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NORM
NORM-VET

Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

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The NORM and NORM-VET programmes are part of the
Norwegian Government's Action Plan against Antimicrobial Resistance (2000 – 2004) issued in 2000, and the
National Strategy for Prevention of Infections in the Health Service and Antibiotic Resistance (2008 – 2012) issued in 2008.

CONTENTS

I. 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 sources. 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 monitoring antimicrobial drug usage and resistance in both human and veterinary medicine and published several reports and recommendations in this regard.

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, a conference organized in September 2004 by the Norwegian Institute of Public Health and supported by the Norwegian government, issued a report, which forms the basis for containment of antimicrobial resistance in the years to come. The need for continued surveillance of both resistance and drug usage was emphasised. An integrated national strategy for prevention of infections in the health service and antibiotic resistance (2008 – 2012) was issued in the summer of 2008.

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 Zoonosis Centre at the Norwegian Veterinary Institute. The usage of antimicrobial agents in humans and animals is based on wholesalers' data reported to the Norwegian Institute of Public Health. This reporting was made mandatory from January 1 2002. Data on the usage of feed additives, i.e. coccidiostatic growth promoters, are collated at the Norwegian Food Safety Authority.

This report, which is the twelfth annual joint report from NORM and NORM-VET, presents data for 2011. 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 the Reference Center for Detection of Antimicrobial Resistance (K-Res) in Tromsø for fruitful cooperation and all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Oslo, August 2012

II. SAMMENDRAG

Dette er den tolvte 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 over forekomst av antibiotikaresistens og forbruk av antibiotika til mennesker og dyr i 2011. Data fra relevante prosjekter som ikke er med i de kontinuerlige overvåkingsprogrammene, presenteres også.

Både NORM og NORM-VET programmene er 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 Zoonosesenteret ved Veterinærinstituttet i Oslo. Programmene har et godt samarbeid og 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 2011 var 6271 kg. Fra 1993 til 2011 er salget av veterinære antibiotika til landdyr redusert med 39 %. For preparater som nesten utelukkende benyttes til produksjonsdyr (landdyr), er reduksjonen på 42 %, mens salget av veterinære antibakterielle preparater som kun brukes til kjæledyr, har økt med 36 % (fra 417 til 567 kg).

Forbruksmønsteret til produksjonsdyr har utviklet seg i gunstig retning siden 1993 idet andelen av rene penicillinpreparater har økt betraktelig parallelt med at bruk av kombinasjonspreparater med penicillin og dihydro-streptomycin har gått ned. Siden det første penicillinpreparatet til smådyr kom på markedet i Norge i 1994 har bruk av veterinære penicillinpreparater (målt i kg) til smådyr økt fra 1 til 64 % av totalsalget av slike preparater markedsført kun til kjæledyr.

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.

Totalsalget av veterinære antibiotika til terapeutisk bruk hos oppdrettsfisk i Norge var i 2011 på 549 kg aktiv substans, hvorav 39 % var kinoloner. 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 har i de senere årene utgjort hovedparten av forbruket. Salgstallene, i kg aktiv substans, er mer enn fordoblet siden forbudet mot bruk av antibakterielle vekstfremmere, noe som kan forklares ved økt produksjon av broilere. Forbruksmønstret for koksidiostatika er endret fra monensin til narasin etter 1996.

Forbruk av antibiotika hos mennesker

I 2011 var humant forbruk av antibiotika til systemisk bruk 20,6 DDD/1000 innbyggere/dag. Dette er en økning på 5 % sammenliknet med 2010. Antibiotikaforbruket var 17,2 DDD/1000 innbyggere/dag når man trekker fra metenamin. Totalforbruket av antibiotika har vært stabilt 2007-2010, og økningen over det siste året er derfor bekymringsverdig.

Gjennom de siste 10 årene har salget av penicilliner og kinoloner økt jevnt, mens salg av sulfonamider og trimetoprim har gått ned. Fra 2010 til 2011 ble det påvist en betydelig økt forskrivning av makrolider (+ 15 %) og tetracykliner (+ 11 %) som kan skyldes en lands-omfattende epidemi av *Mycoplasma pneumoniae* infeksjoner. Det urinveisantiseptiske middelet metenamin har de seneste årene økt kraftig, og i 2011 utgjorde metenamin 17 % av totalt salg målt i DDD.

I 2011 utgjorde penicillinene 41 % av det totale antibiotikaforbruket i Norge målt i DDD. Som i de foregående år ble det sett en økende forskrivning av bredspektrede og penicillinase stabile penicilliner. Tetracykliner utgjorde 17 % av totalforbruket i 2011. Forbruket av makrolider og linkosamider utgjorde 11 % av totalt salg i 2011. Salget av cefalosporiner, monobaktamer og karbapenemer utgjør kun 3 % av totalsalget. Over år har det vært en markant økning i forbruket av fluorokinoloner. Denne gruppen utgjorde kun 4 % av totalforbruket i 2011, men salget er mer enn doblet siden 2000.

Bruken av antibakterielle midler varierer avhengig av kjønn, alder og bosted. Salget til sykehus og primærhelsetjenesten utgjorde i 2011 henholdsvis 7 % og 84 %. I sykehus brukes penicilliner i stor grad; 45 % av antibiotikasalget målt i DDD til sykehus. Tilsvarende andel for allmennpraksis er 41 %. De viktigste andre gruppene på sykehus var cefalosporiner (19 %) og kinoloner (7 %), mens det i allmennpraksis var tetracykliner (19 %) og makrolider (12 %).

Resistens hos kliniske isolater fra dyr

Kliniske isolater av *E. coli* (n=38) fra broiler med sepsis ble undersøkt. Forekomsten av antibiotikaresistens var moderat til høy; 36,8 % av isolatene var følsomme for alle undersøkte antibiotika. Vel 21 % av isolatene var resistente mot ett antibiotikum (hovedsakelig sulfonamider), mens vel 15 % var samtidig resistente mot to (hovedsakelig ampicillin og tetracyklin eller sulfonamider). Ett isolat hadde nedsatt følsomhet for tredje generasjons cefalosporiner, og bla_{CMY-2} genet ble påvist.

Resistens hos indikatorbakterier fra dyr

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

I 2011 ble *E. coli* isolert fra avføringsprøver fra svin (192 isolater) og blindtarminnhold fra broiler (208 isolater) resistenstestet. For begge dyrearter var det en moderat forekomst av resistente bakterier; cirka 75 % av isolatene var følsomme for alle antibiotika i testpanelet. Hos svin ble resistens mot ett antibiotikum påvist hos 9,9 % av

isolatene og hyppigst mot streptomycin. Det ble kun påvist et fåtall multiresistente isolater. Ett isolat hadde nedsatt følsomhet for tredje generasjons cefalosporiner. Videre undersøkelser indikerte at dette var forårsaket av kromosomal AmpC produksjon. Ved bruk av selektiv metode var ett isolat identifisert som ESBL positiv, og bla_{TEM-52} genet ble påvist. Dette er den første påvisningen av ESBL positiv *E. coli* fra gris i Norge.
Hos broiler ble resistens mot ett antibiotikum påvist hos 16,4 % av isolatene og hyppigst mot ampicillin. Det ble kun påvist et fåtall multiresistente isolater. To isolater hadde nedsatt følsomhet for tredje generasjons cefalosporiner med en ikke selektiv metode, og bla_{CMY-2} genet ble påvist. Ved bruk av selektiv metode hadde 43 % av prøvene ESBL positive *E. coli* isolater, og samtlige inneholdt bla_{CMY-2} genet. Cefalosporinholdige medisiner blir ikke brukt i norsk broilerproduksjon. Sannsynligvis avspeiler resultatene situasjonen internasjonalt. Norge er avhengig av import av avlsdyr. For øvrig har prevalensen av resistens mot forskjellige antibakterielle midler vært stabil og lav til moderat hos *E. coli* fra både svin og broiler i perioden 2000 til 2011.
Til sammen ble det undersøkt 62 isolater av *Enterococcus faecalis* og 176 isolater av *E. faecium* fra broiler. I alt var 45,2 % og 14,4 % følsomme for alle antibiotika for henholdsvis *E. faecalis* og *E. faecium*. *E. faecalis* var oftest resistent mot tetracyklin (45,2 % av isolatene), mens *E. faecium* oftest var resistent mot narasin (68,8 % av isolatene). Bruk av narasin som fôrtilsetning mot kokksidier i broilerproduksjonen kan medføre et seleksjonspress. Ingen vankomycinresistente enterokokker ble påvist med ikke-selektiv isolasjonsmetode. Med selektiv metode var imidlertid 15,9 % av isolatene vankomycinresistente, og alle *vanA* positive isolater var *E. faecium*. Samtlige var dessuten resistente mot narasin.

Resistens hos zoonosebakterier og andre enteropatogene bakterier

I 2011 ble det resistenstestet 49 *Salmonella* spp. isolater fra norske dyr. Resistens mot tetracykliner, ampicillin, streptomycin og sulfonamider ble observert i cirka en tredjedel av isolatene, noe som kan forklares med funn av multiresistent *S. enterica* serovar 4,[5],12:i- isolert fra flere dyrearter. To isolater viste resistens mot fluorokinoloner. Isolater av *S. diarizonae* sau innsamlet fra sau i perioden 2006-2011 ble resistenstestet. Samtlige isolater var følsomme for antibiotika i testpanelet bortsett fra for streptomycin, der 7,5 % var resistente.
I et prøvemateriale av 48 isolater av *Campylobacter jejuni* fra broiler var nesten 90 % av isolatene følsomme for alle antibiotika i testpanelet. Et fåtall isolater (1-3 av 48) var resistente mot kinoloner, streptomycin eller tetracykliner. I perioden 2000 til 2011 har andelen følsomme isolater for alle undersøkte antibiotika holdt seg relativt stabil.
I alt 1033 nesesvabere fra griser tilhørende 207 besetninger ble innsamlet på slakterier og undersøkt for MRSA. Seks isolater (3 %) ble påvist, og alle stammet fra prøver innsamlet ved det samme slakteriet. Alle isolatene hørte til ST398 *spa* type t034. Dette er første påvisning av såkalt dyre-assosiert MRSA hos gris i Norge. Isolatene var samtidig resistente mot tetracyklin, fluorokinolon, klindamycin og erythromycin (4 av 6 isolater). Studien var anonymisert slik at det ikke var mulig å spore prøvene tilbake til opprinnelsesbesetningen(e). Tilsvarende resistensmønster er ikke påvist tidligere hos bakterier isolert fra gris i Norge.

Siden referanselaboratoriet for enteropatogene bakterier, som resistenstester human-isolater, per 01.01.11 gikk over til EUCAST sin standardiserte metode for antimikrobiell resistenstesting, er vurderinger vedrørende eventuelle statistisk signifikante endringer av resistens fra foregående år lite relevant å rapportere. For *Salmonella og Shigella* var det en forskyvning av sonedistribusjon mot venstre, og dette kan ha maskert reell økning av resistens, mens det motsatte var tilfelle for patogene *Yersinia enterocolitica.* Til tross for denne usikkerheten er sterke trender kommentert.
For *Salmonella* er det gjennomgående at forekomsten av resistens i *S.* Typhimurium-gruppen (som inkluderer *S. enterica* serovar 4,[5],12:i:-) er høyere for flere antibiotika enn for andre *Salmonella* serovarer, samt at resistensen er økende. Dette gjelder både for innenlandssmittede og pasienter som er smittet i utlandet.
Det var enda færre isolater med *Yersinia enterocolitica* enn året før (37 i 2011 mot 53 i 2010), og vurderingene blir dermed mer usikre enn tidligere. Det ser imidlertid ut til at forekomsten av resistens holder seg stabilt lav, bortsett fra for ampicillinresistens, som holder seg stabilt høy. Dette skyldes at nesten alle *Yersinia* har kromsomalt kodet betalaktamresistens.
De fleste tilfeller av *Shigella*-infeksjoner i Norge kan knyttes til smittekilder i utlandet. Antibiotikaresistens var utbredt hos *Shigella* isolater, spesielt hos *Shigella flexneri,* i likhet med det som rapporteres fra andre land. Forekomsten synes imidlertid rimelig stabil, kanskje bortsett fra resistens mot fluorokinoloner, som synes å ha økt hos *S. sonnei.*
Når det gjelder ESBL hos tarmpatogene bakterier, synes det å være en økning. I 2011 ble det påvist 13 *Salmonella* med $ESBL_A$ mot 9 året før, samt 3 $ESBL_M$ (ble ikke undersøkt i 2010). Tre *Shigella*-isolater hadde ESBL, hvorav to var $ESBL_A$ og ett isolat hadde $ESBL_M$.
Det har også vært en mindre endring i metoden for resistenstesting av *Campylobacter*, ved skifte av produsent av MIC-strips. Foreløpige resultater fra metode-evalueringen tyder på en forskyvning mot lavere MIC-verdier. Metodeendringen kan altså underestimere reell økning i resistens. Dette kan forklare mangel på signifikant endring av fluorokinolonresistens hos *C. jejuni* siden 2010, men endringen er høysignifikant når det gjøres sammenlikning med tall fra 2008. Når det gjelder erytromycin og gentamicin, er økningen signifikant selv ved sammenlikning av tallene fra 2010 og 2011. For øvrig er resistens mot fluorokinoloner og tetracyclin klart hyppigere i utenlandssmittede isolater.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterie-isolater fra mennesker var, som i de foregående år, meget lav i 2011. Det ble påvist fem tilfeller av meticillin-resistente *Staphylococcus aureus* (MRSA) blant de 1084 blodkulturisolater (0,5 %) som ble inkludert i NORM-protokollen. Dette samsvarer med at syv av 1457 (0,5 %) *S. aureus* blodkulturisolater i laboratorienes datasystemer ble rapportert som MRSA. I 2011 var dermed åtte av 1468 (0,5 %) *S. aureus* fra blodkultur og spinalvæske MRSA. Andelen er på samme nivå som tidligere år (2010:1,0 %, 2009: 0,5 %, 2008: 0,7 %). Meldesystemet for infeksjons-sykdommer (MSIS) registrerte 563 tilfeller av MRSA-

infeksjon i 2011 mot 431 i 2010. Hele 79 % av tilfellene var pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (12/915, 1,3 %) men viste en økning fra 0,6 % i 2010. MSIS registrerte videre 496 tilfeller av MRSA-kolonisering i 2011 mot 481 tilfeller i 2010 og 402 i 2009. Det totale antallet MRSA-meldinger økte dermed fra 912 meldinger i 2010 til 1059 i 2011 (+16,1 %). Resultatene fra overvåkingen viser at det totale antallet personer med påvist infeksjon eller kolonisering med MRSA fortsetter å øke, men at antallet med alvorlige infeksjoner er stabilt på et lavt nivå.

Nedgangen i forekomst av fusidinresistens blant *S. aureus* isolater fra sårprøver har nå stabilisert seg på 9,9 % sammenliknet med 7,7 % i 2010.

Blodkulturisolater av *E. coli* og *Klebsiella* spp. var som tidligere stort sett følsomme for bredspektrede antibiotika. Forekomsten av resistens og nedsatt følsomhet for gentamicin hos *E. coli* var 4,7 % sammenliknet med 5,2 % i 2010 og 4,0 % i 2009. Forekomsten av resistens og nedsatt følsomhet for ciprofloxacin i *E. coli* fortsatte å øke til 9,1 % i 2011. Tallene er justert i henhold til nye brytningspunkter. Det er en klar samvariasjon mellom forbruket av fluorokinoloner og nedsatt følsomhet for denne antibiotikagruppen. *Klebsiella* spp. hadde lavere forekomst av resistens mot 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 48/1438 *E. coli* (3,3 %) og 25/596 (4,2 %) *Klebsiella* spp. isolater fra blodkultur ble rapportert som ESBL positive. For *E. coli* var forekomsten av ESBL litt høyere enn i 2010 (3,0 %). Forekomsten av ESBL blant *Klebsiella* spp. var igjen økende etter en forbigående reduksjon i 2010 (1,5 %). De fleste isolatene kunne verifiseres som ESBL positive ved molekylære analyser, og det er derfor grunn til å følge utviklingen med spesiell oppmerksomhet. Andelen av ESBL positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (3,3 %) enn fra urinprøver (1,6 %). Det ble ikke påvist karbapenemaseproduserende isolater i NORM i 2011, men Kompetansesenteret for påvisning av antibiotikaresistens (K-Res) mottar jevnlig slike stammer. Fra juli 2012 vil karbapenemaseproduserende isolater være nominativt meldepliktige til MSIS.

Det ble påvist fem *Enterococcus faecium* isolater med klinisk signifikant VanB vankomycinresistens i 2011, sannsynligvis tilknyttet et større sykehusutbrudd på Vestlandet. Forekomsten av nedsatt følsomhet for ampicillin i *Enterococcus faecium* ligger fortsatt på rundt 80 %, og høygradig gentamicinresistens ble påvist i hele 26 % av *E. faecalis* og 50 % av *E. faecium*. Alle *E. faecium* isolater med høygradig gentamicinresistens hadde samtidig nedsatt følsomhet for ampicillin. Alle enterokokkisolatene var følsomme for linezolid.

Streptococcus pneumoniae fra blodkultur og spinalvæske var generelt følsomme for alle relevante antibiotika. Trettien av 727 isolater (4,3 %) hadde nedsatt følsomhet for penicillin G, og dette er en økning fra 2,9 % i 2009 og 3,0 % i 2010. Det var imidlertid kun tre isolater som hadde samtidig redusert følsomhet for cefalosporiner, og ingen isolater var høygradig resistente mot beta-laktamer. Forekomsten av makrolidresistens blant systemiske pneumokokkisolater har stabilisert seg på rundt 4,0 % etter toppåret 2006 (12,4 %).

Haemophilus influenzae luftveisisolater var generelt følsomme for kloramfenikol, ciprofloxacin og tetracyklin. Forekomsten av betalaktamaseproduksjon har økt jevnt fra 7,0 % i 2000 til 12,3 % i 2011. Påvisning av kromosomal resistens mot betalaktamer er metodologisk utfordrende. Resultatene for 2011 indikerer at forekomsten ligger i størrelsesorden 10-20 %, og at 1-2 % av isolatene har kombinert betalaktamaseproduksjon og PBP endringer.

I alt 362 tilfeller av tuberkulose ble meldt til MSIS i 2011. Det ble utført resistensbestemmelse av 261 *Mycobacterium tuberculosis* isolater. Kun fire isolater fra pasienter smittet i henholdsvis Afrika (n=3) og Europa utenfor Norge (n=1) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 189 blodkulturisolater av *Candida albicans* (n=139), *C. glabrata* (n=25), *C. tropicals* (n=12) og *C. parapsilosis* (n=13). Alle *C. albicans* isolater var følsomme for amphotericin B, fluconazol og voriconazol, mens to isolater var resistente mot anidulafungin som klasserepresentant for echinocandinene. Det ble påvist høy forekomst av resistens mot fluconazol og voriconazol blant *C. glabrata* isolater. Amfotericin B viste høy aktivitet mot alle de undersøkte soppisolatene. Resultatene er i samsvar med tidligere studier fra Norge.

Overvåking av resistens mot antivirale midler omfattet i 2011 både influensavirus og HIV, men resultatene for HIV er foreløpig ikke blitt analysert. Influensasesongen 2011/2012 ble i Norge dominert av influensa A(H3N2) med begrenset spredning av influensa type B og kun spredte enkeltisolater av pandemisk influensa A(H1N1). Alle isolater av influensa A(H3N2) og A(H1N1)pdm var resistente mot M2-blokkere men følsomme for neuraminidasehemmerne oseltamivir og zanamivir. Alle isolater av influensa B var følsomme for neuraminidase-hemmere.

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.

III. SUMMARY

This is the 12th joint report from the NORM surveillance programme for antimicrobial resistance in human pathogens and the NORM-VET monitoring programme for antimicrobial resistance in animal pathogens and the food production sectors. The report presents data on the occurrence of antimicrobial resistance and the usage of antimicrobial agents in humans and animals for the year 2011. The NORM and NORM-VET programmes are 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 Zoonosis Centre, Norwegian Veterinary Institute, Oslo. Successful collaboration has been established between NORM and NORM-VET and a joint 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 2011, the total sales of antimicrobial VMPs for terrestrial animals were 6,271 kg. The annual sales, in kg active substance, of antimicrobial VMPs for use in terrestrial animals decreased by approximately 39% from 1993 to 2011. The reduction in use is accounted for by a reduction in the use in food producing animals (42% reduction) while for antimicrobial VMPs marketed for companion animals an increase of 36% in the sales is observed. The sales patterns of antimicrobial VMPs for terrestrial animals have gradually become more favourable as the proportion of penicillin use has increased; the proportion accounted for by pure penicillin preparations rose from 29% of total sales in 1993 to 51% in 2011. In this period the sales of aminoglycosides decreased from 32% to 25% of total sales; this is due to a reduction in the use of combination preparations of penicillin and dihydro-streptomycin in food producing animals. 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 organizations and the Norwegian Medicine Authority during the second part of the 1990s. Furthermore, a target set by the Norwegian husbandry organizations to reduce the sales by 25% with 1995 as the reference year is thought to have had a major impact on this decrease. In 2011, the total sales of antimicrobial agents for therapeutic use in farmed fish were 549 kg of active substance of which quinolones accounted for 39%. The sales of antimicrobial VMPs in Norwegian aquaculture declined by approximately 99% from a peak in 1987 to 1996 and has thereafter remained relatively constant. This reduction is mainly attributed to the introduction of effective vaccines in salmonids. In 2011, the total sales of ionophore coccidiostat feed additives, in kilograms of active substance, was more than twice the amounts used prior to the withdrawal of the antimicrobial growth promoters in 1995. This is explained by increased production of broilers. While monensin was the most frequently used ionophore in poultry in 1995, the usage of coccidiostats has since then been dominated by narasin.

Usage of antimicrobial agents in humans

In 2011, the overall sale of antibacterials for systemic use in humans was 20.6 DDD/1,000 inhabitants/day, an increase of 5% compared to 2010. When methenamine is excluded, the level of antibiotic use in 2011 was 17.2 DDD/1,000 inhabitants/day. Since 2007 the sales have been relatively stable, and the increase from 2010-2011 is therefore cause for concern.

Over the last decade the sales of penicillins and quinolones have increased, while sales of sulfonamides and trimethoprim have decreased. From 2010 to 2011 there has also been a marked increase in the sales of macrolides (+ 15%) and tetracyclines (+ 11%) which may in part be explained by a national epidemic of *Mycoplasma pneumoniae* infections. The use of the urinary antiseptic agent methenamine still increases and accounted for 17% of total sales in 2011, measured in DDDs.

In 2011, 41% of the total antibiotic human use, measured in DDDs, was penicillins. As in 2010, an increase in the use of penicillins with extended specter and beta-lactamase resistant penicillins was observed. Tetracyclines accounted for 17% of total consumption in 2011. The consumption of macrolides and lincosamides accounted for 11% of total sales. Sales of cephalosporins, monobactams and carbapenems constitute 3% of total sales. Over the years there has been a marked increase in quinolone use. This group accounted for only 4% of total consumption in 2011, but sales have more than doubled since 2000.

The use of antibacterials varies according to gender, age and area of residence. Sales to hospitals and ambulatory care accounted for 7% and 84%, respectively. Penicillins accounted for around 45% of sales to hospitals and 41% to ambulatory care. The other main groups in hospitals were cephalosporins (19%) and quinolones (7%), while in ambulatory care the most important other groups were tetracyclines (19%) and macrolides and lincosamides (12%).

Resistance in animal clinical isolates

Clinical isolates of *E. coli* (n=38) from broiler with septicaemia were included in the survey. The prevalence of antimicrobial resistance was moderate to high. In total, 36.8% of the isolates were susceptible to all antimicrobial agents in the test panel. Approximately 21% of the isolates were resistant to one antimicrobial agent (mainly sulfonamides), and approximately 15% were resistant to two (ampicillin and tetracycline or sulfonamides). One isolate was resistant to third generation cephalosporins and contained the $bla_{\text{CMY-2}}$ gene.

Resistance in indicator bacteria from animals

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

In 2011, *E. coli* isolated from faecal samples from swine (192 isolates) and from caecal content of broiler (208 isolates) were included. For both animal species the prevalence of resistant *E. coli* was moderate and approximately 75% of the isolates were susceptible to all antimicrobials included in the test panel.

In swine, resistance to one of the antimicrobial agents was identified in 9.9% of the isolates and most prevalent was resistance to streptomycin. Only a few isolates were multi-resistant. One isolate had reduced susceptibility to third generation cephalosporins, further investigations indicated increased chromosomal AmpC production. By using a selective method for detection of ESBL producing *E. coli*, one isolate was resistant to third generation cehpalosporins and contained the bla_{TEM-52} gene. This is the first detection of an ESBL producing *E. coli* from swine in Norway.

In broiler, resistance to one of the antimicrobial agents was identified in 16.4% of the isolates and most prevalent was resistance to ampicillin. Few isolates were multi-resistant. Two isolates were resistant to third generation cephalosporins (non-selective method) and both contained the bla_{CMY-2} gene. By using a selective method for detection of ESBL producing *E. coli*, 43% (108 out of 252 samples) of the samples were positive. All isolates had a beta-lactam resistance profile corresponding to an AmpC phenotype. PCR and sequencing showed that all isolates contained the bla_{CMY-2} gene. Drugs containing cephalosporins are not used in Norwegian broilers. The results probably mirror the international situation as Norway is dependent on import of breeder birds.

In broiler, isolates of *Enterococcus faecalis* (n=62) and *E. faecium* (n=176) were examined for susceptibility to antimicrobial agents. In total, 45.2% and 14.4% of the isolates of *E. faecalis* and *E. faecium*, respectively, were susceptible to all agents in the test panel. Resistance to tetracycline dominated in *E. faecalis* (45.2% of isolates) and resistance to the coccidiostat narasin dominated in *E. faecium* (68.8%). Narasin is used routinely as feed additive in broiler production and exerts a selection pressure. Vancomycin resistant enterococci (VRE) were not detected by using a non-selective method. However, by the selective method, VRE were identified in 15.9% of the samples. All isolates contained the *vanA* gene and belonged to *E. faecium* and were also resistant to narasin.

Resistance in zoonotic and non-zoonotic enteropathogenic bacteria

In 2011, a total of 49 *Salmonella* spp. isolates from Norwegian animals were susceptibility tested. Resistance to tetracyclines, ampicillin, streptomycin or sulfonamides was observed in nearly one third of isolates, which was explained by the emerging multi-resistant *S. enterica* serovar 4,[5],12:i- detected from several animal species. Two isolates were resistant to fluoroquinolones.

Isolates of *S. diarizonae* from sheep were collected in the period 2006 to 2011 and tested for susceptibilty to antimicrobial agents. All isolates were susceptible to the antimicrobials included in the test panel except for streptomycin, 7.5% were resistant to this agent. In a study including 48 *Campylobacter jejuni* isolates from broiler, the majority (90%) were susceptible to the antimicrobials included in the test panel. In the period 2000 to 2011 this favourable situation has been relatively stable.

A total of 1,033 slaughter pigs were sampled using nasal swabs and examined for Methicillin Resistant *Staphylococcus aureus* (MRSA). The animals originated from 207 different farms. The investigation was anonymous. MRSA was detected in six pooled samples (3%), all originating from animals slaughtered at the same slaughterhouse. All isolates belonged to ST398 *spa* type t034. In addition to resistance against beta-lactams, all isolates presented a multiresistant profile including resistance to the antimicrobials tetracycline, fluoro-quinolones, clindamycin and erythromycin (four of six isolates). This is the first time the livestock-associated MRSA has been isolated from swine in Norway.

In 2011, the reference laboratory on human isolates of enteropathogenic bacteria changed methodology to the EUCAST standardised method for antimicrobial susceptibility testing of fastidious *Enterobacteriaceae.* Thus, the judgments regarding possible changes over time may be based on false prerequisites. The crude results from disc diffusion zone diameters show a left shift regarding *Salmonella* and *Shigella,* whereas for *Yersinia enterocolitica* there was a slight shift to the right for some of the antimicrobials tested. Consequently, changes in resistance rates in *Salmonella* and *Shigella* may be underestimated and changes in resistance rates in *Yersinia enterocolitica* may be slightly overestimated. In spite of these uncertainties, changes have been commented on.

Antimicrobial resistance in the *S.* Typhimurium-group (including *S. enterica* serovar 4,[5],12:i-) seems to be on a higher level than for other serovars., and the resistance is increasing. This applies to domestically acquired strains as well as to strains acquired abroad.

Shigella flexneri seems to be resistant to more anti-microbials than *Shigella sonnei.* The rates of resistance seem, however, stable except for resistance to flouro-quinolones, which may have increased in *Shigella sonnei.*

The absolute number of tested pathogenic *Yersinia enterocolitica* is even lower than in 2010, and evaluation of the results is therefore more unreliable than in previous years. It seems, however, that resistance rates are stably low, except for resistance to ampicllin which is stably high due to intrinsic resistance.

The number of ESBL-carrying fastidious enteropathogenic bacteria seems to have increased. In 2011 thirteen strains of *Salmonella* were verified to carry $ESBL_A$, and three carried $ESBL_M$, whereas two *Shigella*-isolates carried $ESBL_A$ (AmpC) and one isolat had $ESBL_M$.

Susceptibility testing of *Campylobacter* was slightly modified by a change of supplier of MIC strips. Preliminary evaluation of the reliability study may indicate a shift to lower MIC-values (more sensitive strains). This may underestimate possibly true increases in resistance and may explain the lack of significance for the apparent increase in resistance to flouroquionlones in *Campylobactrer jejuni* from 2010 to 2011. When comparing with 2008 numbers, however, the change is highly significant. In spite of a possible underestimation of the increase in resistance, the change did reach statistical significance for erythromycin and gentamicin when comparing 2010 and 2011. Resistance to fluoroquinolones and tetracycline is more prevalent in strains acquired abroad than among those acqiured in Norway. The prevalences of resistance towards all antimicrobials tested are stable in strains acquired abroad.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still very low in Norway in 2011. Only five methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among the 1,084 strains included in the NORM protocol (0.5%), and seven out of 1,457 (0.5%) *S. aureus* isolates were reported as MRSA from the laboratories´ information systems. The total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 1,468 including

eight MRSA strains (0.5%). This prevalence is at the same level as in 2010 (1.0%), 2009 (0.5%) and 2008 (0.7%). The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 563 cases of MRSA infections in 2011 compared to 431 in 2010. A majority of the MRSA cases (79%) were reported to be wound infections and/or abscesses. Conversely, the prevalence of MRSA among non-invasive *S. aureus* isolates is still very low at 1.3% (12/915) but increased from 0.6% in 2010. Furthermore, MSIS registered 496 cases of MRSA colonisation compared to 481 in 2010 and 402 in 2009. The total number of MRSA notifications thus increased from 912 in 2010 to 1,059 in 2011 (+16.1%). The results indicate an increasing number of MRSA infections and colonisations, while the prevalence of invasive disease remains stable at a low level. The decline in the epidemic of fusidic acid resistant *S. aureus* wound isolates has now stabilised at 9.9% compared to 7.7% in 2010.

E. coli and *Klebsiella* spp. blood culture isolates were generally susceptible to broad-spectrum antimicrobials. The prevalence of gentamicin non-susceptibility in *E. coli* was 4.7% compared to 5.2% in 2010 and 4.0% in 2009. The increasing prevalence of *E. coli* non-susceptibility to fluoroquinolones continued and reached 9.1% in 2011. The figures have been adjusted for changes in microbiological breakpoints. There is a clear correlation between the total usage of fluoroquinolones and non-susceptibility to these agents. The prevalence of resistance to 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 48/1,438 (3.3%) *E. coli* and 25/596 (4.2%) *Klebsiella* spp. blood culture isolates were reported with this phenotype in 2011. For *E. coli*, this is a slight increase from 2010 (3.0%). The prevalence of ESBL production in *Klebsiella* spp. is again increasing after a temporary decline in 2010 (1.5%). As most of these isolates were verified by molecular methods, the trend should be closely monitored. The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (3.3%) than among urinary tract isolates (1.6%). No carbapenemase producing isolates were included in the NORM protocol in 2011, but occasional isolates have been received at the Reference Center for Detection of Antimicrobial Resistance (K-Res). From July 2012, carbapenemase producing isolates should be individually reported to MSIS.

Five *Enterococcus faecium* isolates with clinically significant VanB vancomycin resistance were detected in 2011, presumably linked to a major hospital outbreak in the Western part of the country. The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilised around 80%, and high-level gentamicin resistance (HLGR) was detected in 26% of *E. faecalis* and 50% of *E. faecium*. All HLGR *E. faecium* isolates were also non-susceptible to ampicillin. All enterococcal isolates were susceptible to linezolid.

Streptococcus pneumoniae from blood cultures and cerebrospinal fluids were generally susceptible to all relevant antimicrobials. Thirty-one out of 727 isolates (4.3%) displayed reduced susceptibility to penicillin G, and this is an increase from 2.9% in 2009 and 3.0% in 2010. However, only three isolate were non-susceptible to cephalosporins, and no isolates displayed high-level resistance to beta-lactam antibiotics. The prevalence of macrolide resistance among pneumococcal blood culture isolates has now stabilised at 4.0% after a peak of 12.4% in 2006.

Haemophilus influenzae respiratory tract isolates were generally susceptible to chloramphenicol, ciprofloxacin and tetracycline. The prevalence of beta-lactamase production has steadily increased from 7.0% in 2000 to 12.3% in 2011. The detection of chromosomally encoded beta-lactam resistance in *H. influenzae* is technically challenging. The results from 2011 indicate a prevalence anywhere in the range between 10-20%, and the combination of beta-lactamase production and PBP changes apparently occurs in 1-2% of isolates.

A total of 362 cases of tuberculosis were reported to MSIS in 2011. Susceptibility tests were performed on 261 *Mycobacterium tuberculosis* isolates. Only four isolates, originating from Africa (n=3) and Europe outside Norway (n=1), were classified as multidrug-resistant (MDR).

Susceptibility testing was performed on 189 blood culture isolates of *Candida albicans* (n=139), *C. glabrata* (n=25), *C. tropicals* (n=12) and *C. parapsilosis* (n=13). All *C. albicans* isolates were susceptible to amphotericin B, fluconazole and voriconazole, while two isolates were resistant to anidulafungin as a class representative for echinocandins. A high prevalence of resistance to fluconazole and voriconazole was detected in *C. glabrata* isolates. Amphotericin B was active against all yeast isolates. The results are in accordance with previous studies from Norway.

Surveillance data on resistance to antiviral agents included both influenza virus and HIV in 2011, but the HIV data have as yet not been analysed. The 2011/2012 influenza season was dominated by influenza A(H3N2) with limited circulation of influenza type B and only occasional isolates of pandemic influenza A(H1N1). All isolates of influenza A(H3N2) and the few pandemic A(H1N1)pdm isolates were uniformly resistant to M2 blockers but fully susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. All influenza B isolates were susceptible to neuraminidase inhibitors.

Conclusion

Antimicrobial resistance is still a limited problem in Norway. The relatively low usage of antimicrobial agents as well as the appropriate patterns of use must be maintained to preserve this favourable situation. The data presented in this report show that Norwegian antimicrobial policies in food production and health care 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.

IV. 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, 2012.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	310,767	159,663	151,104
5 to 14 years	612,808	313,431	299,377
15 to 24 years	655,585	336,180	319,405
25 to 44 years	1 373,016	703,481	669,535
45 to 64 years	1 265,680	645,761	619,919
65 years and older	768,054	340,355	427,659
All age groups	4 985,910	2 498,871	2 486,999

TABLE 2. Livestock population in Norway in 2011.
Data provided by the Register of Production Subsidies as of 31 July, 2011.

	Number* of	
Animal category	Herds	Animals
Cattle	16,100	862,000
Dairy cows only**	9,600	209,000
Suckling cow only**	4,200	63,400
Combined production (cow)**	920	32,600
Goat	1,300	66,900
Dairy goat**	380	35,400
Sheep	14,600	2 291,000
Breeding sheep > 1 year**	14,500	882,000
Swine	2,300	839,000
Breeding animal > 6 months**	1,300	56,000
Fattening pigs for slaughter**	2,100	460,000
Poultry		
Egg laying hen (> 20 weeks of age)	1,700	3 778,000
Flocks > 250 birds**	580	3 756,000
Broiler	590#	-
Turkey, ducks and geese for slaughter	150	372,000
Flocks > 25 birds**	52	371,000

* Numbers >100 rounded to the nearest ten, numbers > 1000 rounded to the nearest hundred.
** Included in above total.
#Number tested in the surveillance for Campylobacter.

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2011. *Data provided by the Norwegian Directorate of Fisheries.*

Year	Atlantic salmon (ton)	Rainbow trout (ton)	Cod (ton)	Arctic char (ton*)	Halibut (ton*)	Blue mussels (ton)	Scallops[1] (ton)	Oysters (ton)
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	1 059,958	58,311	15,249	276	2,767	1,742	12.7	1.7

[1]From the wild population. *After 2001 in numbers of 1,000 individuals.

Import of live animals

Import of live animals (excluding fish and companion animals) to Norway in 2011 was limited to one cattle, 39 sheep, 108 reindeer for slaughter and 45,029 day old chicks.

V. USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

Kari Grave

Therapeutic usage of veterinary antimicrobial agents

Total sales (in kg active substance) in Norway of antimicrobial veterinary medicinal products (VMPs) for therapeutic use split into sales for use in food producing animals and companion animals in the period 1993-2011 are shown in Figure 1. The data are based on sales from drug wholesalers to Norwegian pharmacies and from feed mills to fish farmers (see Appendix 1) of veterinary antimicrobial agents for therapeutic use 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).

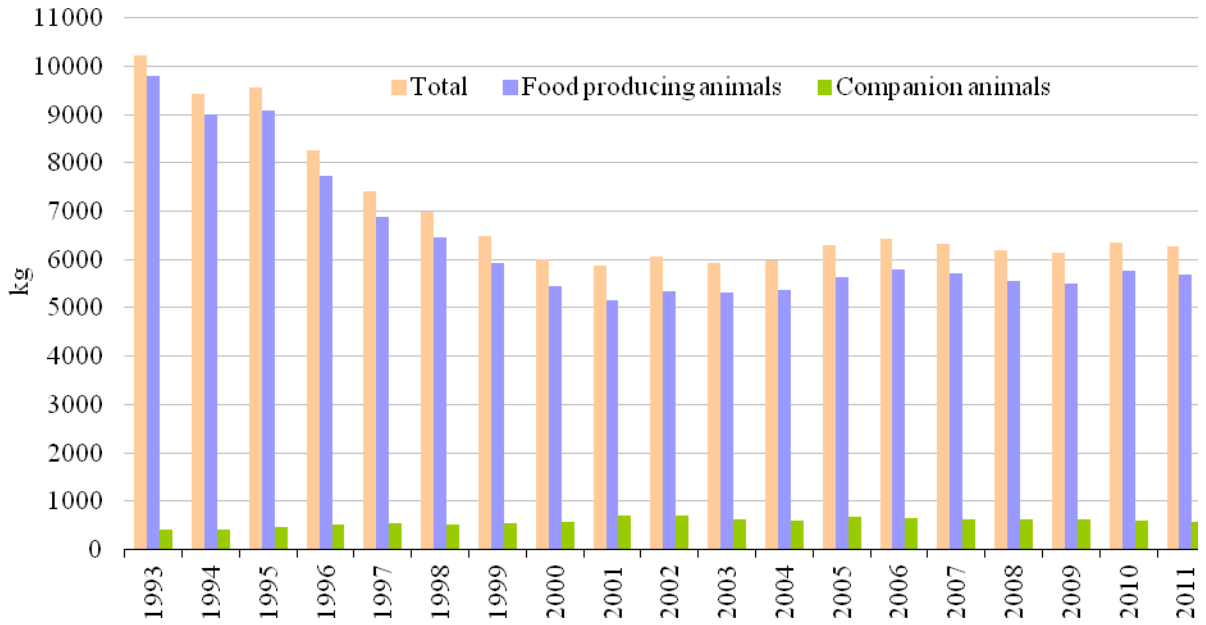

FIGURE 1. Total sales, in kilograms active substance, and estimated sales for food producing animals and companion animals of antimicrobial veterinary medicinal products (VMP) for therapeutic in Norway for the years 1993-2011 (farmed fish not included).

In the period 1993-2011 the total sales of antimicrobial VMPs for use in terrestrial animals decreased by 39%. Of antimicrobial VMPs used almost solely for food production animals the reduction was 42%, while for products used in companion animal only an increase of 36% was observed (Figure 1).

An increase in the sales of penicillin VMPs is observed for the period 1993-2011 from 29% to 51% of total sales and this is accounted for by products used in food producing and in companion animals (Figures 2-3). In this period the sales of aminoglycosides decreased from 32% to 25% of the total sales; this is due to a reduction in the use of combination preparations of penicillin and dihydro-streptomycin in food producing animals (Figure 2).

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 3).

The sales of the antimicrobial VMPs defined by the World Health Organization (WHO) as critically important in human medicine are negligible, i.e. 3rd and 4th generation cephalosporins, fluoroquinolones and macrolides (Figures 2-3). There are no cephalosporin VMPs marketed in Norway for food producing animals and only one such product for companion animals (3rd generation cephalosporin).

The reduced sales of antimicrobial VMPs in food producing animals as well as the favourable prescribing patterns are mainly explained by a campaign on prudent use of antimicrobials conducted by the Norwegian husbandry organizations and Norwegian Medicine Authority during the second part of the 1990s. Furthermore, a target set by the Norwegian husbandry organizations to reduce the sales by 25% with 1995 as the reference year is thought to have had a major impact on this decrease.

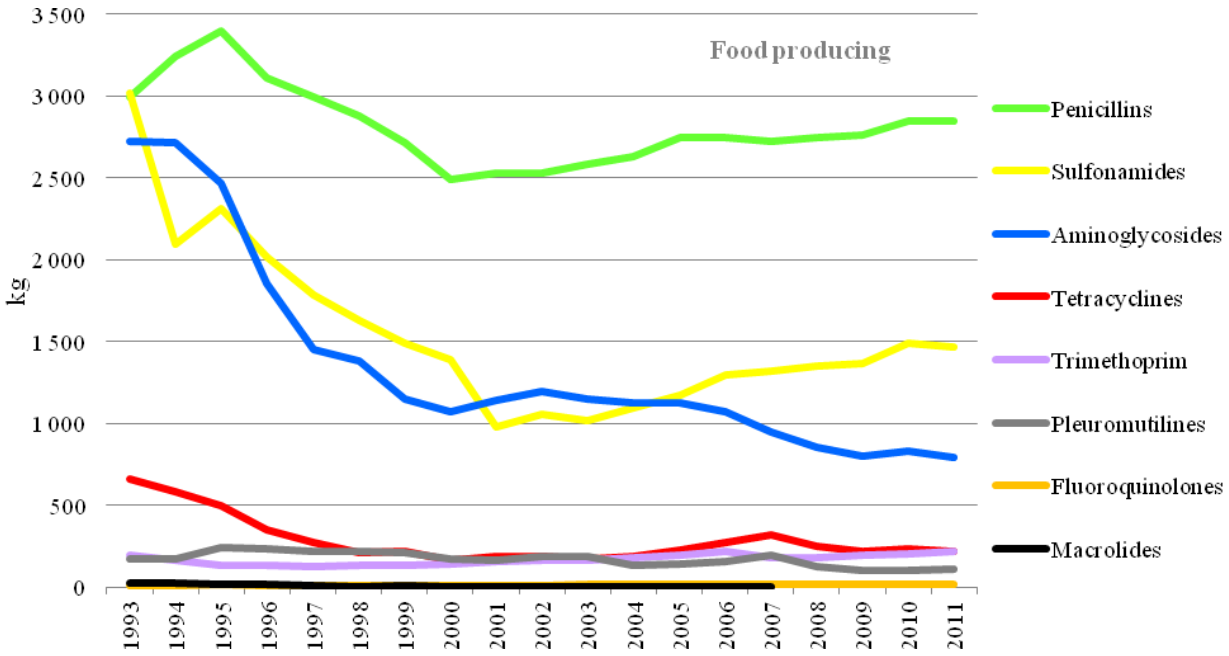

FIGURE 2. Sales in Norway (kilograms active substance) of antimicrobial veterinary medicinal products (VMP) mainly for therapeutic used in food producing animals for the years 1993-2011 (farmed fish not included). In addition, minor amounts of amphenicols (19, 24, 26 and 24 kg) were sold in 2008, 2009, 2010 and 2011, respectively.

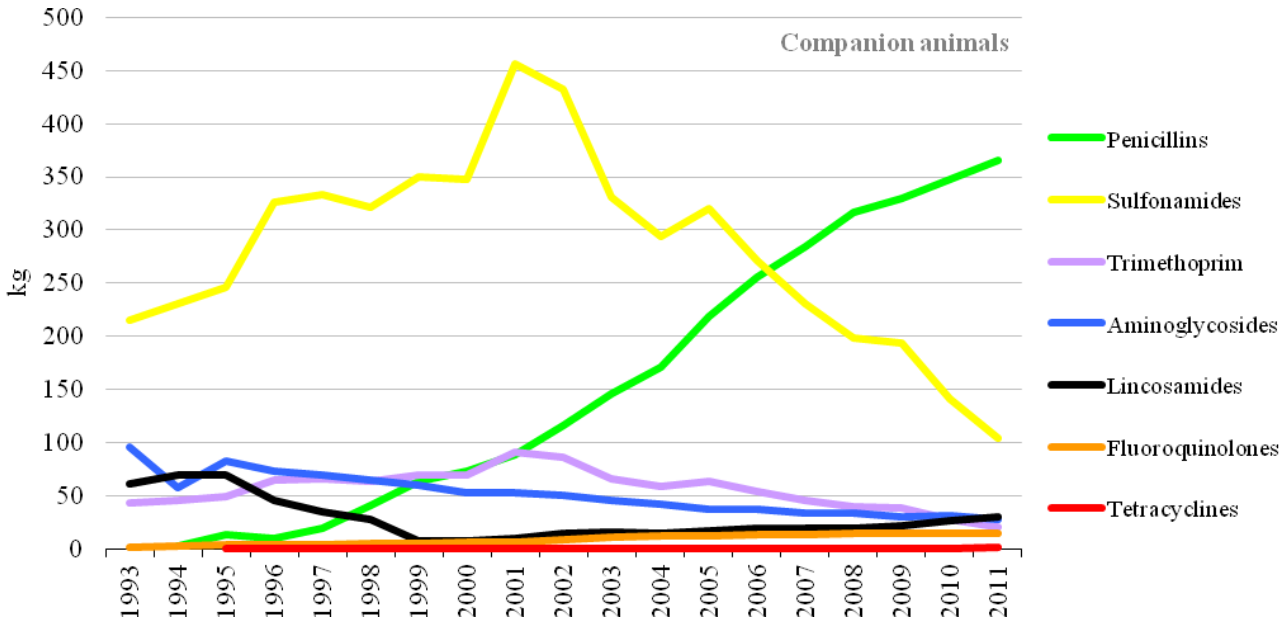

FIGURE 3. Sales in Norway, in kilograms active substance, of antimicrobial veterinary medicinal products (VMP) marketed for therapeutic use in companion animals for the years 1993-2011. In addition, minor amounts of a 3rd generation cephalosporin (1 kg) were sold annually during 2008-2011.

An increase of 36% in the sales, in kg active substance, from 417 to 567 kg of antimicrobial VMPs marketed for companion animals from 1993-2011 is observed (Figure 3). This increase is mainly accounted for by penicillins, and in 2011 approximately 88% of the penicillins sold for companion animals was as a combination of amoxicillin and a beta-lactamase inhibitor (Figure 4).

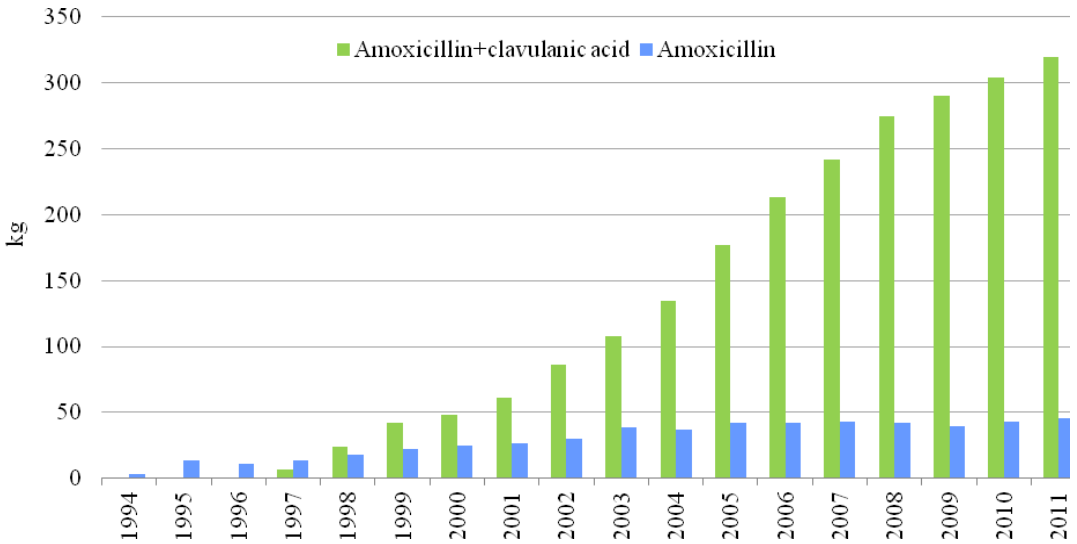

FIGURE 4. Sales, in kg active substance, of penicillin veterinary medicinal products for companion animals 1994-2011.

The annual sales of antimicrobial VMPs for use in farmed fish peaked in 1987 when the sales amounted to 48 tons (Figure 5). In 2011, the sales of antimicrobial VMPs for use in farmed fish were 549 kg active substance, of which 39% were quinolones (Table 4); this implies that the sales have declined by approximately 99% from 1987.

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.

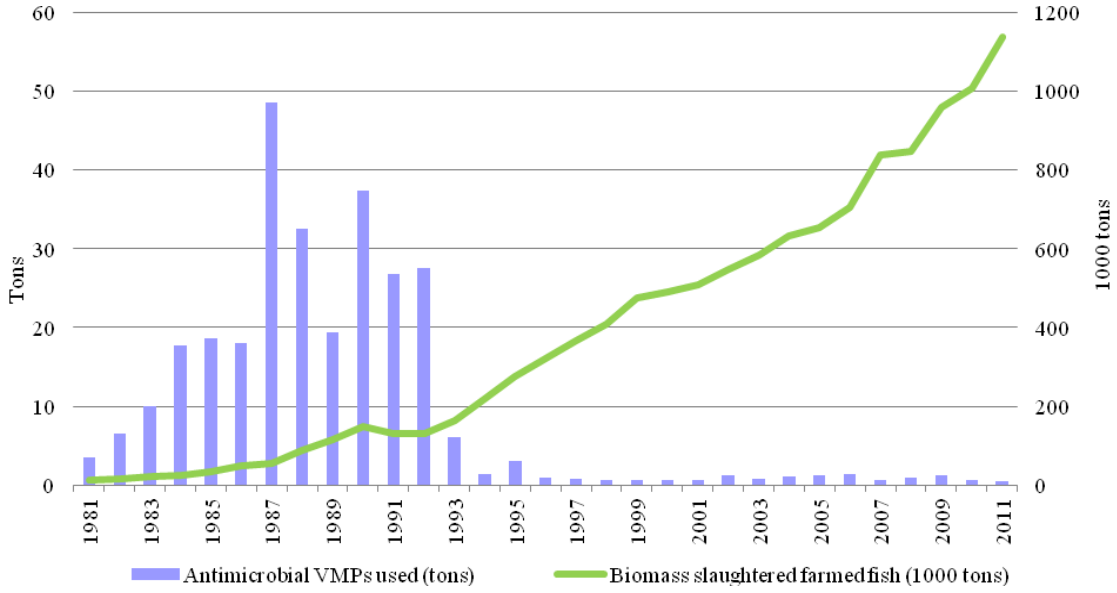

FIGURE 5. Total sales, in tons of active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 1981-2011 versus produced biomass (slaughtered) farmed fish.

TABLE 4. Total sales, in kilograms of active substance, of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 2000-2011.

Group of substances/active substance	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Tetracyclines												
Ox tetracycline	15	12	11	45	9	8	0	19	23	40	10	1
Amphenicols												
Florfenicol	148	109	205	154	111	202	302	139	166	303	275	336
Quinolones												
Flumequine	52	7	5	60	4	28	7	18	1	1	0	0
Oxolinic acid	470	517	998	546	1,035	977	1,119	406	681	926	308	212
Combinations												
Spectinomycin + lincomycin (2+1)	0	0	0	0	0	0	50	66	70	43	57	0
Total	**685**	**645**	**1,219**	**805**	**1,159**	**1,215**	**1,478**	**648**	**941**	**1,313**	**649**	**549**

Antimicrobial and coccidiostatic feed additives

Data on the sales of various substances and categories of feed additives (Table 5) were obtained through annual reports from the Norwegian Agricultural Inspection Service (2000-2002) and the Norwegian Food Safety Authority (2003-2011).
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, including avoparcin. These measures resulted in an immediate reduction in the usage of these substances (Figur 6). No antimicrobial growth promoters have been used in animals in Norway since 1997.

TABLE 5. Total sales, in kilograms of active substance, of coccidiostats as feed additives in Norway 2000-2011. Data were obtained through annual reports from the Norwegian Agricultural Inspection Service (2000-2002) and the Norwegian Food Safety Authority (2003-2011).

Active substance	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Lasalocid	80	96	514	108	173	37	13	17	16	63	0	0
Monensin	776	629	521	717	817	852	889	919	897	885	805	1,060
Salinomycin	233	12	0	0	0	0	0	0	0	0	0	0
Narasin	4,486	4,195	4,470	5,067	5,270	5,318	5,615	7,065	9,212	8,621	9,080	9,394
Total ionophore coccidiostats	**5,575**	**4,932**	**5,505**	**5,892**	**6,260**	**6,207**	**6,517**	**8,001**	**10,125**	**9,569**	**9,885**	**10,454**
Amprolium/etopabat	135	159	74	42	0.8	0	0	0	0	0	0	0
Total others	**135**	**159**	**74**	**42**	**0.8**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

The total sales of ionophore coccidiostats (kilograms of active substance) have been doubled since the withdrawal of antimicrobial growth promoters in 1995 and have since then almost totally been dominated by narasin (Table 5, Figur 6). The sales of ionophore coccidiostats are highly correlated to the number of slaughtered chicken produced in this period.

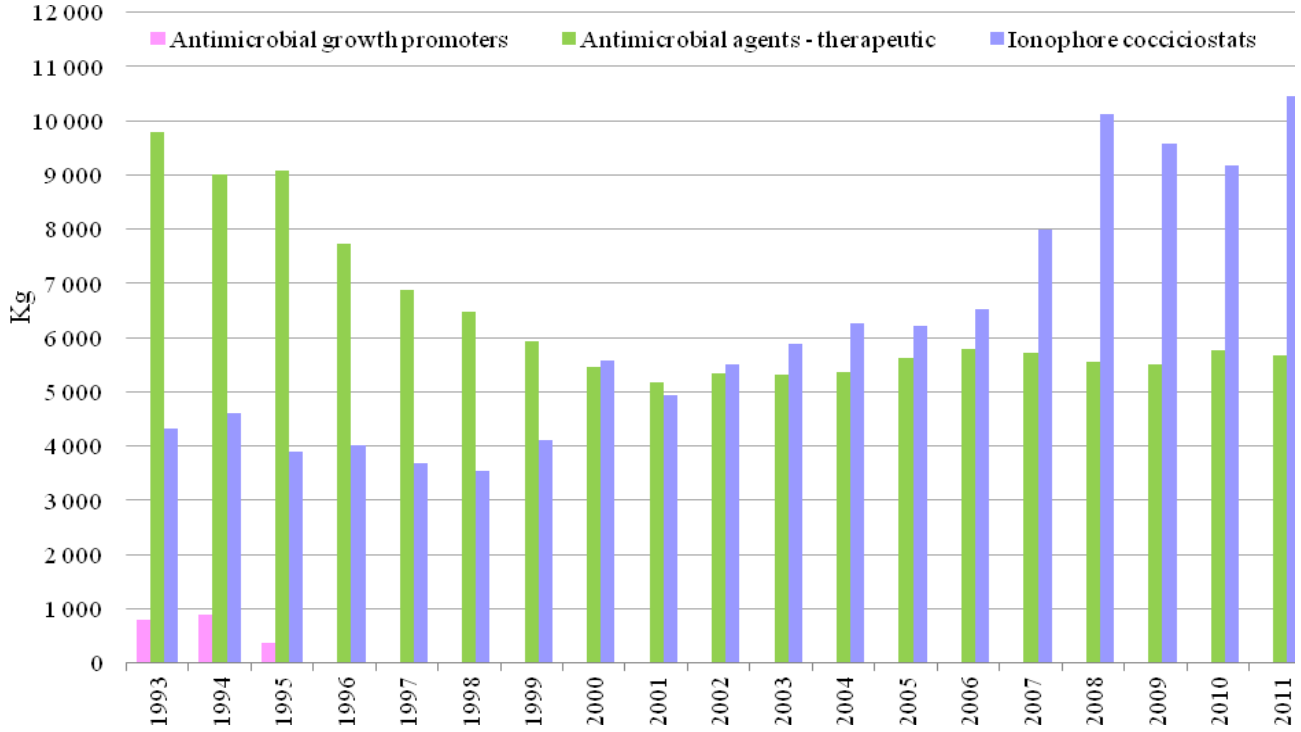

FIGURE 6. Sales, in kg active substance, of antimicrobial veterinary medicinal products (antimicrobial growth promoters, therapeutic antimicrobial agents and ionophore coccidiostats) for food producing animals in Norway during 1994-2011.

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

In 2011, the overall sales in Norway of antibacterials for use in humans, terrestrial animals and farmed fish measured in weight of active substance were 58.1 tons (Figure 7). Human use accounted for 88.2% of the total use, terrestrial animal use for 10.9% and the use in aquaculture only for 1% of total use. The increase of 16% (in tons) from 2005 is solely caused by increased use in humans. When excluding methenamine, the five year increase was 11% (from 41.0 tons in 2005 to 45.4 tons in 2011).

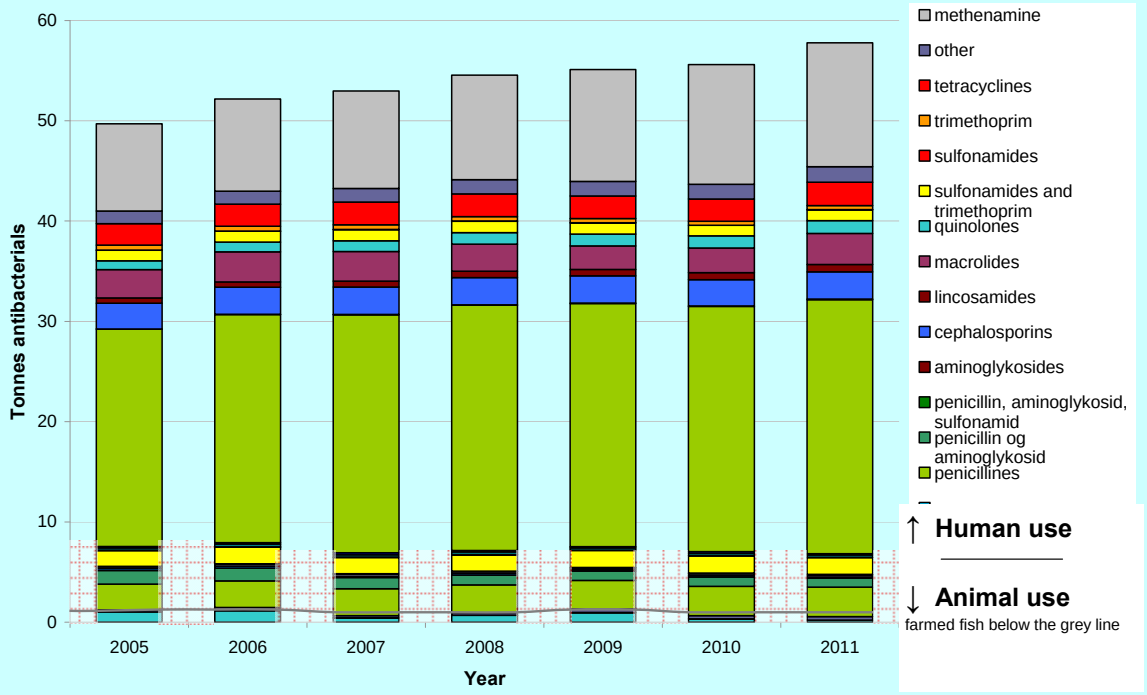

FIGURE 7. Sales, in tons of active substance, of human and veterinary antibacterials, for the years 2005-2011. Use in farmed fish is included and appears below the grey line.

As seen in Table 6, oral formulations are dominating in human medicine while for veterinary medicine the dominating formulations are the parenteral ones. The oral formulations of human antibacterials represent 78% the total weight. The other dominant formulations are parenteral formulations (human and animals) and oral formulations in animals. Use of other formulations e.g. for eye, ear and skin is limited.

TABLE 6. Sales, in kilograms of active substance, of human and veterinary antibacterials according to formulation in 2011.

Formulation	Humans	Terrestrial animals	Farmed fish
Dermal	108	3	
Oral	45,354	2,398	549
Parenteral	5,685	3,283	
Eye / ear	37	11	
Intramammary		461	
Others	50	129	
Total	51,234	6,285	549

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USAGE IN HUMANS

Hege Salvesen Blix

In 2011, the overall sales of antibacterials for systemic use in humans were 20.6 DDD/1,000 inhabitants/day, an increase of 5% compared to 2010. Since 2004, total sales of antibacterials have been increasing, mainly due to the penicillin group and to increased use of methenamine. When methenamine is excluded, the level of antibiotic use in 2011 was 17.2 DDD/1,000 inhabitants/day. The increase observed in 2011 is mainly due to an increase for the macrolides and the tetracyclines (Table 7, Figure 8).

TABLE 7. Human usage of antibacterial agents in Norway 2004-2011 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2010-2011. Collection methodology of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2004	2005	2006	2007	2008	2009	2010	2011	Change (%) 2010-2011
J01A	Tetracyclines	2.97	3.11	3.24	3.32	3.22	3.09	3.12	3.47	+ 11
J01B	Amphenicols	0.001	0.001	0.002	0.001	0.001	0.002	0.001	0.001	-
J01CA	Penicillins with extended spectrum	2.37	2.53	2.74	2.93	3.09	3.15	3.19	3.21	+ 1
J01CE	Beta-lactamase sensitive penicillins	4.23	4.55	4.63	4.70	4.71	4.47	4.44	4.47	+ 1
J01CF	Beta-lactamase resistant penicillins	0.63	0.56	0.66	0.72	0.77	0.80	0.82	0.88	+ 8
J01CR	Combination of penicillins	0.01	0.01	0.01	0.02	0.02	0.02	0.03	0.03	-
J01D	Cephalosporins, monobactams, carbapenems	0.61	0.57	0.60	0.60	0.60	0.58	0.55	0.56	+ 2
J01E	Sulfonamides and trimethoprim	1.09	1.06	1.04	1.02	0.98	0.94	0.87	0.87	-
J01F	Macrolides, lincosamides and streptogramins	1.89	2.12	2.24	2.30	2.13	1.89	2.01	2.31	+ 15
J01G	Aminoglycosides	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.07	-
J01M	Quinolones	0.52	0.57	0.62	0.67	0.70	0.71	0.73	0.75	+ 2
J01X*	Other antibacterials	2.83	3.05	3.18	3.30	3.48	3.65	3.84	3.93	+ 2
	Total exclusive of methenamine	**14.8**	**15.6**	**16.3**	**16.9**	**16.8**	**16.2**	**16.3**	**17.2**	**+ 5**
	Total all antimicrobial agents	**17.2**	**18.2**	**19.0**	**19.7**	**19.8**	**19.4**	**19.7**	**20.6**	**+ 5**

* J01X includes glycopeptides, colistin, fusidic acid, metronidazol (i.v.), nitrofurantoin, linezolid and methenamine. Of total J01X, methenamine constitutes 3.44 DDD/1000 inhabitants/day.

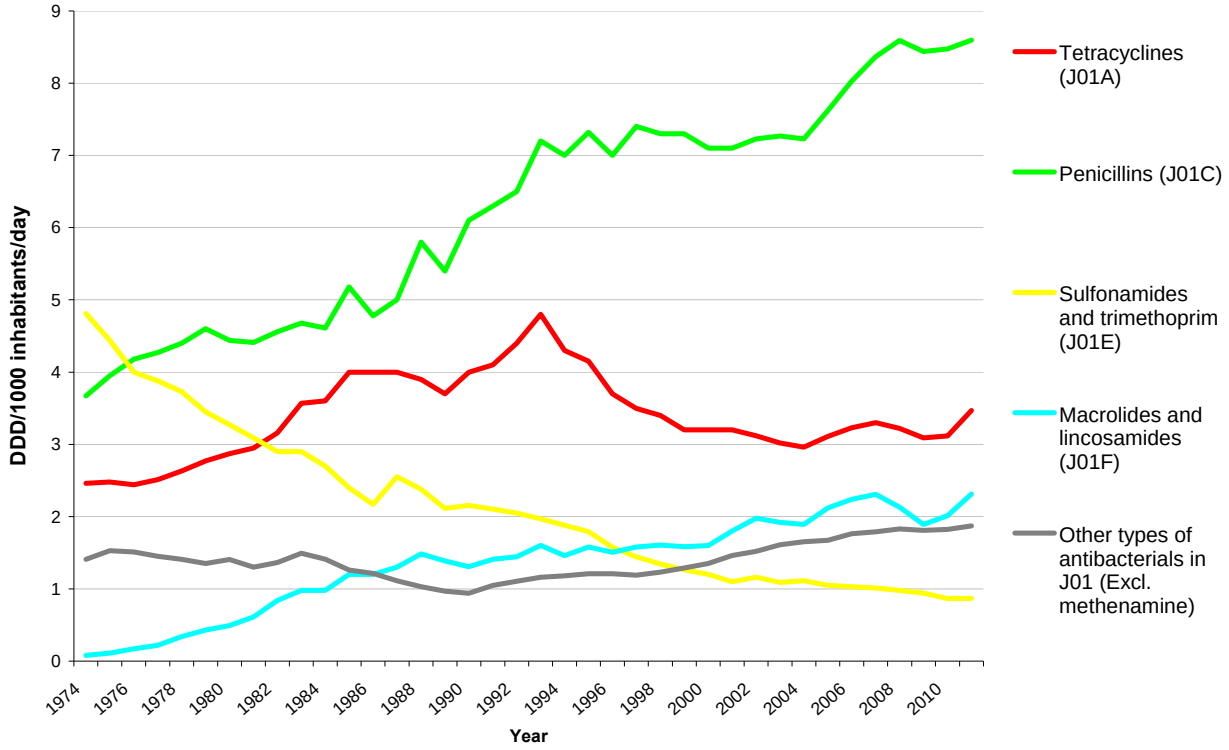

FIGURE 8. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E) and other antibacterials in Norway 1974-2011. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05).

In 2011, the penicillins (ATC group J01C) accounted for 41% of the total antibacterial use in Norway (Figure 8). Within the penicillins the beta-lactamase sensitive penicillins (J01CE) is the largest subgroup. Over the years there has been a shift towards use of more broadspectered penicillins. Penicillins with extended spectre (J01CA) now represent 37% of the penicillin group compared to 29% a decade ago, in 2001 (Figure 10). This is mainly due to increasing use of pivmecillinam, that has become a prominent choice for urinary tract infections at the expense of the subgroup of sulfonamides and trimethoprim, which has decreased over the years (Figure 8).

An epidemic of *Mycoplasma pneumoniae* was noted in Norway in late autumn 2011. The epidemic resulted in shortage of erythromycin and the use of alternative antibiotics such as tetracyclines was recommended. This epidemic is probably the reason for the increase in macrolides (J01FA) and tetracyclines (J01A) in 2011. Tetracyclines increased by 11%, compared to 2010 and represent 17% of total use, while the macrolides, lincosamides and streptogramins (J01F) increased by 15% and accounted for 11% of total use in 2011 (Table 7 and Figure 9).

The use of of the group J01F macrolides, lincosamides and streptogramins has followed a wavy pattern over the years although the internal pattern within the group has remained relatively unchanged over the years (Figure 11). The shifts in use could be explained to some degree by the recurrent epidemics of *M. pneumoniae* in Norway, occurring with five- to seven-year intervals, at least for the years 2011/12 and 2006. In year 2000, an epidemic was noted, but this can not be identified through the drug use data.

In the latest years, sales of cephalosporins, monobactams and carbapenems have been stable and this group represents 3% of the total sales of antibacterials (Figure 9). The internal subgroup pattern has changed since 1996 (Figure 12). First and third generation cephalosporins hold 48% and 28% of ATC group J01D. In 2001 the proportions were 58% for first and 13% for third generation cephalosporins.

The use of quinolones is increasing. Still, it represents only a small fraction (4%) of total antibacterial sales, but the sales have more than doubled since 2000. Ciprofloxacin is the main substance accounting for 95% of the quinolone group in 2011 (Table 7-8).

The increase of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, accounting for 17% of total antibacterial use (Figure 9).

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. There is a trend of the same high-use and low-use counties over the years. The use has increased from 2010-2011 in all counties (Figure 13).

Antibacterials are prescription-only drugs in Norway. Eigthy-four percent of the total human sales of antibacterials are used outside institutions (hospitals and nursing homes). Physicians are the main prescribers to humans, but dentists prescribe 5% (measured in DDDs) of antibiotics (J01) to humans in ambulatory care. Dentists most often prescribe phenoxymethylpenicillin (78% of all antibiotic-DDDs prescribed by dentists) followed by amoxicillin (9%) and clindamycin (5%).

In ambulatory care in 2011, the most important antibiotic groups were penicillins J01C (41% of DDDs), tetracyclins J01A (19%) and macrolides and lincosamides J01F (12%).

Females use more antibiotics than males. Thirty percent of the females purchased at least one antibiotic course in 2011 compared to 21% of the males. The gender pattern is similar in all regions in the country (Figure 14). The highest use is found among young children, young women and the elderly (Figure 15). Among those who use antibacterials, the elderly use more, both with regard to amount (measured in DDDs) and to the number of prescriptions. For those above 65 years of age, 2-3 prescriptions are dispensed every year compared to 1-2 for younger persons. When 0-4 year olds are prescribed antibacterials, the average prescription number is two per year. Since the dosages for young children are much lower than in adults, the amount DDD per user will be less than in adults (Figure 16).

In 2011, the antibacterial sales (in DDDs) to hospitals represented 7.2% 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 17). Penicillins (J01C) represent around 45% of the use measured in DDDs in hospitals (J01CE 19%, J01CA 15% and J01CF 10%). The second largest group is the cephalosporins; 19% of all DDDs, the dominant subgroup being third generation cephalosporins (J01DD) (9%). In 2011, three single substances accounted for 30% of all antibacterial use in hospitals; benzylpenicillin (15%), cefotaxime (7.5%) and cloxacillin (7.2%). Four selected groups mainly used in hospitals are shown in Figure 18. Since 2006, there has been a stable increase in the use of third generation cephalosporins, carbapenems and piperacillin and enzyminhibitor, while the use of second generation cephalosporins has decreased over the years.

Updated National Guidelines for antibiotic use are available for ambulatory care and nursing homes. A new Guideline for hospital use is planned to be published in fall 2012, see page 31. A national Centre of excellence; Antibiotics Center for Primary Health Care, was established in 2006 and a National Centre for Antibiotic Use in Hospitals was established in 2011. These centres will, among other tasks, be responsible for updating national guidelines and this will hopefully have a positive impact on therapy traditions and antibacterial prescribing in Norway.

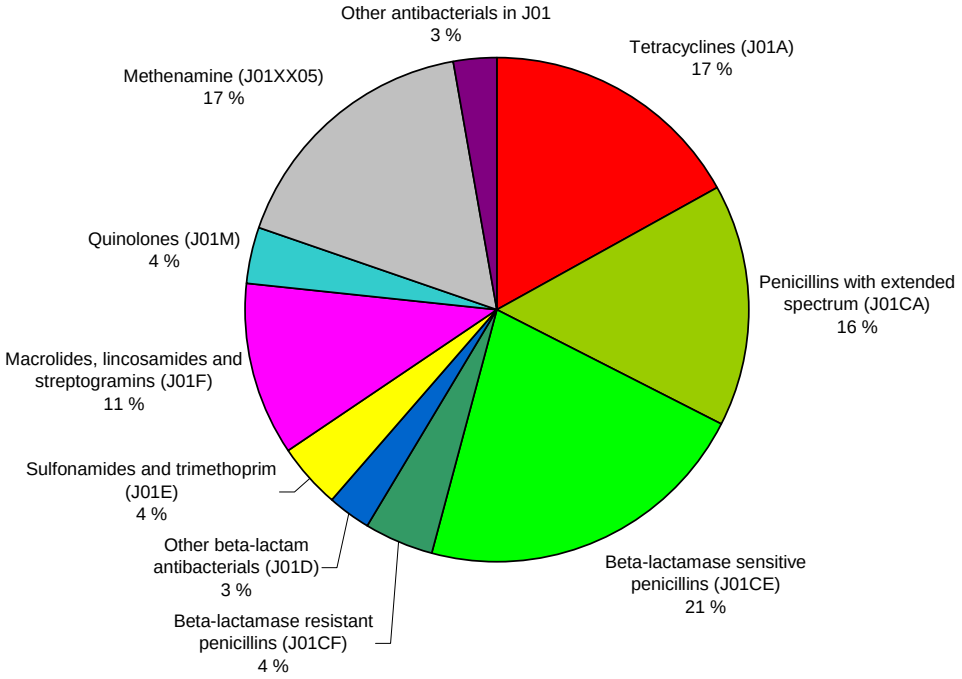

FIGURE 9. Relative amount of antibacterial agents for systemic use in 2011 in Defined Daily Doses (DDD) (total sale in the country).

TABLE 8. Human usage of single antimicrobial agents for systemic use in Norway. 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	Substance	2003	2004	2005	2006	2007	2008	2009	2010	2011
J01A A02	Doxycycline	1.93	1.80	1.89	1.97	2.0	1.9	1.78	1.83	2.09
J01A A04	Lymecycline	0.30	0.34	0.39	0.45	0.51	0.52	0.54	0.59	0.76
J01A A06	Oxytetracycline	0.19	0.20	0.20	0.19	0.18	0.17	0.16	0.15	0.03
J01A A07	Tetracycline	0.60	0.62	0.64	0.63	0.63	0.62	0.60	0.54	0.58
J01AA07*	Minocycline			0.0003	0.0003	0.0001	0.0002	0.0003	0.001	0.002
J01AA12	Tigecycline				0.0001	0.0002	0.0004	0.0005	0.0004	0.0002
J01B A01	Chloramphenicol	0.002	0.001	0.002	0.002	0.001	0.001	0.002	0.0007	0.0005
J01C A01	Ampicillin	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09	0.09
J01C A02*	Pivampicillin	0.09	0.08	0.07	0.06	0.01				
J01C A04	Amoxicillin	0.95	0.94	1.06	1.11	1.26	1.34	1.31	1.34	1.39
J01C A08	Pivmecillinam	1.14	1.25	1.29	1.46	1.55	1.65	1.72	1.75	1.73
J01C A11*	Mecillinam	0.005	0.005	0.006	0.006	0.006	0.008	0.008	0.008	0.008
J01C E01	Benzylpenicillin	0.25	0.24	0.26	0.26	0.25	0.24	0.28	0.22	0.24
J01C E02	Phenoxymethylpenicillin	4.13	3.99	4.29	4.37	4.45	4.46	4.19	4.22	4.23
J01C E08*	Benzathine benzylpenicillin	0.0001	0.0002	0.0001	0.0002	0.0001	0.0001	0.0002	0.0002	0.0001
J01C F01	Dicloxacillin	0.48	0.51	0.41	0.54	0.61	0.64	0.67	0.70	0.74
J01C F02	Cloxacillin	0.11	0.11	0.15	0.12	0.12	0.13	0.13	0.12	0.14
J01C F05*	Flucloxacillin	0.0002	0.0002	0.0001	0.0001	0.0003	0.0005	0.0007	0.0005	0.0003
J01C R02*	Amoxicillin and enzyme inhibitor	0.01	0.0003	0.0000	0.0001	0.0001	0.0012	0.003	0.003	0.002
J01C R05	Piperacillin and enzyme inhibitor	0.0024	0.005	0.01	0.01	0.02	0.02	0.02	0.02	0.03

ATC	Substance	2003	2004	2005	2006	2007	2008	2009	2010	2011
J01D B01	Cefalexin	0.3	0.29	0.24	0.26	0.25	0.23	0.21	0.20	0.19
J01D B03	Cefalotin	0.06	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.08
J01D B04*	Cefazolin			0.002	0.002	0.001	0.001			
J01D C01*	Cefoxitin	0.0001								
J01D C02	Cefuroxim	0.15	0.14	0.13	0.12	0.12	0.11	0.10	0.09	0.09
J01D D01	Cefotaxim	0.07	0.07	0.08	0.09	0.09	0.10	0.11	0.11	0.12
J01D D02	Ceftazidim	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01D D04	Ceftriaxone	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.03
J01D F01	Aztreonam	0.001	0.001	0.0005	0.0008	0.0008	0.0007	0.0006	0.0006	0.0005
J01D H02	Meropenem	0.02	0.02	0.026	0.031	0.035	0.037	0.042	0.041	0.043
J01D H03	Ertapenem				0.000	0.001	0.001	0.002	0.002	0.002
J01D H51	Imipenem and enzyme inhibitor	0.006	0.005	0.005	0.004	0.004	0.003	0.002	0.002	0.002
J01E A01	Trimethoprim	0.74	0.76	0.73	0.70	0.68	0.64	0.60	0.56	0.55
J01E E01	Sulfamethoxazol and trimethoprim	0.34	0.34	0.33	0.34	0.34	0.34	0.33	0.31	0.32
J01F A01	Erythromycin	1.09	1.03	1.16	1.24	1.21	1.08	0.92	0.94	1.18
J01F A02	Spiramycin	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01F A09	Clarithromycin	0.37	0.37	0.39	0.40	0.43	0.37	0.31	0.34	0.37
J01F A10	Azithromycin	0.26	0.28	0.32	0.34	0.39	0.38	0.37	0.41	0.44
J01FA15*	Telithromycin	0.0003	0.0003							
J01F F01	Clindamycin	0.19	0.20	0.23	0.25	0.26	0.28	0.28	0.31	0.32
J01GA01*	Streptomycin	0.0004	0.0004	0.0002	0.0003	0.0002	0.0003	0.0002	0.0002	0.0002
J01G B01	Tobramycin	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
J01G B03	Gentamicin	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04	0.05
J01G B06*	Amikacin	0.0008	0.0003	0.0004	0.0009	0.0003	0.0007	0.0008	0.0009	0.001
J01M A01	Ofloxacin	0.05	0.05	0.05	0.04	0.04	0.04	0.03	0.03	0.03
J01M A02	Ciprofloxacin	0.42	0.47	0.52	0.57	0.62	0.66	0.67	0.70	0.71
J01MA12*	Levofloxacin	0.0003		0.0003	0.0003	0.0008	0.0008	0.004	0.003	0.002
J01MA14*	Moxifloxacin					0.0007	0.001	0.001	0.004	0.006
J01X A01	Vancomycin	0.006	0.007	0.007	0.008	0.01	0.01	0.01	0.01	0.01
J01X A02	Teicoplanin	0.0009	0.0007	0.0008	0.0008	0.0007	0.001	0.0007	0.0008	0.0008
J01X B01	Colistin	0.002	0.003	0.004	0.005	0.004	0.004	0.005	0.004	0.004
J01X C01	Fusidic acid	0.007	0.008	0.006	0.006	0.006	0.006	0.005	0.004	0.005
J01X D01	Metronidazole	0.07	0.08	0.08	0.07	0.07	0.07	0.07	0.07	0.07
J01X E01	Nitrofurantoin	0.35	0.36	0.36	0.37	0.36	0.36	0.36	0.37	0.39
J01X X05	Methenamin	2.18	2.37	2.59	2.71	2.84	3.02	3.19	3.37	3.44
J01XX08	Linezolid	0.004	0.006	0.007	0.006	0.006	0.007	0.008	0.009	0.01
J01XX09	Daptomycin					0.000	0.000	0.000	0.0001	0.0004
D06AX09/ R01AX06*	Mupirocin in kg ointment/cream (2%)	3.0	3.0	3.4	4.3	4.0	3.9	5.1	4.5	4.6
J04A**	Rifampicin	0.049	0.068	0.077	0.082	0.092	0.092	0.127	0.126	0.122
A07AA09	Vancomycin	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
A07AA11*	Rifaximin							0.0005	0.0013	0.0022
P01AB01	Metronidazole	0.19	0.20	0.20	0.20	0.21	0.21	0.22	0.23	0.24

* Drugs not licensed at the Norwegian marked in 2010.
** Given as the amount of rifampicin in plain and combination products.

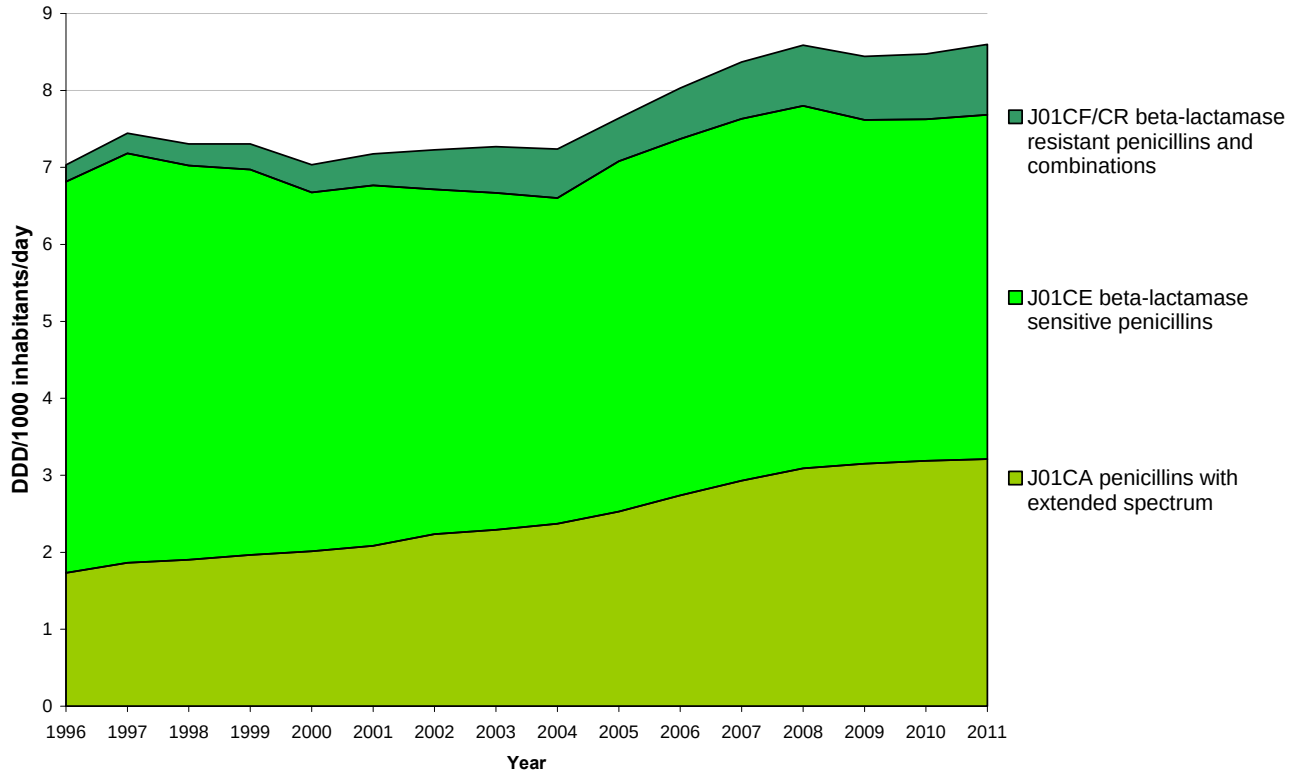

FIGURE 10. Sales of penicillins (J01C) in Norway 1996-2011 and changes within groups of penicillins.

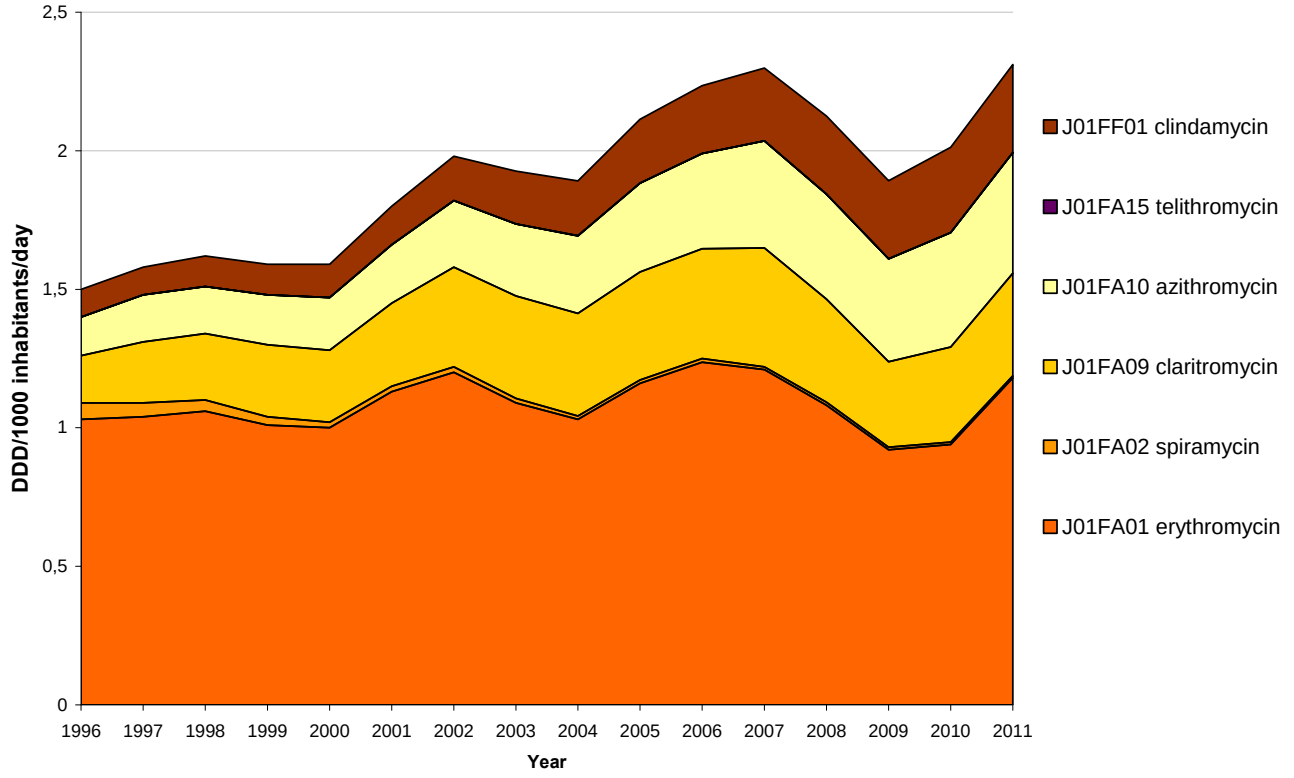

FIGURE 11. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1996-2011.

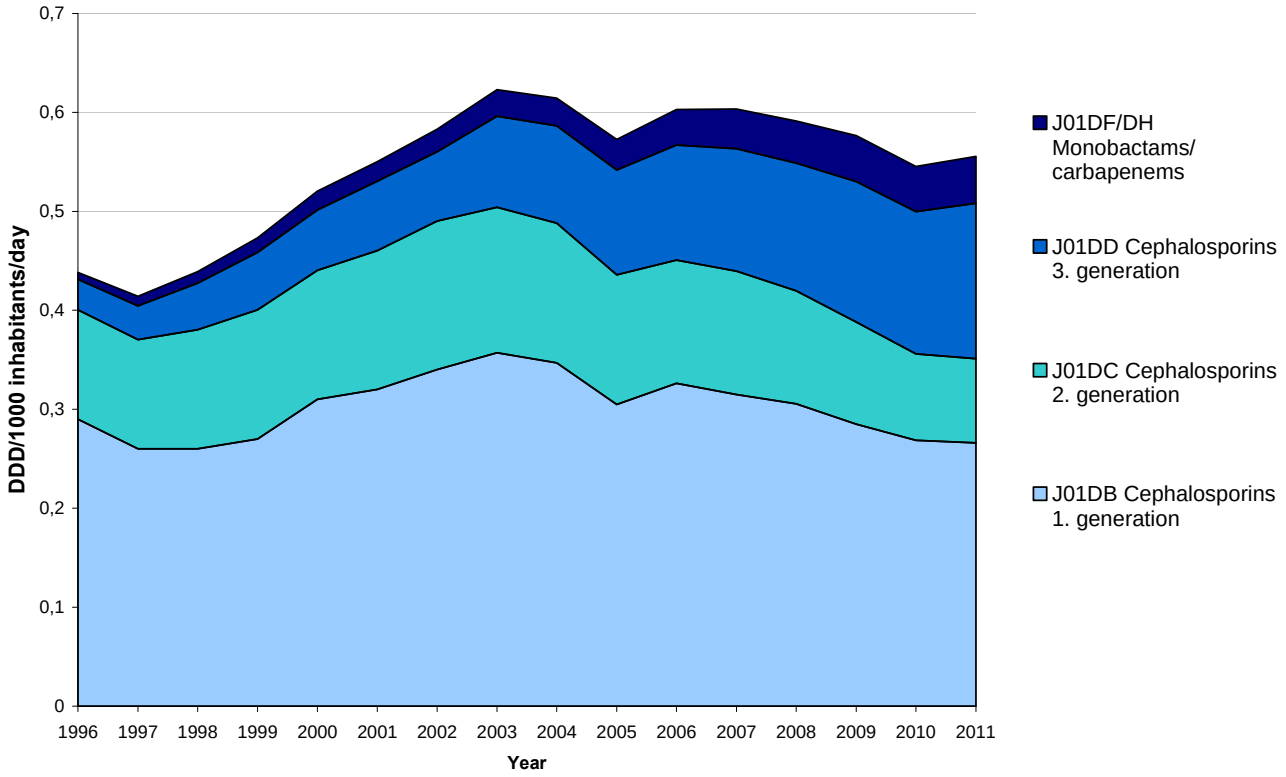

FIGURE 12. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2011 and changes between generations of cephalosporins and monobactams/carbapenems.

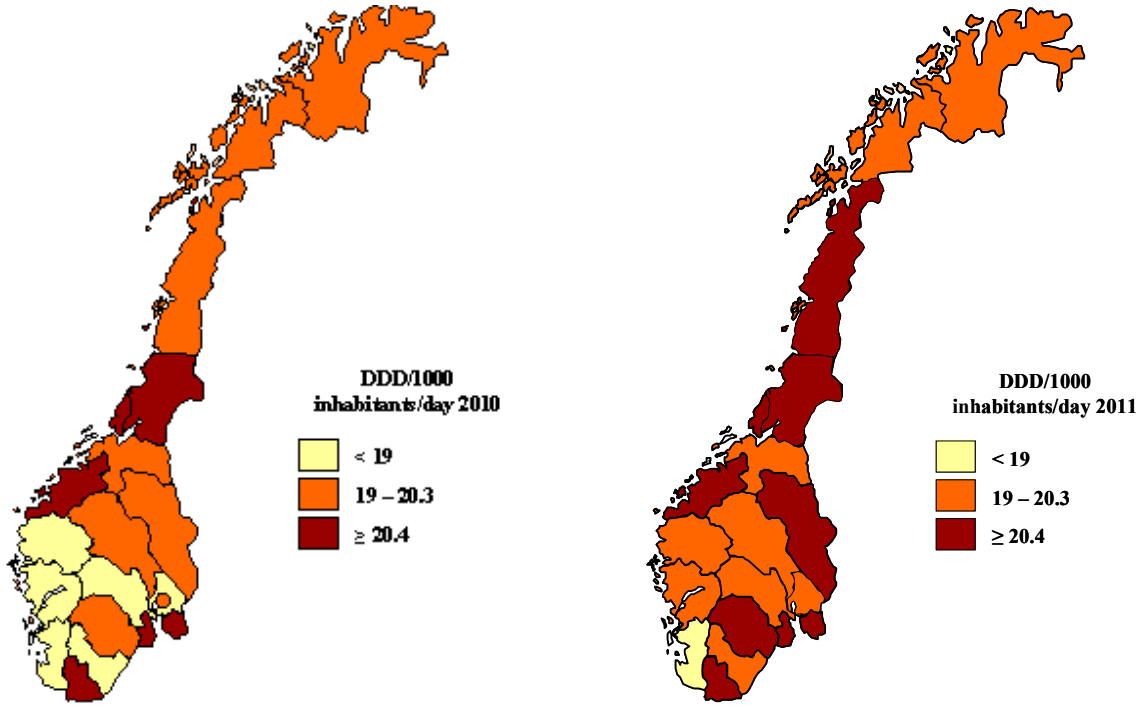

FIGURE 13. Sales of antibacterial agents for systemic use (ATC group J01) in the different counties of Norway in 2010 and 2011.

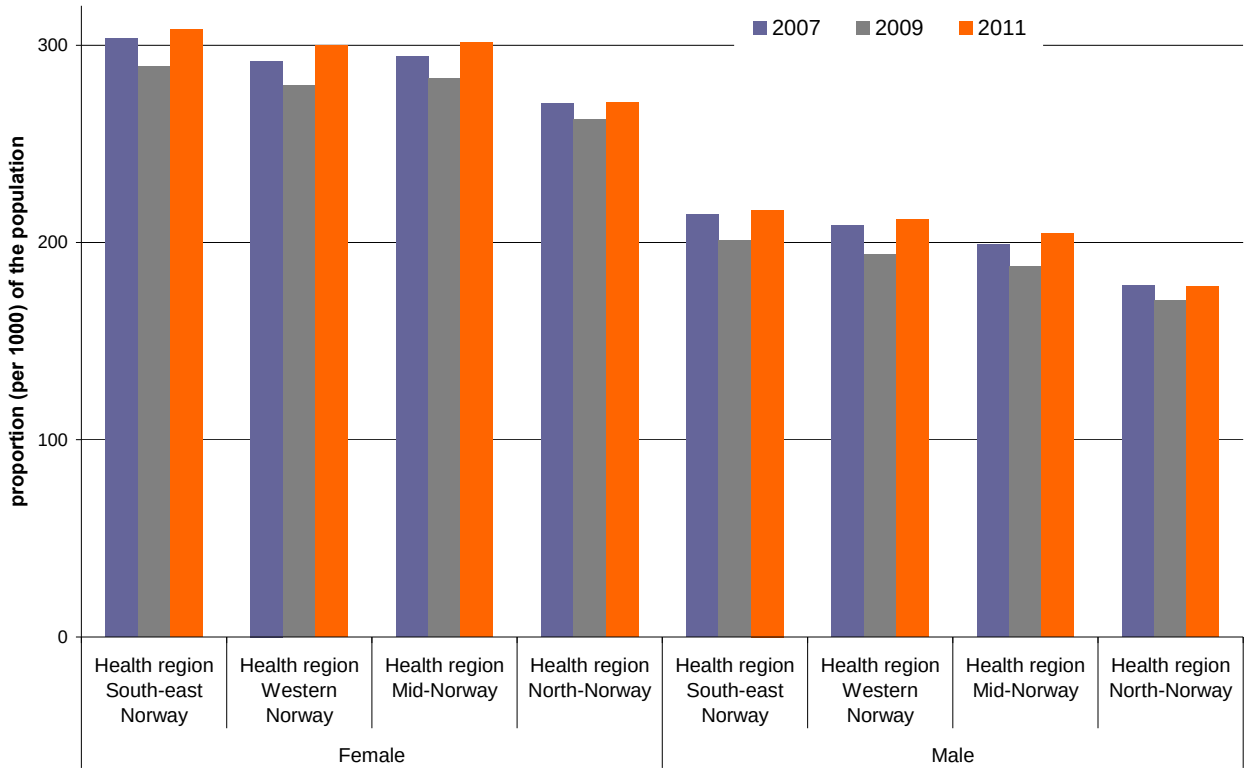

FIGURE 14. One year prevalence of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2007, 2009 and 2011. Antibacterials for systemic use include ATC group J01, vancomycin (A07AA09) and metronidazole (P01AB01).

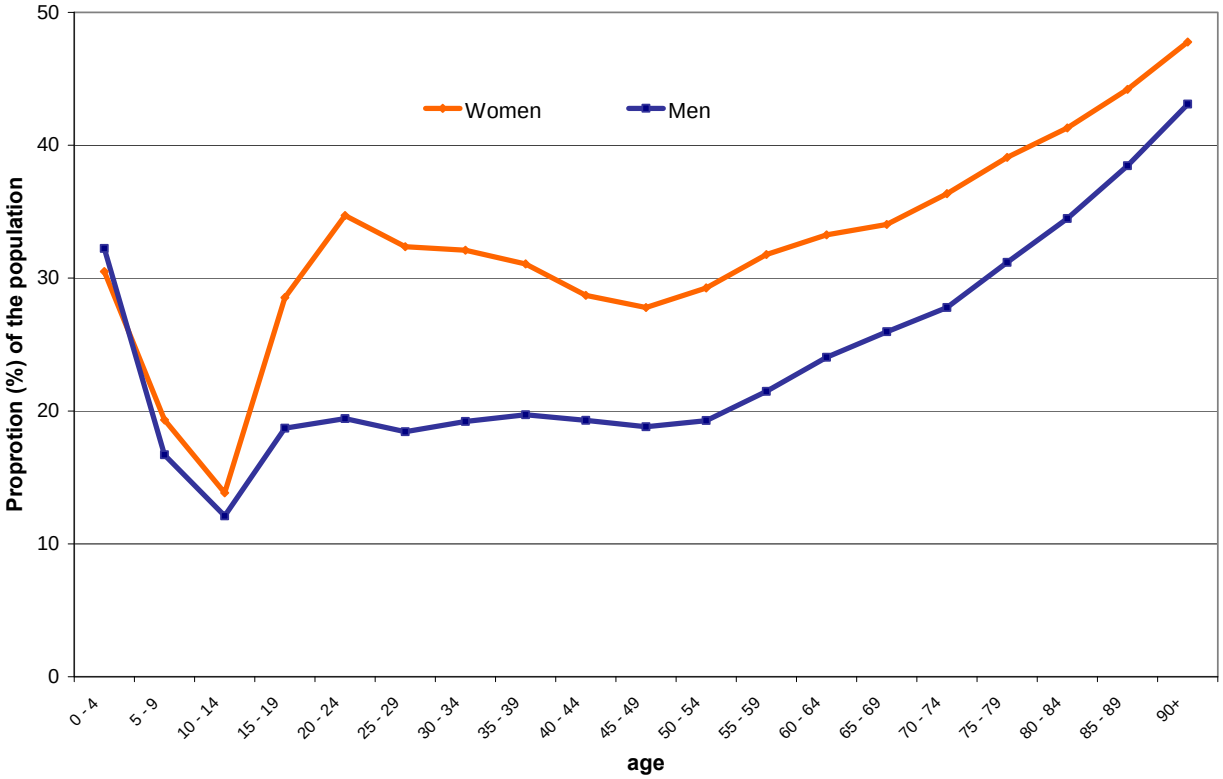

FIGURE 15. Proportion (%) of the population having dispensed at least one prescription of antibacterials (one year prevalence) in ambulatory care by gender and age (from 1 year to 90+ years) in Norway, 2011. Antibacterials included are antibacterials for systemic use (ATC group J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01). Prevalence in age groups above 65+ is adjusted according to persons from these age groups living outside institutions.

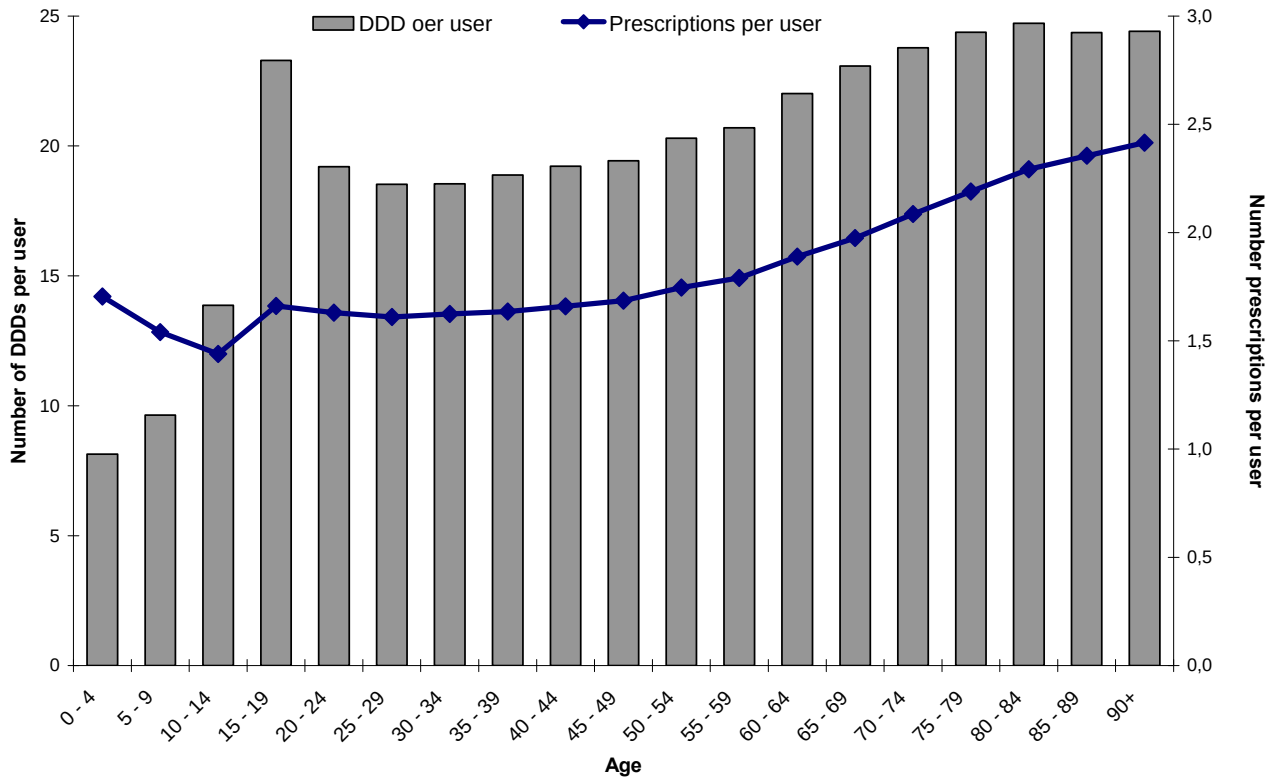

FIGURE 16. Mean number of prescriptions per user and mean number of DDDs per user of antibacterials in ambulatory care by age (from 1 year to 90+ years) in Norway, 2011. Antibacterials included are antibacterials for systemic use (ATC group J01, excl. methenamine).

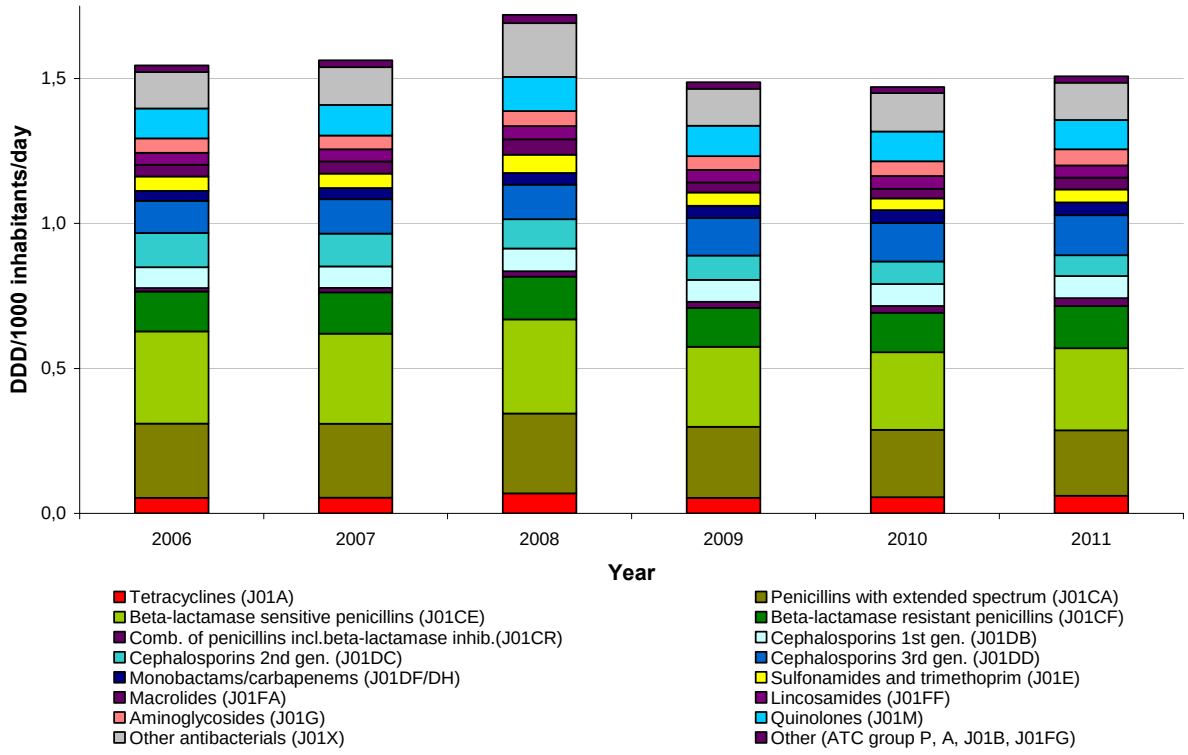

FIGURE 17. Distribution of antibacterial agents for systemic use in Norwegian hospitals 2006-2011, measured in DDD/1,000 inhabitants/day.

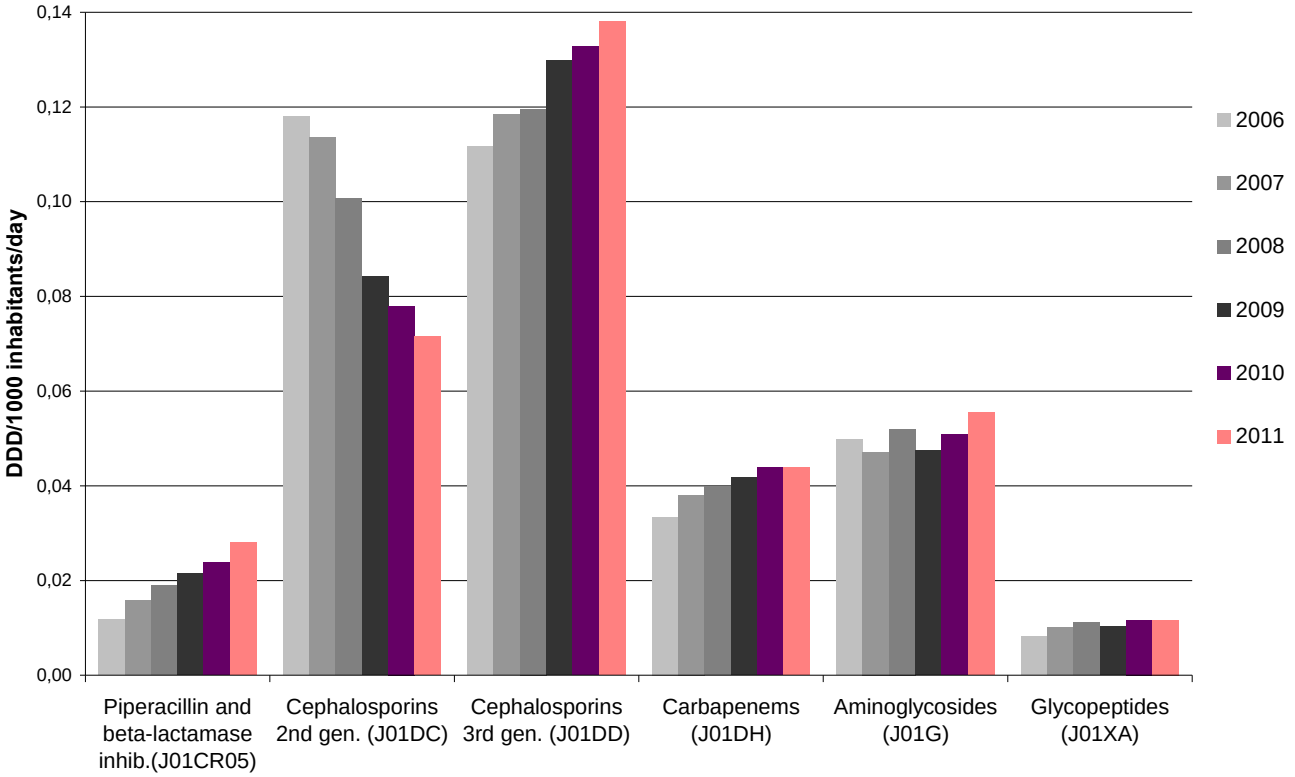

FIGURE 18. Distribution of selected antibacterial agents for systemic use in Norwegian hospitals 2006-2011, measured in DDD/1,000 inhabitants/day.

Elucidating the 2011/2012 *M. pneumoniae* epidemic by changes in antimicrobial prescriptions

In fall 2011, an epidemic increase of *Mycoplasma pneumoniae* was observed in Norway, as well as in other Nordic and Northern-European countries (1). The increased activity of *M. pneumoniae* was noted both at distinct laboratories and through monthly laboratory-based reporting of positive test results for certain viral and bacterial infections to the Norwegian Institute of Public Health. The reporting of positive laboratory results is voluntary, and although the majority of diagnostic laboratories in Norway submit reports to this system, it cannot capture the full picture of the epidemic. In order to assess the magnitude of the epidemic further, an *ad hoc* query of the overall number of samples received, analysed and tested positive for *M. pneumoniae* was made to the medical microbiological laboratories. By this survey, the burden of the epidemic was assumed to be highest in southern and western Norway (2).

If treatment of respiratory tract infections caused by *M. pneumoniae* is indicated, erythromycin or doxycycline is recommended as drugs of choice according to Norwegian guidelines. Further, clarithromycin is recommended as second line treatment. All drugs dispensed to residents living in Norway are recorded in the nationwide Prescription Database (NorPD). Data from this population based surveillance can be used to elucidate and complete the description of the *M. pneumoniae* epidemic with regard to age and gender of the patients and geographical variation of disease burden.
From 2010 to 2011, the use of erythromycin, clarithromycin and doxycycline measured in DDDs increased dramatically, by 26%, 9% and 14%, respectively, see Tables 7 and 8. The use of erythromycin is highly prevalent in young children, more so among boys than girls. From 13 years on the girls/women use more than boys/men (Figure 19). The peak for the 19-years old reflects a general high use of antibiotics in May, linked to graduation from Norwegian upper secondary schools (3).
The use in the 2011/12 season increased for all age groups. The highest increase in prevalence, almost 8 times, was observed in the age groups 2-10 years and for women 30-40 years, more than three times. The lower level of use for men aged 30-40 years, may suggest a lower exposure rate for men compared to women. This may indicate that the mothers and grandmothers are those being in closest contact with children. An increased use of erythromycin was observed from the early autumn of 2011. The use of erythromycin peaked in December 2011 for all age groups. By April 2012 the use had declined to a level comparable with previous years.

The geographical variation in use of erythromycin and clarithromycin among children aged ≤ 2 years was studied in the 19 counties of Norway by comparing the change in use from one year to another; July 2010 - April 2011 and July 2011 - April 2012 (Figure 20). The use increased in 15 of the 19 counties, the increase being greater than 15% in 12 counties. The largest proportional (%) increase was seen for counties in the south and west of Norway and the lowest in the north. In some counties a decrease was observed, which might reflect a shift of therapy preference.

In conclusion, the use of erythromycin and clarithromycin increased dramatically between September 2011 and April 2012, with a peak in December 2012. The geographical variation indicates that the disease burden was highest in the south and west of Norway. This observation corresponds nicely with data on testing activity and positivity rates, with positivity rates up to 25% at microbiological laboratories in the south and west of Norway. Thus, data on antimicrobial prescription may be used as a proxy to describe the epidemic of *M. pneumoniae*, and can elucidate the spread and disease burden.

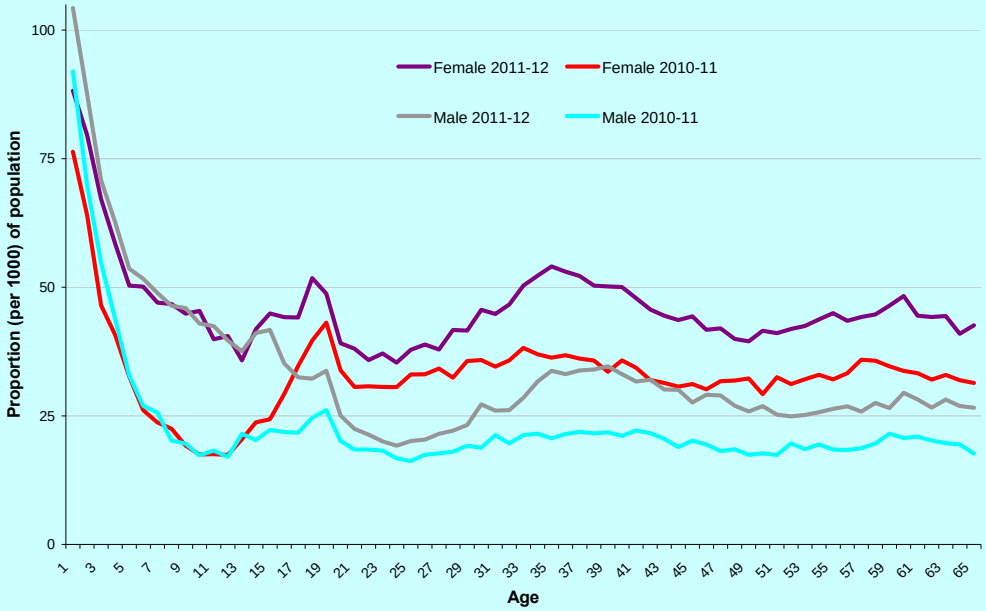

FIGURE 19. Proportion (per 1,000) of the population having dispensed at least one prescription of erythromycin in ambulatory care by gender and age in Norway. Shown for the period May 2010-April 2011 and May 2011-April 2012.

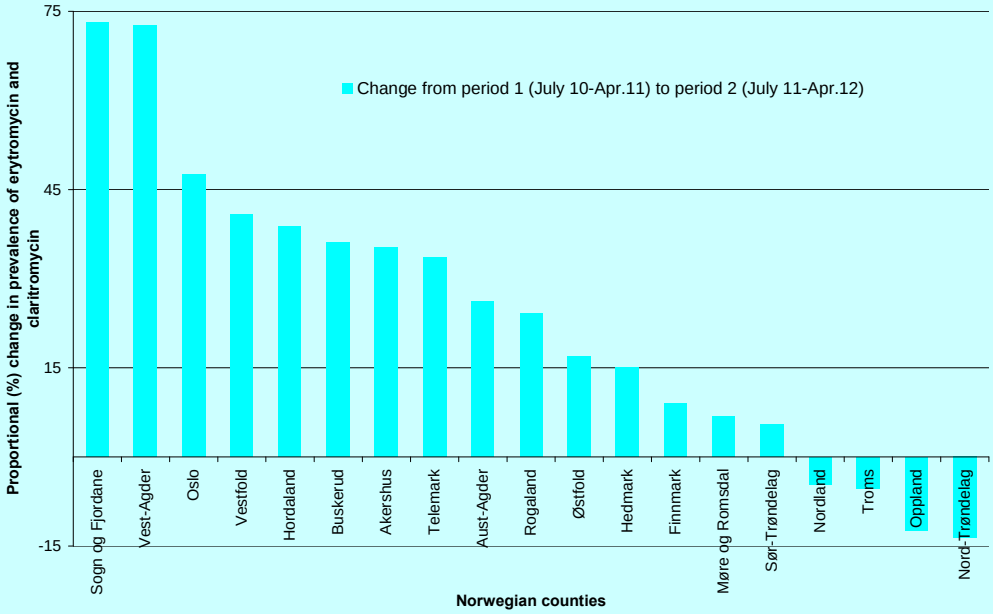

FIGURE 20. Proportional (%) change in prevalence between the period July 2010- April 2011 and July 2011- April 2012 in the use of erythromycin and clarithromycin for the 0-2 year population in ambulatory care by county.

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A new national guideline for the use of antibiotics in hospitals

A national handbook on antibiotic use in hospitals was published in 2001 but was never revised (1). Since then, each of four Regional Health Authorities in Norway have released their own hospital guidelines, and a national guideline for primary care was published in 2008 (2). Authorative national recommendations have been in demand and two successive national strategic plans to combat antibiotic resistance have emphasised the need for a national hospital guideline (3).

The Norwegian Health Directorate is the only official body empowered to publish national guidelines. In January 2011 the Directorate appointed an Editorial Board with a mandate and resources to write an evidence-based (EvB) antibiotic guideline (AG). The AG should be limited to adult hospitalized patients and encompass systemic bacterial and fungal infections as well as acute and serious tropical diseases.

The work has been led by a part-time engaged project leader and an Editorial Board with seven expert representatives from the four Health Regions, members appointed from various official health institutions, as well as patient representatives. Sixteen guideline panels have elaborated on antibiotic therapies while one large group has covered the subject of antibiotic prophylaxis in surgery. Geographical and specialty representation has been important in assembly of these working groups as a means of securing consensus and credibility, and to ensure optimal acceptance and support by the users. Overall, more than 80 writers ("content experts") and a number of librarians, but only one part-time GRADE methodologist, have been at work for 18 months. This is a very short time for development of an extensive new guideline, also considering that most participants have done this work in addition to their duties as full-time clinicians.

The Directorate has decided that GRADE (Grading of Recommendations, Assessment, Development and Evaluation) is the EvB framework that shall be used for guideline development in Norway (4). However, all actors in this AG process had severely underestimated the amount of time required to complete GRADE and the challenges that arise when attempting to apply GRADE on the topic of antibiotic use. There is a well-documented scarcity of high-quality literature (RCTs) in the field of infectious diseases (5) and, furthermore, a unique Norwegian situation of low antimicrobial resistance renders many international drug effectiveness studies unsuitable to support recommendations in our setting.

As of June 2012, the guideline has been through an official hearing and is projected for release on January 1st 2013 provided that allocation of resources will allow for a smooth process. This first version of the guideline has only been able to apply GRADE to a few topics but still the unanimous decision has been to publish it. It is planned an entirely Web-based guideline, and, equally important, a short handbook offering advice on empiric antibiotic regimens for acute infectious conditions. Moreover, collaboration has been established between the Health Directorate/AG Editorial Board and a Norwegian dominated, international group which is developing a GRADE-oriented guideline authoring software. This promises to be an invaluable tool in our effort to maintain and revise the guideline and properly apply GRADE.

Numerous positive effects have resulted from our guideline activities, most importantly 1) a boost for the entire infectious diseases milieu as a unifying project which has been perceived as very meaningful; 2) that a complete guideline is about to be released and, although not evidence based according to initial intentions, it is more elaborated in that regard than the predecessors; and 3) that valuable experience is accumulated which should benefit the Health Directorate in their strategies for future clinical guideline work. An obvious benefit of our guideline effort, however not thoroughly discussed, is the potential to identify useful scientific projects on antibiotic treatment and prophylaxis and to enable a basis for guideline implementation studies.

We aim to continuously improve, upgrade and revise the guideline. To succeed, one key element will be an upgrade of the support offered to the guideline panelists by the Health Directorate. What seems most urgently in demand is method experts who may aid in the practical application of EvB principles. Large resources and extensive use of methodologists are needed in clinical guideline development based on GRADE, as is most convincingly accounted for in a recent publication describing the ACCP 9th revision of antithrombotic guidelines (6).

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Variations in Norwegian GPs' antibiotic prescription habits for respiratory tract infections

About 90% of all Norwegian antibiotic prescriptions are issued in primary health care (1) and more than half of them for respiratory tract infections (RTIs) (2), which accounts for about 15% of all patient encounters (3). The Norwegian guidelines recommend penicillin V as the drug of choice for the majority of these. Striking variations have been observed between otherwise comparable GPs when it comes to their antibiotic prescription patterns (4-6). The reasons for these variations are not fully explored.

The Norwegian Prescription Peer Academic Detailing (Rx-PAD) study aimed at describing some of this variation in detail. It was conducted from the Department of General Practice/ Family Medicine at the University of Oslo in collaboration with the Antibiotic Centre for Primary Care in Oslo from 2004 to 2007. The two topics of the study were: Antibacterial prescribing in respiratory tract infections, and prescribing of potentially harmful drugs and combination of drugs for elderly patients above 70 years. The evaluation of this model was conducted as an intervention trial based on cluster randomisation (a peer group representing a cluster). Outcome data from the participants' EPR systems were collected from 440 GPs in Southern Norway, representing about one tenth of the Norwegian GPs. The aim of the intervention in the groups working with antibiotics was to harmonise prescription habits with the national guidelines, and then compare the effect of intervention with antibiotic prescription habits in the control group (those working with prescribing of potentially harmful prescription in the elderly).

A description of the baseline data from the 440 GPs was published in 2011 (6). One of the findings was the great variation in the antibiotic prescription rates for RTIs, illustrated in Figure 21. The GPs with the lowest prescription rates issued an antibiotic in only one out of ten RTI episodes, while the high prescribers had a rate of about seven out of ten. The variations became even more evident when analysing the proportion of non-penicillin V when an antibiotic was prescribed for an RTI. Some GPs very rarely prescribed non-penicillinV for RTIs, while others did this almost consistently, Figure 22.

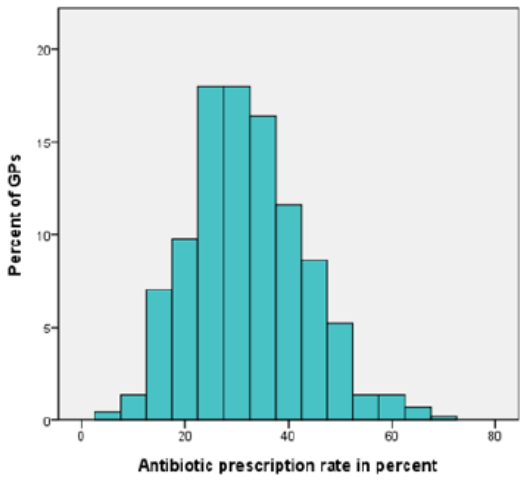

FIGURE 21. Distribution of antibiotic prescription rates among 440 GPs. Baseline from the Rx-PAD study.

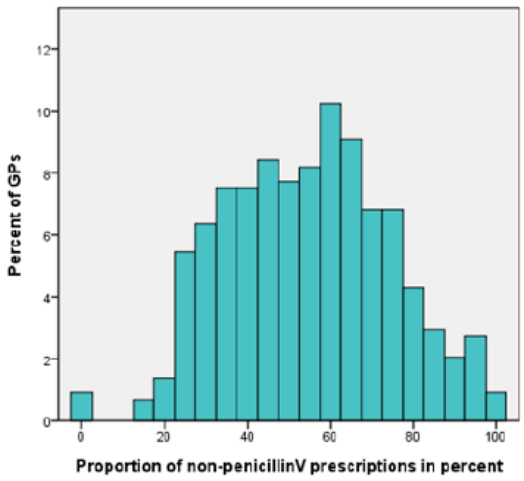

FIGURE 22. Distribution of non-penicillin V proportion among 440 GPs. Baseline from the Rx-PAD study.

Other interesting findings were that GPs in the highest quintile of annual office patient consultations had 66% higher odds for prescribing an antibiotic compared to those in the lowest quintile. Furthermore, the quintile of GPs with the highest prescribing rate had 270% higher odds for prescribing a non-penicillinV antibiotic when an antibiotic was issued, compared to those in the lowest quintile. These variations are not explainable by differences in disease scope or practice population, but rather by the GPs' individual habits and beliefs. A qualitative study from general practice in the UK describes some of the considerations that influence GP's prescription habits when choosing an antibiotic (7). More qualitative studies are required in order to further investigate these important considerations. The data describing the effects of the intervention in the Rx-PAD project will be published this year.

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VI. OCCURRENCE OF ANTIMICROBIAL RESISTANCE

A. ANIMAL CLINICAL ISOLATES

Marianne Sunde, Madelaine Norström, Jannice Schau Slettemeås, Arve Lund

Escherichia coli from septicaemia in broiler

A total of 38 isolates of *Escherichia coli* from clinical cases of septicaemia in poultry were susceptibility tested. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Table 9 and in the text.

TABLE 9. Antimicrobial resistance in isolates of *Escherichia coli* (n=38) from septicaemia in broiler collected 2008-2011.

		Distribution (n) of MIC values (mg/L)															
Substance	Resistance (n)	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	8							15	15				4	4			
Chloramphenicol	1								6	29	2				1		
Florfenicol	0									26	12						
Ampicillin	14							2	17	5				1	1	12	
Cefotaxime	1		3	20	14					1							
Ceftazidim	3					22	13	2			1						
Sulfamethoxazole	16										5	11	6				16
Trimethoprim	8				5	9	10	6				8					
Gentamicin	0						18	19	1								
Streptomycin	4									19	14	1	1		1	2	
Kanamycin	0										38						
Ciprofloxacin	3		11	24			2	1									
Nalidixic acid	3							7	24	4					2	1	
Colistin	0						36	2									

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

RESULTS AND COMMENTS

In total, 36.8% of the isolates were susceptible to all antimicrobial agents included. The following proportions of isolates were resistant to one or more antimicrobial agents: 21.1% were resistant to one (mainly sulfonamides), 15.8% to two (mainly ampicillin and tetracyclines or sulfonamides), 13.2% to three and 13.2% to four or more antimicrobial agents. *E. coli* isolates from septicaemia in poultry were surveyed in 2004 and 68.4% were susceptible to all antimicrobials included. The current data indicate a moderate to high occurrence of resistance among *E. coli* isolates from diseased poultry. However, it is not possible to conclude regarding the trend, because the number of isolates was low both in 2004 and 2011. Interestingly, one of the isolates had reduced susceptibility to third generation cephalosporins and was shown to contain the bla_{CMY-2} gene. Combination of virulence and resistance properties in the same isolate is a hazard with a dangerous potential. Three isolates (7.9%) were resistant to nalidixic acid and ciprofloxacin. In comparison, 5 of 18 isolates from poultry with septicaemia in 2004 were fluoroquinolone resistant. Although the number of isolates tested was limited, the findings may indicate that fluoroquinolone resistance in poultry is emerging. No preparations containing quinolones are licensed for use in poultry in Norway. However, veterinarians may apply for authorisation to use drugs for which no marketing authorisation has been granted. Sulfaclozin (1996-2002) and minor amounts of enrofloxacin (1992-2004) in preparations intended for flock treatment of poultry, has been sold in Norway with such exemption. In addition, flumequine (cross-resistance with nalidixic acid) was used for clinical purposes to a very limited extent in the 1980s and the early 1990s.

B. INDICATOR BACTERIA FROM ANIMALS

Marianne Sunde, Madelaine Norström, Jannice Schau Slettemeås, Arve Lund

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 resistance situation, detect trends and evaluate the effects of interventions.

In NORM-VET, *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria. In 2011, *E. coli* from faecal samples and boot swabs from pigs and poultry respectively, were included. The substances included in the test panels might not always be those used in veterinary medicine, but are included because of their importance for human health. Some of the cut-off values defining resistance applied in NORM-VET have been changed over the years. To facilitate comparisons in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2011. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from swine and poultry

A total of 194 faecal samples from swine were examined, and *E. coli* was isolated from 99% of the samples. Altogether 252 samples from poultry were examined and *E. coli* isolates were obtained from 208 samples (82.5%).

One isolate per positive sample was susceptibility tested. The results are presented in Table 10 and Figures 23-25, and in the text.

TABLE 10. Antimicrobial resistance in isolates of *Escherichia coli* from faecal samples from swine (n=192) and broiler (n=208) in 2011.

Substance	Sample	Resistance (%) [95% CI*]		Distribution (%) of MIC values (mg/L)															
				0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Swine	9.4	[5.7-14.4]							35.4	55.2				2.1	4.2	3.1		
	Broiler	4.3	[2.0-8.1]							30.8	64.9				1.4	2.9			
Chloramphenicol	Swine	0.5	[0.0-2.9]								7.3	66.1	25.5	0.5			0.5		
	Broiler	0.5	[0.0-2.6]								7.2	73.6	18.8				0.5		
Florfenicol	Swine	0.0	[0.0-1.9]									44.3	54.2	1.6					
	Broiler	0.0	[0.0-1.8]									51.4	46.6	1.9					
Ampicillin	Swine	7.8	[4.4-12.6]							20.8	57.8	13.0	0.5				1.0	6.8	
	Broiler	15.4	[10.8-21.0]							20.7	52.4	11.1	0.5				1.9	13.5	
Cefotaxime	Swine	0.5	[0.0-2.9]	0.5	11.5	74.0	13.5			0.5									
	Broiler	1.0	[0.1-3.4]		7.2	68.8	21.6	1.4				1.0							
Ceftazidime	Swine	0.5	[0.0-2.9]					75.5	24.0			0.5							
	Broiler	1.0	[0.1-3.4]					66.3	32.7				0.5	0.5					
Sulfamethoxazole	Swine	10.4	[6.5-15.6]										38.5	39.1	10.9	1.0			10.4
	Broiler	9.6	[6.0-14.5]										30.3	42.8	15.4	1.9			9.6
Trimethoprim	Swine	7.3	[4.9-11.9]				5.2	41.7	44.3	1.0	0.5			0.5	6.8				
	Broiler	5.8	[3.1-9.9]				8.7	41.8	42.8	1.0					5.8				
Gentamicin	Swine	0.0	[0.0-1.9]					1.6	65.6	31.8	1.0								
	Broiler	0.0	[0.0-1.8]					0.5	63.6	34.6	1.4								
Streptomycin	Swine	17.2	[12.1-23.3]									51.0	30.2	1.6	3.1	3.1	5.7	4.7	0.5
	Broiler	4.8	[3.0-9.9]								0.5	61.1	33.2	0.5	1.9	1.0	1.0	0.5	0.5
Kanamycin	Swine	1.6	[0.3-4.5]										98.4		1.6				
	Broiler	1.9	[0.5-4.9]										98.1	0.5	1.4				
Ciprofloxacin	Swine	0.0	[0.0-1.9]	0.5	67.7	31.8													
	Broiler	1.9	[0.5-4.9]	0.5	57.2	40.4			1.4	0.5									
Nalidixic acid	Swine	0.0	[0.0-1.9]							3.1	63.5	32.8	0.5						
	Broiler	1.9	[0.5-4.9]							5.3	59.6	32.7		0.5				1.9	
Colistin	Swine	0.0	[0.0-1.9]						90.6	8.9	0.5								
	Broiler	0.0	[0.0-1.8]						92.3	7.7									

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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.

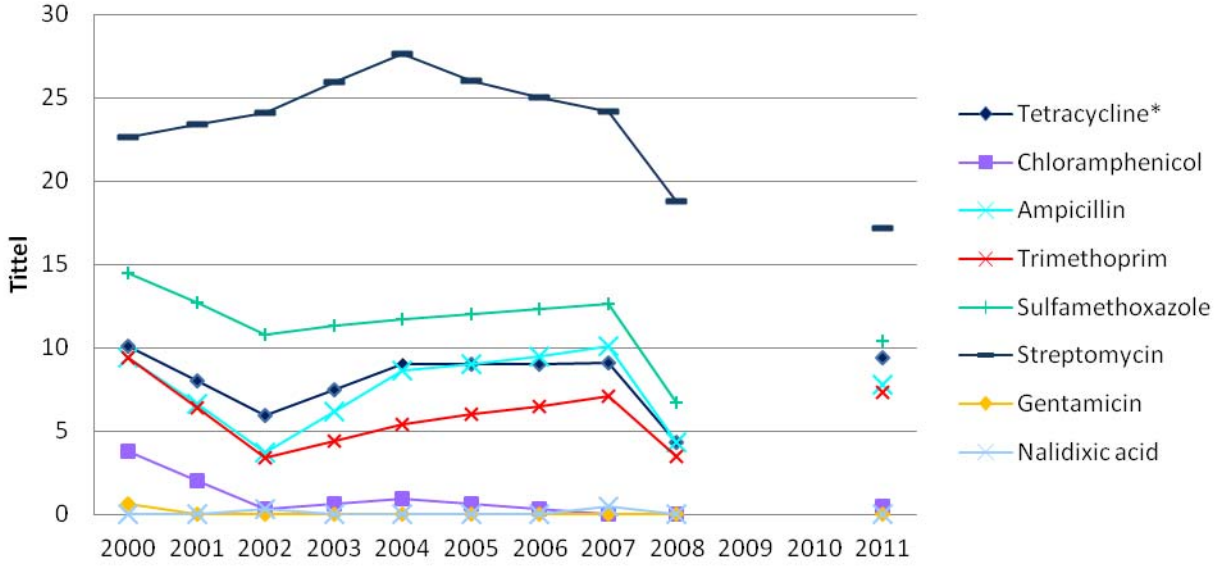

FIGURE 23. Prevalence of resistance to various antimicrobials in *E. coli* from swine isolates (faecal samples) 2000-2011. The cut-off values used in NORM-VET 2011 were applied. *Oxytetracycline instead of tetracycline in 2002 and 2004.

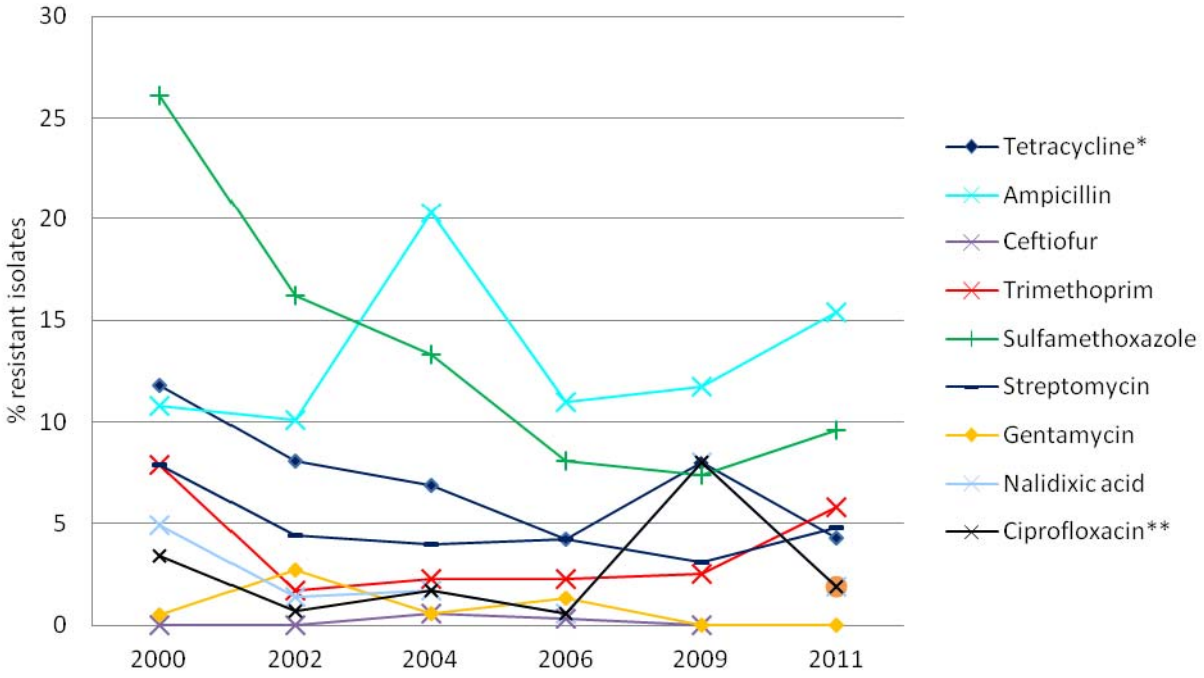

FIGURE 24. Prevalence of resistance to various antimicrobials in *E. coli* from broiler isolates in 2000-2011. The cut-off values used in NORM-VET 2011 were applied. *Oxytetracycline in 2002 and 2004. **Enrofloxacin before 2006.

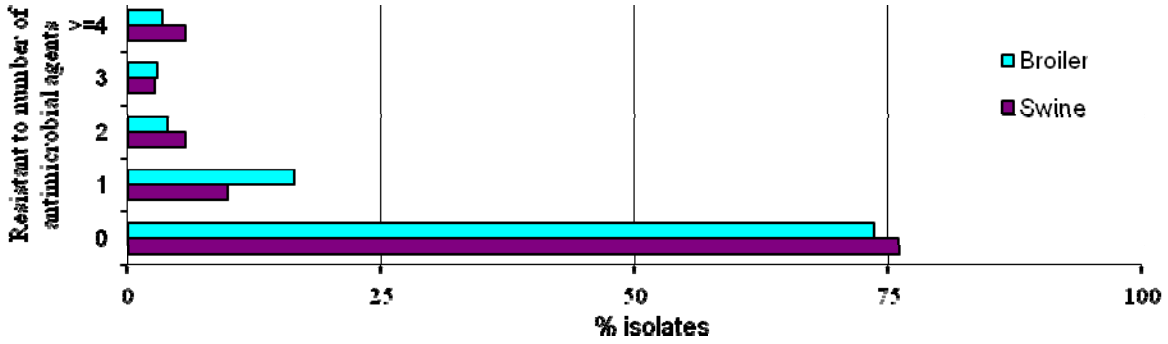

FIGURE 25. Antimicrobial resistance profile for *E. coli* from faecal isolates from broiler (n=208) and swine (n=192) in 2011. Proportions of isolates susceptible to all or resistant to one, two, three and four or more antimicrobial agents are illustrated.

RESULTS AND COMMENTS

SWINE

The data indicate a moderate to low occurrence of resistance among *E. coli* from faecal samples, 76.0% of the isolates were susceptible to all antimicrobial agents included. As in 2008, resistance to streptomycin was the most frequently identified resistance determinant, followed by sulfamethoxazole, tetracycline and ampicillin. Altogether, 9.9% were resistant to one (predominantly streptomycin), 5.7% to two (mainly tetracycline and streptomycin), 2.6% to three and 5.7% to four or more antimicrobial agents (Figure 25). All these antimicrobial agents are used for clinical purposes in swine. By using a non-selective method, one isolate was resistant to third generation cephalosporins. Further investigation indicated that this was caused by increased chromosomal AmpC production.

None of the isolates were resistant to chloramphenicol. Veterinary drugs containing chloramphenicol were withdrawn from the Norwegian market in 1992. Moreover, no resistance to the fluoroquinolone ciprofloxacin or to the quinolone nalidixic acid was observed. The usage of fluoroquinolones in food production animals in Norway is very limited. Over the years 2000 to 2011, the prevalence of resistance to various antimicrobials in *E. coli* isolates has been rather stable. Guidelines for use of antimicrobial agents in swine and close follow-up by the Norwegian Pig Health Service and veterinarians are important to maintain this favourable situation.

BROILER

The data indicate a moderate occurrence of resistance among *E. coli* from broiler faecal samples. In total, 73.6% of the isolates were susceptible to all antimicrobial agents included. Altogether, 16.4% of the isolates were resistant to one antimicrobial agent (predominantly ampicillin), 3.9% to two (mainly ampicillin and sulfamethoxazole), 2.9% to three and 3.4% to four antimicrobial agents (Figure 25). Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to sulfamethoxazole, trimethoprim and streptomycin. Over the years 2000 to 2011, the decreasing trend regarding resistance to sulfamethoxazole seems to level off.

Resistance to the fluoroquinolone ciprofloxacin and to the quinolone nalidixic acid was identified in 2% of the isolates compared to 8% in 2009 (Figure 24).

By using a non-selective method, two isolates were resistant to third generation cephalosprins, the $bla_{\text{CMY-2}}$ gene was identified in both. A selective method was used to detect ESBL/AmpC positive *E. coli* in the same material (see separate presentation page 40).

Extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* from swine

A total of 194 faecal swabs from swine were screened for the presence of ESBL producing *E. coli* by using a selective method. *E. coli* resistant to third generation cephalosporins was found in 0.5% [95% CI: 0.0-2.9] (1 out of 194 samples). Further investigations showed that the isolate contained a $bla_{\text{TEM-52}}$ gene. This is the first detection of an ESBL positive *E. coli* from swine in Norway. In a previous survey (2009), no such isolates were detected.

Enterococcus spp. from broiler

A total of 252 samples from poultry were collected. *E. faecium* or *E. faecalis* was identified in 238 of the samples (94.4%). One isolate per positive sample was susceptibility tested. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Tables 11-12, Figure 26, and in the text.

TABLE 11. Antimicrobial resistance in *E. faecalis* spp. (n=62) from broiler in 2011.

	Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance		[95% CI*]	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	45.2	[32.5-58.3]			53.2	1.6			1.6		11.3	29.0	3.2				
Chloramphenicol	11.3	[4.7-21.9]			1.6		3.2	67.7	16.1			11.3					
Ampicillin	0	[0.0-5.8]		1.6	12.9	82.3	3.2										
Erythromycin	25.8	[15.5-38.5]			24.2	16.1	14.5	19.4	1.6	3.2	3.2		17.7				
Streptomycin	16.1	[8.0-27.7]									3.2	37.1	41.9	1.6			16.1
Gentamicin	0	[0.0-5.8]						1.6	37.1	56.5	4.8						
Kanamycin	0	[0.0-5.8]								6.5	11.3	74.2	6.5	1.6			
Vancomycin	0	[0.0-5.8]				53.2	40.3	6.5									
Bacitracin#	19.4	[10.4-31.4]					1.6	14.5	54.8	8.1	1.6		11.3	8.1			
Linezolid	0	[0.0-5.8]				56.5	43.5										
Virginiamycin	NR	NR						3.2	33.9	51.6	11.3						
Narasin	4.8	[1.0-13.5]	67.7	17.7		4.8	4.8	4.8									

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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. # Measured in U/ml.

TABLE 12. Antimicrobial resistance in *E. faecium* (n=176) from broiler in 2011.

	Resistance (%)		Distribution (n) of MIC values (mg/L)														
Substance		[95% CI*]	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	11.4	[7.1-17.0]			85.8	1.7		1.1	1.1	0.6	2.8	6.3	0.6				
Chloramphenicol	0	[0.0-2.1]			1.1	0.6	11.4	76.1	9.7	1.1							
Ampicillin	0.6	[0.0-3.1]		9.7	27.8	43.2	15.9	2.8	0.6								
Erythromycin	5.7	[2.8-10.2]			19.3	49.4	11.4	14.2	3.4	0.6	0.6		1.1				
Streptomycin	0.6	[0.0-3.1]								2.3	29.0	64.8	3.4				0.6
Gentamicin	0	[0.0-2.1]					1.1	13.1	64.2	20.5	1.1						
Kanamycin	0.6	[0.0-3.1]								1.1	2.3	26.3	44.0	22.3	3.4	0.6	0.6
Vancomycin	0	[0.0-2.1]				80.7	15.9	3.4									
Bacitracin#	38.1	[30.9-45.7]				26.7	1.7	3.4	9.7	12.5	8.0	18.8	2.8	16.5			
Linezolid	0	[0.0-2.1]			0.6	24.4	71.6	3.4									
Virginiamycin	0	[0.0-2.1]			18.2	37.5	34.7	9.7									
Narasin	68.8	[61.3-75.6]	6.3	5.7	4.0	2.8	12.5	63.6	5.1								

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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. # Measured in U/ml

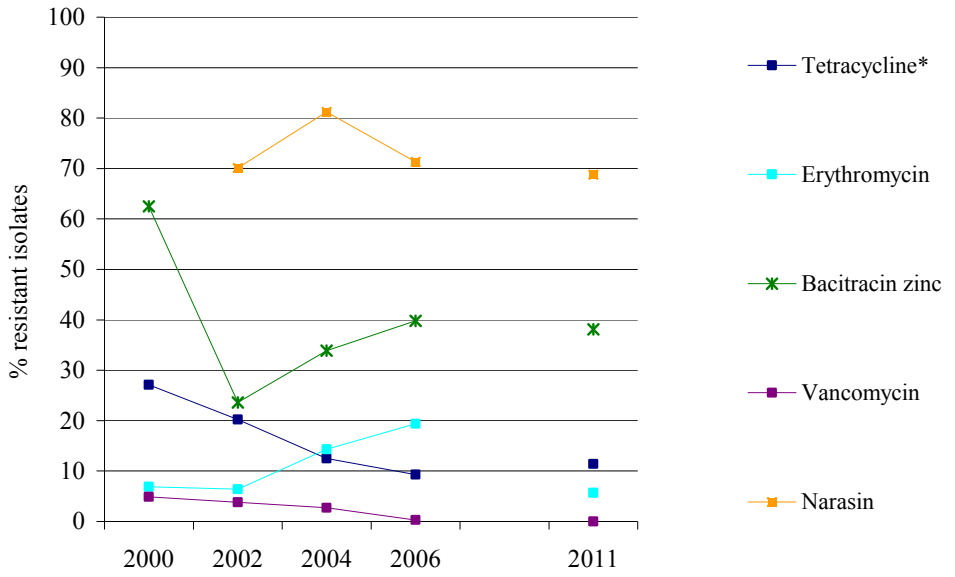

FIGURE 26. Prevalence of resistance to various antimicrobials in *E. faecium* from broiler (meat and faecal samples) 2000-2011. The breakpoints used in NORM-VET 2011 were applied. * Oxytetracycline in 2002 and 2004.

RESULTS AND COMMENTS

E. faecalis is known to be inherently resistant to the streptogramin virginiamycin, while *E. faecium* is known to be susceptible to this antimicrobial agent. Virginiamycin is therefore not included in the following comments. The resistance profiles of the two bacterial species are rather different and therefore presented separately.

E. faecalis: In total 45.2% of the isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to one (mainly tetracycline) and two (mainly tetracycline and bacitracin) antimicrobial agents was detected in 17.7% and 19.3%, respectively. In addition, 4.8% and 12.9% of the isolates were resistant to three and four antimicrobial agents, respectively.

E. faecium: In total 14.2% of the isolates were susceptible to all antimicrobial agents included in the test panel. Resistance to one (mainly narasin) and two (mainly narasin and bacitracin) antimicrobial agents was detected in 5.2% and 29.0%, respectively. In addition, 4.6% and 0.6% of the isolates were resistant to three and four antimicrobial agents, respectively.

Coccidiostats are routinely used in Norwegian broiler production, and since 1996 such use has been dominated by the ionophore narasin. The selection pressure exerted by the use of narasin in broiler production is probably the reason why narasin resistance is frequently observed among enterococci from broilers, *E. faecium* in particular. The prevalence of resistance to the other antimicrobial agents among *E. faecalis* and *E. faecium* from healthy broilers is considered moderate.

No vancomycin resistant isolates of *E. faecium* or *E. faecalis* were detected by random selection. Avoparcin, which induces cross-resistance to vancomycin, was routinely used as a growth promoter in Norwegian broiler and turkey production from 1986 until it was banned in 1995. Studies have shown that this use has selected for an extensive reservoir of vancomycin resistant enterococci (VRE) in Norwegian broiler production. The reservoir has persisted after the ban was implemented (see data for selective screening for VRE below).

Surprisingly there is a high frequency of tetracycline resistance specifically among *E. faecalis* (45%) despite insignificant use of oxytetracycline for clinical purposes in Norwegian broiler production. Resistance to erythromycin has decreased compared to the survey in 2006 but is still fairly common in particular for *E. faecalis*. Erythromycin has never been used in broilers in Norway. However, resistance may have been acquired by former use of spiramycin as cross-resistance between erythromycin and spiramycin is common. Spiramycin was licensed for use in poultry until 1998 when it was withdrawn due to limited sales.

The findings in 2011 confirm that resistance to bacitracin persists among enterococci from broiler and is fairly prevalent, especially in *E. faecalis*. Bacitracin was formerly used as a growth promoter, but was negligible during the 1990s. No use of bacitracin has been recorded in animal production in Norway after 1997.

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

A total of 252 boot swab samples from broiler flocks were screened for the presence of VRE. The results are presented in Table 13. Laboratory methods and data processing are described in Appendix 3.

TABLE 13. Antimicrobial resistance in vancomycin reistant *Enterococcus faecium* (n=40) from boot swab samples in broiler holdings in 2011.

		Distribution (%) of MIC values (mg/L)													
Substance	Resistance (n)	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	3		36	0	1	0	0	0	1	2					
Chloramphenicol	0				5	32	3								
Ampicillin	3	12	2	3	4	16	1	1	1						
Erythromycin	2		32	3	3	0	0	2							
Streptomycin	0							2	18	19	1				
Gentamicin	0					7	24	9							
Kanamycin	0									17	15	6	1	1	
Vancomycin	40											40			
Bacitracin[#]	0			21	2	0	0	15	2						
Linezolid	0			21	19										
Virginiamycin	1		1	8	29	1	1								
Narasin	40					34	6								

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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. [#] Measured in U/ml.

RESULTS AND COMMENTS

A total of 40 (15.9%, 95% CI: 11.6-21.0) samples were positive for VRE. All *vanA* positive isolates were identified as *E. faecium*. All isolates were also resistant to narasin. Three isolates showed additional resistance to tetracycline and ampicillin and two were resistant to erythromycin.

Compared to the previous survey in 2006, the number of VRE positive samples has increased in 2009 and 2011. This might be a result of improved sampling method using boot swabs (per flock) instead of faecal samples (from groups of broilers). Boot swab sampling mirrors the prevalence in the broiler house and not the actual prevalence in the live birds.

ESBL and AmpC producing *Escherichia coli* in Norwegian broiler production

Acquired resistance to cephalosporins among Gram negative bacteria has become almost epidemic in recent years. Production of extended-spectrum beta-lactamases (ESBLs) or transferable AmpC production are major mechanisms behind such resistance. Among production animals, poultry seems to be associated with the highest frequencies of *Escherichia coli* and *Salmonella* producing ESBLs/AmpC.

In Norway, the situation regarding antimicrobial resistance in food production animals is favourable when compared to many other countries. However, in the NORM-VET 2006 programme a single ESBL positive *E. coli* was detected from the intestinal flora of a healthy broiler. This finding may be regarded as an "early warning" that poultry production could be associated with bacteria expressing resistance to critically important antimicrobial agents. The isolate contained an incI1 plasmid carrying a $bla_{\text{TEM-20}}$ gene. Comparative studies showed that a closely related plasmid was present in *Salmonella* Paratyphi B dT^{+} from broilers in The Netherlands, suggesting a wide distribution of this ESBL encoding plasmid among bacteria from poultry. Import of breeding animals was suspected as a possible source.

In NORM-VET, *E. coli* from the intestinal flora of healthy broilers has been investigated in five previous years. Inclusion of isolates was based on random selection after growth on agar with no antimicrobials. In 2011, a selective method for detection of ESBL/AmpC positive *E. coli* was applied for the first time on faecal material from broilers. Testing of *E. coli* with a non-selective procedure was performed in parallel. The material consisted of boot swabs (see Appendix 3).

TABLE 14. Antimicrobial resistance in isolates of *Escherichia coli* with ESBL $bla_{\text{CMY-2}}$ from boot swab samples from broiler holdings (n=108) in 2011.

	Resistance (%)		Distribution (%) of MIC values (mg/L)															
Substance	[95% CI*]		0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycine	2.8	[0.6-7.9]							36.1	61.1					2.8			
Chloramphenicol	0.0	[0.0-3.4]								12.0	81.5	6.5						
Florfenicol	0.0	[0.0-3.4]									55.6	43.5	0.9					
Ampicillin	100	[96.6-100]												2.8	20.4	45.4	31.5	
Cefotaxime	100	[96.6-100]						0.9			99.1							
Cefotaxime	100	[96.6-100]									15.7	50.9	29.6	3.7				
Sulfamethoxazole	9.3	[3.2-14.1]										35.5	46.7	7.5	1.9	0.9		7.5
Trimethoprim	0.9	[0.02-5.1]				14.8	37.0	41.7	5.6					0.9				
Gentamicin	0.9	[0.02-5.1]						39.8	56.5	3.7								
Streptomycin	2.8	[0.6-7.9]									40.7	55.6	0.9	2.8				
Kanamycin	0.9	[0.02-5.1]										99.1	0.9					
Ciprofloxacin	3.7	[1.0-9.2]		23.1	73.1	1.9		1.9										
Nalidixic acid	1.9	[0.2-6.5]							2.8	76.9	17.6	0.9				1.9		
Colistin	0.0	[0.0-3.4]						97.2	2.8									

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested 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 discussion

By use of the selective method, *E. coli* resistant to third generation cephalosporins were found in 43% [95% CI: 36.7-49.2] of the broiler samples. All isolates had a beta-lactam resistance profile corresponding to an AmpC phenotype. PCR and sequencing showed that all isolates contained the $bla_{\text{CMY-2}}$ gene. By using the non-selective procedure, two cephalosporin resistant isolates (1.0%; 95% CI: 0.1-3.4), also containing the $bla_{\text{CMY-2}}$ gene, were found.

Like the situation in many other countries, broiler production in Norway has a high prevalence of *E. coli* resistant to third generation cephalosporins. This situation is surprising as there is no selection pressure from cephalosporin usage. No commercial preparations for livestock containing cephalosporins are available on the market. The poultry production in Norway is dependent on import of breeding animals and these animals are a likely source of resistant bacteria. A similar situation is also reported from other Scandinavian countries.

The presence of bacteria resistant to cephalosporins in food production animals is of concern. Resistant bacteria in the food chain may have an impact on resistance development in human bacterial populations and it should be an overall goal to keep the level of resistant bacteria in production animals and through the meat processing chain at the lowest possible level. Further studies are needed in order to fully understand the role of resistant bacteria in food and their impact on the resistance epidemiology in humans.

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C. ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

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Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum. In Norway, *Salmonella* isolates from control programmes concerning feed samples, animals and food products, as well as diagnostic samples are monitored for antimicrobial resistance. Additionally in 2011, antimicrobial resistance in isolates of *Campylobacter jejuni* from broiler was included. Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates. Sampling, laboratory methods and data processing are described in Appendix 4.

The NORM results on human isolates of enteropathogenic *Enterobacteriaceae* are interpreted according to the clinical breakpoints given by the Norwegian Working Group for Antibiotics (NWGA) and by the corresponding Nordic group (NordicAST). In case of missing clinical breakpoints, epidemiological breakpoints (ECOFFs) are used. Multi-drug resistance (MDR) was defined as resistance to three or more antimicrobial categories according to the 2011 EDCD/CDC joint definitions.
From 2011 on, the EUCAST protocol for antimicrobial resistance (AMR) testing of non-fastidious bacteria has been used. Therefore, differences in proportions of resistance between 2011 and earlier years may be due to methodological issues rather than true shifts in resistance. That is why the judgements regarding changes over time are rather conservative.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food production animals in Norway is very good 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 (index isolates) to the Norwegian Veterinary Institute. Additionally, isolates of *Salmonella diarizonae* from sheep collected during the period 2006-2011 were included. The data are presented in Tables 15-16 and in the text.

TABLE 15. Antimicrobial resistance in *Salmonella* spp. (n=49) from animals (cattle=12, dog=17, alpaca=1, cat=5, broiler=2, turkey=1, swine=5, horse=5, deer=1); *S.* Typhimurium (n=22) and other *Salmonella* spp. (n=27) in 2011.

	Resistance (n)	Distribution (n) of MIC values (mg/L)															
Substance		0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	15							17	17			1	2		12		
Chloramphenicol	2								4	31	12					2	
Florfenicol	2								4	36	7		2				
Ampicillin	15						4	29	1						15		
Cefotaxime	0			26	20	3											
Sulfamethoxazole	15												10	20	4		15
Trimethoprim	0					32	16	1									
Gentamicin	0						32	16	1								
Streptomycin	16									2	24	7		1	4	7	4
Kanamycin	0								40	9							
Ciprofloxacin	2		13	34		1	1										
Nalidixic acid	2								1	37	9				1	1	

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

TABLE 16. Antimicrobial resistance in *Salmonella diarizonae* (n=67) of diagnostic submissions from sheep during the years 2006-2011.

	Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	[95% CI*]		0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	0	[0.0-5.4]						9.0	89.6	1.5								
Chloramphenicol	0	[0.0-5.4]								58.2	41.8							
Florfenicol	0	[0.0-5.4]								49.3	50.7							
Ampicillin	0	[0.0-5.4]						56.7	43.3									
Cefotaxime	0	[0.0-5.4]			97.0	3.0												
Sulfamethoxazole	0	[0.0-5.4]										40.3	7.5	23.9	28.4			
Trimethoprim	0	[0.0-5.4]					53.7	46.3										
Gentamicin	0	[0.0-5.4]					62.7	37.3										
Streptomycin	7.5	[2.5-16.5]										4.5	88.1	7.5				
Kanamycin	0	[0.0-5.4]						9.0	89.6	1.5								
Ciprofloxacin	0	[0.0-5.4]		89.6	10.4													
Nalidixic acid	0	[0.0-5.4]								9.0	89.6	1.5						

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

RESULTS AND COMMENTS

ANIMALS

In 2011, a total of 49 isolates of *Salmonella* spp. were susceptibility tested. The 22 isolates of *S.* Typhimurium included seven from cattle and one from broiler, two from swine, one from each of alpaca and red deer, and five from each of dogs and cats. The remaining isolates belonged to several different serovars and originated from dogs (n=12), cattle (n=5), swine (n=3), horses (n=5) and one each from turkey and broiler. Resistance to tetracyclines, ampicillin, streptomycin and sulfamethoxazole was occurring in about a third of the isolates. Two isolates showed resistance to fluoroquinolones. The data, although limited, indicate that resistance in *Salmonella* spp. occasionally isolated in Norwegian animals seems to be increasing. The emerging multi-resistant *S. enterica* serovar 4,[5],12:i- was isolated from different animal species including cattle, horse, dog and broiler. All were resistant to tetracycline, ampicillin, streptomycin and sulfametoxazole.

SHEEP

The isolates of *Salmonella diarizonae* from sheep were susceptible to the substances included in the panel except for streptomycin, 7.5% were classified as resistant. *S. diarizonae* has been isolated from cases of abortion, stillbirth and diarrhoea in sheep.

Salmonella from human clinical specimens

In 2011 the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) performed antimicrobial resistance (AMR) testing on a total of 1,271 unique *Salmonella* isolates from human infections. As indicated in Table 17, 22.6% was reported as acquired in Norway, 69.2% was acquired abroad, whereas the place of origin was unknown for 8.3%.

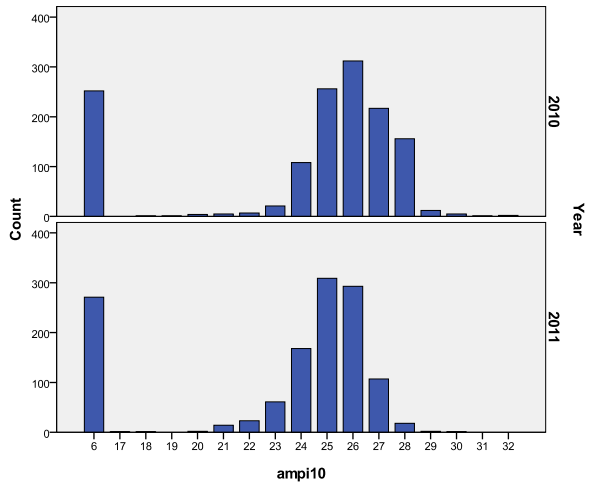
A total of 75 strains were isolated from blood culture; 10 strains of *S.* Typhimurium and its monophasic variant, 17 *S.* Enteritidis, 25 *S.* species, and, not surprisingly, most of the *S.* Typhi (n= 13 of the total 15) and all the Paratyphi (n=10).

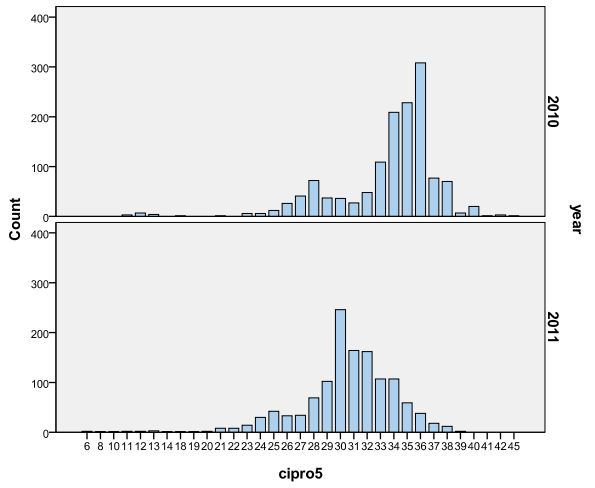
TABLE 17. Distribution of human isolates of *Salmonella* serovar (n=1,271) in 2011 according to geographical origin of acquisition.

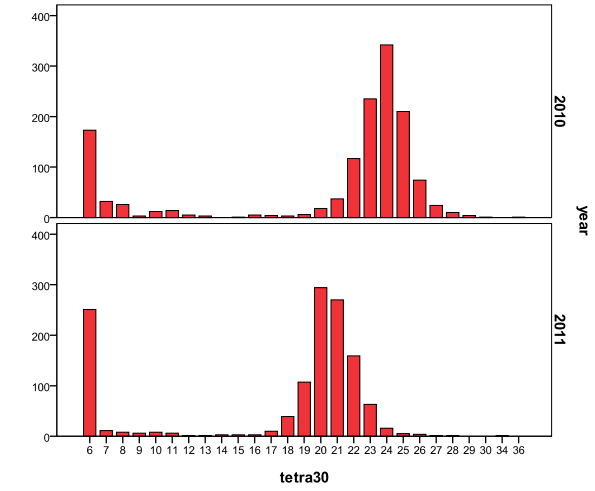
	Place of acquistion		
	Norway	Abroad	Unknown
S. Typhimurium including *S. enterica* serovar 4,[5],12:i- (n=300)	138	128	34
S. Enteritidis (n=478)	43	405	30
S. Typhi (n=15)	1	14	0
S. Paratyphi (n=11)	0	11	0
Other *Salmonella* (n=467)	105	321	41
Total (n=1,271)	**287** (22.6%)	**879** (69.2%)	**105** (8.3%)

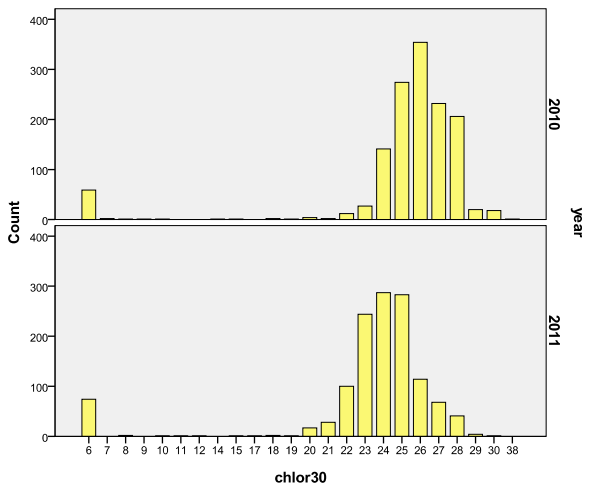
The dominating serovars are *S.* Typhimurium (n=173) and its monphasic variant (n=127), with 300 (23.6%) of the isolates, and *S.* Enteritidis with 478 (37.6%) of the isolates. Of these, 142 (47.3%), and 43 (9.0%) were reported as infected in Norway, respectively. From 2010 on, phage typing has not been performed, and thus results on *S.* Typhimurium definite phage type (DT) 104 is not available. DT 104 is of special concern, however, because of carriage of a specific pattern of MDR, namely resistance to ampicllin, chloramphenicol, streptomycin, sulfonamides, and tetracycline, thus the term ACSSuT resistance profile. To mirror, to some extent, the development regarding *S.* Typhimurium DT 104, numbers are given for isolates showing the ACSSuT resistance profile.

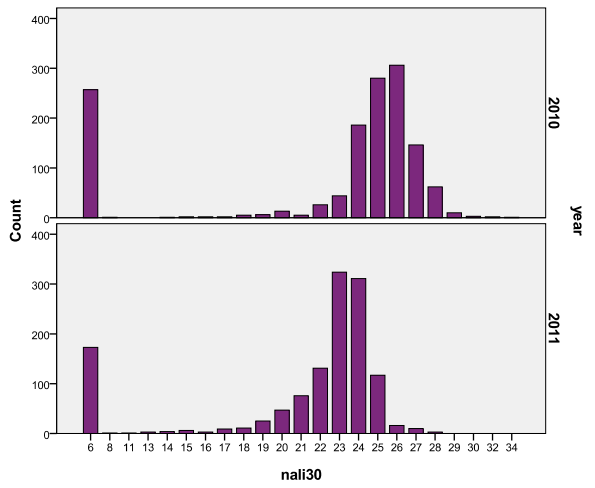
Because of the change of resistance testing method, the distributions of disc diffusion zones for each antibiotic against all serovars of *Salmonella* are shown below.

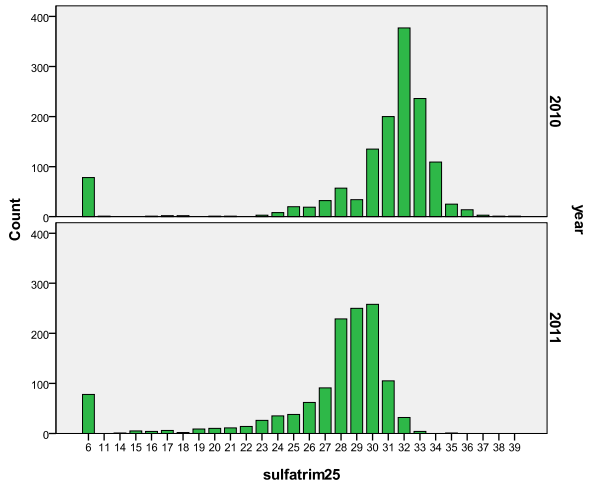












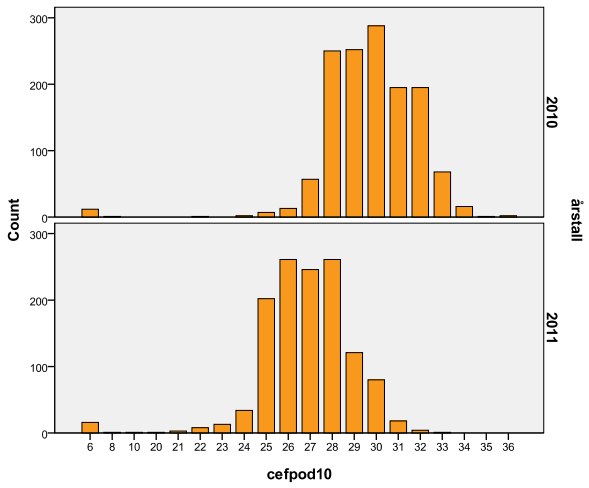


FIGURE 27. Distribution of zone diameters for *Salmonella* isolates (all serovars) included in NORM 2010 and 2011.

As seen in the figure, there is a general tendency that distributions have shifted to the left from 2010 to 2011. Thus, comparisons of AMR results between 2010 and 2011 must be treated with caution.

The results of the AMR for 2011 strains are presented in Tables 18-21, in Figures 28-33, and in the text. Sampling, laboratory methods, and data handling are described in Appendix 4.

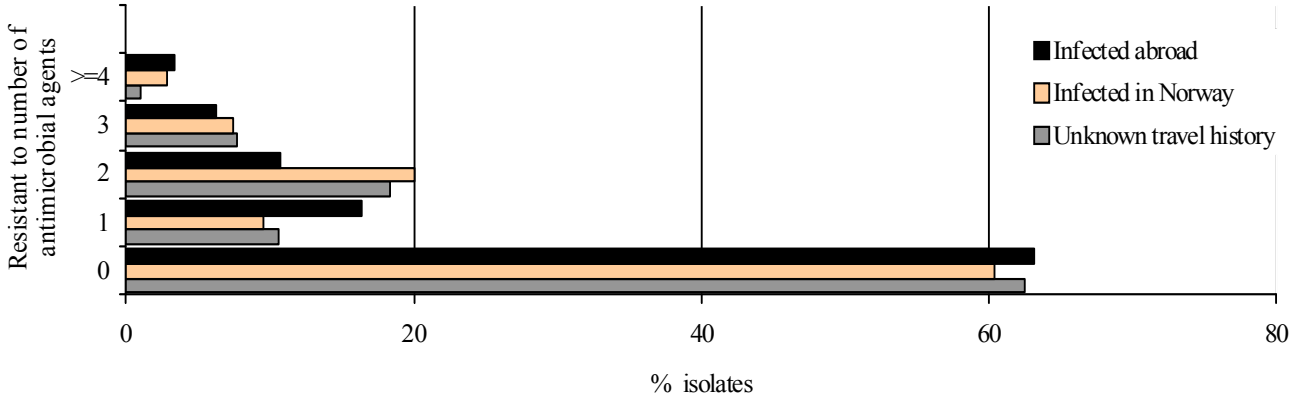


FIGURE 28. Antimicrobial resistance profiles for all *Salmonella* serovars from humans infected in Norway, abroad, and with unknown travel history. Proportion of isolates in 2011 resistant to none, one, two, three, or four or more antimicrobial agents are illustrated.

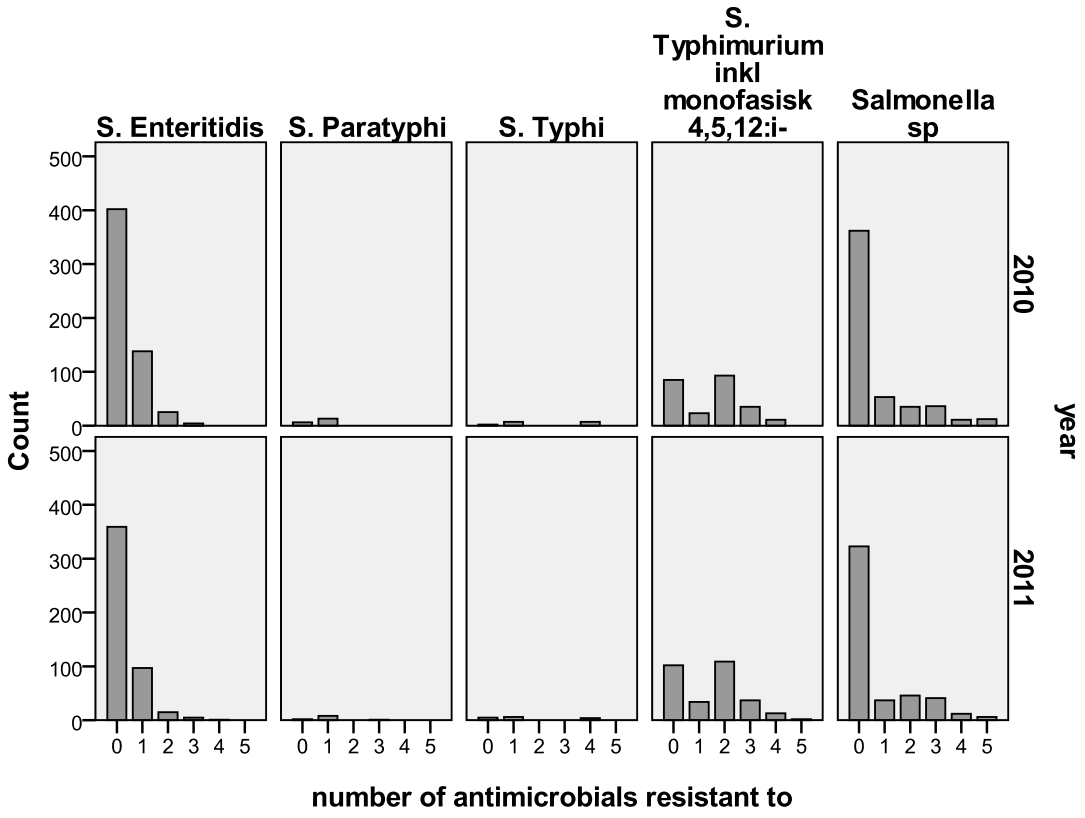


FIGURE 29. Distribution of number of antimicrobials that *Salmonella* were resistant to; by groups of serovars; and by years.

TABLE 18. Human isolates of domestically acquired isolates of *Salmonella* Typhimurium-group (n=138) during 2011, including domestically acquired *S. enterica* serovar 4,[5],12:i:- (n=52), and isolates of either of the two serovars with the ACSSuT resistance profile (n=16). 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 [1]	≤ 8	> 8	44.2	-	55.8
Chloramphenicol [1]	≤ 8	> 8	87.2	-	12.3
Tetracycline [2]	≥ 17	< 17	46.4	-	53.6
Nalidixic acid [2]	≥ 19	< 19	94.9	-	5.1
Ciprofloxacin [2]	≥ 23	< 23	97.8	-	2.2
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	97.1	0.0	2.9

[1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

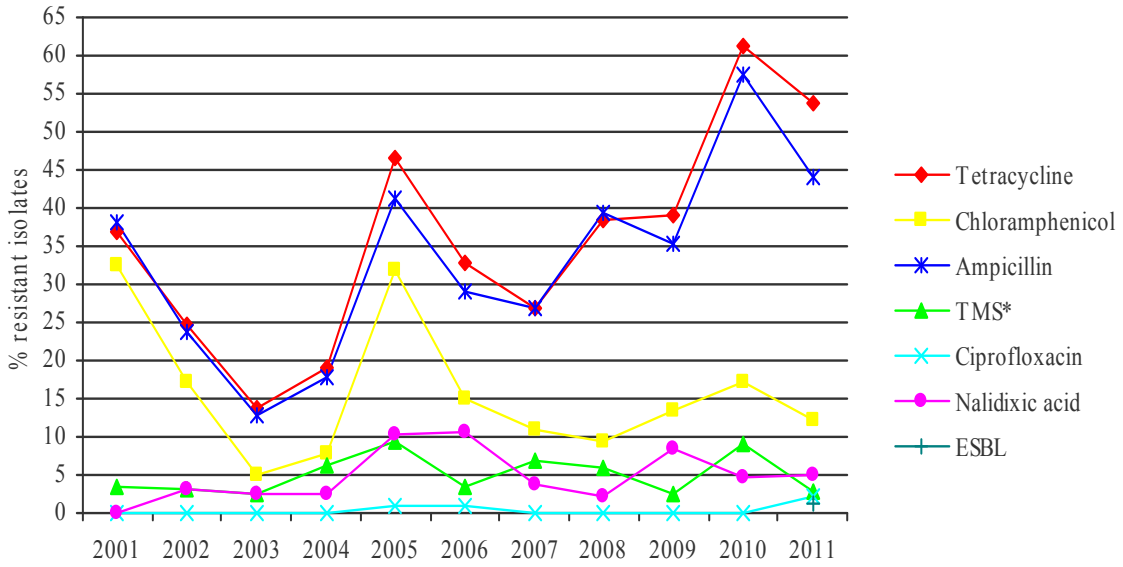


FIGURE 30. Percentage of resistance to various antimicrobial agents in *Salmonella* Typhimurium-group (including *S. enterica* serovar 4,[5],12:i:- and isolates with the ACSSuT resistance profile) from humans infected in Norway 2001-2011 (n=138). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 19. Human isolates of *Salmonella* Typhimurium-group acquired abroad during 2011 (n=128), including *S. enterica* serovar 4,[5],12:i:- (n=59) and isolates of either of the two serovars with the ACSSuT resistance profile (n=15). 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 [1]	≤ 8	> 8	43.0	-	57.0
Chloramphenicol [1]	≤ 8	> 8	82.8	-	17.2
Tetracycline [2]	≥ 17	< 17	39.8	-	60.2
Nalidixic acid [2]	≥ 19	< 19	89.1	-	10.9
Ciprofloxacin [2]	≥ 23	< 23	96.9	-	2.2
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	91.4	0.0	8.6

[1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

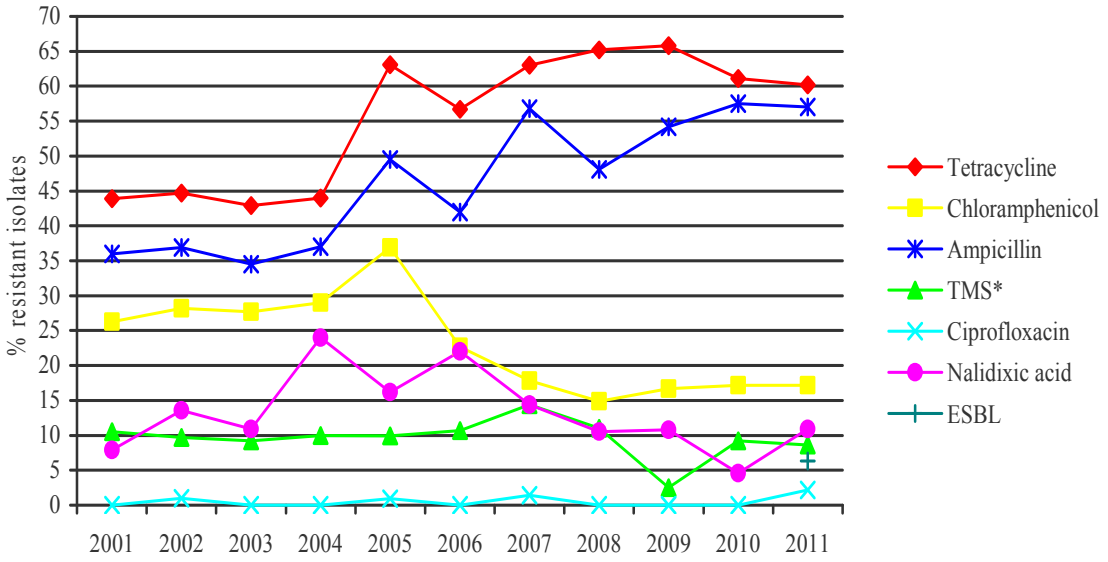


FIGURE 31. Percentage of resistance to various antimicrobial agents in human *Salmonella* Typhimurium-group (including *S. enterica* serovar 4,[5],12:i:- and isolates of either of the two serovaras with the ACSSuT resistance profile) from humans infected outside Norway 2001-2011 (n=128). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 20. Human isolates of *Salmonella* Enteritidis (n=478[#]), acquired during 2011, 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 [1]	≤ 8	> 8	94.1	-	5.9
Chloramphenicol [1]	≤ 8	> 8	99.4	-	0.6
Tetracycline [2]	≥ 17	< 17	95.6	-	4.4
Nalidixic acid [2]	≥ 19	< 19	81.4	-	18.6
Ciprofloxacin [2]	≥ 23	< 23	99.4	-	0.6
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	99.0	0.0	1.0

Place of infection; Norway (n=43), abroad (n=405), unknown (n=30). [1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

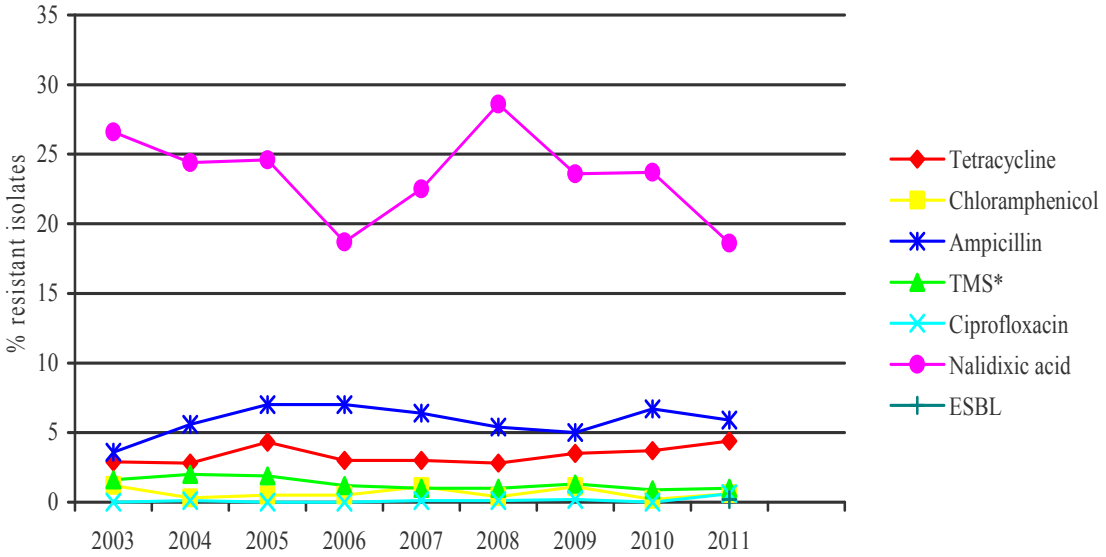


FIGURE 32. Percentage of resistance to various antimicrobial agents in *Salmonella* Enteritidis from humans in 2003-2011 (n=478). *TMS=Trimethoprim-sulfamethoxazole. Place of infection; Norway (n=43), abroad (n=405), unknown (n=30).

TABLE 21. Human isolates of *Salmonella* spp. (including *S.* Paratyphi B variant Java, but excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi) (n=467[#]), acquired during 2011, 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 [1]	≤ 8	> 8	85.7	-	14.3
Chloramphenicol [1]	≤ 8	> 8	93.8	-	6.2
Tetracycline [2]	≥ 17	< 17	77.7	-	22.3
Nalidixic acid [2]	≥ 19	< 19	82.9	-	17.1
Ciprofloxacin [2]	≥ 23	< 23	96.4	-	3.6
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	88.6	0.0	11.4

Place of infection; Norway (n=105), abroad (n=321), unknown (n=41). [1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

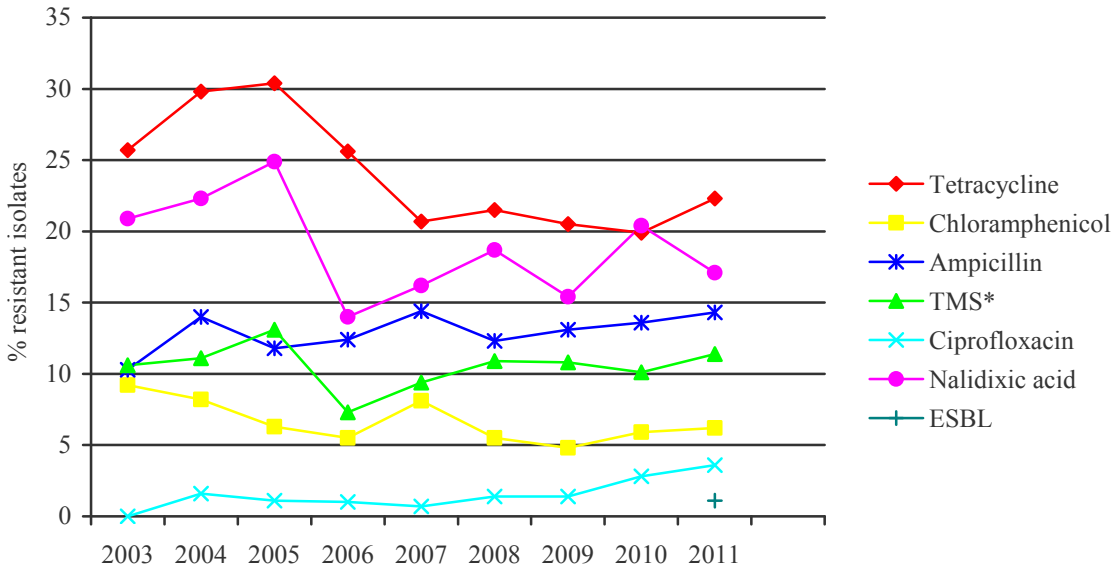


FIGURE 33. Percentage of resistance to various antimicrobial agents in *Salmonella* spp. (including *S.* Paratyphi B variant Java; but excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi) from humans in 2003-2011 (n=467). *TMS=Trimethoprim-sulfamethoxazole. Place of infection; Norway (n=105), abroad (n=321), unknown (n=41).

RESULTS AND COMMENTS

The formerly mentioned change in AMR test method; which has resulted in an apparent shift of distribution to the left for all antimicrobials tested, may underestimate changes from 2010 to 2011. This must be taken into account when evaluating the results and comments that follow. In particular, this point may be true for Figure 29, where there is no apparent shift to the right in crude number of antimicrobials that *Salmonella* show resistance to. Moreover, resistance to nalicixid acid and/or ciprofloxacin was counted as fluoroquinolone resistance in the calculations of MDR instead of only ciprofloxacin. On the other hand, cefpodoxime was not included in the calculations. Thus, the numbers may not be directly comparable to the results from other countries.

The overall tendencies were that most resistance was found in the *Salmonella* Typhimurium-group (as the y-axis of Figures 30 and 31 reaches a higher level than that of Figures 32 and 33), and that the resistance in *S.* Typhimurium-group seems to have increased. As Figure 30 and 31 shows, this appears to be true for both domestically acquired strains and strains acquired abroad. In Figure 30 both ampicillin and tetracycline started oscillating around 25% resistance and have ended at around 45%, whereas in figure 31 resistance to both antimicrobials started at a higher level and have increased not as much, now oscillating around 55% resistance.

Several countries have reported a distressing increase in multiresistant *S. enterica* serovar 4,[5],12:i-). In Norway, the number of this serovar has increased steadily over the last years; with 59, 43, 87 and 127 isolates in 2008, 2009, 2010 and 2011, respectively. The corresponding proportions of this serovar within the *Salmonella* Typhimurium-group were around 20% in 2008 and 2009, 35.2% in 2010 and 42.3% in 2011. However, MDR seems to be at about the same level in *S. enterica* serovar 4,[5],12:i- and *S.* Typhimurium; 15.0% and 20.8% respectively.

The majority of *S.* Enteritidis isolates were acquired abroad (n=405 compared to 43 acquired in Norway). The proportions of *S.* Enteritidis isolates resistant to the different antimicrobial agents included were, except for nalidixic acid, considerably lower than for *S.* Typhimurium (Figure 32). There is still a very low level of resistance to ciprofloxacin, and the resistance to ampicillin is well below 10%. The prevalence of antimicrobial resistance in *S.* Enteritidis seems quite stable.

With regard to *Salmonella* spp. (including 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 over the last years (Table 21 and Figure 33). Resistance to nalidixic acid was most common, followed by resistance to tetracycline and ampicillin. Resistance to ciprofloxacin was observed in 3.6% of the isolates, whereas 14.3% were resistant to ampicillin.

Among the few isolates of *S.* Typhi (n=15) in 2011, 4 were MDR. The proportions of resistance to particular antimicrobials were as follows: ampicillin 26.7%, ciprofloxacin 13.3%, chloramphenicol 26.7%, nalidixic acid 66.7%, trimethoprim-sulfamethoxazole 26.7%, and tetracycline 100%. All infections with these serovar were acquired abroad. Four isolates (26.7%) were resistant to four or more of the antimicrobial agents included in the survey. The isolates of *S.* Paratyphi A (n=9) and *S.* Paratyphi B (n=2), however, showed overall low rates of resistance, except for one of the isolates of *S.* Paratyphi B, which was resistant to three antimirobials.

In 2011, the detection of possible extended spectrum beta-lactamases (ESBL) was based on reduced zone diameters for cefpodoxime. Eighteen isolates had reduced susceptibility to cefpodoxime. Thirteen were fenotypically characterised to carry $ESBL_A$ (inhibited by clavulanic acid) and three as $ESBL_M$ (AmpC)-producers. The $ESBL_A$-positive strains were *S.* Typhimurium-group (n=9) and *S.* Saintpaul (n=4), whereas the $ESBL_M$-producers were *S.* Enteritidis (n=1), *S.* Newport (n=1) and *S.* Typhimurium (n=1). Three of the strains were domestically acquired; two were of the *S.* Typhimurium group and one was *S.* Newport.

Livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) detected for the first time in swine in Norway

During the last years a new livestock-associated MRSA variant has emerged among animals in several European countries, particularly among pigs. These MRSA isolates usually belong to sequence type 398 (ST398). The animals are often asymptomatic carriers, and MRSA is seldom isolated from pathological lesions in animals. MRSA ST398 can spread from animals to humans and therefore has zoonotic potential.

In two previous screenings for MRSA in swine herds in Norway (2008) no isolates of the livestock-associated MRSA were found. However, from one holding MRSA ST8, *spa* type t008 was detected. This ST is commonly found in humans and follow-up investigations of family members on the farm revealed that two persons carried the same clone. Human-to-animal transmission was the most likely explanation for the positive finding in this herd.

In 2011, screening for MRSA in swine was included in the NORM-VET programme. A total of 1,033 slaughter pigs were sampled using nasal swabs at ten different slaughterhouses. The animals originated from 207 different farms. The investigation was anonymous and tracing of positive isolates to herds was not possible.

Results and comments

MRSA was detected in six pooled samples (3%), all originating from animals slaughtered at the same slaughterhouse. All isolates belonged to ST398 *spa* type t034. In addition to resistance against beta-lactams, all isolates presented a multiresistant profile including resistance to tetracycline, fluoroquinolone, clindamycin and erythromycin (four of six isolates).

There are two possible ways that the swine became colonised with MRSA; the pigs may have originated from MRSA-colonised herds supplying pigs to the slaughterhouse, or the pigs may have been colonised during the transport to or during the stay at the slaughterhouse. The multiresistant profile of these isolates has not been observed in pigs from Norway before, suggesting that the clone might have been introduced from abroad.

The Norwegian swine industry and the Norwegian Food Safety Authority have decided to follow up the findings with investigations in swine holdings and slaughterhouses. Both stakeholders have a common goal to keep the Norwegian swine population free from the livestock-associated MRSA.

References

1. European Food Safety Authority (EFSA). Analysis of the baseline survey on the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008. EFSA Journal 2009; 7: 1376.
2. Sunde et al.. Detection of methicillin resistant *Staphylococcus aureus* sequence type 8 in pigs, production environment and human beings. J Vet Diagn Invest 2011; 23: 348-50.
3. Weese, J. S., van Duijkeren E.. Methicillin-resistant *Staphylococcus au*reus and *Staphylococcus pseudintermedius* in veterinary medicine. Vet Microbiol 2009; 140: 418-429.

Arve Lund, Madelaine Norström, Jannice Schau Slettemeås, Bjørn Lium and Marianne Sunde, Norwegian Veterinary Institute, Oslo. Lillian Marstein and Trond Jacobsen, St. Olavs University Hospital, Trondheim.

CAMPYLOBACTER SPP.

Campylobacter spp. from broiler

The isolates of *Campylobacter jejuni* in broilers originate from caecal samples collected by the "Norwegian action plan against *Campylobacter* spp. in broiler meat production". All broiler flocks slaughtered before 50 days of age are tested for the presence of *Campylobacter* spp.

In 2011, one *C. jejuni* isolate per positive flock was submitted for susceptibility testing. A total of 48 isolates were susceptibility tested. The results are presented in Table 22 and Figure 34, and in the text.

TABLE 22. Antimicrobial resistance in *Campylobacter* spp. (n=48) from broiler in 2011.

	Resistance	Distribution (n) of MIC values (mg/L)													
Substance	(n)	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	1		35	8	1	3					1				
Erythromycin	0				36	11	1								
Streptomycin	1					8	39						1		
Gentamicin	0			10	32	6									
Ciprofloxacin	2	3	37	5	1					2					
Nalidixic acid	3						3	37	5				3		

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 prevalence of antimicrobial resistance among *C. jejuni* isolates from Norwegian broilers is low. A total of 89.6% of the included isolates were susceptible to all antimicrobial agents tested. One to three isolates of 48 tested were resistant to quinolones, streptomycin or tetracycline.

Antimicrobial agents except coccidiostats are rarely used in broiler production, and only for treatment. If used, the aminopenicillin amoxicillin or the tetracycline oxytetracycline are the drugs of choice. Nalidixic acid is not used in poultry. Over the years, the trend has been rather stable and results obtained in 2011 are no exception (Figure 34).

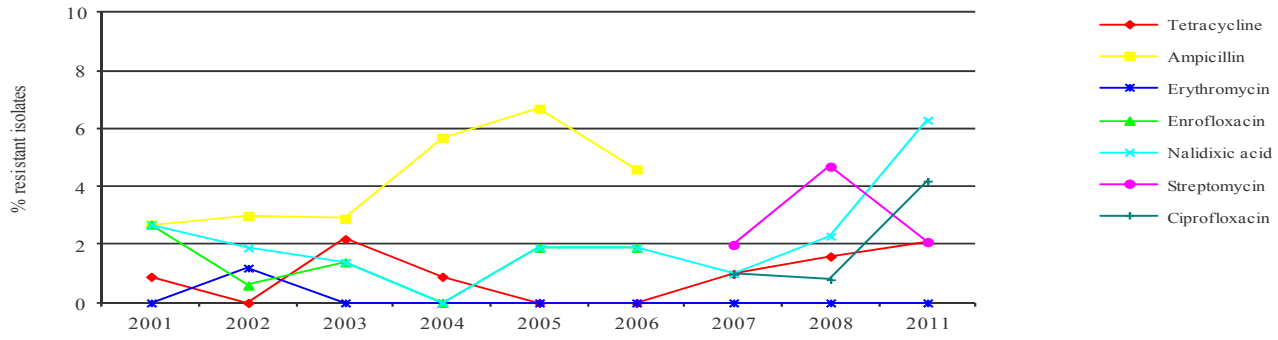


FIGURE 34. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers 2001-2011. The breakpoints for resistance defined in NORM-VET 2006 were applied for the data generated before 2007.

Campylobacter spp. from human clinical specimens

Of the 3,005 cases of human campylobacteriosis registered in Norway in 2011 (incidence rate 60.4 per 100,000), 61.0% were reported as acquired abroad. Based on epidemiological data on patients, the vast majority of cases were judged as sporadic. However, only a fraction of the isolates are forwarded to the NRL. Consequently, quality assured species diagnoses, complete AMR data and molecular epidemiology data on *Campylobacter* isolates are lacking due to resource limitations. Thus outbreaks with less clear epidemiological links may very well have been overlooked, and the AMR results presented may therefore be underestimated or overestimated.

Susceptibility testing was performed on a total of 276 isolates of *C. jejuni* (110 from patients infected in Norway, 147 from patients infected abroad and 19 from patients where the origin of infection was unknown), 11 *C. coli* isolates and 3 *C. lari* isolates. Clinical breakpoints have been worked out by EUCAST for ciprofloxacin and erythromycin. For other antimicrobials epidemiological breakpoints (ECOFFs) have been used, in agreement with the Norwegian Working Group for Antibiotics (NWGA). The results for *C. jejuni* are presented in Tables 23-26, Figures 35-37, and in the text.

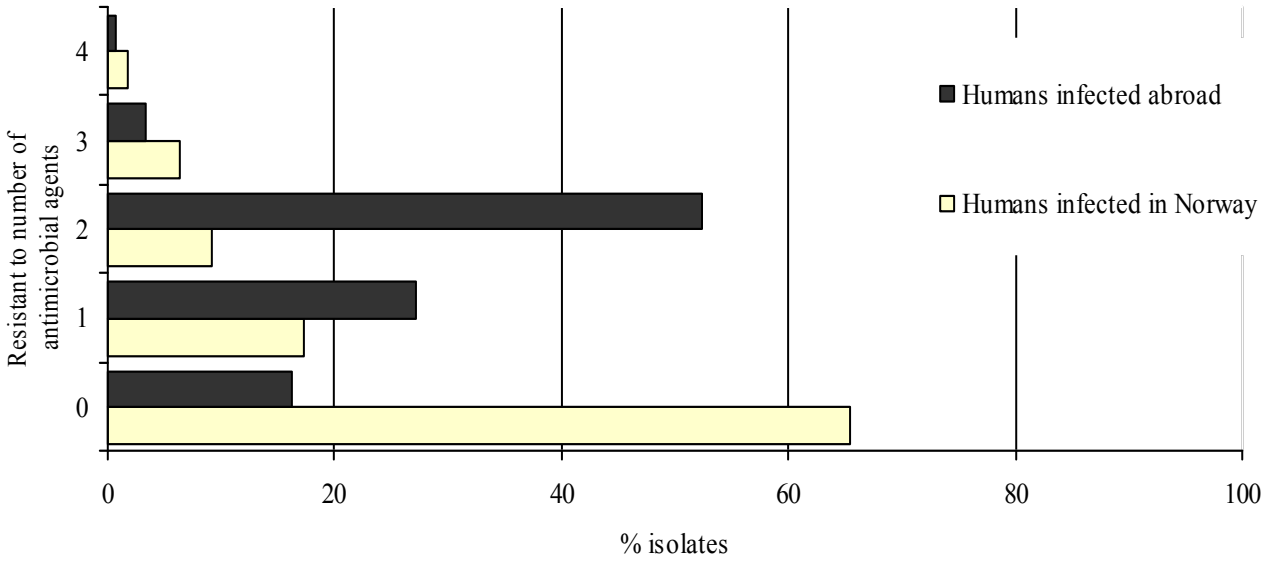


FIGURE 35. Antimicrobial resistance profiles for *Campylobacter jejuni* from humans infected in Norway (n=110) and humans infected abroad (n=147). Proportion of isolates resistant to none, one, two, three, or four or more antimicrobial agents respectively are illustrated. The isolates from humans were tested for susceptibility to tetracycline, erythromycin, gentamicin, ciprofloxacin and nalidixic acid.

TABLE 23. *Campylobacter jejuni* isolates from patients infected in Norway (n=110). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 1	> 1	86.4	-	13.6
Erythromycin	≤ 4	> 4	93.6	-	6.4
Gentamicin	≤ 2	> 4	88.2	7.3	3.6
Nalidixic acid	≤ 16	> 16	70.9	-	29.1
Ciprofloxacin	≤ 0.5	> 1	78.2	0.0	21.8

TABLE 24. *Campylobacter jejuni* isolates from patients infected in Norway (n=110). Distribution (%) of MICs (mg/L).

	≤ 0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Tetracycline		1.8	14.5	37.2	24.5	8.1	4.5	0.9	0.9		0.9	4.5	0.9	0.9
Erythromycin			0.9	4.5	6.4	51.8	22.6	7.3	2.7	0.9	1.8			0.9
Gentamicin				0.9	19.1	39.1	29.1	7.3	3.6					
Nalidixic acid						0.9	9.1	38.2	15.4	7.2	3.6	4.5		2.9
Ciprofloxacin	0.9	9.1	48.2	17.3	2.7		0.9				29.9			

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

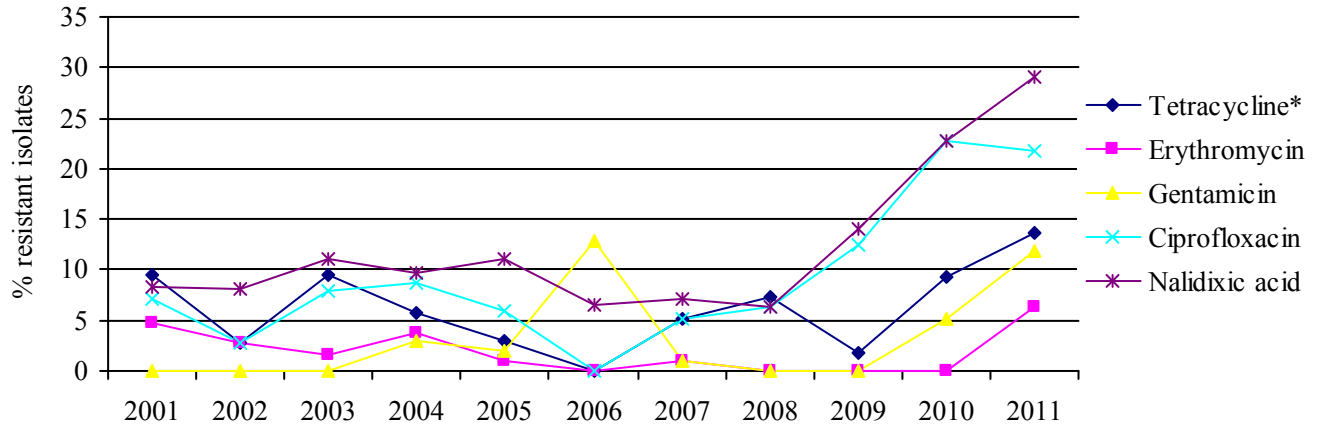


FIGURE 36. Prevalence of resistance in *Campylobacter jejuni.* isolated from humans infected in Norway 2001-2011 (n=110), to various antimicrobials. * Doxycycline before 2006.

TABLE 25. *Campylobacter jejuni* isolates from patients infected outside Norway (n=147). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 1	> 1	38.8	-	61.2
Erythromycin	≤ 4	> 4	95.9	-	4.1
Gentamicin	≤ 2	> 4	95.9	4.1	0.0
Nalidixic acid	≤ 16	> 16	25.2	-	74.8
Ciprofloxacin	≤ 0.5	> 1	24.5	0.0	75.5

TABLE 26. *Campylobacter jejuni* isolates from patients infected outside Norway (n=147). Distribution (%) of MICs (mg/L).

	≤ 0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Tetracycline			6.8	18.4	8.2	5.5	2.7	0.7	0.7	7.4	11.6	17.7	5.5	15.0
Erythromycin				1.4	22.4	32.3	31.3	5.4	1.4	0.7		0.7		1.4
Gentamicin				2.7	32.0	44.9	16.3	4.1						
Nalidixic acid							0.7	17.6	4.7	2.1	0.7			74.1
Ciprofloxacin		4.1	12.3	7.4	0.7			0.7	1.4	2.1	71.4			

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.

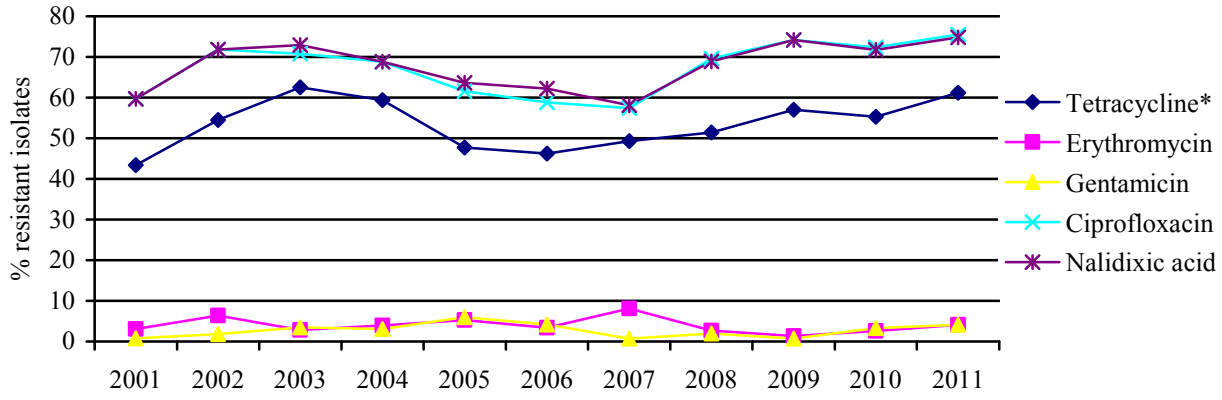


FIGURE 37. Prevalence of resistance to various antimicrobial agents in *Campylobacter jejuni* from humans infected outside Norway 2001-2011 (n=147). *Doxycycline before 2006.

RESULTS AND COMMENTS

In January 2011 the NRL changed from Etests (bioMérieux; formerly AB Biodisk) to MIC test strips from Liofilchem. Preliminary results from the reliability study indicate that MIC test strip may give slightly lower MIC-values than Etests, and thus real increases in resistance may have been underestimated or even masked. However, differences within 2011 data can be made without hesitation.

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 17.0% of isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 67.9% of the isolates from patients infected in Norway ($p<0.001$). The main differences between the two groups were seen for quinolones (ciprofloxacin/ nalidixic acid) with 75.5% resistance in isolates acquired abroad versus 30.0% resistance in isolates acquired in Norway ($p<0.001$), and tetracycline with 61.2% resistance in isolates acquired abroad versus 13.6% resistance for those acquired in Norway ($p<0.001$).

For strains acquired abroad, there is no significant change in resistance rates to any antimicriobials tested, but, as pointed out earlier, the lack of significant increases may not be true due to methodological change.

For domestically acquired strains, however, changes did reach statistical significance for erythromycin ($p=0.01$) and gentamicin ($p<0.001$), and in the proportion of MDR (from 0% in 2010 to 5.5% in 2011, $p=0.005$). On the other hand, even when comparing 2011 numbers to the numbers in 2008, the apparent increase in tetracycline resistance shown in Figure 36 did not reach statistical significance. Yet there are highly significant changes for both ciprofloxacin ($p=0.003$) and nalidixin ($p<0.001$) when comparing to 2008 data.

Eight *C. coli* isolates were acquired abroad, and three were acquired in Norway. All eight isolates acquired abroad were resistant to at least one of the antimicrobial agents tested. *C. coli* isolates are typically associated with pigs and pork. Three *C. lari* isolates were acquired in Norway and were sensitive to the antibiotics tested except for quinolones.

Yersinia enterocolitica from human clinical specimens

A total of 37 strains of pathogenic *Yersinia enterocolitica* were analysed in 2011. Thirty belonged to serogroup 3 (13 acquired in Norway, 12 abroad and 5 with unknown place of acquisition). Six strains belonged to serogroup 9, of which four were acquired in Norway (including an outbreak strain linked to imported radiccio rosso), one strain was acquired abroad, and one strain was from a case with unknown travel history. One single strain belonged to serogroup 5.27 biotype 2 and was acquired abroad. All *Y. enterocolitica* isolates were susceptibility tested. The results are presented in Table 27 and Figure 39.

Because the laboratory changed AMR testing method to the EUCAST protocol, the distributions of zone diameters for each antimicrobial tested are shown below.

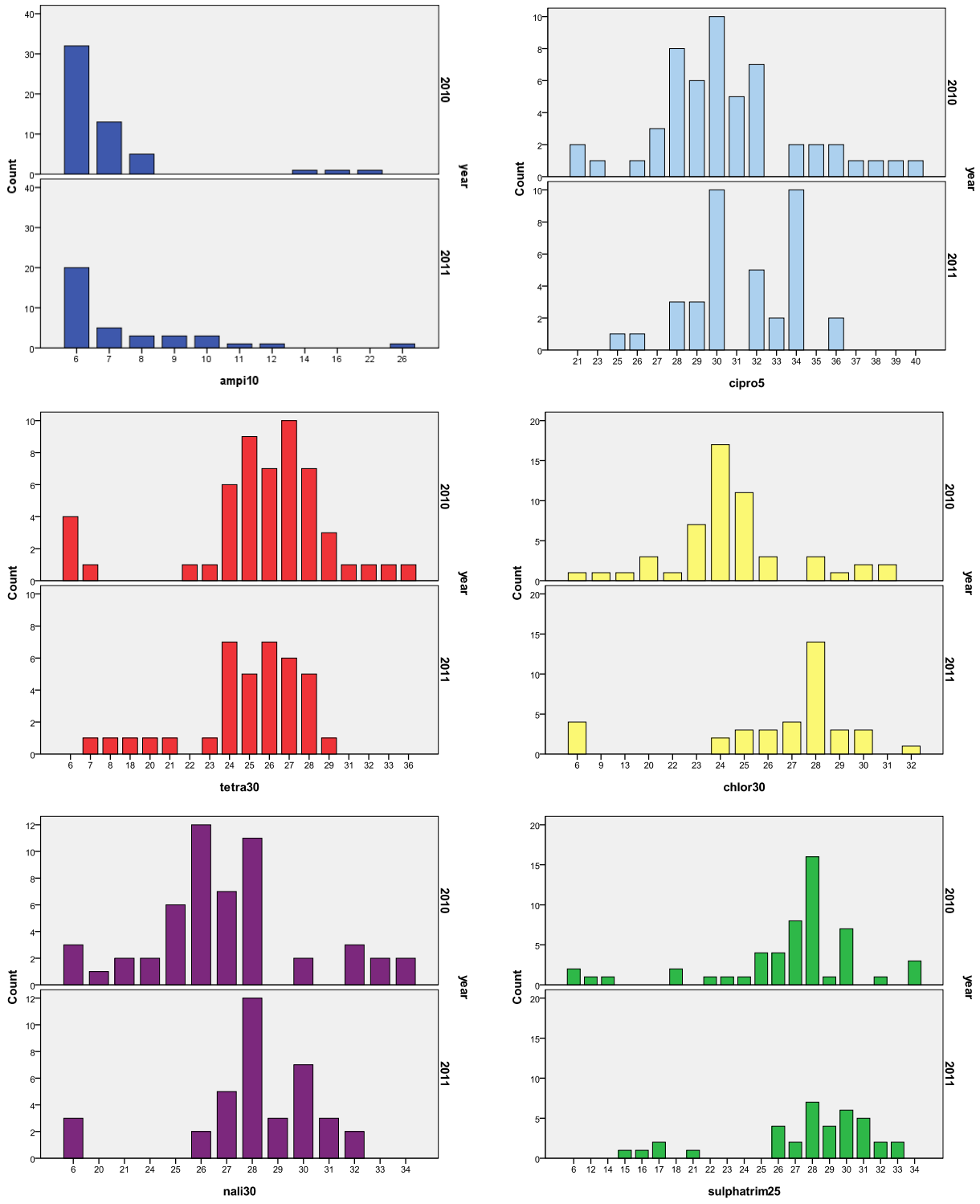


FIGURE 38. Distribution of zone diameters for *Yersinia enterocolotica* isolates included in NORM 2010 and 2011.

As seen in Figure 38, there is a general tendency of a shift to the right, rather than to the left as was seen in *Salmonella* and *Shigella.* This methodolocial issue may lead to false statements about possible increases in AMR for *Yersinia enterocolitica.* Thus, evaluations of the results, regarding changes over time, must be treated with caution. Moreover, the crude number of isolates is quite low, and judgments should consequently be even more conservative regarding AMR results for *Yersinia enterocolitica* than for the other enteropathogenic bacteria reported on.

TABLE 27. *Yersinia enterocolitica* serogroups O:3, O:9 and O:5,27 isolates from human clinical cases (n=37[#]). Distribution (%) 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 (mm) *		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≥ 14	< 14	2.7	-	97,3
Chloramphenicol	≥ 23	< 23	89.2	-	10.8
Tetracycline	≥ 19	< 19	91.9	-	8.1
Nalidixic acid	≥ 21	< 21	91.9	-	8.1
Ciprofloxacin	≥ 23	< 23	100.0	-	0.0
Trimethoprim-sulfamethoxazole **	≥ 24	< 24	86.5	-	13.5

[#] Place of acquisition Norway (n=17), abroad (n=14) or unknown (n=6). * As of June 2012 EUCAST has developed neither clinical nor epidemiological breakpoints for *Yersinia enterocolitica.* The breakpoints used are therefore based on evaluations of the distribution of zone diameters for each antimicriobial. ** Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

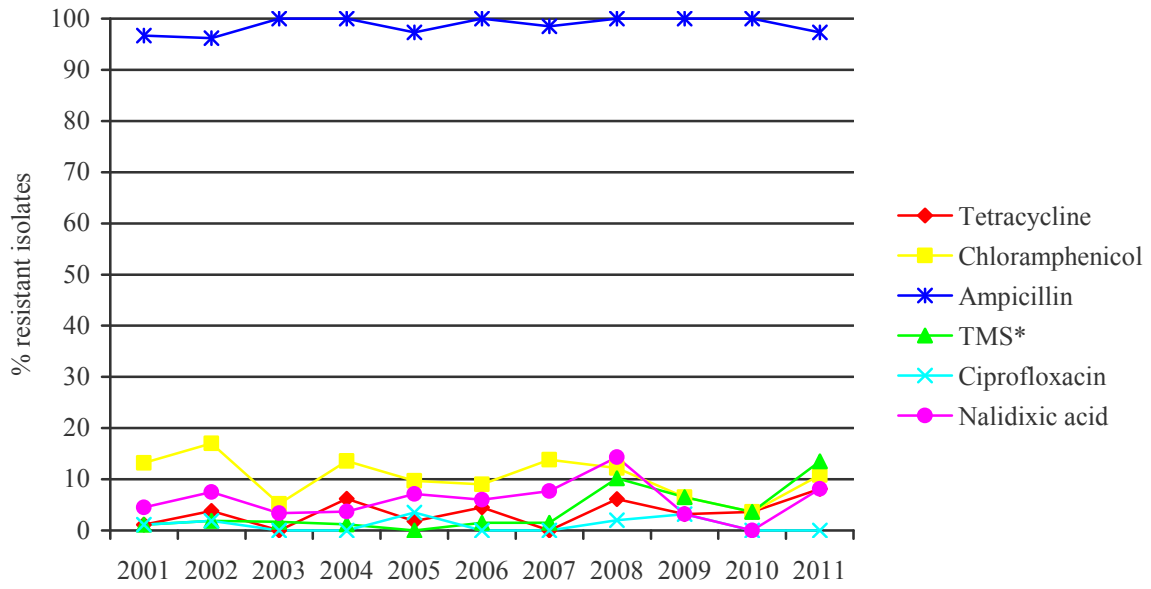


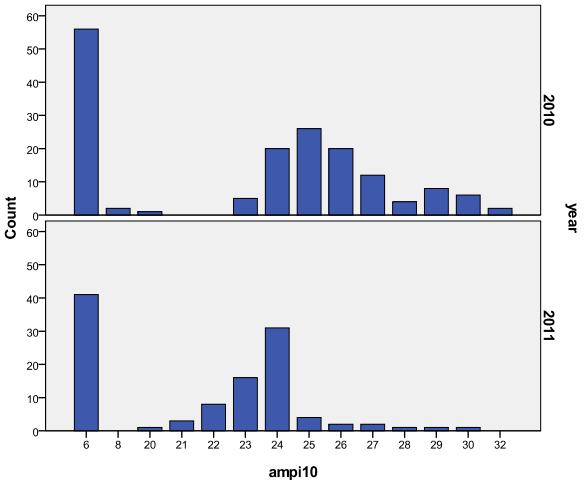
FIGURE 39. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2011 (n=37). *TMS=Trimethoprim-sulfamethoxazole.

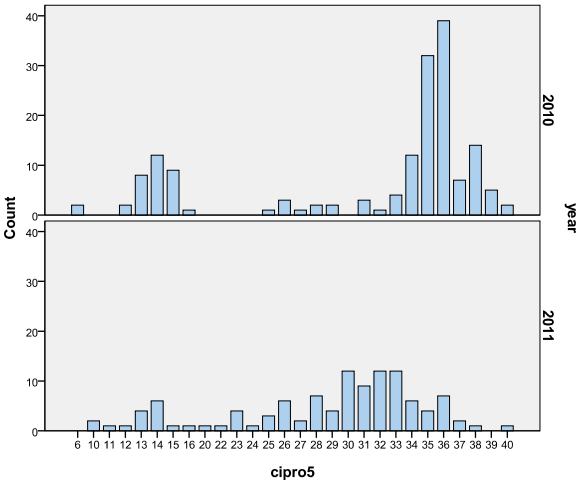
RESULTS AND COMMENTS

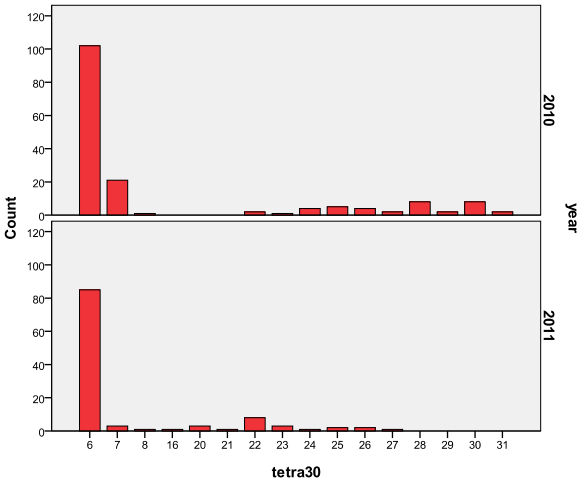
Almost all isolates of pathogenic *Yersinia enterocolitica* expressed intrinsic resistance to ampicillin. In accordance with the data on zone diameters published on the EUCAST reference database, there is a tiny number of strains lacking this attribute. This is also in agreement with a study screening for *blaA* genes *(Sharma S. et al. FEMS Microbiol Lett 2006;257:319-327).* The prevalence of resistance to other antimicrobial agents seems to be fairly stable during the years 2001-2011. However, when EUCAST has gathered enough data to establish breakpoints for *Yersinia enterocolitica*, it will be possible to judge with more statistical weight on this matter.

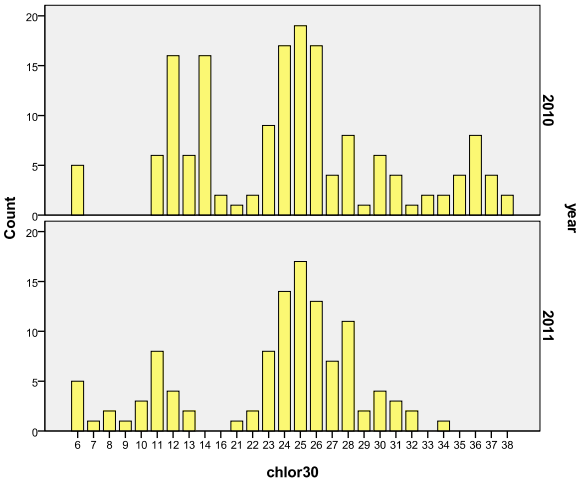
Shigella spp. from human clinical specimens

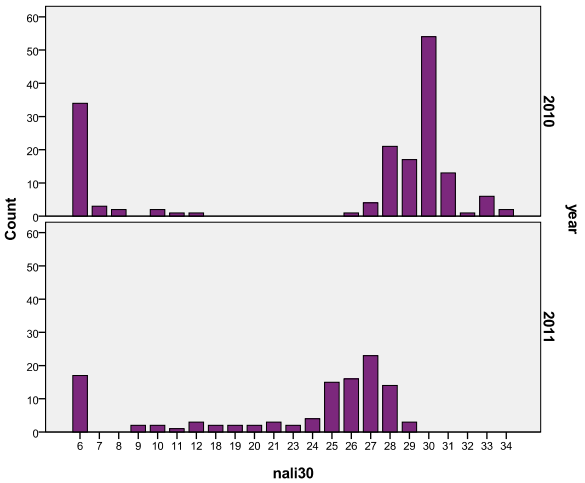
It should be emphasised that almost all reported *Shigella* infections in Norway are acquired abroad. In 2011, thirteen (11.7%) of the 111 unique isolates *of Shigella* were domestically acquired, including an outbreak strain linked to imported fresh basil, affecting 46 cases. The remaining domestically acquired strains were most probably 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 111 *Shigella* isolates that were susceptibility tested was as follows: *S. sonnei* 63 (56.8%); *S. flexneri* 41 (36.9%); *S. boydii* 6 (5.4%); and *S. dysenteriae* 1 (0.9%). Multi-resistance was defined as resistance to three or more antimicrobial categories. As with *Salmonella* and *Yersinia,* the method for AMR testing was changed to the EUCAST method and distributions of disc diffusion zones for each antimicrobial are therefore shown below.

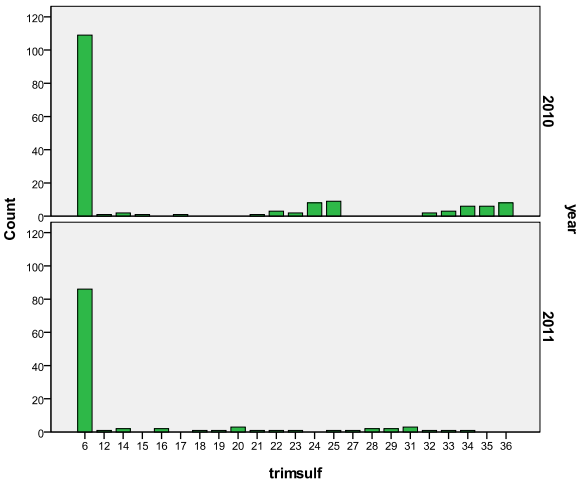












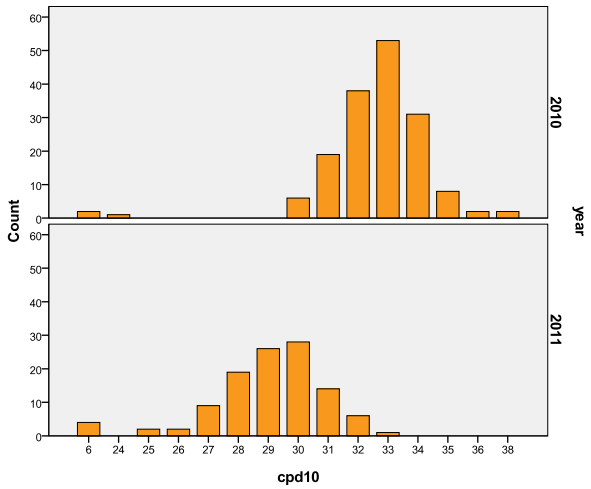


FIGURE 40. Distribution of zone diameters for *Shigella* spp. included in NORM 2010 and 2011.

The same tendency of a left shift as seen for *Salmonella* was observed in the distributions, meaning that a possibly true increase in resistance may have been underestimated. The results for *S. sonnei* and *S. flexneri* are presented in Tables 28 and Figure 43 and in Table 29 and Figure 43, respectively.

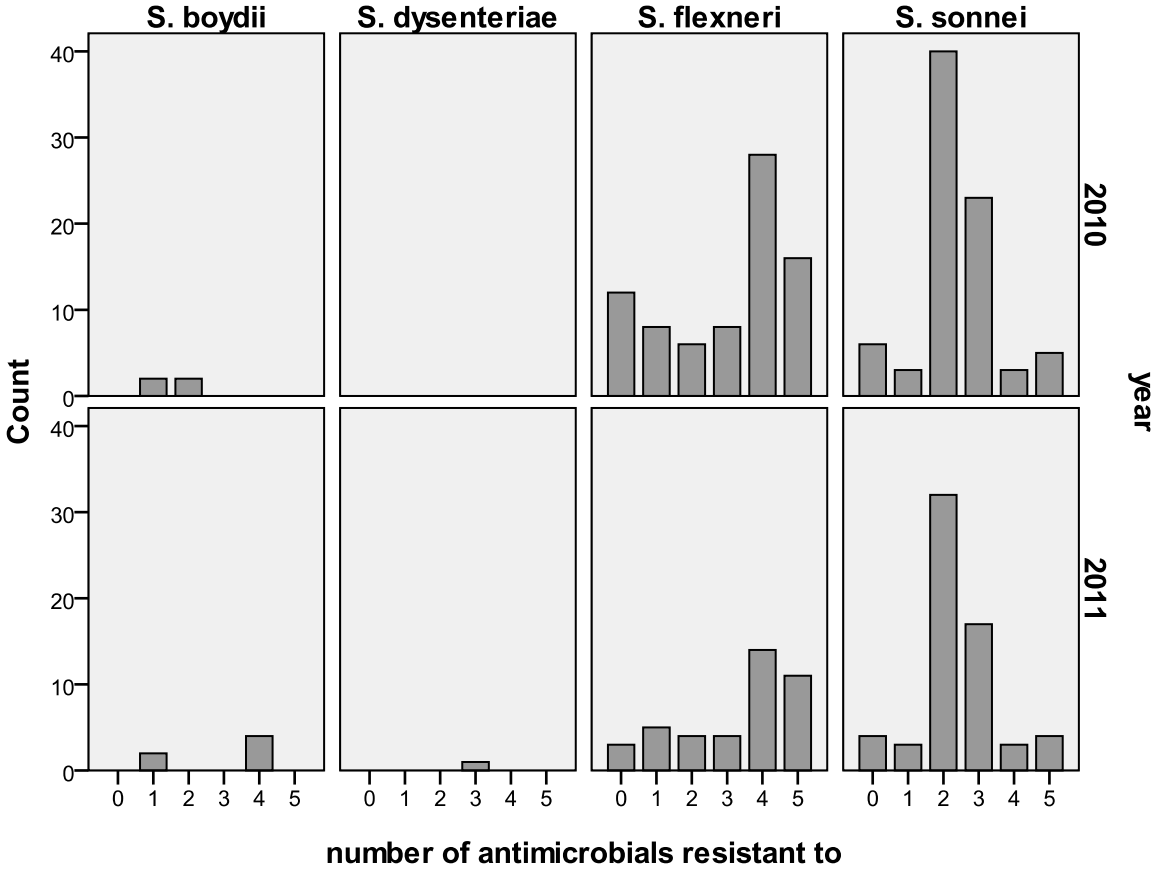


FIGURE 41. Distribution of number of antimirobials that *Shigella* isolates were resistant to; by species and by year.

TABLE 28. *Shigella sonnei* isolates from human clinical cases (n=63). 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 [1]	≤ 8	> 8	84.1	-	15.9
Chloramphenicol [1]	≤ 8	> 8	93.7	-	6.3
Tetracycline [2]	≥ 19	< 19	15.9	-	84.1
Nalidixic acid [2]	≥ 19	< 19	68.3	-	31.7
Ciprofloxacin [1]	≤ 0.5	> 1	81.0	0.0	19.0
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	7.9	3.2	88.9

[1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

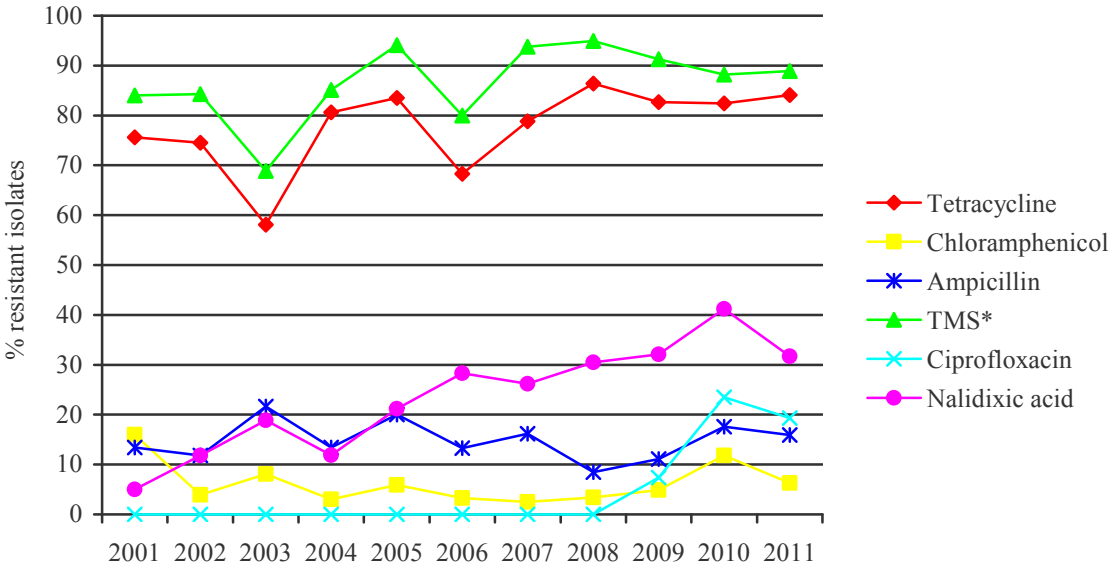


FIGURE 42. Prevalence of resistance to various antimicrobial agents in *Shigella sonnei* from humans in Norway 2001-2011 (n=63). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 29. *Shigella flexneri* isolates from human clinical cases (n=41). 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 [1]	≤ 8	> 8	36.6	-	63.4
Chloramphenicol [1]	≤ 8	> 8	46.3	-	53.7
Tetracycline [2]	≥ 19	< 19	19.5	-	80.5
Nalidixic acid [2]	≥ 19	< 19	76.9	-	23.1
Ciprofloxacin [1]	≤ 0.5	> 1	90.2	0.0	9.8
Trimethoprim-sulfamethoxazole [1,*]	≤ 2	> 4	39.0	0.0	61.0

[1] NordicAST clinical breakpoint for *Enterobacteriaceae* 2012. [2] Epidemiological breakpoint based on zone-distribution evaluations. *Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

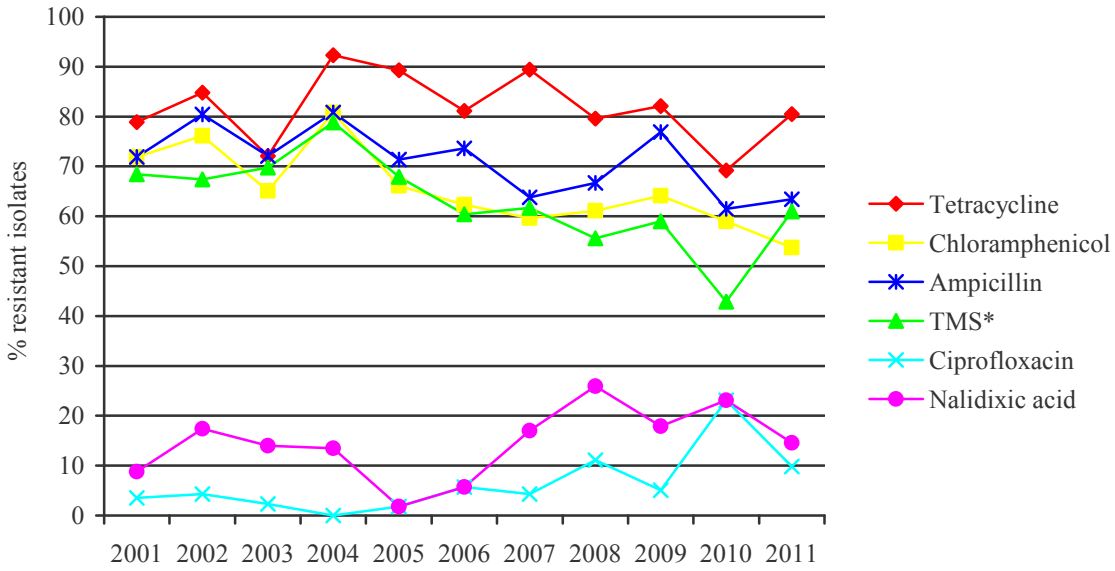


FIGURE 43. Prevalence of resistance to various antimicrobial agents in *Shigella flexneri* from humans in Norway 2001-2011 (n=41). *TMS=Trimethoprim-sulfamethoxazole.

RESULTS AND COMMENTS

The resistance patterns for *S. sonnei* have been fairly stable during the period 2001-2011, but for resistance to fluoroquinolones. The tendency of increase in resistance to nalidixic acid seems to have been going on from 2001, whereas resistance to ciprofloxacin started to rise in 2008/2009. For both substances, the percentages decreased slightly from last year, but this is most likely due to the change in AMR testing methodology mentioned earlier.

Almost the same pattern appears to be true for *S. flexneri.* For the latter, percentages of fluoroquinolon resistance in 2010 have been corrected (Figure 43), and obviously the apparent tendency of increasing resistance to fluoroquinolones described in the 2010 report was based on false results.

As shown in Figure 41 multi-resistance is frequent for all *Shigella* tested; also for the few isolates of *S. dysenteriae* (n=1) and *S. boydii* (n=6). The percentages of resistance to three or more categories of antimicrobials in *S. sonnei* and *S. flexneri* were 38.1% and 70.7% respectively. Four of the six *S. boydii* isolates were MDR, and the single strain of *S. dysenteriae* was MDR as well.

Three strains had reduced susceptibility to cefpodoxime. All three were *S. sonnei*. Two of them were fenotypically characterised as $ESBL_A$ producers with inhibitory effect of clavulanate acid, whereas one was an $ESBL_M$ producer (AmpC).

D. HUMAN CLINICAL ISOLATES

Gunnar Skov Simonsen, Karin Rønning, Cecilie Torp Andersen

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 30, 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 *Propioni-bacterium* 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 30. Number of blood culture isolates in 2011, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) 2007-2011. The table is based on data from the information systems of all laboratories in Norway in 2011.

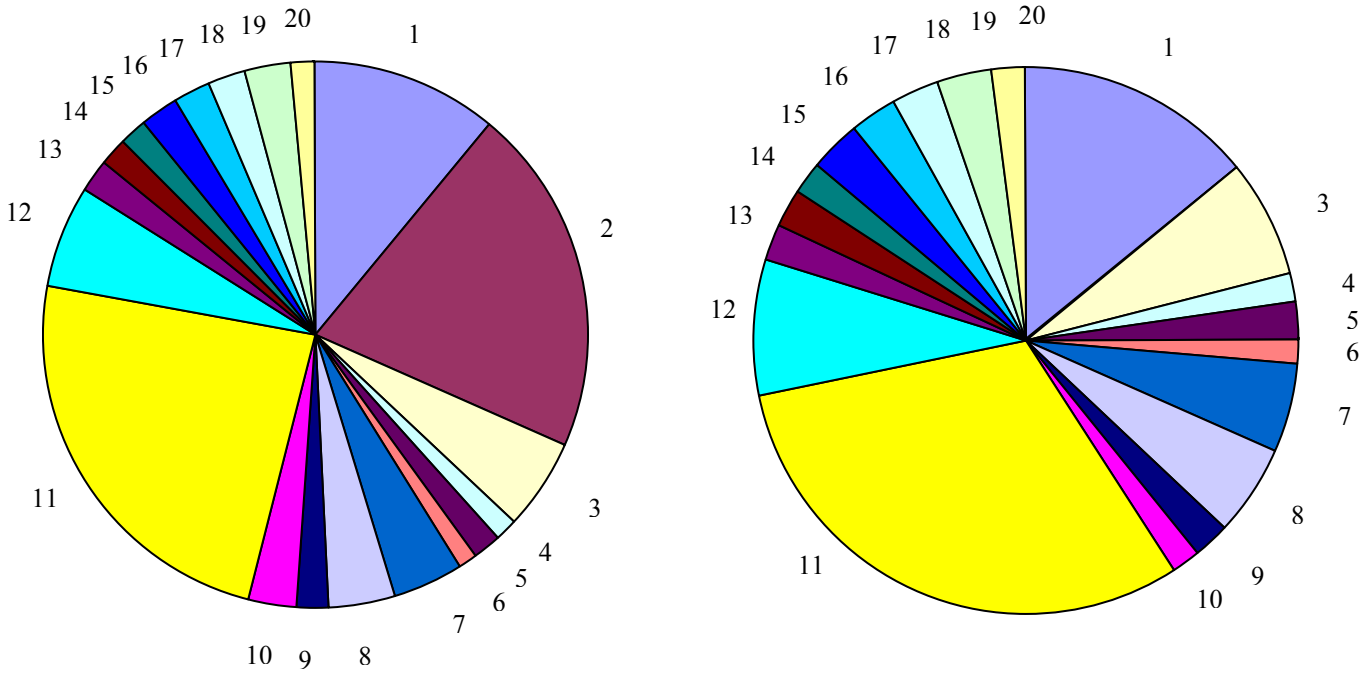
Species	No. of isolates 2011	% of all isolates					% of isolates excluding skin flora				
		2007	2008	2009	2010	2011	2007	2008	2009	2010	2011
Staphylococcus aureus	1,467	10.1	10.6	10.6	11.4	11.0	13.3	13.9	13.9	14.5	14.2
Coagulase negative staphylococci	2,739	21.6	21.3	22.3	19.3	20.6	-	-	-	-	-
Streptococcus pneumoniae	703	7.8	6.6	6.2	5.7	5.3	10.2	8.7	8.2	7.3	6.8
Streptococcus pyogenes	182	1.1	1.3	1.3	1.3	1.4	1.5	1.7	1.7	1.6	1.8
Streptococcus agalactiae	213	1.7	1.6	1.4	1.5	1.6	2.2	2.0	1.8	1.9	2.1
Beta-haemolytic streptococci group C and G	162	0.9	1.4	1.1	1.3	1.2	1.1	1.9	1.4	1.7	1.6
Viridans- and non-haemolytic streptococci	541	3.7	3.9	3.5	4.7	4.1	4.8	5.1	4.7	5.9	5.2
Enterococcus faecalis	539	4.3	4.0	4.6	4.6	4.1	5.7	5.2	6.0	5.9	5.2
Enterococcus faecium	240	1.4	1.4	1.3	1.7	1.8	1.8	1.9	1.7	2.1	2.3
Other Gram positive aerobic bacteria	390	3.4	3.4	2.7	2.8	2.9	2.1	1.5	1.5	1.4	1.6
Escherichia coli	3,188	22.3	22.8	23.0	23.4	24.0	29.2	29.9	30.2	29.6	30.9
Klebsiella spp.	814	6.0	5.8	6.5	6.8	6.1	7.9	7.6	8.6	8.7	7.9
Enterobacter spp.	240	1.8	1.9	1.9	1.6	1.8	2.3	2.5	2.5	2.1	2.3
Proteus spp.	225	1.7	1.5	1.5	1.7	1.7	2.2	2.0	2.0	2.2	2.2
Other *Enterobacteriaceae*	298	2.2	2.1	1.9	2.3	2.2	2.9	2.8	2.6	2.9	2.9
Pseudomonas spp.	202	1.6	1.8	1.9	1.8	1.5	2.1	2.4	2.5	2.2	2.0
Other Gram negative aerobic bacteria	294	2.1	2.1	1.9	2.3	2.2	2.7	2.8	2.5	2.9	2.8
Bacteroides spp.	297	2.2	2.3	2.2	2.0	2.2	2.9	3.0	2.9	2.6	2.9
Other anaerobic bacteria	377	2.5	2.5	2.3	2.3	2.8	2.9	2.8	2.8	2.6	3.4
Yeasts	193	1.7	1.8	1.9	1.5	1.5	2.3	2.3	2.5	1.9	1.9
Total	**13,304**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 30 and Figure 44, aerobic Gram positive and Gram negative bacteria represented 54.0% and 39.5% of all isolates, respectively. The predominance of Gram positives among all isolates was at the same level as in previous years. The most common Gram positive species were coagulase negative staphylococci which represented 20.6% of all isolates. 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 40.8% aerobic Gram positives and 51.0% aerobic Gram negatives.

Among the aerobic Gram positives, the prevalence of *S. pneumoniae* has steadily declined even when skin contaminants are excluded, from 12.1% in 2005 to 6.8% in 2011. The prevalence of viridans and non-haemolytic streptococci declined in 2011 to the same level as in previous years (5.2%). The prevalence of coagulase negative staphylococci also stabilised at around 20%.

E. coli (30.9%) and other *Enterobacteriaceae* (15.3%) accounted for the vast majority of aerobic Gram negative isolates, but the proportions have remained relatively unchanged since 2005. *Pseudomonas* spp. (2.0%) 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 5.0% (6.3% excluding skin flora) which is an increase from 4.3% (5.2% excluding skin flora) in 2010. Yeasts accounted for 1.5% (1.9% excluding skin flora) which is unchanged from earlier years. The major pathogens among anaerobes were members of *Bacteroides* spp. (2.2%/2.9%) and among yeasts *Candida albicans* (1.0%/1.3%). 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 44. Distribution of all blood culture isolates (left, n=13,304) and blood culture isolates excluding common skin contaminants (right, n=10,306) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. Data were retrieved from the information systems of all Norwegian laboratories in 2011.

Escherichia coli in blood cultures

TABLE 31. *Escherichia coli* blood culture isolates (n=1,438). 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	60.4	-	39.6
Piperacillin-tazobactam	≤ 8	> 16	95.7	2.7	1.6
Cefuroxime*	≤ 0.5	> 8	2.8	91.8	5.4
Cefotaxime	≤ 1	> 2	96.1	0.4	3.5
Ceftazidime	≤ 1	> 4	96.2	0.9	2.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	95.3	0.3	4.4
Nalidixic acid	≤ 16	> 16	84.5	-	15.5
Ciprofloxacin	≤ 0.5	> 1	90.9	0.2	8.9
Tigecycline	≤ 1	> 2	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	75.2	0.7	24.1
ESBL	Negative	Positive	96.7	-	3.3

*The wild type is defined as intermediately susceptible indicating that the drug is active at low dosage in urinary tract infections and at high dosage in systemic infections. **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* correspond to EUCAST breakpoints except for cefuroxime where the wild type is defined as intermediately susceptible by NWGA. The wild type was recategorised as susceptible to ampicillin from 2012 which is in line with EUCAST. The methodology for susceptibility testing was changed to EUCAST standard in 2011, and minor changes in resistance rates may be due to this transition. Breakpoints are presented in Table 31.

The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobial agents such as cefotaxime (96.1%), ceftazidime (96.2%), gentamicin (95.3%), piperacillin-tazobactam (95.7%), meropenem (100.0%) and tigecycline (100.0%) (Table 31). However, for several of these agents there was a reduction in the prevalence of susceptibility by approximately one percentage point from 2010 to 2011.

The increasing prevalence of non-susceptibility to gentamicin noted from 2004 to 2010 was reversed with 0.3% I and 4.4% R in 2011 compared to 0.4% I and 4.8% R in 2010, see Figure 45), but this change was not significant.

The prevalence of non-suscpetibility to ciprofloxacin was 9.1% in 2011 (0.2% I and 8.9% R), the highest rate ever recorded in NORM. The steadily increasing proportion of non-susceptibility to ciprofloxacin in *E. coli* blood culture isolates corresponds to the situation in almost all other European countries. The temporal association between ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 46. A similar association between quinolone use and resistance in systemic *E. coli* isolates is also reported internationally. The prevalence of resistance to the indicator antibiotic nalidixic acid (15.5%) is at the same level as in 2010, whereas the figures for ampicillin (39.6%) and trimethoprim-sulfamethoxazole (24.1%) are slowly increasing.

In 2011, the 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 Etests. A total of 48 isolates (3.3%) were reported as ESBL positive which is a slight increase from 3.1% in 2010 (Figure 48). The isolates originated from 14 different hospitals with up to six isolates from each institution. All ESBL isolates were resistant to ampicillin and cefuroxime, and most of them were also non-susceptible to cefotaxime (45/48) and ceftazidime (42/48). Many isolates were intermediately (4/48) or even fully susceptible (37/48) to piperacillin-tazobactam, but most displayed co-resistance to ciprofloxacin (35/48), gentamicin (17/48) and/or trimethoprim-sulfamethoxazole (31/48). All were fully susceptible to tigecycline and meropenem. Fourteen additional isolates were reported as non-susceptible to cefotaxime (n=10) and/or ceftazidime (n=13) without being confirmed as ESBL producers.

All *E. coli* ESBL isolates were molecularly characterised by PCR and DNA sequencing which revealed a predominance of CTX-M groups 1 (n=31) and 9 (n=9), as well as one isolates containing enzymes from both genotypes. The remaining seven isolates harboured TEM (n=1), derepressed chromosomally encoded AmpC (n=3), or plasmid encoded CMY (n=1) or DHA (n=1) enzymes. A single isolate displayed a phenotypical ESBL profile but was negative in CTX-M, SHV and TEM PCRs and will be investigated further.

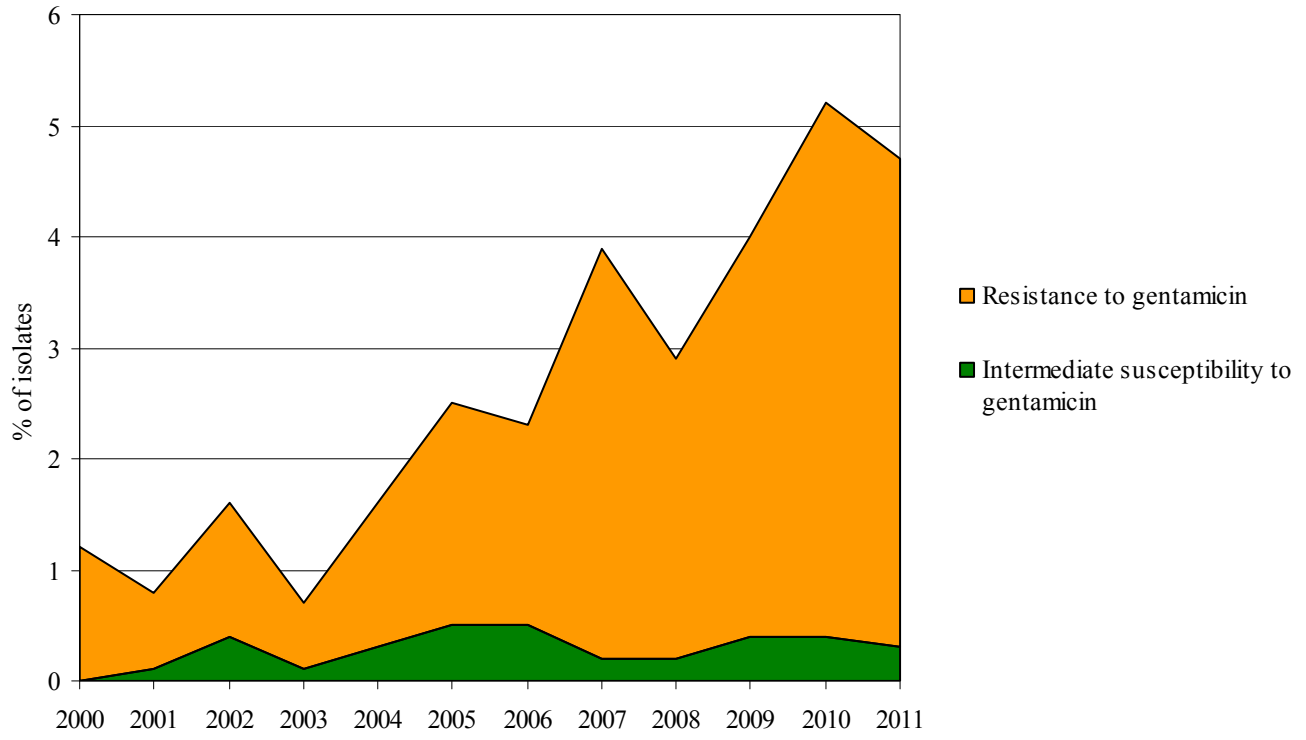


FIGURE 45. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2011.

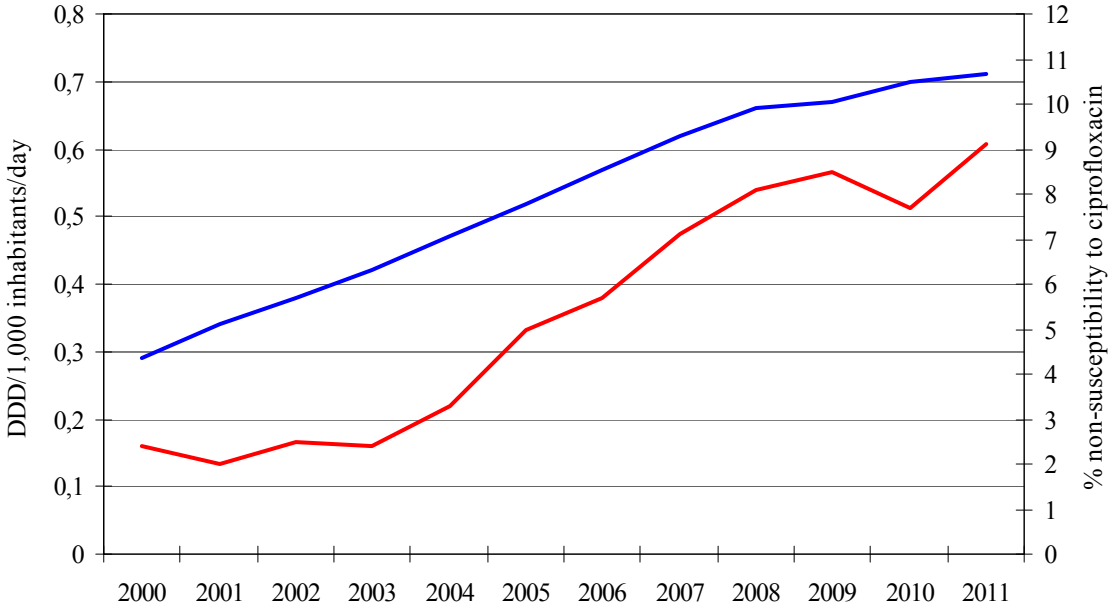


FIGURE 46. Usage of ciprofloxacin (blue) and prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2012 breakpoints (red) 2000-2011.

Escherichia coli in urine

TABLE 32. *Escherichia coli* urinary tract isolates (n=940). 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	64.3	-	35.7
Mecillinam	≤ 8	> 8	91.3	-	8.7
Cefuroxime*	≤ 0.5	> 8	2.8	94.5	2.8
Cefotaxime	≤ 1	> 2	98.4	0.1	1.5
Ceftazidime	≤ 1	> 4	98.3	0.3	1.1
Gentamicin	≤ 2	> 4	97.6	0.3	2.1
Nalidixic acid	≤ 16	> 16	88.1	-	11.9
Ciprofloxacin	≤ 0.5	> 1	94.6	0.4	5.0
Nitrofurantoin	≤ 64	> 64	98.5	-	1.5
Trimethoprim	≤ 2	> 4	77.2	0.5	22.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	78.4	1.1	20.5
ESBL	Negative	Positive	98.4	-	1.6

*The wild type is defined as intermediately susceptible indicating that the drug is active at low dosage in urinary tract infections and at high dosage in systemic 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 prevalences of resistance for 2011 are shown in Table 32 and the results 2000-2011 are shown in Figure 47. As for *E. coli* blood culture isolates, the wild type isolates were reclassified as susceptible to ampicillin from 2012 and the results since 2000 have been recalculated accordingly.

The resistance rates among urinary tract isolates have remained relatively stable over the last ten years. The prevalence of resistance to ampicillin has gradually increased from approximately 25% to 30%. A little more than 20% of *E. coli* isolates are resistant to trimethoprim and trimethoprim-sulfamethoxazole. The prevalence of resistance to mecillinam increased from 4.4% in 2010 to 8.7% in 2011, but this may at least in part be explained by the transition to EUCAST methodology in 2011. Susceptibility test results are notoriously difficult to reproduce for this agent.

Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. The prevalence of non-susceptibility has been relatively stable around 3.5-5.5% over the last years. The prevalence in 2011 was 5.4% with 0.4% intermediate susceptibility and 5.0% resistance. This is essentially unchanged from 5.8% non-susceptibility in 2010. The corresponding rates for blood culture isolates were 0.2% intermediate susceptibility and 8.9% resistance in 2011. The difference between isolates from systemic and localized infections was also seen for nalidixic acid with 11.9% resistance in urinary tract isolates and 15.5% resistance in bloodstream infections. One may speculate that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and topoisomerase genes, whereas urinary tract isolates are more representative of the wild type normal flora. Nevertheless, the prevalence of first-step mutations in both bloodstream and urinary tract isolates is cause for great concern.

In total, 15 isolates (1.6%) were reported as ESBL producers. This prevalence is at the same level as in 2010 (1.4%), but confirms the increase from 2009 (0.5%). As seen in Figue 48, the prevalence of *E. coli* ESBL is still significantly lower in urine than in blood culture isolates (3.4%), but there is an increasing trend in both specimen types. The isolates were retrieved from eight different laboratories in all parts of the country. Four isolates were found in hospitalized patients, while the others were detected in samples submitted from outpatient clinics (n=2), nursing homes (n=1) or general practitioners (n=8). The ESBL strains were generally resistant to ampicillin (15/15), cefuroxime (15/15), cefotaxime (14/15) and ceftazidime (10/15), but a majority (10/15) was registered as susceptible to mecillinam. The clinical relevance of this finding is not known. Most of the ESBL isolates were non-susceptible to quinolones (n=8) and trimethoprim-sulfamethoxazole (n=10), but remained susceptible to nitrofurantoin (n=13) and gentamicin (n=11). Carbapenems were not included in the 2011 protocol. By molecular characterisation of 13 isolates it was found that they harboured resistance determinants from CTX-M groups 1 (n=8) and 9 (n=3), as well as plasmid encoded CMY (n=1) and TEM-1 hyperproduction (n=1). This is in accordance with findings in blood culture isolates and previous surveys.

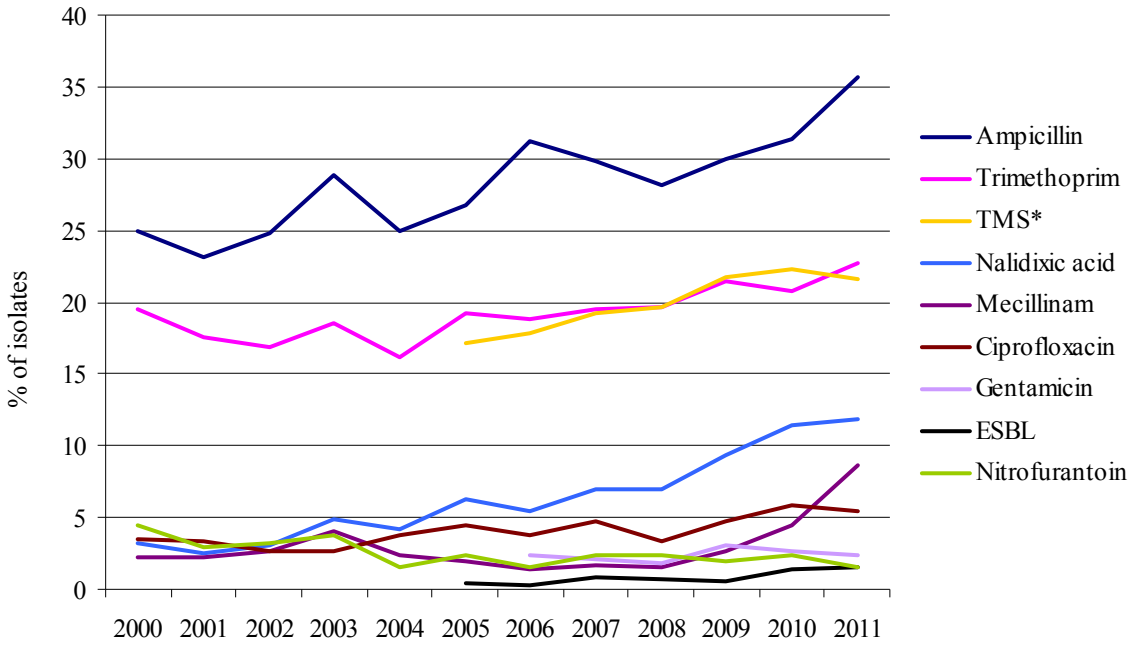


FIGURE 47. Prevalences of resistance to various antimicrobial agents in urinary tract *E. coli* isolates 2000-2011. The breakpoint for resistance to ampicillin was changed fram R > 16 mg/L to R > 8 mg/L in 2005. For all years, isolates previously classified as intermediately susceptible have been categorised as susceptible according to 2012 EUCAST guidelines. The results from 2000-2004 thus indicate proportion of isolates with MIC > 16 mg/L and since 2005 MIC > 8 mg/L. *TMS=Trimethoprim-sulfamethoxazole.

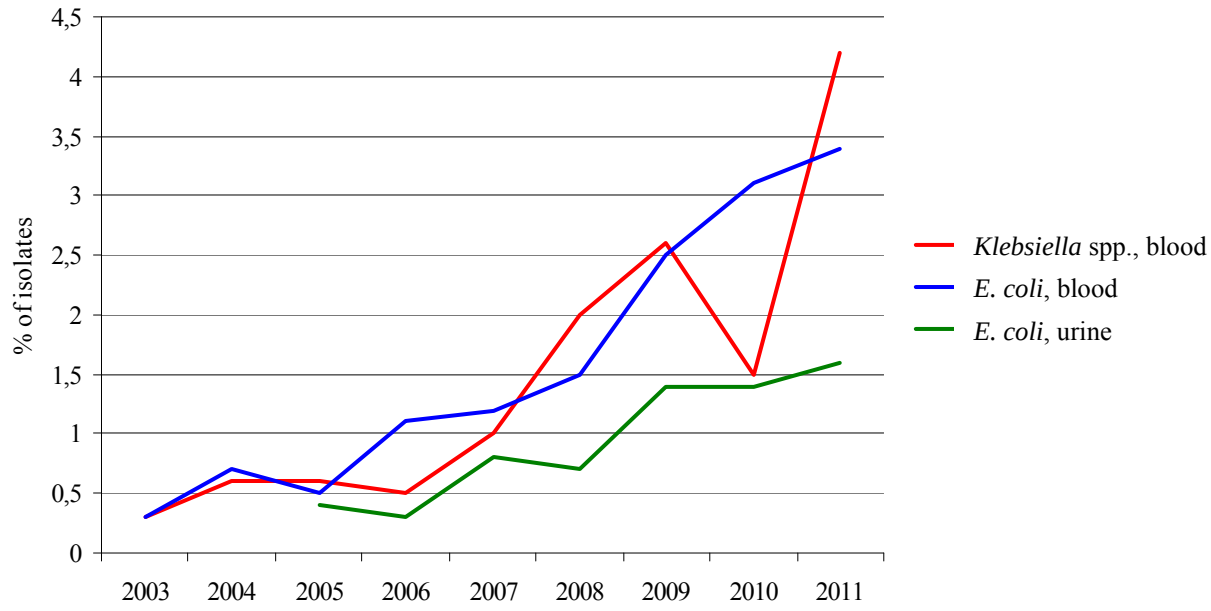


FIGURE 48. Prevalences of ESBL production among *Klebsiella* spp. blood culture isolates and *E. coli* isolates from blood and urine 2003-2011.

Klebsiella spp. in blood cultures

TABLE 33. *Klebsiella* spp. blood culture isolates (n=596). 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	89.4	7.7	2.9
Cefuroxime*	≤ 0.5	> 8	3.0	86.4	10.6
Cefotaxime	≤ 1	> 2	95.3	0.0	4.7
Ceftazidime	≤ 1	> 4	94.3	1.5	4.2
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	95.4	0.7	3.9
Nalidixic acid	≤ 16	> 16	87.6	-	12.4
Ciprofloxacin	≤ 0.5	> 1	94.3	1.0	4.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	82.9	1.7	15.4
ESBL	Negative	Positive	95.8	-	4.2

*The wild type is defined as intermediately susceptible indicating that the drug is active at low dosage in urinary tract infections and at high dosage in systemic infections. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 34. *Klebsiella pneumoniae* blood culture isolates (n=454). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	88.3	9.0	2.6
Cefuroxime*	≤ 0.5	> 8	2.4	86.1	11.5
Cefotaxime	≤ 1	> 2	94.3	0.0	5.7
Ceftazidime	≤ 1	> 4	92.5	2.0	5.5
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	94.3	0.9	4.8
Nalidixic acid	≤ 16	> 16	86.6	-	13.4
Ciprofloxacin	≤ 0.5	> 1	93.0	1.3	5.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	79.1	2.2	18.7
ESBL	Negative	Positive	94.5	-	5.5

*The wild type is defined as intermediately susceptible indicating that the drug is active at low dosage in urinary tract infections and at high dosage in systemic infections. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 35. *Klebsiella oxytoca* blood culture isolates (n=127). 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	93.0	3.1	3.9
Cefuroxime*	≤ 0.5	> 8	5.5	86.6	7.9
Cefotaxime	≤ 1	> 2	99.2	0.0	0.8
Ceftazidime	≤ 1	> 4	100.0	0.0	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	99.2	0.0	0.8
Nalidixic acid	≤ 16	> 16	91.3	-	8.7
Ciprofloxacin	≤ 0.5	> 1	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.3	0.0	4.7
ESBL	Negative	Positive	100.0	-	0.0

*The wild type is defined as intermediately susceptible indicating that the drug is active at low dosage in urinary tract infections and at high dosage in systemic infections. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

The surveillance of *Klebsiella* spp. in blood cultures included 454 *K. pneumoniae* (76.2%), 127 *K. oxytoca* (21.3%), and 15 (2.5%) isolates not identified to the species level, giving a total of 596 *Klebsiella* spp. isolates (Tables 33-35). The species distribution was not significantly changed from 2010. As for *E. coli*, the Norwegian Working Group for Antibiotics (NWGA) has defined the *Klebsiella* spp. wild type as intermediately susceptible to cefuroxime. The breakpoints for antimicrobial agents included in the *Klebsiella* surveillance protocol were not changed in 2010. The SIR distribution for cefpirome and tigecycline are not given as EUCAST has not defined breakpoints for these agents. The *E. coli* breakpoints for tigecycline intersected the wild type population and were clearly not suitable for *Klebsiella* spp. (data not shown).

The majority of *Klebsiella* spp. isolates remained fully susceptible to aminoglycosides, but the prevalence of non-susceptibility to gentamicin continued to increase from 1.0% in 2008, 1.4% in 2009 and 2.2% in 2010, to 4.6% in 2011. Aminoglycoside resistance was detected in 0.8% of *K. oxytoca* isolates compared to 1.8% in 2010. When analysing *K. pneumoniae* separately, the prevalence of non-susceptibility to gentamicin reached 5.7%, which is at the same level as in *E. coli* blood culture isolates (4.7%). It thus appears that around 5% of invasive isolates of the two major pathogens in the *Enterobacteriaceae* family now harbour clinically significant aminoglycoside resistance. This is cause for great concern as aminoglycosides have traditionally been used in the empirical regimen for septiceamia in Norway.

The overall prevalence of resistance to ciprofloxacin has generally been stable at 3-4% when taking into account the changes in breakpoints and interpretive rules, but the increase from 5.2% to 5.7% non-susceptibility to ciprofloxacin in *Klebsiella* spp. (6.1% to 7.0% in *K. pneumoniae*) from 2010 to 2011 confirms the gradually increasing trend over the last years. Non-susceptibility to trimethoprim-sulfamethoxazole stabilised at 17.1% in 2011 compared to 17.9% in 2010. There was still a significant difference in the prevalence of non-susceptibility to ciprofloxacin and trimethoprim-sulfamethoxazole between *K. pneumoniae* and *K. oxytoca*. All *K. oxytoca* were fully susceptible to ciprofloxacin and only 4.7% were non-susceptible to trimethoprim-sulfamethoxazole, compared to 7.0% and 20.9% for *K. pneumoniae,* respectively. A comparison of ESBL rates and non-susceptibility to beta-lactam antibiotics is complicated by the diagnostic challenges of the chromosomal K1 beta-lactamase in *K. oxytoca*.

Most *Klebsiella* spp. isolates were susceptible to cefotaxime (95.3%), ceftazidime (94.3%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (89.4%, Figure 49). However, the rates of non-susceptibility to third generation cephalosporins increased by approximately two percentage points in 2011 and reached the highest levels ever recorded in NORM (Figures 48-49).

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 Etests. The increasing prevalence of phenotypically confirmed ESBL isolates seen from 2006 to 2009 resumed with an increase from 1.5% in 2010 to 4.2% in 2011. The 25 ESBL isolates originated from ten different laboratories and were all identified as *K. pneumoniae*, thus constituting 5.5% in this species. The ESBL isolates were generally non-susceptible to cefuroxime (25/25), ceftazidime (25/25) and cefotaxime (24/25), and co-resistance was common to ciprofloxacin (17/25), trimethoprim-sulfamethoxazole (21/25) and gentamicin (16/25). Many isolates were intermediately (9/25) or even fully (9/25) susceptible to piperacillin-tazobactam. Molecular characterisation of the isolates at the Reference Centre for Detection of Antimicrobial Resistance (K-Res) confirmed the presence of CTX-M groups 1 (n=18) and 9 (n=1). The remaining isolates contained broad-spectrum SHV variants alone (n=4) or in combination with DHA (n=1). A single isolate harboured a CMY sequence only. All isolates were fully susceptible to meropenem, and no carbapenemase resistance determinants were detected.

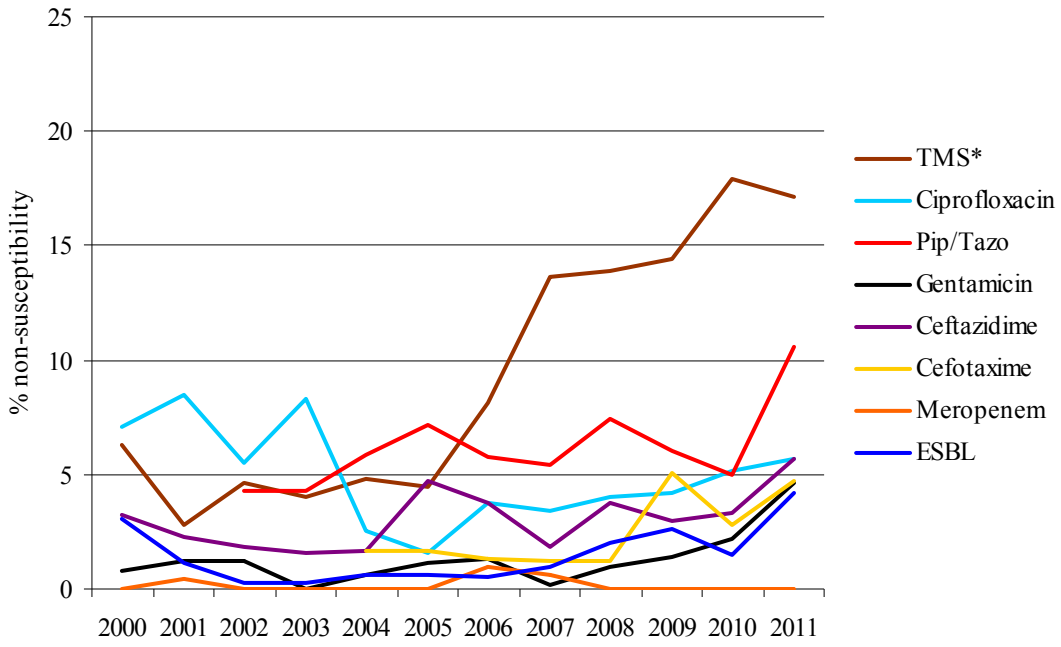


FIGURE 49. Prevalence of non-susceptibility to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2011. *TMS=Trimethoprim-sulfamethoxazole.

Haemophilus influenzae in respiratory tract specimens

TABLE 36. *Haemophilus influenzae* in respiratory tract specimens (n=677). 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	81.7	-	18.3
Amoxicillin-clavulanic acid	≤ 2	> 2	93.8	-	6.2
Cefuroxime	≤ 1	> 2	75.3	7.7	17.0
Cefotaxime	≤ 0.12	> 0.12	100.0	-	0.0
Ciprofloxacin	≤ 0.5	> 0.5	99.9	-	0.1
Chloramphenicol	≤ 2	> 2	99.3	-	0.7
Tetracycline	≤ 1	> 2	96.2	3.4	0.4
Trimethoprim-sulfamethoxazole	≤ 0.5	> 1	75.6	2.4	22.0
Nalidixic acid (mm)	≥ 23	< 23	99.7	-	0.3
Beta-lactamase	Negative	Positive	87.7	-	12.3

TABLE 37. *Haemophilus influenzae* in respiratory tract specimens (n=677). Distribution (%) of MICs (mg/L) and zone diameters for nalidixic acid (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					0.1	3.2	23.5	43.3	11.5	6.9	1.6	1.8	2.1	1.8	0.7	3.3
Amoxi-clav**					0.3	0.7	5.2	50.2	28.1	9.3	3.2	1.8	1.0	0.1		
Cefuroxime				0.1		0.7	1.0	16.2	57.2	7.7	5.2	8.9	2.8	0.1		
Cefotaxime	1.0	4.1	46.1	32.3	12.0	4.4										
Ciprofloxacin	0.3	9.5	68.8	20.4	0.7		0.1							0.1		
Chloramph.								8.7	74.2	16.4	0.3		0.4			
Tetracycline					0.1	0.3	2.7	47.1	45.9	3.4	0.3	0.1				
TMS***			1.3	12.1	30.9	22.2	5.0	4.1	2.4	2.7	3.1	2.7	0.9	12.7		
	< 11	11	12	13	14	15	16	17	18	19	20	21	22	23	24	≥ 25
Nalidixic acid	0.1		0.1											0.1	0.1	99.6

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

RESULTS AND COMMENTS

Haemophilus influenzae respiratory tract isolates were included in the NORM surveillance protocol in 2001, 2004 and 2007. MIC results from previous years have been recategorised according to the 2012 EUCAST breakpoint protocol.

Beta-lactam resistance in *H. influenzae* may be mediated by beta-lactamases or chromosomal alterations in genes encoding penicillin-binding proteins (PBPs). In 2011, 12.3% of isolates were beta-lactamase positive compared to 7.0% in 2001, 8.8% in 2004 and 10.5% in 2007 (Figure 50). The prevalence of chromosomal beta-lactam resistance is difficult to assess as different substrates will display divergent results depending on the underlying genetic changes. Ampicillin resistance exceeded the prevalence of beta-lactamases by 6.0 percentage points in 2011 compared to 2.9 in 2007, whereas the combination of amoxicillin and the beta-lactamase inhibitor clavulanic acid indicated a prevalence of PBP-mediated resistance of 6.2% compared to 8.0% in 2007. The prevalence of cefuroxime resistant isolates (MIC > 2 mg/L) has been suggested as the most sensitive indicator for alterations in the wild type sequence of PBP3, and this rate has increased slightly from 16.3% in 2007 to 17.0% in 2011. The proportion of concomitant beta-lactamase production and PBP-mediated resistance increased from 0.7% in 2007 to 1.0% in 2011 when measured by amoxicillin-clavulanic acid. The combination of beta-lactamase production and cefuroxime resistance increased from 1.5% in 2007 to 2.4% in 2011. There were no isolates with reduced susceptibility to cefotaxime. Only a few isolates with high level resistance to cephalosporins have so far been isolated from clinical samples in Norway.

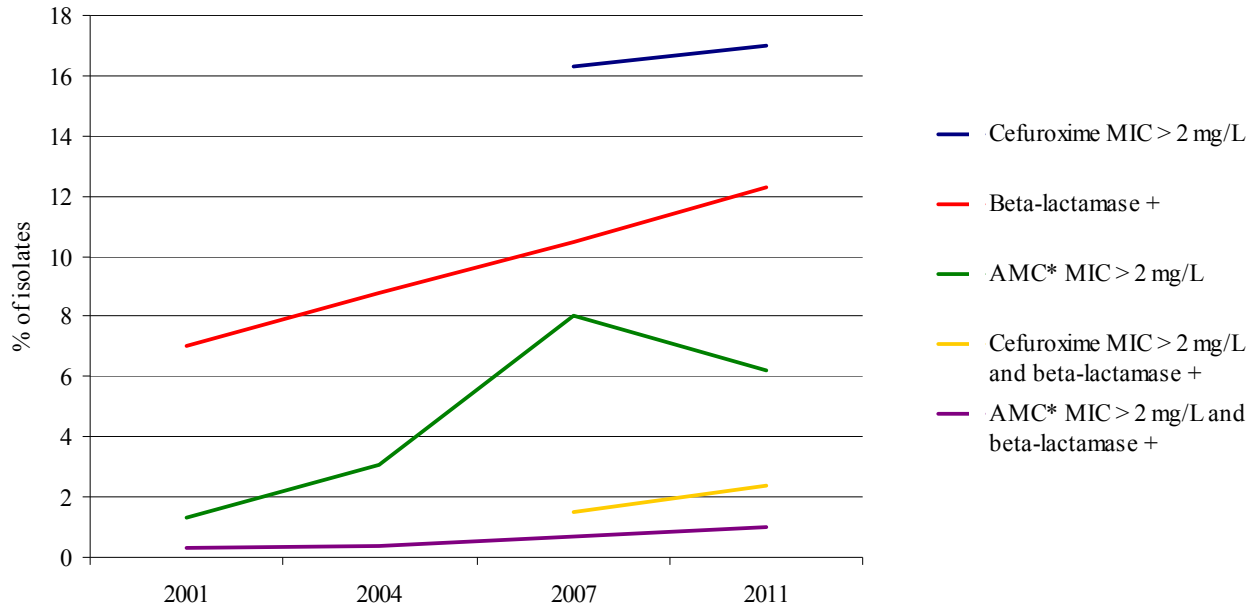


FIGURE 50. Prevalence of beta-lactamase production, chromosomally encoded beta-lactam resistance, and combination of both mechanisms in *Haemophilus influenzae* respiratory tract isolates 2001-2011. The time intervals on the x-axis are not identical. *AMC=Amoxicillin-clavulanic acid.

Different substrates have been suggested for screening of beta-lactam resistance in *H. influenzae*. The 1 IU penicillin G disk (PcG 1) is recommended for initial screening, with subsequent beta-lactamase testing and cefaclor 30 µg disk diffusion for beta-lactamase positive isolates. All beta-lactamase producing isolates (n=83) except two had PcG 1 zone diameters below 12 mm, thus indicating high sensitivity for this mechanism (data not shown). Figure 51 depicts the correlation between PcG 1 zone diameters and cefuroxime MIC among beta-lactamase negative isolates (n=594). PcG 1 identified 86 of the 99 cefuroxime resistant isolates (sensitivity 86.9%). However, 62 additional cefuroxime intermediately susceptible (n=18) or susceptible (n=44) isolates were positive in the screening test, giving a specificity of 87.5% when cefuroxime resistance according to current EUCAST breakpoints is used as the gold standard. The underlying data indicate that there may be quality differences between disk manufacturers with respect to the PcG 1 disk.

The zone breakpoints for cefaclor 30 µg disk are calibrated for beta-lactamase positive isolates. The correlation between cefuroxime MIC and cefaclor 30 µg is shown for this subpopulation (n=83) in Figure 52. Only 2/16 cefuroxime resistant isolates were missed by cefaclor (sensitivity 87.5%), whereas 8/67 cefuroxime intermediately susceptible (n=3, MIC 2 mg/L) or susceptible isolates (n=5, MIC 1 mg/L) were "falsely" identified as positive by the cefaclor test (specificity 91.0%). The results illustrate the continuing challenges in beta-lactam susceptibility testing in *H. influenzae.*

The results for non-beta-lactam agents are shown in Tables 36-37. The breakpoints for tetracycline and trimethoprim-sulfamethoxazole have been adjusted since 2007. When applying 2012 EUCAST breakpoints, the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole has increased from 21.2% in 2007 (18.6% R and 2.6% I) to 24.4% in 2011 (22.0% R and 2.4% I). Conversely, the prevalence of non-susceptibility to tetracycline has decreased from 7.3% in 2007 (2.5% R and 4.8% I) to 3.8% (0.4% R and 3.4% I). Chloramphenicol and ciprofloxacin were not included in previous surveys, but the rates of resistance in 2011 were very low (0.7% and 0.1%, respectively). The nalidixic acid screening disk identified two suspicious isolates, one of which was the only ciprofloxacin resistant isolate in the survey. Beta-lactamase producing isolates were more often resistant to trimethoprim-sulfamethoxazole (30.1% vs 20.9%), chloramphenicol (3.6% vs 0.3%) and tetracycline (3.6% vs 0.0%) compared to beta-lactamase negative isolates.

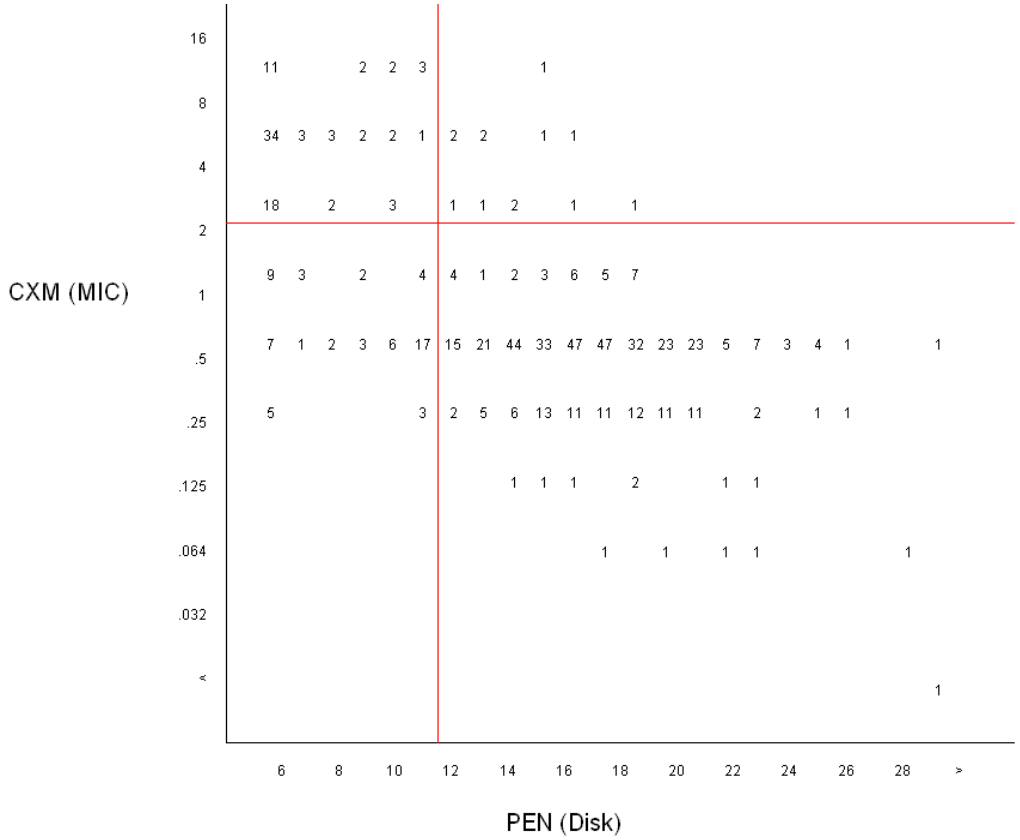


FIGURE 51. Correlation between zone diameters for the penicillin G 1 IU disk and cefuroxime MIC among beta-lactamase negative *Haemophilus influenzae* respiratory tract isolates in 2011 (n=594). Horizontal and vertical red lines indicate the EUCAST clinical MIC I/R breakpoint for cefuroxime (R > 2 mg/L) and the NordicAST zone breakpoint for penicillin G 1 U intended for screening (R < 12 mm), respectively. The results are presented as number of isolates. Further details are given in the text.

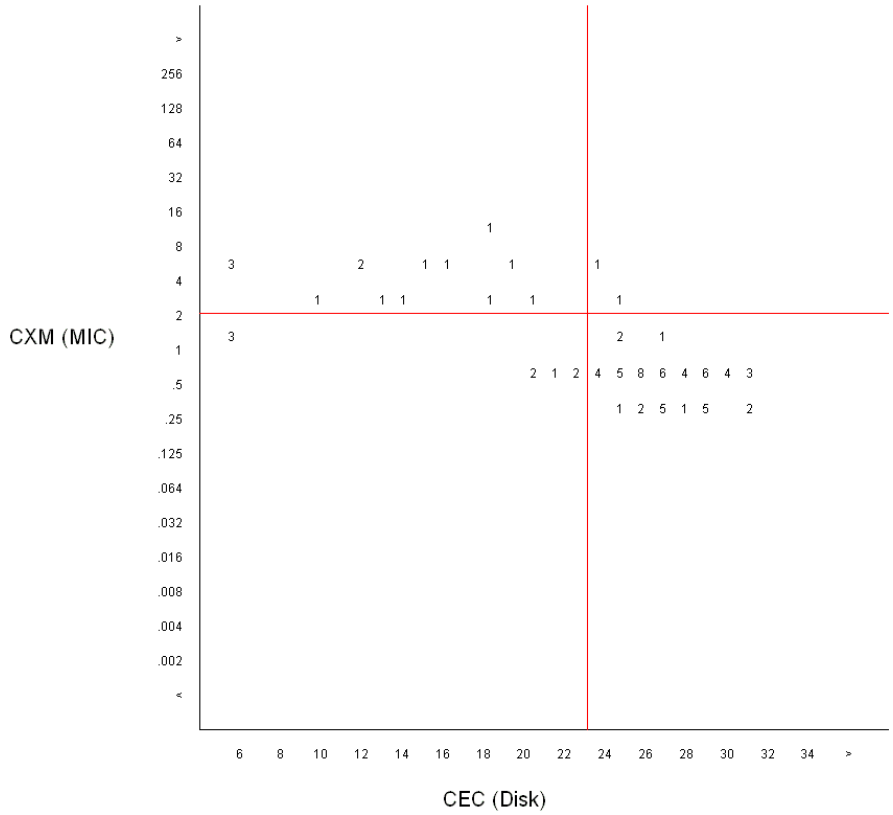


FIGURE 52. Correlation between zone diameters for cefaclor 30 µg disks and cefuroxime MIC among beta-lactamase positive *Haemophilus influenzae* respiratory tract isolates in 2011 (n=83). Horizontal and vertical red lines indicate the EUCAST clinical MIC I/R breakpoint for cefuroxime (R > 2 mg/L) and the NordicAST zone breakpoint for cefaclor 30 µg intended for screening (R < 23 mm), respectively. The results are presented as number of isolates. Further details are given in the text.

Staphylococcus aureus in blood cultures

TABLE 38. *Staphylococcus aureus* blood culture isolates (n=1,084). 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	95.7	0.0	4.3
Clindamycin	≤ 0.25	> 0.5	97.6	0.2	2.2
Fusidic acid	≤ 1	> 1	95.8	-	4.2
Ciprofloxacin	≤ 1	> 1	98.0	-	2.0
Gentamicin	≤ 1	> 1	99.2	-	0.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.5	0.3	0.2
Tetracycline	≤ 1	> 2	95.8	0.3	3.9
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.6	0.2	0.2
Beta-lactamase	Negative	Positive	26.9	-	73.1
Cefoxitin screen	Negative	Positive	99.5	-	0.5
MRSA (*mecA*)	Negative	Positive	99.5	-	0.5

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

RESULTS AND COMMENTS

Five methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2011 (Table 38) corresponding to a prevalence of 0.5%. This is at the same level as 0.7% in 2008, 0.4% in 2009 and 1.0% in 2010. The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from four different hospitals.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. All MRSA isolates had cefoxitin zone diameters below the screening breakpoint. One MRSA isolate displayed co-resistance to ciprofloxacin as well as inducible MLS_B resistance, whereas three other isolates were tetracycline resistant. All MRSA isolates were fully susceptible to gentamicin, linezolid, rifampicin, vancomycin and trimethoprim-sulfamethoxazole. No methicillin susceptible *S. aureus* (MSSA) isolates displayed reduced cefoxitin zone diameters.

The findings are in accordance with reports from the databases of the participating laboratories where seven out of 1,457 (0.5%) *S. aureus* blood culture isolates were MRSA. One of the eleven *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 8/1,468 (0.5%). The Norwegian Surveillance System for Communicable Diseases (MSIS) reported a total number of 1,059 MRSA cases in 2010. This is a 16% increase from 912 cases in 2010. However, the cases reported to MSIS were predominantly skin and soft tissue infections (79% of infections) and colonisations (n=496). The number of MRSA infections increased to 563 in 2011 compared to 431 in 2010 (+31%) and 414 in 2009, and the number of MRSA colonisations from 402 in 2009 and 481 in 2010 to 496 in 2011 (+3%). Further information about MRSA cases in MSIS is presented on page 74.

A total of 47 *S. aureus* isolates (4.3%) were non-susceptible to erythromycin. This is a slight decrease from 2010 (5.4%). The macrolide resistance phenotypes were determined by the double disk diffusion (DDD) test. Ten (21%) were constitutively MLS_B resistant, 31 (66%) were inducibly MLS_B resistant and six (13%) displayed efflux mediated M type resistance. These figures represent 0.9%, 2.9% and 0.6% of all *S. aureus* isolates from blood cultures, respectively. The distribution of macrolide resistance phenotypes was similar to the results from previous years.

The prevalence of resistance to fusidic acid was at the same level (4.2%) as in 2009 (4.5%) and 2010 (3.4%). This may indicate that the epidemic of fusidic acid resistant *S. aureus* in Norway has now passed. The prevalence of ciprofloxacin resistance decreased from 3.9% in 2010 to 2.0% in 2011. There were no significant changes for gentamicin, rifampicin or trimethoprim-sulfamethoxazole, and all isolates were fully susceptible to linezolid. Vancomycin was not included in the susceptibility test panel for all isolates in 2011.

Figure 53 shows the prevalences of non-susceptibility to various antimicrobials. A total of 73.1% of the isolates were beta-lactamase positive which is unchanged from previous years. A subgroup analysis revealed that beta-lactamase positive isolates were more often resistant than beta-lactamase negative isolates to ciprofloxacin (2.3% vs 1.4%), erythromycin (4.8% vs 3.1%), clindamycin (2.5% vs 1.4%), and tetracycline (4.2% vs 3.1%).

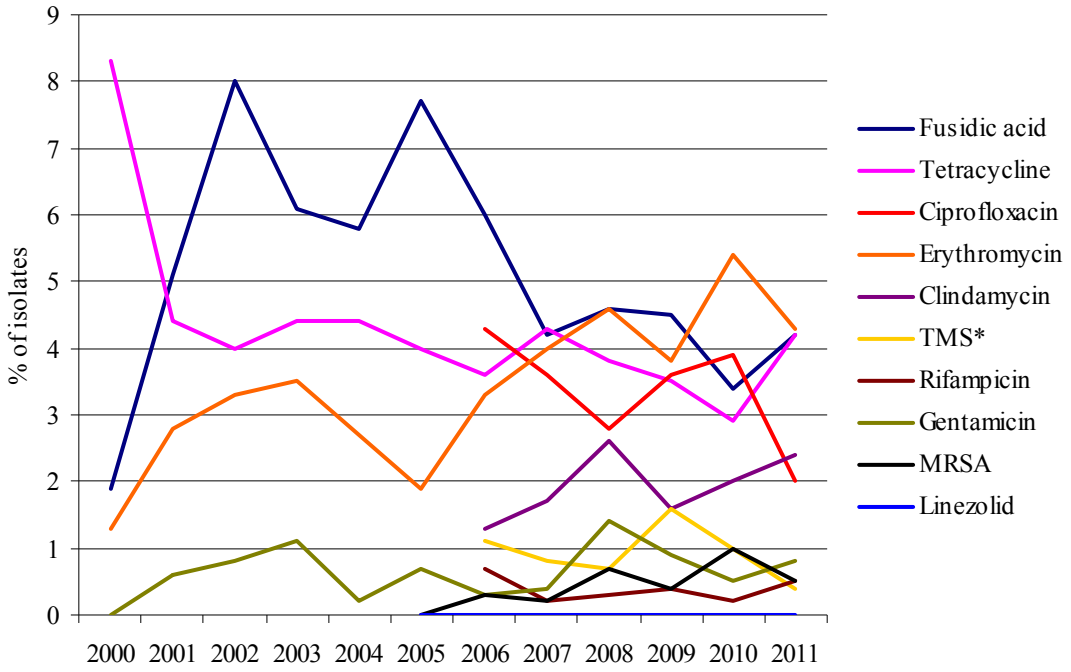


FIGURE 53. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* blood culture isolates 2000-2011. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 39. *Staphylococcus aureus* isolates from wound specimens (n=915). 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	93.5	0.1	6.4
Clindamycin	≤ 0.25	> 0.5	96.3	0.4	3.3
Fusidic acid	≤ 1	> 1	90.1	-	9.9
Ciprofloxacin	≤ 1	> 1	98.3	-	1.7
Gentamicin	≤ 1	> 1	99.2	-	0.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.7	0.1	0.2
Tetracycline	≤ 1	> 2	95.1	0.3	4.6
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.1	0.7	0.2
Beta-lactamase	Negative	Positive	25.2	-	74.8
Cefoxitin screen	Negative	Positive	98.7	-	1.3
MRSA (*mecA*)	Negative	Positive	98.7	-	1.3

*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. Twelve out of 915 (1.3%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence was higher than in 2010 (0.6%) and also higher than in blood cultures (0.5%, see above). Further surveillance is needed to evaluate whether this trend reflects the emergence of community-acquired skin and soft tissue MRSA infections as opposed to systemic bloodstream infections. The MRSA isolates originated from patients admitted to hospital (n=4), outpatient clinics (n=3), nursing homes (n=1) and general practitioners (n=4) in different parts of the country. Six MRSA isolates were co-resistant to erythromycin and five were concomitantly resistant to clidamycin. Four of the same isolates were also resistant to tetracycline. All MRSA isolates were susceptible to fusidic acid, trimethoprim-sulfamethoxazole, rifampicin, linezolid and vancomycin. None of 903 MSSA isolates were falsely positive in the cefoxitin test.

The high prevalence of resistance to fusidic acid in *S. aureus* wound isolates displayed a slight increase from 7.7% in 2010 to 9.9% in 2011 (Table 39 and Figure 54). This may indicate 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 (4.2%).

For other antimicrobial agents such as trimethoprim-sulfamethoxazole, gentamicin, rifampicin, and tetracycline there were only minor changes from 2010 to 2011, and the prevalences of non-susceptibility were in general similar for blood culture isolates and isolates from wound specimens. A total of 60 (6.5%) isolates were non-susceptible to erythromycin which is an increase from 4.9% in 2010. Fifty-eight of these isolates were further examined for determination of resistance phenotype. The majority (30/58, 52% of macrolide resistant isolates) were inducibly resistant to clindamycin, thus representing the $iMLS_B$ phenotype. Minor proportions were either constitutively resistant to clindamycin (n=15) or low-level resistant to erythromycin (n=13), expressing efflux mediated M type resistance. The findings are in accordance with the results from blood culture isolates.

A total of 74.8% of the isolates were beta-lactamase positive, which is at the same level as in previous years. Resistance to fusidic acid was more common among the 684 beta-lactamase positive isolates (10.5%) than among the 231 beta-lactamase negative ones (8.2%). A similar trend was seen for tetracycline (5.3% vs 2.6%) and ciprofloxacin (2.3% vs 0.0%). There were no significant differences for other antimicrobial agents.

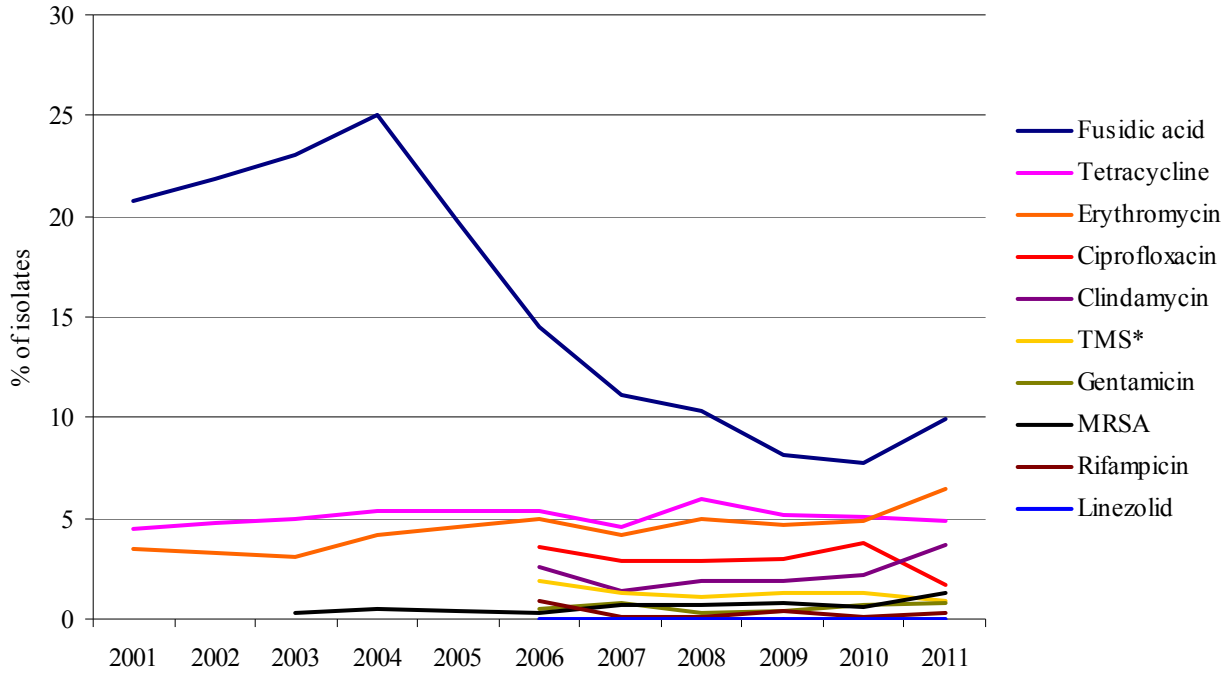


FIGURE 54. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* wound isolates 2000-2011. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

MRSA infections in humans in Norway 2011

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been notifiable in Norway since 1995 and colonisation was made notifiable in 2005. A total of 1,059 cases of MRSA were reported in 2011 (21 per 100,000 person-years). 563 (53 %) of the cases had an infection and 496 were colonised. There was a significant increase in the incidence rate for MRSA infections and for all MRSA cases from 2010 to 2011 (Fig 55). The overall incidence rate per county is shown in Figure 56.

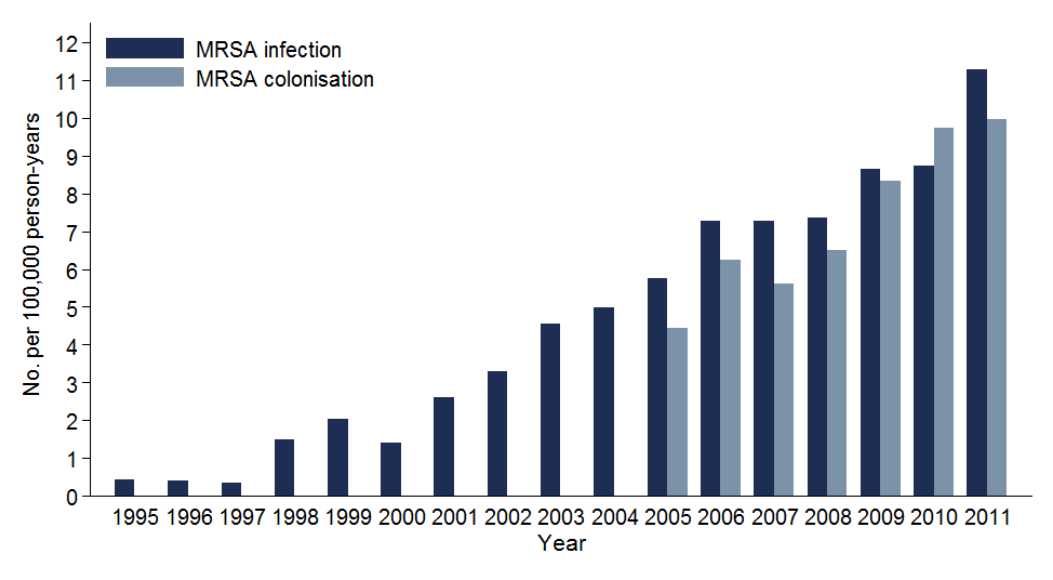


FIGURE 55. Number of MRSA cases per 100,000 person-years in Norway 1995-2011, by infection and colonisation.

Men and women were equally affected. At the time of diagnosis 217 (20 %) were inpatients, 76 (7 %) were residents in nursing homes and 727 (69 %) were diagnosed in the community. Health care workers accounted for 36 of the reported cases. The increase of MRSA cases occurred in cases infected abroad and in the community, while there have been no increase in cases associated to the Norwegian health care (Fig 57). The main objective of the Norwegian MRSA guidelines is to prevent MRSA from becoming endemic in health care institutions. In the last six years the number of hospitalised patients notified with MRSA has been at a stable low level and the number of MRSA-positive nursing home residents has decreased. Ten cases (2%) were reported with systemic infections or infections in inner organs. Of the remaining 553 MRSA-infections, 445 (79%) were reported as either skin- or wound infections. Seven of the 36 cases reported in health care workers were classified as clinical infections. In summary, although the incidence of MRSA in the community is rising, the aim of preventing MRSA from becoming endemic in the health care setting is still holding.

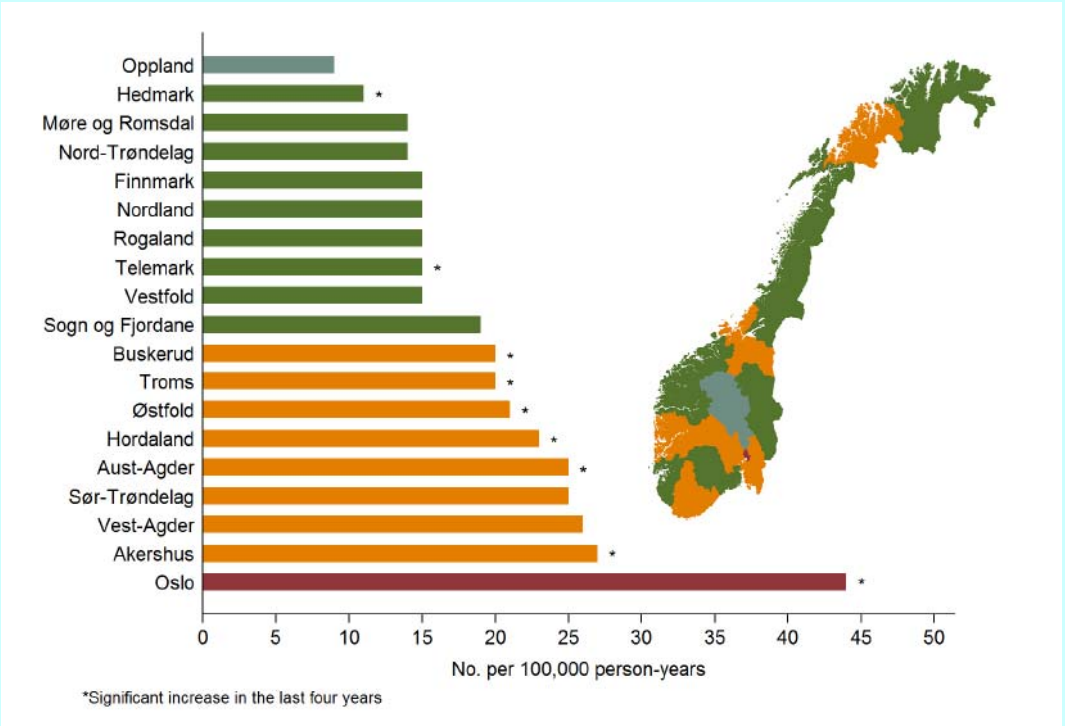


FIGURE 56. Number of MRSA cases per 100,000 person-years by county in Norway, 2011.

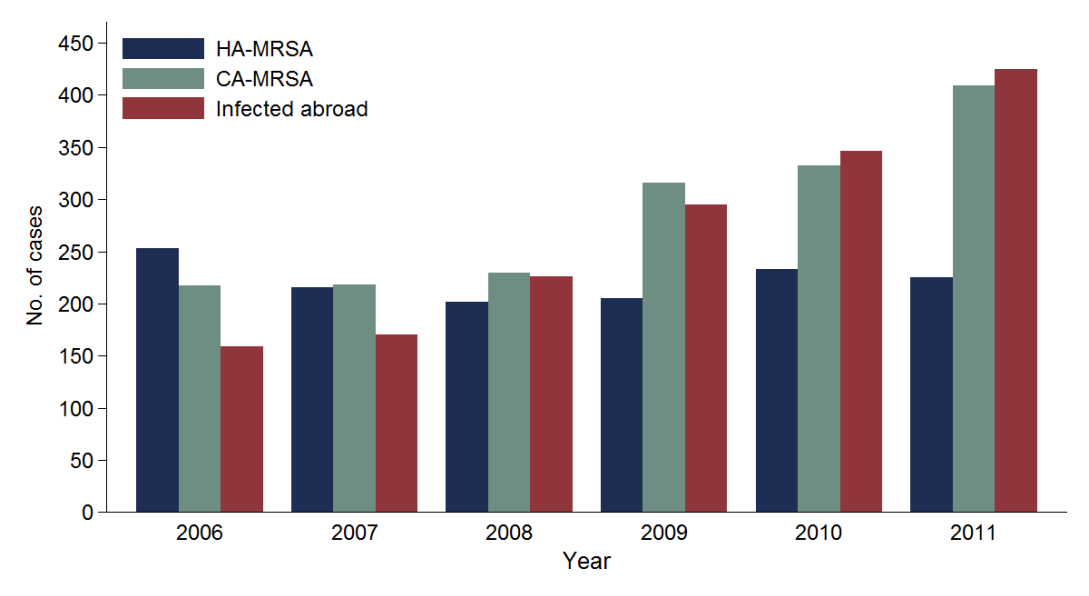


FIGURE 57. Reported cases of MRSA infection and colonisation in Norway 2006-2011, by domestic (health care associated and community associated) and imported cases.

The Reference Laboratory for MRSA, St. Olav University Hospital, Trondheim, received 1,000 MRSA isolates in 2011. Fifty-nine isolates were not sent to the reference laboratory but only reported to MSIS. A total of 195 different spa-types were identified and the six most frequent were (spa-type, n (%)): t019, n=122 (12.2 %), t002, n=111 (11.1 %), t008, n=90 (9.0 %), t044, n=60 (6.0 %), t223, n=36 (3.6 %) and t437, n=32 (3.2 %). A total of 102 spa-types were reported as single events.

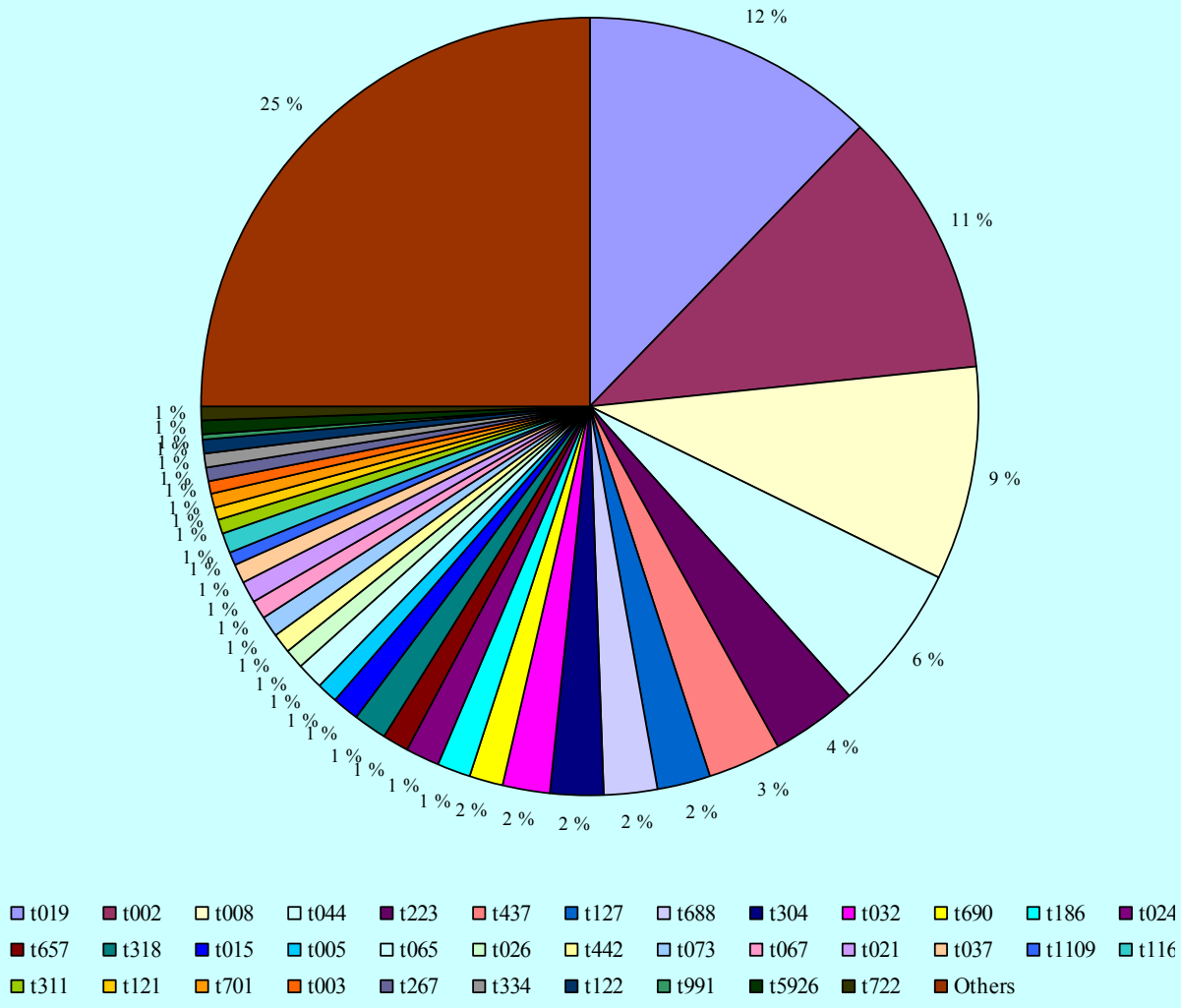


FIGURE 58. Distribution of spa-types in Norwegian MRSA isolates in 2011.

Based on spa-type, all isolates were characterised in MLST clonal complex. A total of 777 isolates (77.7 %) occurred in the six most prevalent clusters (CC, n (%)): CC5, n=196 (19.6 %), CC8, n=177 (17.7 %), CC30, n=169 (16.9 %), CC22, n=96 (9.6 %), CC80, n=71 (7.1 %), and CC45, n=68 (6.8%).

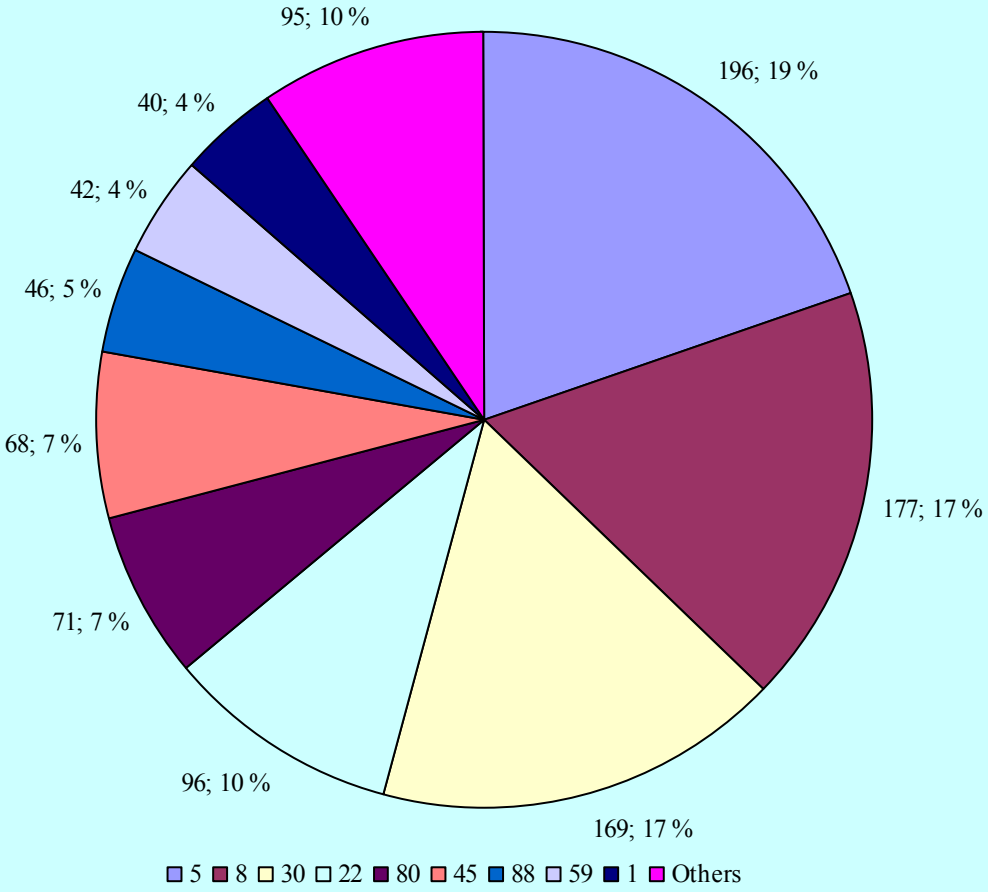


FIGURE 59. Distribution of MLST clonal complex based on spa-type in Norwegian MRSA isolates in 2011.

On the basis of the article "Methicillin-resistant *Staph. aureus* with a novel *mecA* homologue in human and bovine populations in the UK and Denmark: a descriptive study" published in The Lancet Infectious Diseases June 3rd 2011, a new strain of methicillin resistant *S. aureus* was identified. The new strain differs from previous strains by being *mecA* negative, but carries a homologous gene to *mecA* called $mecA_{lga251}$ (named *mec*C, personal communication from Robert Skov, July 2012). This gene encodes a protein that gives the same phenotypic resistance as the *mecA* gene, but shares only 70% nucleotide sequence similarity with *mecA*. The $mecA_{lga251}$ gene is located on a novel *SCCmec* element designated *SCCmec XI*. A PCR to detect $mecA_{lga251}$ was established at the MRSA Reference Laboratory. All laboratories were invited to send strains for detection of this gene. Positive findings of the gene are considered to be MRSA.

To investigate whether any previously received *mecA* negative methicillin resistant strains could possess this gene, all strains previously called BORSA (borderline methicillin resistant *S. aureus*) were tested. In the collection tested (n=15), seven (7) isolates were positive for $mecA_{lga251}$. These isolates were from 2006 (1), 2008 (1), 2009 (3) and 2011 (2) and were spa typed to t843, t1048 and t1535, all associated with multilocus sequence type lineage CC130. This is consistent with the published article.

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Trond Jacobsen, Kjersti Wik Larssen, Lillian Marstein, Anne Kilnes, Hege Snøsen, Frode Width Gran, Norwegian Reference Laboratory for MRSA, St. Olavs University Hospital, Trondheim.

Enterococcus spp. in blood cultures

TABLE 40. *Enterococcus* spp. blood culture isolates (n=596). 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	73.8	0.7	25.5
Gentamicin*	≤ 128	> 128	-	67.3	32.7
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	97.8	-	2.2

*The wild type is defined as intermediately susceptible.

TABLE 41. *Enterococcus faecalis* blood culture isolates (n=381). 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	-	74.0	26.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	100.0	-	0.0

*The wild type is defined as intermediately susceptible.

TABLE 42. *Enterococcus faecium* blood culture isolates (n=180). 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	16.7	2.2	81.1
Gentamicin*	≤ 128	> 128	-	50.0	50.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	97.2	-	2.8

*The wild type is defined as intermediately susceptible.

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a group 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 40. The surveillance in NORM 2011 included 381 (63.9%) *E. faecalis* isolates, 180 (30.2%) *E. faecium* isolates and 35 (5.9%) unspeciated enterococcal isolates. The proportion of *E. faecalis* isolates has thus been further reduced from 73.1% in 2009 and 67.9% in 2010, whereas the proportion of *E. faecium* has increased from 21.1% in 2009 and 26.7% in 2010. The number of isolates not speciated to the genus level or identified as *E. faecalis* or *E. faecium* has decreased over the last five years.

The panel of antimicrobial agents examined and the breakpoints for interpretation remained unchanged from 2010.

E. faecalis was universally susceptible to ampicillin (Table 41). The prevalence of resistance to ampicillin in *E. faecium* remained stable at 81.1% compared to 81.3% in 2010 (Table 42 and Figure 60). The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was 26.0% which is a slight decrease from 29.9% in 2010 (Figure 61), and the prevalence of HLGR in *E. faecium* has apparently stabilised around 45-50%. All (90/90) HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin. Conversely, 90 out of 150 (60%) ampicillin non-susceptible *E. faecium* also displayed HLGR. These findings are similar to the results from previous years.

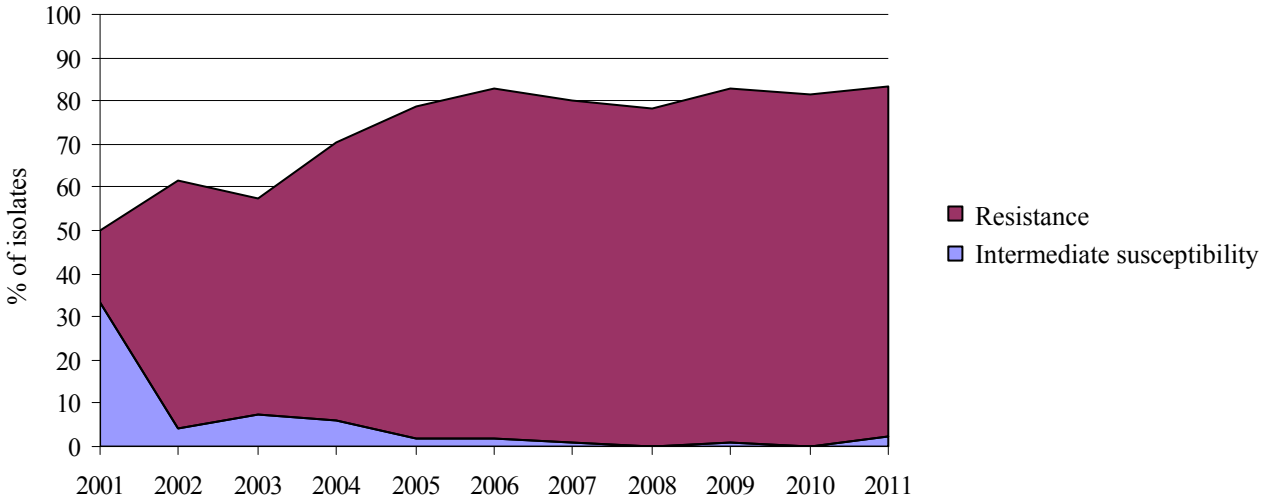

FIGURE 60. Prevalence of intermediate susceptibility and resistance to ampicillin in *E. facium* blood culture isolates 2001-2011. The results are interpreted according to the 2012 breakpoint protocol of S ≤ 4 mg/L and R > 8 mg/L.

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 harbors 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 amino-glycosides 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 a recent outbreak has occurred in the western part of the country. Thirteen isolates were reported as vancomycin resistant (2.2%), but only five *E. faecium* isolates contained transferable glycopeptide resistance confirmed by positive *vanB* PCRs. The five isolates originated from three different hospitals and are probably linked to the hospital outbreak presented on page 79. The remaining vancomycin resistant isolates were registered as either *E. gallinarum* (n=4), *E. casseliflavus* (n=1) or unspeciated *Enterococcus* sp. (n=3) which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All 13 isolates were fully susceptible to linezolid.

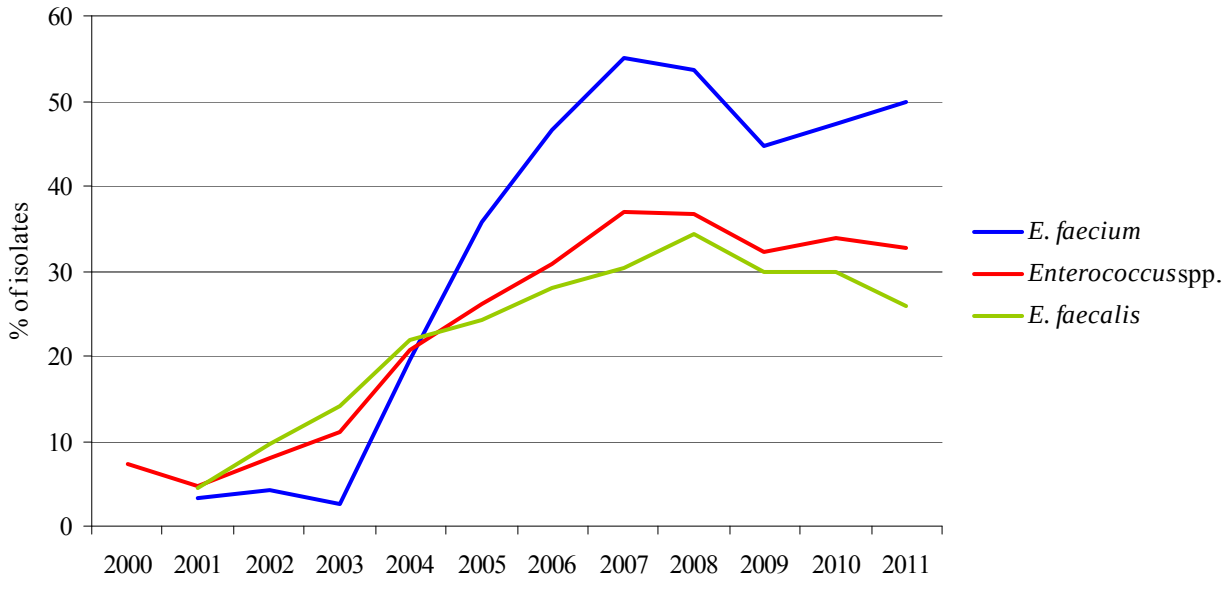

FIGURE 61. Prevalence of high-level resistance to gentamicin in blood culture isolates of *E. faecalis*, *E. faecium* and all enterococci combined during 2000-2011. The breakpoint for high-level resistance was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

First hospital outbreak of *vanB* vancomycin-resistant *Enterococcus faecium* in Norway

Vancomycin resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE) have been rare in Norway with only 0-10 cases reported annually between 2005 and 2009 (0-0.2/100,000 inhabitants). During the summer and fall of 2010, five clinical VRE isolates were detected at Haukeland University Hospital in Bergen, initiating a VRE screening programme in the hospital. A patient with laboratory confirmed VRE from any clinical site was considered a case, thereby including both clinical infection and colonisation in the case definition. The screening programme revealed an ongoing VRE outbreak in the respiratory ward, the gastrointestinal surgical ward, several medical wards as well as sporadic cases in other departments. From June 2010 to June 2012 a total of 326 cases of VRE were reported. More than 90% (307/326) of them were asymptomatic VRE carriers identified through contact tracing or screening.

Typing and antibiotic resistance

All 326 isolates were *E. faecium* with the *vanB* gene, verified by PCR and vancomycin resistance mechanism, involving biochemical identification with Vitek GP cards (bioMérieux) and vancomycin and teicoplanin minimum inhibitory concentrations (MICs) determined by MIC test strips (Liofilchem). Only 6% (n=19) were isolated from clinical samples; 4% (n=13) from urine samples, 1% (n=3) from blood cultures, 0.3 % (n=1) from pleural fluid, 0.3 % (n=1) from bronchial fluid and 0.3 % (n=1) from a tracheal swab. A total of 94 % were identified through screening of asymptomatic patients (stool samples), thus the vast majority of the cases were patients colonised but not infected with VRE. Most of the colonised patients would have gone undetected if active screening for VRE had not been conducted (Figure 62).

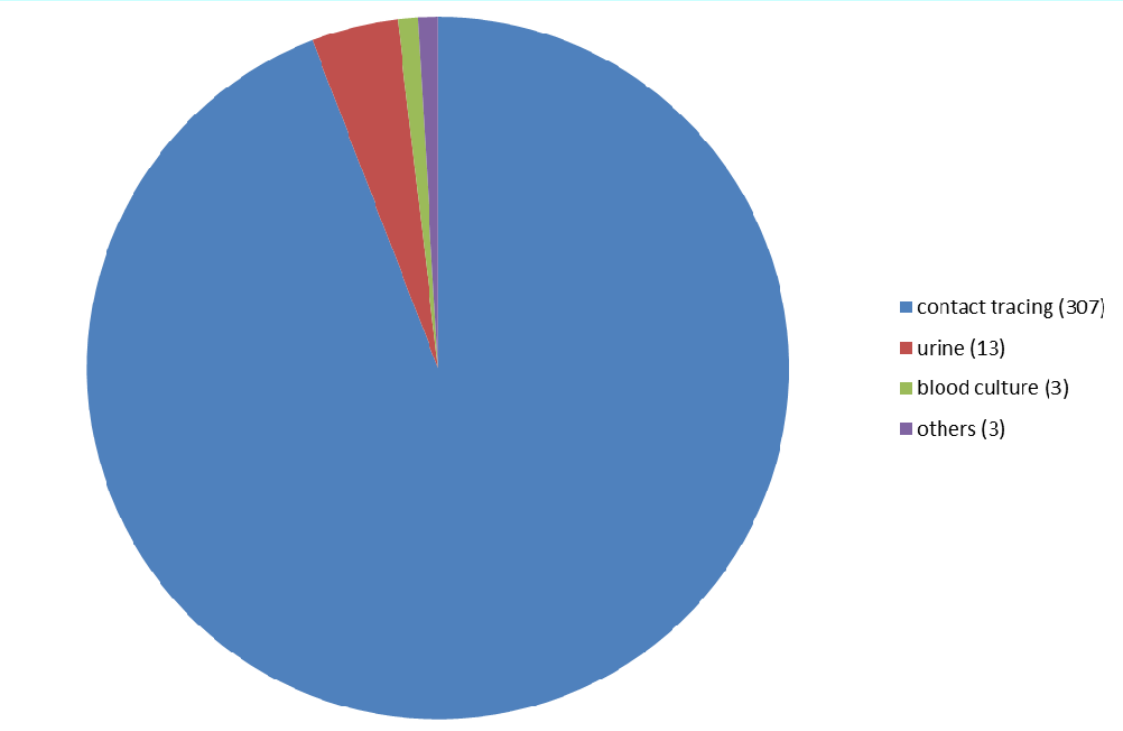

FIGURE 62. Number of VRE isolates found in clinical samples versus screening samples

The VRE isolates were typically resistant to vancomycin with MICs ranging from 8-64 mg/L, but susceptible to teicoplanin (MICs 0.125-1 mg/L). The clinical isolates were resistant to ampicillin, trimethoprim and nitrofurantoin. The blood culture isolates tested also demonstrated reduced susceptibility to gentamicin.
Epidemiological typing of the first *E. faecium* isolates (n=50) has been performed by pulsed-field gel electrophoresis (PFGE). The results so far show that the isolates have identical or closely related PFGE patterns suggesting dissemination of the same strain.

Interventions

Patient-to-patient transmission of VRE in health care settings occurs by contaminated hands of health care workers or indirectly by contaminated medical equipment or environmental surfaces. In order to avoid dissemination of VRE and thus preventing it from becoming endemic in our hospital, we focused our interventions on contact tracing and isolation of hospitalised VRE positive patients, prudent use of antibiotics, reinforcement of standard precautions for infection control including hand hygiene practice, and environmental disinfection.

Conclusions

VRE have not yet been eradicated from our hospital, but the outbreak is brought under control and the total number of detected cases is decreasing (Figure 63). Efforts to reduce the prevalence of colonisation and infection are continuing, taking into consideration the local epidemiology of the spread of VRE in order to yield the best outcomes. As a result of this outbreak, a national guideline on VRE management was developed and published in August 2011.

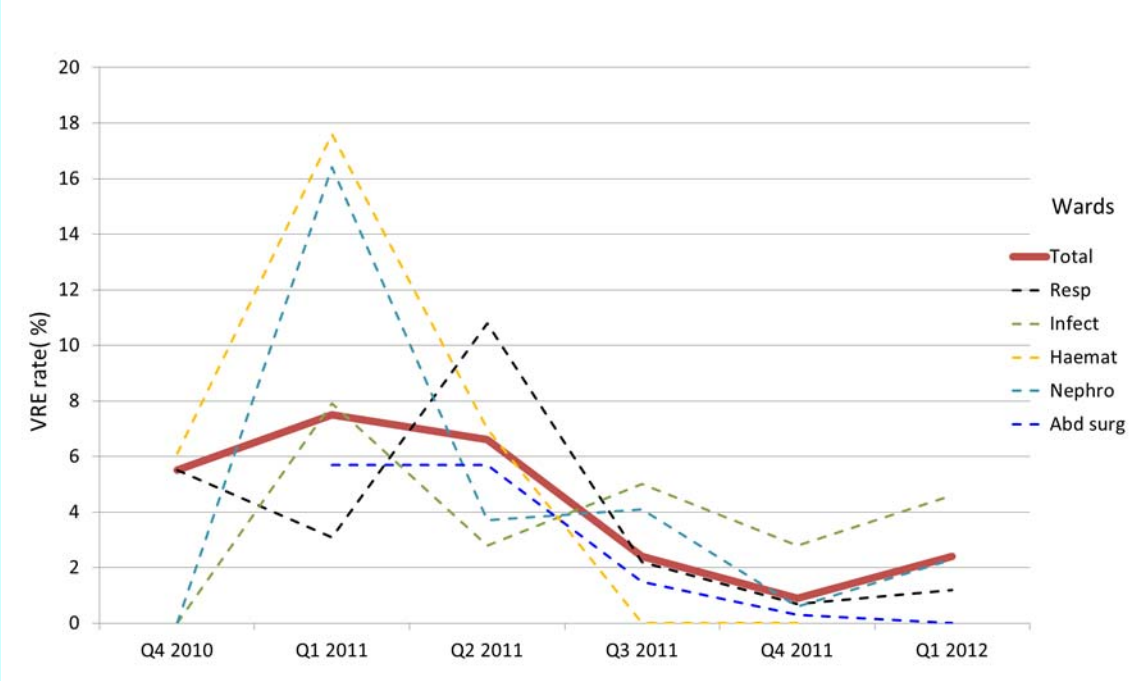

FIGURE 63. Quaterly VRE rate at Haukeland University Hospital, 2010 – 2012.

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Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 43. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=727). 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	95.7	4.3	0.0
Cefotaxime	≤ 0.5	> 2	99.3	0.7	0.0
Ceftriaxone	≤ 0.5	> 2	99.3	0.7	0.0
Erythromycin	≤ 0.25	> 0.5	96.0	0.0	4.0
Clindamycin	≤ 0.5	> 0.5	97.2	-	2.8
Tetracycline	≤ 1	> 2	95.8	0.1	4.1
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	94.3	1.8	3.9
Chloramphenicol	≤ 8	> 8	99.0	-	1.0
Oxacillin screen (mm)	≥ 20	< 20	93.0	-	7.0

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

TABLE 44. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=727). 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		3.2	81.7	7.7	3.2	1.8	1.2	0.3	0.7	0.3						
Cefotaxime		1.1	73.5	17.6	2.2	3.6	0.6	0.8	0.6	0.1						
Ceftriaxone		2.5	77.9	12.2	2.2	3.3	1.0	0.3	0.7							
Erythromycin					17.1	78.1	0.8			0.3	0.1	0.7	0.1	0.1		2.6
Clindamycin					9.1	77.3	10.9									2.8
Tetracycline					2.2	90.4	2.8		0.4	0.1	0.1	1.1	2.6	0.3		
TMS**					0.4	26.8	57.6	5.0	4.5	1.8	2.2	1.0	0.3	0.4		
Chloramph.							0.1		0.1	63.8	34.8	0.1	1.0			
Norfloxacin										5.2	57.2	36.9	0.3		0.1	0.2

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	7.0	0.7	0.4	0.3	1.1	2.8	12.5	12.9	14.7	19.9	11.1	12.1	3.4	0.7	0,3	

*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. 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 summarized in Tables 43-44 and Figures 64-65. All systemic *S. pneumoniae* isolates submitted to the Reference Laboratory for Respiratory Pathogens at the Norwegian Institute of Public Health during 2011 were included in the surveillance protocol. Twenty-seven isolates were recovered from cerebrospinal fluids, and two 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 materials.

Norwegian breakpoints for pneumococci are in accordance with EUCAST and have remained unchanged in 2011. The results for penicillin G, cefotaxime and ceftriaxone were interpreted according to the general breakpoints for pneumococci (R > 2, R > 0.5 and R > 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 4.3% (31/727) *S. pneumoniae* isolates were intermediately susceptible to penicillin G. No fully resistant isolates were detected. None of the non-susceptible isolates were recovered from cerebrospinal fluids. The prevalence of non-susceptibility to penicillin G was higher than in 2009 (2.9%) and 2010 (3.0%). Five penicillin G non-susceptible isolates displayed intermediate susceptibility to cefotaxime and ceftriaxone (MIC 1-2 mg/L). No penicillin G susceptible isolates displayed reduced susceptibility to cephalosporins. The oxacillin screening disk is often used to discriminate between penicillin susceptible and non-susceptible isolates. All penicillin G non-susceptible isolates were resistant to oxacillin. Conversely, 20/696 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test were thus 100.0% and 97.1%, respectively. Many of the penicillin non-susceptible *S. pneumoniae* isolates were also non-susceptible to erythromycin (13/31), trimethoprim-sulfamethoxazole (17/31) and tetracycline (12/31).

The prevalence of macrolide resistance has apparently stabilised after a gradual decline since the peak at 12.4% in 2006 (Figure 65). A total of 4.0% of the isolates were erythromycin resistant in 2011 which is unchanged from 2010. This is consistent with a decline in absolute numbers and proportions of systemic *S. pneumoniae* infections caused by resistant strains belonging to vaccine serotypes following introduction of the 7-valent conjugated pneumococcal vaccine (PCV-7). The macrolide resistance phenotype was further characterised in 23/29 erythromycin non-susceptible isolates. Six (26% of erythromycin non-susceptible isolates, 1.0% of all isolates) displayed a phenotype compatible with efflux-based M-type resistance to erythromycin only. The remaining isolates were either constitutively (n=12, 52% of erythromycin non-susceptible isolates, 2.1% of all isolates) or inducibly (n=5, 22% of erythromycin non-susceptible isolates, 0.9% of all isolates) resistant to clindamycin, thus indicating the presence of *erm*-encoded MLS resistance to both macrolides and lincosamides. The distribution of MLS phenotypes was not significantly altered from 2010.

The 5.7% prevalence of non-susceptibility to trimethoprim-sulfamethoxazole is a slight increase from 3.8% in 2009 and 4.3% in 2010. Similarly, the prevalence of non-susceptibility to tetracycline has increased from 2.8% in 2010 to 4.2% in 2011 (Figure 64). The vast majority of isolates remained susceptible to chloramphenicol which was earlier often used for empirical treatment of meningitis in Norway. The low prevalence of high-level norfloxacin resistance (Table 44) reflects that levofloxacin, moxifloxacin and other "respiratory fluoroquinolones" are not marketed in Norway.

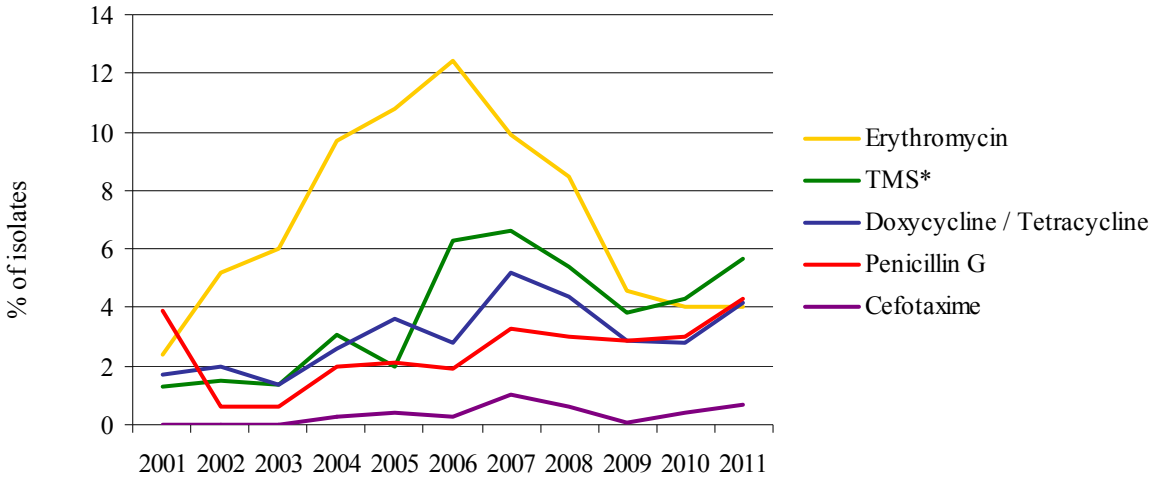

FIGURE 64. Prevalences (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2010. Doxycycline was substituted by tetracycline in 2005. All results are categorised according to the 2012 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

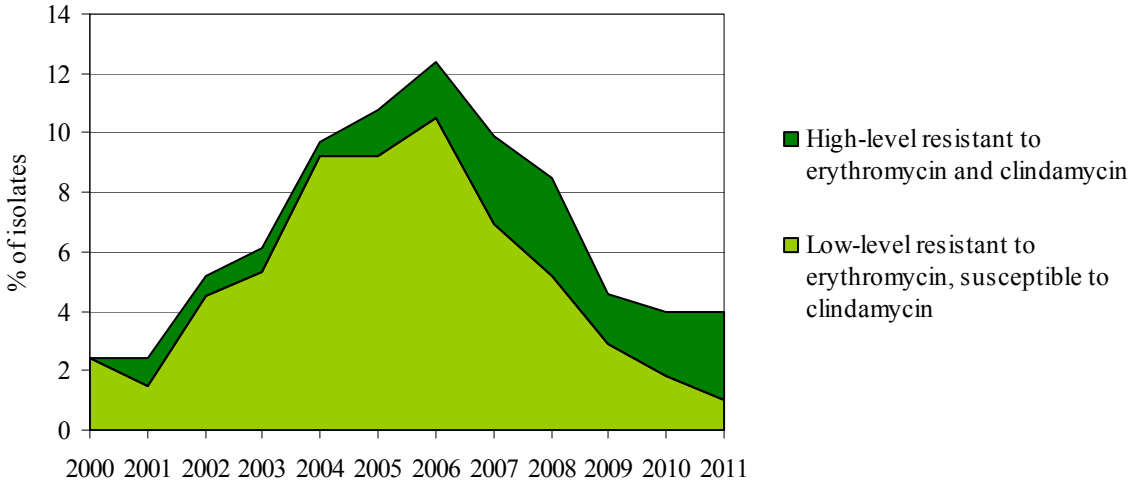

FIGURE 65. Prevalences (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2011. Doxycycline was substituted by tetracycline in 2005. All results are categorised according to the 2012 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

Mycobacterium tuberculosis

A total of 362 cases of infection with *M. tuberculosis* complex (not BCG) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2011. Twenty-nine of the cases had been treated with anti-TB drugs previously. In 17 cases it was not known whether the cases had been previously treated. Three of the four MDR-TB cases were treated for the first time, for the fourth case this was unknown.

Two hundred sixty-one cases were confirmed by culture followed by susceptibility testing of the strain isolated. The results are presented in Table 45. Please note that the numbers for 2010 have been adjusted compared to the previous report. The numbers refer to the year the test was taken.

TABLE 45. Antimicrobial susceptibility of 261 isolates of *M. tuberculosis* complex (not *M. bovis (BCG)*) isolated from human infections in 2011 (2010).

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents (No. of isolates)					
			Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDR TB*
Norway	44 (47)	22 (32)	0 (3)	0 (0)	1(0)	3 (3)	1 (3)	0 (0)
Europe excl. Norway	30 (24)	22 (17)	2 (7)	1 (4)	1 (1)	1(6)	4 (5)	1 (4)
Asia	112 (135)	113 (86)	11 (9)	0 (3)	0 (0)	15 (8)	2 (8)	0 (2)
Africa	170 (129)	129 (113)	19 (17)	3 (2)	1 (1)	19 (19)	9 (8)	3 (2)
America	2 (1)	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)
No information	4 (0)	1 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	362 (336)	261 (276)	32 (36)	4 (1)	3 (2)	39 (36)	16 (24)	4 (8)
Proportion of resistant isolates (%)			12.2 (13.0)	1.5 (0.3)	1.1 (0.7)	14.9 (13.0)	6.1 (8.7)	1.5 (2.9)

*MDR-TB: Multidrug-resistant tuberculosis, resistant to at least rifampicin and isoniazid.

Candida spp. in blood cultures

TABLE 46. 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*/***	≤ 0.03	> 0.03	98.6	-	1.4

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

TABLE 47. *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						2.2	61.4	34.3	2.2								
Fluconazole					0.7	24.1	60.7	13.6	0.7								
Voriconazole	3.4	64.2	28.6	2.7	0.9												
Anidulafungin	77.1	16.4	3.6	1.4	0.7	0.7											
Caspofungin**			0.9	7.2	36.6	45.5	9.8										
Micafungin**	13.6	45.7	33.6	3.6	0.7		0.7			0.7							

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

TABLE 48. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=25). 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	12.0	20.0	68.0
Voriconazole**	≤ 0.125	> 0.125	16.0	-	84.0
Anidulafungin*/***	≤ 0.06	> 0.06	92.0	-	8.0

* Recommended breakpoints by the European Commitee on Antimicrobial Susceptibility Testing – EUCAST.
** There are no EUCAST breakpoints for fluconazol and voriconazol as there is insufficient evidence for their use in treating *C. glabrata* infections. The breakpoints given are those made for *C. albicans*, *C. tropicalis* and *C. parapsilosis* (EUCAST).
*** There are no European breakpoints for caspofungin and micafungin. Strains susceptible to anidulafungin are considered susceptible.

TABLE 49. *Candida glabrata* blood culture isolates (n=25). 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			4.0			8.0	28.0	60.0									
Fluconazole**							4.0			8.0	20.0	24.0	8.0			4.0	32.0
Voriconazole**			4.0		4.0	8.0	24.0	20.0	4.0	4.0	4.0	8.0	20.0				
Anidulafungin		20.0	72.0			4.0		4.0									
Caspofungin***						12.0	80.0	4.0	4.0								
Micafungin***		68.0	28.0							4.0							

*Shaded areas in each row indicate susceptibility (light) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.
** There are no EUCAST breakpoints for fluconazol and voriconazol as there is insufficient evidence for their use in treating *C. glabrata* infection.
*** There are no European breakpoints for caspofungin and micafungin. Strains susceptible to anidulafungin are considered susceptible.

TABLE 50. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates (n=12). 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*/**	≤ 0.06	> 0.06	100.0	-	0.0

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

TABLE 51. *Candida tropicalis* blood culture isolates (n=12). 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							33.3	58.3	8.3								
Fluconazole							41.7	41.7	8.3	8.3							
Voriconazole			8.3	25.0	41.7	25.0											
Anidulafungin		8.3	91.7														
Caspofungin**						58.3	41.7										
Micafungin**			66.7	33.3													

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

TABLE 52. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates (n=13). 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	92.3	7.7	0.0
Voriconazole*	≤ 0.125	> 0.125	100.0	-	0.0

* Recommended breakpoints by the European Commitee on antimicrobial susceptibility testing – EUCAST. Susceptibility testing for anidulafungin is not recommended as this species is a poor target for therapy with this drug. One must assume this also applies to other echinocandins (caspofungin and micafungin).

TABLE 53. *Candida parapsilosis* blood culture isolates (n=13). 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							30.8	53.9	15.4								
Fluconazole						15.4	69.2	7.7			7.7						
Voriconazole	7.7	15.4	69.2	7.7													
Anidulafungin**			7.7					15.4	23.1	30.8	15.4		7.7				
Caspofungin**						7.7	7.7	30.8	46.2	7.7							
Micafungin**			7.7			7.7		61.5	23.1								

*Shaded areas in each row indicate susceptibility (light) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.
** Susceptibility testing for anidulafungin is not recommended as this species is a poor target for therapy with this drug. One must assume this also applies to other echinocandins (caspofungin and micafungin).

RESULTS AND COMMENTS

In 2011, 200 isolates of seven different *Candida* species were isolated from blood stream infections in 190 patients and were received at the National Mycology Reference Laboratory. In 2010, 175 isolates of eight species were received. All isolates were susceptibility tested for amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin by Etest according to the manufacturer's instructions (AB bioMérieux). The results for *Candida albicans*, *C. glabrata*, *C. tropicalis* and *C. parapsilosis* are presented in Tables 46-53.

EUCAST has now determined that isolates categorised as anidulafungin susceptible can be regarded as susceptible to caspofungin and micafungin due to the cross resistance between the three echinocandins. Due to significant inter-laboratory variation in MIC ranges for caspofungin, EUCAST breakpoints have not yet been established, whereas specific breakpoints for micafungin are in preparation.

Candida albicans is still the most common *Candida* species observed (n=139, 69.5%) followed by *C. glabrata* (n=25, 12.4%), *C. parapsilosis* (n=13, 6.5%) and *C. tropicalis* (n=12, 6%). All *C. albicans* and *C. tropicalis* were susceptible to all antifungals tested, with the exception of two isolates of *C. albicans* with slightly elevated MICs to anidulafungin (0.064 and 0.125 mg/L).

The total number of *C. glabrata* (n=25) is slightly lower than in 2010 (n=34). All *C. glabrata* were susceptible to amphotericin B and with two exceptions, to anidulafungin. These two isolates also had slightly elevated MICs towards caspofungin and micafungin as the cross resistance between the echinocandins suggests. Azole resistance is approximately the same as last year. When testing for fluconazole susceptibility, only one isolate (4%) had MIC < 2 mg/L, while eight isolates (32%) had MIC ≥ 256 mg/L compared to 6% and 29% in 2010. Four isolates (16%) had MIC ≤ 0,125 mg/L when testing for voriconazole susceptibility. In 2010 this number was 6%. Heteroresistance to both fluconazole and voriconazole were found in seven isolates of *C. glabrata* (28%). This number is fairly stable compared to 2010 (29%) and 2009 (37%). EUCAST concludes that the epidemiological cut-off values for *C. glabrata* against fluconazole in general are higher than for *C. albicans*. Due to insufficient evidence that *C. glabrata* is a good target for fluconazole treatment, MIC values should be reported without accompanying S, I or R.

The number of blood stream infections with *C. parapsilosis* is still low. *C. parapsilosis* have higher MIC levels for the echinocandins then what we observe for the other *Candida* spp. More then 90% of the isolates had MIC > 0.064 mg/mL for all tree echinocandins. From 2012 EUCAST does not recommend susceptibility testing against anidulafungin as *C. parapsilosis* is a poor target for echinocandin therapy, and the isolates may be reported as resistant without testing.

Resistance in influenza viruses

The Department of Virology at the Norwegian Institute of Public Health (NIPH) functions as a WHO National Influenza Centre (NIC) and is designated by the Ministry of Health as national reference laboratory for influenza. In the latter function lies also the obligation to monitor and assess the occurrence of resistance. In addition to national monitoring, a selection of influenza viruses that are shipped by European NICs to the WHO Collaborating Centre in the United Kingdom is also tested for antiviral susceptibility there.

Background

Two classes of antiviral drugs are being used against influenza virus infections. M2 blockers inhibit replication of influenza type A viruses, while the more recently developed neuraminidase inhibitors (NIs) inhibit the replication of both type A and B. Historically, resistance has been known to develop quite easily against the M2 blockers. Over the last decade, the prevalence of resistance in A(H3N2) viruses due to the S31N substitution has increased and during the last few years almost all circulating H3N2 viruses are resistant (1). Similarly, practically all A(H1N1)pdm09 viruses are resistant, also due to S31N.

The more recently developed NIs initially seemed to be much less affected by resistance development, and resistant mutants in general have seemed less viable. However, an oseltamivir resistant seasonal A(H1N1) virus variant, carrying the neuraminidase mutation H274Y, emerged in 2007 (2,3) and within a year reached almost total predominance among seasonal viruses of this subtype. This global emergence of resistance was discovered first through analysis of viruses from Norwegian influenza surveillance, and it took place with no association to recorded usage of drug. Fortunately, as a consequence of the emergence in 2009 of the pandemic influenza A(H1N1)pdm09 virus, the previously circulating H1N1 viruses which were oseltamivir resistant appear to have become extinct.

During the 2009 A(H1N1)pdm09 pandemic, a substantial peak in NI (primarily oseltamivir) usage was recorded. This, however, did not lead to detectable emergence of resistant viruses. Also globally, very little oseltamivir resistance has been observed. Nonetheless, toward the end of the 2011 influenza season in Australia, local spread of oseltamivir resistant H1N1pdm09 viruses was observed (4). Apparently, these viruses did not spread beyond the initial area and ceased to circulate with the ending of the season there. No corresponding occurrence of resistant viruses has yet been reported from the 2011/12 Northern Hemisphere influenza season. Resistance to the other NI available in Norway, zanamivir, appears to be extremely rare. Community spread of oseltamivir resistant A(H1N1)pdm09 virus still remains a concern, given that data from animal studies suggest that the fitness of the H275Y variant is not significantly compromised and that there indeed was local spread of resistant virus in Australia in 2011.

Surveillance findings

In Norway seasonal H3N2 was the dominating strain in circulation during the 2011/12 season. There was limited circulation during the season of influenza type B, both Yamagata- and Victoria-lineage, representing about 3% of the virus detections. A(H1N1)pdm virus has been encountered only sporadically this season.

Findings from Norwegian surveillance are summarised in Table 54. The few pandemic A(H1N1)pdm09 viruses analysed in 2011/2012 have been 100% susceptible to the neuraminidase inhibitors in the phenotypic assay (MUNANA), but 100% resistant to M2 blockers. The A(H3N2) viruses have remained resistant to the M2 blocker adamantine, but susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. All influenza B viruses that have been analysed are susceptible to both oseltamivir and zanamivir.

TABLE 54. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the NIs oseltamivir and zanamivir during the influenza seasons 2005/06 through 2011/12. Two screening tools were used to determine oseltamivir/zanamivir resistance: sequence analysis of viral genes or a neuraminidase inhibition assay.

	Adamantane resistance		Oseltamivir resistance			Zanamivir resistance		
	A(H1N1)	A(H3N2)	A(H1N1)	A(H3N2)	B	A(H1N1)	A(H3N2)	B
2005/06	ND	75% (n=4)	0% (n=6)	0% (n=13)	0% (n=21)	0% (n=6)	0% (n=13)	0% (n=21)
2006/07	0% (n=6)	90% (n=10)	0% (n=5)	0% (n=10)	ND	0% (n=5)	0% (n=10)	ND
2007/08	0% (n=112)	100% (n=2)	68% (n=272)	0% (n=2)	0% (n=59)	0% (n=114)	0% (n=2)	0% (n=59)
2008/09	0% (n=5)	100% (n=65)	100% (n=33)	0% (n=13)	0% (n=1)	0% (n=5)	0% (n=12)	0% (n=1)
2009-pand*	100% (n=258)	100% (n=2)	0% (n=884)		0% (n=11)	0% (n=36)		0% (n=9)
2010/11*	100% (n=54)	100% (n=10)	1.6%** (n=244)	0% (n=1)	0% (n=30)	0% (n=2)	0% (n=1)	0% (n=24)
2011/12	100% (n=19)	100% (n=56)	0%** (n=27)	0% (n=71)	0% (n=5)		0% (n=59)	0% (n=4)

* During influenza season 2010/11, all A(H1N1) tested were pdmH1. ** A(H1N1)pdm with the mutation 275Y in mixture commonly associated with oseltamivir resistance. NI=Neurominidase inhibitors. ND=Not determined.

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

Data sources

Feed additives

Until 2003, the Norwegian Agricultural Inspection Service was responsible for the collection of data on sales of antimicrobial growth promoters and coccidiostats as feed additives, while from that time the Norwegian Food Safety Authority has been in charge of collecting such data. Reliable data on the use of different substances and categories of feed additives was obtained from these sources.

Antimicrobial agents for therapeutic use

In Norway, veterinary antimicrobial agents for therapeutic use in domestic animals or farmed fish are prescription drugs only. Moreover, veterinary antimicrobial agents have to be dispensed through pharmacies, which are supplied by drug wholesalers only. An exemption from the pharmacy/wholesalers monopoly has been granted for medicated feeds (i.e. feeds into which drugs for therapeutic use are mixed prior to sales). Medicated feeds have to be prescribed by veterinarians and produced by feed mills authorized by the Norwegian Medicines Agency. In Norway, medicated feeds produced and supplied by feed mills are only used for farmed fish. Medicated feeds for livestock are not produced in feed mills due to the small size of livestock herds compared to most other European countries. However, herd/flock treatment of livestock with antimicrobial agents is possible, again subject to veterinary prescription, through the drinking water or as a top dressing on the feed. The sales figures for veterinary antimicrobial agents from wholesalers and feed mills are thought to roughly equal the use of these drugs. Sales figures for veterinary antimicrobial agents are therefore used as a synonym for usage of veterinary antimicrobial agents. Drug wholesalers and feed mills report their sales figures to the Norwegian Institute of Public Health. This reporting was made mandatory from January 1st 2002. Number of items sold for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and calculated to express kg active substance.

Drug classification system

The Anatomical Therapeutic Chemical vet (ATCvet) classification system was used to categorise veterinary medicinal products (http://www.whocc.no/atcvet).

Unit of measurement

The amount of active substance denoted in kilograms was chosen as the unit of measurement. Veterinary antimicrobial drug usage was calculated from sales figures for delivery of antimicrobials from wholesalers to pharmacies, and from feed mills. The data for benzyl penicillin salts and esters (procaine penicillin and penethamate hydriodide) were converted to the corresponding values for benzyl penicillin.

Inclusion criteria – veterinary drugs

The veterinary drugs included for terrestrial animals were all the approved veterinary antimicrobial products belonging to the following ATCvet groups: QA07AA (gastrointestinal infections) (no product in ATCvet group QA07AB on the market in Norway), QG01AA+AE (uterine infections) (no products in ATCvet groups QG51AC, -AE, -AX, -BA, -BC or -BE on the market in Norway), and QJ (antimicrobial agents for systemic use that includes intramammary dose applicators (QJ51)). Additionally, antimicrobial products sold on special exemption from market authorisation have been included following a case by case assessment. Sales of antimicrobial agents as medicated feeds and as premixes, both intended for use in farmed fish, belonging to QJ are presented separately. An exemption has been made for an antimicrobial premix approved for farmed fish only (trimethoprim-sulfadiazine 1:5) but sold solely for use in terrestrial animals since 1995 (unpublished data). Consequently, the sales of the antimicrobial agents in terrestrial animals reported for the years 1993-2005 were underestimated, although only slightly. However, the updated usage figures for 1995-2005 correlated highly positive (r=0.998) with the data reported previously for these years confirming the formerly reported reduction in the usage of antimicrobial agents in terrestrial animals. Dermatological preparations (QD) and preparations intended for sensory organs (QS) are not included in the material. Human antimicrobial preparations are used in small animal practice. However, data on the use of such antimicrobial preparations in animals are not included in this report as such sales cannot be separated from sales intended for use in humans.

Analysis of the data

In order to assess the overall use of antimicrobial VMPs for terrestrial food producing animals and for pets, sales of products approved for companion animals only (tablets and pasta) has been separated form the total sales.

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

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

The wholesales database covers total sales of antibacterials 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. The Norwegian Institute of Public Health collects the data. Data on drug use from wholesalers is available since the beginning of the seventies.

Data on antibacterial use in hospitals are retrieved from *Sykehusapotekenes Legemiddelstatistikk* (the hospital pharmacies drug statistics database) which is a cooperation of LIS, Legemiddel Innkjøp Samarbeid (Drug Purchasing Cooperation) and the four regional pharmaceutical health trusts operating the hospital pharmacies in Norway. *Sykehusapotekenes Legemiddel-statistikk* collects sales data from each pharmacy delivering drugs to hospitals. Data are collected as sales from the pharmacy to wards/hospitals.

Data on the use in ambulatory care are retrieved from NorPD, a nation-wide prescription database. 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. The Norwegian Institute of Public Health collects the data. More information available at www.fhi.no.

Drug Classification
The data is categorised according to the ATC classification system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2011 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 antibacterials are only used in severe infections and their DDDs are assigned accordingly. The DDDs assigned are based on daily treatment.

Inclusion criteria
The antibacterials for human use included in this report belong to ATC group J01 antibacterials for systemic use. Oral vancomycin (A07AA09), rifaximin (A07AA11) and oral and rectal metronidazole (P01AB01) are also included. Of the antimycobacterials, only rifampicin is included and data are presented as total amount rifampicin used. 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 (2011). ATC index with DDDs 2012. WHO Collaborating Centre, Oslo

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

Sampling strategy
Clinical isolates of *Escherichia coli* were collected from poultry with septicaemia. The Norwegian Veterinary Institute (NVI) in Trondheim supplied a majority of the isolates being collected in the period 2008-2011. Some isolates were also submitted from other NVI laboratories. A total of 38 isolates were tested (one isolate per herd).
Indicator *E. coli* from swine were collected from intestinal content of healthy animals admitted to slaughterhouses and collected at random by staff of the Norwegian Food Safety Authority. Altogether 194 herds were included (one sample per herd). The samples were also examined for *E. coli* producing extended-spectrum beta-lactamase (ESBL).
Nasal swabs were obtained from healthy swine admitted to slaughterhouses and examined for methicillin resistant *Staphylococcus aureus* (MRSA). Altogether 207 randomly selected herds were included in the study. From each herd five animals were sampled and subsequently pooled into one sample. The study was anonymous.
The indicator *E. coli* from healthy broilers were collected from samples obtained by the Norwegian *Salmonella* control programme for live animals. A sample from each of the first five flocks to be processed at a specific weekday during the whole sampling period (Jan-Nov) was collected. From each flock a piece of a boot swab was analysed. A total of 252 samples were collected. The samples were also used for isolation of *Enterococcus* spp., and for selective isolation of ESBL producing *E. coli* and vancomycin resistant *Enterococcus* spp. (VRE).

Indicator isolates of *E. coli*
Sample material (boot swabs) from healthy broilers was mixed with sterile distilled water prior to plating onto the surface of lactose-bromthymol blue agar and incubated at 37°C for 24h. Sample material from healthy swine was plated directly onto lactose-bromthymol blue agar. Typical colonies were subcultured on blood agar (Heart infusion agar, Difco) containing 5% bovine blood and incubated at 37°C for 24h. Colonies were identified as *E. coli* by typical appearance, lactose fermentation, a positive indole reaction, and negative citrate and oxidase reactions.

ESBL *producing E. coli*
Sample material (healthy broilers and swine) was plated onto MacConkey agar (Difco) containing 1 mg/L cefotaxime and MacConkey agar containing 2 mg/L ceftazidime. The agar plates were incubated at 37°C for 24-48h. Positive colonies were selected, and the isolates confirmed as *E. coli* using API 20 E (bioMérieux).
Presumptive positive *E. coli* were further investigated by disk diffusion (Beckton Dickinson) and further subjected to PCR (Pérez-Pérez et al, 2002) and DNA sequencing.

***Enterococcus* spp.**
Sample material was plated on Slanetz & Bartley agar (Oxoid) and incubated at 44°C for 24-48h. Colonies from each positive sample were selected, and the isolates confirmed as *Enterococcus* spp. by phenotypic characterisation and negative catalase test. The isolates were further identified to the species level as *E. faecalis* or *E. faecium* using PCR (Dutka-Malen et al. 1995).

Vancomycin resistant *Enterococcus* spp.
Sample material was plated on Slanetz & Bartley agar (Oxoid) with 32 mg/L vancomycin and incubated at 44°C for 48h. Presumptive positive colonies were selected and confirmed as *Enterococcus* spp. by phenotypic characterisation and negative catalase test. The isolates were identified to the species level as *E. faecalis* or *E. faecium* and tested for the *vanA* gene using PCR (Dutka-Malen et al. 1995, Simonsen et al. 2000).

Methicillin resistant *Staphylococcus aureus* (MRSA)
Screening for MRSA from swine was performed by incubation of each of the pooled nasal swabs in Mueller-Hinton broth with 6.5% NaCl. After incubation 1 mL was transferred to 9 mL Trypton-Soya broth with 75 mg/L aztreonam and 3.5 mg/L cefoxitin and incubated at 35°C for 16-20h, followed by plating on Brilliance MRSA agar plates (Oxoid). Suspected colonies were subjected to further identification including PCR for detection of the *mec*A/*nuc* genes (Predari et al. 1991, Brakstad et al. 1992).

Susceptibility testing
Isolates were tested for antimicrobial susceptibility at NVI, Oslo. MIC values were obtained using the VetMIC™ microdilution method (Dep. of Antibiotics, National Veterinary Institute, Sweden).
Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 05.06.2012) were used except for ciprofloxacin for *E. coli* and trimethoprim and clindamycin for *S. aureus*. For these exceptions, and 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
The following susceptible bacteria were included as quality controls on a regular basis: *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *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. faecium* CCUG 33829, *S. aureus* CCUG 35603. 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 (EU CRL for Antimicrobial Resistance in Denmark).

Data processing
Susceptibility data were recorded and stored in the sample registration system at NVI as discrete values (MIC). The data management and analysis were performed in SAS v 9.1 (SAS Institute Inc., Cary, NC, USA) and the 95% confidence intervals were calculated by the exact binomial test using R v. 2.7.1 (R Development Core Team, 2008).

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

Sampling strategy - animals

Salmonella
Samples from animals were collected according to the Norwegian *Salmonella* control programme for live animals. Additional isolates were obtained from animals from clinical submissions or necropsies at the Norwegian Veterinary Institute (NVI). One isolate of each serovar per incident was included for susceptibility testing.
S. diarizonae was isolated from clinical samples of sheep submitted to the NVI laboratories during 2007-2011.

Campylobacter jejuni
Caecal samples were collected from positive flocks of broiler in the Norwegian action plan against *Campylobacter* (www.vetinst.no). One isolate from each flock was included for susceptibility testing.

Sampling strategy - humans

Salmonella, Yersinia enterocolitica* and *Shigella
All human isolates were obtained from clinical specimens. One isolate per patient or one isolate per recognized outbreak was included for susceptibility testing.

Campylobacter
A total of 275 human isolates were obtained from clinical specimens. Five regional laboratories submitted the first five independent isolates each month to the NRL for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Isolation and identification of bacteria
Isolation and identification of *Salmonella* spp. from animals was carried out at the NVI according to ISO 6579:2002/Amd.1:2007: Annex D: Detection of *Salmonella* spp. in animal faeces and in environmental samples from the primary production stage.
Isolation and identification of *Campylobacter jejuni* from broiler was carried at NVI, Oslo. Sample material was plated onto the surface of selective media (CAT, Oxoid) and incubated at 41°C for 48h in microareophilic atmosphere. Suspect isolates were further identified to species level (*C. jejuni*) using standard bacteriological testing.
The NORM data regarding human clinical isolates of enteropathogenic bacteria are based on primary laboratories forwarding all isolates of possible enteropathogenic bacteria to the NRL for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH). The reference analyses are 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
Isolates from animals were tested for antimicrobial susceptibility at NVI, Oslo. MIC values were obtained using the VetMIC™ microdilution method (Dep. of Antibiotics, National Veterinary Institute, Sweden).

Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the NRL for Enteropathogenic Bacteria at NIPH by agar disk diffusion test 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 from Liofilchem.

For animal isolates, epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 05.06.2012) were used. For additional antimicrobial agents not defined in the EUCAST recommendations, cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also Appendix 6).
For human isolates EUCAST or NordicAST clinical breakpoints were used if established, otherwise epidemiological breakpoints were used.

Quality assurance systems
NVI and the Reference Laboratory for Enteropathogenic Bacteria/NIPH have a quality assurance system according to the requirements of NS-EN ISO/IEC 17025.
Campylobacter jejuni subsp. *jejuni* CCUG 11284 was used as quality control strains at NVI on a weekly basis. The participating laboratories at NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in two external quality assurance programmes: For veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit Loughborough, UK) and for resistance monitoring (EU CRL for Antimicrobial Resistance in Denmark).
The NRL for Enteropathogenic Bacteria at 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
Susceptibility data were recorded and stored in the sample registration system at NVI. The susceptibility data were stored as discrete values (MIC). The data management and analysis were performed in SAS v 9.1 (SAS Institute Inc., Cary, NC, USA) and the 95% confidence intervals were calculated by the exact binomial test using R v. 2.7.1 (R Development Core Team, 2008).
The NRL at NIPH stored susceptibility data of human isolates as either millimeter zone diameters or MIC-values. The data managment and analysis were performed in SPSS version 17. (SPSS inc. Chicago, USA).

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

General considerations

NORM is based upon periodic sampling and testing in each participating laboratory of microbial isolates from defined clinical conditions such as respiratory tract infections, wound infections, urinary tract infections, and septicaemiae. For enteric infections see Appendix 4. 2011 was the twelfth year of surveillance, and all 21 laboratories in Norway participated in the surveillance system in addition to the Norwegian Institute of Public Health. All 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 2011 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. in blood cultures (9 months); *Streptococcus pneumonia* from blood cultures and cerebrospinal fluids, and *Candida* spp. in blood cultures (12 months); *Haemophilus influenzae* from respiratory tract specimens (3 weeks); *S. aureus* from wound specimens (1 week); *E. coli* from urinary tract infections (2 days); *Mycobacterium tuberculosis* from all samples (12 months). *S. pneumoniae* from blood cultures and cerebrospinal fluids were further analysed at the the Norwegian Institute of Public Health in Oslo. *Candida* spp. from blood cultures were further analysed at Oslo University Hospital, Rikshospitalet. *M. tuberculosis* was further analysed at the Norwegian Institute of Public Health and Oslo University Hospital (Ullevål and Rikshospitalet).

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp. and *S. aureus* isolates were examined according to the EUCAST disk diffusion standard using antibiotic disks and Mueller Hinton II agar from either Oxoid or Beckton Dickinson. Suitable antibiotics were selected for each bacterial species, and the results were interpreted according to the breakpoints of the Norwegian Working Group on Antibiotics (NWGA). The NWGA breakpoints are harmonised with EUCAST breakpoints with few exceptions as explained in the text. All *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 the clover leaf test. All *Enterococcus* spp. isolates were screened for glycopeptide resistance using a vancomycin 6 mg/L BHI agar. *S. pneumoniae* and *H. influenzae* isolates were susceptibility tested using MIC gradient tests (bioMerieux) on MH II agar supplemented with 5% lysed horse blood (*S. pneumoniae*) or Isovitalex and haemoglobin (*H. influenzae*). Susceptibility testing of *Candida* spp. isolates was performed by MIC gradient tests using RPMI agar containing 2% glucose and MOPS. All resistance values were recorded either as mm inhibition zone sizes or MIC values in order to monitor trends in the occurrence of resistance.

For *M. tuberculosis*, all isolates were tested using the BACTEC 460 or BACTEC MGIT 960 systems. All three test laboratories participate in the WHO external DST quality control programme. The same three laboratories and Haukeland University Hospital also perform tests for mutations in *rpoB* gene to detect resistance to rifampicin.

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 (bioMerieux). ESBL positive strains 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* spp. isolates displaying growth on the vancomycin screening agar were examined by *van* PCRs for confirmation of VRE. Erythromycin resistant *S. pneumonia* and *S. aureus* isolates were analysed for determination of MLS phenotype using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

Quality control

The following strains were used for quality control: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 (ESBL positive), *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. pneumoniae* ATCC 49619, *S. pneumoniae* TIGR4, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. aureus* ATCC 43300 (heterogeneous MRSA), *S. aureus* CCUG 35600 (homogeneous MRSA), *H. influenzae* ATCC 49247, *C. albicans* ATCC 10231.

Data processing

The specially designed eNORM computer programme was used for the registration of patient data, sample data and resistance data. The results were further analysed by WHONET 5.3 with the aid of the NORMlink 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 attempt was made to evaluate the clinical significance of each finding.

Appendix 6:
Cut-off values NORM-VET

Epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 05.06.2012) were used. For additional antimicrobial agents not defined in the EUCAST recommendations, cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.

Antimicrobial	Resistant MIC (mg/L)	*Campylobacter jejuni*	*Salmonella* spp.	*Escherichia coli*	*Enterococcus spp.*	*Staphylococcus aureus*
Ampicillin	>4				■	
	>8		■	■		
Bacitracin*	>32				■	
Cefotaxime	>0.25			■		
	>0.5		■			
Ceftazidime	>0.5			■		
Cefalotin	>1					■
Cefoxitin	>4					■
Chloramphenicol	>16		■	■		■
	>32				■	
Ciprofloxacin	>0.06		■	■		
	>1	■				■
Clindamycin	>0.25					■
Colistin	>2			■		
Erythromycin	>1					■
	>4	■			■	
Florfenicol	>16		■	■		
Fusidic acid	>0.5					■
Gentamicin	>1	■				
	>2		■	■		■
	>32				■	
Kanamycin	>8			■		■
	>16		●			
	>1024				●	

Antimicrobial	Resistant MIC (mg/L)	*Campylobacter jejuni*	*Salmonella* spp.	*Escherichia coli*	*Enterococcus spp.*	*Staphylococcus aureus*
Linezolid	>4			■	■	
Mupirozin	>1					■
Nalidixic acid	>16	■	■	■		
Narasin	>2				■	
Oxacillin	>2					■
Quino-dalfopristin	>1					■
Rifampicin	>0.03					■
Sulfamethoxazole	>64			■		
	>128					■
	>256		●			
Streptomycin	>2	■				
	>16		■	■		■
	>128				■	
Tetracycline	>1					■
	>2	■				
	>4				■	
	>8		■	■		
Tiamulin	>2					■
Trimethoprim	>2		■	■		■
Vancomycin	>2					■
	>4				■	
Virginiamycin	>4				■	

Squares: Cut-off values recommended by EUCAST
Filled circles: Cut-off values not defined by EUCAST - defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.
*Units/mL

Appendix 7: 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.

	MIC values mg/L													
Antimicrobials	S	R	*Escherichia coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Candida albicans* ¤
Amphotericin B	≤ 1	> 1											■
Ampicillin	≤ 1	> 1							■				
	≤ 4	> 8									■		
	≤ 8	> 8	■		■		■						
						■#							
Amoxi-Clav*	≤ 2	> 2							■				
Anidulafungin	≤ 0.03	> 0.03											■
Cefotaxime	≤ 0.125	> 0.125							■				
	≤ 0.5	> 2										■	
	≤ 1	> 2	■	■									
Ceftazidime	≤ 1	> 4	■	■									
Ceftriaxone	≤ 0.5	> 2										■	
Cefuroxime	≤ 0.5	> 8	■	■									
	≤ 1	> 2							■				
Chloramphenicol	≤ 2	> 2							■				
	≤ 8	> 8			■		■					■	
						■#							
Ciprofloxacin	≤ 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						■					
Fluconazole	≤ 2	> 4											■
Fusidic acid	≤ 1	> 1								■			
Gentamicin	≤ 1	> 1								■			
	≤ 2	> 4	■	■				■					
	≤ 128	> 128									■		
Linezolid	≤ 4	> 4								■	■		

Antimicrobials	MIC values mg/L S	R	*Escherichia coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Candida albicans* ¤
Mecillinam	≤ 8	> 8	■										
Meropenem	≤ 2	> 8	■	■									
Nalidixic acid			■#	■#	■#	■#	■#	■#	■#				
Nitrofurantoin	≤ 64	> 64	■										
Oxacillin												■#	
Penicillin G	≤ 0.064	> 2										■	
Piperacillin-Tazo**	≤ 8	> 16	■	■									
Rifampicin	≤ 0.06	> 0.5								■			
Tetracycline	≤ 1	> 1						■					
	≤ 1	> 2			■#	■#	■#		■	■		■	
Tigecycline	≤ 1	> 2	■										
Trimethoprim	≤ 2	> 4	■										
TMS***	≤ 1	> 2							■			■	
	≤ 2	> 4	■	■	■	■#	■			■			
Vancomycin	≤ 4	> 4									■		
Voriconazole	≤ 0.125	> 0.125											■

¤ Breakpoints for *Candida* spp. other than *C. albicans* (*C. glabrata*, *C. tropicalis* and *C. parapsilosis*), details are given in Tables 46-53.
Epidemiological cut-off value based on the wild type distribution by EUCAST. * Amoxi-Clav= Amoxicillin-Clavulanic acid. ** Piperacillin-Tazo=Piperacillin-Tazobactam. *** TMS Trimethoprim-sulfamethoxazole. Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

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