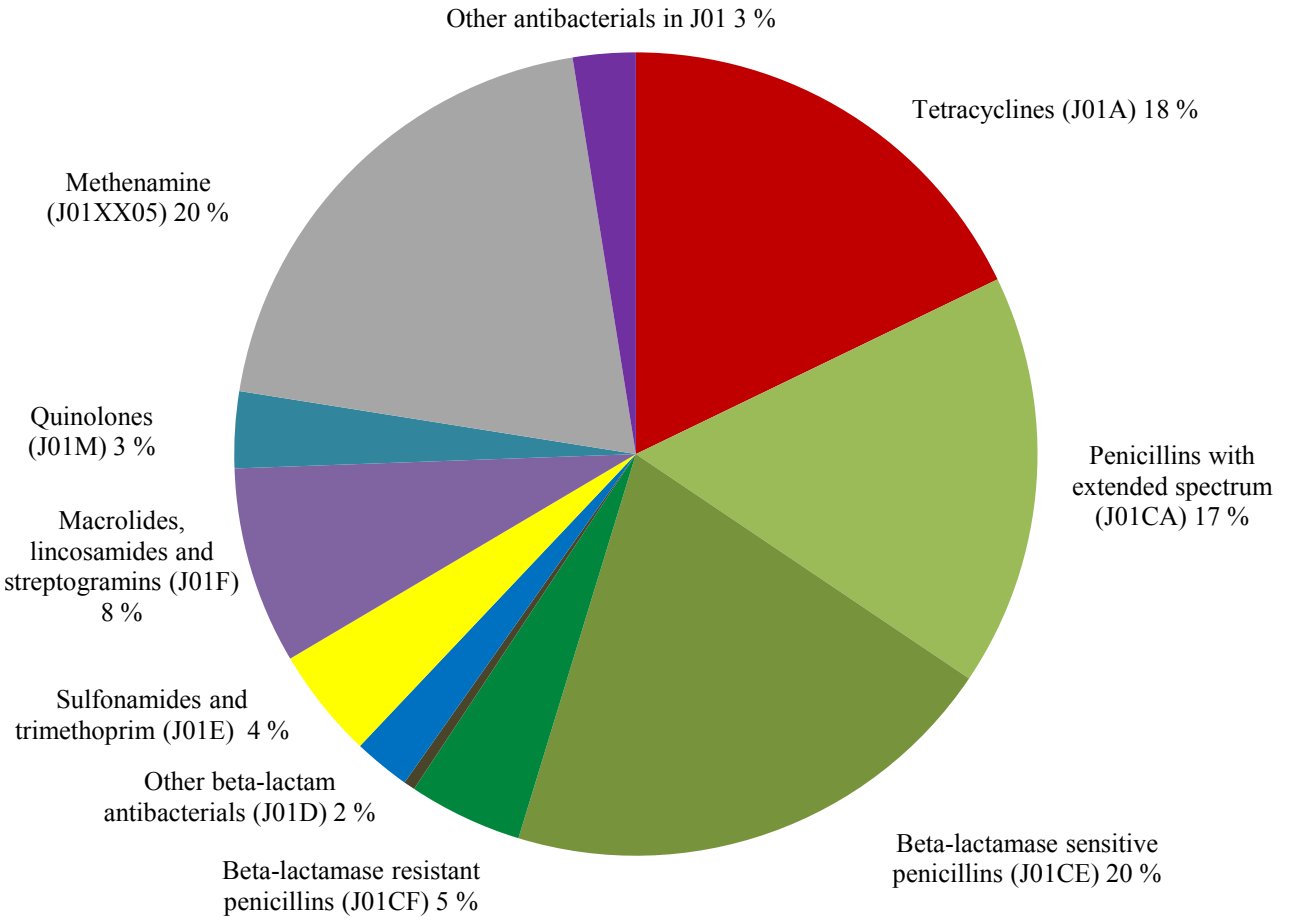

FIGURE 16. Relative amount of antibacterial agents for systemic use in 2015 in Defined Daily Doses (DDDs), total sales in the country.

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

In 2015, the overall sales in Norway of antibacterials for use in humans, terrestrial animals and farmed fish measured in weight of active substance were 57.3 tonnes (Figure 17). Of the total sales of antibacterials in Norway in 2015, sales for human use accounted for 89.3 %, terrestrial animals for 10.2 % and use in fish only for 0.5 %. In 2015, the level of total use in tonnes, when excluding methenamine, is now the same as in 2006. The use in humans increased until 2012, but has decreased since then. During these years the use in terrestrial animals has been low and relatively stable, while the use in aquaculture has varied but is very low.

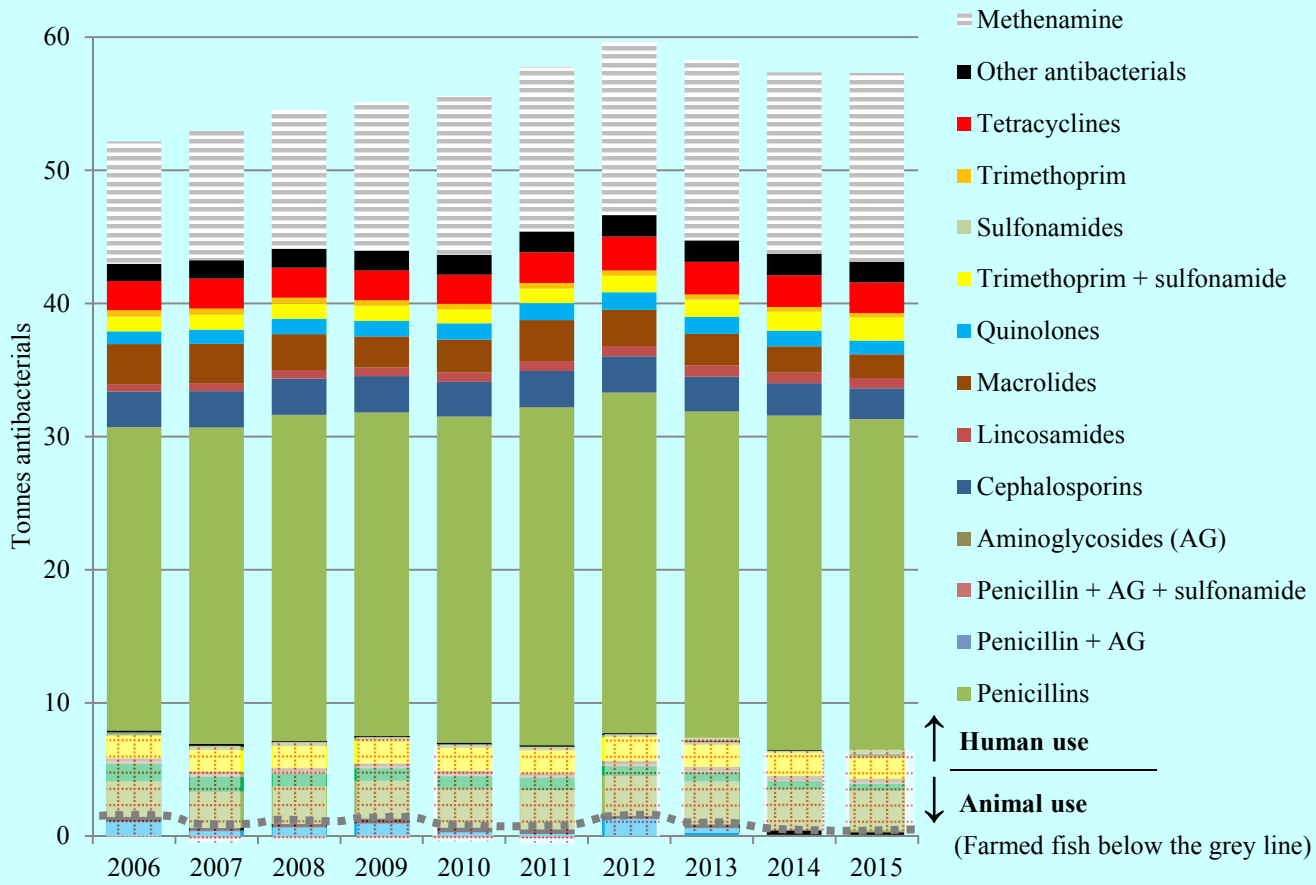

FIGURE 17. Sales, in tonnes of active substance, of antibacterials for humans, animals and fish, for the years 2006-2015. The use in farmed fish is shown below the grey line.

According to Table 7, oral formulations are dominating in human medicine while for veterinary medicine the dominating formulations are the parenteral ones. Sales of other formulations e.g. for eye, ear and skin are limited.

TABLE 7. Sales, in kg of active substance, of human and veterinary antibacterials according to formulation in 2015 (methenamine not included).

Formulation	Humans	Terrestrial animals[1]	Aquaculture
Dermal	108	10	
Oral	29,886	2,084	301[2]
Parenteral	6,880	3,365	
Eye / ear	33	27	
Intramammary		279	
Others	59	97	
Total	36,966	5,862	301

[1] There is a minor discrepancy of 24 kg between the total sales (excluding dermal and eye/ear formulations) between Table 7 and Figure 17; this is due to differences in rounding of calculations. [2] Includes 25 kg oxytetracycline used for cleaner fish that help control salmon lice in salmonid aquaculture.

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TABLE 8. Human usage of single antibacterial agents for systemic use in Norway 2010-2015. Sales are given in DDD/1,000 inhabitants/day. The methodology for collection of data on human usage of antibacterial agents is presented in Appendix 2.

ATC group	ATC code	Substance	2010	2011	2012	2013	2014	2015
J01A - Tetracyclines	J01A A02	Doxycycline	1.83	2.09	2.36	2.02	1.97	1.94
	J01A A04	Lymecycline	0.59	0.76	0.90	1.00	0.96	0.96
	J01A A06*	Oxytetracycline	0.15	0.03	-	<0.001	<0.001	<0.001
	J01A A07	Tetracycline	0.54	0.58	0.62	0.54	0.50	0.45
	J01A A08*	Minocycline	0.001	0.002	0.006	0.009	0.003	0.002
	J01A A12	Tigecycline	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01B - Amphenicols	J01B A01	Chloramphenicol	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CA - Penicillins with extended spectrum	J01C A01	Ampicillin	0.09	0.09	0.09	0.10	0.12	0.11
	J01C A04	Amoxicillin	1.34	1.39	1.45	1.40	1.41	1.33
	J01C A08	Pivmecillinam	1.75	1.73	1.78	1.83	1.80	1.68
	J01C A11	Mecillinam	0.008	0.008	0.008	0.008	0.007	0.006
J01CE - Beta-lactamase sensitive penicillins	J01C E01	Benzylpenicillin	0.22	0.24	0.24	0.22	0.23	0.21
	J01C E02	Phenoxymethyl-penicillin	4.22	4.23	4.07	3.85	3.60	3.61
	J01C E08*	Benzathine benzylpenicillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CF - Beta-lactamase resistant penicillins	J01C F01	Dicloxacillin	0.70	0.74	0.76	0.57	0.71	0.71
	J01C F02	Cloxacillin	0.12	0.14	0.14	0.21	0.18	0.16
	J01C F05*	Flucloxacillin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
J01CR - Combination of penicillins, incl. beta-lactamase inhibitors	J01C R02*	Amoxicillin and enzyme inhibitor	0.003	0.002	0.004	0.007	0.012	0.013
	J01C R05	Piperacillin and enzyme inhibitor	0.02	0.03	0.03	0.04	0.06	0.07
J01DB - First gen. cephalosporins	J01D B01	Cefalexin	0.20	0.19	0.18	0.17	0.14	0.12
	J01D B03	Cefalotin	0.07	0.08	0.08	0.08	0.09	0.09
J01DC - Second gen. cephalosporins	J01D C02	Cefuroxime	0.09	0.09	0.08	0.07	0.05	0.04
J01DD - Third gen. cephalosporins	J01D D01	Cefotaxime	0.11	0.12	0.12	0.12	0.11	0.11
	J01D D02	Ceftazidime	0.01	0.01	0.01	0.01	0.01	0.01
	J01D D04	Ceftriaxone	0.02	0.03	0.03	0.03	0.02	0.02
J01DF - Monobactams	J01D F01	Aztreonam	<0.001	<0.001	<0.001	0.001	0.001	0.001
J01DH - Carbapenems	J01D H02	Meropenem	0.04	0.04	0.05	0.05	0.05	0.04
	J01D H03	Ertapenem	0.002	0.002	0.002	0.002	0.002	0.002
	J01D H51	Imipenem and enzyme inhibitor	0.002	0.002	0.002	0.002	0.002	0.002
J01DI – Other cephalo-sporins and penems	J01DI02	Ceftaroline fosamil					<0.001	<0.001
J01E - Sulfonamides and trimethoprim	J01E A01	Trimethoprim	0.56	0.55	0.51	0.48	0.44	0.40
	J01E E01	Sulfamethoxazole and trimethoprim	0.31	0.32	0.36	0.37	0.40	0.44
J01F - Macrolides, lincosamides and streptogramins	J01F A01	Erythromycin	0.94	1.18	1.06	0.85	0.74	0.67
	J01F A02	Spiramycin	0.01	0.01	0.01	0.01	0.01	0.004
	J01F A06	Roxithromycin				<0.001	<0.001	<0.001
	J01F A09	Clarithromycin	0.34	0.37	0.39	0.30	0.23	0.18
	J01F A10	Azithromycin	0.41	0.44	0.48	0.41	0.35	0.35
	J01FS15	Telithromycin			<0.001	<0.001	<0.001	<0.001
	J01F F01	Clindamycin	0.31	0.32	0.33	0.37	0.33	0.31

ATC group	ATC code	Substance	2010	2011	2012	2013	2014	2015
J01G - Aminoglycosides	J01GA01*	Streptomycin	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	J01G B01	Tobramycin	0.03	0.03	0.03	0.03	0.02	0.02
	J01G B03	Gentamicin	0.04	0.05	0.05	0.05	0.05	0.06
	J01G B06*	Amikacin	0.001	0.001	0.001	0.001	0.001	0.001
J01M - Quinolones	J01M A01	Ofloxacin	0.03	0.03	0.02	0.02	0.01	0.01
	J01M A02	Ciprofloxacin	0.70	0.71	0.72	0.69	0.63	0.56
	J01MA12*	Levofloxacin	0.003	0.002	0.002	0.001	0.002	0.002
	J01MA14*	Moxifloxacin	0.004	0.006	0.004	0.005	0.007	0.008
J01X - Other antibacterials	J01X A01	Vancomycin	0.01	0.01	0.01	0.01	0.02	0.02
	J01X A02	Teicoplanin	0.001	0.001	0.001	0.001	<0.001	<0.001
	J01X B01	Colistin	0.004	0.004	0.004	0.005	0.006	0.005
	J01X C01	Fusidic acid	0.004	0.005	0.005	0.004	0.004	0.004
	J01X D01	Metronidazole	0.07	0.07	0.07	0.06	0.05	0.04
	J01X E01	Nitrofurantoin	0.37	0.39	0.37	0.36	0.33	0.33
	J01XX01	Fosfomycin			<0.001	<0.001	<0.001	<0.001
	J01X X05	Methenamine	3.37	3.44	3.57	3.67	3.65	3.76
	J01XX08	Linezolid	0.009	0.01	0.01	0.007	0.007	0.008
	J01XX09	Daptomycin	<0.001	<0.001	0.001	0.001	<0.001	<0.001
Antibiotics in other ATC groups	J04AB02	Rifampicin	0.004	0.004	0.005	0.004	0.005	0.004
	J04A	Rifampicin**	0.086	0.082	0.086	0.082	0.079	0.073
	A07AA09	Vancomycin	0.001	0.001	0.002	0.002	0.002	0.002
	A07AA11	Rifaximin	0.001	0.002	0.004	0.007	0.01	0.03
	A07AA12	Fidaxomicin			<0.001	<0.001	<0.001	<0.001
	P01AB01	Metronidazole	0.23	0.24	0.23	0.24	0.24	0.23
	D06AX09/ R01AX06*	Mupirocin (grams)	90	93	145	171	170	221

*Drugs not licensed in the Norwegian market in 2015. ** Given as the amount DDD/1,000 inhabitants/day of rifampicin (i.e. total amount in plain and combination products).

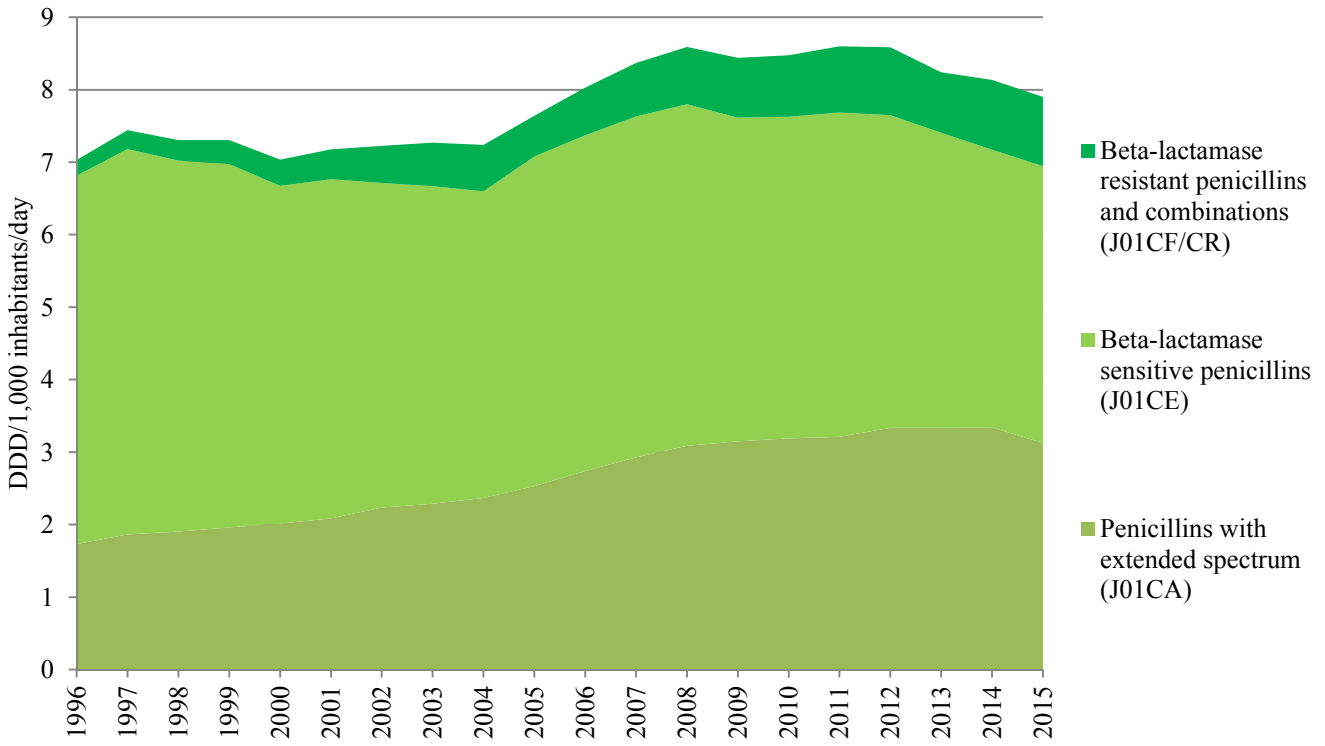

FIGURE 18. Sales of penicillins (J01C) in Norway 1996-2015 and changes within groups of penicillins.

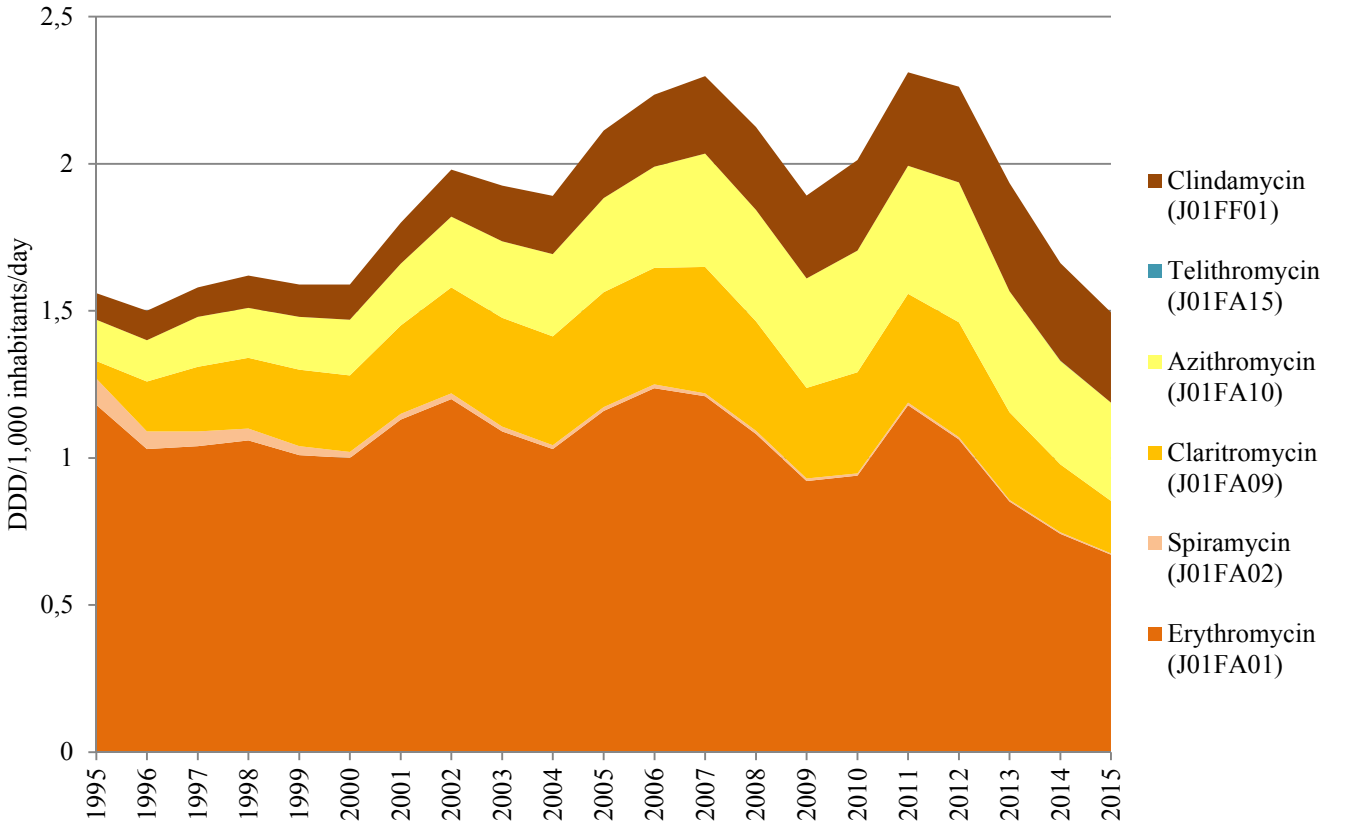

FIGURE 19. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1995-2015.

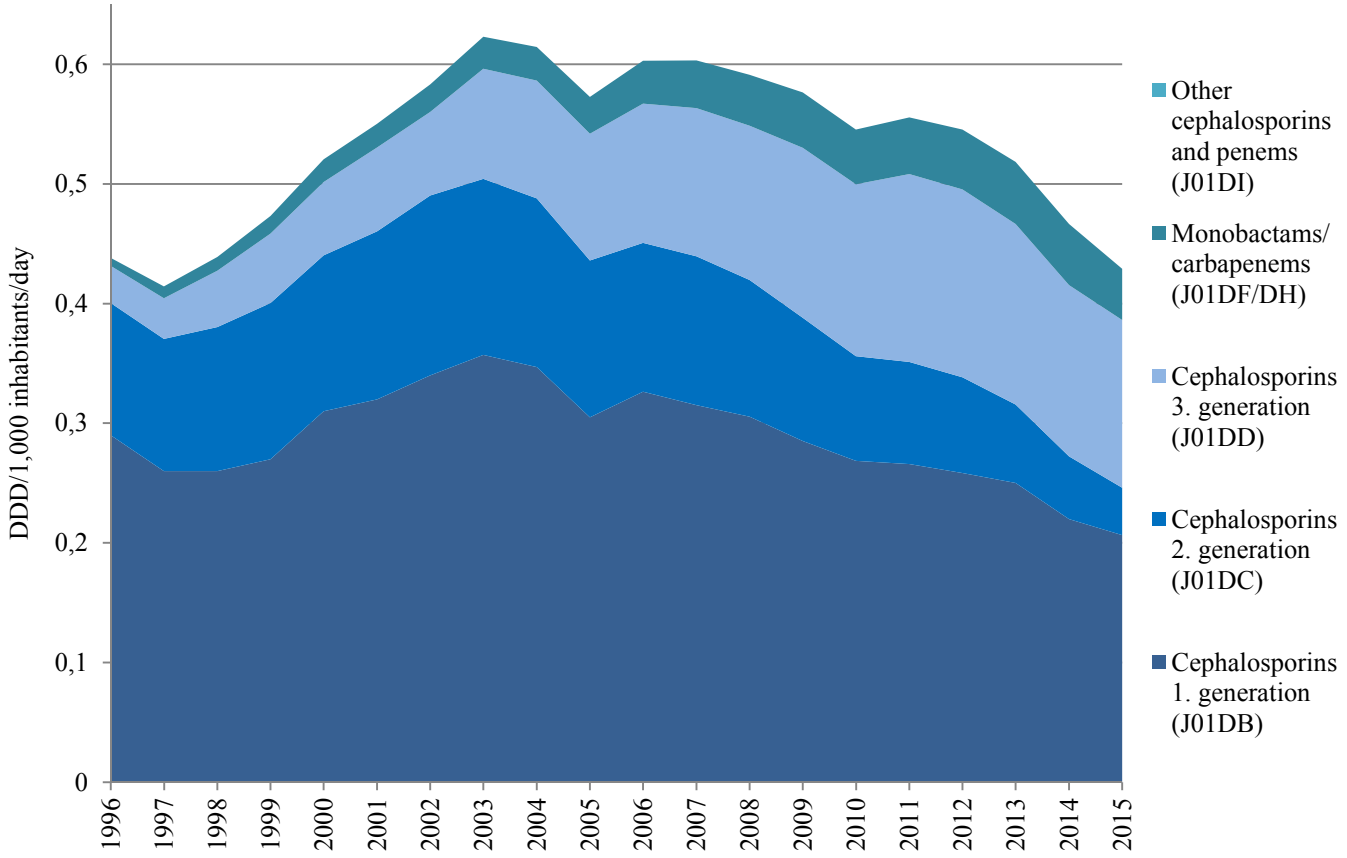

FIGURE 20. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2015 and changes within generations of cephalosporins and monobactams/carbapenems.

Antibiotic usage in primary care

Around 85% of the total human sales of antibacterials are used in primary care, i.e. outside health institutions. Antibacterials are prescription-only drugs in Norway and all prescriptions (including those prescribed from hospitals to out-patients) to persons living in Norway are captured in these figures.

Sales of antibiotics to outpatients have decreased since 2012. For ambulatory care, the most important antibiotic groups in 2015 were penicillins (J01C, 41% of DDDs), tetracyclins (J01A, 19%) and macrolides and lincosamides (J01F, 8%). The four most commonly prescribed antibiotics for outpatients in 2015 were phenoxymethylpenicillin, pivmecillinam, doxycycline, and amoxicillin. These four represented 52% of all prescriptions and 47% of all DDDs. The urinary antiseptic methenamine represented only 8% of prescriptions, but 22% of the DDDs in ATC group J01 antibacterials for systemic use.

Geographical variation

The usage of antibacterials varies among the 19 Norwegian counties. The county using the least is using around 70% (in DDDs) of the county using the most (Figure 21). Over the years, and measured in DDDs, the same counties seem to be high-use counties and low-use counties, respectively. The pattern is almost the same when looking at the number of prescriptions/1,000 inhabitants (Figure 22).

Females use more antibiotics than males; 27% of females purchased at least one antibiotic course in 2015 compared to 18% of males. The gender pattern is similar in all regions in the country (Figure 23). The highest use is found among young children, young women and the elderly (Figure 24). More than one in three elderly are prescribed antibiotics each year. This is also apparent with regard to number of prescriptions and volume (amount measured in DDDs). For those above 75 years of age, 2-2.5 prescriptions are dispensed every year compared to 1.5-2 for younger persons (Figure 25).

Antibiotics prescribed by dentists

Physicians are the main prescribers to humans, but dentists prescribe 5% (measured in DDDs) of antibiotics (J01) to humans in ambulatory care. In 2015, dentists most often prescribed phenoxymethylpenicillin (75% of all antibiotic DDDs prescribed by dentists) followed by amoxicillin (11%) and clindamycin (6%).

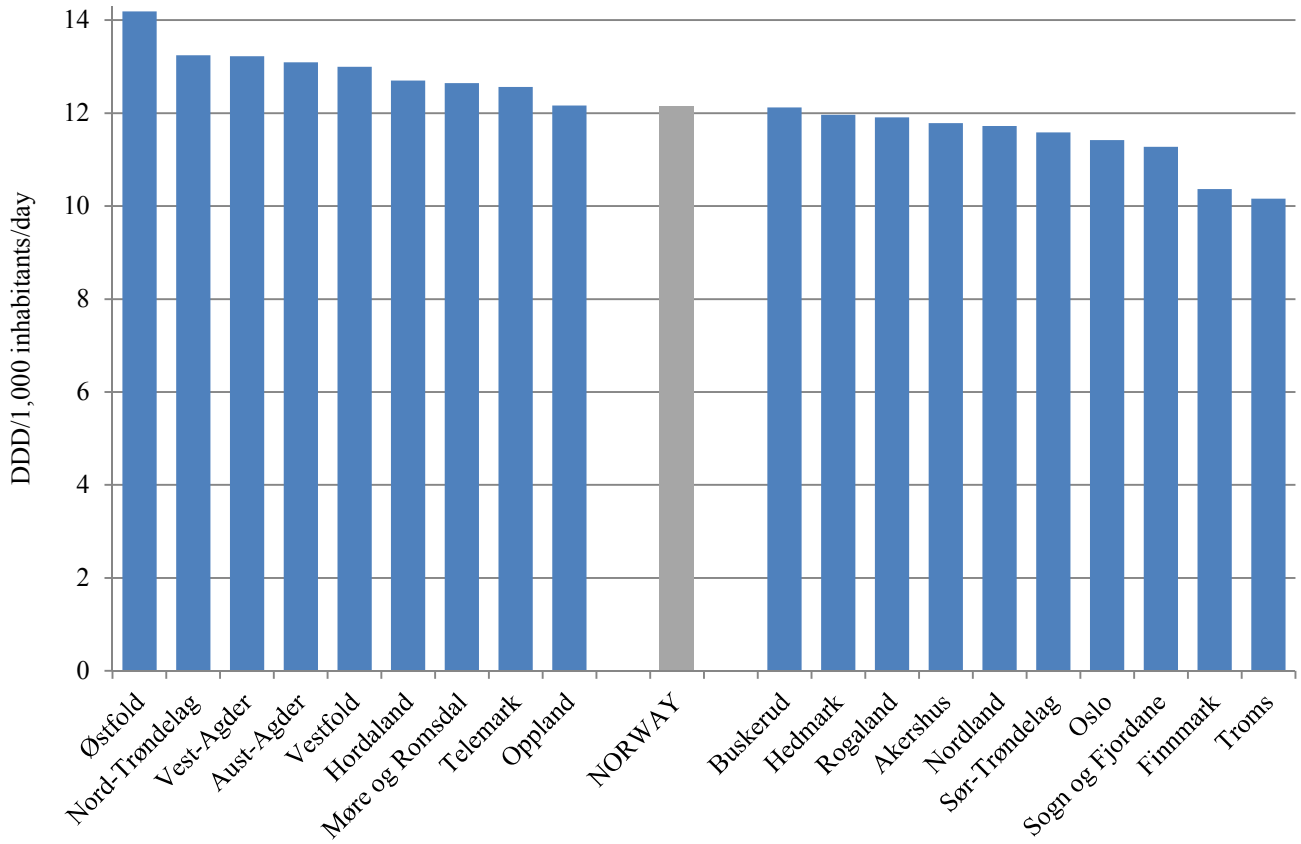

FIGURE 21. Sales of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2015. Measured as number of DDD/1,000 inhabitants/day. Data from NorPD (i.e. health institutions not included).

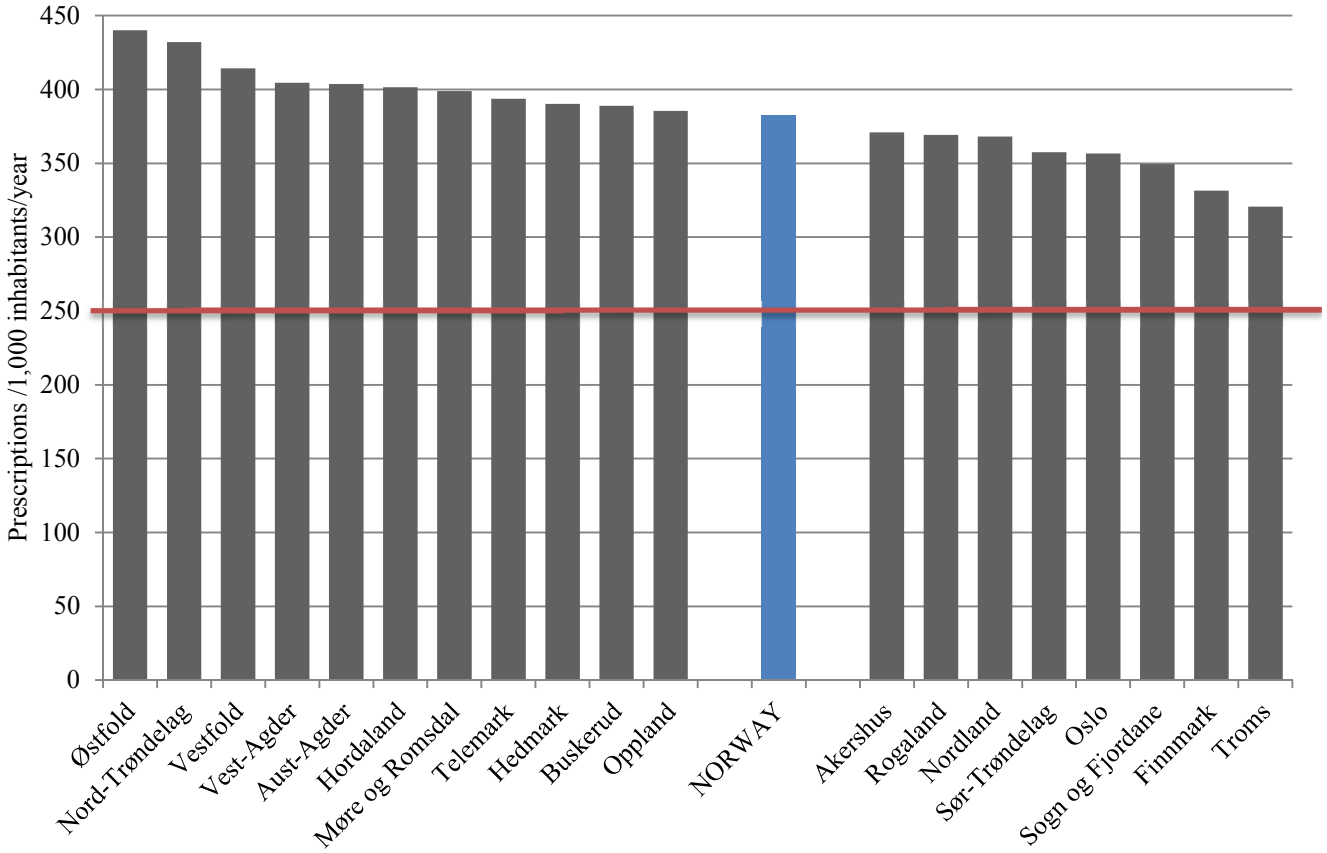

FIGURE 22. Sales of antibacterial agents for systemic use (ATC group J01, excl. methenamine) in outpatients in the different counties of Norway in 2015. Measured as number of prescriptions/1,000 inhabitants. Data from NorPD (excl. health institutions). Red line: goal set by the National Strategy against Antibiotic Resistance 2015-2020.

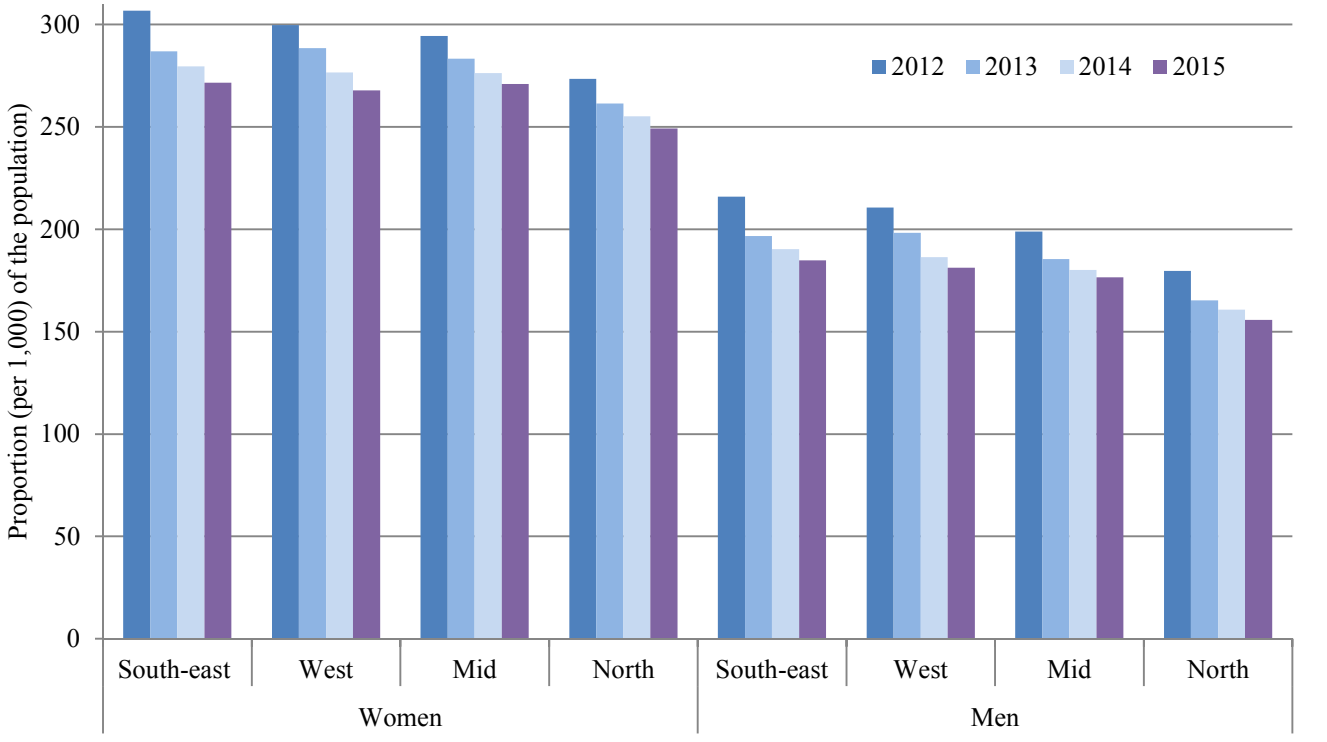

FIGURE 23. One year prevalence of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2012-15. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine), vancomycin (A07AA09), rifaximin (A07AA11), fidaxomicin (A07AA12) and metronidazole (P01AB01).

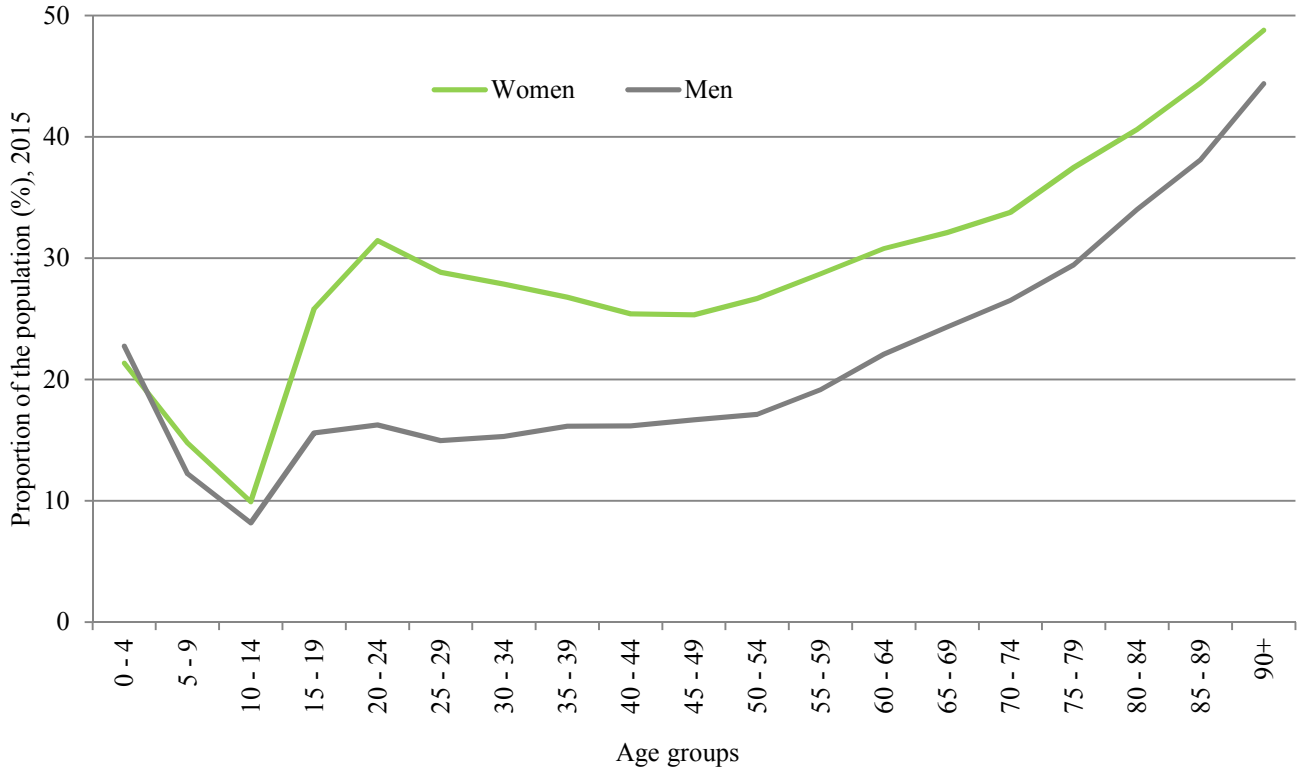

FIGURE 24. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one year prevalence) in ambulatory care by gender and age in Norway, 2015. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine), vancomycin (A07AA09), rifaximin (A07AA11), fidaxomicin (A07AA12) and metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions.

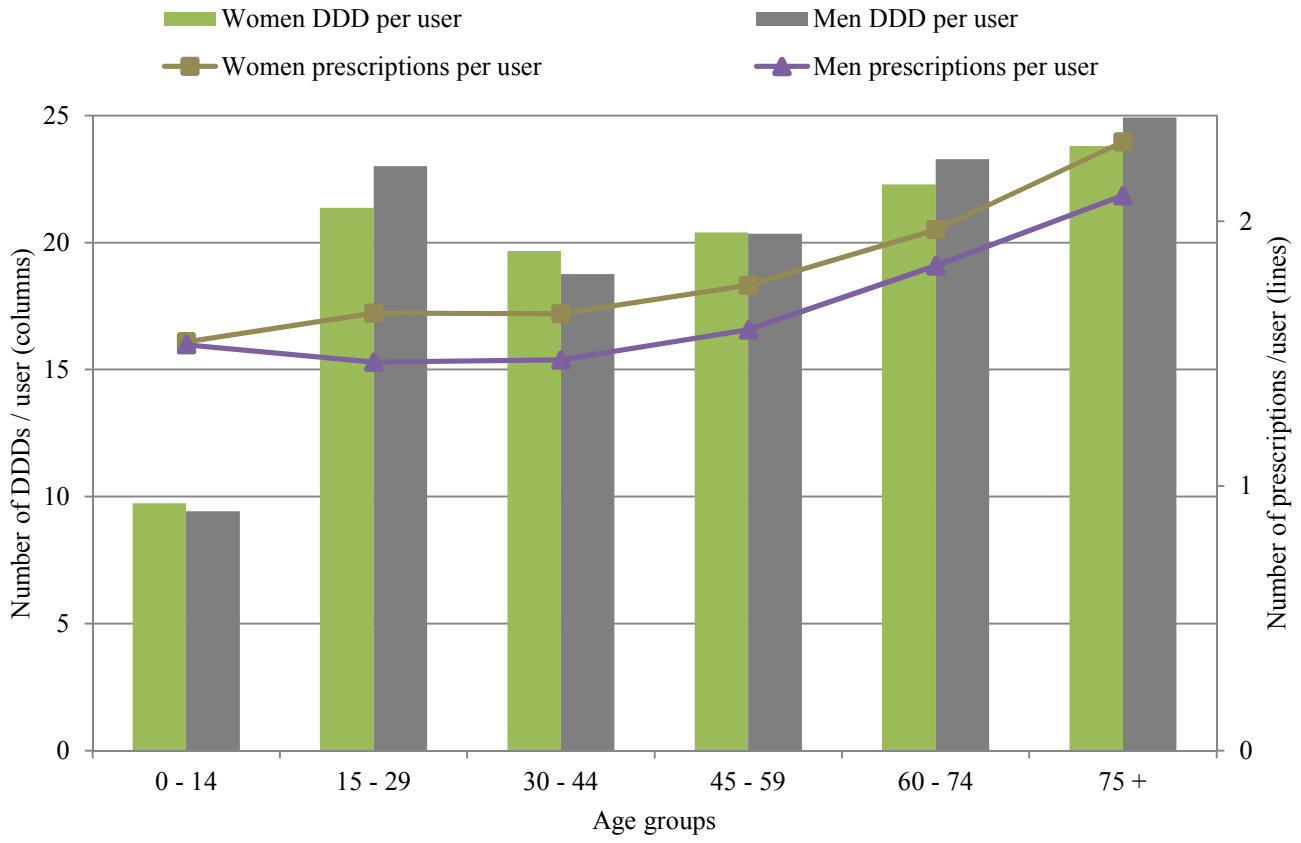

FIGURE 25. Mean number of prescriptions per person and mean number of DDDs per person among users of antibacterials in ambulatory care by gender and age in Norway, 2015. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

Improving fluoroquinolone prescribing in primary care

The Norwegian government has an ambitious plan to improve antibiotic prescribing by 2020. Reduction of total antibiotic prescribing by 30% is the main goal of this initiative (1). An equally important goal is reducing unnecessary broad-spectrum antibiotic prescribing and improving the choice of antibiotic prescribing such that prescribing is in line with the national guidelines. Attaining these goals makes focus on fluoroquinolone prescribing in the primary care essential.

Nearly 90% of antibiotic prescribing occurs in primary care in one of the following three clinical arenas; the family physicians office, the nursing home, or the emergency room (ER). There are salient differences between these three arenas making the need to tailor antibiotic prescribing improvement strategies to these specific differences. Antibiotic stewardship programmes have traditionally focused on the hospital setting, but recently stewardship programmes have been initiated in the nursing home and ER settings (2, 3).

Fluoroquinolones are arguably the broadest spectrum antibiotics primary care physicians can prescribe in Norway. They can also be administered both orally and intravenously. The combination of these factors makes fluoroquinolones a tempting choice for empiric therapy for patients with suspected urosepsis or with an infection of uncertain etiology. This is especially true for elderly, cognitively impaired, patients in whom the clinical presentation can make specific diagnosis difficult. Many of these elderly patients are initially treated in the local hospital, stabilised, and then transferred to a nursing home before completion of antibiotic treatment.

Transfer to the nursing home provides an opportunity to re-evaluate and possibly de-escalate antibiotic therapy. De-escalation refers to shortening the course of antibiotic treatment, reducing the dosage, or changing the antibiotic to a narrower spectrum antibiotic. Switching to a narrower spectrum antibiotic is contingent on adequate microbiologic diagnostics prior to initiation of initial empiric therapy. A recent Norwegian nursing home study demonstrated that at least 38% and perhaps as much as much as 76% of fluoroquinolone prescriptions could have been switched to a narrower spectrum antibiotic(4). Unfortunately, a disappointing 50% of the infections treated with a fluoroquinolone had no form for microbiologic work-up. This inadequacy makes de-escalating of fluoroquinolone therapy difficult.

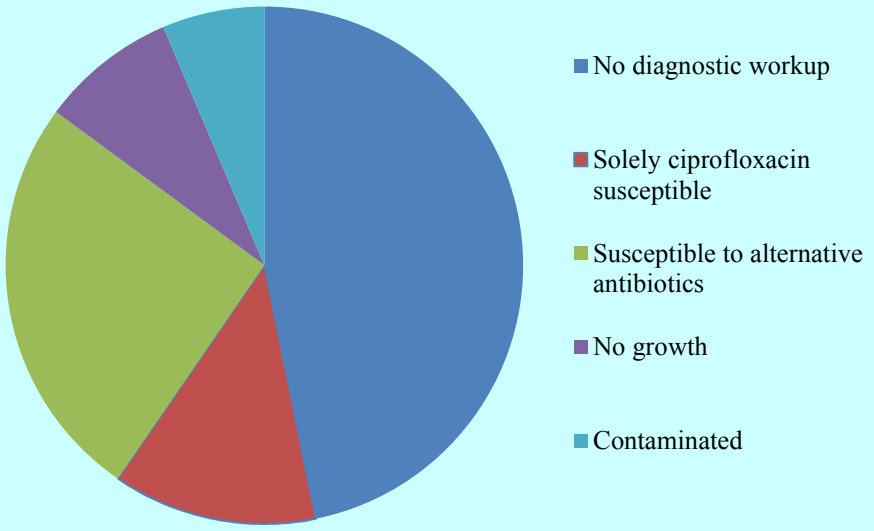

FIGURE 26. The degree of microbiological workup and culture results among nursing home patients treated with a fluoroquinolone.

Evaluating the indication for fluoroquinolone prescribing is another opportunity to reduce unnecessary fluoroquinolone prescribing when patients are transferred to the nursing home. Norwegian guidelines do not recommend fluoroquinolones for treating RTI (5). There is evidence that guideline incongruent fluoroquinolone prescribing in the nursing home is often initiated by hospital physicians but is perpetuated by nursing home physicians (6). This is concerning for two reasons. First, there is a risk that prescribing practices in the local hospital will influence primary care physicians to prescribe fluoroquinolone more liberally. Second, strategies to improve antibiotic prescribing need to aim at both the hospital and the nursing home.

In addition to the nursing home-hospital interface, the emergency room is undoubtedly an area to focus on for improved antibiotic prescribing. It is difficult to know precisely what proportion of antibiotics in general and fluoroquinolones specifically are prescribed in the ER. A conservative estimate is 30% as most physician offices close at 15:00 and are not open on the weekends. A study evaluating the feasibility of restrictions combined with a therapy suggestion list showed a significant reduction in fluoroquinolone prescribing for cystitis and a concomitant increase in mecillinam prescribing (7). The study also showed that the overwhelming majority of prescriptions for cystitis were in line with national guidelines. Nonetheless, the study raises the issue of the necessity of immediate availability of ciprofloxacin in the ER and the use of clinical decision support prompting to reduce fluoroquinolone prescribing (8).

The third arena for improved fluoroquinolone improvement is the general practitioner's office. Studies examining prescribing for respiratory tract infections among Norwegian family physicians demonstrate clear differences in guideline incongruent prescribing (9). It is impossible to extrapolate these observations to the treatment of urinary tract infections, but it is not unreasonable to assume that the same holds true - that certain prescribing physicians have greater guideline incongruent prescribing of fluoroquinolone than others. There is substantial literature documenting inexplicable variation in prescribing practices both on the individual physician level and at the institutional level (10).
In Norway, the national prescription registry registers all prescriptions which are expedited at a pharmacy. Until recently, these prescriptions did not require a diagnosis. This hindered access to valuable information on how specific infections are treated by individual physicians. This information would provide the basis for individual physician feedback and defining targets for improved antibiotic prescribing in general, for example unnecessary fluoroquinolone treatment for uncomplicated cystitis and respiratory tract infections.
The NORM report provides surveillance on the national level. Antibiotic stewardship programmes providing regular periodic surveillance in the ER, in nursing homes and of individual primary care physicians are essential to improve fluoroquinolone prescribing in primary care.

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Measuring the usage of antibiotics in hospitals: Current state-of-the-art in Norway, limitations and challenges

To gauge the extent of antibiotic use is essential for most antibiotic stewardship activities and the study of antibiotic resistance development. This text presents relevant measurements used to survey antibiotic use in hospitals and discusses best practices and current limitations. Possible solutions to major challenges are also addressed, including some that may be particular for Norway. Important issues not considered here are optimal reporting of antibiotic use data and patient case-mix adjustments in efforts to benchmark hospitals.

Antibiotic measurement indices
For surveillance purposes, indices are commonly calculated with aggregated antibiotic doses representing the numerator and measures that relate to the hospital patient population as the denominator. The two main indices recommended for hospitals are Defined Daily Doses (DDDs) per 100 hospital bed days and DDDs per 100 hospital stays (i.e. the number of hospital discharges). The DDD definition is given on page 106 in this report. The index commonly used for antibiotic outpatient surveillance, DDDs per 1,000 inhabitants per day (DID), is unfortunately seldom applicable to hospitals since many institutions have a diverse and fragmented patient catchment area. Typically, this applies to tertiary centers and larger hospitals in densely populated areas. For selected hospitals where these limitations do not apply, and to present overall national antibiotic use, DID may still be a valuable index.

The numerator: aggregated doses of antibiotics
To standardise measures of drug utilisation, the technical unit of DDDs was proposed in the late 1970ies and has since gained an international acceptance. Alterations in DDDs and the Anatomical Therapeutic Chemical (ATC) index are maintained by the WHO [1]. The use of WHO DDDs is mandatory for any international comparisons of antibiotic use. However, in the surveillance of a hospital patient population, there are shortcomings in the WHO assigned DDDs for many narrow-spectrum antibiotics. In particular, this concerns the doses for the penicillins which in general are set far lower than the doses that are actually being used. The effect of recording too high numbers of DDDs for these antibiotics is a skewed surveillance, e.g. by reporting falsely high proportions of narrow-spectrum when compared to the broad-spectrum antibiotics. Some authorities suggest WHO DDD adjustments to establish units that better reflect hospital usage, often denounced Prescribed Daily Doses

[2, 3]. In Germany, a similar unit of RDDs (Recommended Daily Doses) supplements WHO DDDs in national surveillance reports [4]. An alternate measure of hospital-adjusted Daily Doses units has also been evaluated for Norway, using a national surveillance dataset [5]. The acquisition of antibiotic doses is facilitated by a national internet-base database containing sales data from all hospital pharmacies in Norway, which may be downloaded and analysed on a monthly basis.

The denominator: administrative data related to hospital activity

Relating antibiotic consumption to hospital activity parameters is considered a prerequisite for antibiotic surveillance and comparisons of antibiotic use between hospitals and countries. In particular, this is crucial for temporal trend analyses – even when performed within a single hospital – because the average length of stay has decreased significantly in hospitals during the last decade (but to a variable degree) while the number of patient stays has increased. Antibiotic use data should relate both to the number of hospital bed days and the number of hospital stays. In addition to accounting for variations in hospital activity, the two indices may give slightly different information of importance for the interpretation of antibiotic use density in hospitals (6).

The acquisition of the denominator data would appear to be a straightforward process – which may be why the method by which denominator data are collected is often cursory described in scientific papers. However, in Norway this exercise represents a major challenge whenever one attempts to assemble and analyse antibiotic use data at lower levels than whole Health Enterprises (HEs) – i.e., administrative units consisting of one to seven geographically separate hospitals. Such detailed data are not publicly available and, more importantly, no national coding standard exists for HEs administrative unit codes. Moreover, problems arise when one attempts to link activity data from administrative sources to the antibiotic doses sold from hospital pharmacies, where an equal plethora of locally determined and different unit codes exists.

Circumventing the problem?

Considering the ease of access and timeliness of antibiotic sales data in Norway, an additional and straightfoward method of evaluating antibiotic use may be to rank the total number of antibiotic doses through Drug Utilisation (DU) analysis (5, 8). Depending on the number of total registered antibiotics, the most used substances within 75% or 90% of total doses of all antibiotics (DU75%/DU90%) are ranked for a given period. The ranking order may reveal useful information both for intra- and interhospital comparisons. Furthermore, rapid and timely results can be presented since the need for administrative data is obliviated.

Immediate and long-term challenges and prorposed solutions

A national aim has been set from 2016 to reduce consumption of broad-spectrum antibiotics in hospitals by 30% within the year 2020 (7), hence the need for a reliable measurement tool is evident. The next immediate step should be to implement standardised antibiotic surveillance systems at the individual hospital level to permit an effective antibiotic stewardship. Urgent action is called for by relevant stakeholders to assure the availability of essential data sources as described above. Unfortunately, no such initiatives have been undertaken up until now. An effective measure would probably be to allocate some resources to the National Patient Registry and the Health Analytic Section of the National Institute of Public Health where all relevant data and the right expertise co-exists – a combination which may deliver administrative data on a timely and perpetual basis.

In a longer time perspective, the implementation of electronic medication charts ("*elektronisk kurve*") in most or all Norwegian hospitals will represent a paradigm shift for antibiotic stewardship. Antibiotic regimes prescribed and administered may then easily be analysed for individual patients pr as aggregated data, and antibiotic use may subsequently be linked to relevant sources of clinicial information.

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8. Zarb P *et al*. Drug Utilization 75% (DU75%) in 17 European Hospitals (2000 - 2005): Results from the ESAC-2 Hospital Care Sub Project. Current clinical pharmacology. 2011;6(1):62-70.

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Antibiotic usage in hospital care

In 2015, the antibacterial sales (in DDDs) to hospitals represented around 7.4% of total sales of antibacterials for human use in the country. The therapy pattern of antibacterials in hospitals does not change much from one year to another (Figure 27).

Penicillins (J01C) represent 49% of the use measured in DDDs in hospitals (J01CE 17%, J01CA 16%, J01CF 11% and J01CR 5%). The second largest group is the cephalosporins with 17% of all DDDs, the dominant subgroup being 3rd generation cephalosporins (J01DD). In 2015, eight substances accounted for 57% of DDDs used in hospitals. These are benzylpenicillin, cloxacillin, cefotaxime, ampicillin, cefalotin, piperacillin/tazobactam, doxycycline and pivmecillinam. Three single substances accounted for 30% of all antibacterial use in hospitals; benzylpenicillin (14%), cloxacillin (9%) and cefotaxime (7%).

Figure 28 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. In 2015, a mean use of 74 DDD/100 bed days was observed. There has been an increase in mean DDD/100 bed days by 21% over the last 10 years, while the DDD/admission (3.2 in 2015) has increased by 6 % in the same period.

Seven selected groups that are mainly used in hospitals are shown in Figure 29. Since 2006, there has been an increase in the use of carbapenems and the combination of piperacillin/tazobactam. The use of 3rd generation cephalosporins decreased in 2014 and 2015, and the use of 2nd generation cephalosporins has been decreasing over many years. It should be noted that only parenteral formulations of 2nd and 3rd generation cephalosporins as well as carbapenems are lisenced in Norway.

There are large variations between hospitals in the volume of antibiotics used, measured in DDD/100 bed days, as well as in the therapy profile. Figure 30 shows the use of 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 solely by differences in activity or composition of patient populations.

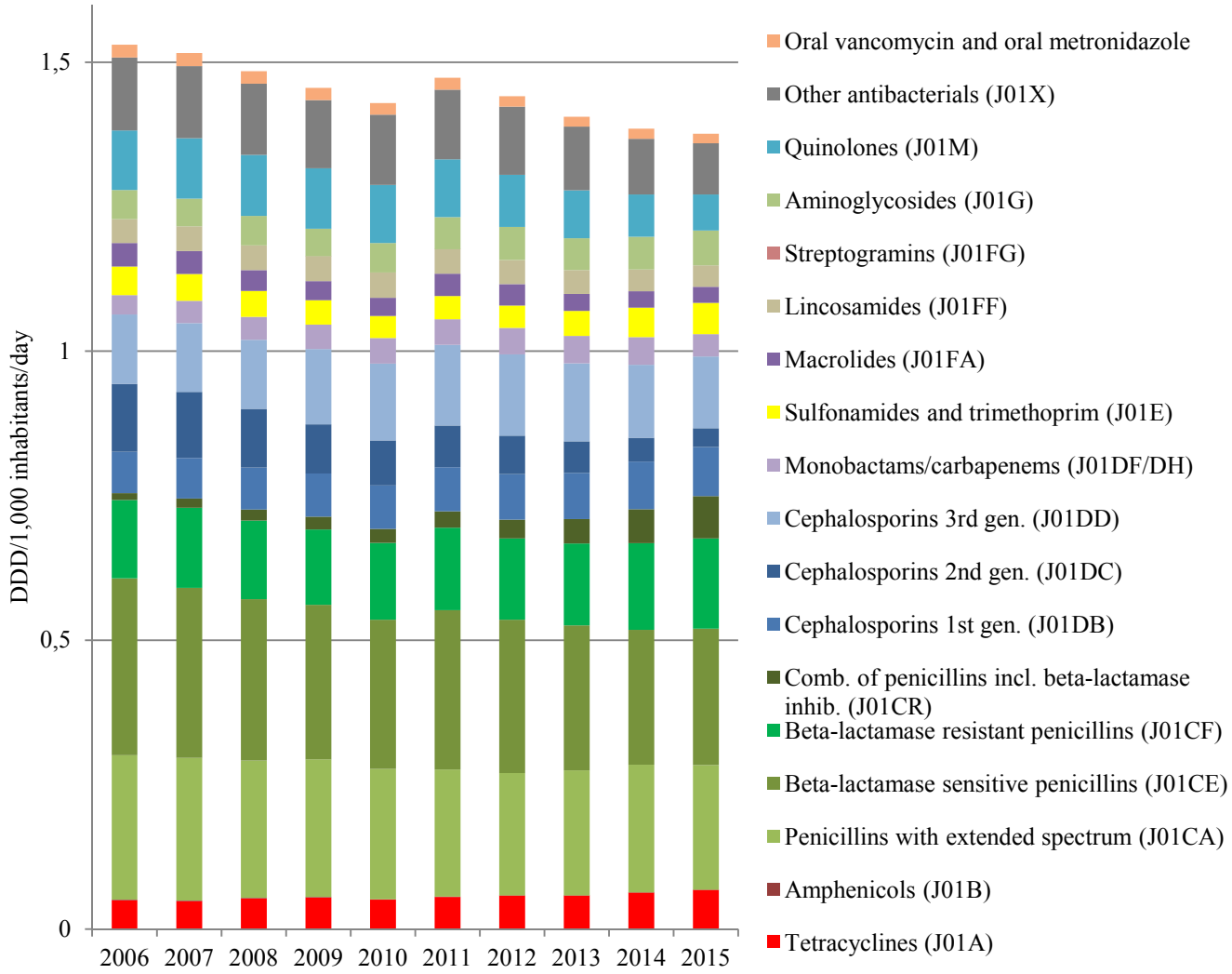

FIGURE 27. Proportions of antibacterial agents for systemic use in Norwegian hospitals 2006- 2015, measured in DDD/1,000 inhabitants/day.

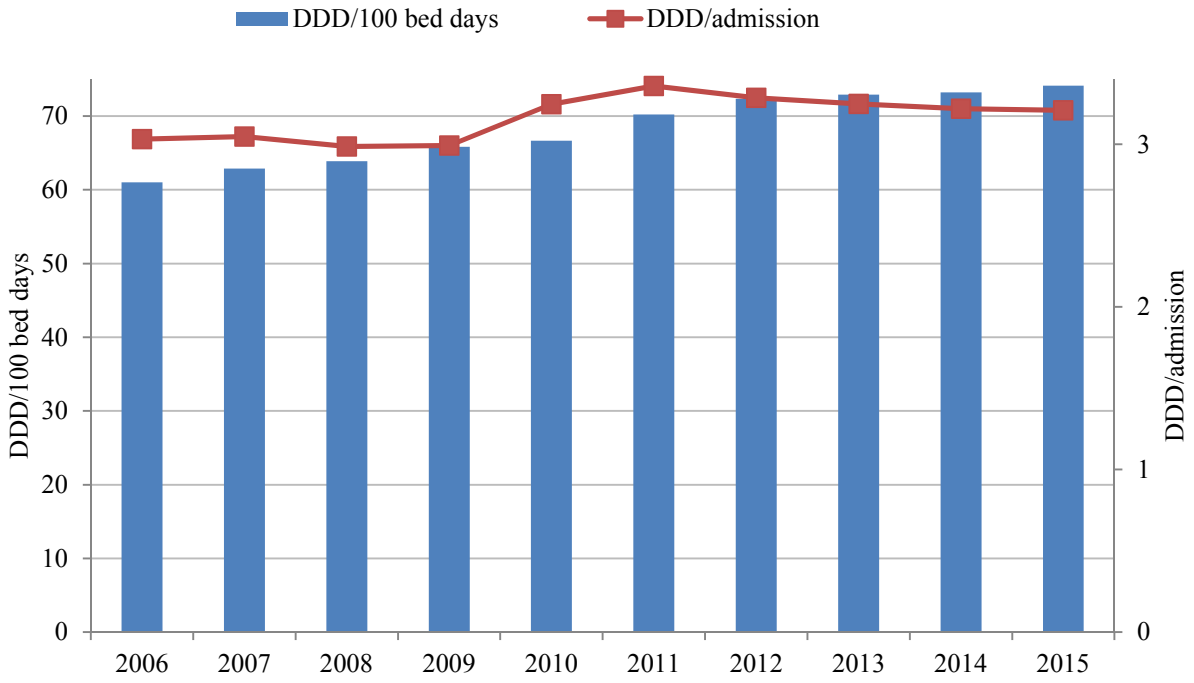

FIGURE 28. Total use of antibiotics in Norwegian somatic hospital 2006-2015, measured in DDD/100 bed days (blue bars) and DDD/admission (red line). Antibiotics are defined as J01 antibacterials for systemic use, A07AA09 vancomycin (oral), A07AA12 fidaxomycin and P01AB01 metronidazole (oral and rectal).

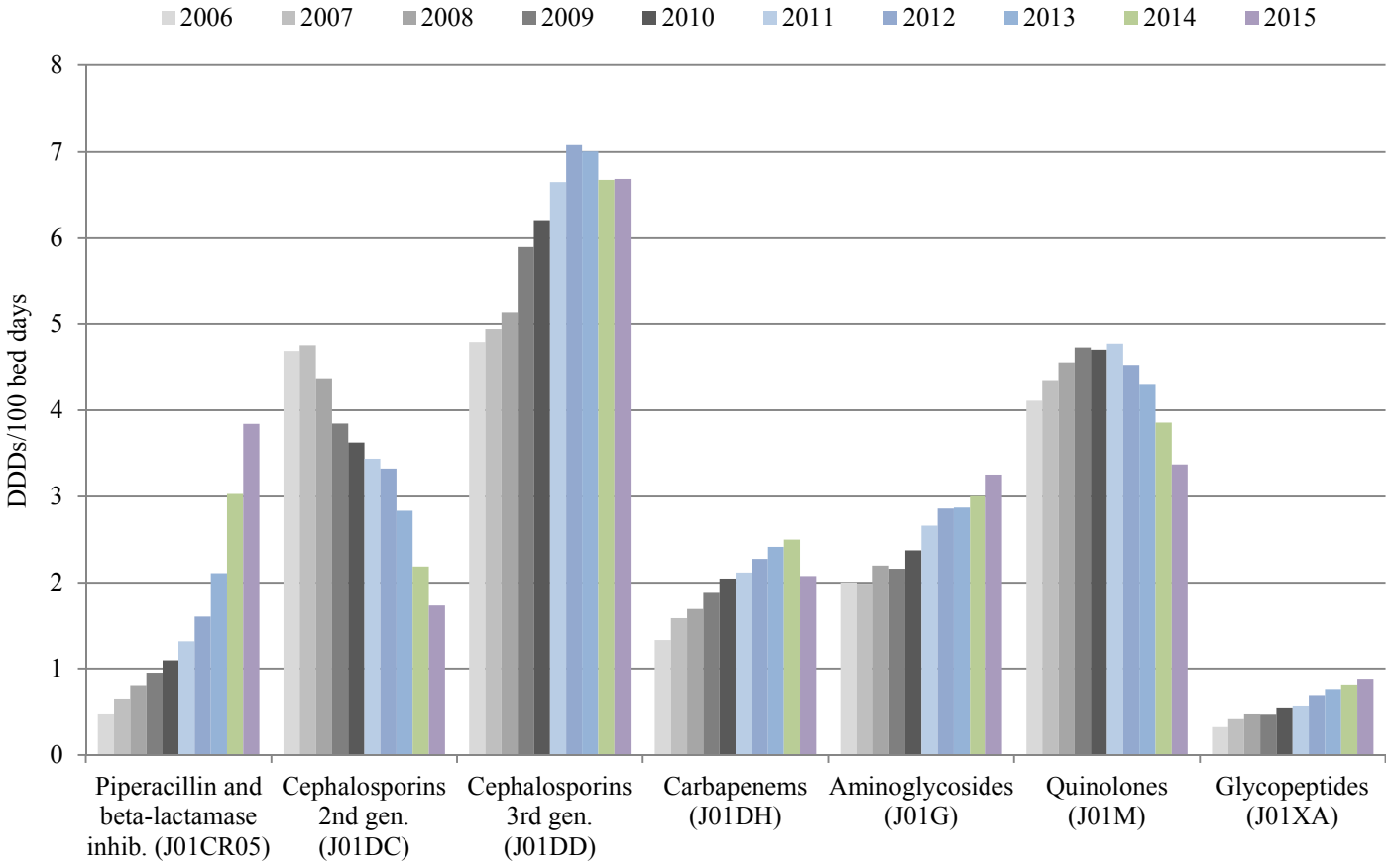

FIGURE 29. Proportions of selected antibacterial agents for systemic use (ATC J01CR05, ATC group J01DC, J01DD, J01DH and J01M) in Norwegian hospitals 2006-2015, measured in DDD/100 bed days.

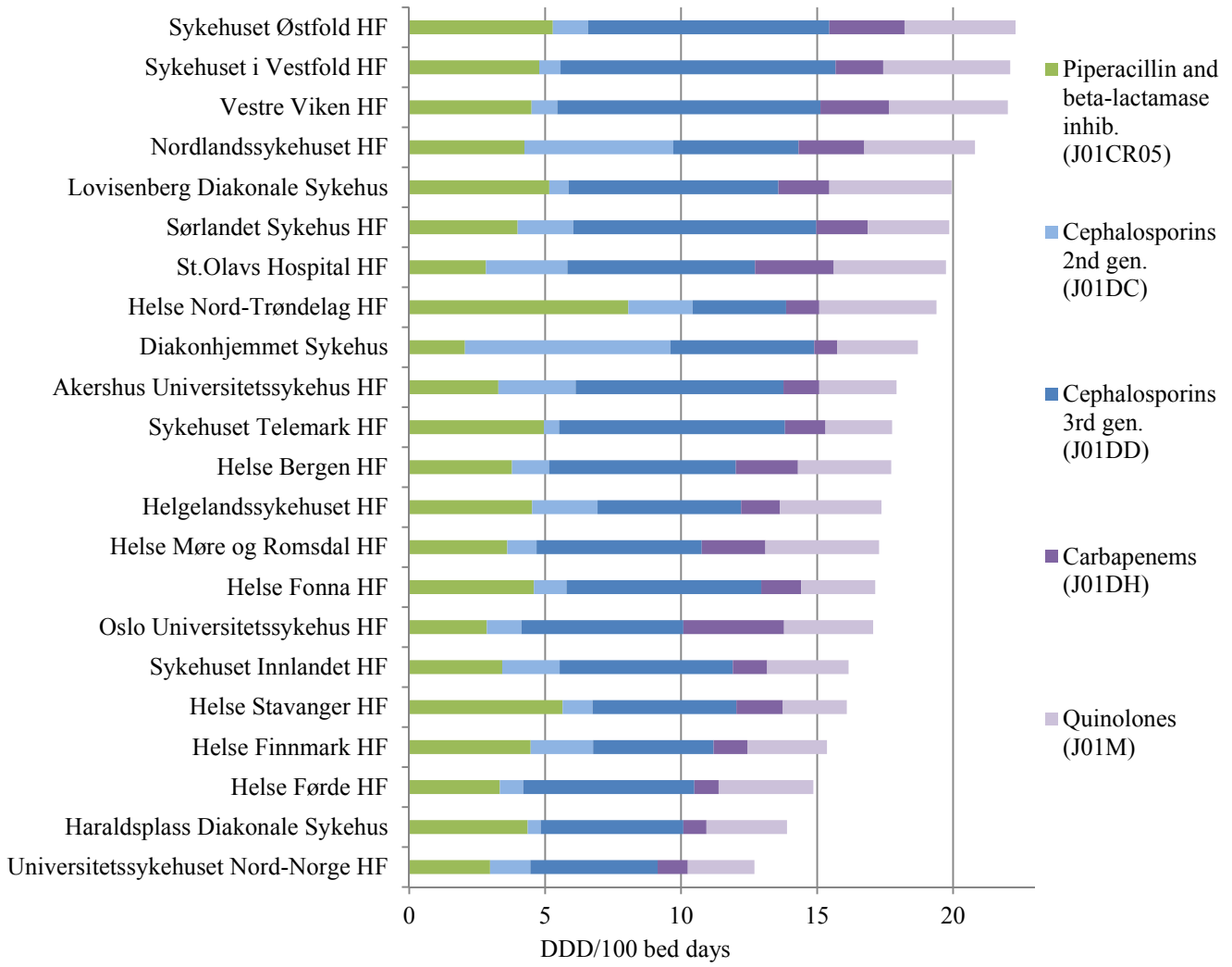

FIGURE 30. Proportions of selected antibacterial agents for systemic use (ATC J01CR05, ATC group J01DC, J01DD, J01DH and J01M) in Norway, presented per hospital/health trust, in 2015, measured in DDD/100 bed days.

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 is reduction of DDDs by 30%. In addition, two sector specific goals in ambulatory care are presented; reduction of average number of prescriptions (target; 250 precriptions per 1,000 inhabitants per year) and the reduction of antibiotics for respiratory infections by 20%. Figure 31 shows total human use (J01) and use of antibiotics for respiratory tract infections in Norway since 2012 according to National targets. Figure 32 shows proportional change (2012-2015) in usage in ambulatory care in Norwegian municipalities with more than 5,000 inhabitants. In many municipalities, the use of anti-bacterials has decreased since 2012, but usage has increased in 13% of the municipalities. Furthermore, since 2012, there has been a reduced prevalence of use in all age groups except for the elderly above 75 years. Moreover, prescription to men is reduced more than in women; 15% reduction in prescriptions pr 1,000 men vs. 10% in women. The largest reduction in prescriptions per 1,000 is seen in children with approximately 21% less prescriptions since 2012 pr 1,000 in 0-14 year olds.

For hospitals, the main target is 30% reduction in combined use of five selected groups of antibiotics. Figure 33 shows the annual variation in total hospital use of these groups in the years 2006-2015 according to the national target. Figure 34 shows how the use of these five groups have changed in different Norwegian hospitals/health trusts in relation to the national target. A reduction by 30 % is marked by a grey line in the figure.

Norway has two national advisory units for antibiotic use. The Antibiotics Center for Primary Health Care (ASP) was established in 2006, whereas the Norwegian National Advisory Unit for Antibiotic Use in Hospitals (KAS) was established in 2011. 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 updated National Antibiotic Treatment Guidelines for ambulatory care, nursing homes, dentists and hospitals.

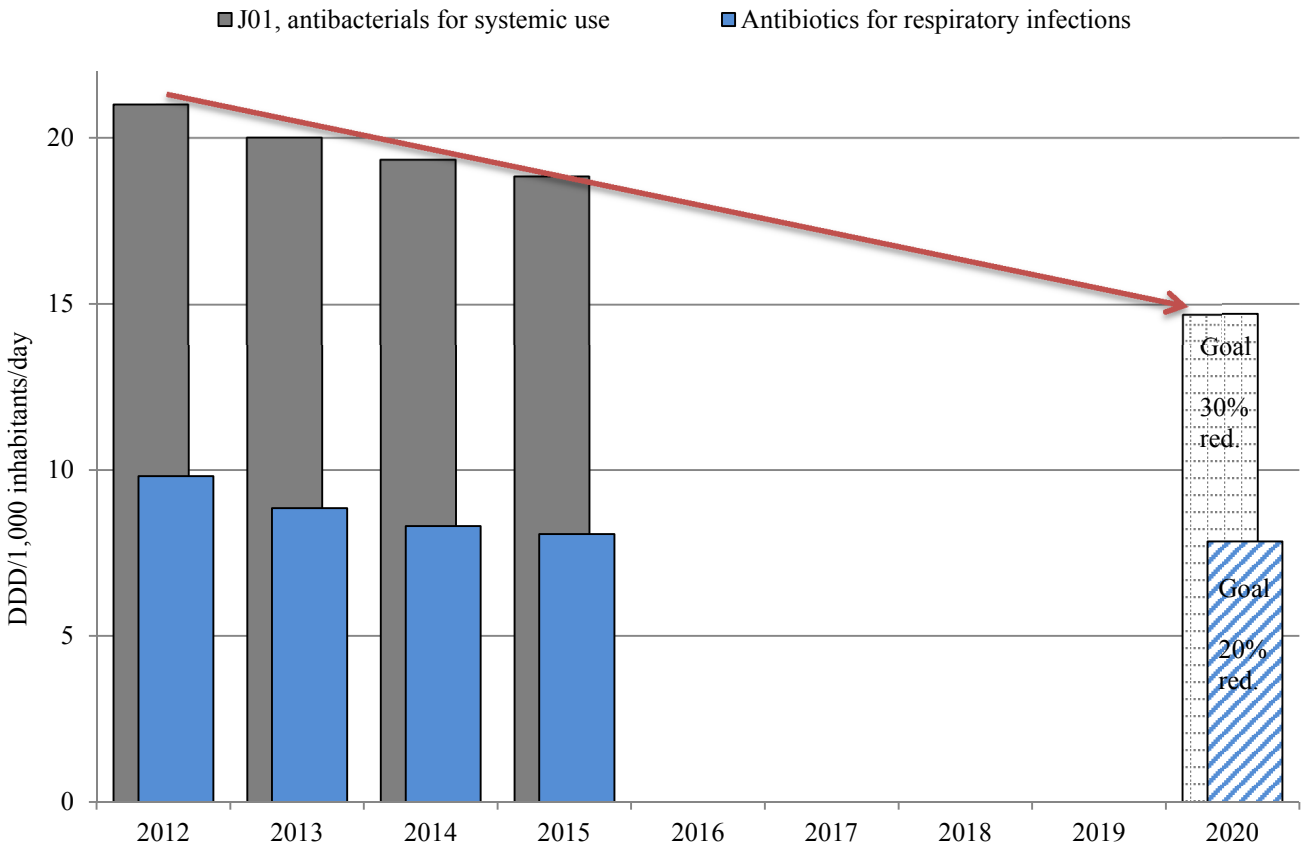

FIGURE 31. Total human sales of antibacterial agents for systemic use (ATC group J01, incl. methenamine) and sales of antibiotics for respiratory tract infections (amoxicillin, phenoxymethylpenicillin, macrolides and doxycycline) in Norway in 2012-2015 measured in DDD/1,000 inhabitants/day. According to the National Action Plan, the target for 2020 is a 30% reduction, measured in DDDs. Bars indicate measured use 2012-2015 (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.

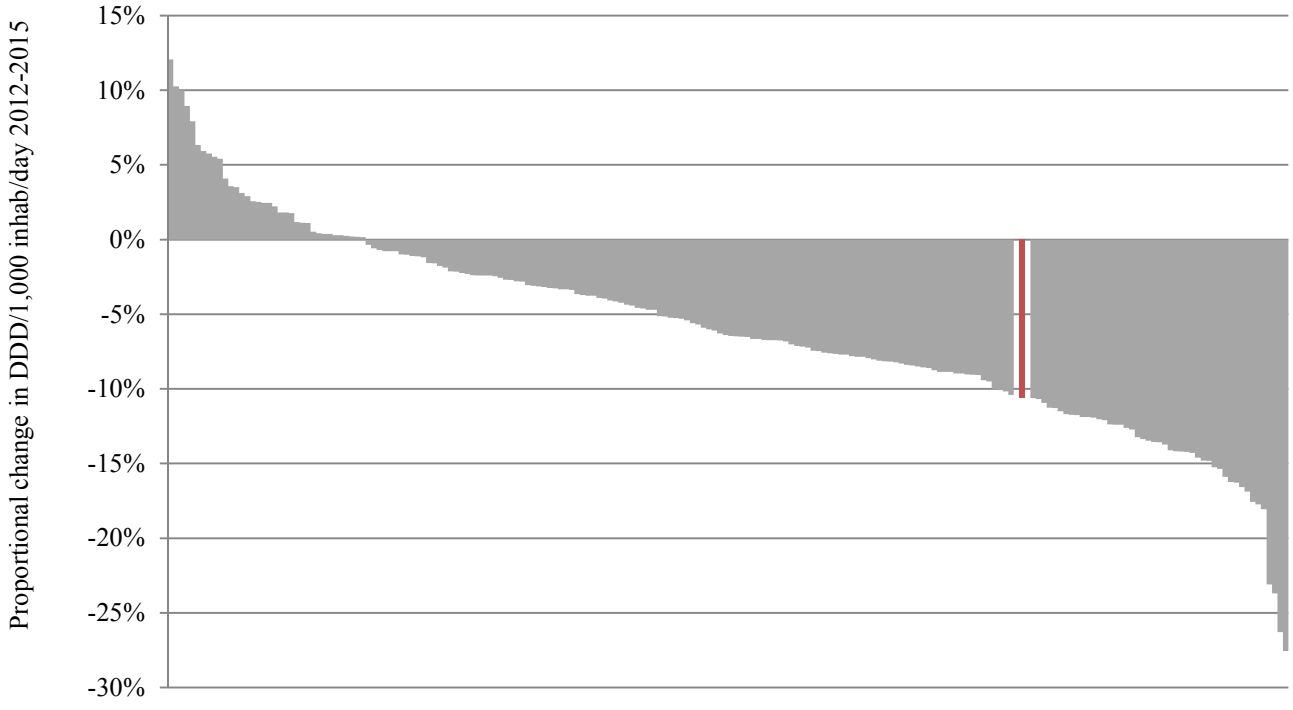

FIGURE 32. Proportional change (%), measured in DDD/1,000 inhabitants/day, of use of antibacterial agents for systemic use (ATC group J01) in outpatients in the 202 largest municipalities (more than 5,000 inhabitants) in Norway in 2012-2015. Data from NorPD (i.e. excl. health institutions). Red line is the national average in 2015 with an 11% reduction since 2012.

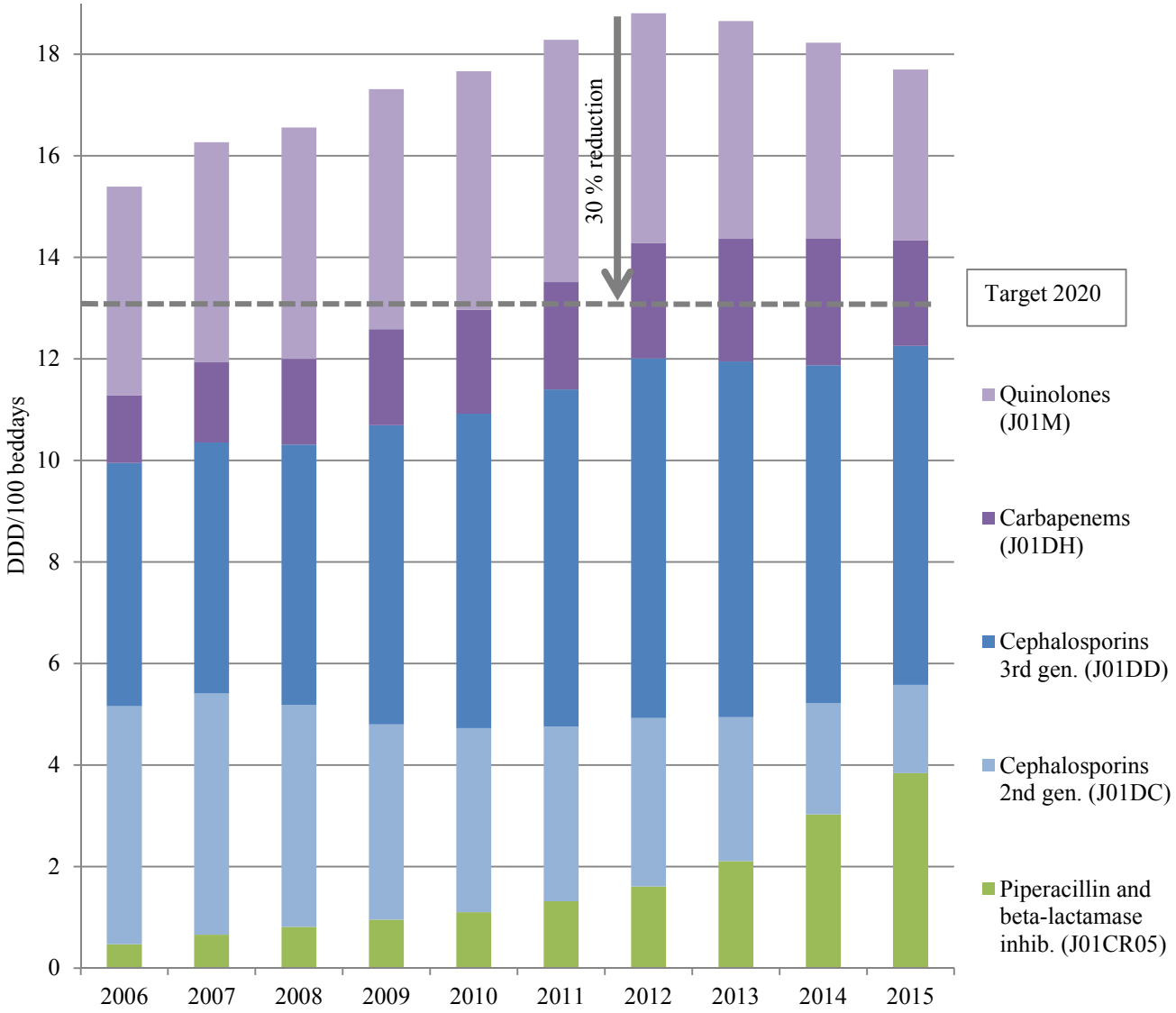

FIGURE 33. Use of selected broad-spectrum antibacterial agents for systemic use (ATC J01CR05, ATC group J01DC, J01DD, J01DH and J01M) in Norwegian hospitals in 2006-2015, measured in DDD/100 bed days. According to the National Action Plan, the target for hospitals is 30% reduction (measured in DDDs) by 2020 compared to 2012.

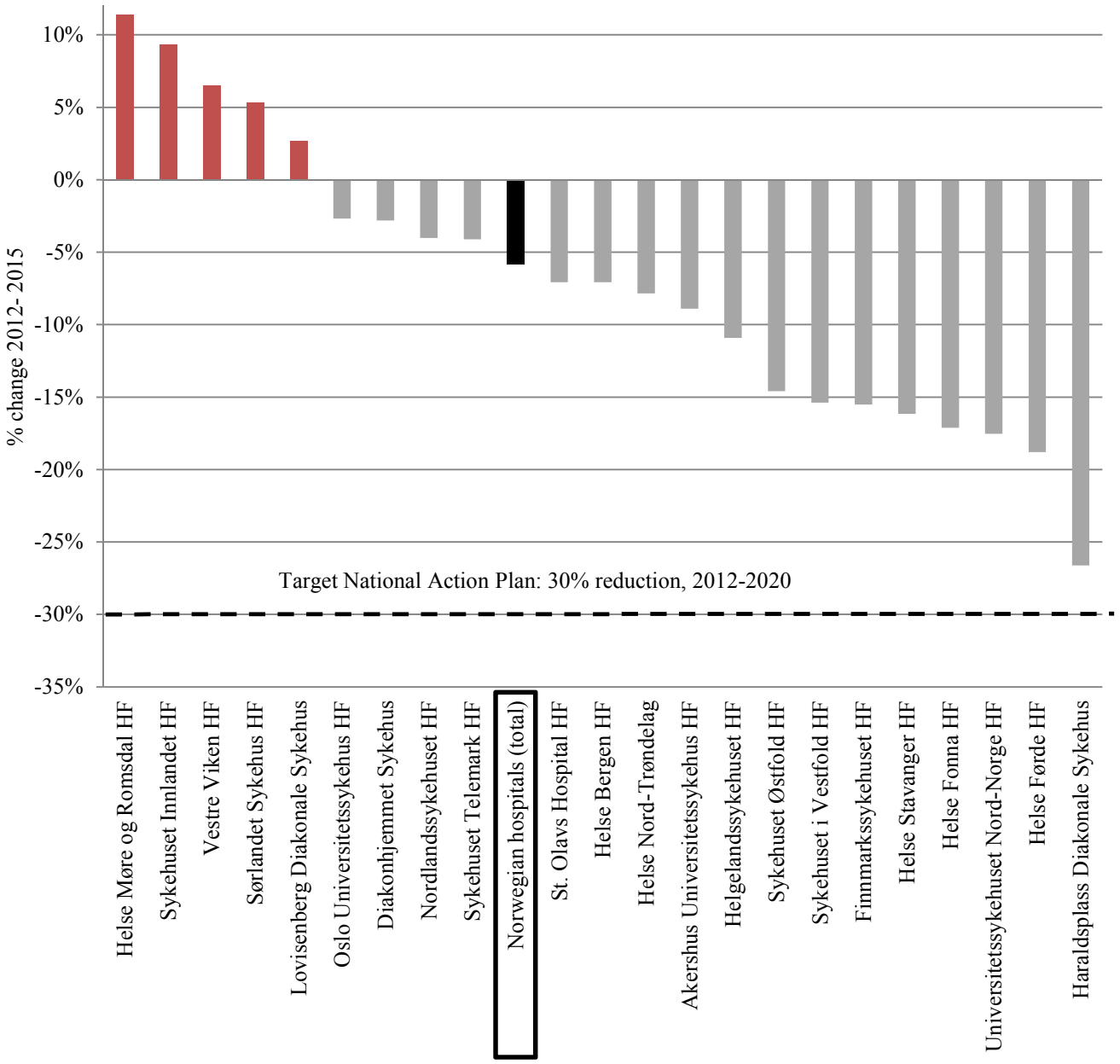

FIGURE 34. Proportional change (%) in DDD/100 bed days in the use of selected broad-spectrum antibacterial agents for systemic use (ATC J01CR05, ATC group J01DC, J01DD, J01DH and J01M) in Norwegian hospitals/health trusts 2012-2015. According to the National Action Plan, the target for hospitals is a 30% reduction, measured in DDDs, by 2020 compared to 2012. Black bar: National average.

Antimycotic usage in Norway

The usage of antimycotics for systemic use has been increasing in Norway, more so in ambulatory care than in hospitals (Figure 35). In 2015, hospital use of antimycotics represented 24% of total use measured in DDDs. Fluconazole is the most used agent in both settings. In July 2013, a warning regarding the use of oral ketoconazole was issued due to increased risk of liver damage. This resulted in decreased use of ketoconazole in ambulatory care (red bars). Oral formulations are most commonly utilised outside hospitals. Only 2% of total DDDs in ambulatory care were for parenteral use, whereas 62% was for parenteral use in hospitals.

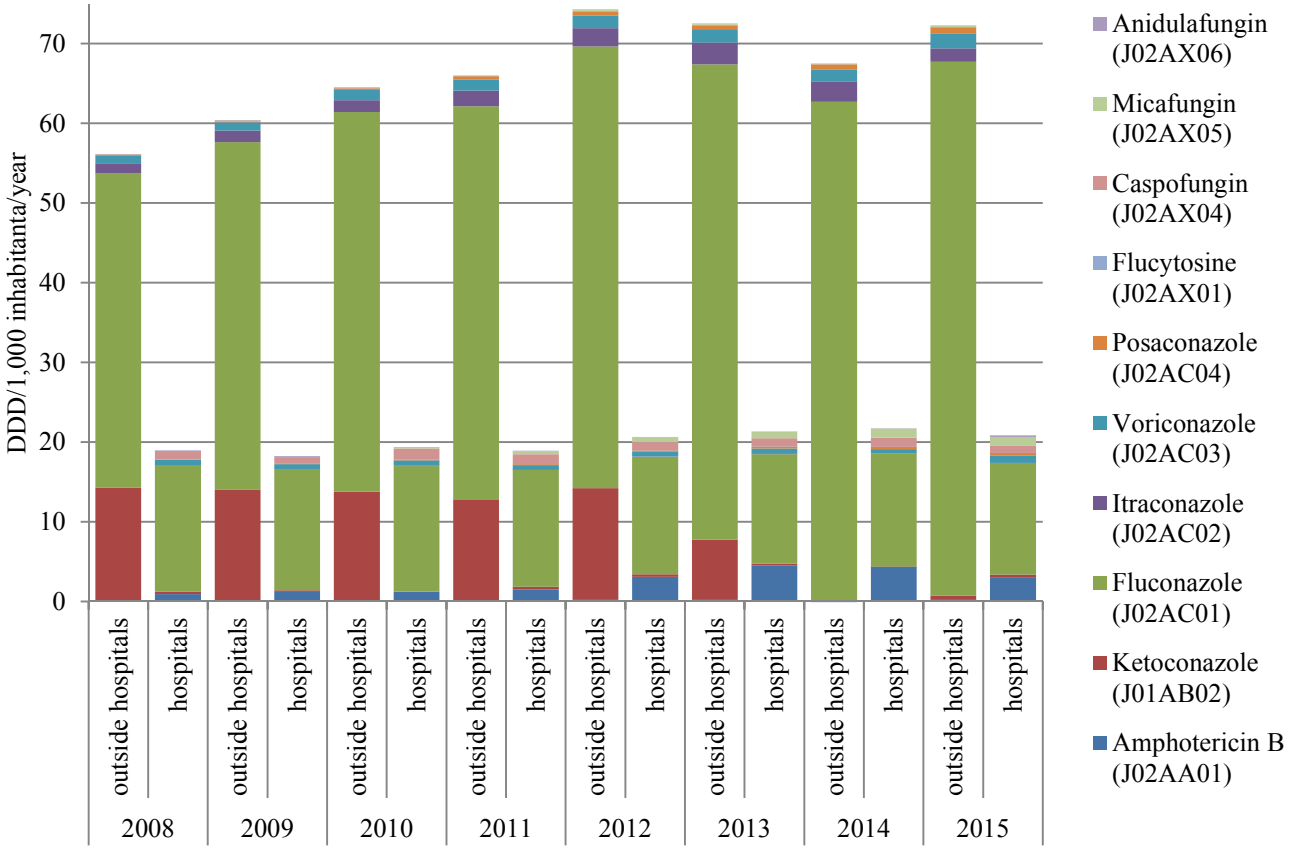

FIGURE 35. Proportions of antimycotics for systemic use in Norway for ambulatory care and hospitals 2008-2015, measured in DDD/1,000 inhabitants/year.

OCCURRENCE OF ANTIMICROBIAL RESISTANCE

INDICATOR BACTERIA FROM ANIMALS AND FOOD

Gro Johannessen, Madelaine Norström, Jannice Schau Slettemeås, 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 antibiotic resistance, detect trends and evaluate effects of interventions.

Bacterial resistance to critically important antimicrobials, such as third generation cephalosporins, quinolones and carbapenems has received special attention over the last years. These are defined by the WHO as critically important for treatment of human infections. Monitoring the resistance to these substances in the bacterial population is therefore of special interest, and their presence in food production animals and the food chain is of concern as they may have an impact on resistance development in human bacterial populations. Therefore, it should be an overall goal to keep the level of such resistant bacteria in production animals and through the food processing chain at the lowest possible level.

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. 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 *E. coli* was implemented as well.

In 2015, *E. coli* from caecal samples of cattle and swine, meat thereof and vegetables were included. In addition, the results from the screening of methicillin resistant *Staphylococcus aureus* in cattle are described under this chapter.

The substances included in the test panels might not always be those used in veterinary medicine, but are selected 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 2015. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from cattle and swine

Caecal samples from a total of 264 cattle and 270 swine were examined, and *E. coli* isolates were obtained from 262 (99.2%) of the cattle and 270 (100%) of the swine samples, respectively. One isolate per positive sample was susceptibility tested. The results are presented in Table 9 and Figures 36-37, and in the text.

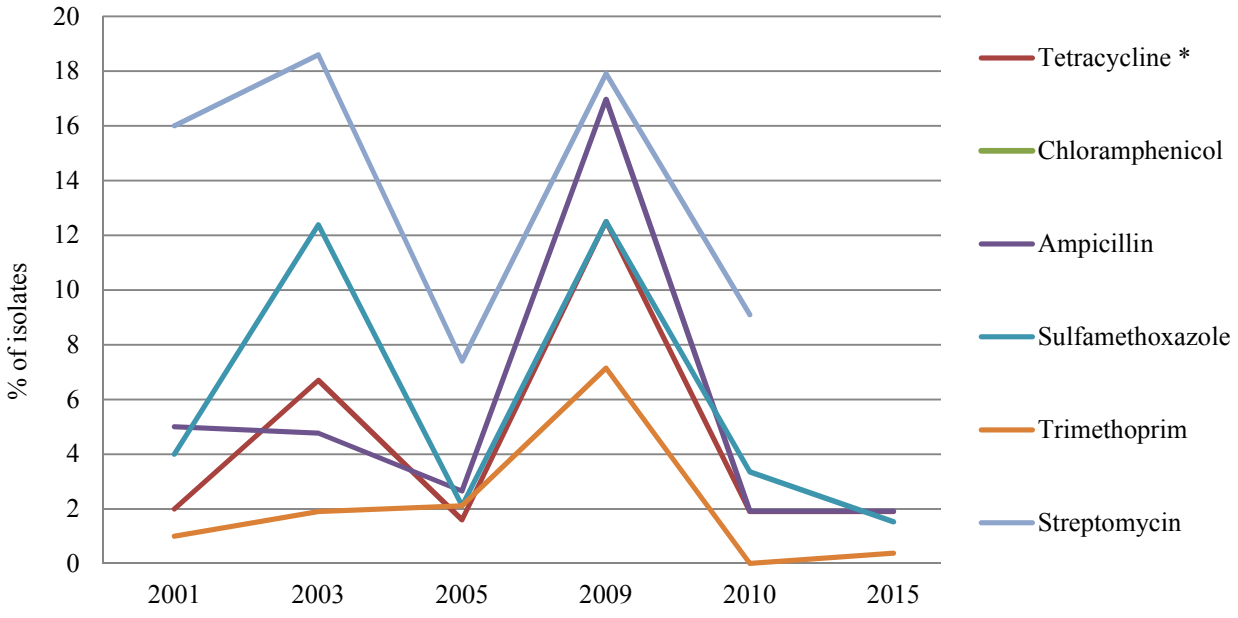

FIGURE 36. Prevalence of resistance to various antimicrobial agents in *Escherichia coli* from bovine samples (faeces and beef samples) collected in 2001-2015. The breakpoints in NORM-VET 2015 were applied. * Oxytetracycline before 2005.

TABLE 9. Antimicrobial resistance in *Escherichia coli* isolates from caecal samples of cattle (n=262) and swine (n=270) in 2015.

		Resistance (%)		Distribution (%) of MIC values (mg/L)*														
Substance	Sample		[95% CI]	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Cattle	1.9	[0.4-3.9]								96.9	1.1				0.4	1.5		
	Swine	9.6	[6.4-13.8]								89.3	0.4	0.7			3.3	6.3		
Tigecycline	Cattle	1.1	[0.2-3.3]					91.2	7.6	1.1									
	Swine	2.2	[0.8-4.8]					91.5	6.3	1.1	1.1								
Chloramphenicol	Cattle	0	[0.0-1.4]										99.6	0.4					
	Swine	2.2	[0.8-4.8]										97.4	0.4		0.4	1.9		
Ampicillin	Cattle	1.9	[0.4-3.9]							0.8	32.4	59.9	5.0	0.8			1.1		
	Swine	11.1	[7.6-15.5]							4.4	31.5	51.1	1.9				11.1		
Cefotaxime	Cattle	0	[0.0-1.4]					100											
	Swine	0.7	[0.1-2.7]					99.3			0.4	0.4							
Ceftazidime	Cattle	0	[0.0-1.4]						100										
	Swine	0.4	[0.0-2.0						99.6				0.4						
Meropenem	Cattle	0	[0.0-1.4]		100														
	Swine	0	[0.0-1.4]		99.6	0.4													
Sulfamethoxazole	Cattle	1.5	[0.2-3.3]										83.2	13.4	1.9				1.5
	Swine	13.7	[9.8-18.4]										74.1	8.5	3.3				13.7
Trimethoprim	Cattle	0.4	[0.0-2.1]					93.9	5.7							0.4			
	Swine	9.6	[6.4-13.8]					84.1	6.3							9.6			
Azithromycin	Cattle	ND	ND								55.3	40.8	3.4	0.4					
	Swine	ND	ND								66.7	31.1	2.2						
Gentamicin	Cattle	0	[0.0-1.4]						29.4	67.2	3.4								
	Swine	0	[0.0-1.4]						38.5	58.5	3.0								
Ciprofloxacin	Cattle	0.4	[0.0-2.1]	97.7	1.9			0.4											
	Swine	0.7	[0.1-2.7]	98.9	0.4			0.4	0.4										
Nalidixic acid	Cattle	0.8	[0.1-2.7]									97.3	1.9		0.4		0.4		
	Swine	0.7	[0.1-2.7]									98.9	0.4		0.4			0.4	
Colistin	Cattle	0	[0.0-1.4]							90.5	9.5								
	Swine	0	[0.0-1.4]							96.7	3.3								

*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.

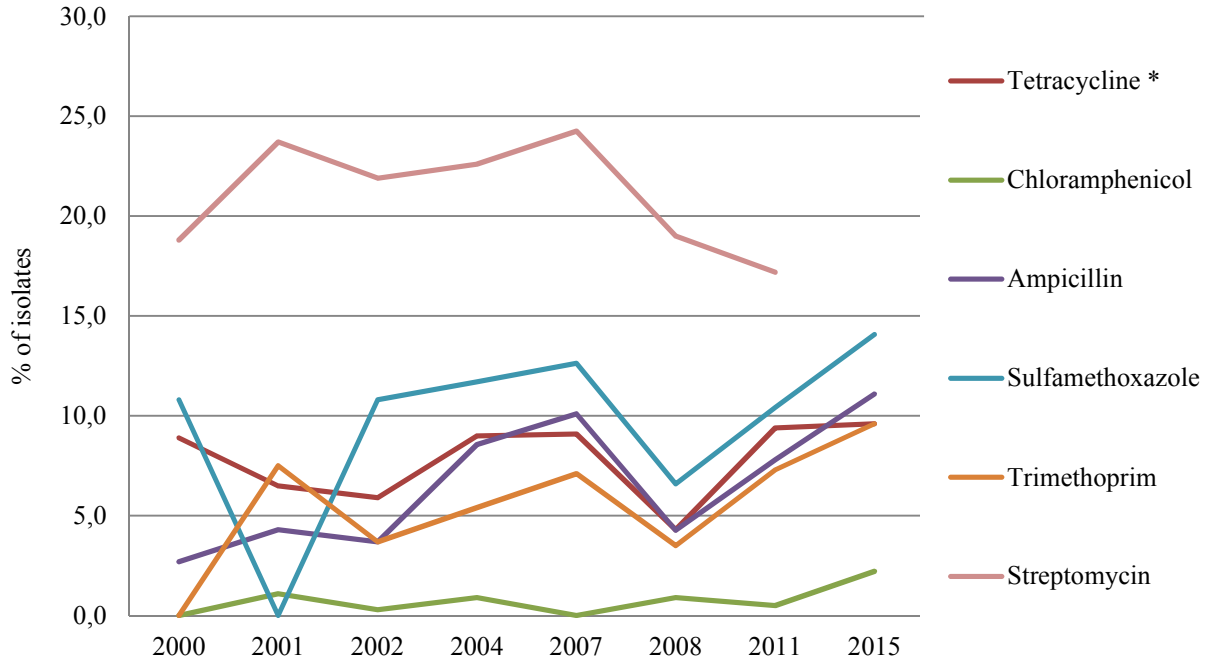

FIGURE 37. Prevalence of resistance to various antimicrobials in *E. coli* from swine (caecal and pork samples) 2000-2015. The breakpoints used in NORM-VET 2015 were applied. * Oxytetracycline before 2005.

RESULTS AND COMMENTS

CATTLE

The data indicate a low occurrence of resistance among *E. coli* from bovine caecal samples. In total, 95.4% of the isolates were susceptible to all antimicrobial agents included. Resistance to one antimicrobial agent occurred in 3.0% of the isolates, while resistance to two and to four or more antimicrobial agents occurred in 0.8% and 0.8% of the isolates, respectively. Resistance to tetracycline and ampicillin were the most frequently identified resistance determinants, followed by resistance to sulfamethoxazole.

Compared to previous data, the proportion of isolates being fully susceptible has increased and the proportion being resistant to one or more than three antimicrobial agents has decreased. However, the observed change is probably due to changes made in the panel of antimicrobial agents tested for. The antimicrobial agent with most resistant isolates from previous years, streptomycin, is no longer included in the test panel. A decrease was observed in resistance to sulfamethoxazole from 3.3% in 2010 to 1.5% in 2015 (p=0.3). The reduction was, however, not statistically significant and further monitoring is needed to see whether there is a true reduction.

None of the isolates displayed any resistance to the third generation cephalosporins cefotaxime or ceftazidime, indicating a prevalence below 1.4%. This is in concordance with the results from previous years. Resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) was very low and identified in two isolates only (0.8%, 95% CI: 0.09-2.7). Previously, quinolone resistance has only been detected in a single isolate in 2001, while the subsequent investigations in 2003, 2005, 2009 and 2010 did not reveal any quinolone resistant isolates. To investigate the reservoirs of resistance to these critically important antimicrobials further, selective methods were applied on the same sample material (see below).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian cattle is low (EFSA and ECDC Summary Report 2013). This situation is due to the limited use of antibiotics in the Norwegian cattle production. Comparison is, however, difficult as sampling regimes have varied between the countries, an aspect that probably will improve after the implementation of the regulative 2013/652/EU.

SWINE

The 2015 data showed that 78.9% of the *E. coli* isolates from swine caecal samples were susceptible to all antimicrobial agents tested. Altogether, 6.3% of the isolates were resistant to one antimicrobial agent, 4.1% to two, 6.7% to three and 4.1% to four or more antimicrobial agents. In total, 21.1% of the isolates were resistant indicating high occurrence of resistance among swine caecal *E. coli* according to the EFSA classification described in Appendix 6. Resistance to sulfamethoxazole was the most frequently identified resistance phenotype, followed by resistance to ampicillin, and tetracycline and trimethoprim.

As for cattle, comparison to previous years has to take into consideration the changes made in the panel of antimicrobial agents tested. The proportion of isolates being fully susceptible may seem to have increased and the proportion being resistant to decrease. However, resistance to streptomycin, which is no longer part of the panel, has traditionally been most frequently identified with 17.2% resistant isolates in 2011. In 2015, the most frequently identified antimicrobial agent was sulfamethoxazole, previously the second most frequently identified (Figure 37). It has, however been a small increase in resistance to sulfamethoxazole from 10.4% in 2011 to 14.1% in 2015 (p=0.00014). In the same time period, sales of sulfonamides in VMPs applicable for use in swine have declined, and further data are needed in order to understand this increase of sulfamethoxazole resistance.

Two of the *E. coli* isolates showed resistance to cephalosporins. One of these contained the $bla_{\text{OXA-1}}$ gene, and displayed resistance to sulfamethoxazole, trimethoprim, chloramphenicol, ampicillin, cefotaxime and cefepime. The other was due to a chromosomal mutation in the promoter sequence of the AmpC gene. Resistance to quinolones (i.e. ciprofloxacin and/or nalidixic acid) was very low and identified in only two isolates (0.7%, 95% CI: 0.09-2.7). To investigate the reservoirs of resistance to these critically important antimicrobials further, selective methods were applied on the same sample material (see below).

In an international perspective, the occurrence of resistance among *E. coli* from Norwegian swine is low, though the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary Report 2013). This favourable situation is due to the rather limited use of antibiotics in the Norwegian swine production.

Cephalosporin resistant *Escherichia coli* from cattle, beef, swine and pork

In 2015, selective screening for *E. coli* resistant to third generation cephalosporins was performed on samples from cattle and swine and meat thereof. A total of 264 cattle caecal and 245 beef samples, and 258 swine caecal and 244 pork samples were screened. Results are presented in the text and in Table 10.

TABLE 10. Overview of *E. coli* resistant to cephalosporins identified in NORM-VET 2015, their source of origin and antimicrobial resistant patterns.

		Resistance to number of antimicrobials														
		4*	4	5	5	5	6	7	7	7	8	9	9**	6*	6*	N
Resistance pattern[1]	Ampicillin	24	1	1	2	1	2	1	1	1	1	1	1	1	1	39
	Cefotaxime	24	1	1	2	1	2	1	1	1	1	1	1	1	1	39
	Ceftazidime	24	1	1	2	1	2	1	1	1	1	1	1			37
	Cefoxitin	24		1	2	1	2		1		1	1				33
	Cefepime		1					1		1			1	1	1	6
	Chloramphenicol							1					1	1	1	4
	Ciprofloxacin								1				1			2
	Ertapenem										1	1				2
	Imipenem			1								1				2
	Nalidixic acid								1				1			2
	Sulfamethoxazole					1	2	1	1	1	1	1	1	1	1	11
	Tetracycline				2		2			1	1	1	1		1	9
	Trimethoprim							1		1	1	1		1		5
No. of isolates	Beef		1				1	1					1			4**
	Cattle caecal samples	1														1
	Pork	1			1											2
	Swine caecal samples	22		1	1	1	1		1	1	1	1		1		31*
	Vegetables														1	1
Genotype	Up-regulated AmpC[2]	24		1	2	1	2		1							31
	bla$_{CTX-M-1}$		1					1								2
	bla$_{CMY-2}$										1	1				2
	bla$_{CTX-M-27}$									1						1
	bla$_{CTX-M-14}$												1			1
	bla$_{OXA-1}$													1	1	2

[1]Resistance is indicated with hatched areas where the number of isolates resistant to the respective antimicrobials are presented.
[2]Up-regulation of chromosomally located AmpC due to mutations in the promoter region.
*One isolate identified only through traditional *E. coli* indicator methods.
**One isolate identified through selective screening for quinolone resistant *E. coli*.

RESULTS AND COMMENTS

E. coli resistant to third generation cephalosporins, i.e. cefotaxime and/or ceftazidime, were found in one cattle caecal (0.4%, 95% CI: 0.0-2.1) and three beef (1.2%, 95% CI: 0.3-3.5) samples, and 29 swine caecal (11.2%, 95% CI: 7.7-15.7) and two pork (0.8%, 95% CI: 0.1-2.9) samples. The resistance genes responsible are shown in Table 10, together with an overview of what other antimicrobial agents the isolates showed decreased susceptibility for. The majority of the isolates showed decreased susceptibility due to mutations in the promoter region for the chromosomally located AmpC gene, though two of the beef isolates (*bla*$_{CTX-M-1}$) and three of the swine caecal isolates (*bla*$_{CMY-2}$ and *bla*$_{CTX-M-27}$) showed decreased susceptibility due to plasmid encoded resistance genes.

None of the isolates showed decreased susceptibility to meropenem, the preferred carbapenem used for detection of carbapenemase production. Although two isolates from swine caecal samples showed decreased susceptibility to imipenem with MIC values above the EUCAST cut-off value at 0.5 mg/L, and two other isolates from swine caecal samples showed decreased susceptibility to ertapenem with MIC values above the EUCAST cut-off value at 0.064

mg/L (data not shown), these were not regarded as true carbapenem resistant isolates as imipenem and ertapenem have lower specificity to detect carbapenemase producing *Enterobacteriaceae* than meropenem (Cohen *et al.* 2010).
Selective methods for isolation of *E. coli* resistant to third generation cephalosporins have not previously been performed on cattle caecal or beef samples, and comparison to previous years is therefore difficult. For swine, on the other hand, selective screening has previously been performed in 2009, 2011 and 2012. The first detection of *E. coli* resistant to third generation cephalosporins due to plasmid encoded resistance genes was in 2011, an isolate containing a $bla_{\text{TEM-52}}$ gene (NORM-VET 2011). The current findings by the selective method may indicate that there has been a small increase with regard to occurrence of plasmid encoded cephalosporin resistant *E. coli* in swine the last few years from 0/183 in 2009, 1/194 in 2011, 0/169 in 2012 and 3 in 2015 (NORM-VET 2009, NORM-VET 2011, NORM-VET 2012). However, this is a non-significant result (p=1). Similarly, the finding of 26 chromosomally encoded cephalosporin resistant *E. coli* may indicate an increase from 18/194 in 2011. As for the plasmid encoded determinants, this is a non-significant result (p=0.9) and further monitoring is needed to follow the situation with regard to both plasmid encoded and chromosomally encoded cephalosporin resistance.
In an international perspective, the occurrence of *E. coli* resistant to third generation cephalosporins in cattle and swine and meat thereof is low in Norway, though the occurrence varies markedly between countries. This low prevalence reflects that use of this antimicrobial subclass for food producing animal species is < 0.01 kg.
A scientific opinion published by The European Food Safety Authorities in 2011 concluded that there is indirect evidence of transmission between food producing animals/foods to humans. The situation regarding *E. coli* resistant to third generation cephalosporins in Norwegian cattle and swine is rather similar to the situation in Sweden (SVARM 2015). A Swedish report from 2014 (Egervärn *et al.* 2014), concludes that food on the Swedish market is a limited contributor to the prevalence of cephalosporin resistant *E. coli* within the human healthcare sector for the time being. However, a continued awareness of animal bacterial reservoirs resistant to third generation cephalosporins is of importance to be able to implement control measures if needed.

Quinolone resistant *Escherichia coli* from cattle, beef, swine and pork

In 2015, selective screening for quinolone resistant *E. coli* was performed on caecal samples from cattle and swine, and meat thereof. A total of 264 cattle caecal, 244 beef, 258 swine caecal and 243 pork samples were screened for the presence of quinolone resistant *E. coli*. The results are presented in Table 11 and in the text.

TABLE 11. Antimicrobial resistance in quinolone resistant *Escherichia coli* isolates from caecal and meat samples of swine and cattle in 2015. In total, 176 isolates (19 and two isolates from cattle caecal and beef samples, respectively, and 140 and 15 isolates from swine caecal and pork samples, respectively).

	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	44.3	[36.8-52.0]								55.1	0.6				14.8	29.5		
Tigecycline	1.1	[0.1-4.0]					90.9	8.0		0.6	0.6							
Chloramphenicol	8.5	[4.8-13.7]										89.8	1.7		1.7	1.7	5.1	
Ampicillin	41.5	[34.1-49.1]							2.8	19.9	35.2	0.6	0.6		0.6	40.3		
Cefotaxime	0.6	[0.0-3.1]					99.4					0.6						
Ceftazidime	0.6	[0.0-3.1]						99.4	0.6									
Meropenem	0.0	[0.0-2.1]		100														
Sulfamethoxazole	45.5	[37.9-53.1]										47.2	6.3	1.1				45.5
Trimethoprim	34.1	[27.1-41.6]					64.8	1.1							34.1			
Azithromycin		ND								36.4	51.7	9.7	0.6	0.6	0.6	0.6		
Gentamicin	2.8	[0.9-6.5]						26.1	66.5	4.5			0.6		2.3			
Ciprofloxacin	94.9	[90.5-97.6]		0.6	4.5	15.9	60.2	14.2			0.6	1.7	2.3					
Nalidixic acid	84.7	[78.5-89.6]									2.3	6.3	6.8	5.1	12.5	42.6	24.4	
Colistin	0.0	[0.0-2.1]							96.6	3.4								

*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

A total of 178 *E. coli* isolates were isolated by use of 0.06 mg/L ciprofloxacin added to the selective medium. Of these, 176 isolates were resistant to quinolones when MICs were determined using the Sensititre® TREK EUVSEC plate (Table 11). Quinolone resistance was found in 7.2% (95% CI: 4.4-11.0) and 0.8% (95% CI: 0.1-2.9) of the cattle caecal and beef samples, respectively. From swine, quinolone resistant *E. coli* were detected in 54.3% (95% CI: 48.0-60.5) of the caecal and 6.2% (95% CI: 3.5-10.0) of the pork samples investigated.

In total, 57.9% of the cattle caecal isolates showed decreased sensitivity only to quinolones (ciprofloxacin and/or nalidixic acid). In addition to quinolone resistance, 21.0% were resistant to one or two more antimicrobial agents (mainly tetracycline and/or sulfamethoxazole), while 21.0% were resistant to three, or four or more antimicrobial agents (ampicillin, trimethoprim, tetracycline and sulfamethoxazole). Of the beef isolates, one was resistant to four antimicrobial agents, and one to seven antimicrobial agents, in addition to the decreased sensitivity to quinolones. This last one showed resistance to the third generation cephalosporins cefotaxime and ceftazidime due to the presence of a $bla_{\text{CTX-M-14}}$ gene (Table 10). None of the isolates showed decreased susceptibility to the carbapenem meropenem.

A total of 35.7% of the swine caecal isolates were resistant only to quinolones (ciprofloxacin and/or nalidixic acid). Additional resistance to one or two antimicrobial agents was found in 24.3% of the isolates (mainly tetracycline and/or sulfamethoxazole, then ampicillin), 35.0% showed resistance to additionally three or four, and 5.0% showed resistance to additionally five or six antimicrobial agents. Among the pork isolates, 33.3% showed decreased susceptibility only to quinolones, while 33.3% of the isolates were resistant to two additional antimicrobial agents (tetracycline and ampicillin, sulfamethoxazole and trimethoprim or tigecycline), and 33.3% to three other antimicrobial agents (ampicillin, sulfamethoxazole and trimethoprim).

Resistance to quinolones in bacteria is usually caused by mutations in the quinolone resistance determining region (QRDR) involving the genes *gyrA*, *gyrB*, *parC,* and *parE*. In addition, plasmid-mediated quinolone resistance (PMQR) genes (*qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, *qepA*, *aac(6')-1b-cr, oqxAB*) are responsible for low-level resistance to quinolones in isolates without chromosomal mutations. In total, 20.5% of the isolates had low MIC values for both ciprofloxacin and nalidixic acid, or high MIC values for both (4.5%), which might indicate presence of plasmid-mediated resistance genes. However, the majority of the isolates (75.0%) had high MIC values only for nalidixic acid. In cases of concomitant mutations and plasmid-mediated resistance, the presence of PMQR cannot be discovered by MIC profiles and further characterisation of the isolates will be performed to investigate these aspects in depth.

Selective methods for isolation of quinolone resistant *E. coli* have not previously been performed on samples from cattle and swine, and comparison to previous years is therefore difficult. However, through the years from 2000, the prevalence of resistance to quinolones among indicator *E. coli* from both cattle and swine has been low and stable. Although the selective method detects quinolone resistant *E. coli* in about half of the swine caecal samples, only a few isolates are usually detected by the non-selective procedure, showing that the within-herd prevalence of quinolone resistant *E. coli* in general is low. Also in an international perspective, the occurrence of quinolone resistant *E. coli* in Norwegian cattle and swine is low, though the occurrence varies markedly between countries. Moreover, the finding of quinolone resistant *E. coli* in only 6.2% of the pork samples, indicates that the hygienic measures taken during slaughter prevents extensive contamination to meat through the slaughtering process.

Carbapenemase producing *Escherichia coli* from cattle, beef, swine and pork

A total of 264 caecal samples from cattle, 244 beef samples, 270 caecal samples from swine and 243 pork samples were screened for the presence of carbapenemase producing *Escherichia coli.* No carbapenemase producing *E. coli* 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 appropriate to follow the situation in the years to come.

Escherichia coli from vegetables

A total of 243 samples of leafy salads were screened for the presence of indicator *E. coli*, *E. coli* resistant to third generation cephalosporins, quinolone resistant *E. coli* and for the presence of carbapenemase producing *E. coli*. The results are presented in Table 12 and in the text.

TABLE 12. Antimicrobial resistance in isolates of *Escherichia coli* (n= 73) from leafy salads in 2015.

Substance	Resistance (%) [95% CI]		Distribution (%) of MIC values (mg/L)*															
			0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	5.5	[1.5-13.4]								90.4	4.1					5.5		
Tigecycline	0.0	[0.0-4.9]					86.3	13.7										
Chloramphenicol	1.4	[0.0-7.4]										97.3	1.4				1.4	
Ampicillin	10.9	[4.9-20.5]							2.7	24.7	56.2	5.5			1.4	9.6		
Cefotaxime	1.4	[0.0-7.4]					98.6		1.4									
Ceftazidime	0.0	[0.0-4.9]						100										
Meropenem	0.0	[0.0-4.9]		98.6	1.4													
Sulfamethoxazole	6.9	[2.2-15.3]										80.8	9.6	2.7				6.9
Trimethoprim	0.0	[0.0-4.9]					93.2	4.1	2.7									
Azithromycin		ND																
Gentamicin	0.0	[0.0-4.9]						21.9	75.3	2.7								
Ciprofloxacin	0.0	[0.0-4.9]	97.3	2.7														
Nalidixic acid	0.0	[0.0-4.9]									100							
Colistin	0.0	[0.0-4.9]							95.9	4.1								

*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

E. coli was detected in 30.0% of the leafy salad samples. The data indicate a moderate occurrence of resistance among *E. coli* from these samples. In total, 82.2% of the isolates were susceptible to all antimicrobial agents included. Altogether, 13.7% of the isolates were resistant to one antimicrobial agent, 2.7% to two, and 1.4% to five antimicrobial agents. Due to rather extensive sample variability and limited findings, any possible associations to sample origin could not be investigated thoroughly.

Among the *E. coli*, one isolate was resistant to the third and fourth generation cephalosporins cefotaxime and cefepime, respectively. The isolate carried the bla_{OXA-1} gene, and was showing additional resistance to tetracycline, chloramphenicol, ampicillin and sulfamethoxazole. The selective screening for *E. coli* resistant to third generation cephalosporins did, however, not reveal any isolates, indicating that the finding was a random finding and present at very low levels. No carba-penemase producing *E. coli* were detected. Quinolone resistant *E. coli* were detected from two samples by selective screening (0.8%, 95% CI: 0.1-2.9). One of these had low MIC values for both ciprofloxacin and nalidixic acid, which might indicate presence of a plasmid-mediated resistance mechanism. The isolate was in addition resistant to tetracycline, sulfamethoxazole, and trimethoprim.

Leafy salads have not previously been investigated in NORM-VET. During primary production and harvesting, leafy salad can become contaminated with antimicrobial resistant bacteria from animal and human sources. As salad is typically consumed raw and without any heat treatment, presence of antimicrobial resistant bacteria is 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.

Integron, plasmid and host strain characteristics of *Escherichia coli* from humans and food included in the Norwegian antimicrobial resistance monitoring programmes

Monitoring programmes for antimicrobial resistance were established in several countries from the late 90ies. The strain collections obtained in these programmes represent unique materials for further studies as the isolates have been systematically collected over years, originate from a variety of sources and represent the national resistance situation in the respective countries. The NORM and NORM-VET programmes collect resistance data from human pathogens, from zoonotic bacteria, from clinical isolates from animals, as well as from indicator bacteria from healthy animals and domestically produced meat.

In our study we investigated the prevalence of class 1 and class 2 integrons, and characterised the cassettes within them, in *E. coli* from humans with bloodstream infections and in *E. coli* isolated from domestically produced meat. The isolates were collected by NORM and NORM-VET in the years 2000 to 2003. The mapping of integrons in such collections represents a novel approach in describing prevalence and integron characteristics in two different *E. coli* populations, collected within the same geographical area and timeframe. Most bacterial isolates in similar studies have not been collected in a randomised manner, thus making generalisation difficult with regard to prevalence of integrons and occurrence of cassette variants within them. Multi-resistance integrons are of importance in the epidemiology of antimicrobial resistant Gram-negatives. Integrons can incorporate mobile gene cassettes by site-specific recombination. Resistance to important antimicrobials used in both human and veterinary medicine can be conferred via integron cassettes, like resistance to ampicillin, trimethoprim and chloramphenicol. Integrons can also contain genes encoding metallo-beta-lactamases highlighting their role in the dissemination of resistance to last line antimicrobial agents.

Results

Integrons of class 1 and 2 occurred significantly more frequently among human isolates; 45.4% (95% CI: 39.9-50.9) than among meat isolates; 18% (95% CI: 13.2-23.3), ($p<0.01$, Chi-square test). Identical cassette arrays including *dfrA1-aadA1*, *aadA1*, *dfrA12-orfF-aadA2*, *oxa-30-aadA1* (class 1 integrons) and *dfrA1-sat1-aadA1* (class 2 integrons) were detected from both reservoirs. However, the most prevalent cassette array in human isolates, *dfrA17-aadA5*, did not occur in isolates from meat, suggesting a possible linkage between this class 1 integron and a subpopulation of *E. coli* able to cause severe infections, or highly adapted to colonisation of a human host.

Class 1 integrons containing the *drfA1-aadA1* cassette combination or the *aadA1* cassette as the only cassette occurred frequently in both categories. These isolates were investigated further in order to detect similarities with regard to transferability, plasmids and host strain characteristics. We detected closely related IncF plasmids (pMLST: F24:A-:B1) carrying *drfA1-aadA1* integrons in isolates from pork and an unrelated *E. coli* from a human with septicaemia. Furthermore, we showed that most class 1 integrons with the *aadA1* cassette were located on related IncF plasmids (pMLST F51:A-:B10) in human isolates. The plasmid was present in unrelated as well as closely related host strains, demonstrating that dissemination of this integron could be attributed to both clonal spread and dissemination of a resistance plasmid.

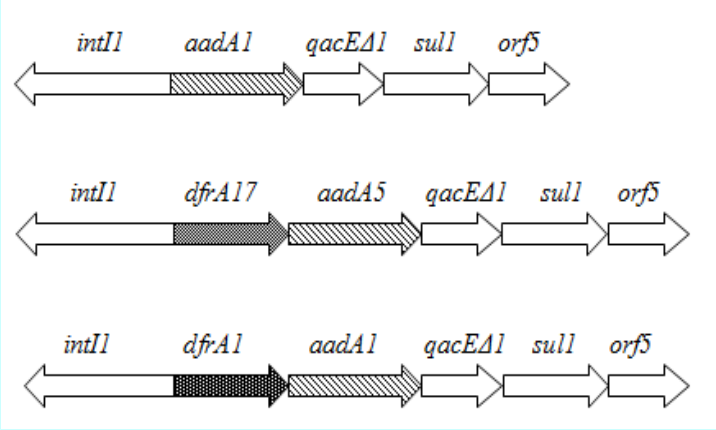

FIGURE 38. Schematic structure of the most commonly occurring class 1 integrons in the study.

Conclusion

Among the systematically collected isolates from two sources, some significant differences concerning integron prevalence and integron variants were observed. However, closely related plasmids as vehicles for specific class 1 integrons in isolates from meat and from a human with bloodstream infection were found, highlighting the role of meat as a possible source of resistance elements for pathogenic bacteria.

The results generated could serve as baseline data from a period predating the ESBL era in Scandinavia. It would be of interest to perform follow-up studies with newer strain collections to investigate changes in integron occurrence, changes in cassette composition, as well as changes in IncF plasmids and their host strains. Such studies would provide valuable data concerning the evolution of antimicrobial resistance taking advantage of strain collections obtained through monitoring programmes.

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Occurrence of *mcr-1* in historical isolates from animals and humans in Norway

In November 2015, the first plasmid-mediated colistin resistance gene, *mcr-1,* was detected in an *Escherichia coli* strain from a pig in China (1). Since then, the *mcr-1* gene has been reported in *Enterobacteriaceae* from various sources in several countries all over the world including several EU/EEA countries. Retrospective studies in China have identified this gene in *E. coli* originally isolated in the 1980ies, while the first European isolate dates back to 2005 (2). From several countries including Denmark and Germany (3, 4), the *mcr-1* gene has been detected in isolates carrying genes encoding extended spectrum beta-lactamases (ESBL). In Norway, the *mcr-1* gene was not detected among the whole genome sequences of all human clinical carbapenemase-producing isolates submitted to the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance during 2007-2014 (personal communication, Ørjan Samuelsen). However, Solheim *et al.* recently found the *mcr-1* gene in an *E. coli* from 2014 isolated from the stool of a subject returning from India with symptoms of traveller's diarrhoea (5). This was, to the author's knowledge, the first report of plasmid encoded colistin resistance in Norway.

In order to acquire more information on the frequency of the *mcr-1* gene in Norway, we performed a small study on historical colistin resistant isolates from NORM-VET and a selection of human ESBL producing *Salmonella* and *Shigella.* These were subjected to *mcr-1* PCR at the Norwegian Veterinary Institute according to the method published by Liu *et al.* 2015 (1).

All NORM-VET isolates with colistin MIC values > 2 mg/L, isolated in the years 2010-2015 were included, nine isolates in total. These comprised four *E. coli* isolates (from two broilers, one turkey and one dog), as well as four *Salmonella* Typhimurium isolates (three feline and one canine) and one *Salmonella* Braenderup from a quail. Furthermore, we included 59 ESBL-producing *Salmonella* and 15 ESBL-producing *Shigella* isolated from humans between 2012 and 2015 that had not been phenotypically tested for colistin resistance.

Neither the isolates from NORM-VET, nor the human ESBL-producing *Salmonella* or *Shigella* carried the *mcr-1* gene. With regard to the importance of preserving colistin as a last-resort drug in human medicine, combined with the dissemination potential of plasmid encoded resistance, further monitoring is recommended to acquire knowledge on the frequency of the *mcr-1* gene in the years to come.

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Methicillin resistant *Staphylococcus aureus* in cattle

Resistance to critically important antimicrobials represents a significant public health problem. Screening for methicillin resistant *Staphylococcus aureus* (MRSA) is annually performed in samples from swine through a separate surveillance programme (see text box page 54). Additionally in 2015, screening for MRSA was performed on samples from cattle dairy herds. Sampling, laboratory methods and data processing are described in Appendix 3. The data are presented in the text.

RESULTS AND COMMENTS

Samples from a total of 179 cattle dairy herds were screened for the presence of MRSA. One positive sample was identified, giving a prevalence of MRSA in Norwegian dairy herds of 0.6% (95% CI: 0.01-3.1). The isolate belonged to clonal complex 1 (CC1), *spa*-type t127. In addition to methicillin, the isolate showed reduced sensitivity to tetracycline, streptomycin, penicillin, kanamycin, erythromycin, and cefoxitin. Selective methods for isolation of MRSA have not previously been performed on samples from cattle herds, and comparison to previous years is therefore difficult. However, *S. aureus* from clinical mastitis in cattle has previously been susceptibility tested for methicillin under the auspices of NORM-VET. No MRSA has been detected among these isolates. MRSA has, however, been detected from a few cattle herds associated with MRSA positive swine herds.

Methicillin resistant *Staphylococcus aureus* in swine in Norway 2015

MRSA belonging to the animal associated clonal complex CC398 spa-type t034 was detected in swine samples for the first time in 2011 (anonymous study). In 2013/14, two clusters of MRSA CC398 t034 positive swine herds were detected, and measures to eradicate livestock associated MRSA (LA-MRSA) from positive swine herds were imposed. The rationale behind this strategy was to avoid the swine population becoming a reservoir of MRSA with the potential of zoonotic transmission, as MRSA is not a health problem in pigs. The LA-MRSA eradication strategy includes restrictions on trade of live animals upon suspicion, depopulation of pigs in LA-MRSA positive swine herds, thorough cleaning and disinfection of premises, negative samples from the environment and mandatory down-time before restocking with pigs from MRSA negative herds. After restocking, samples are collected from animals and the environment several times to assess the effectiveness of MRSA eradication. To the authors' knowledge such a strategy has not been conducted in any other countries.
From 2014, a yearly surveillance programme of MRSA in the swine population was implemented. The objective of the programme is to identify methicillin resistant *Staphylococcus aureus* (MRSA) positive swine herds with the intention of eradication, as the overall goal is to keep the Norwegian pig population free of LA-MRSA. The first year, all sow herds with more than ten sows were examined (n=986 herds) and a single positive herd was identified (4). A few additional herds were not included in the survey as they were sampled in ongoing outbreak investigations in the same time period.

Materials and methods

In 2015, all pure breed nucleus herds and multiplier herds (n=95), as well as all finishing swine herds with an annual production of more than 70 pigs (n=877) the preceding year were to be sampled using sterile SodiBox™ cloths moistened with sterile saline water. A point on the cloth was rubbed firmly against the skin behind both ears of the pig (about 5x5 cm on each side). Each cloth was used for 20 pigs, and a total of three cloths, representing 60 pigs distributed in all rooms and all age groups (except suckling piglets), were taken per herd. The three cloths were analysed as one pooled sample. In addition, in each herd two cloths were used for environmental samples taken in all rooms with pigs. Each cloth was used on about 15 contact points (about 10x10 cm per location) representing furnishings, feeders, water nipples, window sills, door handles, tools, boots, ventilation system etc. These two cloths were analysed as one pooled sample.
The samples were submitted to the Norwegian Veterinary Institute in Oslo and analysed for MRSA by a method described by the EU reference laboratory on antimicrobial resistance (DTU Food, National Food Institute, Copenhagen, Denmark): Pre enrichment in 300 mL Mueller Hinton broth with 6.5% NaCl at 37°C for 16-20 h. Then 1 mL was transferred into 9 mL tryptone soya broth with cefoxitin (3.5 mg/L) and aztreonam (75 mg/L). After incubation at 37°C for 16-20 h, 10 µL were inoculated on Brilliance^{TM} MRSA2 Agar (Oxoid) and incubated at 37°C for 24-48 h. Suspect colonies were isolated on 5% blood agar and submitted to the Norwegian human reference laboratory for MRSA at St. Olavs Hospital in Trondheim for *spa* typing. The 95% confidence interval (CI) was calculated based on a binomial distribution.

Results

A total of 821 herds were included in the 2015 survey, of which 86 were nucleus or multiplier herds and 735 were finishing herds. Of the nucleus or multiplier herds not sampled in the survey, four were sampled in ongoing outbreak investigations in the same time period and three were no longer nucleus or multiplier herds. MRSA was identified in four herds; situated in the counties Rogaland, Hordaland and Nordland (0.5%; 95% CI: 0.01-1.2). From two herds (finishing herds), both samples from animals and the environment were positive, whereas only animal samples were positive for the other two herds (one finishing herd and one multiplier herd). The isolates were typed as CC1, t177 (Rogaland and Hordaland), and CC398, t034 (Rogaland and Nordland). Contact tracing showed that the two herds with MRSA CC1, t177 belonged to the same cluster of positive herds, while the two MRSA CC398, t034 positive herds were not linked. All four herds went through slaughter of animals, thorough cleaning and disinfection of rooms, and restart with MRSA-free pigs in line with the previous strategy for MRSA in swine herds. Contact tracing from these four herds resulted in identification of 13 other MRSA positive pig herds. In addition, 17 pig herds were found positive for CC398, t034 in two separate contact tracings from positive farm workers. Thus, in total 34 pig herds were found positive for LA-MRSA during 2015 through surveillance (n=4) and contact tracing (n=30).

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Action plan against antibiotic resistance within the sector responsibility of the Ministry of Agriculture and Food

The National Strategy against Antibiotic Resistance 2015-2020 was adopted in June 2015. The strategy's main goal is to reduce the total use of antibiotics and to assure responsible use of antibiotics in all sectors, to increase the body of scientific knowledge, and to be an international mobiliser against antibiotic resistance (1). The strategy sets overarching goals for the period, as well as sector-specific goals for the sectors health, food producing animals and household pets, fish and climate and environment.

According to the strategy, the sector-specific goals for food-producing animals and household pets are:

1. Mapping of reservoirs of antibiotic resistant bacteria will be carried out in the most relevant animal populations and plants important to food safety.
2. LA-MRSA will not be established in the Norwegian pig population.
3. ESBL in the Norwegian poultry-production will be reduced to a minimum.
4. The use of antibiotics in terrestrial animals used for food production will be reduced by at least 10 percent compared with 2013.
5. The use of antibiotics in household pets will be reduced by at least 30 percent compared with 2013.
6. Narasin and other coccidiostats with antibacterial properties will be phased out of chicken production, as long as this does not adversely affect animal health and well-being, and does not result in increased use of antibiotics for treatment of infections.

To follow up the national strategy, the Ministry of Agriculture and Food has developed an action plan against antibiotic resistance (2). The action plan is divided into several areas of action with underlying measures as briefly summarised in the text below:

1. Mapping of the reservoir; this action area comprises continued and further development of the monitoring performed within the veterinary sector (animals, feed, food, and environment), and includes normal bacterial flora, animal pathogens and zoonotic bacteria. Introduction of notification obligation for specific resistance mechanisms is also included.
2. Increased control; actions under this area includes continued efforts to prevent MRSA from being established in the Norwegian swine population, continued reduction of the occurrence of ESBL producing intestinal bacteria in poultry, and maintaining of good animal health and hygienic production.
3. Better diagnostic methods; optimise use of new diagnostic methods.
4. Better prescribing and use of antibiotics and other substances; this action area includes among others phasing out of narasin, updated clinical guidelines for prescription, prescribing supervisions, use of VetReg, “wait and see” prescriptions for pets, and limitations for veterinary use of the critically important antibiotics.
5. Other regulatory actions; comprises changes in the regulations regarding compensations due to production losses.
6. Knowledge development, research; this action area comprises strengthening of research and knowledge related to antibiotic resistance, including knowledge on how resistance occurs and disseminates between food, animals and humans. Conducting survey studies within NORM-VET and socio-economic analyses are included.
7. International activities; continued focus on prudent use and increased efforts against antibiotic resistance in international forums such as the EU, FAO, OIE, Codex Alimentarius, etc.

References:

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Streptococcus agalactiae in Norwegian dairy herds

Streptococcus agalactiae (group B streptococcus) is a contagious mastitis pathogen in dairy cows that may reduce milk production and quality and increase the use of antimicrobials. In humans, *S. agalactiae* can colonise the rectovaginal tract without causing disease, but may also cause serious infections particularly in neonates and the elderly.
During the 1950ies and 1960ies, *S. agalactiae* dominated as a cause of intramammary infections (IMI) in Norwegian dairy cattle. An eradication programme was implemented and a marked reduction in the number of infected herds was registered during the 1960ies. However, in recent years, the prevalence of *S. agalactiae* mastitis in dairy cattle has increased again in Norway concomitantly with changes in herd sizes, housing, milking systems and management practices. Similar trends have been reported from other Scandinavian countries.

Some studies have investigated the human reservoir in relation to mastitis in cattle. Although human and bovine strains are found largely different, little is known about the likelihood of transmission between humans and cattle. Dairy cattle are obviously exposed to human *S. agalactiae* strains during milking and similarly, infected cows may represent a source of the bacteria to humans.

While human *S. agalactiae* isolates have been included in NORM in 2006, 2009 and 2012, this is the first time bovine isolates are susceptibility tested in NORM-VET. All the 50 isolates were collected in the research project "Contagious mastitis - a reoccurring threat to Norwegian dairy production" in 2012, and originated from 50 different herds.

Among the isolates, 48.0% (95% CI: 33.7-62.6) showed reduced susceptibility to tetracycline and 2.0% (95% CI: 0.1-10.6) to vancomycin. No isolates showed reduced susceptibility to benzylpenicillin, cefotaxime, erytromycin or clindamycin. Macrolide resistance is frequently reported in human and in bovine isolates from other countries. Also, the prevalence of tetracycline resistance is low compared to what is reported from other countries. This favourable situation is probably due to the limited use of antibiotics in the Norwegian dairy production.

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ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

Nils Olav Hermansen, Madelaine Norström, Jannice Schau Slettemeås, Anne Margrete Urdahl

Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum. In Norway, *Salmonella* isolates from control programmes concerning feed samples, animals and food products, as well as diagnostic samples from animals are monitored for antimicrobial resistance.
Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates.
Sampling, laboratory methods and data processing are described in Appendix 4.
The NORM results on human isolates of enteropathogenic *Enterobacteriaceae* are interpreted according to the clinical breakpoints given by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), while the NORM-VET results are interpreted according to epidemiological cut-off values given by EUCAST. In case of missing clinical breakpoints, epidemiological cut-off values (ECOFFs) were used based on zone-distribution judgments or, as for *Campylobacter*, on ECOFFs given by EUCAST. Multi-drug resistance (MDR) was defined as resistance to three or more antimicrobial categories according to the 2011 ECDC/CDC joint definitions.

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 those detected by clinical submissions to the Norwegian Veterinary Institute. The data are presented in Table 13 and in the text.

TABLE 13. Antimicrobial resistance in *Salmonella* spp. (n=15) from animals (cattle=4, dog=5, poultry=1, cervid=1, bird=3, sheep=1); *S.* Typhimurium (n=11) and other *Salmonella* spp. (n=4) in 2015.

		Distribution (n) of MIC values (mg/L)*																
Substance	n resistant	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	3								11	1					3				
Tigecycline	0					14	1												
Chloramphenicol	2										12	1				2			
Ampicillin	3							6	5		1				3				
Cefotaxime	0					15													
Ceftazidime	0						15												
Meropenem	0			13		2													
Sulfamethoxazole	2										9	4							2
Trimethoprim	0					15													
Azithromycin	ND								10	4	1								
Gentamicin	2						12	1				1		1					
Ciprofloxacin	0		12		2	1													
Nalidixic acid	0									13	2								
Colistin	0							13	2										

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

RESULTS AND COMMENTS

In 2015, a total of 15 *Salmonella* spp. isolates from animals were susceptibility tested. The eleven isolates of *S.* Typhimurium included four dogs, (one monophasic isolate), three birds and four cattle. The remaining four isolates belonged to three different serovars; *S.* Kedougou from a dog, *S.* Havana from a poultry flock and *S.* enterica diarizonae from both one sheep and one cervid flock.

Of the 15 isolates, 12 were fully susceptible, while three isolates were resistant to three, four and five antimicrobial agents, respectively. These three were all *S.* Typhimurium, and were isolated originally from one dog (monophasic isolate) and two cattle.

Salmonella from human clinical specimens

In 2015, the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) performed antimicrobial susceptibility testing on a total of 925 unique *Salmonella* isolates from human infections.
As indicated in Table 14, 21.5% was reported as acquired in Norway, 69.7% was acquired abroad, whereas the place of acquisition was unknown for 8.8%. Travel abroad is considered a risk factor for obtaining bacteria carrying antimicrobial resistance.
All isolates were tested for resistance against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime and meropenem), ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole. In addition, 295 of 925 isolates were tested for nalidixic acid, azithromycin, tetracycline, and chloramphenicol.

TABLE 14. Distribution of human isolates of *Salmonella* serovars (n=925) in 2015 according to place of acquisition.

	Place of acquistion		
	Norway	Abroad	Unknown
S. Typhimurium including *S. enterica* serovar 4,[5],12:i- (n=224)	81	123	20
S. Enteritidis (n=345)	47	271	27
S. Typhi (n=7)	0	5	2
S. Paratyphi (n=7)	0	7	0
Other *Salmonella* (n=342)	71	239	32
Total (n=925)	**199 (21.5%)**	**645 (69.7%)**	**81 (8.8%)**

The dominating serovars were *S.* Typhimurium (n=123) and its monophasic variant (n=101), with 224 isolates (24.2%) of all *Salmonella* isolates, and *S.* Enteritidis with 345 (37.3%) of the isolates. The numbers of *S.* Typhi and *S.* Paratyphi isolates remain low. For 2015 the total numbers of isolates were seven and seven, respectively.
The results of the antimicrobial susceptibility testing for 2015 isolates are presented in Tables 15-18, in Figures 39-46, and in the text.

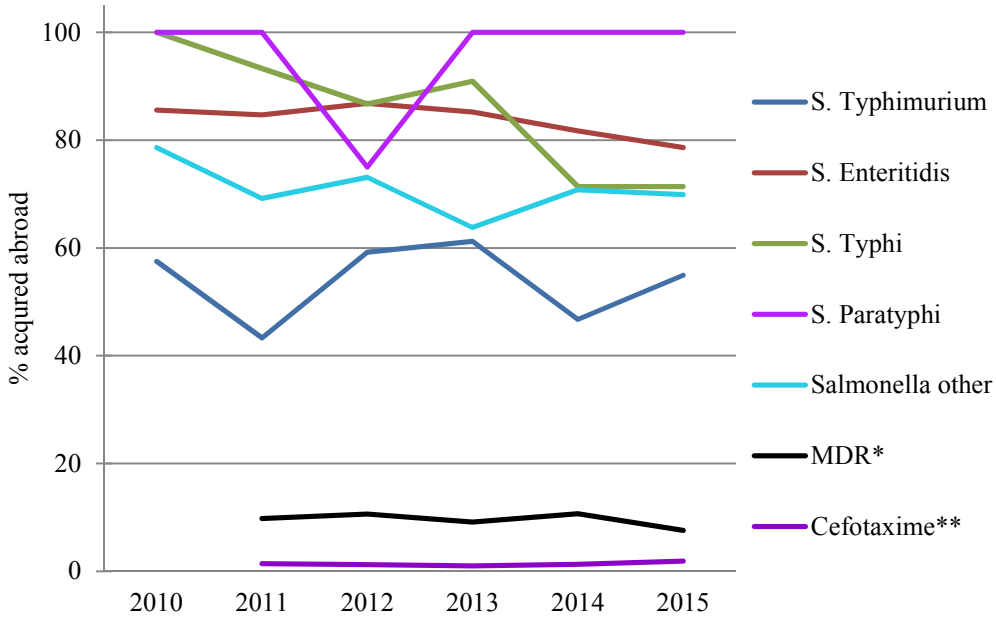


FIGURE 39. Proportion of unique isolates of *Salmonella* acquired abroad, and tested for antimicrobial resistance 2010- 2015 by serovar group, and total results for MDR and cefotaxime. *MDR testing in 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups. **Before 2014 cefpodoxime was tested.

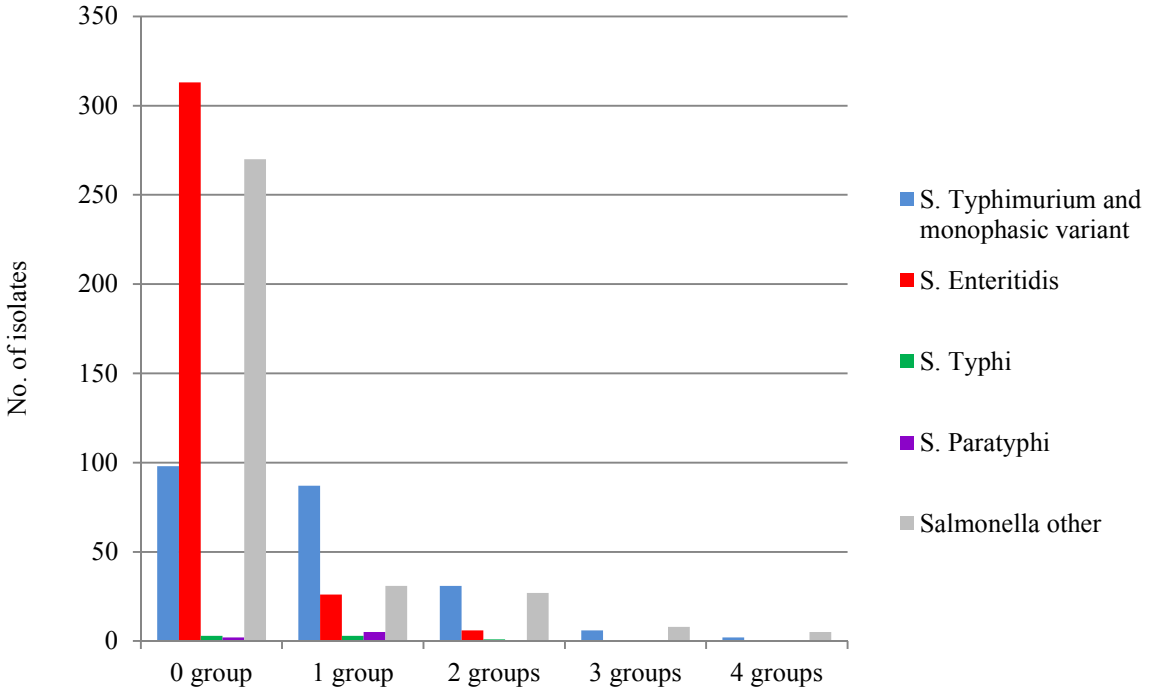


FIGURE 40. Distribution of number of antimicrobials that *Salmonella* isolates from 2015 (n=925) were resistant to; by serovar groups. The four antibiotic groups tested were beta-lactams, aminoglycosides, fluoroquinolones and trimethoprim-sulfamethoxazole.

ANITMICROBIAL RESISTANCE IN BLOOD CULTURE ISOLATES OF SALMONELLA

A total of 46 strains were isolated from blood culture, representing 0.4% of all blood culture isolates when skin contaminants are excluded. There were five *S.* Typhimurium and its monophasic variant, 15 *S.* Enteritidis (32.6%), four *S.* Typhi, six *S.* Paratyphi, and 16 (34.8%) other *Salmonella* isolates (Figure 41) representing eleven different serovars. Most isolates from blood culture were tested against seven groups of antibiotics. The number that each group of *Salmonella* was resistant to is shown in Figure 42. Although the numbers are small, it seems that the most frequent serovar in blood culture, *S.* Enteritidis, is fairly sensitive to all groups of antimicrobials, in spite of having been acquired abroad in more than half of the cases. It should be emphasised that low-level ciprofloxacin resistance is underestimated. When calculating MDR, low-level resistance against nalidixic acid and/or high-level resistance against ciprofloxacin counted as quinolone resistance.

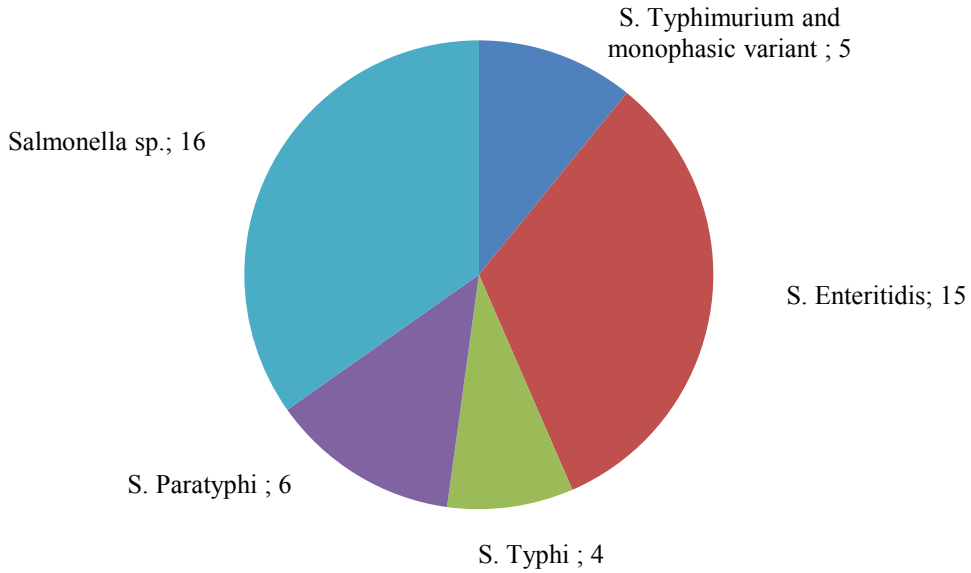


FIGURE 41. Distribution of blood culture isolates of different *Salmonella* serovars (n=46) in 2015.

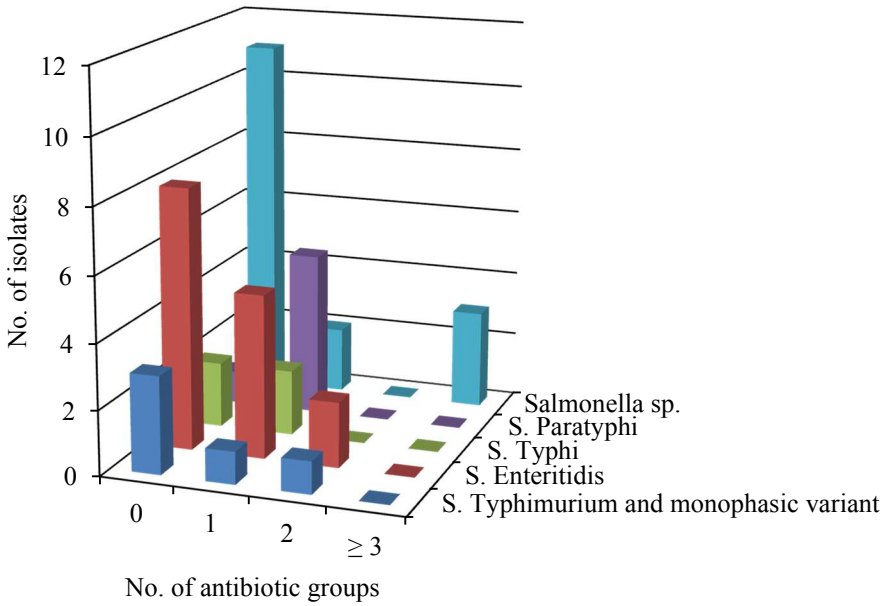


FIGURE 42. Antimicrobial resistance in *Salmonella* isolated from blood culture in 2015 tested against seven antibiotic groups with the number of isolates resistant to none, one, two, or three or more antimicrobial groups, respectively. The seven antibiotic groups tested were beta-lactams, aminoglycosides, fluoroquinolones, trimethoprim-sulfamethoxazole, macrolides, tetracyclines, and chloramphenicol.

RESISTANCE IN SALMONELLA IRRESPECTIVE OF SAMPLE MATERIAL

TABLE 15. Human isolates of domestically acquired *Salmonella* Typhimurium-group (n=59) during 2015, including domestically acquired *S. enterica* serovar 4,[5],12:i:- (n=22). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	66.7	-	33.3
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	98.8	1.2	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin [1]	≤ 0.5	> 1	98.8	1.2	0.0
Nalidixic acid [2] *	≥ 19	< 19	88.2	-	11.8
Gentamicin	≤ 2	> 4	97.5	0.0	2.5
Azithromycin [2] *	≥ 12	<12	100.0	-	0.0
Tetracycline [2] *	≥ 13	< 13	29.4	-	70.6
Chloramphenicol *	≤ 8	> 8	85.3	-	14.7
Trimethoprim-sulfamethoxazole	≤ 2	> 4	97.5	0.0	2.5

[1] Low-level resistance against ciprofloxacin is underestimated by using these breakpoints; EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. [2] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 34/81 isolates.

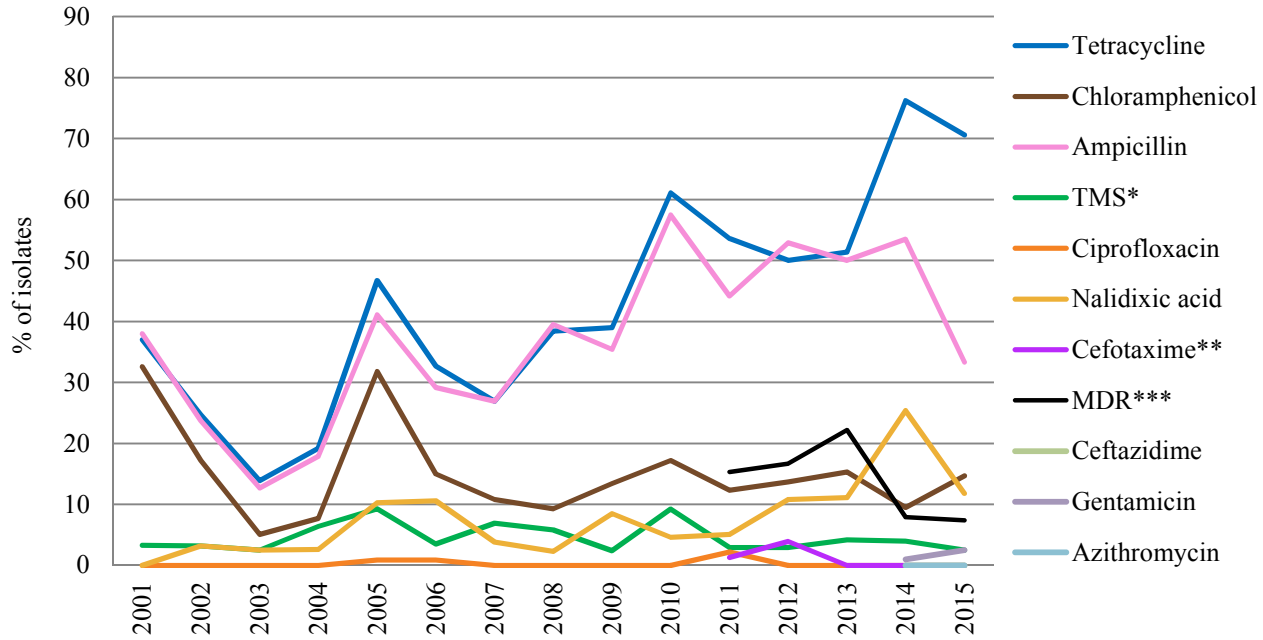


FIGURE 43. Percentage of resistance to various antimicrobial agents in *Salmonella* Typhimurium-group including *S. enterica* serovar 4,[5],12:i:- from humans infected in Norway 2001-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested. ***MDR testing in 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups.

TABLE 16. Human isolates of *Salmonella* Typhimurium-group acquired abroad during 2015 (n=55), including *S. enterica* serovar 4,[5],12:i:- (n=68). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	30.1	-	69.9
Cefotaxime	≤ 1	> 2	96.8	0.0	3.2
Ceftazidime	≤ 1	> 4	94.3	3.3	2.4
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin [1]	≤ 0.5	> 1	99.2	0.8	0.0
Nalidixic acid [2]*	≥ 19	< 19	73.6	-	26.4
Gentamicin	≤ 2	> 4	94.3	0.8	4.9
Azithromycin [2] *	≥ 12	< 12	98.9	-	1.1
Tetracycline [2] *	≥ 13	< 13	11.5	-	88.5
Chloramphenicol *	≤ 8	> 8	73.6	-	26.4
Trimethoprim-sulfamethoxazole	≤ 2	> 4	91.9	0.8	7.3

[1] Low-level resistance against ciprofloxacin is underestimated by using these breakpoints; EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. [2] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 87/123 isolates.

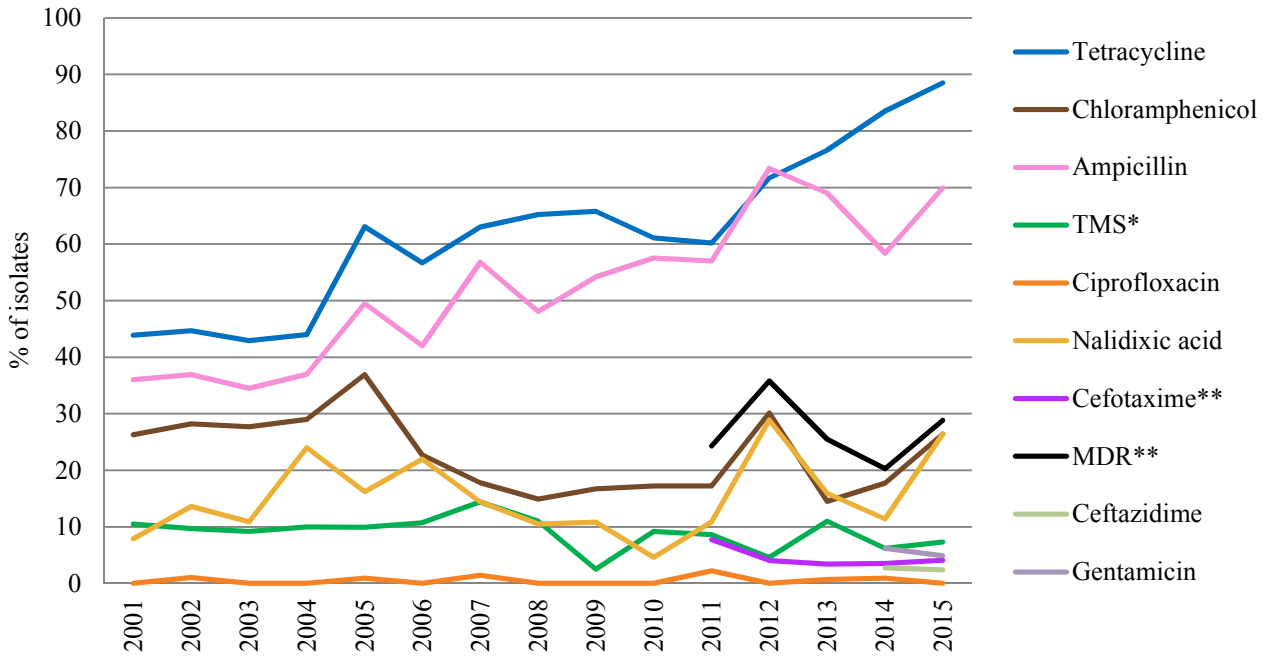


FIGURE 44. Percentage of resistance to various antimicrobial agents in *Salmonella* Typhimurium-group including *S. enterica* serovar 4,[5],12:i:- from humans infected outside Norway 2001-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested. ***MDR testing in 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups.

TABLE 17. Human isolates of *Salmonella* Enteritidis (n=345[#]), acquired during 2015, irrespective of place of acquisition. Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	95.7	-	4.3
Cefotaxime	≤ 1	> 2	99.7	0.3	0.0
Ceftazidime	≤ 1	> 4	99.1	0.9	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin [1]	≤ 0.5	> 1	99.7	0.3	0.0
Nalidixic acid [2]*	≥ 19	< 19	75.8	-	24.2
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [2] *	≥ 12	< 12	100.0	-	0.0
Tetracycline [2] *	≥ 13	< 13	92.4	-	7.6
Chloramphenicol *	≤ 8	> 8	100.0	-	0.0
Trimethoprim-sulfamethoxazole	≤ 2	> 4	99.4	0.0	0.6

[1] Low-level resistance against ciprofloxacin is underestimated by using these breakpoints; EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. [2] Epidemiological cut-off values based on zone distribution evaluations. *Only tested in 66/345 isolates. #Place of acquisition; Norway (n=47), abroad (n=271), unknown (n=27).

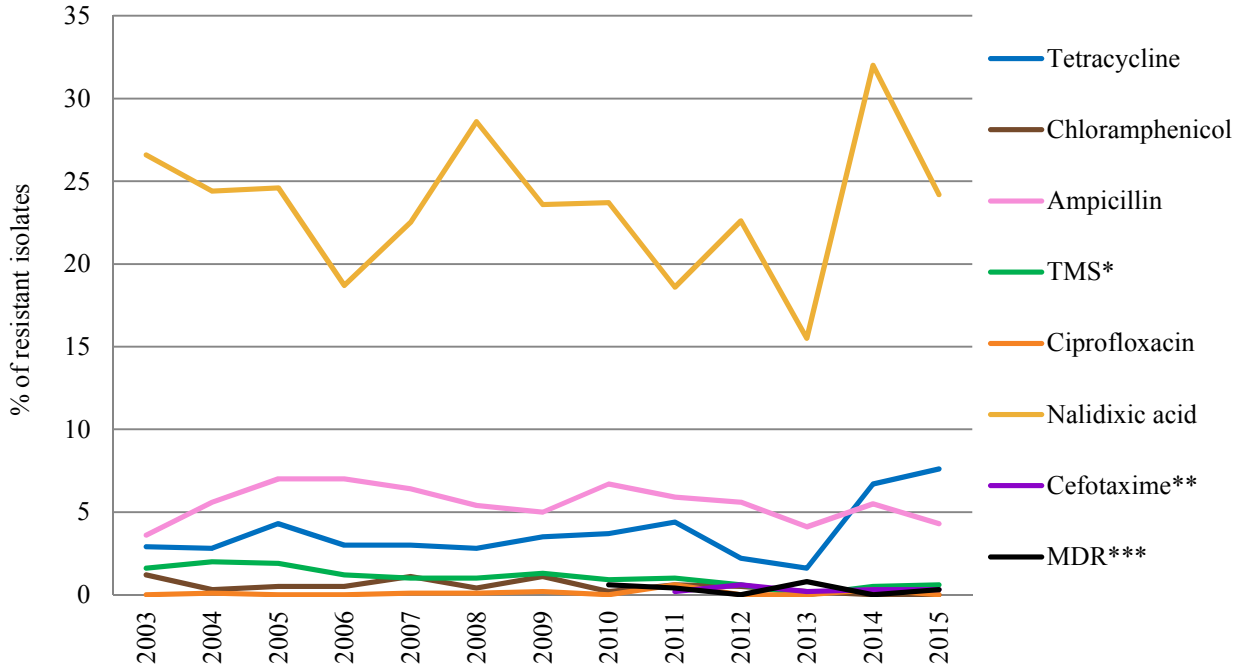


FIGURE 45. Percentage of resistance to various antimicrobial agents in *Salmonella* Enteritidis from humans in 2003-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested. ***MDR testing 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups.

TABLE 18. Human isolates of *Salmonella* spp. including *S.* Paratyphi B variant Java, but excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi (n=342[#]), acquired during 2015, irrespective of place of acquisition. Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	86.2	-	13.8
Cefotaxime	≤ 1	> 2	97.4	0.0	2.6
Ceftazidime	≤ 1	> 4	95.4	2.3	2.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin [1]	≤ 0.5	> 1	95.6	1.2	3.2
Nalidixic acid [2]*	≥ 19	< 19	83.7	-	16.3
Gentamicin	≤ 2	> 4	94.1	0.3	5.6
Azithromycin [2] *	≥ 12	< 12	98.8	-	1.2
Tetracycline [2] *	≥ 13	< 13	87.5	-	12.5
Chloramphenicol *	≤ 8	> 8	92.5	-	7.5
Trimethoprim-sulfamethoxazole	≤ 2	> 4	89.7	0.3	10.0

[1] Low-level resistance against ciprofloxacin is underestimated by using these breakpoints; EUCAST emphasises evidence of poor clinical response in systemic infections with low-level ciprofloxacin resistant *Salmonella*. [2] Epidemiological cut-off values based on zone distribution evaluations. *Only tested in 80/342 isolates. #Place of infection; Norway (n=71), abroad (n=239), unknown (n=32).

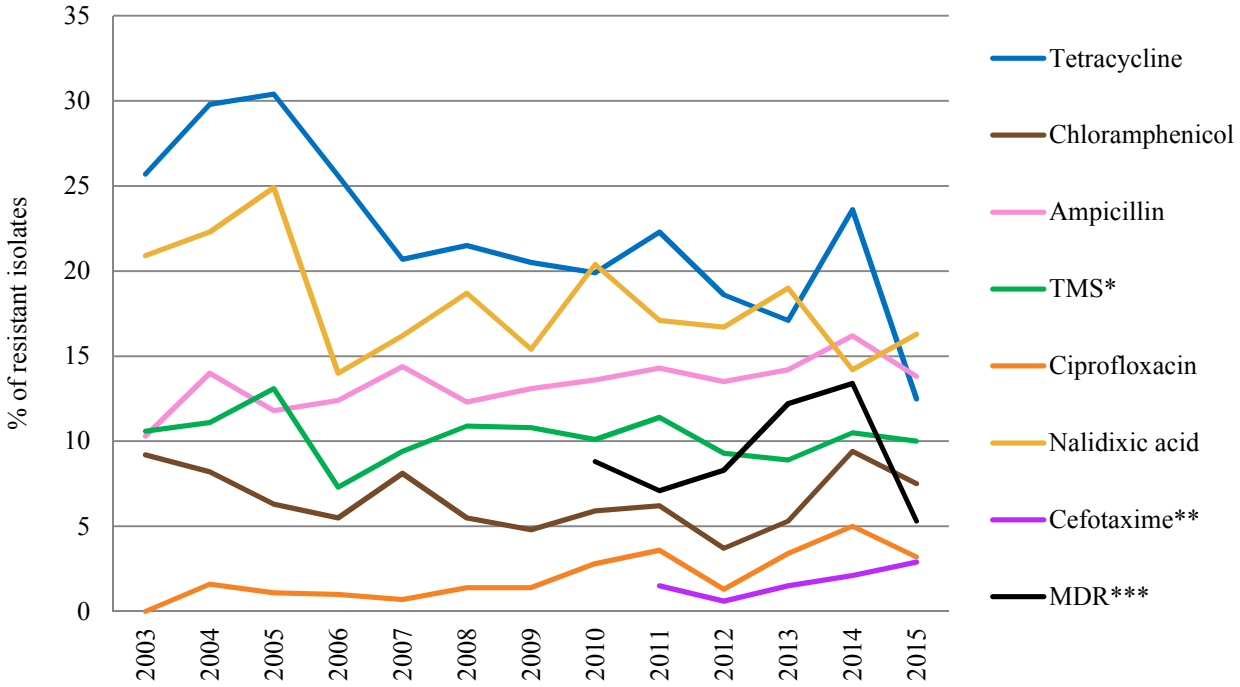


FIGURE 46. Percentage of resistance to various antimicrobial agents in *Salmonella* spp. including *S.* Paratyphi B variant Java; but excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi, from humans in 2003-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested.***MDR testing 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups.

RESULTS AND COMMENTS

As found earlier, the overall impression is that the "*S.* Typhimurium and its monophasic variant" group and the "*Salmonella* other" group are the two most resistant (Figure 40).

Another tendency is that the proportion of strains resistant to ampicillin and tetracycline within the *S.* Typhimurium-group acquired abroad continues to increase. As demonstrated in Figure 44, this trend is apparent for strains acquired abroad. The rates of isolates resistant to ampicillin and tetracycline have practically doubled over the last decade and are now around 50% for domestically acquired isolates and 70-80% in those acquired abroad.

Antimicrobial resistance in *S.* Enteritidis isolates seems fairy stable (Figure 45), possibly due, in part, to a stable proportion of infections acquired abroad (Figure 39). There is still a very low level of resistance to ciprofloxacin. However, the breakpoints used underestimate low-level ciprofloxacin resistance, probably relevant in systemic *Salmonella* infections. There is no clear tendency towards an increase in resistance against nalidixic acid.

With regard to *Salmonella* spp. including *S.* Paratyphi B variant Java, but excluding *S.* Typhimurium-group, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi, most infections were acquired abroad and antimicrobial resistance was moderate and fairly stable, but for a possible decrease in tetracycline resistance and MDR (Table 18 and Figure 46). Also in this group, resistance to ciprofloxacin was still well below 5%, although the same reservations have to be made concerning low-level ciprofloxacin resistant strains in systemic infections.

A total of thirteen strains carried extended spectrum beta-lactamases (ESBL). $ESBL_A$ was carried by five strains of *S.* Typhimurium or its monophasic variant, by three *S.* Infantis, and by one each of *S.* Poona, *S.* Cholerasuis, *S.* Rissen, *S.* Kentuchy and *S.* Anatum, respectively. $ESBL_M$ was not found among *Salmonella* species in 2015.

CAMPYLOBACTER SPP.

Campylobacter coli from swine

Caecal samples from a total of 270 swine were examined, and *C. coli* isolates were obtained from 217 of these (80.4%). The results are presented in Table 19 and in the text.

TABLE 19. Antimicrobial resistance in *Campylobacter coli* (n=217) from swine in 2015.

	Resistance		Distribution (n) of MIC values (mg/L)*												
Substance	(%)	[95% CI]	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Tetracycline	0.5	[0.0-2.5]				98.6	0.5	0.5					0.5		
Erythromycin	0	[0.0-1.7]					99.5	0.5							
Streptomycin	29.5	[8.4-17.6]			0.5		0.5	9.2	60.4	4.1	0.9	24.4			
Gentamicin	0	[23.5-36.0]		0.9	3.2	31.3	63.6	0.9							
Ciprofloxacin	12.0	[8.0-17.1]		87.1	0.9			0.9	3.2	6.5	1.4				
Nalidixic acid	12.4	[8.4-17.6]						1.4	59.0	25.3	1.8	0.9	4.1	7.4	

*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.

RESULTS AND COMMENTS

The data indicate a high occurrence of resistance among *C. coli* from swine. A total of 63.6% of the isolates were susceptible to all antimicrobial agents tested. Altogether, 24.0% were resistant to one antimicrobial agent, 7.0% to two, and 5.5% to three of the antimicrobial agents tested. Resistance to streptomycin was the most frequently identified resistance determinant (29.5%), followed by resistance to nalidixic acid (12.4%) and ciprofloxacin (12.0%). Resistance to erythromycin and gentamicin were not detected.

C. coli has only been investigated once before, in 2009, and an increase in resistance was observed for the three most frequently identified antimicrobial agents compared to the 2009 results. However, these are non-significant results and further monitoring is needed to follow the situation in *C. coli* from swine.

In an international perspective, the occurrence of resistance among *C. coli* from Norwegian swine is low. However, the occurrence varies markedly between countries reporting to EFSA (EFSA and ECDC Summary report 2013). This favourable situation is due to the rather limited use of antibiotics in the Norwegian swine production.

Campylobacter spp. from human clinical cases

Of the 2,307 human campylobacteriosis cases registered in Norway in 2015, 51.1% were reported as acquired abroad. Based on epidemiological data from patients, the vast majority of cases were judged as sporadic. However, only a fraction of the isolates are forwarded to the National Reference Laboratory. Consequently, quality-assured species diagnoses, complete AMR data and molecular epidemiology data on *Campylobacter* isolates are lacking due to resource limitations. Outbreaks with less clear epidemiological links may very well have been overlooked, and the antimicrobial susceptibility testing results presented may therefore be underestimated or overestimated.

Susceptibility testing was performed on a total of 263 *C. jejuni* isolates from 95 patients infected in Norway, 153 infected abroad and 15 where the place of acquisition of infection was unknown, as well as 19 *C. coli* isolates. EUCAST clinical breakpoints and epidemiological cut-off values have been used. The results for *C. jejuni* are presented in Tables 20-21, Figures 47-49, and in the text.

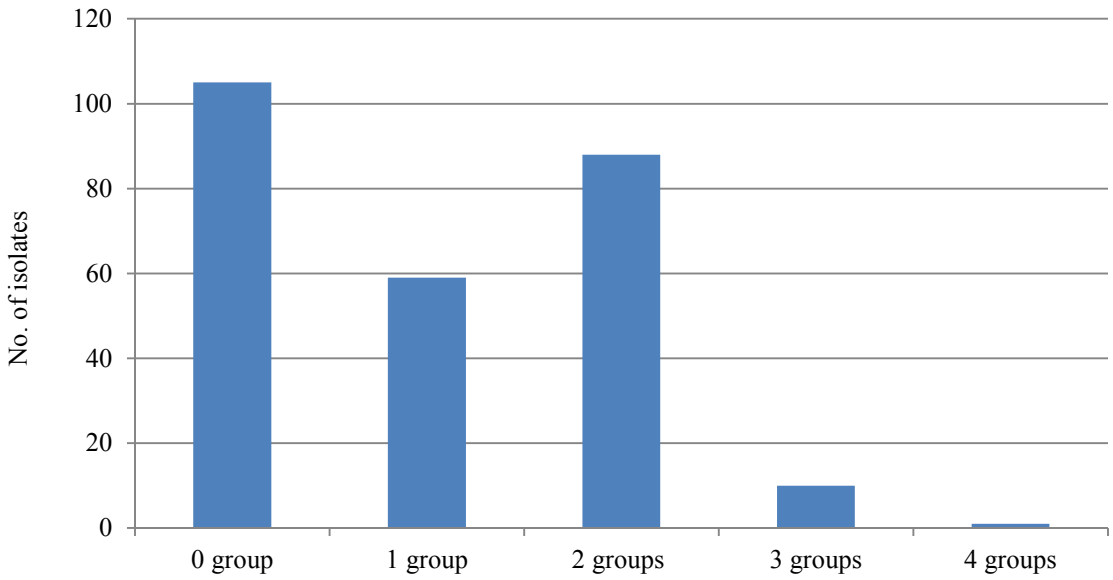


FIGURE 47. Distribution of number of antimicrobials that *Campylobacter jejuni* isolates were resistant to in 2015. The four antibiotic groups tested were tetracycline, fluoroquinolones, aminoglycosides and macrolides.

TABLE 20. *Campylobacter jejuni* isolates from patients infected in Norway in 2015 (n=95). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	86.2	-	13.8
Erythromycin	≤ 4	> 4	97.9	-	2.1
Gentamicin [1]	≤ 2	> 2	97.9	-	2.1
Nalidixic acid [1]	≤ 16	> 16	70.2	-	29.8
Ciprofloxacin	≤ 0.5	> 0.5	73.4	-	26.6

[1] Epidemiological cut-off values according to EUCAST web-pages by July 2014.

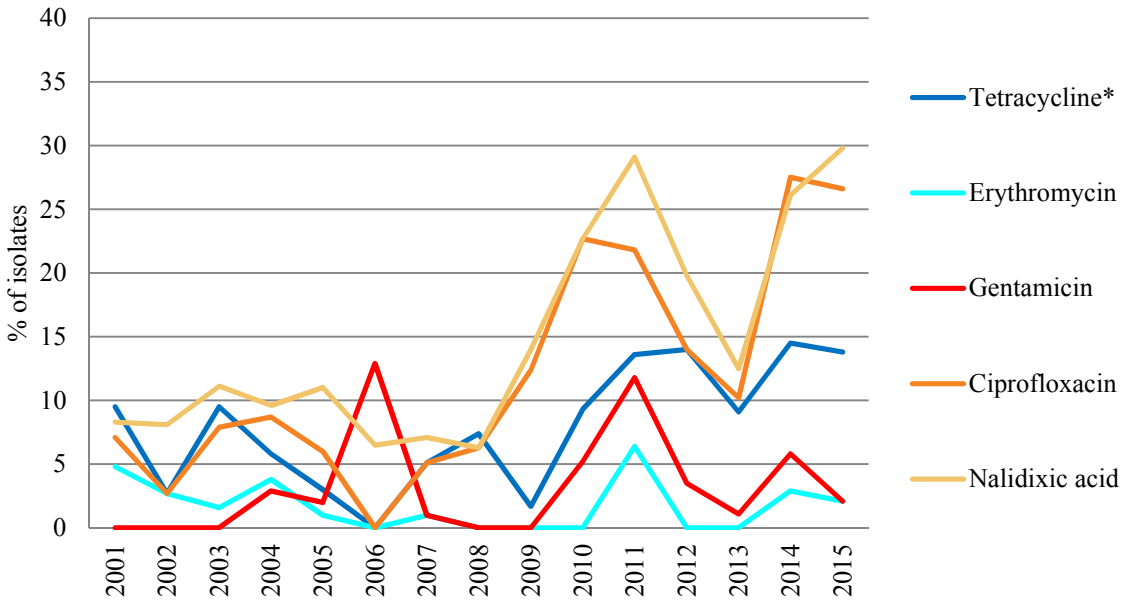


FIGURE 48. Prevalence of resistance in *Campylobacter jejuni* isolated from humans infected in Norway 2001-2015 to various antimicrobials. *Doxycycline before 2006.

TABLE 21. *Campylobacter jejuni* isolates from patients infected outside Norway in 2015 (n=152). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	45.4	-	54.6
Erythromycin	≤ 4	> 4	92.8	-	7.2
Gentamicin [1]	≤ 2	> 2	98.0	-	2.0
Nalidixic acid [1]	≤ 16	> 16	20.4	-	79.6
Ciprofloxacin	≤ 0.5	> 0.5	20.4	-	79.6

[1] Epidemiological cut-off values according to EUCAST web-pages by July 2014.

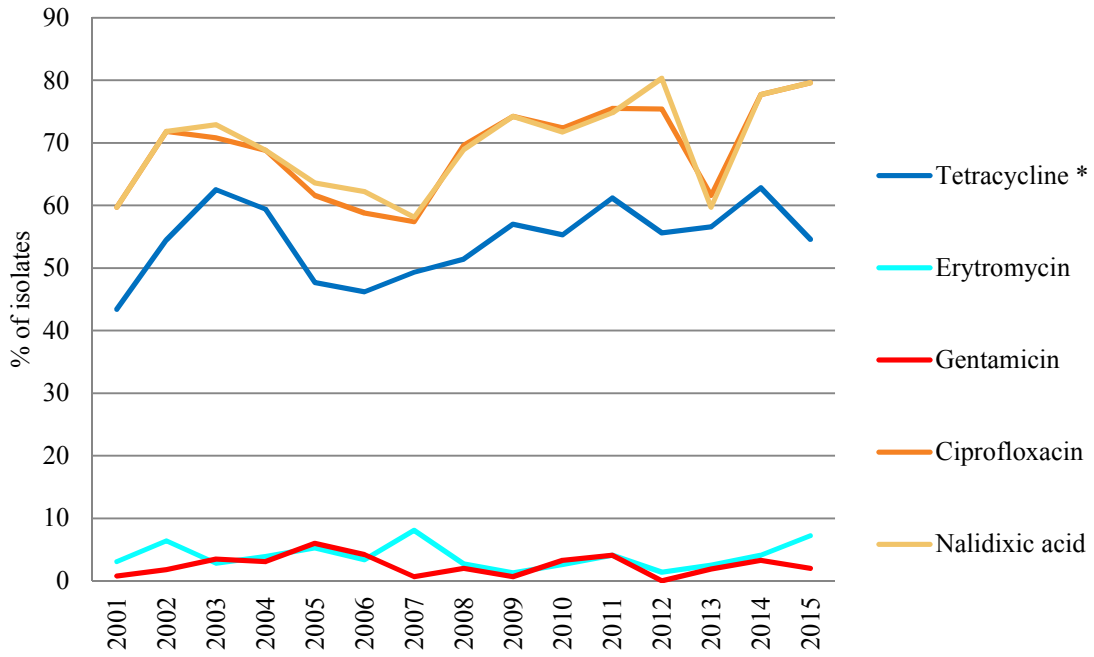


FIGURE 49. Prevalence of resistance to various antimicrobial agents in *Campylobacter jejuni* from humans infected outside Norway 2001-2015. *Doxycycline before 2006.

RESULTS AND COMMENTS

The data clearly show that resistance was more widespread among *C. jejuni* isolates recovered from patients infected abroad than in patients infected in Norway. Only 15.0% of isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 68.4% of the isolates from patients infected in Norway. The main differences between the two groups were seen for ciprofloxacin, nalidixic acid and tetracycline. There was a statistically significant difference in levels of resistance between those isolates acquired abroad compared to those acquired in Norway (p<0.001 for both antimicrobial groups).

For strains acquired abroad, resistance against all antimicrobials seems relatively stable, and for strains acquired in Norway the level of resistance seems to increase, however with broad variations probably due to a low number of strains tested. Furthermore, there might be a tendency towards more resistance against quinolones in isolates acquired in Norway, possibly approaching the level seen in isolates acquired abroad.

Seventeen of the 19 *C. coli* isolates were acquired abroad. All of these seventeen isolates were resistant to at least one of the antimicrobial agents tested.

Yersinia enterocolitica from human clinical cases

A total of 75 unique strains of pathogenic *Yersinia enterocolitica* were analysed in 2015. Fifty-four belonged to serogroup 3 including 36 acquired in Norway, 11 acquired abroad and seven with unknown place of acquisition. Twenty strains belonged to serogroup 9, of which 16 were acquired in Norway, one acquired abroad and three strains were acquired from unknown location. One *Y. pseudotuberculosis* strain was acquired in Norway. All *Y. enterocolitica* isolates were tested for susceptibility to four antimicrobial groups (beta-lactams, quinolones, aminoglycosides, and trimethoprim-sulfamethoxazole) whereas only seven strains were tested against all seven groups. The results are presented in Table 22 and Figures 50-51.

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

TABLE 22. *Yersinia enterocolitica* serogroups O:3, O:9, and *Y. pseudotuberculosis* human cases in 2015 (n=75). Distributions (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	0.0	-	100.0
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.5	> 1	100.0	0.0	0.0
Nalidixic acid [1]*	≥ 19	< 19	85.7	-	14.3
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1] *	≥ 12	< 12	100.0	-	0.0
Tetracycline [1] *	≥ 13	< 13	100.0	-	0.0
Chloramphenicol *	≤ 8	> 8	100.0	-	0.0
Trimethoprim-sulfamethoxazole	≤ 2	> 4	98.7	1.3	0.0

[1] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 7/75 isolates.

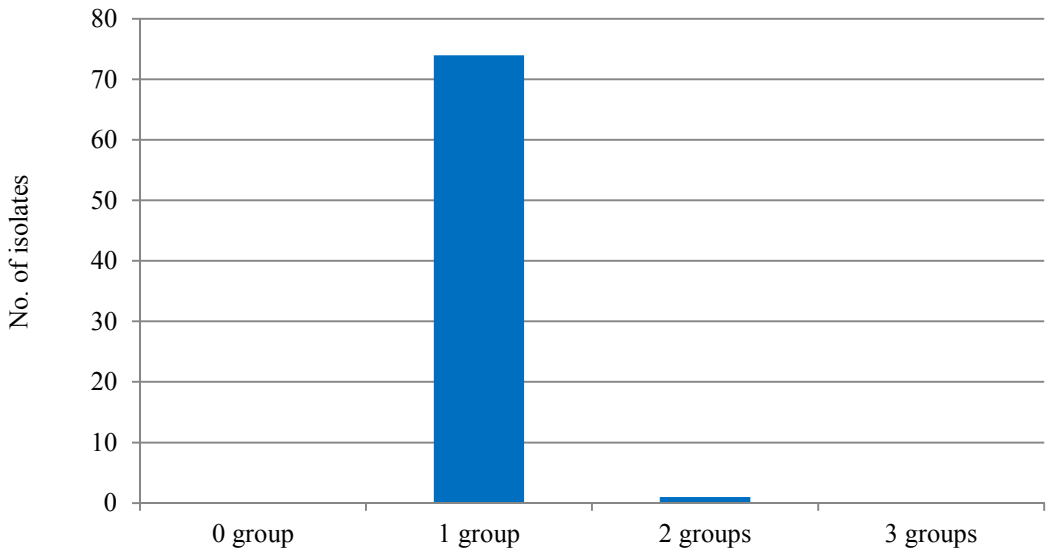


FIGURE 50. Distribution of number of antimicrobials that *Yersinia enterocolitica* isolates were resistant to in 2015.

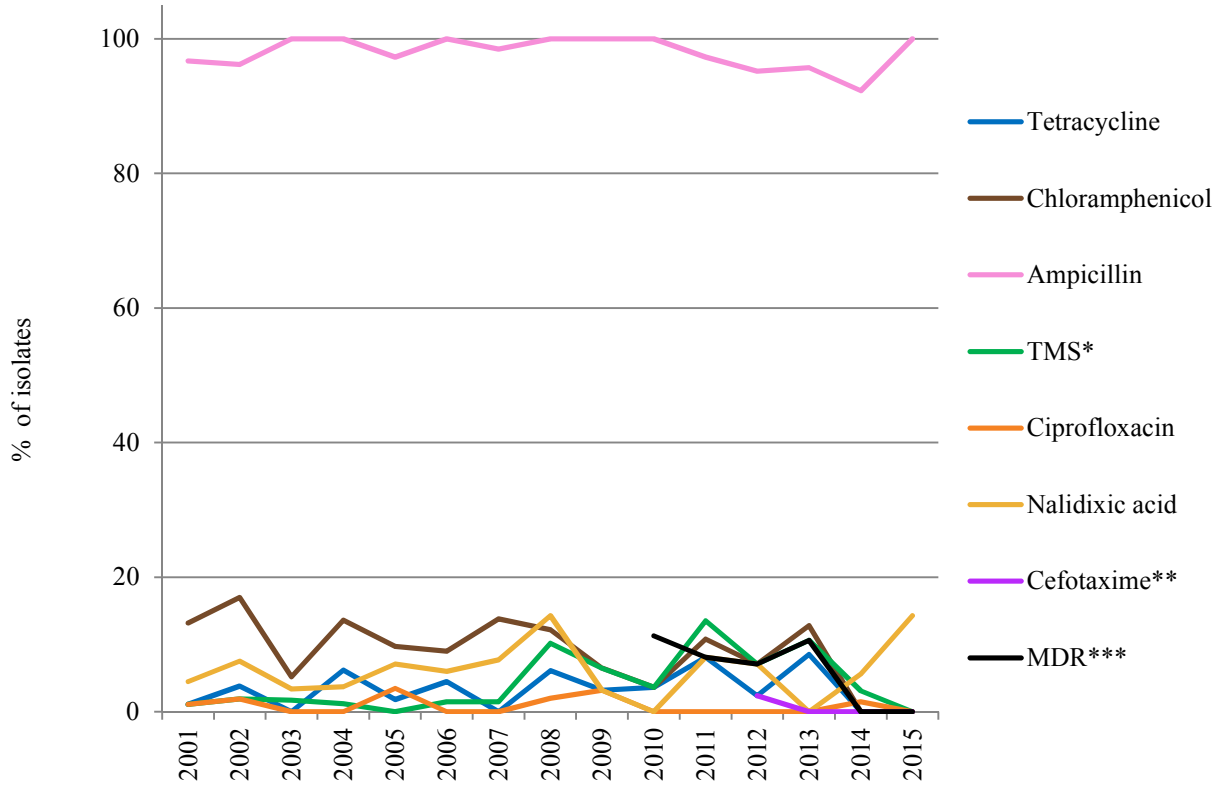


FIGURE 51. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested. ***MDR testing in 2011-2013 was calculated for five groups of antibiotics, whereas from 2014 onwards MDR results shown are for seven groups.

RESULTS AND COMMENTS

All isolates of pathogenic *Yersinia enterocolitica* expressed intrinsic resistance to ampicillin. The prevalence of resistance to other antimicrobial agents appeared stable during the years 2001-2015.

Shigella spp. from human clinical cases

In 2015, 11 (14.3%) of the 77 unique isolates *of Shigella* were domestically acquired. However, the domestically acquired strains were considered secondary to imported cases. Thus, the prevalence of resistance presented in this report predominantly relates to isolates originating from other countries. The species distribution of the 77 *Shigella* isolates that were tested for drug susceptibility was as follows: *S. sonnei* 39 (50.6%); *S. flexneri* 29 (37.7%); *S. boydii* 5 (6.5%); *S. dysenteriae* 2 (2.6%) and *Shigella species* 2 (2.6%). The number of antimicrobial agents that *Shigella* isolates were resistant to are shown in Figure 52.

All isolates were tested for resistance against four different antibiotic groups: beta-lactams (ampicillin, cefotaxime, ceftazidime, and meropenem), ciprofloxacin, gentamicin and trimethoprim-sulfamethoxazole. In addition, eleven of the isolates were tested for nalidixic acid, azithromycin, tetracycline, and chloramphenicol. Multi-resistance was defined as resistance to three or more antimicrobial categories, calculated on the basis of the isolates tested for all seven antibiotic groups. The results for *S. sonnei* and *S. flexneri* are presented in Table 23 and Figure 53, and in Table 24 and Figure 54, respectively.

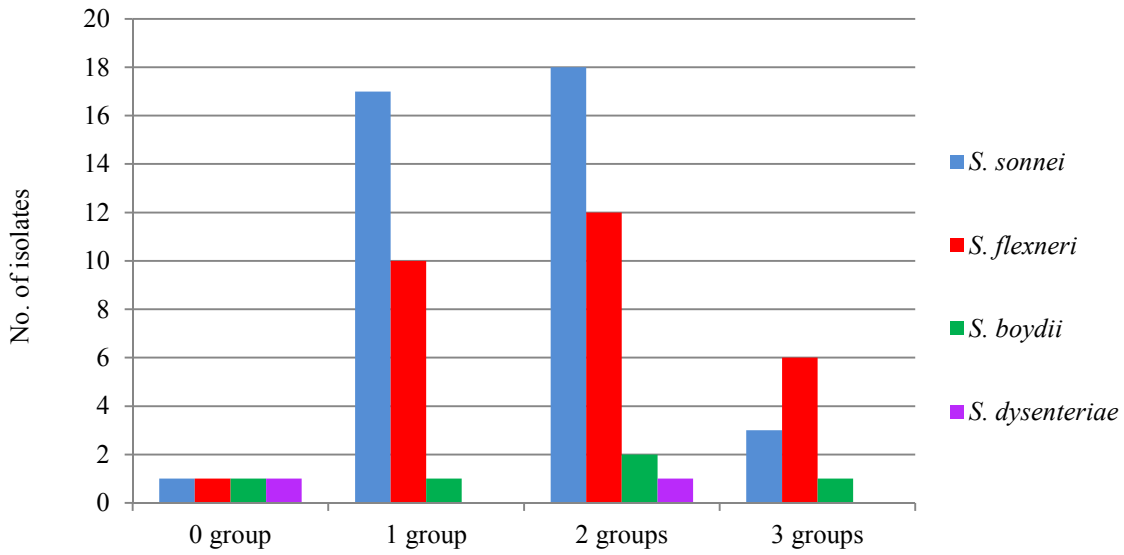


FIGURE 52. Distribution of number of antimicrobials that *Shigella* isolates were resistant to; by species, among all isolates tested against four antibiotic groups.

TABLE 23. *Shigella sonnei* isolates from human cases in 2015 (n=39). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	71.8	-	28.2
Cefotaxime	≤ 1	> 2	76.9	0.0	23.1
Ceftazidime	≤ 1	> 4	94.9	5.1	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.5	> 1	71.8	0.0	28.2
Nalidixic acid [1]*	≥ 19	< 19	25.0	-	75.0
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1] *	≥ 12	< 12	100.0	-	0.0
Tetracycline [1] *	≥ 13	< 13	25.0	-	75.0
Chloramphenicol *	≤ 8	> 8	100.0	-	0.0
Trimethoprim-sulfamethoxazole	≤ 2	> 4	10.3	2.6	87.1

[1] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 4/39 isolates.

TABLE 24. *Shigella flexneri* isolates from human cases in 2015 (n=29). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4.

	Breakpoints (mg/L or mm)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	24.1	-	75.9
Cefotaxime	≤ 1	> 2	93.1	0.0	6.9
Ceftazidime	≤ 1	> 4	93.2	3.4	3.4
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Ciprofloxacin	≤ 0.5	> 1	72.4	0.0	27.6
Nalidixic acid [1]*	≥ 19	< 19	42.9	-	57.1
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Azithromycin [1] *	≥ 12	< 12	100.0	-	0.0
Tetracycline [1] *	≥ 13	< 13	38.6	-	71.4
Chloramphenicol *	≤ 8	> 8	57.1	-	42.9
Trimethoprim-sulfamethoxazole	≤ 2	> 4	41.4	0.0	58.6

[1] Epidemiological cut-off values based on zone distribution evaluations. * Only tested in 7/29 isolates.

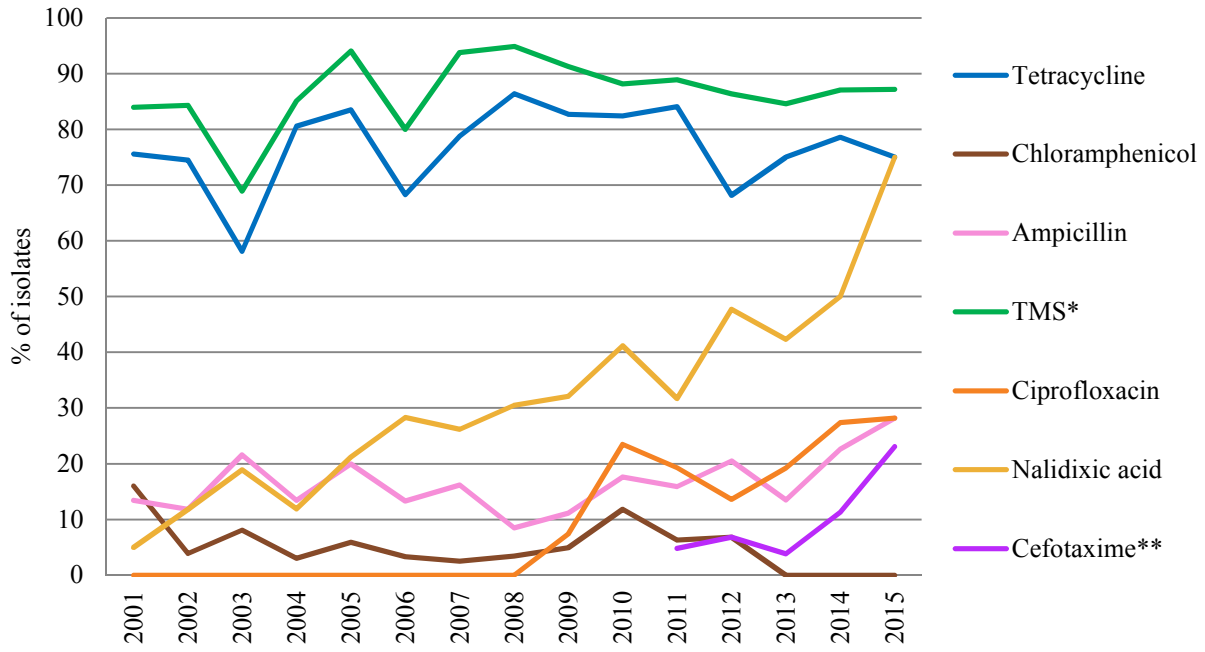


FIGURE 53. Prevalence of resistance to various antimicrobial agents in *Shigella sonnei* from humans in Norway 2001-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested.

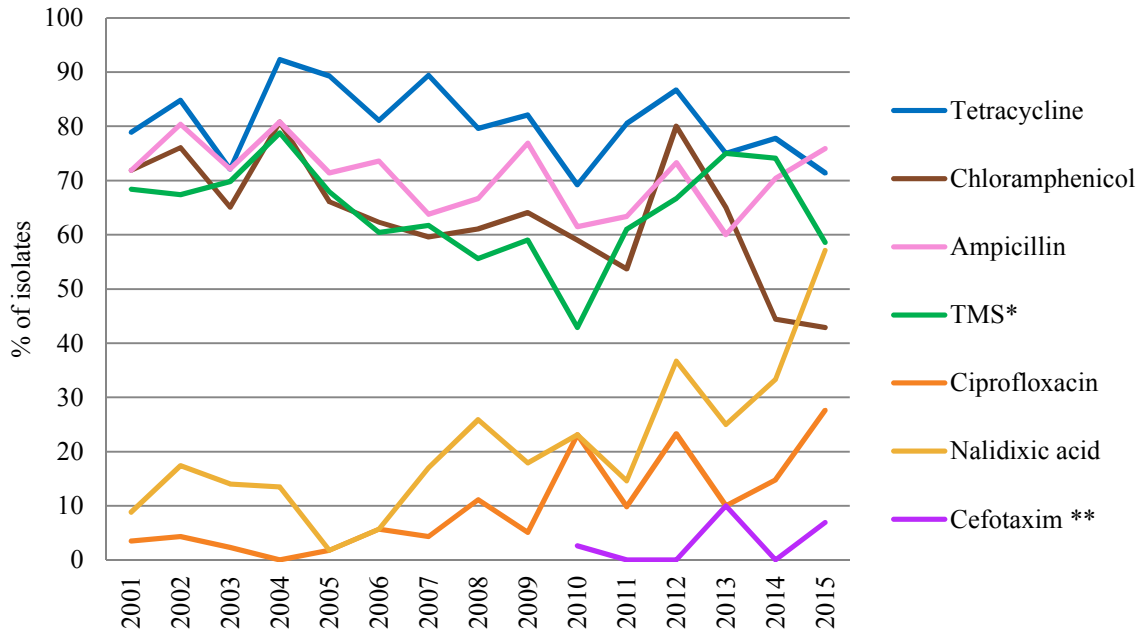


FIGURE 54. Prevalence of resistance to various antimicrobial agents in *Shigella flexneri* from humans in Norway 2001-2015. *TMS=Trimethoprim-sulfamethoxazole. **Before 2014 cefpodoxime was tested.

RESULTS AND COMMENTS

The resistance patterns for *S. sonnei* have been fairly stable during the period 2001-2015. Resistance to nalidixic acid and ciprofloxacin, however, have steadily increased since 2001. A similar development appears for resistance to nalidixic acid and ciprofloxacin in *S. flexneri* isolates. The proportion of multi-drug resistance in both *S. sonnei* and *S. flexneri* (7.7% and 20.7%, respectively) was higher than in *Salmonella* as a whole (6.8%).

Fifteen *Shigella strains* (19.5%) were phenotypically $ESBL_A$ producers with inhibitory effect of clavulanic acid. $ESBL_A$ was carried by nine *Shigella sonnei*, two *Shigella flexneri* and four *Shigella boydii* strains.

HUMAN CLINICAL ISOLATES

Cecilie Torp Andersen, Elisabeth Astrup, Dominique Caugant, Kjersti Wik Larssen, Andreas Radtke, Karin Rønning, Gunnar Skov Simonsen, Dagfinn Skaare, Martin Steinbakk, Didrik Vestrheim, Frode Width-Gran

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

TABLE 25. Number of blood culture isolates in 2015, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) 2011-2015. The table is based on data from the information systems of all laboratories in Norway.

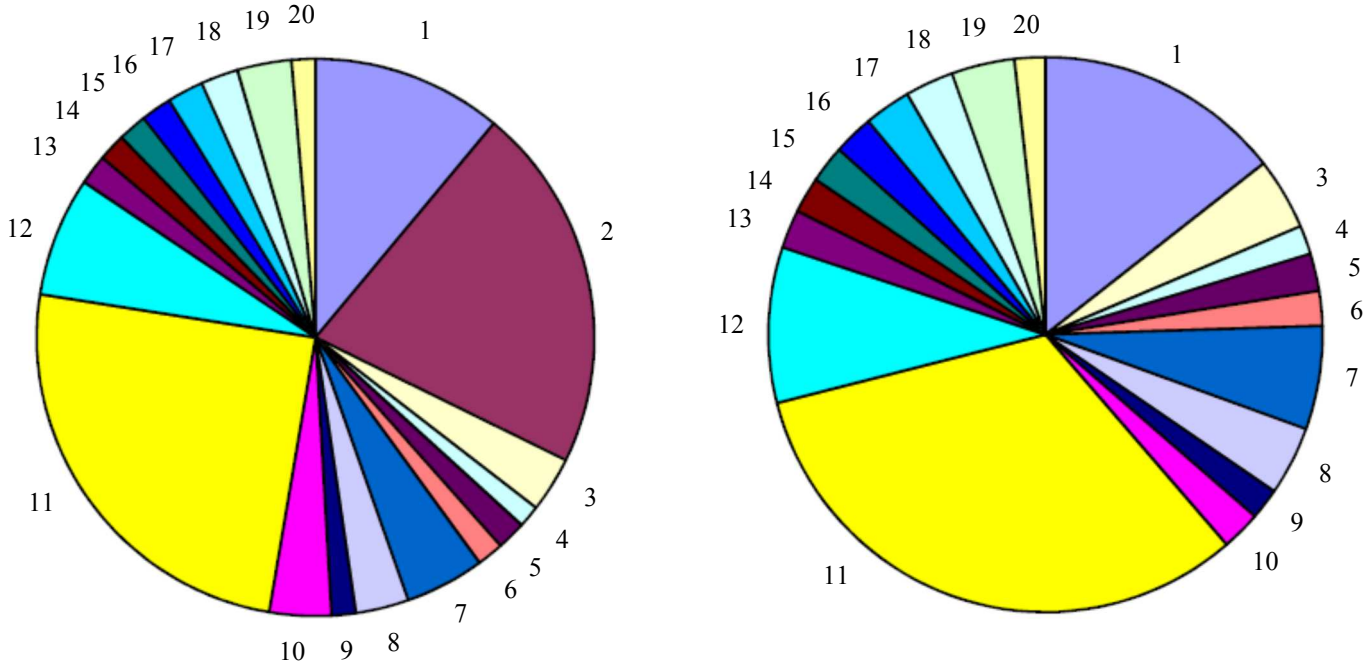
Species	No. of isolates 2015	% of all isolates					% of all isolates excluding skin flora				
		2011	2012	2013	2014	2015	2011	2012	2013	2014	2015
Staphylococcus aureus	1,781	11.0	11.3	11.5	11.0	11.1	14.2	15.0	14.3	14.2	14.4
Coagulase negative staphylococci	3,418	20.6	22.5	17.4	20.4	21.1	-	-	-	-	-
Streptococcus pneumoniae	518	5.3	4.2	4.2	3.6	3.2	6.8	5.6	5.2	4.6	4.2
Streptococcus pyogenes	207	1.4	1.0	1.3	1.1	1.3	1.8	1.3	1.6	1.4	1.7
Streptococcus agalactiae	271	1.6	1.6	1.7	1.6	1.7	2.1	2.1	2.1	2.0	2.2
Beta-haemolytic streptococci group C and G	249	1.2	1.2	1.2	1.2	1.5	1.6	1.6	1.5	1.6	2.0
Viridans- and non-haemolytic streptococci	744	4.1	3.8	5.5	4.6	4.6	5.2	5.1	6.8	5.9	6.0
Enterococcus faecalis	496	4.1	4.0	4.1	3.8	3.1	5.2	5.3	5.1	5.0	4.0
Enterococcus faecium	225	1.8	1.5	1.8	1.6	1.4	2.3	2.0	2.2	2.1	1.8
Other Gram-positive aerobic and facultative bacteria	578	2.9	3.1	3.3	3.5	3.6	1.6	1.9	2.0	2.0	2.3
Escherichia coli	3,999	24.0	23.9	24.4	24.4	24.8	30.9	31.4	30.4	31.5	32.4
Klebsiella spp.	1,118	6.1	6.5	6.8	7.0	6.9	7.9	8.6	8.4	9.0	9.1
Enterobacter spp.	279	1.8	1.9	1.9	1.9	1.7	2.3	2.5	2.4	2.5	2.3
Proteus spp.	258	1.7	1.3	1.7	1.6	1.6	2.2	1.8	2.1	2.1	2.1
Other *Enterobacteriaceae*	288	2.2	2.0	2.3	2.2	1.8	2.9	2.7	2.9	2.9	2.3
Pseudomonas spp.	270	1.5	1.7	1.7	1.8	1.7	2.0	2.2	2.1	2.3	2.2
Other Gram negative aerobic and facultative bacteria	337	2.2	2.0	2.1	2.0	2.1	2.8	2.6	2.6	2.6	2.7
Bacteroides spp.	350	2.2	2.3	2.4	2.2	2.2	2.9	3.0	3.0	2.9	2.8
Other anaerobic bacteria	508	2.8	2.8	3.2	3.1	3.2	3.4	3.3	3.5	3.6	3.7
Yeasts	221	1.5	1.4	1.5	1.4	1.4	1.9	2.0	1.8	1.8	1.8
Total	**16,115**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 25 and Figure 55, aerobic and facultative Gram-positive and Gram-negative bacteria represented 52.6% and 40.6% of all isolates, respectively. The predominance of Gram-positives among all isolates was at the same level as in previous years. The most common Gram-positive species were coagulase negative staphylococci which represented 21.1% of all isolates. This was an increase from 20.4% in 2014, but these fluctuations may result from inconsistent reporting from the laboratories. The difference between aerobic Gram-positives and Gram-negatives was reversed when species of the skin flora (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) were excluded with 38.6% aerobic Gram-positives and 53.1% aerobic Gram-negatives.

Among aerobic Gram-positives, the prevalence of *S. pneumoniae* has steadily declined from 12.1% in 2005 to 4.2% in 2015 (skin contaminants are excluded), following the introduction of the conjugate pneumococcal vaccine in the national childhood immunisation programme. The proportions of other aerobic Gram-positives have remained stable over many years.

E. coli (32.4%) and other *Enterobacteriaceae* (15.8%) accounted for the vast majority of aerobic Gram-negative isolates, but the proportions have remained relatively unchanged over the years. *Pseudomonas* spp. (2.2%) 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 5.4% (6.5% excluding skin flora). Yeasts accounted for 1.4% (1.8% excluding skin flora) which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (2.2%/2.8%) and among yeasts *Candida albicans* (0.9%/1.2%). 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 55. Distribution of all blood culture isolates (left, n=16,115) and blood culture isolates excluding common skin contaminants (right, n=12,349) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. Data for 2015 were retrieved from the information systems of all Norwegian laboratories.

Escherichia coli in blood cultures

TABLE 26. *Escherichia coli* blood culture isolates in 2015 (n=1,952). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	55.9	-	44.1
Piperacillin-tazobactam	≤ 8	> 16	95.0	3.5	1.5
Cefuroxime	≤ 8	> 8	90.7	-	9.3
Cefotaxime	≤ 1	> 2	93.2	0.3	6.5
Ceftazidime	≤ 1	> 4	93.3	1.2	5.5
Cefepime	≤ 1	> 4	94.7	1.1	4.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	93.6	0.5	5.9
Ciprofloxacin	≤ 0.5	> 1	88.1	0.4	11.5
Tigecycline	≤ 1	> 2	99.8	0.2	0.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	72.1	1.0	26.9
ESBL	Negative	Positive	93.5	-	6.5

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

RESULTS AND COMMENTS

The NORM results are interpreted according to the breakpoints of the Norwegian Working Group for Antibiotics (NWGA) at the time of analysis. Norwegian breakpoints for *Enterobacteriaceae* presently correspond to EUCAST breakpoints. All results from previous years have been recategorised to comply with the 2016 EUCAST protocol.

The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobial agents such as cefotaxime (93.2%), ceftazidime (93.3%), cefepime (94.7%), gentamicin (93.6%), piperacillin-tazobactam (95.0%), tigecycline (99.8%) and meropenem (100.0%) (Table 26). There were no significant changes in the prevalence of susceptibility for these agents from 2014 to 2015.

The prevalence of non-susceptibility (intermediate susceptibility and resistance) to gentamicin increased significantly from 5.8% in 2013 to 8.6% in 2014, but declined to 6.4% in 2015 (Figure 56). However, the prevalence of gentamicin resistance is approximately eight times higher than at the turn of the century. A high proportion of gentamicin non-susceptible isolates (50/124, 40.3%) also produced ESBL enzymes. They were retrieved from 19 different laboratories across the country. The prevalence at individual laboratories varied widely due to relatively small numbers. When aggregated by region, the prevalence of gentamicin non-susceptibility was higher in the South-East (7.3%) compared to the Middle (5.6%), North (5.6%) and West (4.4%) regions.

The prevalence of non-suscpetibility to ciprofloxacin was 11.9% (0.4% I and 11.5% R) in 2015 compared to 13.6% (1.0% I and 12.6% R) in 2014. This is the first year with a decline in the proportion of non-susceptibility to ciprofloxacin in *E. coli* blood culture isolates. The temporal association between ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 57. 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 sustained reduction of quinolone resistance rates. The resistance rates for ampicillin (44.1% in 2015, 42.6% in 2014) and trimethoprim-sulfamethoxazole (26.9% in 2015, 27.8% in 2014) are relatively stable.

In 2015, detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidime. All isolates with reduced susceptibility to ceftazidime and/or cefotaxime were further characterised by combination MIC gradient tests. A total of 127 isolates (6.5%) were reported as ESBL positive which is an increase from 5.8% in 2014 (Figure 59). The isolates originated from all 19 participating laboratories across the country. Estimates at laboratory level are uncertain due to small numbers. When aggregated at regional level there were only minor geographical differences in the prevalence of ESBL (South-East 6.5%, West 6.6%, Middle 6.7% and North 6.1%). Almost all ESBL isolates were non-susceptible to ampicillin (126/127), cefuroxime (123/127) and cefotaxime (123/127), and most of them were also non-susceptible to ceftazidime (114/127) and cefepime (97/123). Many isolates were intermediately (20/127) or even fully susceptible (97/127) to piperacillin-tazobactam. Most displayed high level of co-resistance to ciprofloxacin (88/127), gentamicin (50/127) and/or trimethoprim-sulfamethoxazole (83/127). All were fully susceptible to tigecycline and meropenem. Eighteen additional isolates were reported as non-susceptible to cefotaxime (n=9) and/or ceftazidime (n=17) without being confirmed as ESBL producers.

One-hundred twenty-four *E. coli* isolates with suspected ESBL production were molecularly characterised and revealed a predominance of CTX-M groups 1 (n=75) and 9 (n=35). The remaining fourteen isolates harboured derepressed chromosomally encoded AmpC (n=5), CMY (n=3), DHA (n=2), SHV-1 hyperproduction (n=2) and SHV-ESBL (n=2). No isolates with carbapenemase production were detected.

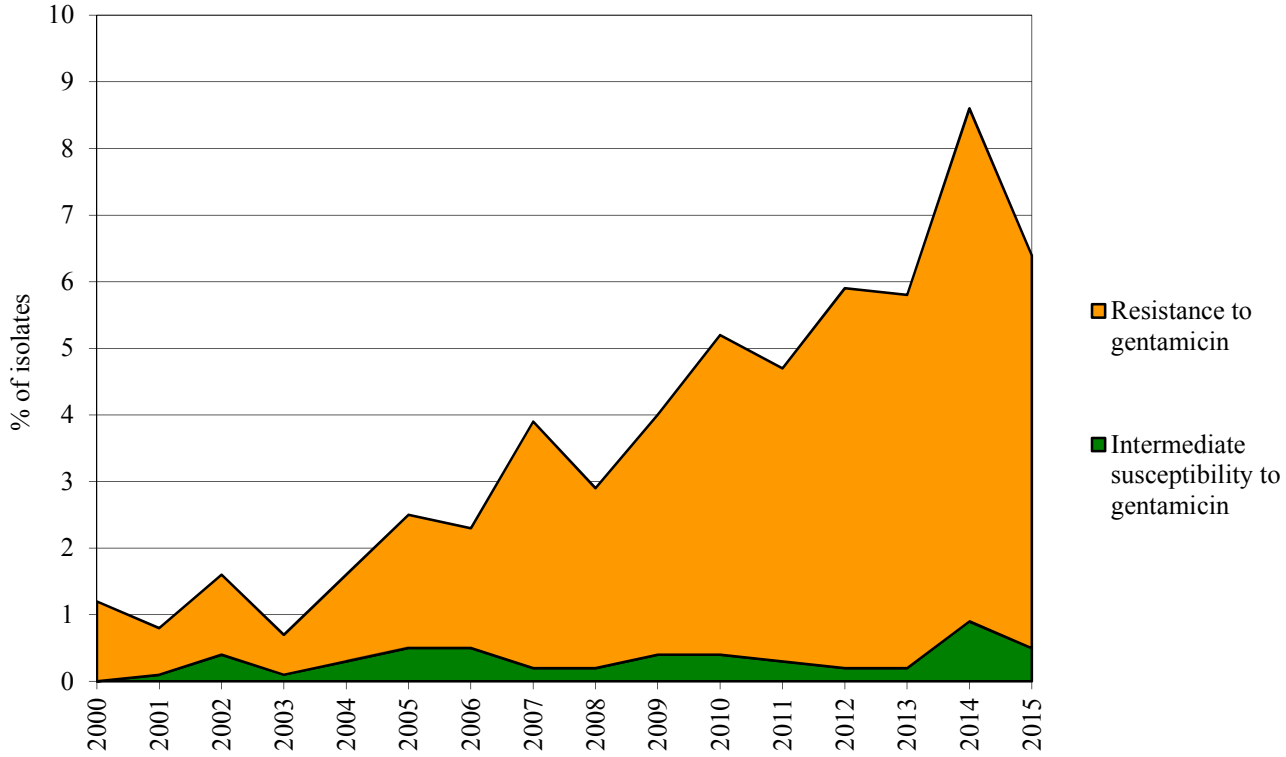


FIGURE 56. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2015.

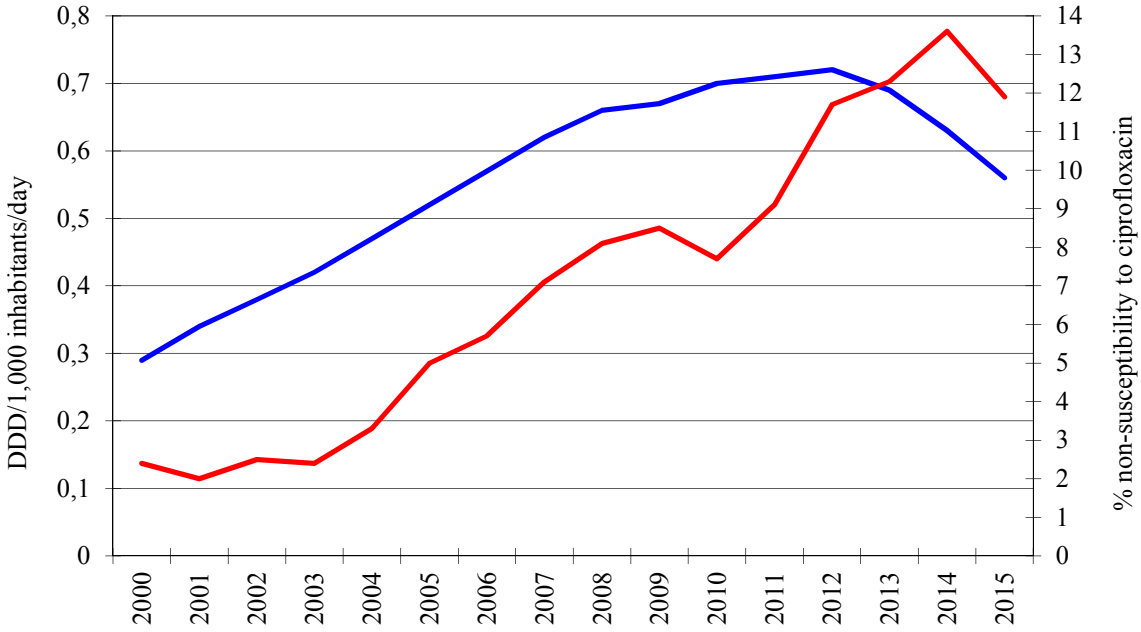


FIGURE 57. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2016 breakpoints (red) 2000-2015.

Escherichia coli in urine

TABLE 27. *Escherichia coli* urinary tract isolates in 2015 (n=1,573). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 8	> 8	65.9	-	34.1
Mecillinam	≤ 8	> 8	94.9	-	5.1
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.9	-	6.1
Cefuroxime	≤ 8	> 8	95.6	-	4.4
Cefotaxime	≤ 1	> 2	96.7	0.1	3.2
Ceftazidime	≤ 1	> 4	96.5	1.0	2.5
Meropenem	≤ 2	> 8	99.9	0.1	0.0
Gentamicin	≤ 2	> 4	96.2	0.4	3.4
Ciprofloxacin	≤ 0.5	> 1	92.4	0.3	7.3
Nitrofurantoin	≤ 64	> 64	99.0	-	1.0
Trimethoprim	≤ 2	> 4	76.9	0.1	23.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	78.4	1.1	20.5
ESBL	Negative	Positive	96.9	-	3.1

*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 2015 is shown in Table 27 and the results for 2000-2015 are shown in Figure 58. All results since 2000 are categorised according to the 2016 EUCAST breakpoint protocol.

The resistance rates among urinary tract isolates have remained relatively stable over the last ten years, but are slowly drifting upward for most antibiotics. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to 35%. Around 20-25% of *E. coli* isolates are resistant to trimethoprim and trimethoprim-sulfamethoxazole. The prevalence of resistance to mecillinam decreased from 6.0% in 2014 to 5.1% in 2015, but susceptibility test results are notoriously difficult to reproduce for this agent and the observed changes may thus not reflect real differences in prevalence.

Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. The prevalence of non-susceptibility was previously stable around 3.5-5.5% but increased to 7.3% in 2013 and 9.4% in 2014. The prevalence in 2015 was 7.6%, with 0.3% intermediate susceptibility and 7.3% resistance. The corresponding rates for blood culture isolates were 0.4% intermediate susceptibility and 11.5% resistance in 2015. 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 are more representative of the wild type normal flora. The slight decrease in resistance from 2014 to 2015 may hopefully indicate a reversal of the steadily increasing rates over many years, but may also be a consequence of variations in case-mix. The prevalence of resistance to amoxicillin-clavulanic acid continued to decrease from 7.9% in 2014 to 6.1% in 2015. The breakpoints used are only valid for uncomplicated urinary tract infections. Almost all isolates (99.0%) remained fully susceptible to nitrofurantoin.

In total, 48 isolates (3.1%) were reported as ESBL producers. This is a decrease from 3.8% in 2014. As seen in Figure 59, the prevalence of *E. coli* ESBL is still lower in urine than in blood culture isolates (6.5%), but there is an increasing trend in both specimen types. The ESBL positive strains were isolated at seventeen different laboratories in all parts of the country. Thirty-one isolates were retrieved from samples submitted by general practitioners, while the others were found in hospitalised patients (n=12), patients visiting outpatient clinics (n=2), and patients in nursing homes (n=3). The ESBL strains were all resistant to ampicillin, cefuroxime and cefotaxime, and non-susceptible to ceftazidime (45/48). Most isolates were registered as *in vitro* susceptible to mecillinam (47/48). The clinical relevance of this finding is doubtful, since mecillinam is not stable for most beta-lactamases. Many of the ESBL isolates were non-susceptible to quinolones (29/48) and trimethoprim-sulfamethoxazole (32/48), but remained susceptible to nitrofurantoin (46/48) and gentamicin (32/48). All ESBL isolates were clinically susceptible to carbapenems.

Molecular characterisation of thirty-seven isolates with phenotypical ESBL production revealed a predominance of CTX-M groups 1 (n=18) and 9 (n=14). A few isolates harboured CMY (n=2), DHA (n=1) or chromosomally encoded AmpC (n=2) enzymes. Three isolates were clinically non-susceptible to meropenem, but they were unfortunately not available for further analysis. Five additional isolates were clinically susceptible, but displayed meropenem zones below the screening breakpoint. They were all susceptible to piperacillin/tazobactam and thus ruled out as possible carbapenemase producers. Two of these isolates were ESBL positive.

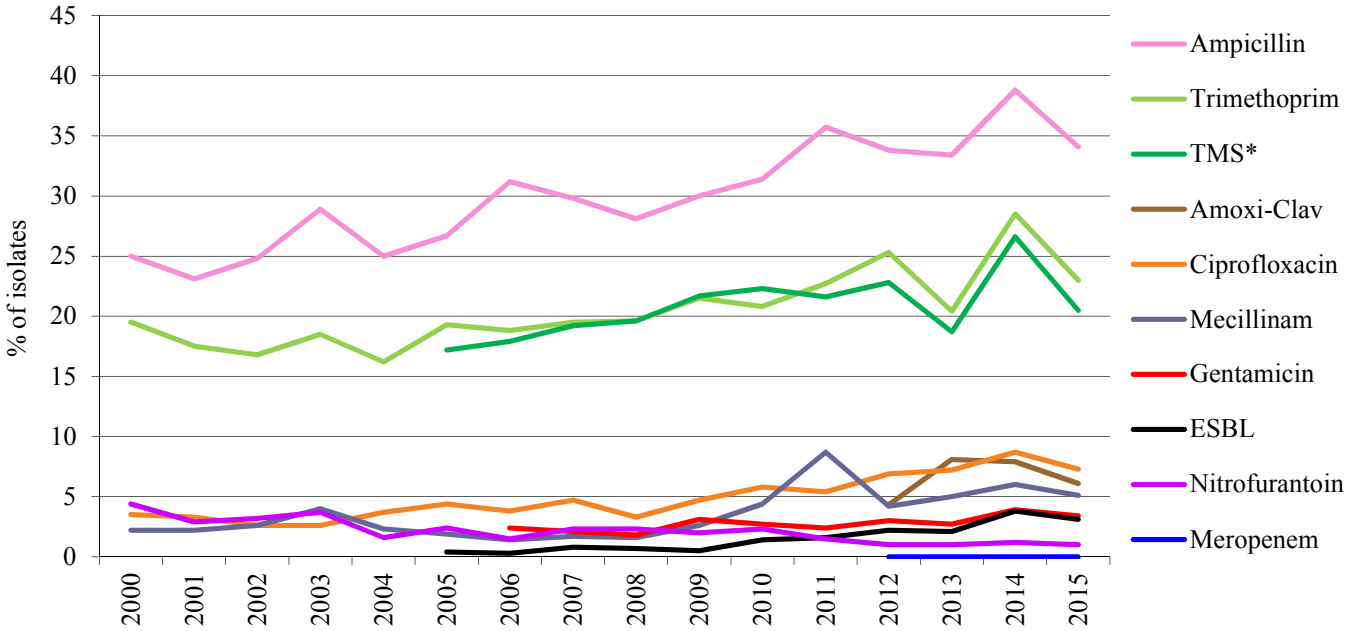


FIGURE 58. Prevalence of resistance to various antimicrobial agents in urinary tract *Escherichia coli* isolates 2000-2015 categorized according to the 2016 EUCAST guidelines. *TMS=Trimethoprim-sulfamethoxazole.

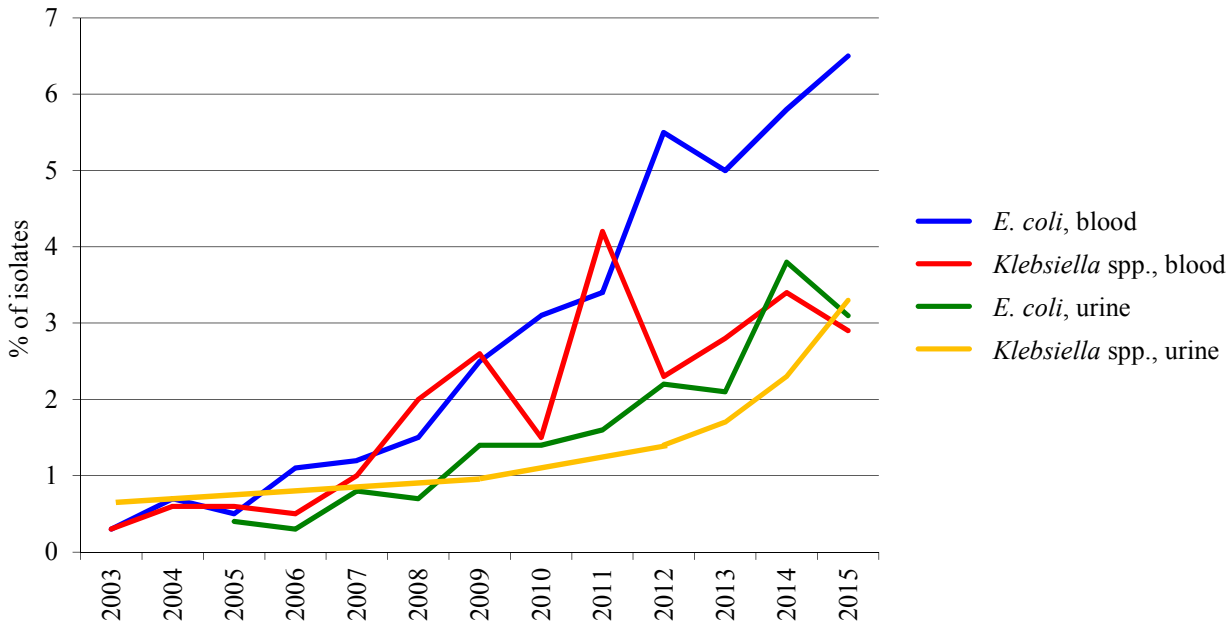


FIGURE 59. Prevalence of ESBL production among *Escherichia coli* and *Klebsiella* spp. isolates from blood and urine 2003-2015.

Klebsiella spp. in blood cultures

TABLE 28. *Klebsiella* spp. blood culture isolates in 2015 (n=823). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	90.1	6.6	3.3
Cefuroxime	≤ 8	> 8	91.7	-	8.3
Cefotaxime	≤ 1	> 2	96.9	0.2	2.9
Ceftazidime	≤ 1	> 4	95.5	1.2	3.3
Cefepime	≤ 1	> 4	96.8	1.0	2.2
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 4	97.2	0.1	2.7
Ciprofloxacin	≤ 0.5	> 1	95.3	1.2	3.5
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	89.6	0.7	9.7
ESBL	Negative	Positive	97.1	-	2.9

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

TABLE 29. *Klebsiella pneumoniae* blood culture isolates in 2015 (n=643). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	90.5	7.2	2.3
Cefuroxime	≤ 8	> 8	92.4	-	7.6
Cefotaxime	≤ 1	> 2	97.0	0.0	3.0
Ceftazidime	≤ 1	> 4	94.8	1.6	3.6
Cefepime	≤ 1	> 4	97.0	0.8	2.2
Meropenem	≤ 2	> 8	99.8	0.0	0.2
Gentamicin	≤ 2	> 4	96.8	0.2	3.0
Ciprofloxacin	≤ 0.5	> 1	94.6	1.2	4.2
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	88.2	0.9	10.9
ESBL	Negative	Positive	97.0	-	3.0

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

TABLE 30. *Klebsiella oxytoca* blood culture isolates in 2015 (n=169). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	89.9	3.0	7.1
Cefuroxime	≤ 8	> 8	90.5	-	9.5
Cefotaxime	≤ 1	> 2	97.0	1.2	1.8
Ceftazidime	≤ 1	> 4	98.8	0.0	1.2
Cefepime	≤ 1	> 4	97.0	1.8	1.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	98.8	0.0	1.2
Ciprofloxacin	≤ 0.5	> 1	98.2	1.2	0.6
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	95.3	0.0	4.7
ESBL	Negative	Positive	98.2	-	1.8

*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 643 *K. pneumoniae* (78.2%), 169 *K. oxytoca* (20.5%), and 11 (1.3%) isolates not identified to the species level, giving a total of 823 *Klebsiella* spp. isolates (Tables 28-30). As for *E. coli*, the breakpoint protocol of the Norwegian Working Group for Antibiotics (NWGA) has been in accordance with EUCAST since 2014.

The majority of *Klebsiella* spp. isolates remains susceptible to aminoglycosides. The prevalence of non-susceptibility increased from 1.0% in 2012 to 4.1% in 2014, but decreased to 2.8% in 2015. *K. oxytoca* isolates are more often susceptible to aminoglycosides (98.8%) than *K. pneumonia* isolates (96.8%). Aminoglycoside resistance in common *Enterobacteriaceae* species is a cause for great concern as these antimicrobials have traditionally been used in the empirical regimen for treatment of septiceamia in Norway.

The overall prevalence of resistance to ciprofloxacin has been stable at 3-4% when taking into account the changes in breakpoints and interpretive criteria. The 4.7% non-susceptibility (1.2% intermediate susceptibility and 3.5% resistance) observed in 2015 is a slight decrease from 5.9% in 2014. Non-susceptibility to ciprofloxacin is more common in *K. pneumoniae* (5.4%) than in *K. oxytoca* (1.8%). Non-susceptibility to trimethoprim-sulfamethoxazole remained stable at 10.4% in 2015 compared to 11.6% in 2014. As for ciprofloxacin, the prevalence of resistance to trimethoprim-sulfamethoxazole was significantly lower in *K. oxytoca* (4.7%) than in *K. pneumoniae* (10.9%).

A comparison of ESBL rates and non-susceptibility to beta-lactam antibiotics between *Klebsiella* species is complicated by the diagnostic challenges of the chromosomal K1 beta-lactamase in *K. oxytoca*. Most *Klebsiella* spp. isolates were susceptible to cefotaxime (96.9%), ceftazidime (95.5%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (90.1%), see Figure 60. The rates of non-susceptibility to third generation cephalosporins were at the same level as in previous years.

As for *E. coli*, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidime disks. Isolates with reduced zone diameters were further characterised by combination MIC gradient tests. The prevalence of phenotypically confirmed ESBL isolates decreased from 3.4% in 2014 to 2.9% in 2015 (Figure 59). The 24 ESBL isolates originated from 10 different laboratories and were identified as *K. pneumoniae* (n=19, 3.0%), *K. oxytoca* (n=3) or *Klebsiella* sp. (n=2). The ESBL isolates were generally non-susceptible to cefuroxime (24/24), ceftazidime (22/24) and cefotaxime (23/24), and co-resistance was frequently seen for ciprofloxacin (19/24), trimethoprim-sulfamethoxazole (19/24) and gentamicin (16/24). Many isolates were intermediately (11/24) or even fully (10/24) susceptible to piperacillin-tazobactam.

Molecular characterisation of 22 isolates with a phenotypic ESBL profile at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-Res) confirmed the predominance of CTX-M groups 1 (n=12) and 9 (n=1). One *K. oxytoca* isolate was a K1 hyperproducer, while a single meropenem resistant *K. pneumoniae* isolate contained both CMY and carbapenemase OXA-48.

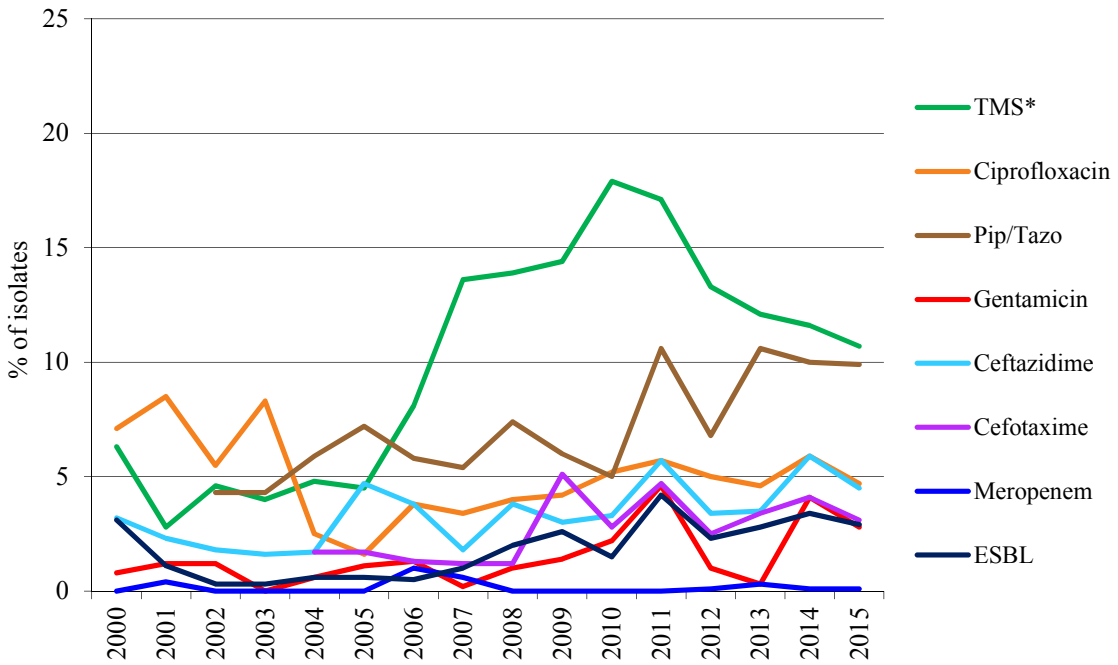


FIGURE 60. Prevalence of non-susceptibility to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2015. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 31. *Klebsiella* spp. urinary tract isolates in 2015 (n=995). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	89.0	-	11.0
Amoxicillin-clavulanic acid*	≤ 32	> 32	93.6	-	6.4
Piperacillin-tazobactam	≤ 8	> 16	89.7	6.3	4.0
Cefuroxime	≤ 8	> 8	91.6	-	8.4
Cefotaxime	≤ 1	> 2	96.3	0.4	3.3
Ceftazidime	≤ 1	> 4	94.1	2.3	3.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.2	0.5	2.3
Ciprofloxacin	≤ 0.5	> 1	94.3	2.2	3.5
Trimethoprim	≤ 2	> 4	79.9	1.7	18.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	84.8	1.7	13.5
ESBL	Negative	Positive	96.7	-	3.3

*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 2012-2014. Due to methodological changes and adjustment of breakpoints 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.

In general, the rates of resistance to urinary tract antibiotics were slightly lower in *Klebsiella* spp. than in *E. coli* isolates (Tables 31-33). The vast majority of isolates are still susceptible to gentamicin (97.2% compared to 98.8% in 2014), ciprofloxacin (94.3% compared to 95.3% in 2014), and meropenem (100.0%). The comparable rates for *E. coli* were 96.1% for gentamicin, 92.4% for ciprofloxacin and 99.9% for meropenem. Susceptibility to trimethoprim (79.9% compared to 81.1% in 2014) and trimethoprim-sulfamethoxazole (84.8% compared to 86.5% in 2014) was higher than in *E. coli* (76.9% and 78.3%, respectively).

All *Klebsiella* isolates are inherently resistant to ampicillin due to the chromosomal SHV beta-lactamase. Wild type

strains have since 2014 been categorised as susceptible to cefuroxime in accordance with the EUCAST protocol. As for *Klebsiella* spp. blood culture isolates, ESBL detection in urinary tract isolates was based on non-susceptibility to cefotaxime and/or ceftazidime and subsequent confirmatory ESBL MIC gradient tests. Thirty-three isolates were reported as ESBL positive of which 29 were *K. pneumonia*, three were *K. oxytoca* and one was unspeciated. The 33 ESBL isolates were retrieved from 15 different laboratories and originated from general practices (n=15), hospitals (n=11), outpatient clinics (n=2) and nursing homes (n=5). The 3.3% ESBL rate (3.8% in *K. pneumoniae*) represented a further increase from 2.3% in 2014, and was at the same level as the 2.9% rate (3.0% in *K. pneumoniae*) found in blood culture isolates. The 33 ESBL isolates were generally non-susceptible to trimethoprim (n=31), trimethoprim-sulfamethoxazole (n=31) and ciprofloxacin (n=26), but many remained susceptible to gentamicin (n=15), mecillinam (n=28) and piperacillin-tazobactam (n=13). Molecular characterisation of 28 isolates with an ESBL phenotype confirmed the presence of CTX-M group 1 (n=24), SHV-ESBL (n=3) and DHA (n=1). No isolates were reported as non-suscpetible to meropenem, and all zone diameters were above the screening breakpoint for carbapenemase production.

TABLE 32. *Klebsiella pneumoniae* urinary tract isolates in 2015 (n=757). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	90.4	-	9.6
Amoxicillin-clavulanic acid*	≤ 32	> 32	94.8	-	5.2
Piperacillin-tazobactam	≤ 8	> 16	89.9	7.1	3.0
Cefuroxime	≤ 8	> 8	91.8	-	8.2
Cefotaxime	≤ 1	> 2	96.2	0.0	3.8
Ceftazidime	≤ 1	> 4	93.6	2.2	4.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.9	0.3	2.8
Ciprofloxacin	≤ 0.5	> 1	93.4	2.2	4.4
Trimethoprim	≤ 2	> 4	77.3	1.8	20.9
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	82.5	2.0	15.5
ESBL	Negative	Positive	96.2	-	3.8

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

TABLE 33. *Klebsiella oxytoca* urinary tract isolates in 2015 (n=139). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	84.9	-	15.1
Amoxicillin-clavulanic acid*	≤ 32	> 32	89.9	-	10.1
Piperacillin-tazobactam	≤ 8	> 16	88.4	2.2	9.4
Cefuroxime	≤ 8	> 8	89.9	-	10.1
Cefotaxime	≤ 1	> 2	94.2	2.9	2.9
Ceftazidime	≤ 1	> 4	96.7	0.8	2.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.9	0.7	1.4
Ciprofloxacin	≤ 0.5	> 1	97.8	2.2	0.0
Trimethoprim	≤ 2	> 4	93.6	1.4	5.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.0	0.7	4.3
ESBL	Negative	Positive	97.8	-	2.2

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

Pseudomonas aeruginosa in blood cultures

TABLE 34. *Pseudomonas aeruginosa* blood culture isolates in 2015 (n=191). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 16	> 16	91.6	-	8.4
Ceftazidime	≤ 8	> 8	93.7	-	6.3
Aztreonam*	≤ 1	> 16	0.0	94.2	5.8
Imipenem	≤ 4	> 8	91.1	1.6	7.3
Meropenem	≤ 2	> 8	84.8	11.5	3.7
Gentamicin	≤ 4	> 4	99.0	-	1.0
Tobramycin	≤ 4	> 4	99.0	-	1.0
Amikacin	≤ 8	> 16	99.0	0.5	0.5
Ciprofloxacin	≤ 0.5	> 1	94.2	2.1	3.7

*The wild type is defined as intermediately susceptible indicating that the drug is moderately active at high dosage in systemic infections.

RESULTS AND COMMENTS

NORM has previously reported on *Pseudomonas aeruginosa* blood culture isolates in 2005 and 2010. These surveys were based on MIC determination, whereas the isolates from 2015 were examined by disk diffusion. However, the breakpoints have not changed in this period and the results are therefore comparable.

Most isolates were susceptible to all relevant anti-microbials, and very few displayed resistance to multiple classes as commonly seen in other countries. The rates of resistance have increased over the last decade for all beta-lactam antibiotics as seen in Figure 61. Of special concern is the relatively high prevalence of meropenem non-susceptibility (11.5% I and 3.7% R) as this substance is often the drug of choice in invasive pseudomonal infections. Many of these isolates were concomitantly non-susceptible to other beta-lactam antibiotics active against wild type *P. aeruginosa*. However, the rates of resistance to aminoglycosides are still very low (0.5-1.0%) and resistance to ciprofloxacin has remained stable at around 4%.

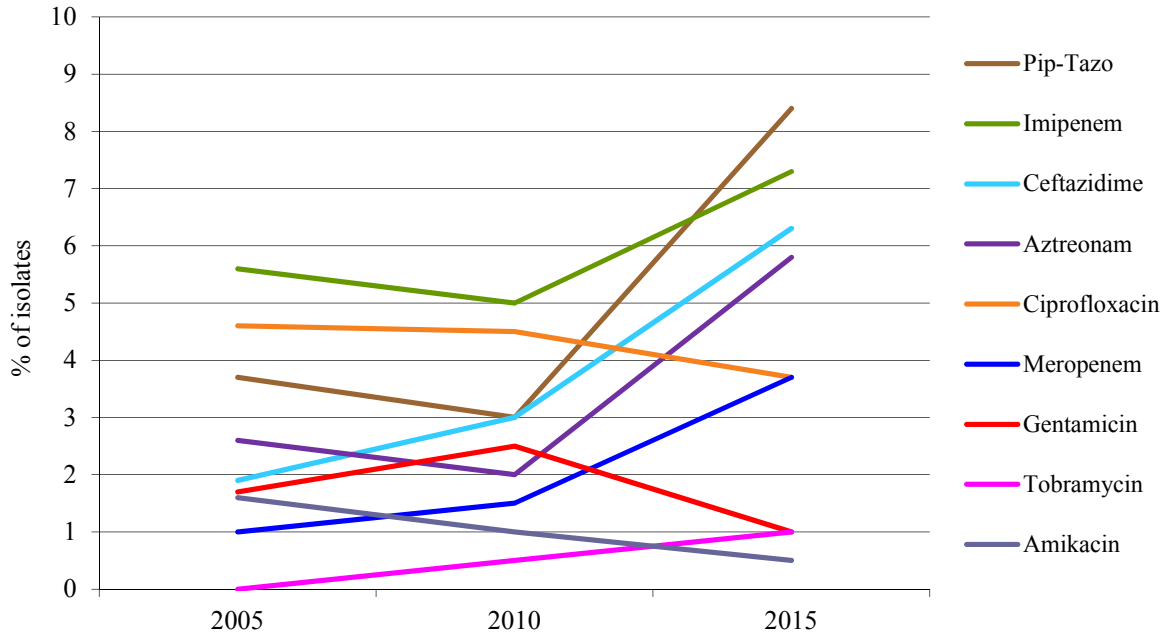


FIGURE 61. Prevalence of resistance to various antimicrobial agents in *Pseudomonas aeruginosa* blood culture isolates 2005-2015.

Update on the ESBL$_{CARBA}$ situation in Norway

ESBL$_{CARBA}$ enzymes are beta-lactamases that hydrolyse and confer resistance/reduced susceptibility to carbapenems. Depending on the substrate profile, resistance to other beta-lactams such as penicillins and cephalo-sporins are expected (1,2). The rapid global dissemination of ESBL$_{CARBA}$ genes among Gram-negative pathogens is a significant threat to patients and healthcare systems (3). ESBL$_{CARBA}$-producing isolates are frequently multi- or extreme-drug resistant. Thus, infections with ESBL$_{CARBA}$-producing Gram-negative bacteria are associated with high mortality rates due to limited treatment options (1,2).

ESBL$_{CARBA}$ enzymes can be divided into three main groups; ESBL$_{CARBA-A}$, ESBL$_{CARBA-B}$ and ESBL$_{CARBA-D}$, according to their amino acid sequence and structure (4). Although the global epidemiology shows a predominance of certain ESBL$_{CARBA}$ beta-lactamases like KPC (ESBL$_{CARBA-A}$), NDM and VIM (ESBL$_{CARBA-B}$) and OXA-48-like (ESBL$_{CARBA-D}$), an increasing number of ESBL$_{CARBA}$ enzymes/variants are continuously being discovered.

ESBL$_{CARBA}$-producing bacteria are notifiable to the Norwegian Surveillance System for Communicable Diseases (MSIS) after confirmation at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance (K-res). Here we summarise the findings of ESBL$_{CARBA}$-producing Gram-negative bacteria in 2015. Isolates from the same patient are included if they were of different species and/or harboured different ESBL$_{CARBA}$ beta-lactamases.

Thirty-seven ESBL$_{CARBA}$-producing *Enterobacteriaceae* from 30 patients were identified in 2015 (Figures 62-63). Compared to 2014, this is a 3-fold increase in the number of patients. Thirty-two percent of the isolates were from fecal/rectal samples. As in previous years, *K. pneumoniae* (n=20) and *E. coli* (n=11) were the dominant species (Figure 62). With respect to specific ESBL$_{CARBA}$ genes a clear trend was observed towards a predominance of *bla*$_{NDM}$ (n=17) and *bla*$_{OXA-48}$-like (n=16). Additionally, one isolate was found to harbour both *bla*$_{NDM}$ and *bla*$_{OXA-48}$-like. This trend reflects the situation elsewhere in Europe (5).

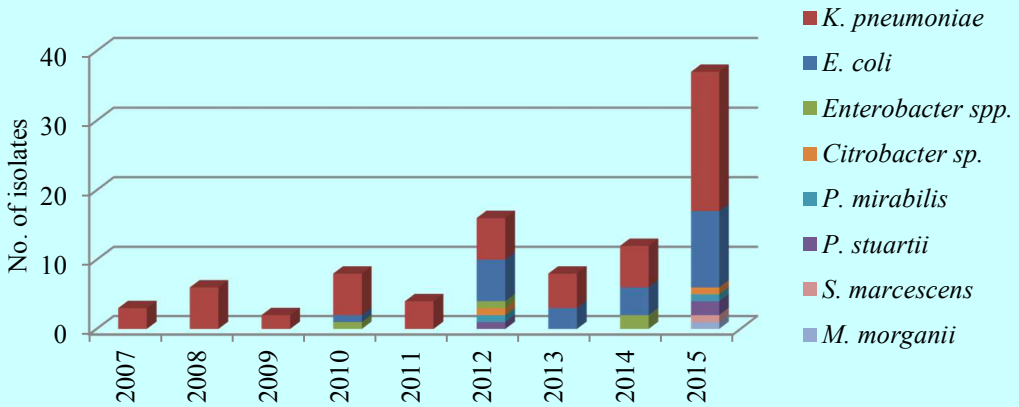


FIGURE 62. ESBL$_{CARBA}$-producing *Enterobacteriaceae* 2007-2015 by species.

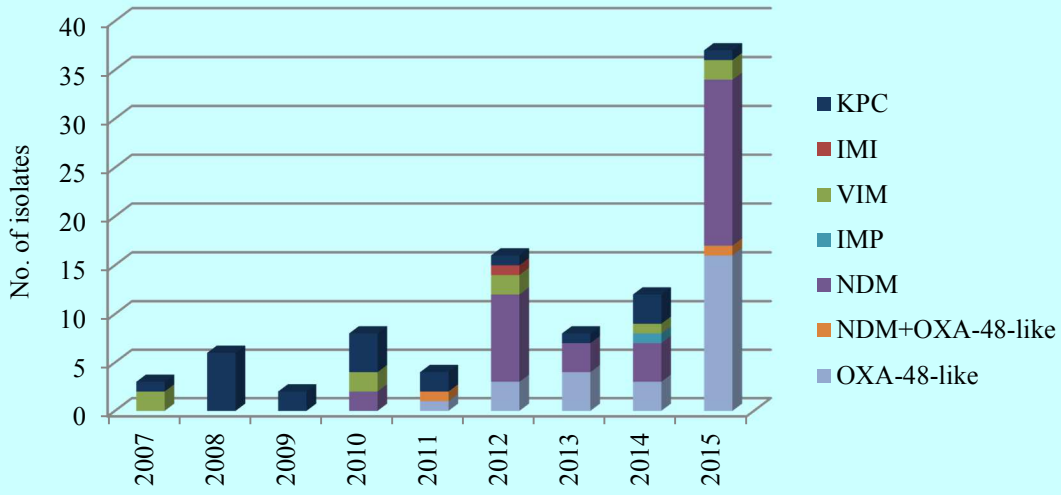


FIGURE 63. ESBL$_{CARBA}$-producing *Enterobacteriaceae* 2007-2015 by ESBL$_{CARBA}$ variant.

No significant change was observed with respect to ESBL$_{CARBA}$-producing *Pseudomonas* spp. and *A. baumannii* compared to 2014 (Figure 64). Fifteen and seven ESBL$_{CARBA}$-producing *A. baumannii* and *Pseudomonas* spp. isolates were identified in 2015, reseptively. As in previous years the dominant ESBL$_{CARBA}$ genes were *bla*$_{OXA-23}$-like among *A. baumannii* (*n*=14) and *bla*$_{VIM}$ among *Pseudomonas* spp. (*n*=6). Single isolates of *A. baumannii* with *bla*$_{OXA-24}$-like and *P. aeruginosa* with *bla*$_{NDM}$ were identified.

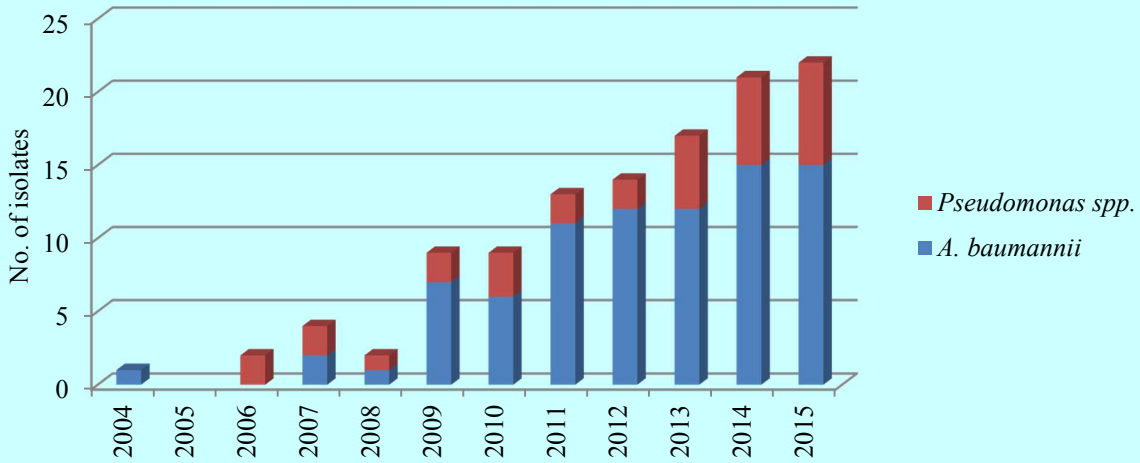


FIGURE 64. Identified ESBL$_{CARBA}$-producing *Pseudomonas* spp. and *A. baumannii* in Norway 2004-2015.

Multiple isolates of diverse species harbouring different ESBL$_{CARBA}$ genes were identified from four patients. For instance, *P. mirabilis* (*bla*$_{NDM}$), *P. stuartii* (*bla*$_{NDM}$), *E. coli* (*bla*$_{OXA-48}$-like), *K. pneumoniae* (*bla*$_{OXA-48}$-like), *M. morganii* (*bla*$_{OXA-48}$-like + *bla*$_{NDM}$) and *P. aeruginosa* (*bla*$_{VIM}$) were identified from one patient (6). This illustrates the promiscuous mobility of carbapenemase genes and challenges with respect to targeted screening. The majority (~73%) of cases were associated with import as in previous years.

Although the number of ESBL$_{CARBA}$-producing isolates in Norway is still low, the 3-fold increase in cases with ESBL$_{CARBA}$-producing *Enterobacteriaceae* is worrying. A similar trend has also been observed in Sweden where 115 patients were identified in 2015 compared to 46 patients in 2014 (7). A significantly higher proportion (71%) of ESBL$_{CARBA}$-producing *Enterobacteriaceae* in Sweden was identified in fecal/rectal samples compared to Norway. Continued surveillance, strict infection control measures as well as high clinical and diagnostic awareness is therefore important to limit the spread and establishment of ESBL$_{CARBA}$-producing Gram-negative bacteria in Norway.

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Haemophilus influenzae in blood cultures and cerebrospinal fluids

TABLE 35. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2015 (n=96). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 1	> 1	86.5	-	13.5
Amoxicillin-clavulanic acid	≤ 2	> 2	100.0	-	0.0
Cefuroxime	≤ 1	> 2	85.5	6.2	8.3
Cefotaxime	≤ 0.125	> 0.125	96.9	-	3.1
Ceftriaxone	≤ 0.125	> 0.125	97.9	-	2.1
Ciprofloxacin	≤ 0.5	> 0.5	99.0	-	1.0
Chloramphenicol	≤ 2	> 2	97.9	-	2.1
Tetracycline	≤ 1	> 2	97.9	0.0	2.1
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 1	85.4	3.1	11.5
Penicillin G (mm)	≥ 12	< 12	79.2	-	20.8
Cefaclor (mm)	≥ 23	< 23	79.2	-	20.8
Beta-lactamase	Negative	Positive	88.5	-	11.5

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

TABLE 36. *Haemophilus influenzae* in blood cultures and cerebrospinal fluids in 2015 (n=96). Distribution (%) of MICs (mg/L) and zone diameters for penicillin G and cefaclor (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Ampicillin						7.3	40.6	29.2	9.4	2.1	1.0		1.0	1.0		8.3
Amoxi-clav**							8.3	55.2	29.2	7.3						
Cefuroxime								17.7	67.7	6.3	2.1	4.2		1.0		1.0
Cefotaxime	1.0	7.3	21.9	46.9	13.5	6.3	1.0		2.1							
Ceftriaxone	33.3	43.8	15.6	4.2	1.0		1.0	1.0								
Ciprofloxacin	5.2	33.3	54.2	6.3										1.0		
Chloramph.								11.5	81.3	5.2	1.0		1.0			
Tetracycline						3.1	31.3	62.5	1.0		1.0		1.0			
TMS***		1.0	15.6	35.4	19.8	7.3	4.2	2.1	3.1	2.1	1.0			8.3		
	< 11	11	12	13	14	15	16	17	18	19	20	21	22	23	24	≥ 25
Penicillin G	19.8	1.0	3.1	6.3	21.9	9.4	7.3	6.3	8.3	6.3	6.3	3.1		1.0		
Cefaclor	9.4						1.0	1.0				2.1	7.3	8.3	10.4	60.4

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

RESULTS AND COMMENTS

Systemic *H. influenzae* isolates were first included in the NORM programme in 2013. Resistance data are provided by the Reference Laboratory at the Norwegian Institute of Public Health on a yearly basis.

In 2015, 96 *H. influenzae* isolates were recovered from blood cultures (n=92) or cerebrospinal fluids (n=4), all representing unique patients (Tables 35-36). Beta-lactamase production was detected in 11.5%, which is at the same level as 13.0% in 2014. A total of 13/96 isolates were resistant to ampicillin, and beta-lactamase production was detected in eleven of them. Two of these isolates were concomitantly non-susceptible to cefuroxime, thus indicating a combination of beta-lactamase production and chromosomal resistance mechanisms. The two beta-lactamase negative, ampicillin resistant strains were both cefuroxime resistant suggesting a chromosomal basis for beta-lactam resistance. They were not resistant to amoxicillin-clavulanic acid.

Cefuroxime MIC > 2 mg/L has been suggested as the most precise indicator for alterations in the wild type PBP3 sequence. Eight isolates (8.3%) displayed this phenotype compared to 13.0% in 2014 and 19.0% in 2013. Some of these isolates remained susceptible to ampicillin (4/8) and amoxicillin-clavulanic acid (8/8). Three isolates from blood culture (n=2) and cerebrospinal fluid (n=1) were resistant to cefotaxime (n=3) and ceftriaxone (n=2). One isolate was resistant to cefotaxime (MIC 0.25 mg/L) and cefuroxime, but remained susceptible to ampicillin and ceftriaxone (MIC 0.064 mg/L) and was beta-lactamase negative. Two isolates were concomitantly resistant to cefotaxime (MIC 1 mg/L) and ceftriaxone (MIC 0.25-0.5 mg/L). One was beta-

lactamase positive and cefuroxime resistant, whereas the other was beta-lactamase negative and cefuroxime susceptible.

Different substrates have been suggested for screening of beta-lactam resistance in *H. influenzae*. The penicillin G 1U disk (PCG1) successfully identified all ampicillin and cefuroxime resistant strains. Nine out of 85 (10.6%) beta-lactamase negative isolates were resistant to PCG1; two of these were resistant to ampicillin and seven were non-susceptible to cefuroxime. The breakpoint for the cefaclor disk test is calibrated for beta-lactamase positive isolates; cefaclor correctly identified two cefuroxime non-susceptible isolates in addition to four isolates where cefuroxime resistance was not verified. The results illustrate the continuing challenges in defining the optimal algorithm for beta-lactam susceptibility testing in *H. influenzae*.

As previously seen in respiratory tract isolates, resistance to ciprofloxacin (1.0%), chloramphenicol (2.1%) and tetracycline (2.1%) was at a very low level. The 11.5% resistance to trimethoprim-sulfamethoxazole was at the same level as 10.1% in systemic isolates in 2014.

Neisseria meningitidis in blood cultures and cerebrospinal fluids

TABLE 37. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2015 (n=10). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.064	> 0.25	20.0	70.0	10.0
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Ciprofloxacin	≤ 0.032	> 0.032	100.0	-	0.0
Chloramphenicol	≤ 2	> 4	100.0	0.0	0.0
Rifampicin	≤ 0.25	> 0.25	100.0	-	0.0

TABLE 38. *Neisseria meningitidis* in blood cultures and cerebrospinal fluids in 2015 (n=10). Distribution (n) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G				2	3	3	1	1								
Ceftriaxone	10															
Ciprofloxacin	5	5														
Chloramph.							1	1	8							
Rifampicin	5	5														
Azithromycin						1	3	2	2	2						
Tetracycline							4	2	4							
Sulfonamide									4						1	5

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

RESULTS AND COMMENTS

N. meningitidis from blood cultures and cerebrospinal fluids were first included in NORM in 2013. As for systemic *H. influenzae* isolates, the Reference Laboratory at the Norwegian Institute of Public Health now provides data on *N. meningitidis* on a yearly basis. The results are presented in Tables 37-38.

A total of 10 isolates were recovered from cerebrospinal fluids (n=2) and blood cultures (n=8). All isolates were from unique patients. The isolates belonged to serogroups B (n=3), C (n=1) and Y (n=6). The serotype Y isolates all belonged to sequence type (ST) 23 (n=5) or the closely related ST2692, but there were no known associations between the cases. Seven isolates displayed penicillin G MICs of 0.125-0.25 mg/L and were thus intermediately susceptible, whereas a single isolate was resistant with an MIC of 0.5 mg/L. The genetic basis for non-susceptibility was not determined, but was most likely caused by alterations in the penicillin-binding protein 2 (PBP2) encoded by *penA*. Sulfonamide resistance has been widespread in *N. meningitidis* since the 1960ies. EUCAST has not defined clinical breakpoints for this agent, but the MIC distributions clearly demonstrate a high prevalence of acquired resistance among Norwegian isolates.

Neisseria gonorrhoeae

TABLE 39. *Neisseria gonorrhoeae* from all specimen types in 2015 (n=259). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.064	> 1	3.1	62.9	34.0
Ceftriaxone	≤ 0.125	> 0.125	100.0	-	0.0
Cefixime	≤ 0.125	> 0.125	98.8	-	1.2
Azithromycin	≤ 0.25	> 0.5	66.4	27.0	6.6
Ciprofloxacin	≤ 0.032	> 0.064	37.8	0.0	62.2
Tetracycline	≤ 0.5	> 1	33.6	13.9	52.5
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Beta-lactamase	Negative	Positive	71.8	-	28.2

TABLE 40. *Neisseria gonorrhoeae* from all specimen types in 2015 (n=259). 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**	0.8	0.4	0.4	1.5	3.1	14.3	21.6	12.4	11.6	9.3	6.9	2.3	1.5	13.9		
Ceftriaxone	25.5	30.1	13.1	16.2	12.7	2.3										
Cefixime			64.5	18.9	10.0	5.4	1.2									
Azithromycin			0.8	1.9	8.5	19.3	35.9	27.0	4.2	1.2			0.4			0.8
Ciprofloxacin	10.0	22.8	3.5	1.5		0.4	0.8	1.2	3.1	9.7	15.4	9.3	1.9	20.5		
Tetracycline					0.8	3.9	7.7	21.2	13.9	15.8	1.5	5.0	13.1	11.2	2.7	3.1
Spectinomycin									0.4		3.1	38.2	51.0	7.3		

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

RESULTS AND COMMENTS

Neisseria gonorrhoeae was surveyed in NORM in 2003 and 2010. Since 2013, Oslo University Hospital has provided resistance data for Norwegian *N. gonorrhoeae* isolates on a yearly basis. All isolates from all specimen types were included in the survey, but only a single isolate was accepted from each patient. The microbiological data could not be linked to information from the Norwegian Surveillance System for Communicable Diseases (MSIS).

In 2015, a total of 259 isolates were available for analysis. The isolates were reported to originate from urethra (n=175), cervix uteri (n=32), anus (n=27), throat (n=10), eye (n=1) or "uknown/others" (n=14). A total of 220 isolates (84.9%) originated from men, 38 (14.7%) from women and one isolate (0.4%) was not specified to 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 within the NORM protocol.

The results from susceptibility testing are presented in Tables 39-40. A majority of the isolates were intermediately susceptible (49.4% in 2014, 62.9% in 2015) or resistant (46.7% in 2014, 34.0% in 2015) to penicillin G. Seventy-three isolates (28.2%) produced beta-lactamase and were phenotypically resistant to penicillin G. This is a slight decrease from 32.4% in 2013 and 30.6% in 2014. Most beta-lactamase positive isolates (69/73, 94.5%) were also non-susceptible to ciprofloxacin. In addition, 19 isolates were resistant and 159 were intermediately susceptible to penicillin G in spite of being beta-lactamase negative. This may be caused by alterations in penicillin binding proteins (PBPs) and/or reduced permeability through the outer cell membrane.

No isolates were categorised as resistant to ceftriaxone. Ceftriaxone resistant isolates from Norway have previously been linked to treatment failure. Three (1.2%) isolates were resistant to the oral cephalosporin cefixime, which is no longer recommended for empirical treatment in Norway. The results confirm the emergence of cephalosporin resistant gonococci in Norway, which is of course extremely alarming from both a clinical and a public health perspective. The current European treatment guidelines consist of a combination of ceftriaxone and azithromycin. It should be noted that 33.6% of the isolates were categorised as non-susceptibilible to azithromycin including one of the three cefixime resistant isolates.

Ciprofloxacin was previously used for empirical treatment of gonorrhoeae acquired outside South-East Asia. The prevalence of ciprofloxacin resistance persisted at a high level (62.2% in 2014). Ciprofloxacin is consequently not a viable alternative except in cases where susceptibility has been documented. All strains were susceptible to the aminoglycoside spectinomycin.

Staphylococcus aureus in blood cultures

TABLE 41. *Staphylococcus aureus* blood culture isolates in 2015 (n=1,277). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	94.5	0.1	5.4
Clindamycin	≤ 0.25	> 0.5	98.0	0.4	1.6
Fusidic acid	≤ 1	> 1	95.2	-	4.8
Ciprofloxacin	≤ 1	> 1	97.7	-	2.3
Gentamicin	≤ 1	> 1	99.8	-	0.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.064	> 0.5	99.2	0.5	0.3
Tetracycline	≤ 1	> 2	96.3	0.2	3.5
Tigecycline	≤ 0.5	> 0.5	99.8	0.0	0.2
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.5	0.2	0.3
Beta-lactamase	Negative	Positive	27.0	-	73.0
Cefoxitin screen	Negative	Positive	99.3	-	0.7
MRSA (*mecA*)	Negative	Positive	99.3	-	0.7

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

RESULTS AND COMMENTS

Nine methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2015, corresponding to a prevalence of 0.7% (Table 41). This is at the same level as in 2013 (0.3%) and 2014 (0.8%). The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from five different hospitals.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. All MRSA isolates had cefoxitin zone diameters below the screening breakpoint. Some MRSA isolates were concomitantly resistant to erythromycin (3/9), clindamycin (1/9), tetracycline (3/9) and/or ciprofloxacin (5/9). All MRSA isolates were susceptible to gentamicin, trimethoprim-sulfamethoxazole, linezolid, rifampicin, tigecycline and fucidic acid. The results from susceptibility testing of all Norwegian MRSA isolates are presented in Table 44 on page 93. No methicillin susceptible *S. aureus* (MSSA) isolates were reported to have cefoxitin zone diameters below the screening breakpoint.

The NORM findings are a bit lower than the reports from the databases of the participating laboratories where 18 out of 1,778 (1.0%) *S. aureus* blood culture isolates were MRSA. One of the 23 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 19/1,801 (1.1%).

Seventy *S. aureus* isolates (5.5%) were non-susceptible to erythromycin. This is a slight increase from 4.1% in 2013 and 4.2% in 2014. The macrolide resistance phenotypes of 69 isolates were determined by the double disk diffusion (DDD) test. Fourteen isolates (20.2%) were constitutively MLS_B resistant, 43 (62.4%) were inducibly MLS_B resistant and 12 (17.4%) displayed efflux mediated M type resistance. These figures represent 1.1%, 3.4% and 1.0% of all *S. aureus* isolates from blood cultures, respectively. The distribution of MLS phenotypes was essentially unchanged from 2014 to 2015.

The prevalence of resistance to fusidic acid at 4.8% was comparable to 4.8 % in 2013 and 4.4% in 2014. The 2.3% prevalence of ciprofloxacin resistance was at the same level as 2.9% in 2013 and 2.8% in 2014. There were no significant changes for gentamicin, rifampicin, tigecycline or trimethoprim-sulfamethoxazole. All isolates were susceptible to linezolid. The general test panel for *S. aureus* did not include vancomycin in 2015.

Figure 65 shows the prevalence of non-susceptibility to various antimicrobials. A total of 73.0% of the isolates were beta-lactamase positive which is unchanged from previous years. Beta-lactamase positive isolates were more likely to be resistant to erythromycin (6.2%), tetracycline (4.3%) and rifampicin (0.9%) compared to beta-lactamase negative isolates (3.2%, 1.4% and 0.1%, respectively). For the other antimicrobials there were only minor differences.

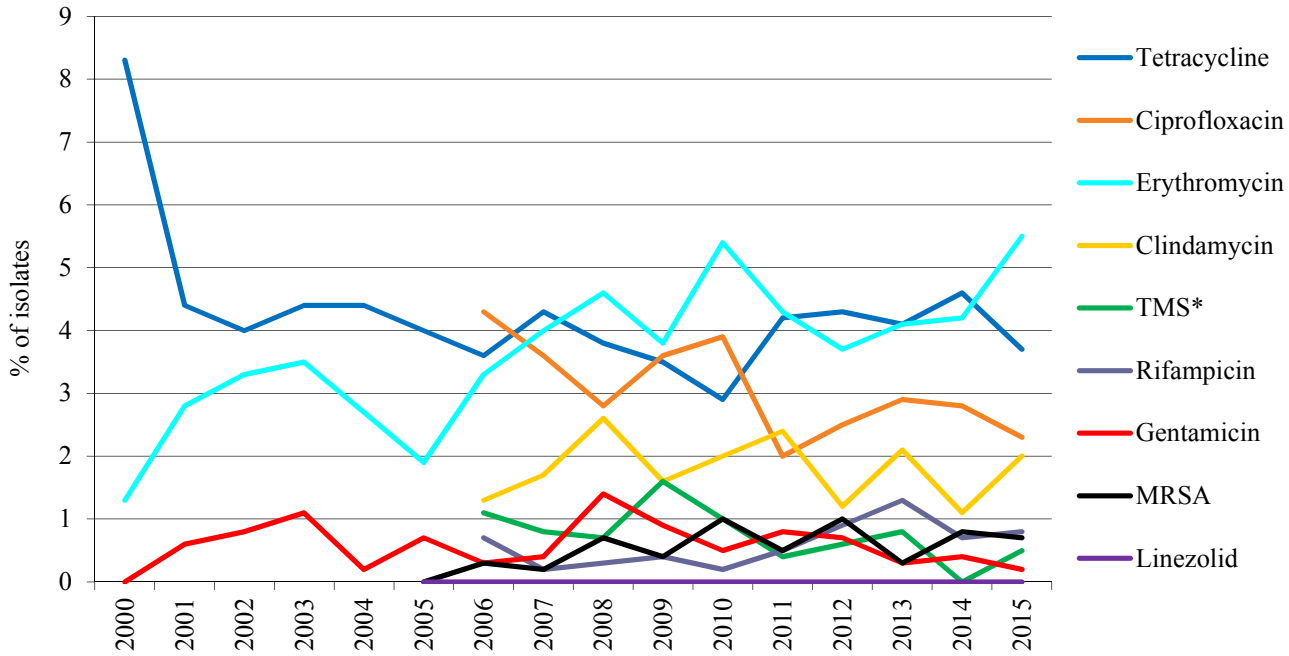


FIGURE 65. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* blood culture isolates 2000-2015. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 42. *Staphylococcus aureus* isolates from wound specimens in 2015 (n=1,125). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	95.0	0.4	4.6
Clindamycin	≤ 0.25	> 0.5	97.4	0.4	2.2
Fusidic acid	≤ 1	> 1	93.2	-	6.8
Ciprofloxacin	≤ 1	> 1	98.5	-	1.5
Gentamicin	≤ 1	> 1	99.8	-	0.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.064	> 0.5	99.6	0.3	0.1
Tetracycline	≤ 1	> 2	95.3	0.2	4.5
Tigecycline	≤ 0.5	> 0.5	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.8	0.2	0.0
Beta-lactamase	Negative	Positive	23.8	-	76.2
Cefoxitin screen	Negative	Positive	98.8	-	1.2
MRSA (*mecA*)	Negative	Positive	98.8	-	1.2

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

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Fourteen out of 1,125 (1.2%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was at the same level as in 2013 (1.2%) and 2014 (1.3%). The MRSA isolates originated from patients admitted to hospitals (n=4), outpatient clinics (n=4), general practitioners (n=5) and a nursing home (n=1) in different parts of the country. Nine MRSA isolates were only resistant to beta-lactam antibiotics. The remaining five isolates displayed reduced susceptibility or co-resistance to tetracycline (n=4), fusidic acid (n=3), erythromycin (n=1) and clindamycin in different combinations. All MRSA isolates were fully susceptible to ciprofloxacin, gentamicin, trimethoprim-sulfamethoxazole, rifampicin, tigecycline and linezolid. No isolates were reported with zone diameters below the cefoxitin screening breakpoint without being confirmed as MRSA by *mecA* PCR. This indicates high specificity of the cefoxitin screen as well as a low prevalence of *mecC* MRSA (see page 93).

The prevalence of resistance to fusidic acid in *S. aureus* wound isolates was slightly reduced at 6.8% compared to 9.0% in 2013 and 8.6% in 2014 (Table 42 and Figure 66). This confirms that the gradually declining prevalence of fusidic acid resistance has now levelled off after the epidemic which peaked at 25.0% in 2004. The prevalence of resistance to fusidic acid is still significantly lower in blood culture isolates (4.8%).

For other antimicrobial agents such as trimethoprim-sulfamethoxazole, gentamicin, rifampicin, and tetracycline there were only minor changes from 2014 to 2015, and the prevalence of non-susceptibility was in general similar for blood culture isolates and isolates from wound specimens. All isolates were susceptible to linezolid.

A total of 56 (5.0%) isolates were non-susceptible to erythromycin which is at the same level as 5.8% in 2014. Fifty-five isolates were further examined for determination of resistance phenotype. The majority were inducibly (23/55, 42% of macrolide resistant isolates) or constitutively (13/55, 24% of macrolide 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 (19/55, 34% of macrolide resistant isolates) compatible with efflux mediated M type resistance. The findings are in accordance with the results from previous years.

A total of 76.2% of the isolates were beta-lactamase positive compared to 76.4% in 2014. Beta-lactamase positive isolates were more likely to be resistant to erythromycin (5.3%), tetracycline (5.0%) and fusidic acid (7.8%) compared to beta-lactamase negative isolates (2.6%, 3.0% and 3.4%, respectively). For the other antimicrobials there were only minor differences.

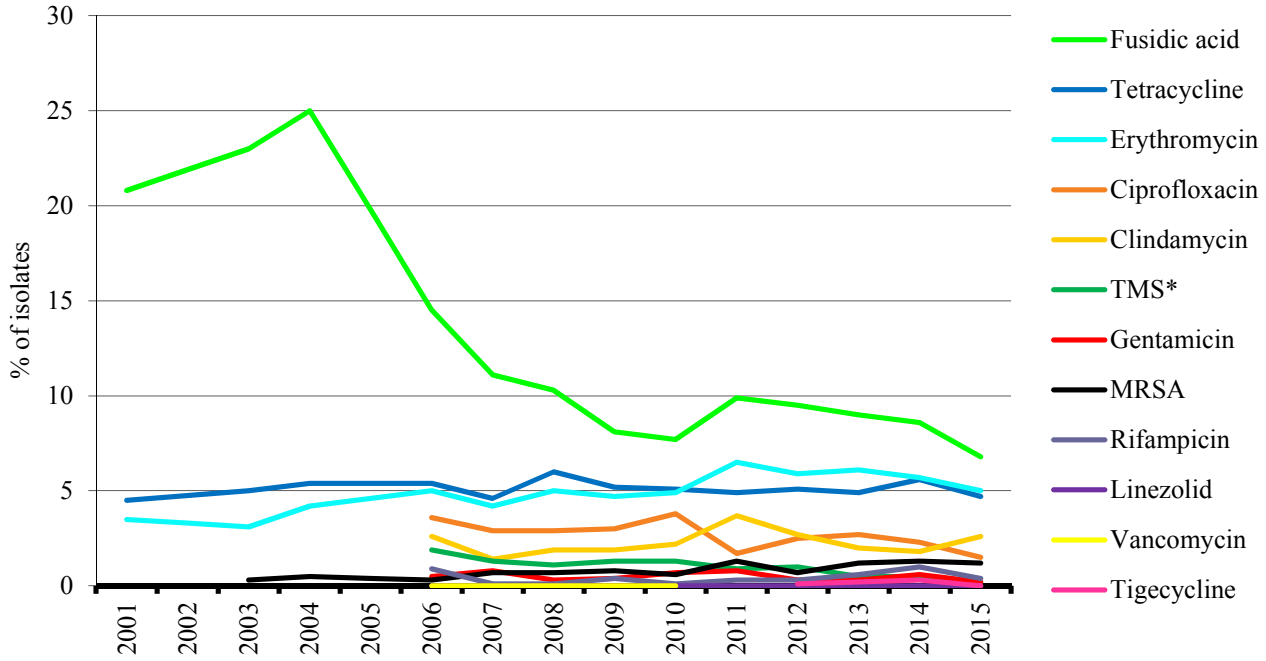


FIGURE 66. Prevalence of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* wound isolates 2001-2015. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

Methicillin resistant *Staphylococcus aureus* (MRSA) infections in Norway 2015

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been notifiable in Norway since 1995 and colonisation since 2005. In all, 2,233 cases of MRSA were reported in 2015 (43 per 100,000 person-years). Of these, 785 (35%) cases were infections while 1,448 were colonised (Figure 67).

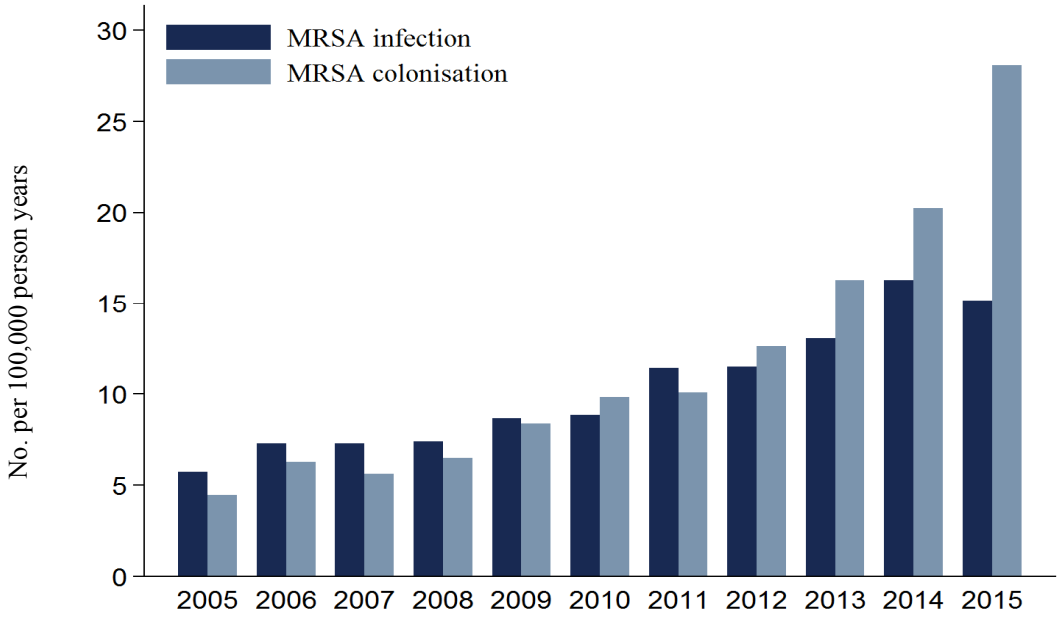


FIGURE 67. Number of MRSA cases per 100,000 person-years in Norway 2005-2015, by infection and colonisation.

Although the notification rate of MRSA increased by 20% from 2014 to 2015, for the first time we saw a decrease in the number of infections. In 2015, 785 cases of MRSA infection were reported, compared to 833 cases in 2014. Accordingly, the increase last year is seen among notified cases of MRSA colonisation. There was a clear increase in notifications during the last three months of the year. This coincided with a greater influx of migrants from areas with higher prevalence of resistant microbes, and the increase may reflect higher testing activity. Again, it is worth noticing that also during this period the incidence of infections did not increase, only colonisation.

The main objective of the Norwegian MRSA infection control measures is to prevent MRSA from becoming endemic in healthcare institutions. 451 (20%) of persons notified with MRSA in 2015 were inpatients at the time of diagnosis, while 76 (3.4 %) were residents in nursing homes and 1,644 (73.6%) were diagnosed in the community. For 64 persons we lack information. However, these numbers only reflect where the MRSA infection/colonisation was diagnosed, not where it was acquired. Eighty-one of the reported MRSA cases in 2015 were found in healthcare workers. We have seen a significant increase in healthcare associated cases the last two years, but the absolute numbers in this group remain small, making changes from one year to another difficult to interpret (Figure 68).

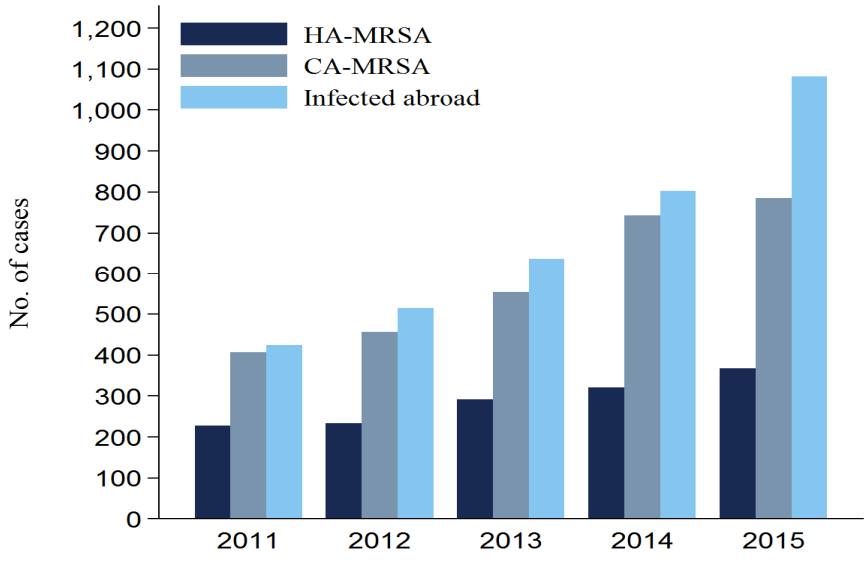


FIGURE 68. Reported cases of MRSA infections and colonisations in Norway 2011-2015, by healthcare associated (HA), community associated (CA) and imported cases.

Livestock associated MRSA (LA-MRSA) was first reported in Norwegian pig herds in 2013. The livestock associated MRSA outbreak within Norwegian pig farms which ran from 2013-2014 is now under control and is not thought to be spreading further. Of all the notifications of LA-MRSA, in the period from 2011 up to and including 2015, 32 (29%) were reported as clinical infections (Table 43).

TABLE 43. Proportion of LA-MRSA among total MRSA.

Year	No of LA MRSA cases (%)	Total number of MRSA cases
2011	2 (0.2%)	1,060
2012	5 (0.4%)	1,206
2013	46 (3.1%)	1,483
2014	25 (1.3%)	1,869
2015	34 (1.5%)	2,235

The Reference Laboratory for MRSA, St. Olav University Hospital, Trondheim, received 2,220 MRSA isolates from different patients in 2015. 349 different *spa*-types were identified and the six most frequent were (*spa*-type, n (%)): t002, n=237 (10.7%), t223, n=167 (7.5%), t019, n=148 (6.7%), t008, n=138 (6.2%), t127, n=113 (5.1%) and t304, n=97 (4.4%). 173 *spa*-types were reported as single events. Based on *spa*-type, all isolates were characterised in MLST clonal complex. 1,601 isolates (72.1%) occurred in the six most prevalent clusters (CC, n (%)): CC5, n=399 (17.8%), CC22, n=339 (15.3%), CC8, n=252 (11.4%), CC30, n=247 (11.1%), CC1, n=220 (9.9%), and CC88, n=144 (6.5%).
The Reference Laboratory found 34 LA-MRSA (CC398) in humans (*spa* t034 (n=32), t899 (n=1) and t8588 (n=1)). *spa* t034 was the tenth most common *spa*-type in Norway in 2015. Three isolates were found positive for *mecC* (*spa*-type t6292, t10765 and t843).

Susceptibility testing was performed on 2,202 MRSA isolates collected in 2015 with the EUCAST 2015 disk diffusion method and analysed with breakpoints from NordicAST 2015. 708 strains (32.2%) were sensitive to all antibiotics tested except beta-lactams. The highest proportions of resistance were found for erythromycin (29.3%), followed by tetracycline (24.6%) and norfloxacin (21.3%). 20.3% of the strains were resistant to clindamycin, of which 64.5% were inducibly resistant by D-test. The lowest rates of resistance were found towards rifampicin (0.6%) and mupirocin (0.9%) and trimethoprim-sulfamethoxazole (1.6%). No strains were resistant to linezolid.

TABLE 44. Susceptibility characterisation of methicillin resistant *Staphylococcus aureus* (MRSA) from 2015 (n=2,202). Standard disk diffusion method ad modum EUCAST 2015. Breakpoints from NordicAST 2015.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	70.5	0.2	29.3
Clindamycin	≤ 0.25	> 0.5	77.9	1.8	20.3
Fusidic acid	≤ 1	> 1	87.7	-	12.3
Norfloxacin	≤ 4	> 4	78.7	-	21.3
Gentamicin	≤ 1	> 1	89.7	-	10.3
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.064	> 0.5	98.7	0.7	0.6
Tetracycline	≤ 1	> 2	75.2	0.2	24.6
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	94.8	3.6	1.6
Mupirocin	≤ 1	> 256	80.4	18.7	0.9

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

Enterococcus spp. in blood cultures

TABLE 45. *Enterococcus* spp. blood culture isolates in 2015 (n=600). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	75.0	0.2	24.8
Imipenem	≤ 4	> 8	74.2	0.5	25.3
Gentamicin*	≤ 128	> 128	-	80.2	19.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.5	99.8	0.2	0.0
Vancomycin (any genotype)	≤ 4	> 4	97.8	-	2.2
Vancomycin (Van A or VanB)	Negative	Positive	99.8	-	0.2

*The wild type is defined as intermediately susceptible.

TABLE 46. *Enterococcus faecalis* blood culture isolates in 2015 (n=383). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Imipenem	≤ 4	> 8	99.7	0.3	0.0
Gentamicin*	≤ 128	> 128	-	86.9	13.1
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.5	100.0	0.0	0.0
Vancomycin (VanA or VanB)	Negative	Positive	100.0	-	0.0

*The wild type is defined as intermediately susceptible.

TABLE 47. *Enterococcus faecium* blood culture isolates in 2015 (n=175). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	14.9	0.6	84.5
Imipenem	≤ 4	> 8	13.7	0.0	86.3
Gentamicin*	≤ 128	> 128	-	60.6	39.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Tigecycline	≤ 0.25	> 0.5	100.0	0.0	0.0
Vancomycin (VanA or VanB)	Negative	Positive	99.4	-	0.6

*The wild type is defined as intermediately susceptible.

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a genus and separately for *E. faecalis* and *E. faecium*. The results for each species are microbiologically more valid as resistance rates differ significantly between *E. faecalis* and *E. faecium*. However, overall rates of resistance are of interest when formulating empirical treatment strategies because they include the probability of systemic infections with each enterococcal species. The overall results for enterococci are presented in Table 45. The surveillance in NORM 2015 included 383 (63.8%) *E. faecalis* isolates (67.2% in 2014), 175 (29.2%) *E. faecium* isolates (28.7% in 2014) and 42 (7.0%) unspeciated enterococcal isolates (4.1% in 2014). 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 2.2 in 2015 which is comparable to previous years. The number of isolates not speciated to the genus level or identified as *E. faecalis* or *E. faecium* has generally decreased over the last five years. The panel of antimicrobial agents examined and the breakpoints for interpretation remained unchanged from 2014 to 2015.

E. faecalis was universally susceptible to ampicillin (Table 46). The prevalence of resistance to ampicillin in *E. faecium* remained unchanged at 84.5% (Table 47). As expected, the results for imipenem closely mirrored those for ampicillin.

The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 13.1%, which is a decrease from 23.6% in 2013 and 18.7% in 2014 (Figure 69). The prevalence of HLGR in *E. faecium* also decreased slightly from 40.8% in 2014 to 39.4%, the lowest level recorded in a decade. All 69 HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin. Conversely, 69 of 149 (46.3%) ampicillin non-susceptible *E. faecium* also displayed HLGR. These findings are similar to the results from previous years. The strong linkage between ampicillin resistance and HLGR may indicate the continuing presence of the internationally disseminated *E. faecium* clonal complex (CC) 17 which is non-susceptible to ampicillin and often harbours high-level resistance to aminoglycosides and vancomycin. The wide dissemination of high-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and beta-lactams often used for treatment of severe enterococcal infections.

Transferable vancomycin resistance has not yet been endemically established in clinical enterococcal isolates in Norway, but recent outbreaks have occurred in different parts of the country. Twelve blood culture isolates were reported as vancomycin resistant in NORM 2015 (2.2%), but only a single *E. faecium* VanB isolate contained transferable glycopeptide resistance confirmed by positive PCR. The remaining eleven vancomycin resistant isolates were registered as *E. gallinarum* (n=7) and *E. casseliflavus* (n=4), which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All enterococcal isolates in NORM 2015 were fully susceptible to linezolid as opposed to previous years when several resistant isolates have been detected.

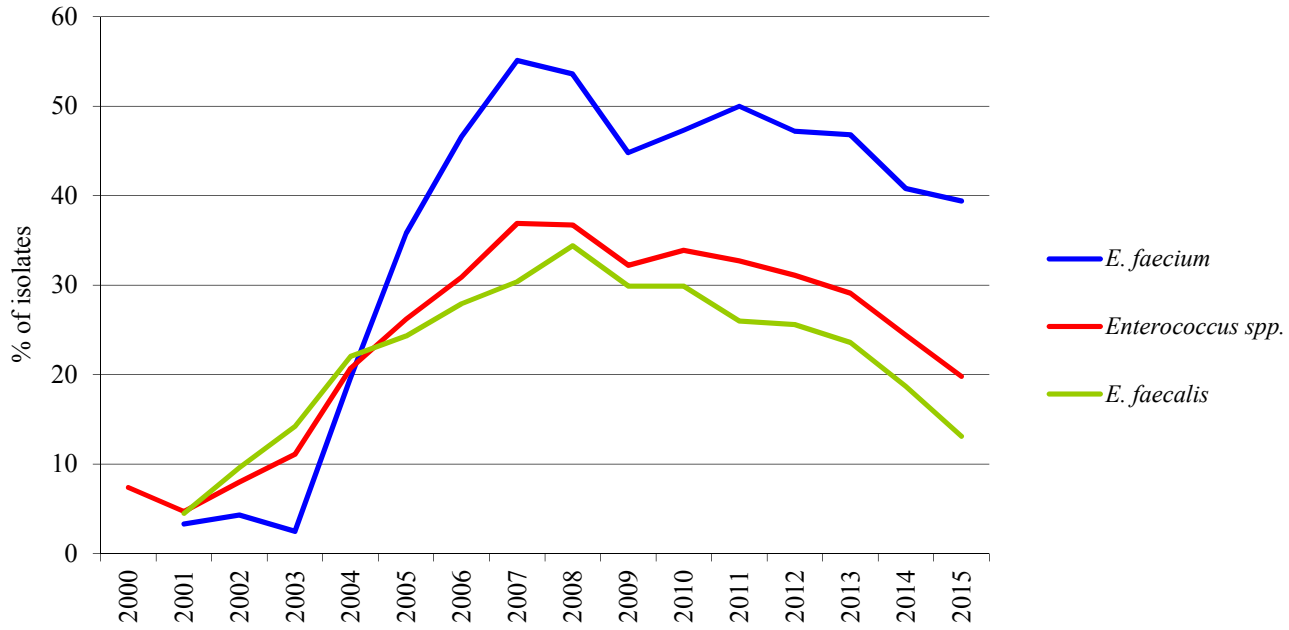


FIGURE 69. Prevalence of high-level resistance to gentamicin in blood culture isolates of *Enterococcus faecalis*, *E. faecium* and all enterococci combined during 2000-2015. The breakpoint for high-level resistance was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Enterococcus spp. in urine

TABLE 48. *Enterococcus* spp. urine isolates in 2015 (n=1,260). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	94.4	0.2	5.4
Gentamicin*	≤ 128	> 128	-	84.2	15.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Trimethoprim*	≤ 0.032	> 1	0.0	79.0	21.0
Trimethoprim-sulfamethoxazole*/**	≤ 0.032	> 1	0.0	85.0	15.0
Vancomycin (any genotype)	≤ 4	> 4	100.0	-	0.0
Vancomycin (Van A or VanB)	Negative	Positive	100.0	-	0.0

*The wild type is defined as intermediately susceptible. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 49. *Enterococcus faecalis* urine isolates in 2015 (n=1,176). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Gentamicin*	≤ 128	> 128	-	86.0	14.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Nitrofurantoin	≤ 64	> 64	99.6	-	0.4
Trimethoprim*	≤ 0.032	> 1	0.0	82.8	17.2
Trimethoprim-sulfamethoxazole*/**	≤ 0.032	> 1	0.0	89.1	10.9
Vancomycin (any genotype)	≤ 4	> 4	100.0	-	0.0
Vancomycin (Van A or VanB)	Negative	Positive	100.0	-	0.0

*The wild type is defined as intermediately susceptible. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 50. *Enterococcus faecium* urine isolates in 2015 (n=82). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	14.6	2.4	82.9
Gentamicin*	≤ 128	> 128	-	58.5	41.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Trimethoprim*	≤ 0.032	> 1	0.0	22.2	77.8
Trimethoprim-sulfamethoxazole*/**	≤ 0.032	> 1	0.0	24.7	75.3
Vancomycin (any genotype)	≤ 4	> 4	100.0	-	0.0
Vancomycin (Van A or VanB)	Negative	Positive	100.0	-	0.0

*The wild type is defined as intermediately susceptible. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

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

The proportion of *E. faecalis* was higher (93.3%) among urinary tract isolates than in blood cultures (63.8%). *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 (13.1%), but lower than in urinary tract isolates from 2010 (21.2%). The prevalence of HLGR and ampicillin resistance was also similar in *E. faecium* urinary tract and blood isolates (approximately 40% and 80%, respectively). The clinical benefit of trimethoprim and trimethoprim-sulfamethoxazole in the treatment of enterococcal infections is uncertain, and the agents are only recommended for uncomplicated cystitis. Wild type enterococci are classified as intermediately susceptible by EUCAST. As seen in Tables 48-50, the prevalence of *in vitro* resistance was significantly higher in *E. faecium* than in *E. faecalis*. The results for both species are comparable to 2010.

Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 51. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2015 (n=519). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.064	> 2	92.5	7.5	0.0
Cefotaxime	≤ 0.5	> 2	99.8	0.0	0.2
Ceftriaxone	≤ 0.5	> 2	99.8	0.2	0.0
Erythromycin	≤ 0.25	> 0.5	95.2	0.0	4.8
Clindamycin	≤ 0.5	> 0.5	96.3	-	3.7
Tetracycline	≤ 1	> 2	93.1	1.5	5.4
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	88.3	2.3	9.4
Chloramphenicol	≤ 8	> 8	99.0	-	1.0
Oxacillin screen (mm)	≥ 20	< 20	90.6	-	9.4

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

TABLE 52. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids in 2015 (n=519). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G		0.4	59.0	30.1	3.1	1.7	3.5	1.0	0.8	0.6						
Cefotaxime		5.8	78.4	6.2	2.9	4.0	1.2	1.3			0.2					
Ceftriaxone		9.6	72.6	8.1	2.7	4.8	1.0	1.0		0.2						
Erythromycin					7.3	81.3	6.6			0.6	0.2	0.4				3.7
Clindamycin					19.3	67.6	9.2	0.2								3.7
Tetracycline					3.3	84.6	4.8		0.4	1.5	0.8	1.0	1.5	2.1		
TMS**						11.2	58.8	14.8	3.5	2.3	1.7	1.9	1.3	4.4		
Chloramph.										38.9	59.5	0.6	1.0			
Norfloxacin										2.7	48.6	47.4	0.6	0.2	0.2	0.4

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	9.2	0.4	0.8	0.4	0.6	3.9	10.2	12.3	20.2	18.3	11.4	10.8	1.2		0.2	

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

RESULTS AND COMMENTS

The results are summarised in Tables 51-52 and Figures 70-71. All systemic *S. pneumoniae* isolates submitted to the National Reference Laboratory for Pneumococci at the Norwegian Institute of Public Health during 2015 were included in the surveillance protocol. Seventeen strains were isolated from cerebrospinal fluids, and eight of these were found in patients who concomitantly had positive blood cultures. Both blood culture isolates and isolates from cerebrospinal fluids were included from patients with positive cultures from both specimen types. In addition, six systemic isolates were recovered from pleural effusions (n=3), synovial fluids (n=2) and a brain biopsy (n=1).

Norwegian breakpoints for pneumococci are in accordance with EUCAST, and these remained unchanged in 2015 as defined by MIC values. The results for penicillin G, cefotaxime and ceftriaxone were interpreted according to the general breakpoints for pneumococci (R > 2 mg/L for all three substances; S ≤ 0.06, S ≤ 0.5 and S ≤ 0.5 mg/l, respectively). The isolates from cerebrospinal fluids were in addition categorised according to breakpoints for meningitis (R > 0.064, R > 0.5 and R > 0.5 mg/L, respectively).

A total of 7.5% (39/519) of *S. pneumoniae* isolates were intermediately susceptible to penicillin G (MIC 0.125-2

mg/L), no isolates were classified as resistant. A single penicillin intermediate blood culture isolate (MIC 2 mg/L) was also resistant to cefotaxime (MIC 4 mg/L) and non-susceptible to ceftriaxone (MIC 2 mg/L). Four of the isolates intermediately susceptible to penicillin were recovered from cerebrospinal fluid, and as they displayed MIC values of 0.125-0.5 mg/L they should clinically be categorised as resistant. The prevalence of non-susceptibility to penicillin G was higher than in 2013 (3.2%) and 2014 (5.3%).

The oxacillin screening disk is often used to discriminate between penicillin susceptible and non-susceptible isolates. Among 39 penicillin G non-susceptible isolates, 37 were resistant to oxacillin. Conversely, 12/480 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 94.9% and 97.5%, respectively. Many of the penicillin non-susceptible *S. pneumoniae* isolates were also non-susceptible to erythromycin (15/39), tetracycline (22/39), trimethoprim-sulfamethoxazole (24/39) and/or chloramphenicol (5/39).

The prevalence of macrolide non-susceptibility remained stable at 4.8% compared to 4.5% in 2014. Most of these isolates (19/25, 76% of macrolide non-susceptible isolates, 3.7% of all isolates) were concomitantly high-level resistant to erythromycin and clindamycin which is compatible with a constitutive MLS_B phenotype. The remaining six isolates (24% of macrolide non-suscpetible isolates, 1.1% of all isolates) were low-level resistant to erythromycin and susceptible to clindamycin as seen in the efflux-based M-type resistance. The distribution of MLS phenotypes was not significantly altered from 2014 to 2015. The results may suggest a continuing predominance of *erm*-mediated macrolide resistance as opposed to the *mef*-dominated peak 2002-2009 (Figure 71).

The 11.7% non-susceptibility to trimethoprim-sulfamethoxazole is a further increase from 8.5% in 2014. The prevalence of non-susceptibility to tetracycline increased from 5.2% in 2014 to 6.9% in 2015 (Figure 70). The vast majority of isolates (99.0%) remained 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.

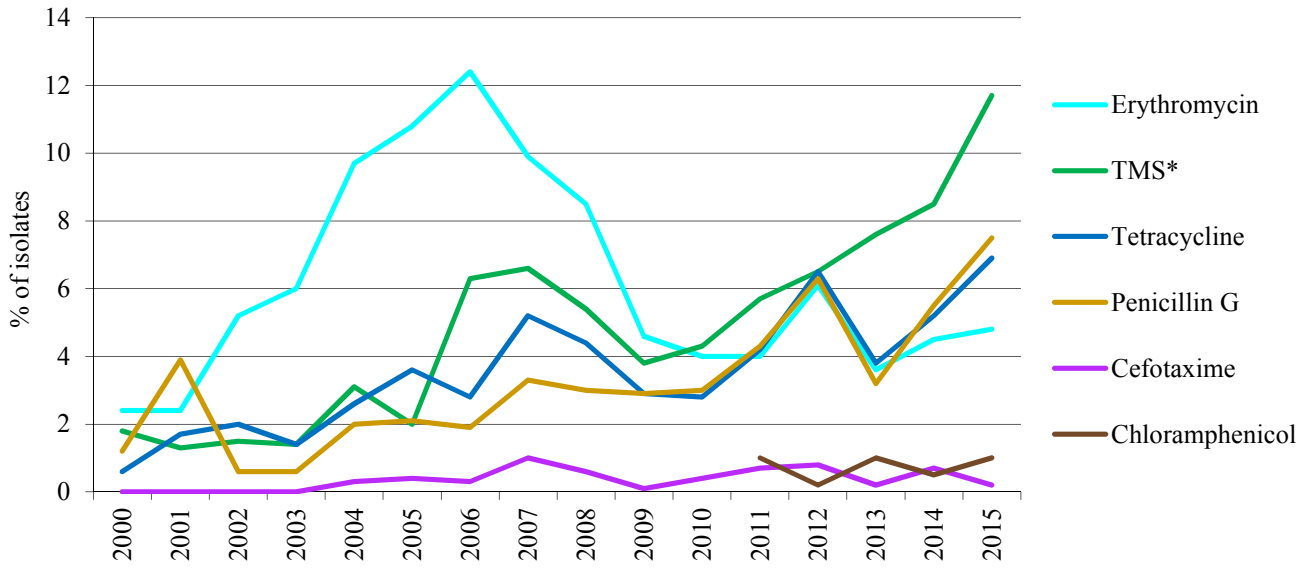


FIGURE 70. Prevalence (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2015. Doxycycline was substituted by tetracycline in 2005. All results are categorised according to the 2016 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

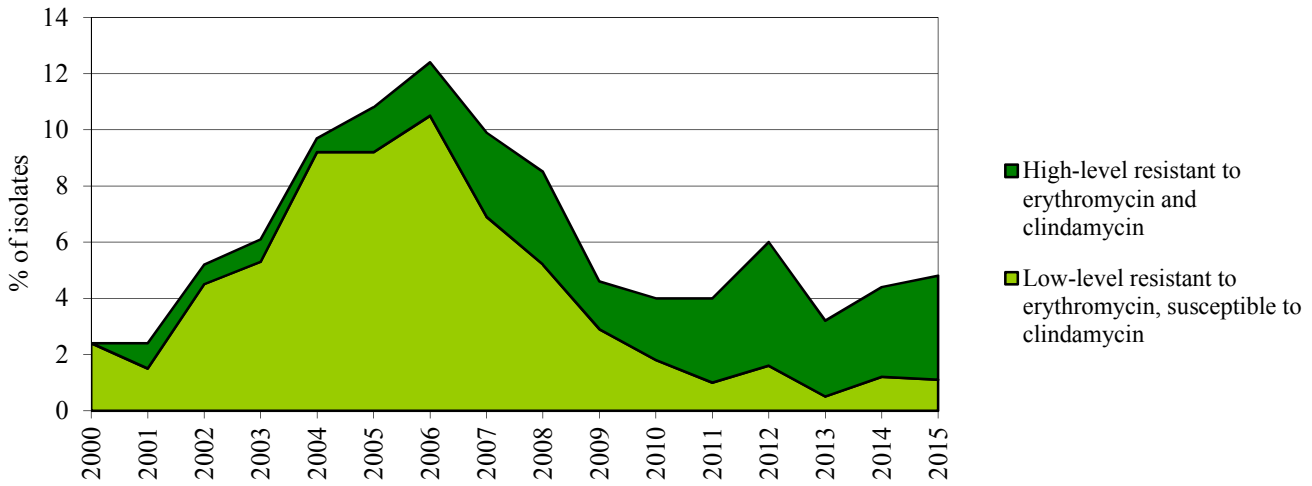


FIGURE 71. Prevalence (%) of non-susceptibility to erythromycin and clindamycin in *Streptococcus pneumoniae* blood culture isolates during 2000-2015.

Streptococcus pyogenes in blood cultures

TABLE 53. *Streptococcus pyogenes* in blood cultures in 2015 (n=200). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	96.5	0.0	3.5
Clindamycin	≤ 0.5	> 0.5	98.0	-	2.0
Tetracycline	≤ 1	> 2	80.0	0.0	20.0
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	98.0	0.0	2.0

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

TABLE 54. *Streptococcus pyogenes* in blood cultures in 2015 (n=200). 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		11.0	86.5	2.5												
Erythromycin					15.5	78.5	2.5				0.5		0.5			2.5
Clindamycin				0.5	36.5	60.5	0.5									2.0
Tetracycline					17.5	58.0	4.5					0.5	4.5	13.0	2.0	
TMS**					8.0	30.0	36.5	22.0	1.5					2.0		

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

RESULTS AND COMMENTS

The Reference Laboratory at the Norwegian Institute of Public Health provides resistance data for systemic *S. pyogenes* isolates on a yearly basis. The Norwegian breakpoints for haemolytic streptococci are in accordance with EUCAST. All comparisons in this report are based on interpretations using the present recommendations.

As expected, all isolates were fully susceptible to penicillin G (Tables 53-54). The prevalence of resistance to erythromycin (3.5%) and clindamycin (2.0%) was unchanged from 2014 (3.7% and 2.1%, respectively). Four of the seven macrolide resistant isolates were concomitantly high-level resistant to clindamycin. The prevalence of tetracycline resistance has increased from 16.5% in 2014 to 20.0% in 2015, whereas the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole has remained relatively stable at 2.0% in 2015 compared to 3.8% in 2014.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 55. *Streptococcus agalactiae* isolates from sterile sites in 2015 (n=279). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	73.1	9.0	17.9
Clindamycin	≤ 0.5	> 0.5	86.0	-	14.0
Tetracycline	≤ 1	> 2	19.0	0.0	81.0
Vancomycin	≤ 2	> 2	100.0	-	0.0

TABLE 56. *Streptococcus agalactiae* isolates from sterile sites in 2015 (n=279). 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				9.0	76.7	14.3										
Erythromycin						11.5	61.6	9.0	0.4	1.1	2.2	2.2	2.5	1.8	0.7	7.2
Clindamycin					10.4	69.2	5.7	0.7	2.5	2.5	0.4		0.7			7.9
Tetracycline					15.8	2.9			0.4		0.4	5.0	41.6	31.5	2.2	0.4
Vancomycin					0.4	11.5	60.9	22.9	4.3							
Gentamicin												0.4	2.9	12.9	60.6	23.3

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).

RESULTS AND COMMENTS

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

Relevant breakpoints have remained unchanged since 2009. A total of 279 strains were included in 2015. Fifty isolates originated from neonates and small children < 1 year of age. In seven cases the age of the patient was not recorded. Most isolates (93.5%) were recovered from blood cultures, but there were also isolates from cerebrospinal fluids (n=2) and various tissues and body fluids (n=16).

As seen in Tables 55-56 there were no isolates with reduced susceptibility to penicillin G or vancomycin. Fifty isolates (17.9%) were resistant to erythromycin compared to 18.1% in 2014. In addition, 9.0% were only intermediately susceptible compared to 2.9% in 2014. Seventy-three erythromycin non-susceptible isolates were analysed for MLS resistance phenotype. Fourty-three displayed constitutive (n=32) or inducible (n=11) MLS_B resistance indicating the presence of an *erm* determinant. The remaining thirty isolates had a resistance pattern in accordance with an efflux-mediated M phenotype encoded by a *mef* gene. Four isolates were recorded as clindamycin resistant (MIC 1-2 mg/L) in spite of erythromycin susceptibility (MIC 0.125-0.25 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. High-level resistance to gentamicin (MIC ≥ 128 mgL) was detected in 23.3% of the isolates. The prevalence of resistance to tetracycline (81.0%) was at the same level as in 2014 (73.7%) with the majority of isolates displaying MIC values of 16-32 mg/L (Table 56).

Mycobacterium tuberculosis

A total of 318 cases of tuberculosis disease (TB) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2015. Of these, 36 cases were born in Norway. Twenty-two cases had been treated with anti-TB drugs previously, and ten additional cases had been diagnosed with TB but had not been treated. Two hundred and fifty-nine cases had TB for the first time.

Two hundred and forty-five cases were confirmed infections with *M. tuberculosis* complex by culture followed by susceptibility testing. The results are presented in Table 57. Cases are registered in MSIS the year in which the first culture positive test was taken. There were five MDR-TB* cases. None of them were co-resistant to moxifloxacin and/or amicacin, hence no cases were categorised as XDR-TB** in 2015. All the five MDR-TB cases had TB for the first time and were previously untreated.

TABLE 57. Antimicrobial susceptibility of 245 isolates of *Mycobacterium tuberculosis* complex (not *M. bovis* (BCG)) from human infections in 2015. Figures from 2014 are shown in parentheses.

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents (No. of isolates)					
			Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDR-TB*
Norway	36 (23)	22 (35)	1 (0)	0 (0)	0 (0)	1 (0)	3 (0)	0 (0)
Europe excl. Norway	27 (29)	22 (28)	1 (5)	0 (2)	0 (2)	1 (4)	0 (2)	0 (2)
Asia	115 (98)	88 (106)	9 (8)	2 (2)	0 (2)	12 (7)	5 (8)	1 (2)
Africa	137 (175)	111 (142)	11 (21)	4 (3)	0 (3)	21 (17)	4 (9)	4 (6)
America	3 (2)	2 (4)	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)	0 (0)
Total	318 (327)	245 (265)	22 (34)	6 (10)	0 (7)	35 (28)	12 (19)	5 (10)
Proportion resistant isolates (%)			9.0 (12.8)	2.4 (3.8)	0.0 (2.6)	14.3 (10.6)	4.9 (7.2)	2.0 (3.8)

* 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 58. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=139). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	100.0	0.0	0.0
Voriconazole*	≤ 0.125	> 0.125	100.0	-	0.0
Anidulafungin*/**	≤ 0.032	> 0.032	98.6	-	1.4
Micafungin*/**	≤ 0.016	> 0.016	98.6	-	1.4

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

TABLE 59. *Candida albicans* blood culture isolates (n=139). 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				0.7	1.4	9.4	52.5	36.0									
Fluconazole					2.2	15.1	59.0	22.3	1.4								
Voriconazole	10.8	73.4	14.4	0.7		0.7											
Anidulafungin	79.9	17.3	1.4				0.7	0.7									
Micafungin	2.1	48.2	48.2						1.4								
Caspofungin**			0.7	3.6	41.0	40.3	10.1		2.9			1.4					

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

TABLE 60. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=35). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 0.002	> 32	0.0	74.3	25.7
Anidulafungin*/**	≤ 0.064	> 0.064	97.1	-	2.9
Micafungin*/**	≤ 0.032	> 0.032	97.1	-	2.9

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

TABLE 61. *Candida glabrata* blood culture isolates (n=35). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B					2.9	8.6	14.3	62.9	11.4								
Fluconazole									2.9	8.6	25.7	8.6	25.7	2.9			25.7
Voriconazole**				5.7	14.3	14.3	22.9	14.2		2.9	2.9	2.9		20.0			
Anidulafungin	2.9	22.9	71.4				2.9										
Micafungin		22.9	57.1	17.1		2.9											
Caspofungin***						22.9	54.3	20.0		2.9							

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.
**There is insufficient evidence that *C. glabrata* is a good target for therapy with voriconazol 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 anidulafungine are considered susceptible.

TABLE 62. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates (n=9). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	88.9	11.1	0.0
Voriconazole*	≤ 0.125	> 0.125	88.9	-	11.1
Anidulafungin*/**	≤ 0.064	> 0.064	100.0	-	0.0

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

TABLE 63. *Candida tropicalis* blood culture isolates (n=9). 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							1	3	5								
Fluconazole							4	4			1						
Voriconazole			2	4	2		1										
Anidulafungin		2	7														
Micafungin**			2	7													
Caspofungin***					1	2	6										

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.
**There is insufficient evidence that *C. tropicalis* is a good target for therapy with micafungin 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 anidulafungine are considered susceptible to caspofungin.

TABLE 64. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates (n=8). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B*	≤ 1	> 1	100.0	-	0.0
Fluconazole*	≤ 2	> 4	87.5	-	12.5
Voriconazole*	≤ 0.125	> 0.125	87.5	-	12.5
Anidulafungin*/**	≤ 0.002	> 4	0.0	75.9	25.0
Micafungin*/**	≤ 0.002	> 2	0.0	100.0	0.0

* Recommended breakpoints by the European Commitee on antimicrobial susceptibility testing - EUCAST.
** There are no European breakpoints for caspofungin. Strains intermediate to anidulafungin and micafungin can be considered intermediate to caspofungin.

TABLE 65. *Candida parapsilosis* blood culture isolates (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				1		1	2	2	1								
Fluconazole							2	4		1		1					
Voriconazole		3	3	1			1										
Anidulafungin								2	1	3	2						
Micafungin								5	3								
Caspofungin**								3	5								

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

RESULTS AND COMMENTS

In 2015, The National Mycology Reference Laboratory received 210 *Candida* isolates of eleven different *Candida* species isolated from bloodstream infections in 200 patients compared to 210 isolates of nine different *Candida* species in 2014. *Candida albicans* is the most common species (n=139, 66.2 %). We received 71 non-albicans isolates (33.8%) compared to 64 isolates (30.5%) in 2014. The number of *Candida glabrata* is still low (n=35, 16.8 %) followed by *Candida dubliniensis* (n=9, 4.3%), *Candida tropicalis* (n=9, 4.3%), *Candida parapsilosis* (n=8, 3.8 %) and ten isolates of other *Candida* spp (n=1-3). Five mixed infections with two or more different *Candida* spp. and seven persistent infections with the same species more than four weeks apart were observed in 2015.

All isolates were susceptibility tested for amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin by Etest according to the manufacturer's instructions (AB bioMérieux). Unexpected susceptibility patterns were confirmed by EUCAST standardised broth microdilution method at Statens Serum Institut in Copenhagen. The results are presented in Tables 58-65.

Acquired resistance is rare and species identification predicts the susceptibility pattern of *Candida* species. With the exception of two echinocandin resistant isolates (1.4 %), all *C. albicans* isolates were susceptible to all drugs tested. Echinocandin resistance was also found in one *C. dublinienis* and one *C. glabrata* isolate. *C. parapsilosis* (n=8) has higher echinocandin MICs resulting from naturally occurring amino acid substitutions within a hot-spot region of the Fks1p target protein. All isolates received in 2015 belonged to the wild type, categorised as inter-mediately susceptible. EUCAST has still not established breakpoints for caspofungin. *C. parapsilosis* isolates intermediately susceptible to anidulafungin and micafungin are regarded intermediately susceptible, and *C. albicans*, and *C. glabrata* isolates susceptible to anidulafungin and micafungin are regarded susceptible to caspofungin. *C. tropicalis* and *C. krusei* strains sensitive to anidulafungin are considered susceptible to caspofungin. The MICs of micafungin for *C. tropicalis* and *C. krusei* are higher than for *C. albicans*, but there is insufficient evidence to indicate whether the wild type population of these pathogens can be considered susceptible to micafungin or not.

Unexpected high MICs of fluconazole (2 mg/L) and voriconazole (0.25 mg/L) were observed in one *C. tropicalis* isolate, and heteroresistance was observed in one *C. parapsilosis* isolate in a patient with persistent infection. Otherwise observed reduced susceptibility to fluconazole is due to intrinsic resistance in *C. krusei* (n=2), *C. pelliculosa* (n=1) and *C. glabrata* (n=35). Nine (25.7%) of the *C. glabrata* isolates were categorised as resistant. Breakpoints for fluconazole ($S \leq 0.002$, $R > 32$) in *C. glabrata* categorise the wild type as intermediately suscpetible. There is still insufficient evidence that *C. glabrata* and *C. krusei* are good targets for therapy with voriconazole, and no breakpoints are set. EUCAST recommends reporting the MIC value without S, I and R categorisation. Except for these species, all isolates were found susceptible to voriconazole. In 2015, isavuconazole has been added to the EUCAST breakpoint table for *Candida* spp., but there is insufficient evidence that *Candida* spp. is a good target for therapy with the drug and breakpoints have not been set. The number of *C. dubliniensis* isolates is the same as the number of *C. tropicalis* (n=9), but this species has no breakpoints except for the non-species related breakpoint of fluconazole. *C. dubliniensis* is therefore not shown in the tables.

All but one of the isolates tested were susceptible to amphotericin B. *Candida lipolytica* (*Yarrowia lipolytica*) found in mixed culture had MIC of 2 mg/L. Amphotericin B is not recommended treatment of *C. lusitaniae* (n=3) infections as *C. lusitaniae* has high MICs or develops resistance during treatment. *C. kefyr* (n=1) might also develop high MICs on amphotericin B therapy. Decreased susceptibility to different antifungal classes is common in some of the species not shown in the figures. *C. guilliermondii* (n=2), a species without any breakpoints, is 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. Collection of data
Veterinary Medicinal Products (VMPs)

Sales data,
In Norway, all veterinary medicinal products (VMPs) are prescription-only medicines, and have to be dispensed through pharmacies, which are supplied by drug wholesalers only or by feed mills. Veterinarians are not allowed to dispense VMPs except in emergency situations in the field, in which case they have to be sold at cost price. Premixes/medicated feeds are currently only used for farmed fish; this is due to the small size of livestock herds (terrestrial animals) in Norway. Group/flock treatment of livestock (terrestrial animals) with antimicrobial agents is subjected to administration through drinking water or as top-dressing on the feed.
Wholesalers and feed mills in Norway have from 1 January 2012 been mandated to provide sales statistics for veterinary medicinal products, as well as for medicated feedingstuffs, to the Norwegian Institute of Public Health (NIPH). The data on sales of each product presentation (name, form, strength and pack size of the included VMPs) were obtained from the Norwegian Institute of Public Health (NIPH), which collects the data from the wholesalers and feed mills.

Prescription data
For 2015, prescription data for farmed fish have been obtained from the Veterinary Prescription Register (VetReg) that was implemented by the Norwegian Food Safety Authority 1 January 2011. The VetReg data provide information about, among, others fish species and production stage.

Feed additives
Until 2003, the Norwegian Agricultural Inspection Service was responsible for the collection of data on sales of antimicrobial growth promanalyzeoters and coccidiostat feed additives, while from that time the Norwegian Food Safety Authority has been in charge of collecting such data. Data on the sales of the different active substances were obtained from these sources.

Veterinary medicinal products included in the data set
The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to identify the veterinary medicinal products (http://www.whocc.no/atcvet) to be included in the data. The ATCvet codes for which the data were requested from the NIPH for terrestrial animals are shown in the table, which is identical to the inclusion criteria by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000302.jsp).

Note that in Norway, veterinary antimicrobials are currently not marketed for all ATCvet codes for antibacterials for intestinal and intrauterine infections.

Antimicrobial VMPs included in the data

Categories	ATCvet codes
Intestinal infections	QA07AA;QA07AB
Uterine infections	QG01AA; QG01AE, QG01BA; QG01BE; QG51AA; QG51AG
Sysetmic infecttions	QJ01
Intramamm. infections	QJ51
Antibacterials used as antiparasitic agents	QP51AG

Antimicrobial products sold on special exemption from market authorisation are included in the data. Dermatological preparations (QD) and preparations for sensory organs (QS) are not included in the data. Human medicinal products (HMPs) are to some extent used in small animal practice; however, data on sales of HMPs to animals are not included in this report as such sales cannot be separated from sales intended for use in humans.

Analysis and reporting of the data
The sales data for each product presentation were calculated to express weigth of active substance sold. In order to comply with the ESVAC standards, sales of prodrugs – e.g. procaine benzylpenicillin and penethamate hydriodide were converted to the corresponding values for the active ingredient, here benzylpenicillin.
The sales data of antimicrobial VMPs for terrestrial animals has been stratified into food producing animals and companion animals – i.e by stratifying tablets, oral solution and oral paste approved for companion animals only; in addition dihydrostreptomycin tablets of pack size 10 pieces have been included. Sales of VMPs for food producing animals have been stratified into VMPs for treatment of individual food producing animals - bolus, injectables, intramammary preparations, intrauterine preparations and some tablets (dihydrostreptomycin – packsizes of 100 and 20 pieces) and for group treatment (oral solution and oral powder). There is some use of injectable VMPs in companion animals. The usage for this animal category is slightly underestimated and overestimated for food producing animals. However, it is thought that the stratified data give a valid picture of the development of the usage in companion and food producing animals.
For 2010-2015, a separate analysis normalising the sales for terrestrial foor producing animals by the population-at-risk – i.e. a population correction factor (PCU) is provided. The animal categories included in the PCU as well as the calculation are identical to what is used by ESVAC and is decribed in detail in Annex 1 of the first ESVAC report (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500112309.pdf).

Appendix 2:
Collection of data on human usage of antimicrobial agents

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 70ies.

Data on antibacterial use in hospitals are retrieved from *Sykehusapotekenes Legemiddelstatistikk* (the hospital pharmacies drug statistics database) which is a cooperation of LIS, Legemiddel Innkjøp Samarbeid (Drug Purchasing Cooperation) and the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. *Sykehusapotekenes Legemiddelstatistikk* collects sales data from each pharmacy delivering drugs to hospitals. Data are collected as sales from the pharmacy to hospital wards. Data have been available since 2006. *Nasjonal kompetanse-tjeneste for antibiotikabruk i spesialisthelsetjenesten* (Norwegian National Advisory Unit for Antibiotic Use in Hospitals) has analysed the data according to activity (admission and bed days).

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

Data on the use in ambulatory care are retrieved from NorPD, a nation-wide prescription database situated at the Norwegian Institute of Public Health. This database includes all prescriptions being prescribed to out-patients in Norway. These data give us the exact population prevalence of antibacterial use 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 2016 is used.

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

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

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

Inclusion criteria
The antibacterials for human use included in this report belong to ATC group J01 *antibacterials for systemic use*. Oral vancomycin (A07AA09), rifaximin (A07AA11) and oral and rectal metronidazole (P01AB01) are also included. For antifungals, only ATC-group J02 *antimycotics for systemic use* is included. Of the antimycobacterials (ATC J04), only rifampicin is included. The content of rifampicin has been calculated in plain products and in combinations and data is presented as total amount of rifampicin. Antibacterials used in dermatological preparations (ATC group D) and preparations intended for sensory organs (ATC group S) are not included in the material, except for mupirocin, which is included in one table.

References
1. WHO Collaborating Centre for Drug Statistics Methodology. ATC index with DDDs 2016. WHO Collaborating Centre, Oslo
2. Definitions Norwegian Directorate of Health https://volven.helsedirektoratet.no/begrep.asp?id=452&catID=12.

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

Sampling strategy
Caecal samples from cattle under one year of age and finishing swine were collected at slaughter throughout the year by The Norwegian Food Safety Authorities (NFSA), following the specifications set by the European Food Safety Authorities (EFSA Journal 2014;12(5):3686). Only one individual caecal samples were included per herd, and in total 264 and 270 samples from cattle and swine, respectively, were collected. The included indicator bacteria *Escherichia coli* were retrieved from these caecal samples. The caecal samples were also used for selective isolation of *E. coli* resistant to third generation cephalosporins, quinolone resistant *E. coli* (QREC), and for carbapenemase producing *E. coli* (CPE). In addition, the caecal samples from swine were used for selective isolation of *Campylobacter coli*.
Beef, pork and vegetables (leafy salads), 245, 244 and 243 respectively, 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 taken without taking place of origin into account. All samples were collected by the NFSA. Only one sample from each production batch was included. All the food samples were analysed using selective isolation of *E. coli* resistant to third generation cephalosporins, QREC and CPE. In addition, *E. coli* indicator bacteria were isolated from vegetables. The vegetable samples comprised both imported and domestically produced, washed and unwashed, leafy salads, and included a variety of salad types.
Samples from 179 random cattle dairy herds with > 25 cows were obtained at the farm by the NFSA and examined for methicillin resistant *Staphylococcus aureus* (MRSA). From each herd, animals were sampled by rubbing a 25 cm^2 area behind the axilla of a total of ten animals with a cloth moistened with sterile water (one sample per herd). In addition a moistened cloth was used to sample the environment at 15 places of about a 100 cm^2 area.

Indicator isolates of *E. coli*
Sample material, i.e. caecal content from one cattle and one finishing swine per herd were plated directly onto MacConkey agar and incubated at 41.5±0.5°C for 20±2h. From vegetable samples, 25±0.5 g sample material was incubated in 225 mL buffered peptone water (BPW-ISO) at 37±1°C for 20±2h according to the protocol from the European Union Reference Laboratory for Antimicrobial Resistance (EURL-AR; http://www.crl-ar.eu/233-protocols.htm). From the overnight broth 10 µL were plated onto MacConkey agar. 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 and confirmed using MALDI-TOF MS (Bruker Daltonics GmbH, Bremen, Germany).

Cephalosporin resistant *E. coli*
Sample material from cattle and swine herd used for *E. coli* isolation, was incubated 1 g in 9 mL BPW-ISO at 37±1°C for 20±2h according to the protocol from EURL-AR (http://www.crl-ar.eu/233-protocols.htm). Similarly, sample material from vegetables, beef and pork (25±0.5 g each), were incubated in 225 mL buffered peptone water (BPW-ISO) at 37±1°C for 20±2h. A total of 10 µL from the overnight broths for all sample types (caecal, meat and vegetable) were plated onto each of MacConkey agar containing 1 mg/L cefotaxime and MacConkey agar containing 2 mg/L ceftazidime. The agar plates were incubated at 41.5±0.5°C for 24-48h. Presumptive cephalosporin resistant *E. coli* were subcultured on blood agar, confirmed as *E. coli* using MALDI-TOF MS (Bruker Daltonics GmbH, Bremen, Germany) and further tested for extended spectrum beta-lactamase production.

Quinolone resistant *E. coli*
Sample material from the overnight BPW-ISO broth from caecal and food (meat and vegetable) samples were plated onto MacConkey agar containing 0.06 mg/L ciprofloxacin. Plates were incubated at 41.5±0.5°C for 24-48h and presumptive QREC were subcultured on blood agar and confirmed as *E. coli* using MALDI-TOF MS.

Carbapenemase producing *E. coli*
Sample material from the overnight BPW-ISO broth from caecal and food samples were plated onto chromID™ CARBA and chromID™ OXA-48 agar (bioMérieux, Marcy l'Etoile, France). Plates were incubated at 37±1°C for 24-48h. Presumptive CPE were subcultured on blood agar, confirmed as *E. coli* using MALDI-TOF MS.

MRSA
With the exception of samples from 12 herds where the cloths were analysed as one pooled sample, the cloths were analysed separately. The sample cloths were analysed for MRSA by incubation in Mueller-Hinton broth with 6.5% NaCl. After incubation 1 mL was transferred to 9 mL Tryptone-Soya broth containing 75 mg/L aztreonam and 3.5 mg/L cefoxitin and incubated at 35°C for 18±2h, followed by plating on Brilliance™ MRSA2 agar plates (Oxoid, Oslo, Norway) (EFSA journal 2012: 10 (10):2897). Suspected colonies were subjected to further identification including PCR for detection of the *mec*A/*nuc* genes (http://www.crl-ar.eu/233-protocols.htm, Stegger et al. 2012).

Genotyping
For the presumptive cephalosporin resistant *E. coli*, PCR was performed for the identification of the genotypes bla_{CTX-M}, bla_{TEM}, bla_{SHV}, multiplex PCR to look for plasmid-mediated AmpC genes, or real-time PCR for the bla_{CMY-2} gene (Pérez-Pérez et al. 2002, Hasman et al. 2005, Briñas et al. 2002, Schmidt et al. 2014). For isolates with an AmpC resistance profile where no plasmid-mediated genes were found, amplification of the promoter region of the chromosomal AmpC gene was performed (Agersø et al. 2012, Peter-Getzlaff et al. 2011 Tracz et al. 2007). Two isolates with unusual phenotypic profiles were subjected to whole genome sequencing at the EURL-AR in Lyngby, Denmark.

Susceptibility testing
Isolates were tested for antimicrobial susceptibility at NVI, Oslo. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacteria to be tested. Epidemiological cut-

off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 19.05.2016) were used, except for azithromycin for *E. coli*. See Appendix 6 for definitions of cut-off values.

Quality assurance systems

The following susceptible bacteria were included as quality controls on a regular basis: *E. coli* ATCC 25922, *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* 16874 (OXA-48), *E. coli* TZ 3638 (GES-5, CARBA), *S. aureus* CCUG 35603 (MRSA). 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-AR, Denmark).

Data processing

Susceptibility data were recorded and stored in the sample registration system at NVI as discrete MIC values. Data management and analysis was performed in SAS-PC System® v 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). The 95% confidence intervals were calculated by the exact binomial test using R version 3.3.0 for Windows (R Development Core Team, 2016).

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

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

*(X) = Only isolates suspected to be resistant to third generation cephalosporins tested as described in Commission implementing decision of 12. Nov 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria (2013/652/EU), data not shown in the report tables.

Appendix 4:
Sampling, microbiological methods and data processing of zoonotic and non-zoonotic enteropathogenic bacteria in NORM and NORM-VET

NORM-VET enteropathogenic bacteria
Sampling strategy - animals

Salmonella
Samples from animals were collected according to the Norwegian *Salmonella* control programme for live animals. Additional isolates were obtained from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). One isolate of each serovar per incident was included for susceptibility testing.

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

Susceptibility testing animal isolates
Isolates were tested for antimicrobial susceptibility at NVI, Oslo. MIC values were obtained using plates from Sensititre® (TREK Diagnostic LTD) with different panels depending on the bacteria to be tested.
For animal isolates, epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 19.05.2016) were used, except for tigecycline for *Salmonella* spp. where EFSA recommended cut-off was used, and for azithromycin and colistin for *Salmonella* spp. for which cut-off values are not defined. For additional antimicrobial agents not defined in the EUCAST recommendations, cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also Appendix 6).

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

Data processing animal isolates
Susceptibility data were recorded and stored in the sample registration system at NVI. The susceptibility data were stored as discrete MIC values. Data management and analysis was performed in SAS-PC System® v 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). The 95% confidence intervals were calculated by the exact binomial test using R version 3.3.0 for Windows (R Development Core Team, 2016).

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

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

Susceptibility testing human isolates
Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the NRL for Enteropathogenic Bacteria at the NIPH by agar disk diffusion tests according to the EUCAST standardised method for AMR testing of non-fastidious bacteria. *Campylobacter* isolates from humans were tested for antimicrobial susceptibility using MIC Test Strips (Liofilchem).
For human isolates EUCAST clinical or epidemiological breakpoints for *Enterobacteriaceae*, version 5.0 2015 were used if established, otherwise local epidemiological cut-off values were used (nalidixic acid, azithromycin and tetracycline). Isolates with reduced susceptibility to cefotaxime or ceftazidime were tested for the presence of $ESBL_A$ by a double disk approximation test (BD Sensidisc), and for the presence of $ESBL_M$ by an AmpC detection test (Liofilchem MIC-test strips). Isolates with reduced susceptibility to meropenem were forwarded to the Norwegian National Advisory Unit on Detection of Antimicobial Resistance (K-Res) for further analyses.

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

Data processing human isolates
The NRL at the NIPH stored susceptibility data of human isolates as either millimeter zone diameters or MIC values. The results were further analysed by WHONET 5.6 with the aid of the BacLink programme, both developed by Dr. John Stelling.

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

General considerations

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. 2015 was the sixteenth 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 2015 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus, Enterococcus* spp. and *Pseudomonas aeruginosa* in blood cultures (9 months); *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Haemophilus influenzae*, *Neisseria meningitidis* and *Candida* spp. from blood cultures and cerebrospinal fluids (12 months); *S. aureus* from wound specimens (1 week); *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, H. influenzae* and *N. meningitidis* from blood cultures and cerebrospinal fluids were analysed at the the Norwegian Institute of Public Health in Oslo. *Candida* spp. isolates from blood cultures were analysed at Oslo University Hospital, Rikshospitalet. *N. gonorrhoeae* isolates were characterised at Oslo University Hospital, Ullevål. MRSA and *S. agalactiae* isolates were analysed at St. Olav University Hospital in Trondheim. ESBL-producing *Enterobacteriaceae* were genetically characterised at University Hospital of North Norway in Tromsø. *M. tuberculosis* isolates were analysed at the Norwegian Institute of Public Health and Oslo University Hospital (Ullevål and Rikshospitalet).

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp., *S. aureus* and *P. aeruginosa* 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 breakpoints of the Norwegian Working Group on Antibiotics (NWGA). The NWGA breakpoints are harmonised with EUCAST. *S. aureus* isolates were tested for beta-lactamase production by nitrocefin disks, acidometric agar plates (3.6 mg/L penicillin G and phenol red) or clover leaf test. *Enterococcus* strains were screened for glycopeptide resistance using vancomycin 6 mg/L BHI agar. *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *H. influenzae*, *N. meningitides,* and *N. gonorrhoeae* were susceptibility tested using MIC gradient tests (bioMerieux or Liofilchem) on MH II agar supplemented with 5% lysed horse blood or GC agar with 1% haemoglobin and Isovitalex (*N. gonorrhoeae*). Susceptibility testing of *Candida* spp. isolates was performed by MIC gradient tests using RPMI agar containing 2% glucose and MOPS. Resistance values were recorded as mm inhibition zone sizes or MIC values in order to monitor trends in the occurrence of resistance.

M. tuberculosis isolates were tested using BACTEC MGIT 960 systems. All three test laboratories participate in the WHO external DST quality control programme. They also tested for mutations in the *rpoB* gene to detect rifampicin resistance.

Confirmation of resistance phenotypes

E. coli and *Klebsiella* spp. with reduced susceptibility to third generation cephalosporins were examined for ESBL production using ESBL combination MIC gradient tests according to the instructions of the manufacturer (Liofilchem). ESBL positive strains from blood cultures were subjected to PCR and DNA sequencing for determination of ESBL genotype. *S. aureus* isolates with reduced susceptibility to cefoxitin were examined by *mecA* PCR for confirmation of methicillin resistance (MRSA). *Enterococcus faealis* and *E. faecium* isolates displaying growth on the vancomycin screening agar were examined by *van* PCRs. Erythromycin non-susceptible *S. pneumoniae*, *S. aureus, S. pyogenes* and *S. agalactias* 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), *N. gonorrhoeae* CCUG 41811, *P. aeruginosa* ATCC 27853, *C. albicans* ATCC 90028.

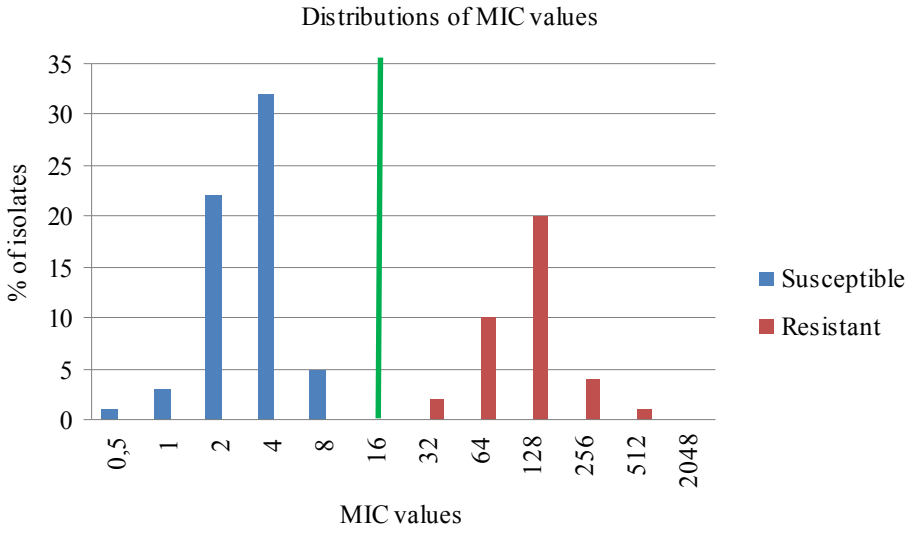
Data processing

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 programme are not directly comparable. This is because the sampling between the programmes and also the classification of resistance differ between the programmes. Clinical breakpoints are used for the classification within NORM, while epidemiological cut-off values are used for the classification of resistance within NORM-VET. EUCAST definitions of clinical breakpoints and epidemiological cut-off values are presented at the web page: http://www.srga.org/Eucastwt/eucastdefinitions.htm. The terms and usage of these two ways of classification of resistance are further explained below. The epidemiological breakpoint would normally be lower for MIC values and higher for disk diameters than the clinical breakpoints. However this is not always the case.

Epidemiological cut-off values
The epidemiological cut-off values are mainly used by epidemiologists and could indicate emerging resistance in the bacterial populations. Based on the distribution of the minimum inhibitory concentration (MIC) or the inhibition zone diameter distribution, each bacterial population could (in an ideal case) be divided into two populations by a biphasic curve as shown in the example below. 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 epidemiological cut-off 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 epidemiological cut-off values recommended by EUCAST. However, for some combinations of bacteria and antimicrobial agents, these were not applicable to our data. In these cases epidemiological cut-off 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 a 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 2013 by EFSA Journal 2015; 13(2):4036 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 19.05.2016) 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*	*Campylobacter coli*	*Staphylococcus aureus*
Ampicillin	> 8	■	■		
Azithromycin*	ND	X	X		
Benzylpenicillin	>0.125				■
Cefotaxime	> 0.25		■		
	> 0.5	■			
Cefoxitin	> 4				■
Ceftazidime	> 0.5		■		
	> 2	■			
Chloramphenicol	> 16	■	■		■
Ciprofloxacin	> 0.06	■	■		
	> 0.5			■	
	> 1				■
Clindamycin	> 0.25				■
Colistin	> 2		■		
	ND	X			
Erythromycin	> 1				■
	> 8			■	
Fusidic acid	> 0.5				■
Gentamicin	> 2	■	■	■	■
Kanamycin	>8				■

Antimicrobials	Resistant MIC (mg/L)	*Salmonella* spp.	*Escherichia coli*	*Campylobacter coli*	*Staphylococcus aureus*
Linezolid	> 4				■
Meropenem	> 0.125	■	■		
Moxifloxacin	> 0.5				
Mupirocin	> 1				■
Nalidixic acid	> 16	■	■	■	
Oxacillin	> 2				
Quinupristin/dalfopristin	> 1				■
Rifampicin	> 0.032				■
Streptomycin	> 4			■	
	>16				■
Sulfamethoxazole	> 64		■		
	> 128				■
	> 256	●			
Tetracycline	> 1				■
	> 2			■	
	> 8	■	■		
Tiamulin	> 2				■
Tigecycline	> 0.5	■	■		
Trimethoprim	> 2	■	■		■
Vancomycin	> 2				■

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

Appendix 8: Breakpoints NORM

NORM data are categorised according to the breakpoints of the Norwegian Reference Group on Antibiotic Susceptibility Testing (NWGA) which are harmonised with EUCAST breakpoints. NWGA breakpoints are available at www.antibiotikaresistens.no.

Antimicrobials	MIC (mg/L)		*Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
	S	R																			
Amicacin	≤ 8	> 16			■																
Amphotericin B	≤ 1	> 1																■	■	■	■
Ampicillin	≤ 1	> 1								■											
	≤ 4	> 8												■							
	≤ 8	> 8	■			■	■	■													
Amoxi-Clav*	≤ 2	> 2								■											
	≤ 32	> 32	■	■																	
Anidulafungin	≤ 0.002	> 4																			■
	≤ 0.032	> 0.032																■			
	≤ 0.064	> 0.064																	■	■	
Azithromycin	≤ 0.25	> 0.5				■[#]	■[#]	■[#]				■									
Aztreonam	≤ 1	> 16			■																
Cefaclor										■[#]											
Cefepime	≤ 1	> 4	■	■																	
Cefixime	≤ 0.125	> 0.125										■									
Cefoxitin													■[#]								
Cefotaxime	≤ 0.125	> 0.125								■											
	≤ 0.5	> 2													■						
	≤ 1	> 2	■	■		■	■	■													
Ceftazidime	≤ 1	> 4	■	■		■	■	■													
	≤ 8	> 8			■																
Ceftriaxone	≤ 0.125	> 0.125								■	■	■									
	≤ 0.5	> 2													■						
Cefuroxime	≤ 1	> 2								■											
	≤ 8	> 8	■	■																	
Chloramphenicol	≤ 2	> 2								■											
	≤ 2	> 4									■										
	≤ 8	> 8				■	■	■							■						
Ciprofloxacin	≤ 0.032	> 0.032									■										
	≤ 0.032	> 0.064										■									
	≤ 0.5	> 0.5							■	■											
	≤ 0.5	> 1	■	■	■	■	■	■													
	≤ 1	> 1											■								
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.	*Pseudomonas aeruginosa*	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
Fluconazole	≤ 0.002	> 32																	■		
	≤ 2	> 4																■		■	■
Fusidic acid	≤ 1	> 1											■								
Gentamicin	≤ 1	> 1											■								
	≤ 2	> 2							■#												
	≤ 2	> 4	■	■		■	■	■													
	≤ 4	> 4			■																
	≤ 128	> 128												■							
Imipenem	≤ 4	> 8			■									■							
Linezolid	≤ 4	> 4											■	■							
Mecillinam	≤ 8	> 8	■	■																	
Meropenem	≤ 2	> 8	■	■	■	■	■	■													
Micafungin	≤ 0.002	> 2																			■
	≤ 0.016	> 0.016																■			
	≤ 0.032	> 0.032																	■		
Mupirocin	≤ 4	> 256											■#								
Nalidixic acid	≤ 16	> 16							■#												
						■#	■#	■#													
Nitrofurantoin	≤ 64	> 64	■																		
Norfloxacin	≤ 4	> 4											■#								
Oxacillin															■#						
Penicillin G	≤ 0.064	> 0.25									■										
	≤ 0.064	> 1										■									
	≤ 0.064	> 2													■						
	≤ 0.25	> 0.25														■	■				
										■#											
Pip-Tazo**	≤ 8	> 16	■	■																	
	≤ 16	> 16			■																
Rifampicin	≤ 0.064	> 0.5											■								
	≤ 0.25	> 0.25									■										
Spectinomycin	≤ 64	> 64										■									
Tetracycline	≤ 0.5	> 1										■									
	≤ 1	> 2								■			■		■	■	■				
	≤ 2	> 2							■												
						■#	■#	■#													
Tigecycline	≤ 0.25	> 0.5												■							
	≤ 0.5	> 0.5											■								
	≤ 1	> 2	■		■																
Tobramycin	≤ 4	> 4																			
Trimethoprim	≤ 0.032	> 32												■							
	≤ 2	> 4	■	■																	

Antimicrobials	MIC (mg/L)		*Escherichia coli*	*Klebsiella* spp.	*Pseudomonas aeruginosa*	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Neisseria meningitidis*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Streptococcus agalactiae*	*Candida albicans*	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*
	S	R																			
TMS***	≤ 0.032	> 1												■							
	≤ 0.5	> 1								■											
	≤ 1	> 2													■	■					
	≤ 2	> 4	■	■		■	■	■					■								
Vancomycin	≤ 2	> 2															■				
	≤ 4	> 4												■							
Voriconazole	≤ 0.125	> 0.125															■		■	■	

[#] Epidemiological cut-off value based on the wild type distribution by EUCAST. * Amoxi-Clav= Amoxicillin-Clavulanic acid. ** Pip-Tazo=Piperacillin-Tazobactam. *** TMS Trimethoprim-sulfamethoxazole. Breakpoints for the e combination are given for the trimethoprim component only.

Appendix 9:
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