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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 recognized 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 eleventh annual joint report from NORM and NORM-VET, presents data for 2010. 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 in Tromsø for fruitful cooperation and all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Oslo, September 2011

II. SAMMENDRAG

Dette er den ellevte 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 2010. 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 2010 var 6347 kg. Fra 1993 til 2010 ble salget av veterinære antibiotika til landdyr redusert med 38 %. For preparater som nesten utelukkende benyttes til produksjonsdyr (landdyr) er reduksjonen på 41% mens salget av veterinære antibakterielle preparater som kun brukes til kjæledyr har økt med 42 % (fra 417 til 591 kg).

Forbruksmønsteret til produksjonsdyr har utviklet seg i gunstig retning siden 1993 idet andelen av rene penicillin-preparater har økt betraktelig parallelt med at bruk av kombinasjonspreparater med penicillin og dihydrostreptomycin har gått ned. Siden det første penicillinpreparatet til smådyr kom på markedet i Norge i 1994 har bruk av penicillinpreparater, i kg aktiv substans, økt fra 1 % til 59 % 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 2010 på 649 kg aktiv substans, hvorav 47 % 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 doblet 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 2010 var humant forbruk av antibiotika til systemisk bruk 19,7 DDD/1000 innbyggere/dag. Det samlede forbruket har vært forholdsvis stabilt gjennom mange år, men det har skjedd en gradvis forskyvning mellom de ulike antibakterielle undergrupper. Fra 2004 til 2006 økte totalforbruket av antibiotika jevnt. Siden 2007 har salget vært stabilt.

Salget av penicilliner og kinoloner øker jevnt, mens salg av sulfonamider og trimetoprim synker. Fra 2009 til 2010 har vi sett en økning av makrolider og tetracykliner mens salg av cefalosporiner har gått ned. Det urinveisantiseptiske middelet metenamin har de seneste årene økt kraftig og i 2010 utgjorde metenamin 17 % av totalt salg målt i DDD.

I 2010 utgjorde penicillinene 43 % av det totale antibiotikaforbruket i Norge målt i DDD. I 2010, som i 2009, så vi en økning av bredspektrede og penicillinase stabile penicilliner og en nedgang i betalaktamase følsomme penicilliner. Tetracykliner utgjorde 16 % av totalforbruket i 2010. Forbruket av makrolider og linkosamider utgjorde 10 % av totalt salg i 2010. 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 2010, men salget er mer enn doblet på 10 år.

Bruken av antibakterielle midler varierer avhengig av kjønn, alder og bosted. Salget til sykehus og primærhelsetjenesten utgjorde i 2010 henholdsvis 7,5 % og 84 %. I sykehus brukes penicilliner i stor grad (45 % av antibiotikasalget målt i DDD til sykehus). Tilsvarende andel for allmennpraksis er 42 %. De viktigste andre gruppene på sykehus var cefalosporiner (19 %) og kinoloner (7 %), mens det i allmennpraksis var tetracykliner (18 %) og makrolider (11 %).

Resistens hos kliniske isolater fra dyr

Kliniske isolater av *S. aureus* fra kyr med mastitt ble undersøkt. Forekomsten av antibiotikaresistens var lav; 97,4 % av isolatene var følsomme for alle undersøkte antibiotika. Ingen av de undersøkte isolatene viste økt toleranse for de desinfeksjonsmidlene som det ble undersøkt for. Det har vært en lav og stabil forekomst av resistens over det siste tiåret.

Enterococcus hirae ble isolert fra sykdomsutbrudd hos broiler. Resistens mot narasin forekom hyppigst og ble påvist i 27 av 41 isolater. Narasin blir brukt som fôrtilsetning, og dette innebærer et seleksjonspress for utvikling av resistente bakterier.

Vibrio anguillarum isolert fra sykdomsutbrudd hos torsk og laks 2000-2009 ble undersøkt. Ettersom det ikke foreligger brytningspunkter for denne bakterien, kunne forekomsten av resistens ikke estimeres.

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 2010 ble *E. coli* isolert fra avføringsprøver fra storfe og tarminnhold fra rødrev resistenstestet. For begge dyrearter var det en lav forekomst av resistente bakterier, cirka 91 % av isolatene var følsomme for alle antibiotika i testpanelet. Hos storfe ble resistens mot ett antibiotikum påvist hos 4,8 % av isolatene og hyppigst mot streptomycin. Det ble kun påvist et fåtall multiresistente isolater. Sammenligning med resultater fra tidligere år viser en lav og stabil forekomst av resistente *E. coli*. Det ble påvist resistente *E. coli* i prøver fra åtte av 88 rødrev. Multiresistente isolater ble påvist hos fire dyr og blant disse også resistens mot fluorokinoloner og gentamicin. Dette er bekymringsfullt og indikerer spredning av resistens i miljøet mot viktige antibiotika til behandling av mennesker og dyr.

Resistens hos zoonosebakterier og andre enteropatogene bakterier

I 2010 ble 21 *Salmonella* spp. isolater fra norske dyr resistenstestet. Forekomst av resistens mot tetracykliner, ampicillin og sulfonamider ble observert i nærmere en tredjedel av isolatene. Ett isolat viste resistens mot fluorokinoloner. Til tross for et lavt prøveantall indikerer resultatene en mulig økning av resistens, spesielt blant *Salmonella* spp. isolert fra hund.
Isolater av *S.* Typhimurium fra ville fugler innsamlet i perioden 2006-2010 ble undersøkt for resistens. Samtlige isolater var følsomme for antibiotika i testpanelet.
I et prøvemateriale av 323 avføringsprøver fra storfe, ble det påvist kun 11 isolater av *Campylobacter jejuni*. Ti av disse var følsomme for alle antibiotika i testpanelet. Materialet er for lite til å trekke noen konklusjoner om resistensutviklingen hos denne bakteriearten hos storfe.

Av de humane salmonellosetilfellene som ble rapportert i 2010, var 79,3 % oppgitt å ha blitt smittet i utlandet. For *S.* Typhimurium er det en klar tendens til at innenlands smittede stammer er mer resistente enn i fjor. Andelen innenlandssmittede *S.* Typhimurium isolater som var følsomme for alle antibiotika har sunket fra 57,3 % til 35,6 %, mens multiresistens hos de innenlands smittede stammene har økt fra 29,3 % til 57,5 %. Dette kan skyldes tilsynelatende etablering i Norge av den nokså resistente monofasiske varianten av *S.* Typhimurium (*S. enterica* serovar 4,[5],12:i:-). For *S.* Enteritidis var forekomsten av antibiotikaresistens fortsatt betydelig lavere enn hos *S.* Typhimurium med unntak av nalidiksinsyre. Til sammen 23,7 % av *S.* Enteritidis isolatene var resistente mot nalidiksinsyre. Andelen av ciprofloxacinresistente *S.* Enteritidis var på samme nivå som i 2009

Andelen *C. jejuni* fra pasienter smittet i utlandet som var følsomme for alle undersøkte antibiotika, lå på samme, relativt lave nivå som i fjor, mens for isolater fra pasienter smittet i Norge synes dessverre andelen å ha sunket (85,1% i 2009 mot 61,9% i 2010).

Smitte med *Yersinia enterocolitica* skjer hovedsakelig innenfor Norges grenser, og den vanligste serogruppen er O:3. Resistens mot kloramfenikol og trimetoprim-sulfamethoxazole er hyppigst påvist. De fleste tilfeller av *Shigella*-infeksjoner i Norge kan knyttes til smittekilder i utlandet. Antibiotikaresistens var utbredt hos *Shigella* isolater i likhet med det som rapporteres fra andre land.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterie-isolater fra mennesker var, som i de foregående år, meget lav i 2010. Det ble påvist 10 tilfeller av meticillin-resistente *Staphylococcus aureus* (MRSA) blant de 1005 blodkulturisolater (1,0 %) som ble inkludert i NORM-protokollen. Dette er i samsvar med at 14 av 1426 (1,0 %) *S. aureus* blodkulturisolater i laboratorienes datasystemer ble rapportert som MRSA. I 2010 var dermed 14 av 1442 (1,0 %) *S. aureus* fra blodkultur og spinalvæske MRSA. Andelen er en svak økning fra tidligere år da man fant 0,5 % i 2009, 0,7 % i 2008 og 0,4 % i 2007. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 431 tilfeller av MRSA-infeksjon i 2009 mot 414 i 2009. Hele 82 % av tilfellene var pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (6/937, 0,6 %). MSIS registrerte videre 481 tilfeller av MRSA-kolonisering i 2010 mot 402 tilfeller i 2009 og 304 i 2008. Det totale antallet MRSA-meldinger økte dermed fra 816 meldinger i 2009 til 912 i 2010 (+11,8 %). 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. Det er dermed et åpent spørsmål om det økende antall meldinger er uttrykk for epidemiologiske endringer eller bedret diagnostikk. Blant *S. aureus* isolater fra sårprøver fortsatte nedgangen i andelen med fucidinresistens fra 14,5 % i 2006 til 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 5,2 %. Dette er en økning fra 4,0 % i 2009, og man bør vurdere om aminoglykosider fortsatt er egnet som empirisk behandling ved sepsis av ukjent årsak. Økningen av resistens og nedsatt følsomhet for ciprofloxacin i *E. coli* fra 3,3 % i 2004 til 8,6 % i 2009 ble i 2010 snudd til nedgang med 7,7 %. 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 aminoglykosider og fluorokinoloner enn *E. coli*.

Produksjon av bredspektrede beta-laktamaser (ESBL) er blitt et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 41/1359 *E. coli* (3,0 %) og 9/599 (1,5 %) *Klebsiella* spp. fra blodkulturer ble rapportert som ESBL positive. For *E. coli* var forekomsten av ESBL høyere enn i 2009 (2,5 %). Forekomsten av ESBL blant *Klebsiella* spp. ble redusert fra 2,6 % i 2009 til 1,5 % i 2010. 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 (3,0 %) enn fra urinprøver (1,4 %). I 2010 ble det for første gang påvist et tilfelle av New Dehli-1 (NDM-1) karbapenemase i *E. coli* i Norge.

Det ble påvist bare ett enkelt enterokokkisolat med klinisk signifikant vankomycinresistens i 2010. Forekomsten av nedsatt følsomhet for ampicillin i *Enterococcus faecium* ligger fortsatt rundt 80 %, og høygradig gentamicin-resistens ble påvist i 29,9 % av *E. faecalis* og 47,3 % av *E.*

faecium. De aller fleste (70 av 71) *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. Tjueto av 730 isolater (3,0 %) hadde nedsatt følsomhet for penicillin G, og kun tre isolater hadde samtidig redusert følsomhet for cefalosporiner. Andelen isolater med nedsatt følsomhet for penicillin G var på samnme nivå som i 2009 (2,9 %). Forekomsten av makrolidresistens blant systemiske pneumokokkisolater fortsatte nedgangen fra toppåret 2006 (12,4 %) til 4,0 % i 2010. Nedgangen må sees i sammenheng med innføringen av den konjugerte pneumokokkvaksinen i barnevaksinasjonsprogrammet i juli 2006.

Pseudomonas aeruginosa fra blodkultur var generelt følsomme for relevante antibiotika, men i alt 19 % viste ulike former for ervervet resistens. Enkeltisolater var resistente mot praktisk talt alle antibiotika som er aktuelle ved behandling av alvorlige infeksjoner med *P. aeruginosa*.

Forekomsten av resistens hos *Neisseria gonorrhoeae* har vært et økende globalt problem gjennom mange år. Epidemiologien i Norge gjenspeiler i det vesentlige forholdene internasjonalt. Forekomsten av betalaktamase-produksjon (28,4 %) og redusert følsomhet for penicillin G (97,7 %) gjør det helt uaktuelt å benytte dette middelet ved behandling av gonorré. Resistens mot ciprofloxacin (61,1 %) er likeledes så utbredt at det empiriske behandlingsregimet i Norge nå må endres. Det kan se ut til at det også foregår en økende resistensutvikling mot cefalosporiner slik at man i første omgang må øke doseringen for å sikre terapeutisk effekt.

I alt 342 tilfeller av tuberkulose ble meldt til MSIS i 2009. Det ble utført resistensbestemmelse av 277 *Mycobacterium tuberculosis* isolater fra pasienter som ikke hadde blitt behandlet for tuberkulose tidligere. Ni isolater fra pasienter smittet i henholdsvis Afrika (n=3), Asia (n=2) og Europa utenfor Norge (n=4) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 165 blodkulturisolater av *Candida albicans* (n=112), *C. glabrata* (n=34), *C. tropicals* (n=12) og *C. parapsilosis* (n=7). Alle *C. albicans* isolater var følsomme for amphotericin B, fluconazol, voriconazol, caspofungin og micafungin, mens to isolater var resistente mot anidulafungin. Det ble påvist høy forekomst av resistens mot fluconazol og voriconazol blant *C. glabrata* isolater. Amfotericin B og echinocandinene viste høy aktivitet mot alle de undersøkte soppartene. Resultatene er i samsvar med tidligere studier fra Norge.

Overvåking av resistens mot antivirale midler omfattet i 2010 både influensavirus og HIV, men resultatene for HIV er foreløpig ikke blitt analysert nærmere. Influensa-sesongen 2010/2011 ble i Norge dominert av influensa B med et visst innslag av pandemisk influensa A(H1N1). Pandemisk influensa A(H1N1) var som tidligere resistent mot M2-blokkere, og det ble også påvist enkelttilfeller med mutasjoner som koder for nedsatt følsomhet for oseltamivir. Alle isolater av influensa B var følsomme for neuraminidasehemmere.

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 når det gjelder 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 11th 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 2010. 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 2010, the total sales of antimicrobial VMPs for terrestrial animals were 6,347 kg. The annual sales of antimicrobial VMPs for use in terrestrial animals have decreased by approximately 38% from 1993 to 2010. The reduction in use is accounted for by a reduction in the use in food producing animals (41% reduction) while for antimicrobial VMPs marketed for companion animals only, an increase of 42% 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 2010. In this period the sales of aminoglycosides decreased from 32% to 26% of total sales; this is due to a reduction in the use of combination preparations of penicillin and dihydrostreptomycin 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 2010, the total sales of antimicrobial drugs for therapeutic use in farmed fish were 649 kg of active substance of which quinolones accounted for 47%. The sales of antimicrobial VMPs in Norwegian aquaculture peaked in 1987 and then declined by approximately 99% until 1996, and has thereafter remained relatively constant. This reduction is mainly attributed to the introduction of effective vaccines in salmonids.

In 2010, 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 2010, the overall sales of antibacterials for systemic use in humans was 19.7 DDD/1,000 inhabitants/day. The total consumption has been relatively stable over many years, although there has been a gradual shift among the various subgroups. From 2004, the total consumption of antibiotics has increased steadily. Since 2007 the sales have been stable.

Sales of penicillins and quinolones are increasing, while sales of sulfonamides and trimethoprim drop. From 2009 to 2010 an increase in macrolides and tetracyclines has been observed while sales of cephalosporins have decreased. The use of the urinary antiseptic agent methenamine still increases and, in 2010, accounted for 17% of total sales, measured in DDDs.

In 2010, 43% of the total antibiotic human use, measured in DDDs, was penicillins. As in 2009, an increase in the use of penicillins with extended specter and beta-lactamase resistant penicillins was observed, and, moreover, a decrease in the use of beta-lactamase sensitive penicillins. Tetracyclines accounted for 16% of total consumption in 2010. The consumption of macrolides and lincosamides accounted for 10% of total sales. Sales of cephalosporins, monobactams and carbapenems constitute 3% of total sales. Over years, there has been a marked increase in quinolone use. This group accounted for only 4% of total consumption in 2010, but sales have more than doubled in 10 years.

The use of antibacterials varies according to gender, age and residence. Sales to hospitals and ambulatory care accounted for 7.5% and 84%, respectively. Penicillins accounted for around 45% of the sales to hospitals and 42% to ambulatory care. The main other groups in hospitals were cephalosporins (19%) and quinolones (7%), while in ambulatory care the most important other groups were tetracyclines (18%) and macrolides and lincosamides (11%).

Resistance in animal clinical isolates

Clinical isolates of *S. aureus* from cattle with mastitis were included in the survey. The prevalence of antimicrobial resistance was low. In total, 97.4% of *S. aureus* isolates were susceptible to all antimicrobial agents in the test panel. None of the isolates exhibited an increased tolerance to the disinfection agents tested for. Occurrence of resistant isolates has been low and stable over the last decade.

Enterococcus hirae was isolated from specimens collected in disease outbreaks in broiler production. Resistance to the coccidiostat narasin was detected in 27 of 41 isolates. Narasin is used as a feed additive, and this exposure represents a selection pressure for development of resistance.

During the period 2000 to 2009 a number of isolates of *Vibrio anguillarum* were obtained from disease outbreaks in farmed cod and salmon and submitted to susceptibility testing. As there are no breakpoints for this organism, the prevalence of resistance to antibiotics in the test panel could not be estimated.

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 2010, *E. coli* isolated from faecal samples from cattle and wild red fox (*Vulpes vulpes*) was included. For both animal species the prevalence of resistant *E. coli* was low and approximately 91% of the isolates were suceptible to all antimicrobials included in the test panel. In cattle, resistance to one of the antimicrobial agents was only identified in 4.8% of the isolates and most prevalent was resistance to streptomycin. Only few isolates were multi-resistant. In comparison with results from the last decade, the prevalence of resistant *E. coli* is low and stable. When screening for resistant *E. coli* in faecal samples from fox, resistant isolates were detected in eight of 88 animals. Of special concern was resistance to antimicrobial agents such as fluoroquinolones and gentamicin, indicating dissemination into the environment of resistance to critically important drugs.

Resistance in zoonotic and non-zoonotic enteropathogenic bacteria

In 2010, a total of 21 *Salmonella* spp. isolates from Norwegian animals were susceptibility tested.

The occurrence of resistance to tetracyclines, ampicillin and sulfonamides was observed in nearly one third of the examined isolates. One isolate showed resistance to fluoroquinolones. In spite of a low sample size, this indicates a possible increase of resistance, especially among *Salmonella* spp. from dogs.

Isolates of *S*. Typhimurium from diseased wild birds collected in the period 2006 to 2010 were tested for susceptibility to antimicrobial agents. All isolates were susceptible to the antimicrobials included in the test panel.

In a study including 323 faecal samples from cattle, *Campylobacter jejuni* was isolated from 11 animals. Ten isolates were susceptible to the antimicrobials included in the test panel. The sample size is too small to draw any conclusions about the status for this organism.

In 2010, 79.3% of the human cases of salmonellosis were reported as being infected abroad. Compared to 2009, there is a clear tendency that the domestically acquired *S.* Typhimurium strains are getting more resistant. The proportion of domestically acquired *S.* Typhimurium sensitive to all antibiotics tested fell from 57.3 % in 2009 to 35.1 % in 2010, and conversely, the proportion of multiresistant strains increased from 29.3% til 57.5%. This phenomenon may be caused by an increase in the proportion of the relatively resistant monophasic variant of *S.* Typhimurium (i. e *S. enterica* serovar 4,[5],12:i:-). The prevalence of resistance was considerably lower in *S.* Enteritidis isolates than in *S.* Typhimurium except for nalidixic acid. In total, 23.7% of *S.* Enteritidis isolates were resistant to nalidixic acid. The prevalence of resistance to ciprofloxacin was unchanged from 2009 to 2010.

The proportion of *C. jejuni* isolates aquired abroad that was susceptible to all antibiotics tested was unchanged from 2009, whereas for the domestically acquired isolates the proportion fell from 85.1% in 2009 to 61.9% in 2010.

Infections with *Yersinia enterocolitica* are typically obtained domestically, and the most common serotype is O:3. Resistance to chloramphenicol and trimethoprim-sulfamethoxazole was most frequently identified. In 2010, the majority of *Shigella* isolates were acquired outside Norway, and, as reported by other countries, antimicrobial resistance was commonly identified.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still very low in Norway in 2010. Only ten methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among the 1,005 strains included in the NORM protocol (1.0%), and 14 out of 1,426 (1.0%) *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 1,442 including 14 MRSA strains (1.0%). This prevalence is a slight increase from 2009 (0.5%), 2008 (0.7%) and 2007 (0.4%). The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 431 cases of MRSA infections in 2010 compared to 414 in 2009. A majority of the MRSA cases (82%) were reported to be wound infections and/or abscesses. Conversely, the prevalence of MRSA among non-invasive *S. aureus* isolates is still very low (6/937, 0.6%). Furthermore, MSIS registered 481 cases of MRSA colonisation compared to 402 in 2009 and 304 in 2008. The total number of MRSA notifications thus increased from 816 in 2009 to 912 in 2010 (+11.8%). The results indicate an increasing number of MRSA infections and colonisations, while the prevalence of invasive disease remains stable at a low level. It is an open question whether the increasing prevalence is due to changes in the epidemiology of MRSA or improved diagnostic practices. The prevalence of resistance to fusidic acid among *S. aureus* wound isolates continued to decrease from 14.5% in 2006 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 5.2% in 2010. This is an increase from 4.0% in 2009, and it should be considered whether aminoglycosides are still suitable for empirical treatment of septicaemia of unknown origin. The increasing prevalence of *E. coli* non-susceptibility to fluoroquinolones from 3.3% in 2004 to 8.6% in 2009 was reversed to 7.7% in 2010. 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 aminoglycosides and fluoroquinolones was lower in *Klebsiella* spp. isolates than in *E. coli*.

Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, and occasional cases have also been reported from Norway. A total of 41/1,359 (3.0%) *E. coli* and 9/599 (1.5%) *Klebsiella* spp. blood culture isolates were reported with this phenotype. For *E. coli*, this is an increase from 2009 (2.5%). The prevalence of ESBL production in *Klebsiella* spp. decreased from 2.6% in 2009 to 1.5% in 2010. 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 (3.0%) than among urinary tract isolates (1.4%). The first case in Norway of an *E. coli* strain containing a New Dehli-1 (NDM-1) carbapenease was found in 2010.

Only a single isolate with clinically significant vancomycin resistance was detected in enterococci in 2010. The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilized around 80%, and high-level gentamicin resistance (HLGR) was detected in 29.9% of *E. faecalis* and 47.3% of *E. faecium*. Virtually all (70 out of 71) 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. Twenty-two out of 730 isolates (3.0%) displayed reduced susceptibility to penicillin G, and only three isolate were also non-susceptible to cefalosporins. The proportion of penicillin non-susceptible isolates was on the same level as in 2009 (2.9%). The prevalence of macrolide resistance among pneumococcal blood culture isolates continued to decrease from a peak of 12.4% in 2006 to 4.0% in 2010. This reduction may be due to the conjugated pneumococcal vaccine which was introduced into the childhood vaccination programme in July 2006.

Pseudomonas aeruginosa blood culture isolates were generally susceptible to all relevant antimicrobials, but a total of 19% displayed some sort of acquired resistance. A few individual isolates were resistant to practically all antibiotics used for treatment of invasive *P. aeruginosa* infections.

The increasing prevalence of resistance in *Neisseria gonorrhoeae* has been a global health problem over many years. The epidemiology in Norway reflects the international situation. The prevalence of beta-lactamase production (28.4%) and reduced susceptibility to penicillin G (97.7%) precludes the use of this substance for treatment of gonorrhoeae. Resistance to ciprofloxacin (61.1%) is similarly so widespread that the empirical regimen in Norway now must be changed. Apparently, the prevalence of reduced susceptibility to cephalosporins is also increasing thus necessitating increased dosing to ensure clinical efficacy.

A total of 342 cases of tuberculosis were reported to MSIS in 2010. Susceptibility tests were performed on 277 *Mycobacterium tuberculosis* primary isolates. Only nine isolates, originating from Africa (n=3), Asia (n=2) and Europe outside Norway (n=4), were classified as multidrug-resistant (MDR).

Susceptibility testing was performed on 165 blood culture isolates of *Candida albicans* (n=112), *C. glabrata* (n=34), *C. tropicals* (n=12) and *C. parapsilosis* (n=7). All *C. albicans* isolates were susceptible to amphotericin B, fluconazole, voriconazole, caspofungin and micafungin, while two isolates were resistant to anidulafungin. A high prevalence of resistance to fluconazole and voriconazole was detected in *C. glabrata* isolates. Amphotericin B and the echinocandins were 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 2010, but the HIV data have as yet not been analysed. The 2010/2011 influenza season was dominated by influenza B with a certain proportion of pandemic influenza A(H1N1). Pandemic influenza A(H1N1) was, as previously, uniformly resistant to M2 blockers, and a few isolates with mutations encoding reduced susceptibility to oseltamivir were also detected. 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 succeeded. 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, 2011.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	308,826	158,452	150,374
5 to 14 years	612,883	313,608	299,275
15 to 24 years	642,640	329,377	313,263
25 to 44 years	1 359,107	694,431	664,676
45 to 64 years	1 254,606	639,044	615,562
65 years and older	742,243	325,937	416,306
All age groups	4 920,305	2 460,849	2 459,456

TABLE 2. Livestock population in Norway in 2010.
Data provided by the Register of Production Subsidies as of 31 July, 2010.

	Number* of	
Animal category	Herds	Animals
Cattle	16,800	872,100
Dairy cows only**	10,200	213,800
Suckling cow only**	4,200	61,500
Combined production (cow)**	950	32,100
Goat	1,300	67,600
Dairy goat**	400	36,900
Sheep	14,800	2 296,900
Breeding sheep > 1 year**	14,600	887,600
Swine	2,400	846,700
Breeding animal > 6 months**	1,400	57,800
Fattening pigs for slaughter**	2,200	461,400
Poultry		
Egg laying hen (> 20 weeks of age)	1,800	3 830,800
Flocks > 250 birds**	660	3 808,900
Broiler	600	-
Turkey, ducks and geese for slaughter	120	363,200
Flocks > 25 birds**	50	362,600

* Numbers >100 rounded to the nearest ten, numbers > 1000 rounded to the nearest hundred.
** Included in above total.

TABLE 3. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2010. *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	927,876	54,448	21,240	492	1,610	1,930	10.3	2.1

[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 2010 was limited to 49 sheep and 24,600 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 1993-2010 are shown in Figure 1. The data are based on sales from drug wholesalers to Norwegian pharmacies (see Appendix 1) of veterinary antimicrobial agents for therapeutic use and includes pharmaceutical formulations approved for food producing animals, including horses, and companion animals. Thus, the figures represent national sales data for veterinary antimicrobial agents (see Appendix 1 for inclusion criteria).

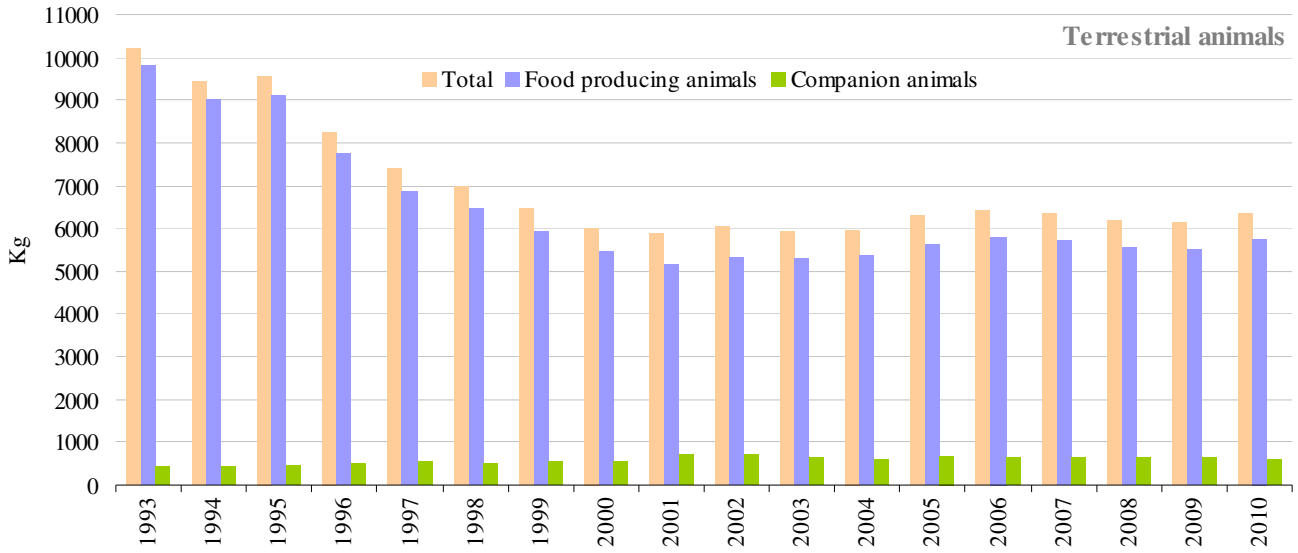

FIGURE 1. Total sales (kilograms active substance) and estimated sales for food producing animals and companion animals of antimicrobial veterinary medicinal products (VMP) for therapeutic in Norway for the years 1993-2010 (farmed fish not included)

In the period 1993-2010 the total sales of antimicrobial VMPs for use in terrestrial animals decreased by 38%. Of antimicrobial VMPs used almost solely for food production animals the reduction was 41%, while for products used in companion animal only an increase of 42% was observed (Figure 1).

An increase in the sales of penicillins is observed for the period 1993-2010 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 26% 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 approved for companion animals in 2001-2002 is probably due to some 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 medicines 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.

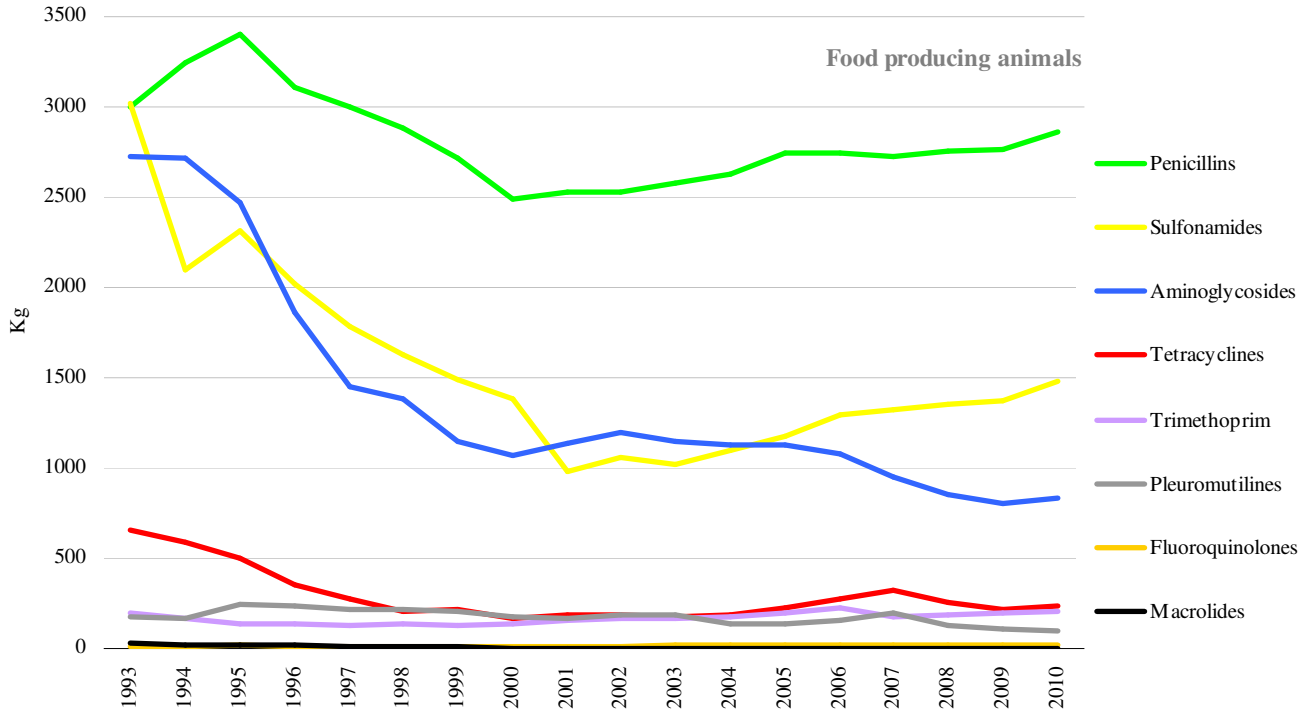

FIGURE 2. Sales in Norway (kilograms active substance) of antimicrobial veterinary medicinal products (VMP) for therapeutic mainly used in food producing animals for the years 1993-2010 (farmed fish not included). In addition, minor amounts of amphenicols, 19, 24 and 26 kg, were sold in 2008, 2009 and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

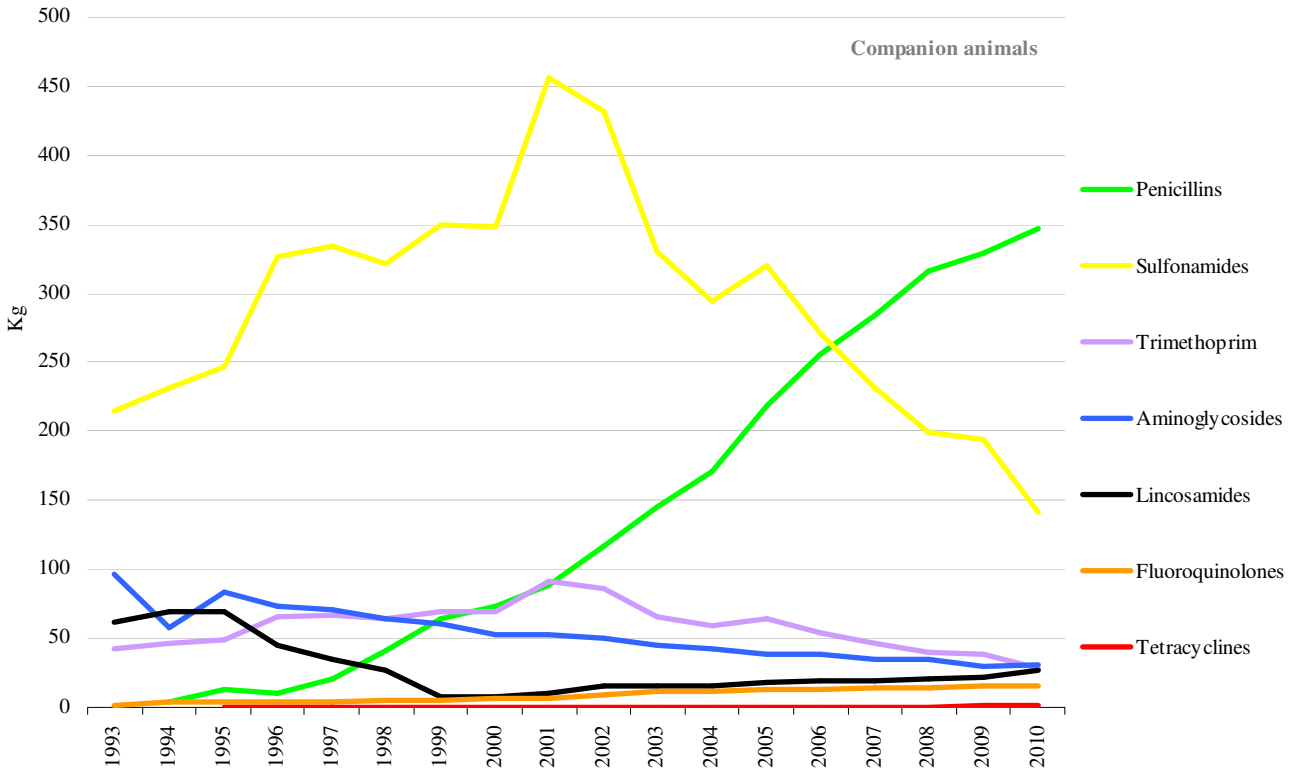

FIGURE 3. Sales in Norway (kilograms active substance) of antimicrobial veterinary medicinal products (VMP) marketed for therapeutic use in companion animals for the years 1993-2010. In addition, minor amounts of a 3rd generation cephalosporin (1 kg) were sold annually during 2008-2010.

An increase of 42% in the sales, in kg active substance, from 417 to 591 kg of antimicrobial VMPs marketed for companion animals from 1993-2010 is observed (Figure 3). This increase is mainly acoounted for by penicillins, and in 2010 approximately 88% of the penicillins sold for companion animals were the combination of amoxicillin and a beta-lactamase inhibitor (Figure 4).

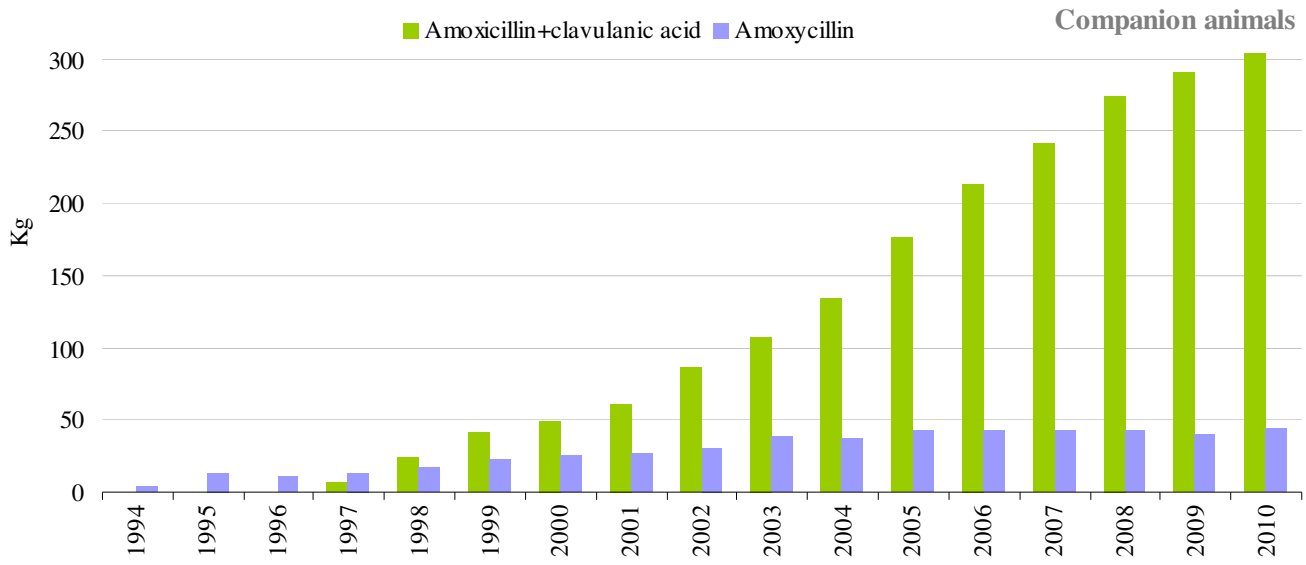

FIGURE 4. Sales (kg active substance) of penicillin veterinary medicinal products for companion animals during 1994-2010.

The annual sales of antimicrobial VMPs for use in farmed fish peaked in 1987 when the sales amounted to 48 tonnes (Figure 5). In 2010, the sales of antimicrobial VMPs for use in farmed fish were 649 kg active substance, of which 47% 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 in the period 1987 to 1996 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.

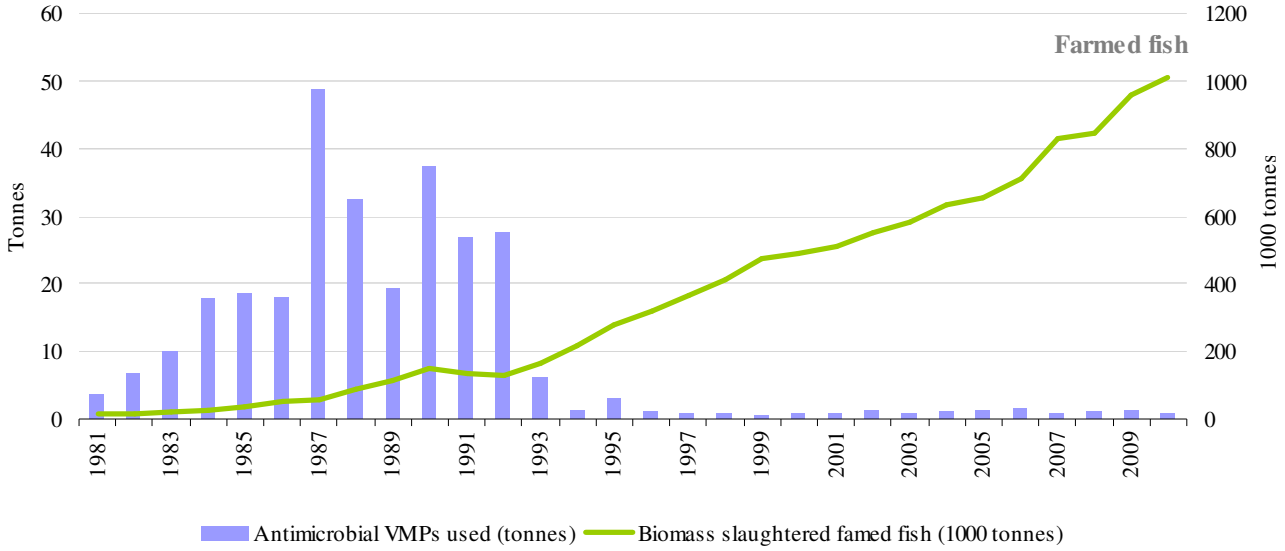

FIGURE 5. Total sales (kilograms of active substance) of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 1981-2010 versus produced biomass (live weight slaughtered) farmed fish. Preliminary data for 2010 for slaughtered biomass.

TABLE 4. Total sales (kilograms of active substance) of antimicrobial veterinary medicinal products (VMPs) for therapeutic use in farmed fish in Norway in the period 2000-2010.

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

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 (2003-2010).
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 (kilograms of active substance) of coccidiostats as feed additives in Norway 2000-2010. Data were obtained through annual reports from the Norwegian Agricultural Inspection Service (2000-2002) and the Norwegian Food Safety Authority (2003-2010).

Active substance	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Lasalocid	80	96	514	108	173	37	13	17	16	63	0
Monensin	776	629	521	717	817	852	889	919	897	885	95
Salinomycin	233	12	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
Total ionophore coccidiostats	**5,575**	**4,932**	**5,505**	**5,892**	**6,260**	**6,207**	**6,517**	**8,001**	**10,125**	**9,569**	**9,175**
Amprolium/etopabat	135	159	74	42	0.8	0	0	0	0	0	0
Total others	**135**	**159**	**74**	**42**	**0.8**	**0**	**0**	**0**	**0**	**0**	**0**

The total sales of ionophore coccidiostats (kilograms of active substance) have been doubled since the withdrawal on antimicrobial growth promoters in 1995 and has 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.

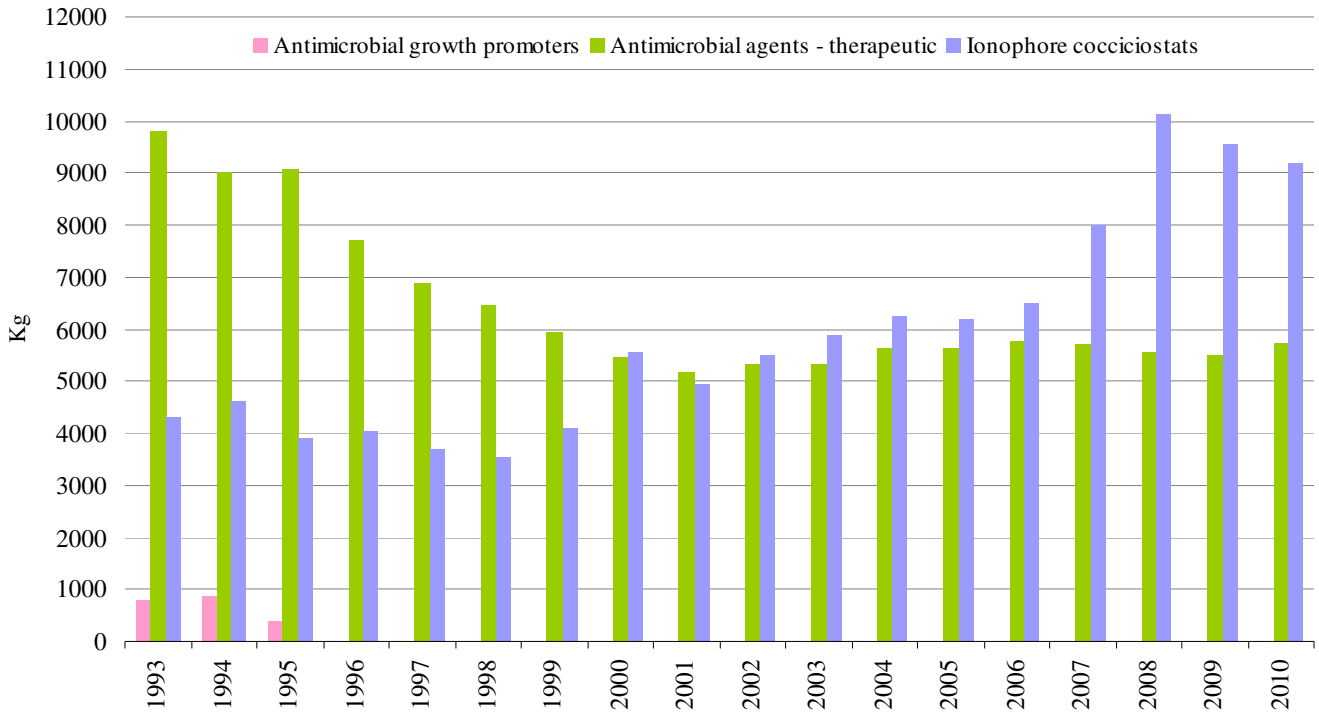

FIGURE 6. Sales (kg active substance) of antimicrobial veterinary medicinal products for food producing animals, antimicrobial growth promoters and ionophore coccidiostats in Norway during 1993-2010.

USAGE IN HUMANS

Hege Salvesen Blix

In 2010, the overall sales of antibacterials for systemic use in humans were 19.7 DDD/1,000 inhabitants/day. Since 2004, total sales of antibacterials have been increasing, mainly due to the penicillin group and to increased use of methenamine. In 2009, a decrease in antibiotic use was observed. When methenamine is excluded, the level of antibiotic use in 2010 was the same as in 2006.

The macrolides have increased over many years, but decreased in 2008 and 2009 by 7% and 11%, respectively. In 2010, however, an increase of 6% was seen. The use of quinolones is steadily increasing (Table 6, Figure 7).

TABLE 6. Human usage of antibacterial agents in Norway 2003-2010 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2009-2010. Collection methodology of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2003	2004	2005	2006	2007	2008	2009	2010	Change (%) 2009-2010
J01A	Tetracyclines	3.03	2.97	3.11	3.24	3.32	3.22	3.09	3.12	- 1
J01B	Amphenicols	0.002	0.001	0.001	0.002	0.001	0.001	0.002	0.001	-
J01CA	Penicillins with extended spectrum	2.29	2.37	2.53	2.74	2.93	3.09	3.15	3.19	+ 1
J01CE	Beta-lactamase sensitive penicillins	4.38	4.23	4.55	4.63	4.70	4.71	4.47	4.44	- 1
J01CF	Beta-lactamase resistant penicillins	0.59	0.63	0.56	0.66	0.72	0.77	0.80	0.82	+ 3
J01CR	Combination of penicillins	0.01	0.01	0.01	0.01	0.02	0.02	0.02	0.03	-
J01D	Cephalosporins, monobactams, carbapenems	0.62	0.61	0.57	0.60	0.60	0.60	0.58	0.55	- 5
J01E	Sulfonamides and trimethoprim	1.08	1.09	1.06	1.04	1.02	0.98	0.94	0.87	- 7
J01F	Macrolides, lincosamides and streptogramins	1.92	1.89	2.12	2.24	2.30	2.13	1.89	2.01	+ 6
J01G	Aminoglycosides	0.07	0.06	0.07	0.07	0.07	0.07	0.07	0.07	-
J01M	Quinolones	0.48	0.52	0.57	0.62	0.67	0.70	0.71	0.73	+ 3
J01X	Other antibacterials	2.63	2.83	3.05	3.18	3.30	3.48	3.65	3.84	+ 5
	Total exclusive of methenamine	**14.9**	**14.8**	**15.6**	**16.3**	**16.9**	**16.8**	**16.2**	**16.3**	**+ 1**
	Total all antimicrobial agents	**17.1**	**17.2**	**18.2**	**19.0**	**19.7**	**19.8**	**19.4**	**19.7**	**+ 2**

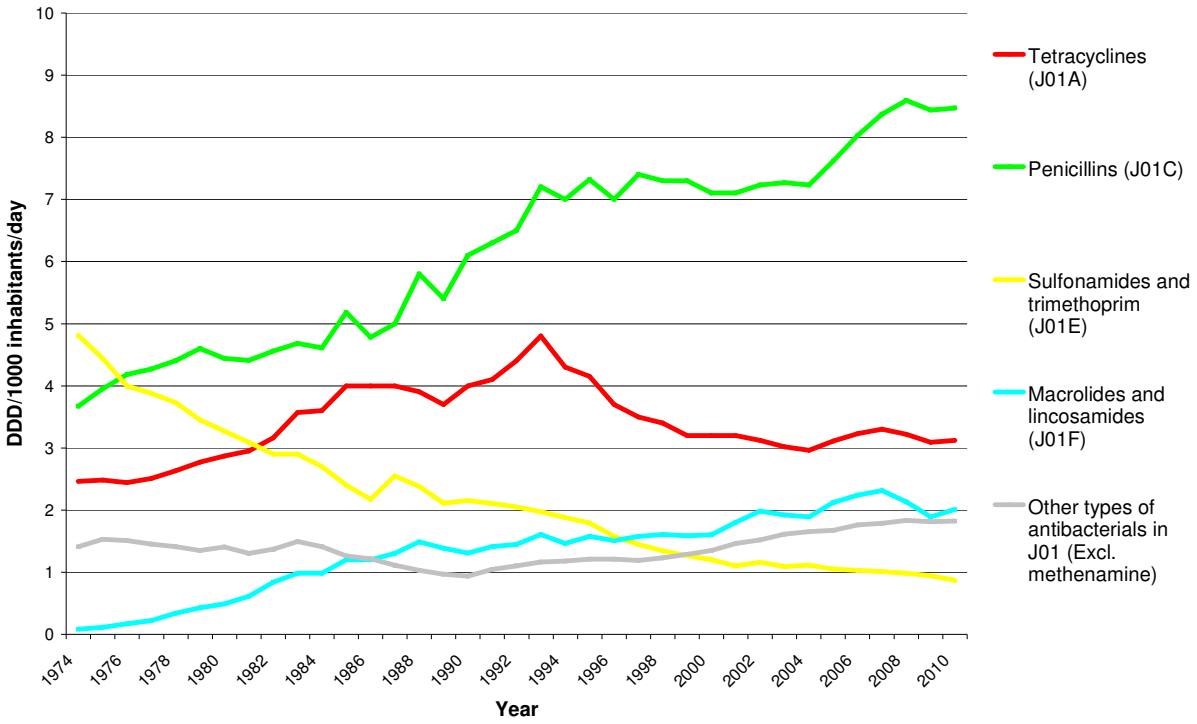

FIGURE 7. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E), and other antibacterials in Norway 1974-2010. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05).

In 2010, the penicillins (ATC group J01C) accounted for 43% 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 it has been a shift towards use of more broad-spectered penicillins. Penicillins with extended spectre (J01CA) now represent 38% of the penicillin group compared to 29% a decade ago (Figure 9). 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.

The tetracyclines (J01A) represent 16% of total use. The sales have been relatively stable over time.

The macrolides, lincosamides and streptogramins (J01F) accounted for 10% of total use in 2010. Although the use increased in 2010 compared to 2009, the level of use is now at the same level as in 2005. The internal pattern of group J01F has remained relatively unchanged over the years although erythromycin, which is most frequently used (47% of subgroup J01F), now seems to be less used (Figure 10).

In the latest years, sales of cephalosporins, monobactams and carbapenems have been stable; a small decrease was seen in 2010. This group represents 3% of the total sales of antibacterials. The internal subgroup pattern has changed since 1996 (Figure 11). First and 3rd generation cephalosporins hold 49% and 26% of ATC group J01D, respectively.

The use of quinolones is increasing. Still, they represent only a minor fraction (4%) of total antibacterial sales, but the sales have more than doubled since 2000.

The increase of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, accounting for 17% of total antibacterial use. The sales of methenamine have increased by 72% since 2000.

The usage of antibacterials vary among the 19 Norwegian counties, the county using the least is using 68% (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 2009-2010 in all counties except Buskerud, Hedmark and Oslo (Figure 12). However, compared to 2005, the use has increased in all counties by 0.2%-23%.

Antibacterials are prescription-only drugs in Norway. Eighty-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%).

In ambulatory care, the most important antibiotic groups in 2010 were penicillins (J01C, 42% of DDDs), tetracyclins (J01A, 18%) and macrolides and lincosamides (J01F, 11%).

Females use more antibiotics than males. Twenty-nine percent of females purchased at least one antibiotic course in 2010 compared to 20% of males. The gender pattern is seen in all regions of the country (Figure 13). The highest use is found among young children, young adults, and the elderly (Figure 14).

In 2010, the antibacterial sales (in DDDs) to hospitals represented 7.5% 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 15). Penicillins (J01C) represent around 45% of the use measured in DDDs in hospitals (J01CE 19%, J01CA 16% and J01CF 9%). The second largest group is the cephalosporins; 19% of all DDDs, the dominant subgroup being 3rd generation cephalosporins (J01DD) (9%). In 2010, three substances accounted for 28% of all antibacterial use in hospitals; benzylpenicillin (14%), cefotaxime (7%) and ciprofloxacin (7%).

Updated National Guidelines for antibiotic use are available for ambulatory care and nursing homes, but not for hospitals (latest national version 2001). The Antibiotics Center for Primary Health Care was established in 2006, and a national centre for antibiotic use in hospitals was appointed in 2010. These centres will, among other tasks, be responsible for updating national guidelines and hopefully have a positive impact on antibacterial prescribing practices in Norway.

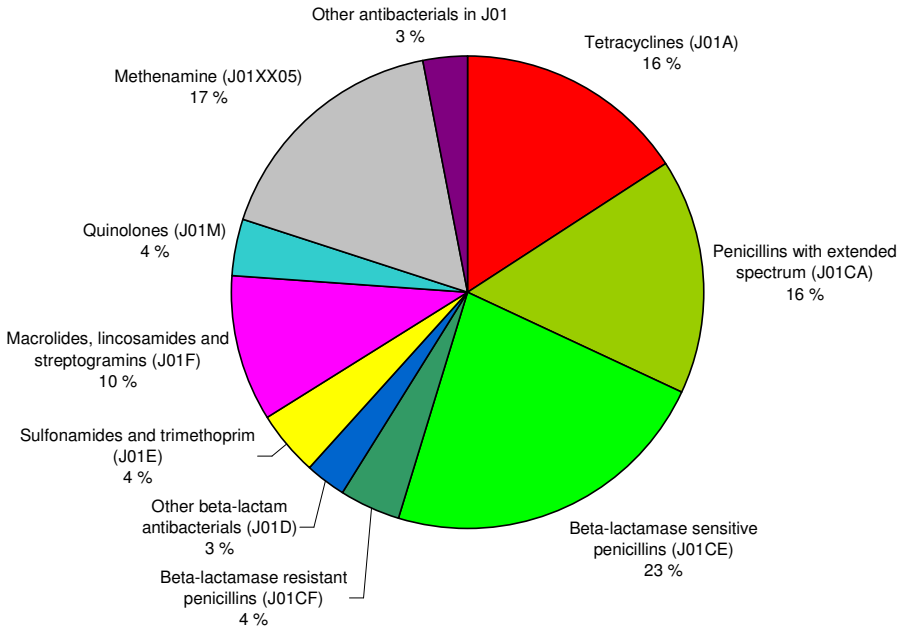

FIGURE 8. Relative amount of antibacterial agents for systemic use in 2010 in Defined Daily Doses (DDD).

TABLE 7. 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	2002	2003	2004	2005	2006	2007	2008	2009	2010
A07A A09	Vancomycin	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
J01A A02	Doxycycline	2.03	1.93	1.80	1.89	1.97	2.0	1.9	1.78	1.83
J01A A04	Lymecycline	0.26	0.30	0.34	0.39	0.45	0.51	0.52	0.54	0.59
J01A A06	Oxytetracycline	0.21	0.19	0.20	0.20	0.19	0.18	0.17	0.16	0.15
J01A A07	Tetracycline	0.62	0.60	0.62	0.64	0.63	0.63	0.62	0.60	0.54
J01AA07*	Minocycline				0.0003	0.0003	0.0001	0.0002	0.0003	0.001
J01AA12	Tigecycline					0.0001	0.0002	0.0004	0.0005	0.0004
J01B A01	Chloramphenicol	0.002	0.002	0.001	0.002	0.002	0.001	0.001	0.002	0.0007
J01C A01	Ampicillin	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.09
J01C A02*	Pivampicillin	0.11	0.09	0.08	0.07	0.06	0.01			
J01C A04	Amoxicillin	0.94	0.95	0.94	1.06	1.11	1.26	1.34	1.31	1.34
J01C A08	Pivmecillinam	1.09	1.14	1.25	1.29	1.46	1.55	1.65	1.72	1.75
J01C A11*	Mecillinam	0.005	0.005	0.005	0.006	0.006	0.006	0.008	0.008	0.008
J01C E01	Benzylpenicillin	0.24	0.25	0.24	0.26	0.26	0.25	0.24	0.28	0.22
J01C E02	Phenoxymethylpenicillin	4.24	4.13	3.99	4.29	4.37	4.45	4.46	4.19	4.22
J01C E08*	Benzathine benzylpenicillin	0.0001	0.0001	0.0002	0.0001	0.0002	0.0001	0.0001	0.0002	0.0002
J01C F01	Dicloxacillin	0.39	0.48	0.51	0.41	0.54	0.61	0.64	0.67	0.70
J01C F02	Cloxacillin	0.11	0.11	0.11	0.15	0.12	0.12	0.13	0.13	0.12
J01C F05*	Flucloxacillin	0.0001	0.0002	0.0002	0.0001	0.0001	0.0003	0.0005	0.0007	0.0005
J01C R02*	Amoxicillin and enzyme inhibitor	0.01	0.01	0.0003	0.0000	0.0001	0.0001	0.0012	0.003	0.003
J01C R05	Piperacillin and enzyme inhibitor	0.0014	0.0024	0.005	0.01	0.01	0.02	0.02	0.02	0.02
J01D B01	Cefalexin	0.29	0.3	0.29	0.24	0.26	0.25	0.23	0.21	0.20
J01D B03	Cefalotin	0.05	0.06	0.06	0.06	0.06	0.07	0.07	0.07	0.07
J01D B04*	Cefazolin				0.002	0.002	0.001	0.001		
J01D C01*	Cefoxitin	0.0002	0.0001							
J01D C02	Cefuroxim	0.15	0.15	0.14	0.13	0.12	0.12	0.11	0.10	0.09
J01D D01	Cefotaxim	0.05	0.07	0.07	0.08	0.09	0.09	0.10	0.11	0.11
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	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02
J01D F01	Aztreonam	0.001	0.001	0.001	0.0005	0.0008	0.0008	0.0007	0.0006	0.0006
J01D H02	Meropenem	0.017	0.02	0.02	0.026	0.031	0.035	0.037	0.042	0.041
J01D H03	Ertapenem					0.000	0.001	0.001	0.002	0.002
J01D H51	Imipenem and enzyme inhibitor	0.005	0.006	0.005	0.005	0.004	0.004	0.003	0.002	0.002
J01E A01	Trimethoprim	0.8	0.74	0.76	0.73	0.70	0.68	0.64	0.60	0.56
J01E E01	Sulfamethoxazol and trimethoprim	0.36	0.34	0.34	0.33	0.34	0.34	0.34	0.33	0.31
J01F A01	Erythromycin	1.2	1.09	1.03	1.16	1.24	1.21	1.08	0.92	0.94
J01F A02	Spiramycin	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01F A09	Clarithromycin	0.36	0.37	0.37	0.39	0.40	0.43	0.37	0.31	0.34
J01F A10	Azithromycin	0.24	0.26	0.28	0.32	0.34	0.39	0.38	0.37	0.41
J01FA15*	Telithromycin	0.0001	0.0003	0.0003						
J01F F01	Clindamycin	0.16	0.19	0.20	0.23	0.25	0.26	0.28	0.28	0.31
J01GA01*	Streptomycin	0.0015	0.0004	0.0004	0.0002	0.0003	0.0002	0.0003	0.0002	0.0002
J01G B01	Tobramycin	0.04	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03

ATC	Substance	2002	2003	2004	2005	2006	2007	2008	2009	2010
J01G B03	Gentamicin	0.02	0.03	0.03	0.03	0.04	0.04	0.04	0.04	0.04
J01G B06*	Amikacin	0.0009	0.0008	0.0003	0.0004	0.0009	0.0003	0.0007	0.0008	0.0009
J01G B07*	Netilmicin	0.007				0.0001				
J01M A01	Ofloxacin	0.05	0.05	0.05	0.05	0.04	0.04	0.04	0.03	0.03
J01M A02	Ciprofloxacin	0.38	0.42	0.47	0.52	0.57	0.62	0.66	0.67	0.70
J01MA12*	Levofloxacin	0.001	0.0003		0.0003	0.0003	0.0008	0.0008	0.004	0.003
J01MA14*	Moxifloxacin						0.0007	0.001	0.001	0.004
J01X A01	Vancomycin	0.006	0.006	0.007	0.007	0.008	0.01	0.01	0.01	0.01
J01X A02	Teicoplanin	0.0013	0.0009	0.0007	0.0008	0.0008	0.0007	0.001	0.0007	0.0008
J01X B01*	Colistin	0.003	0.002	0.003	0.004	0.005	0.004	0.004	0.005	0.004
J01X C01	Fusidic acid	0.01	0.007	0.008	0.006	0.006	0.006	0.006	0.005	0.004
J01X D01	Metronidazole	0.07	0.07	0.08	0.08	0.07	0.07	0.07	0.07	0.07
J01X E01	Nitrofurantoin	0.35	0.35	0.36	0.36	0.37	0.36	0.36	0.36	0.37
J01X X05	Methenamin	2.13	2.18	2.37	2.59	2.71	2.84	3.02	3.19	3.37
J01XX08	Linezolid	0.002	0.004	0.006	0.007	0.006	0.006	0.007	0.008	0.009
J01XX09	Daptomycin						0.000	0.000	0.000	0.0001
D06AX09/ R01AX06*	Mupirocin in kg ointment/cream (2%)	1.3	3.0	3.0	3.4	4.3	4.0	3.9	5.1	4.5
P01AB01	Metronidazole	0.19	0.19	0.20	0.20	0.20	0.21	0.21	0.22	0.23
J04AB**	Rifampicin	0.043	0.049	0.068	0.077	0.082	0.092	0.092	0.127	0.126

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

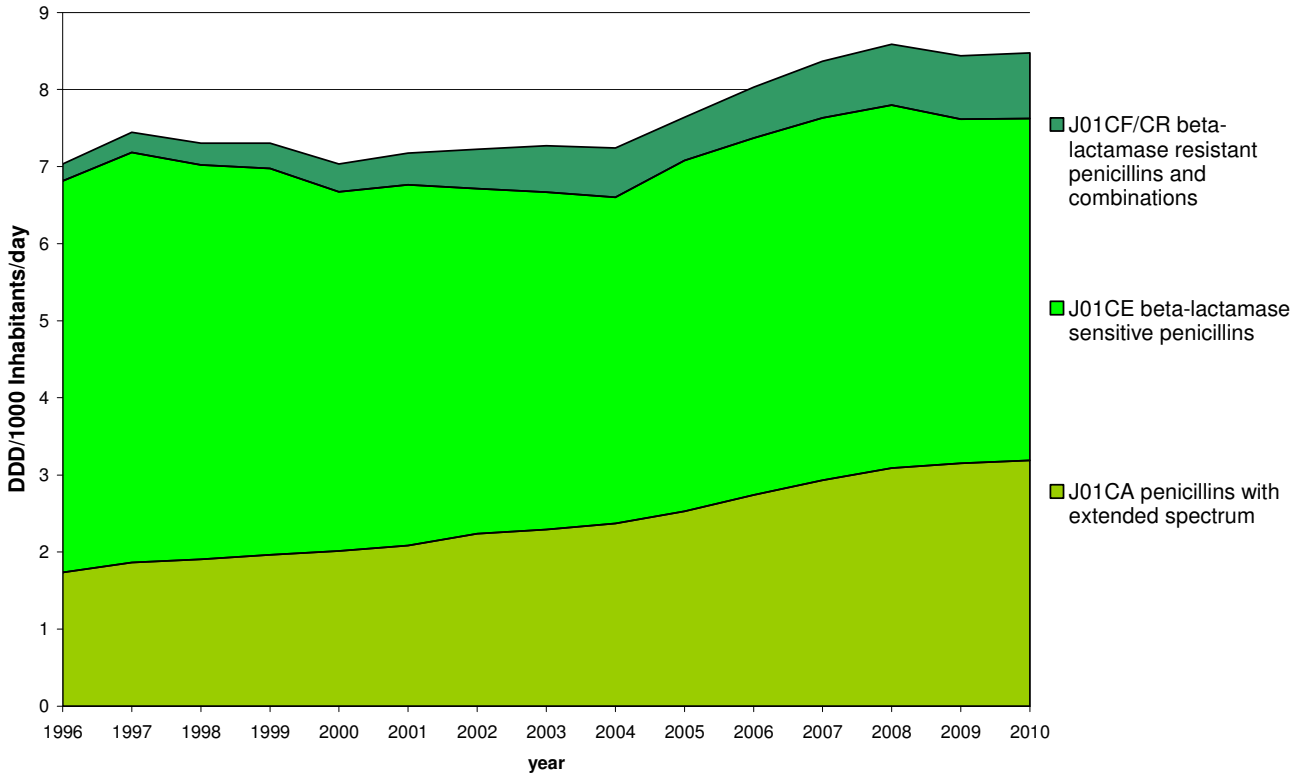

FIGURE 9. Sales of penicillins (J01C) in Norway 1996-2010 and changes within groups of penicillins.

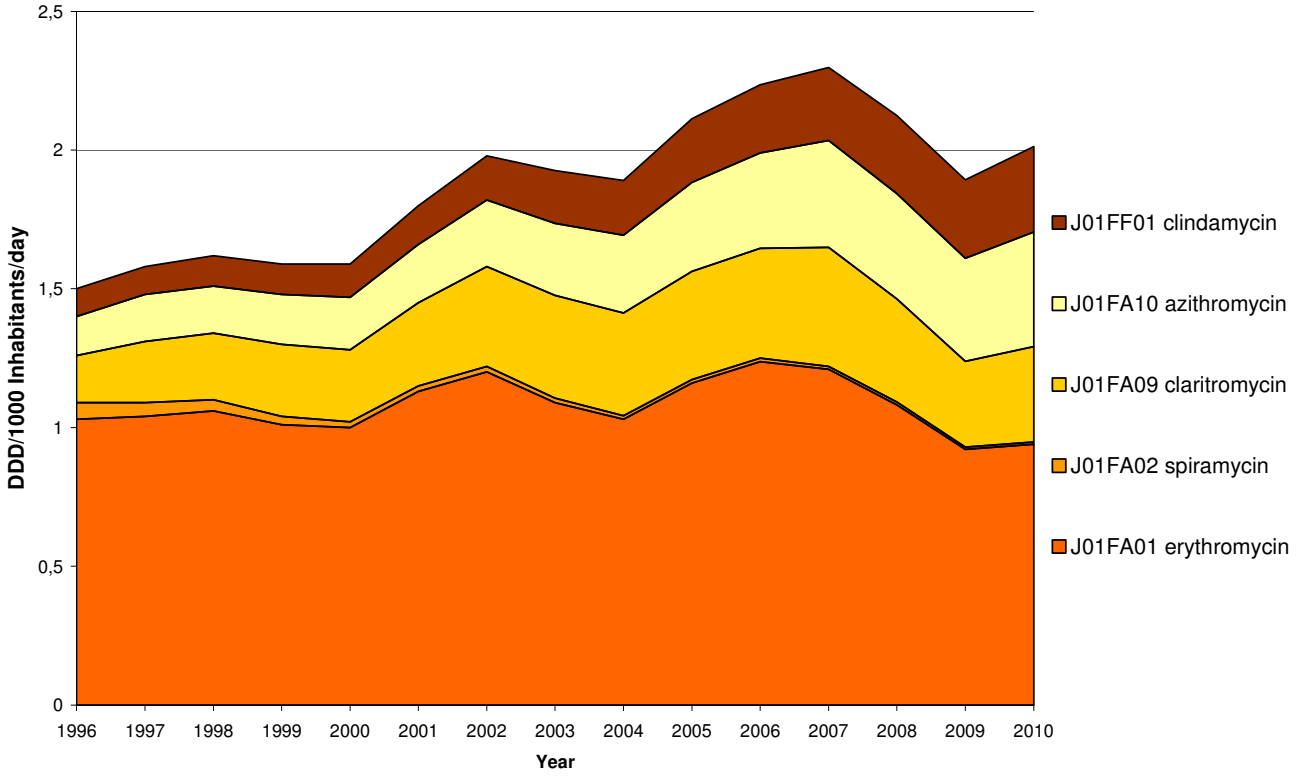

FIGURE 10. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1996-2010.

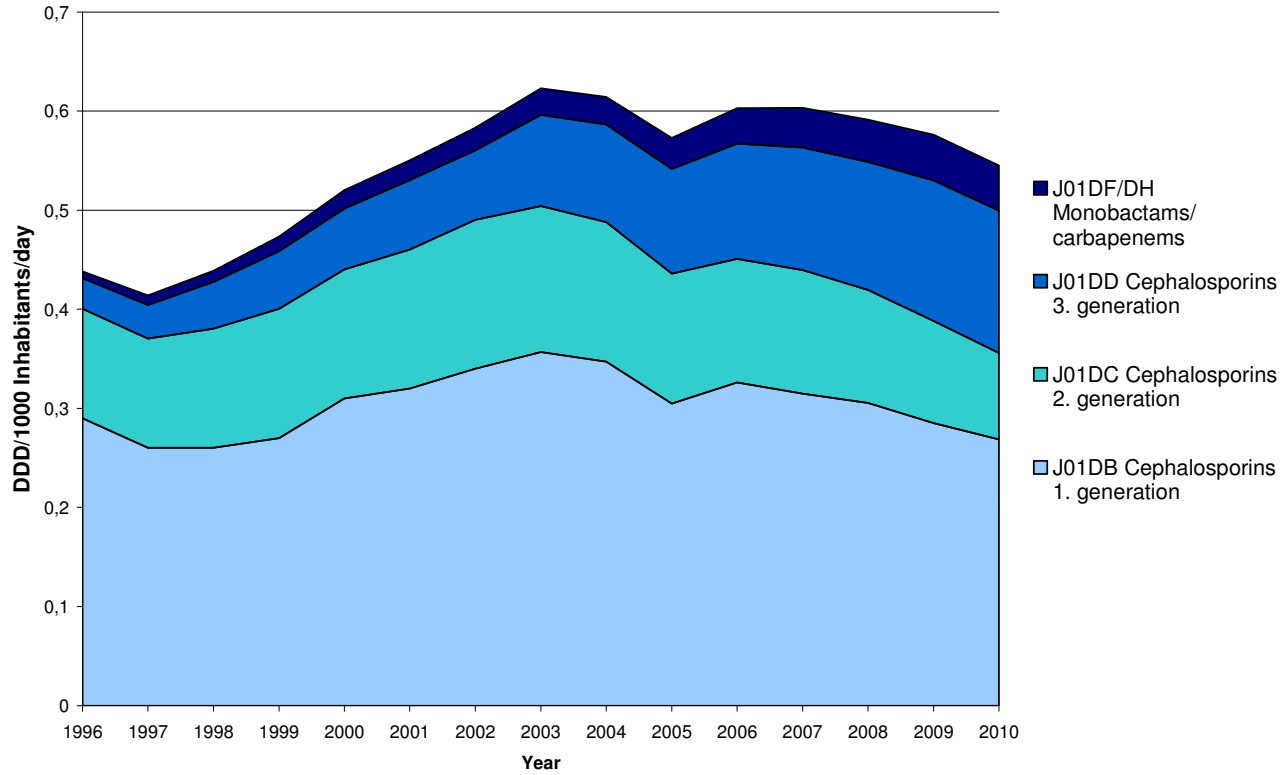

FIGURE 11. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2010 and changes between generations of cephalosporins and monobactams/carbapenems.

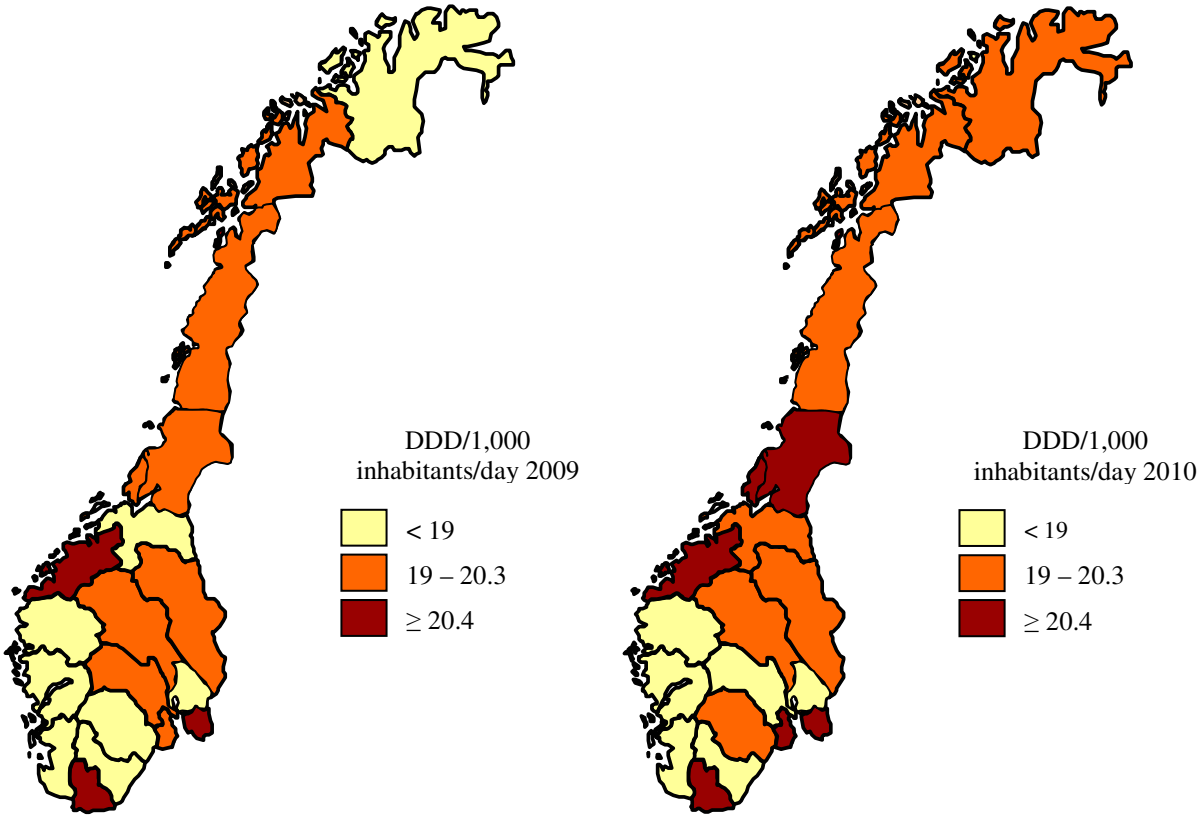

FIGURE 12. Sales of antibacterial agents for systemic use (ATC group J01) in the different counties of Norway in 2009 and 2010.

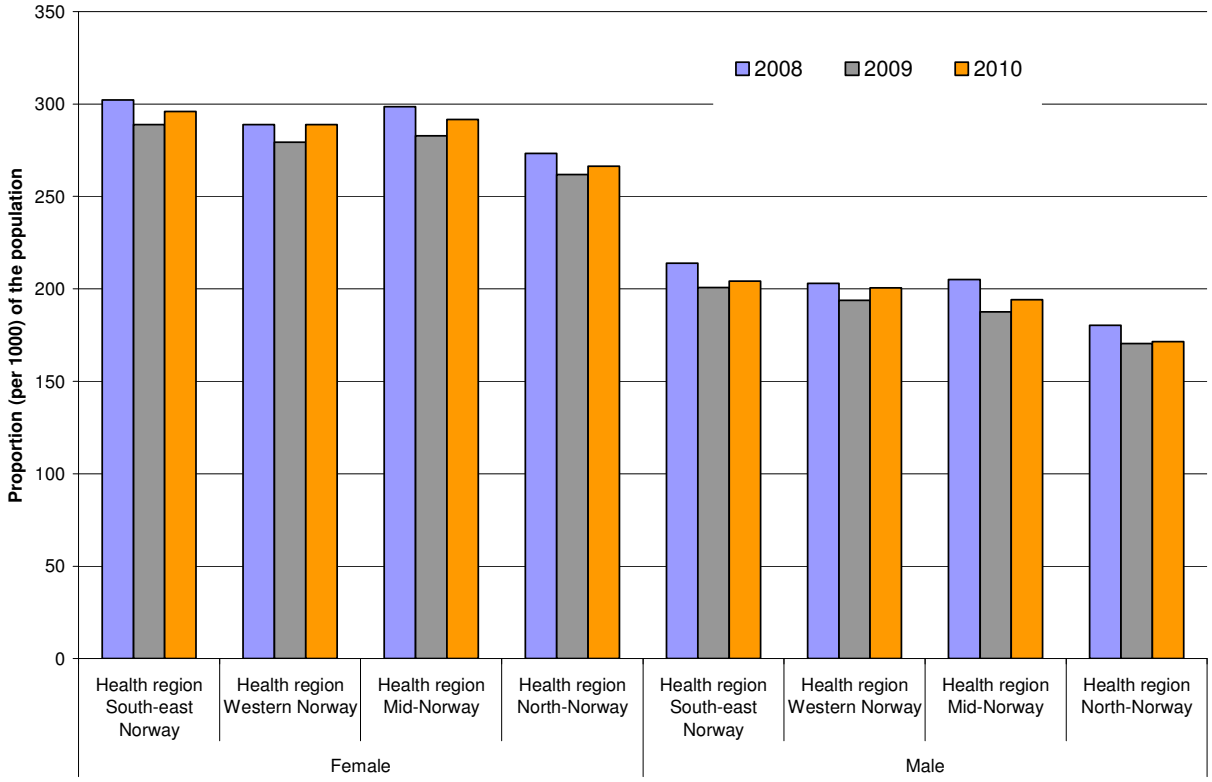

FIGURE 13. One year prevalence of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2008, 2009 and 2010. Antibacterials for systemic use include ATC group J01, oral vancomycin (A07AA09) and oral metronidazole (P01AB01).

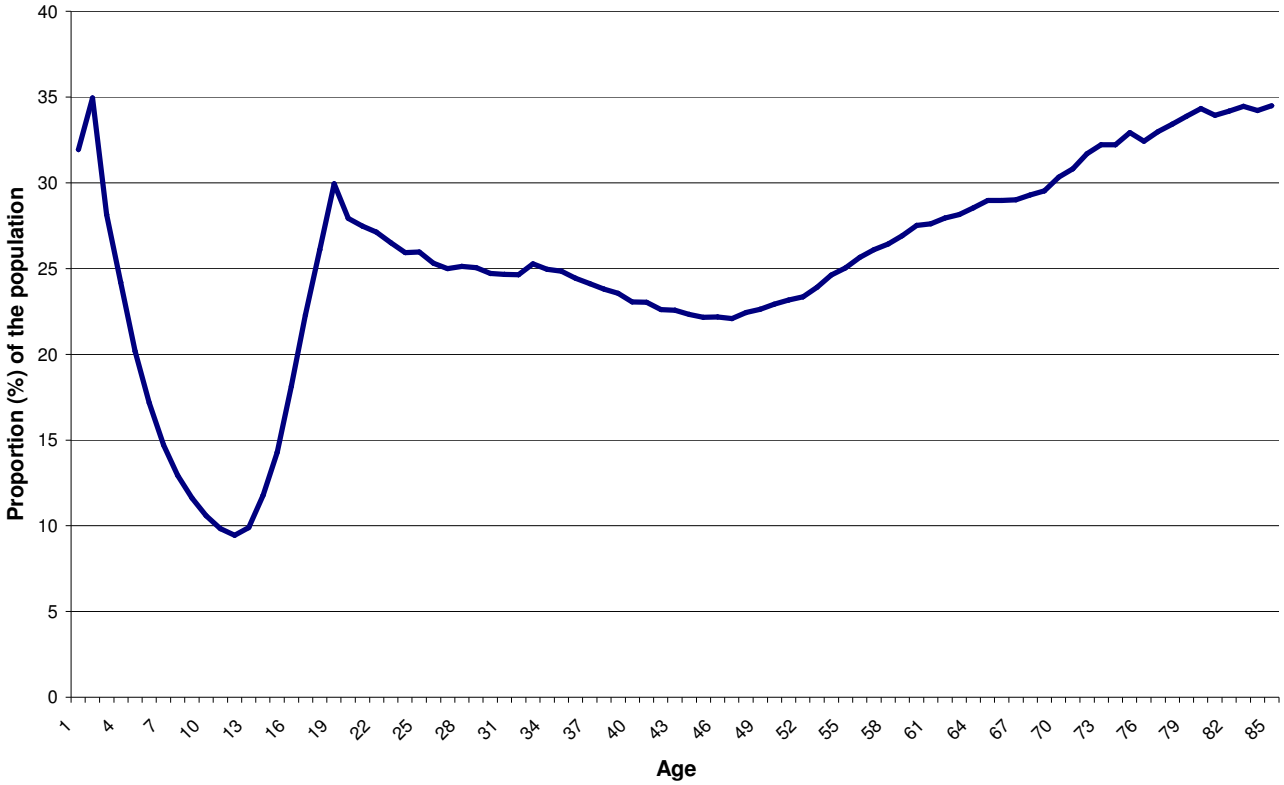

FIGURE 14. One year prevalence (%) of antibacterial use in ambulatory care by age (from 1 year to 85+ years) in Norway in 2010. Antibacterials included are antibacterials for systemic use (ATC group J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01).

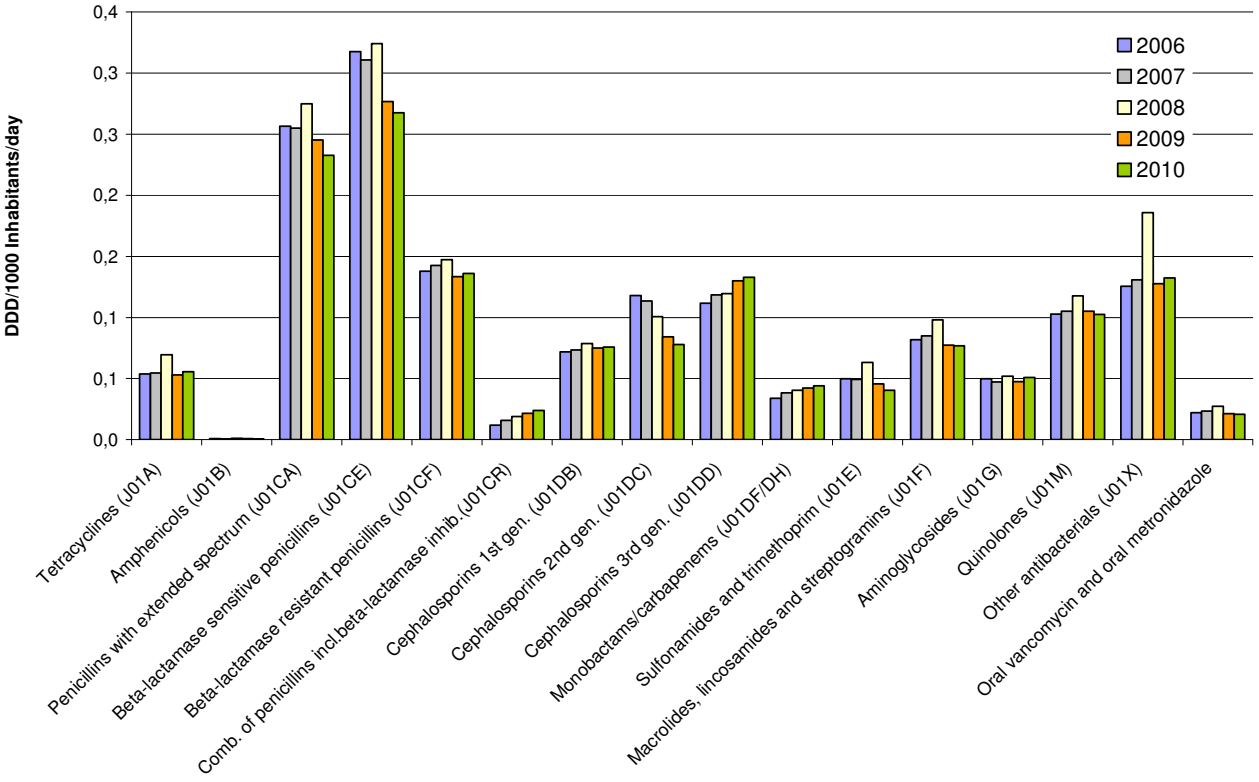

FIGURE 15. Proportions of antibacterial agents for systemic use in Norwegian hospitals 2006 – 2010, measured in DDD/1,000 inhabitants/day.

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

In 2010, the overall sales in Norway of antibacterials for use in humans, terrestrial animals and farmed fish measured in weight of active substance were 55.5 tonnes (Figure 16 and Table 8). Human use accounted for 87.6% of total use, terrestrial animal use for 11.3% and use in aquaculture only 1.2%. The increase of 12% from 2005 to 2010 was solely caused by increased use in humans and is due to an increased population in this period. When excluding methenamine, the 5 year increase was 6% (from 41.0 tons in 2005 to 43.5 tons in 2010).

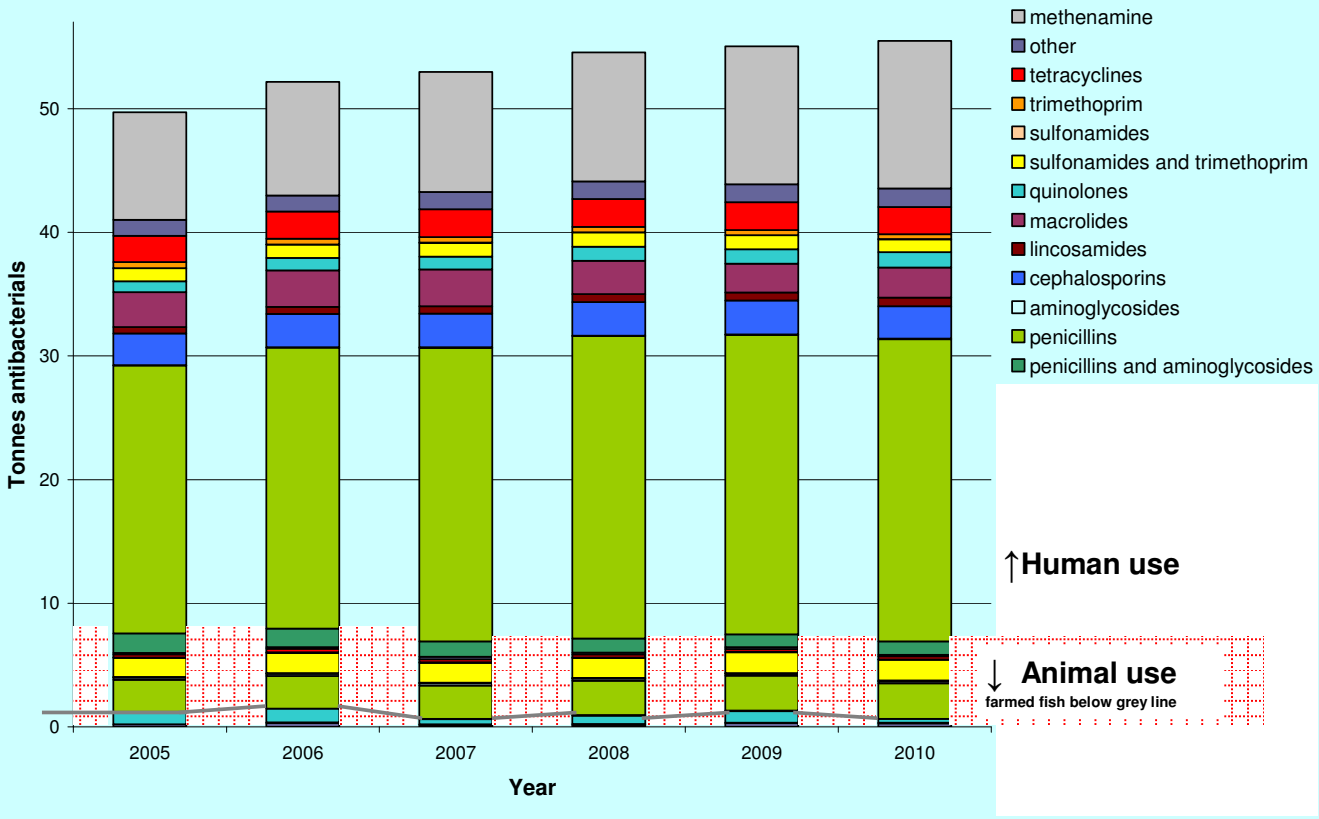

FIGURE 16. Sales, in tonnes of active substance, of human and veterinary antibacterials, for the years 2005-2010. Use in farmed fish is included and appears below the grey line.

According to Table 8, 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 8. Sales, in kilograms of active substance, of human and veterinary antibacterials according to formulation in 2010.

Preparation	Human use	Animal use	Acquaculture
Dermal	105	3	
Oral	43,153	2,389	
Parenteral	5233	3,194	
Eye / ear	39	10	
Intramammarian	49	143	
Others	0	507	649
Total	48,578	6,246	649

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VI. OCCURRENCE OF ANTIMICROBIAL RESISTANCE

A. ANIMAL CLINICAL ISOLATES

Madelaine Norström, Marianne Sunde, Arve Lund

Staphylococcus aures from bovine mastitis

A total of 195 isolates of *Staphylococcus aureus* from clinical mastitis in cattle were susceptibility tested. Additionally, all isolates were tested for an increased tolerance to disinfection agents. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Table 9, Figures 17-18, and in the text.

TABLE 9. Antimicrobial resistance in *Staphylococcus aureus* from bovine mastitis (n=195) in 2010.

	Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	[95% CI*]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	0	[0.0-1.9]				0.5	94.9	4.6									
Chloramphenicol	0	[0.0-1.9]							1.5	75.4	23.1						
Penicillin G**	2.1	[0.5-5.2]	15.4	66.7	14.9	1.0	0.5	0.5		1.0							
Oxacillin***	0	[0.0-1.9]			3.6	28.2	44.1	23.1	1.0								
Cephalothin	0	[0.0-1.9]			6.7	37.9	53.8	1.5									
Trimethoprim	0	[0.0-1.9]					0.5	4.1	39.0	55.9	0.5						
Erythromycin	0	[0.0-1.9]				22.1	75.9	2.1									
Clindamycin	0	[0.0-1.9]				96.4	3.6										
Gentamicin	0	[0.0-1.9]					95.9	4.1									
Kanamycin	0	[0.0-1.9]				7.7	54.9	31.3	5.1	1.0							
Ciprofloxacin	0	[0.0-1.9]		2.6	76.4	20.5	0.5										
Fusidic acid	1.0	[0.1-3.7]		1.5	25.6	61.0	10.8	0.5			0.5						

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. *CI = Confidence interval. ** Classification of resistance to penicillin G was based on beta-lactamase production. All isolates with a positive beta-lactamase test had a MIC-value > 0.125 mg/L, and all beta-lactamase negative isolates had a MIC-value ≤ 0.25 mg/L. *** Resistance to methicillin was investigated using cefoxitin disk diffusion test.

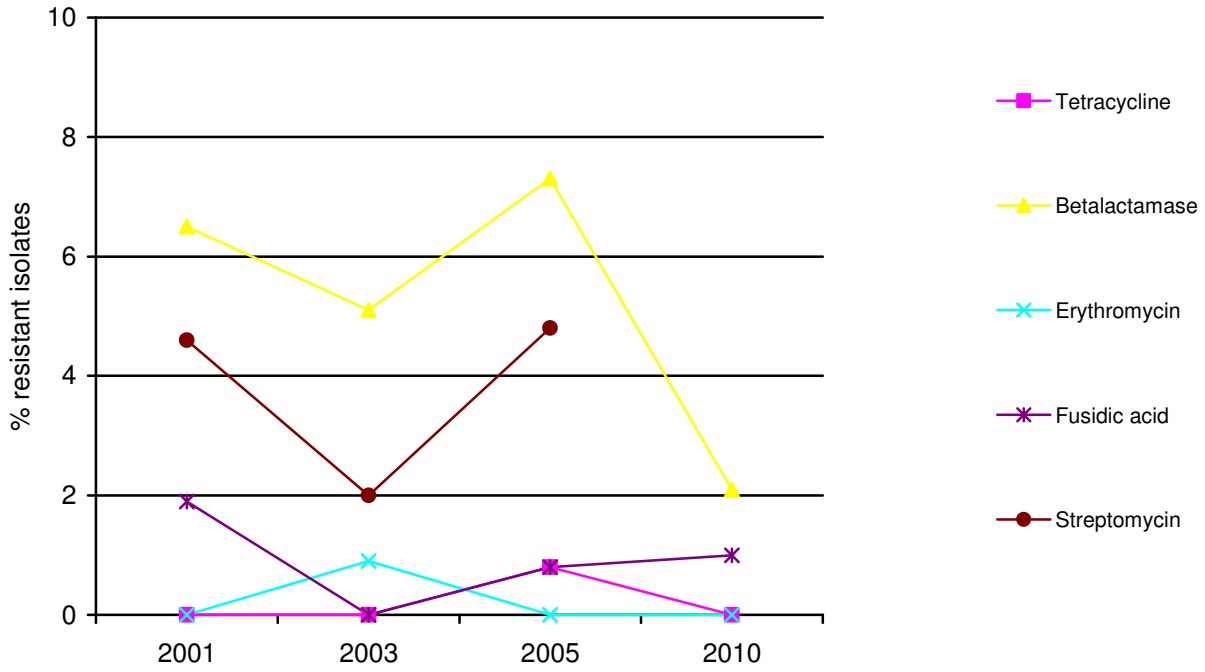

FIGURE 17. Prevalence of resistance to various antimicrobials in *Staphylococcus aureus* from bovine clinical mastitis isolates examined in 2001, 2003, 2005 and 2010. The breakpoints in NORM-VET 2010 were applied.

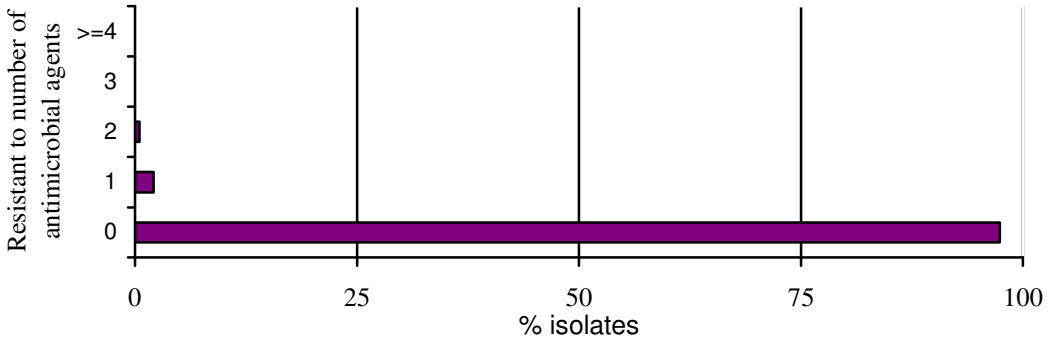

FIGURE 18. Antimicrobial resistance profile for *Staphylococcus aureus* from bovine mastitis (n=195) in 2010. Proportions of isolates susceptible to all or resistant to one, two and three or more antimicrobial agents are illustrated.

RESULTS AND COMMENTS

The occurrence of resistance among *S. aureus* isolates from bovine mastitis was low. In total, 97.4% of the isolates were susceptible to all antimicrobial agents included. Resistance to one antimicrobial agent (penicillin or fusidic acid) occurred in 2.1% of the isolates, and 0.5% were resistant to two (penicillin and fusidic acid) (Figure 18). Methicillin resistance was not detected. None of the isolates exhibited increased tolerance to disinfection agents. Penicillin and streptomycin are among the most commonly used antimicrobial agents for clinical purposes in cattle. Occurrence of resistance among *S. aureus* isolates has remained at approximately the same low level during the last decade (Figure 17). Guidelines and sustained focus on correct use among stakeholders are factors contributing to the favourable situation.

Enterococcus hirae from broiler

A total of 41 isolates of *Enterococcus hirae* from broiler samples were tested. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Table 10 and in the text.

TABLE 10. Antimicrobial resistance in *Enterococcus hirae* (n=41) from broiler in 2010.

		Distribution (n) 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	2		36	3				2							
Chloramphenicol	0				13	28									
Ampicillin	0		8	31	1	1									
Erythromycin	6		34		1						6				
Streptomycin	0								5	10	27				
Gentamicin	0					3	9	28	1						
Kanamycin	0							1	7	25	8				
Vancomycin	0			28	11	2									
Bacitracin[#]	1			35	1	1		1	2			1			
Linezolid	0		1	26	14										
Virginiamycin	0		4		35	2									
Narasin	35		5	1		9	26								

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

In total, five of the isolates were susceptible to all antimicrobial agents included, whereas 28 isolates were resistant to one antimicrobial agent (narasin 27 isolates, tetracycline one isolate). Eight isolates were resistant to two antimicrobial agents (narasin and erythromycin: six isolates; narasin and tetracycline: one isolate; and narasin and bacitracin: one isolate).

Narasin is used as a feed additive in most of the broiler production in Norway and represents a selection pressure for resistance. The low frequency of tetracycline resistance is explained by insignificant use of oxytetracycline for clinical purposes in Norwegian broiler production. Erythromycin has never been used in broilers in Norway. However, as cross-resistance between erythromycin and spiramycin is common, the resistance to erythromycin acquired by *E. hirae* may be explained by former use of spiramycin in broilers (licensed for use in poultry until 1998 when withdrawn due to limited sales).

Bacitracin was formerly used as a growth promoter, but the product was withdrawn from the market in 1997 due to negligible use during the 1990s. Thus, the observed resistance towards bacitracin may indicate prolonged persistence of such resistance.

Vibrio anguillarum from fish

A total of 103 isolates of *Vibrio anguillarum* were collected from diagnostic submissions mainly from farmed cod and salmon during the period 2004-2009. A single isolate from 2000 was also included. The isolates belong to serotypes O1 and O2 which have slightly different wild type distributions for some of the substances in the panel. However, due to the lack of epidemiological cut-off values for this organism, we decided to present only the MIC distributions for each of the substances in the panel and without any distinction between serotypes. This is the first time *V. anguillarum* has been included in NORM-VET. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Table 11, and in the text

TABLE 11. Antimicrobial resistance in *Vibrio anguillarum* (n=103) from farmed cod and salmon obtained in 2000 (one isolate) and during the years 2004-2009.

	Distribution (%) of MIC values (mg/L)																
Substance	0.004	0.008	0.16	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline									100									
Chloramphenicol										100								
Florfenicol											100							
Ampicillin									1.0						24.3	74.8		
Cefotaxime			1.0		1.0	17.5	14.6	4.9	7.8	53.4								
Sulfamethoxazole												52.4	44.7	1.9	1.0			
Trimethoprim								8.7	83.5	7.8								
Gentamicin									11.7	65.0	22.3	1.0						
Streptomycin											1.0	54.4	36.9	7.8				
Kanamycin												96.1	3.9					
Ciprofloxacin	14.6			53.4	2.9	28.2			1.0									
Nalidixic acid									89.3	1.0		1.0	7.8			1.0		
Colistin								66.0	10.7	1.0	22.3							

No microbiological cut-off values are given. 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 distributions of MIC-values show a unimodal pattern with the exception of cefotaxime and ciprofloxacin. The isolates of V. *anguillarum* included in this study were collected in a period with very limited use of anti-microbials in salmonid aquaculture. Vaccination has been (and is) the prevailing preventive measure against a number of bacterial diseases including *V. anguillarum*, since the early 1990s. Consequently, the selection pressure from use of antimicrobials in salmonids has been low, and this is likely to impact on the prevalence of resistance against antimicrobials.

B. INDICATOR BACTERIA FROM ANIMALS

Marianne Sunde, Jarle Mikalsen, Madelaine Norström, 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 so-called indicator bacteria of the normal enteric microflora from healthy animals, as well as indicator bacteria from feed and food, is important to get a better 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 2010, *E. coli* from faecal samples from cattle and wild red foxes were included.
The substances included in the test panels might not always be substances 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 2010. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from cattle

A total of 323 faecal samples from cattle were examined and *E. coli* was isolated from 209 (64.7 %) of the samples. One isolate per positive sample was susceptibility tested.

The results are presented in Table 12 and Figure 19, and in the text.

TABLE 12. Antimicrobial resistance in isolates of *Escherichia coli* (n=209) from faecal samples from cattle in 2010.

Substance	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	1.9	[0.5-4.8]							80.9	17.2				0.5	1.0	0.5		
Chloramphenicol	0.0	[0.0-1.7]								8.6	60.3	31.1						
Florfenicol	0.0	[0.0-1.7]									41.1	58.4	0.5					
Ampicillin	1.9	[0.5-4.8]							14.4	73.7	8.6	1.4				1.9		
Cefotaxime	0.5	[0.0-2.6]	0.5	6.2	78.5	14.4		0.5										
Sulfamethoxazole	3.3	[1.3-6.8]										48.8	40.7	7.2				3.3
Trimethoprim	0.0	[0.0-1.7]				14.8	49.3	35.4	0.5									
Gentamicin	0.0	[0.0-1.7]					1.0	67.0	32.1									
Streptomycin	9.1	[5.6-13.8]								3.3	61.7	25.8			5.3	3.3	0.5	
Kanamycin	0.0	[0.0-1.7]										100						
Ciprofloxacin	0.0	[0.0-1.7]	3.3	70.8	25.8													
Nalidixic acid	0.0	[0.0-1.7]							12.4	31.6	55.0	1.0						
Colistin	0.0	[0.0-1.7]						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.

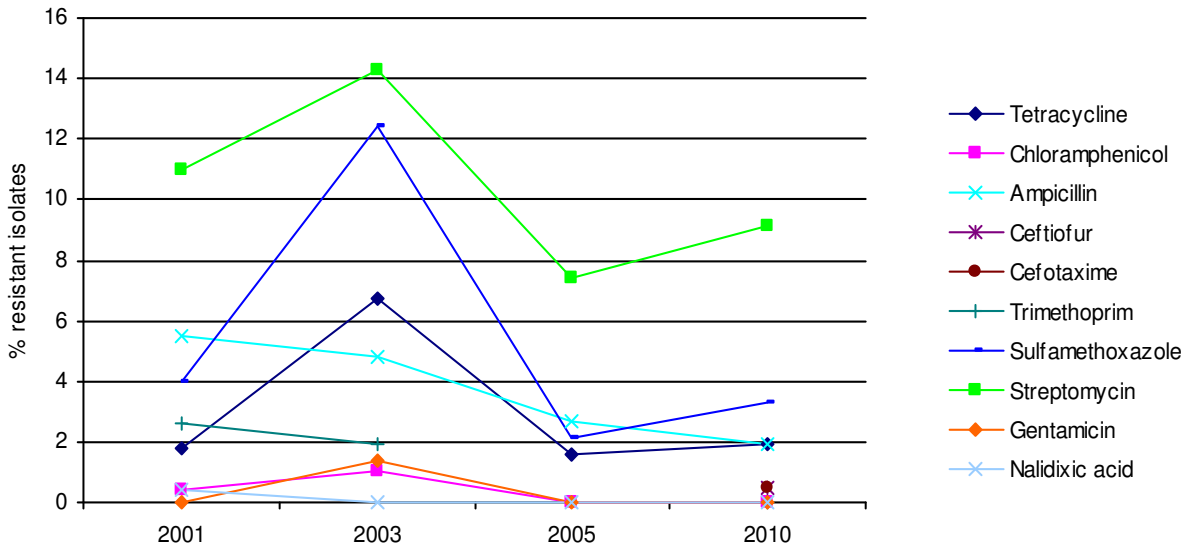

FIGURE 19. Prevalence of resistance to various antimicrobials in *Escherichia coli* from bovine samples (meat and faeces) collected in 2001, 2003, 3005 and 2010. The breakpoints in NORM-VET 2010 were applied.

Escherichia coli from wild red fox

A total of 88 intestinal samples from wild red foxes from Hedmark county shot during the hunting season of 2010, were investigated. *E. coli* was isolated from 55 (62.5%) samples. One isolate per positive sample was susceptibility tested. The results are presented in Table 13 and Figure 20, and in the text. The samples were also examined using a selection method (see textbox page 33).

TABLE 13. Antimicrobial resistance in isolates of *Escherichia coli* (n=55) from intestinal samples of wild red fox in 2010.

Substance	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	1.8	[0.04-9.7]							63.6	32.7	1.8			1.8				
Chloramphenicol	0.0	[0.0-6.5]								7.3	60.0	32.7						
Florfenicol	0.0	[0.0-6.5]									41.8	58.2						
Ampicillin	1.8	[0.04-9.7]							14.5	72.7	7.3	3.6				1.8		
Cefotaxime	0.0	[0.0-6.5]		1.8	78.2	20.0												
Sulfamethoxazole	5.5	[1.1-15.1]										54.5	38.2		1.8			5.5
Trimethoprim	1.8	[0.04-9.7]				1.8	69.1	25.5	1.8				1.8					
Gentamicin	0.0	[0.0-6.5]				1.8	5.5	69.1	23.6									
Streptomycin	3.6	[0.4-12.5]								5.5	67.3	21.8	1.8		1.8	1.8		
Kanamycin	0.0	[0.0-6.5]										100						
Ciprofloxacin	1.8	[0.04-9.7]	1.8	81.8	14.5		1.8											
Nalidixic acid	1.8	[0.04-9.7]							3.6	36.4	58.2					1.8		
Colistin	0.0	[0.0-6.5]						85.5	10.9	3.6								

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.

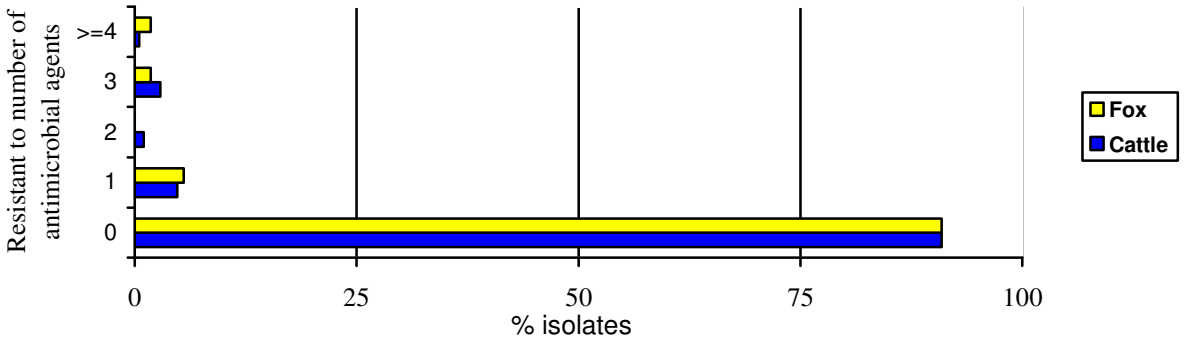

FIGURE 20. Antimicrobial resistance profile for *Escherichia coli* from cattle (n=209) and wild red fox (n=55) in 2010. Proportions of isolates susceptible to all or resistant to one, two, three and four or more antimicrobial agents are illustrated.

Resistant *Escherichia coli* in wild red foxes

Animals examined
During the hunting season in 2010, the carcasses of red foxes were submitted to the Norwegian Veterinary Institute for further investigation. The animals were supplied from the county of Hedmark. The material was primarily used for examination of *Trichinella* spp. and in addition, faecal material was obtained for isolation of resistant *Escherichia coli.* Samples from 88 foxes were included in this study.

Methodology
Fecal material was plated directly on five different selective agar plates (MacConkey) containing the following antimicrobial agents and concentrations: Ampicillin (8 mg/L), tetracycline (8 mg/L), nalidixic acid (16 mg/L), cefotaxime (1 mg/L) and sulfamethoxazole (256 mg/L). The plates were incubated in aerobic atmosphere for 48 hours at 37°C. Colonies with a typical appearance were subcultured in pure culture and further species identification was performed as described for *E. coli* (Appendix 3). Susceptibility testing of isolates identified as *E. coli* was performed by using a broth micro dilution method (VetMIC^{TM}) as described. Resistant *E. coli* isolates grew on several of the selective agar plates from four faecal samples. These isolates were subjected to pulsed-field gel electrophoresis (PFGE) in order to evaluate if the isolates were multi-resistant clonal derivatives of each other able to grow on different selective plates.

Results
From eight out of 88 animals examined, resistant *E. coli* isolates were found. Most commonly observed was resistance to sulphonamides, followed by resistance to tetracycline and streptomycin, then to ampicillin, trimethoprim, quinolones and gentamicin. Multi-resistant strains (resistant to more than two antimicrobial agents) were isolated from four of the animals. From two animals, isolates with different resistance profiles were obtained. These isolates produced distinct PFGE patterns, thus indicating the presence of several resistant *E. coli* clones in the intestinal flora of the same animal.

Conclusion
This study shows that wild foxes in Norway can be colonised with resistant *E. coli*. Resistance to broad-spectrum and critically important antimicrobials agents such as fluoroquinolones and gentamicin was detected, indicating that resistance to such antimicrobial agents is disseminating in the environment.

M. Sunde, H. Fanuelsen, A. S. Barstad, R. Davidson, Norwegian Veterinary Institute, Oslo.

RESULTS AND COMMENTS

CATTLE

The data indicate low occurrence of resistance among *E. coli* from cattle faecal samples. In total, 90.9% of the isolates were susceptible to all antimicrobial agents included. Resistance to one antimicrobial agent (predominantly streptomycin) occurred in 4.8% of the isolates, resistance to two in 1.0% (mainly streptomycin and sulfamethoxazole), to three in 2.9% and to four antimicrobial agents in 0.5% of the isolates (Figure 20). Resistance to streptomycin was the most frequently identified resistance determinant, followed by resistance to sulfamethoxazole and tetracycline. One isolate was multi-resistant to three antimicrobial substances; ampicillin, streptomycin and cefotaxime (only one step above cut-off value). Further investigations showed that this isolate was not an ESBL producer. No quinolone resistance was observed. The results are similar to those presented in previous NORM/NORM-VET reports as seen in Figure 19.

WILD RED FOX

The data indicate low occurrence of resistance among *E. coli* isolated from faecal samples of wild red fox. In total, 90.9% of the isolates were susceptible to all antimicrobial agents included (randomly selected colonies). Three isolates were resistant to one antimicrobial agent (streptomycin), one isolate to three (nalidixic acid, ciprofloxacin and tetracycline) and one to four antimicrobial agents (Figure 20).
By using selective media to screen for resistant *E. coli* in the faecal samples, resistant isolates were detected in samples from eight animals (see textbox above). Of special concern was resistance to antimicrobial agents such as fluoroquinolones and gentamicin, indicating dissemination into the environment of resistance to critically important antimicrobial agents.

C. ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

Trine-Lise Stavnes, Astrid Louise Wester, Madelaine Norström, Marianne Sunde, Arve Lund

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 2010, antimicrobial resistance in *Campylobacter jejuni* from cattle 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 breakpoints of the Norwegan Working Group for Antibiotics (NWGA). These breakpoints diverge significantly from the EUCAST protocol regarding ampicillin, mainly because the officially approved doses for this agent are considerably lower than in other European countries. Thus, the NWGA has decided the wild type of *Enterobacteriaceae* to be intermediately susceptible to ampicillin. This breakpoint issue results in high percentages of intermediately susceptible isolates of *Enterobacteriaceae.* The breakpoint for resistance to ampicillin in *Enterobacteriaceae*, however, is identical to that of EUCAST. The percentages of enteropathogenic *Enterobacteriacea*, therefore, should be comparable to European conditions.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food producing 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, in addition to selected isolates from other relevant projects, as well as those detected by clinical submissions (index isolates) to the Norwegian Veterinary Institute. Additionally, selected isolates from other relevant projects are included. The data are presented in Tables 14-15, and in the text.

TABLE 14. Antimicrobial resistance in *Salmonella* spp. (n=21) from animals (cattle=3, dog=11, cat=1, broiler=2, swine=3, quail=1); *S.* Typhimurium (n=3) and other *Salmonella* spp. (n=18).

		Distribution (n) of MIC values (mg/L)															
Substance	Resistance (n)	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	6						2	11	2					2	4		
Chloramphenicol	0									18	3						
Florfenicol	0									14	7						
Ampicillin	5							14	2						5		
Cefotaxime	0			6	15												
Sulfamethoxazole	4											1	10	6			4
Trimethoprim	3					13	5							3			
Gentamicin	1						18	2						1			
Streptomycin	5									3	12	1		2	2		1
Kanamycin	0							2	17		2						
Ciprofloxacin	1		13	7			1										
Nalidixic acid	1								1	16	3						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 15. Antimicrobial resistance in *Salmonella* Typhimurium (n=70) from diagnostic submissions of wild birds during the years 2006-2010.

	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	[0.0-5.1]						1.4	94.3	4.3								
Chloramphenicol	0.0	[0.0-5.1]								50.0	50.0							
Florfenicol	0.0	[0.0-5.1]								7.1	92.9							
Ampicillin	0.0	[0.0-5.1]						4.3	95.7									
Cefotaxime	0.0	[0.0-5.1]			47.1	51.4	1.4											
Sulfamethoxazole	0.0	[0.0-5.1]											7.1	62.9	3.0			
Trimethoprim	0.0	[0.0-5.1]					81.4	18.6										
Gentamicin	0.0	[0.0-5.1]					1.4	92.9	5.7									
Streptomycin	0.0	[0.0-5.1]										87.1	12.9					
Kanamycin	0.0	[0.0-5.1]							5.7	92.9	1.4							
Ciprofloxacin	0.0	[0.0-5.1]		87.1	12.9													
Nalidixic acid	0.0	[0.0-5.1]								5.7	94.3							

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.

*CI = Confidence interval.

RESULTS AND COMMENTS

ANIMALS

In 2010, a total of 21 isolates of *Salmonella* spp. were susceptibility tested. Three isolates were *S.* Typhimurium including two from swine and one from a dog. The remaining isolates belonged to several different serovars and orginated from dogs (n=10), cattle (n=3), swine (n=1), broiler (n=2), quail (n=1) and a cat (n=1). Resistance to tetracyclines, ampicillin and sulfamethoxazole occurred in about a third of the isolates. One isolate showed resistance to fluoroquinolones. The data, although very limited, indicate that resistance in *Salmonella* occasionally isolated in Norwegian animals, seems to be increasing, especially in *Salmonella* spp. isolated from dogs.

WILD BIRDS

All isolates of *Salmonella* Typhimurium from wild birds were susceptible to the substances included in the panel. These isolates have been genotyped at the Norwegian Institute of Public Health and were all shown to belong to an endemic *Salmonella* Typhimurium genotype present in Norwegian birds. Previous studies have shown that these isolates usually have a fully susceptible antimicrobial resistance profile.

Salmonella from human clinical specimens

In 2010 the National Reference Laboratory (NRL) for Enteropathogenic Bacteria at the Norwegian Institute of Public Health (NIPH) performed antibiotic resistance testing (AST) on a total of 1,394 unique *Salmonella* isolates from human infections. As indicated in Table 16, 15.5% was reported as acquired in Norway, 79.3% was acquired abroad, whereas the place of origin was unknown in 5.1%.

TABLE 16. Distribution of human isolates of *Salmonella* serovar (n=1,384) in 2010 according to geographical origin of acquisition.

	Place of acquistion		
	Norway	Abroad	Unknown
S. Typhimurium including *S. enterica* serovar 4,[5],12:i- (n=247)	87	142	18
S. Enteritidis (n=569)	46	487	26
S. Typhi (n=16)	0	16	0
S. Paratyphi (n=19)	0	19	0
Other *Salmonella* (n=543)	82	434	27
Total (n=1,394)	**215**	**1,098**	**71**

Altogether 247 (17.7%) of the isolates were *S.* Typhimurium, whereas 569 (40.8%) of the isolates were *S.* Enteritidis. Of these 87 (35.2%), and 46 (8.1%) were reported as infected in Norway, respectively. The relatively high proportion of domestically acquired *S.* Typhimurium infections is mainly explained by the endemic occurrence of specific clones of this serovar in Norwegian wildlife.

From 2010 on, phage typing is not performed, and thus results on *S.* Typhimurium definite phage type (DT) 104 is not available. DT 104 is of special concern, because of carriage of multi-resistance. To mirror, to some extent, the development regarding *S.* Typhimurium DT 104, numbers

are given, however, for isolates showing the same resistance profile as that of DT 104 (i.e. resistant to ampicillin, tetracycline, chloramphenicol, sulfadiazine and streptomycin). Furthermore, we have chosen to include *Salmonella enterica* serovar 4,[5],12:i:- as a variant of *S.* Typhimurium, in spite of the ongoing discussion whether this is correct or not.

The results of the AST are presented in Tables 17-20, in Figures 21-25, and in the text. Sampling, laboratory methods, and data handling are described in Appendix 4. Multi-resistance was defined as resistance to two or more antimicrobial agents. The proportion of domestically acquired *S.* Typhimurium (including *Salmonella enterica* serovar 4,[5],12:i:-) that showed a resistance profile similar to that of DT 104 was 5.2% (3% in 2009). The corresponding proportion from infections acquired abroad was 5.6% (5.1% in 2009).

Several European countries have reported a worrisome increase in multi-resistant *S. enterica* serovar 4,[5],12:i:-. In Norway, the absolute number of *Salmonella enterica* serovar 4,[5],12:i:- was 87 in 2010 compared to 43 in 2009 and 59 in 2008. The percentage of this serovar among all *S.* Typhimurium isolates was 35.2% in 2010, compared to around 20% in 2008 and 2009. Nienty-two percent were multi-resistant in 2010, compared to 96% in 2009 and 72% in 2008. Fifty-five isolates were acquired abroad and 29 were acquired in Norway.

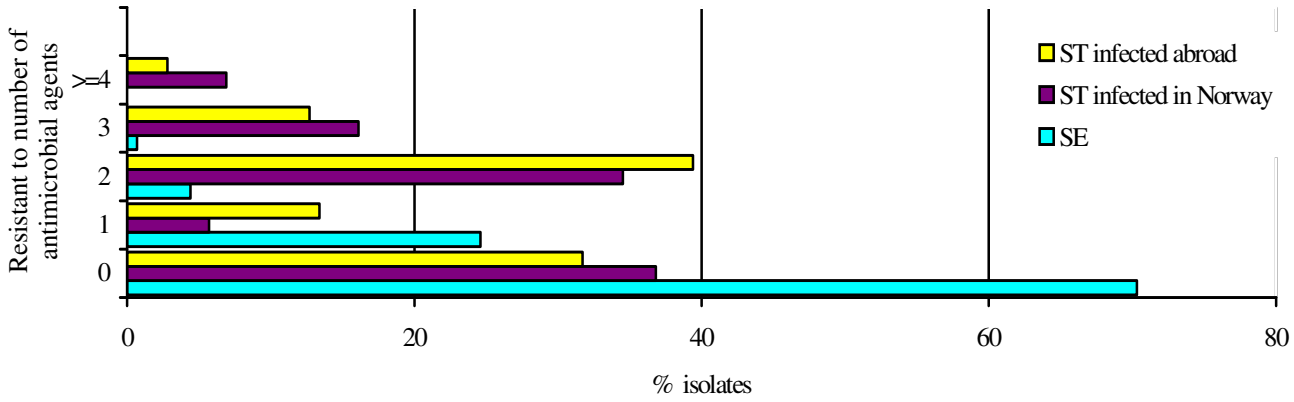

FIGURE 21. Antimicrobial resistance profiles for all *Salmonella* Enteritidis (SE) from humans (n=569) and for *Salmonella* Typhimurium (ST) (including isolates with at resistance profile similar to DT 104, and *S. enterica* serovar 4,[5],12:i:-) from humans infected in Norway (n=87) and abroad (n=142), respectively. Proportion of isolates in 2010 resistant to none, one, two, three, or four or more antimicrobial agents are illustrated.

TABLE 17. Human isolates of domestically acquired *Salmonella* Typhimurium isolates (n=87) during 2010, including isolates with a resistance profile similar to DT 104 (n=12) and the domestically acquired *S. enterica* serovar 4,[5],12:i:- (n=29). 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	42.5	57.5
Chloramphenicol	≤ 8	> 8	82.8	-	17.2
Tetracycline*	≤ 4	> 8	37.9	-	62.1
Nalidixic acid	≤ 16	> 16	95.4	-	4.6
Ciprofloxacin	≤ 0.5	> 1	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	90.8	0.0	9.2

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

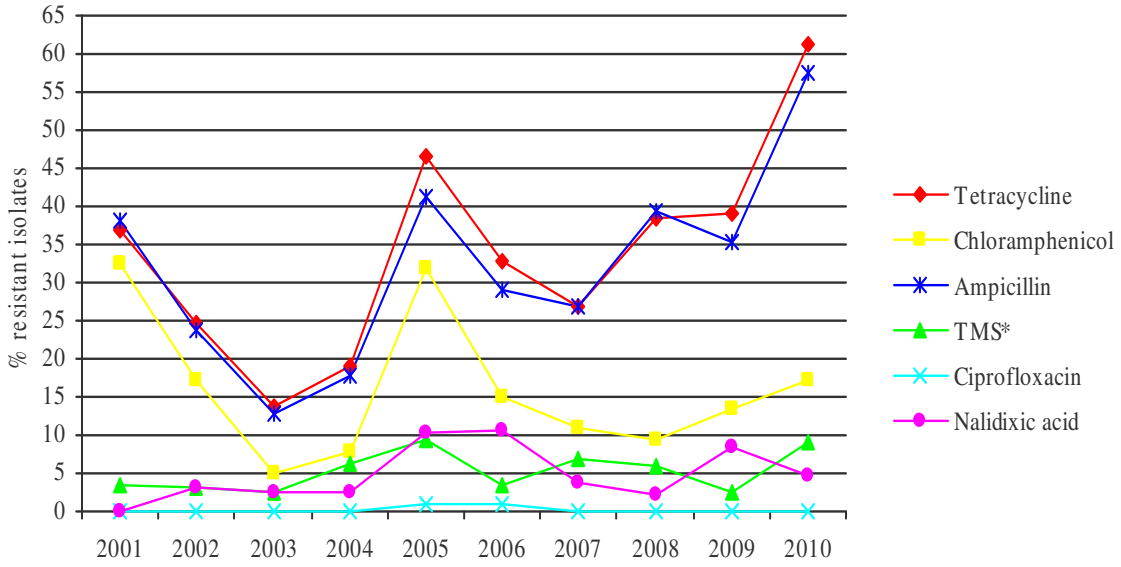

FIGURE 22. Percentage of resistance to various antimicrobial agents in *Salmonella* Typhimurium (including isolates with a resistance profile similar to DT 104 and *S. enterica* serovar 4,[5],12:i:-) from humans infected in Norway 2001-2010 (n=87). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 18. Human isolates of *Salmonella* Typhimurium acquired abroad during 2010 (n=142), including isolates with a resistance profile similar to DT 104 (n=9), and *S. enterica* serovar 4,[5],12:i:- (n=55). 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	44.4	55.6
Chloramphenicol	≤ 8	> 8	89.4	-	10.6
Tetracycline*	≤ 4	> 8	38.7	-	61.3
Nalidixic acid	≤ 16	> 16	93.0	-	7.0
Ciprofloxacin	≤ 0.5	> 1	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	93.0	0.0	7.0

*The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

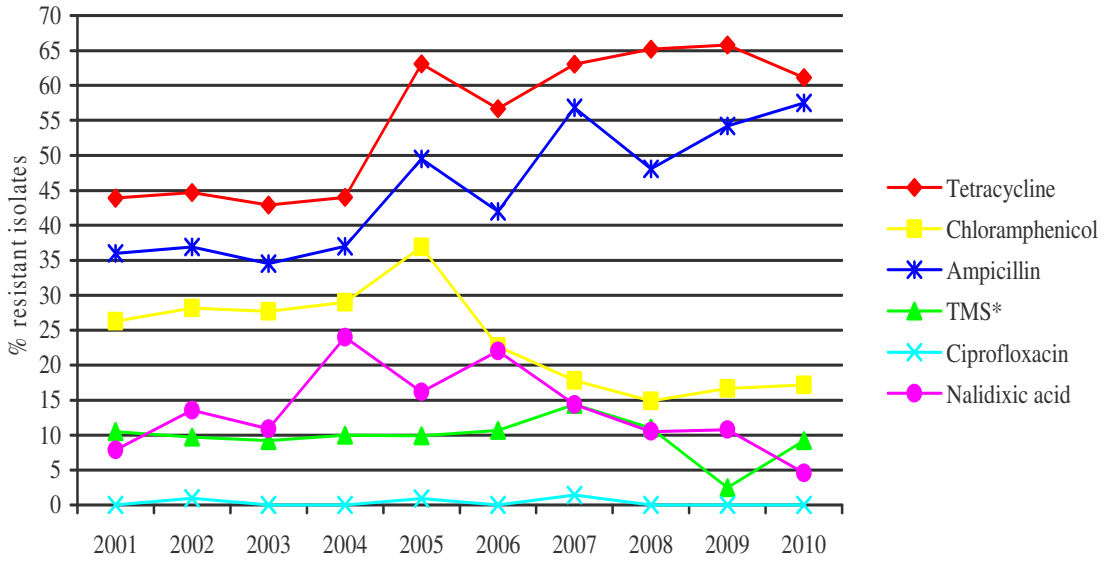

FIGURE 23. Percentage of resistance to various antimicrobial agents in human *Salmonella* Typhimurium (including isolates with a resistance profile similar to DT 104, and *S. enterica* serovar 4,[5],12:i:-) from humans infected outside Norway 2001-2010 (n=142). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 19. Human isolates of *Salmonella* Enteritidis (n=569[#]), acquired during 2010, irrespective of place of acquisition. 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	93.3	6.7
Chloramphenicol	≤ 8	> 8	99.8	-	0.2
Tetracycline*	≤ 4	> 8	96.3	-	3.7
Nalidixic acid	≤ 16	> 16	76.3	-	23.7
Ciprofloxacin	≤ 0.5	> 1	99.8	0.2	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	99.1	0.0	0.9

Place of infection; Norway (n=56), abroad (n=487), unknown (n=26). * The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **According to NWGA and EUCAST, breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

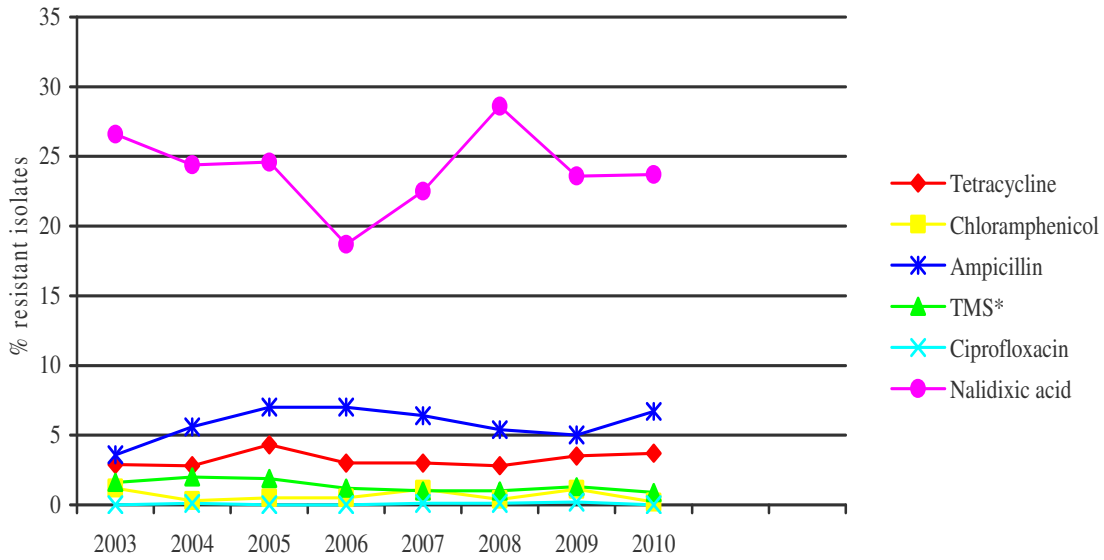

FIGURE 24. Percentage of resistance to various antimicrobial agents in *Salmonella* Enteritidis from humans in 2003-2010 (n=569). *TMS=Trimethoprim-sulfamethoxazole. #Place of infection; Norway (n=56), abroad (n=487), unknown (n=26).

TABLE 20. Human isolates of *Salmonella* spp. (excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi) (n=543[#]), acquired during 2010, irrespective of place of acquisition. 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	86.4	13.6
Chloramphenicol	≤ 8	> 8	94.1	-	5.9
Tetracycline*	≤ 4	> 8	80.1	-	19.9
Nalidixic acid	≤ 16	> 16	79.6	-	20.4
Ciprofloxacin	≤ 0.5	> 1	97.2	0.0	2.8
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	89.7	0.2	10.1

Place of infection; Norway (n=82), abroad (n=434), unknown (n=27). * The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this drug is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

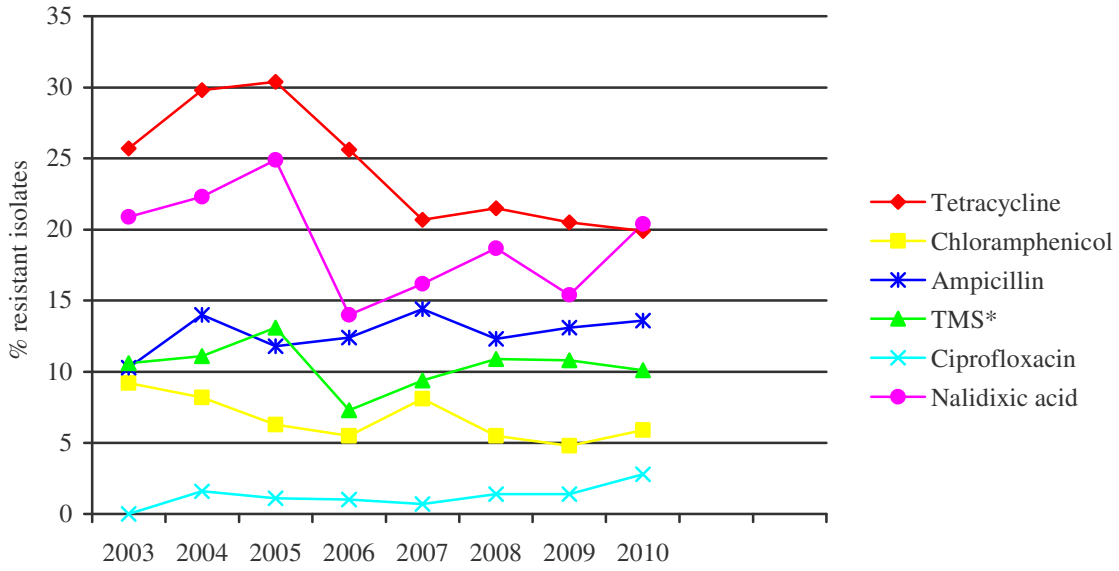

FIGURE 25. Percentage of resistance to various antimicrobial agents in *Salmonella* spp. (excluding *S*. Typhimurium, *S*. Enteritidis, *S*. Typhi and *S*. Paratyphi) from humans in 2003-2010 (n=543). *TMS=Trimethoprim-sulfamethoxazole. . # Place of infection; Norway (n=82), abroad (n=434), unknown (n=27).

RESULTS AND COMMENTS

Because of breakpoint issues regarding ampicillin, the percentage of intermediately susceptible isolates may seem high. The percentages of isolates resistant to ampicillin, however, are of more concern.

The overall tendencies were that most resistance was found in *S.* Typhimurium and that the resistance in S. Typhimurium seems to have increased. This is especially true for the domestically acquired strains. The proportion of domestically acquired *S.* Typhimurium isolates sensitive to all antibiotis declined from 57.3% in 2009 to 35.6% in 2010, and conversely, the proportion of domestically acquired multiresistant *S.* Typhimurium increased from 29.3% in 2009 to 57.5% in 2010. This domestically increase in resistance may be due to an increase in multi-resistant *S. enterica* serovar 4,[5],12:i:- (results not shown).

As shown in Figures 22 and 23, the most commonly observed resistance in *S.* Typhimurium was towards tetracycline, followed by resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and nalidixic acid. The prevalence of resistance for the years 2001-2010 to various antimicrobial agents in human isolates of *S.* Typhimurium, acquired in Norway (Figure 22) and acquired abroad (Figure 23), shows an increasing trend regarding resistance towards tetracycline and ampicillin, whereas for the other antibiotics tested there is no clear trend.

The majority of *S.* Enteritidis isolates was acquired abroad (Table 19). The proportion of *S.* Enteritidis isolates resistant to the different antimicrobial agents included was, except for nalidixic acid, considerably lower than for *S*. Typhimurium (Figure 24). There is still a very low level of resistance to ciprofloxacin, and the resistance to ampicillin is below 10%. The antimicrobial resistance in *S.* Enteritidis seems quite stable.

With regard to *Salmonella* spp. isolates other than *S.* Typhimurium and *S.* Enteritidis, most infections have been acquired abroad and antimicrobial resistance was moderate and fairly stable over the last five years (Table 20 and Figure 25). Resistance to nalidixic acid was most common, followed by resistance to tetracycline and ampicillin. Resistance to ciprofloxacin was observed in 2.8% of the isolates, whereas 13.6% were resistant to ampcillin.

The few isolates of *S.* Typhi (n=16) in 2010 indicate that multi-resistance, including resistance to nalidixic acid, is relatively common in these serovars (results not shown). All infections with these serovar were acquired abroad. Seven isolates (43.7%) were resistant to four or more of the antimicrobial agents included in the survey. The isolates of *S.* Paratyphi A (n=17) and *S*. Paratyphi B (n=2), however, showed overall low rates of resistance, except for resistance to nalidixin in *S.* Paratyphi A, where 76.5% were resistant.

In 2010, the marker for possible extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefpodoxime. All isolates with reduced susceptibility to cefpodoxime were further characterised in order to verify the presence of ESBL. A total of nine isolates displayed reduced susceptibility to cefpodoxime; seven were identified as ESBL producers.

CAMPYLOBACTER SPP.

Campylobacter coli from cattle

A total of 323 faecal samples from healthy cattle were examined. *Campylobacter jejuni* was isolated from 11 samples, and these were susceptibility tested. The data are presented in Table 21 and in the text.

TABLE 21. Antimicrobial resistance in *Campylobacter jejuni* (n=11) from cattle in 2010.

	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	0		2	7	2										
Erythromycin	0				8	3									
Streptomycin	1					2	8						1		
Gentamicin	0				6	5									
Ciprofloxacin	1	1	6	3						1					
Nalidixic acid	1							4	4	2			1		

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

Ten of 11 isolates were susceptible to all antimicrobial agents tested. One isolate was resistant to ciprofloxacin, nalidixic acid and streptomycin. Due to the low number of *Campylobacter jejuni* isolates obtained and susceptibility tested, it is not possible to draw any firm conclusions regarding the prevalence of resistance for this organism in cattle.

Campylobacter spp. from human clinical specimens

Of the 2,673 cases of human campylobacteriosis registered in Norway in 2010 (incidence rate 54.5 per 100,000), 51% were reported as acquired abroad. Based on epidemiological data on patients, the vast majority of cases were judged as sporadic. However, only a small number of the isolates are forwarded to the NRL. Consequently, quality assured species diagnoses, complete AST data and molecular epidemiology data on *Campylobacter* lack due to resource priority matters. Thus outbreaks with less clear epidemiological links may very well have been overlooked, and thus, the results presented may be underestimated or overestimated. Susceptibility testing was performed on a total of 262 isolates of *C. jejuni* (97 from patients infected in Norway, 152 from patients infected abroad and 13 from patients where the origin of infection was unknown), 12 *C. coli* isolates and one *C. lari* isolate. Multi-resistance was defined as resistance to two or more antimicrobial agents. The results for *C. jejuni* are presented in Tables 22-25, Figures 26-28, and in the text.

TABLE 22. *Campylobacter jejuni* isolates from patients infected in Norway (n=97). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	90.7	-	9.3
Erythromycin	≤ 4	> 4	100.0	-	0.0
Gentamicin	≤ 2	> 4	94.8	0.0	5.2
Nalidixic acid	≤ 16	> 16	77.3	-	22.7
Ciprofloxacin	≤ 0.5	> 1	77.3	0.0	22.7

TABLE 23. *Campylobacter jejuni* isolates from patients infected in Norway (n=97). 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	1.0	13.4	23.7	34.1	15.4	2.1	1.0			1.0	2.1	3.1		3.1
Erythromycin					9.3	57.7	32.0	1						
Gentamicin			1	7.2	47.5	39.1	5.2							
Nalidixic acid						1	27.8	38.2	9.3	1				22.7
Ciprofloxacin		17.6	45.4	14.4				1	1		20.6			

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.

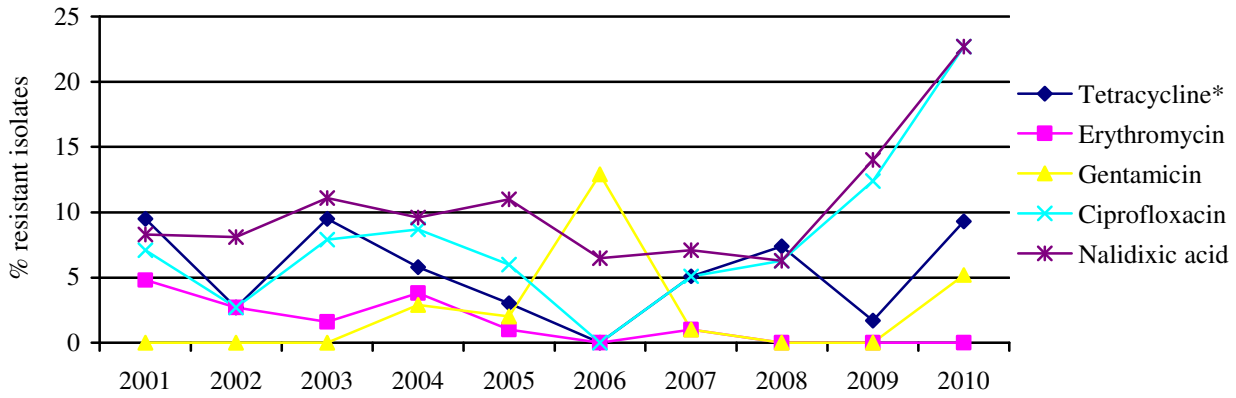

FIGURE 26. Prevalence of resistance in *Campylobacter jejuni.* isolated from humans infected in Norway 2001-2010 (n=97), to various antimicrobials. * Doxycycline before 2006.

TABLE 24. *Campylobacter jejuni* isolates from patients infected outside Norway (n=152). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	44.7	-	55.3
Erythromycin	≤ 4	> 4	97.4	-	2.6
Gentamicin	≤ 2	> 4	96.7	-	3.3
Nalidixic acid	≤ 16	> 16	28.3	-	71.7
Ciprofloxacin	≤ 0.5	> 1	27.6	-	72.4

TABLE 25. *Campylobacter jejuni* isolates from patients infected outside Norway (n=152). 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			12.5	23.7	7.9	0.7		1.3	0.7	8.5	8.5	12.5	9.2	14.5
Erythromycin				1.4	11.8	44.0	31.6	8.5	0.7		0.7			1.3
Gentamicin			0.7	4.6	40.7	50.7	2.0							1.3
Nalidixic acid							6.6	18.4	2	1.3				71.7
Ciprofloxacin		7.3	17.7	2.0	0.7		0.7	0.7	2	2.7	66.2			

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

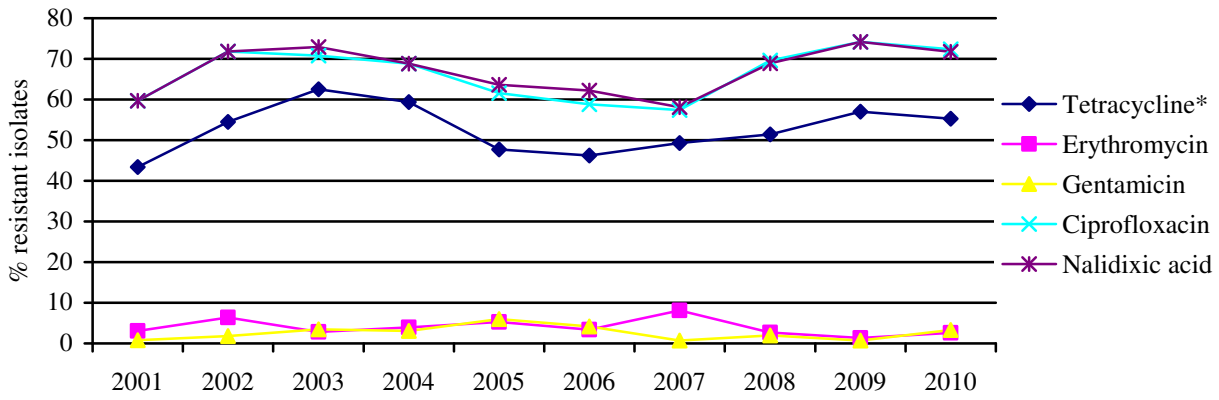

FIGURE 27. Prevalence of resistance to various antimicrobial agents in *Campylobacter jejuni* from humans infected outside Norway 2001-2010 (n=152). *Doxycycline before 2006.

RESULTS AND COMMENTS

Clinical breakpoints have not yet been worked out by EUCAST. Epidemiological breakpoints have therefore been used, in agreement with the Norwegian Working Group for Antibiotics (NWGA).

The data show that resistance was more widespread among *C. jejuni* isolates recovered from patients infected abroad than in patients infected in Norway. Only 16.4% of isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 61.9% of the isolates from patients infected in Norway (Figure 28). The main differences between the two groups were seen for quinolones (ciprofloxacin/nalidixic acid) with 72.4% resistance in isolates acquired abroad versus 22.7% resistance in isolates acquired in Norway, and tetracycline with 55.3% resistance in isolates acquired abroad versus 9.3% resistance for those acquired in Norway.

The prevalences of resistance to various antimicrobial agents for *C. jejuni* acquired inside and outside Norway (Figure 26 and 27) were fairly stable during the period 2001-2008 except for an unexplained increase in the resistance to gentamicin in domestic isolates in 2006, and maybe also an increase again from 2009 to 2010. For the domestically acquired isolates there is an increase in resistance to tetracycline, but only to reach the pre-2009 level again. There is, however, a very steep rise in resistance to quinolones since 2008, which needs attention. These changes may be due to unknown methodological problems. Alternatively, it may be explained by a selection bias, or it may reflect a real increase in the prevalence of a *C. jejuni* clone with this specific resistance pattern. One could also speculate that this may be due to an undetected outbreak of a specific strain.

Twelve *C. coli* isolates were acquired abroad, and none was acquired in Norway. All 12 isolates acquired abroad were resistant to at least one of the antimicrobial agents, mainly to quinolones or tetracycline. *C. coli* are typically associated with pigs and pork. One *C. lari* acquired in Norway was resistant to three antimicrobial agents.

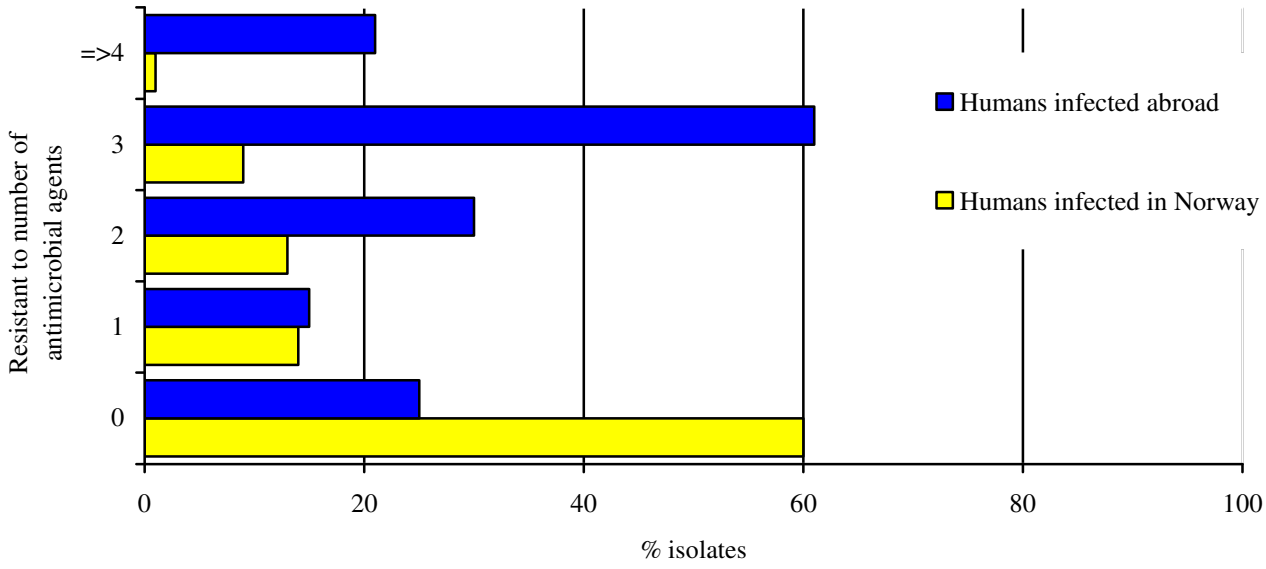

FIGURE 28. Antimicrobial resistance profiles for *Campylobacter jejuni* from humans infected in Norway (n=97) and humans infected abroad (n=152). Proportion of isolates resistant to none, one, two, three, or four or more antimicrobial agents respectively are illustrated. The isolates from humans were tested for susceptibility to tetracycline, erythromycin, gentamicin, ciprofloxacin and nalidixic acid.

Yersinia enterocolitica from human clinical specimens

Most cases of *Yersinia enterocolitica* infections in Norway are domestically acquired. A total of 53 cases of yersiniosis were reported in 2010, which is the exact same number as in 2009. The incidence rate is 1.1 per 100,000. Of the 53 cases, 47 belonged to serogroup 3 (25 acquired in Norway, 10 abroad and 12 with unknown place of infection), three belonged to serogroup 9 (two acquired in Norway and one abroad), one belonged to serogroup 8, one belonged to serogroup 5.27 and one belonged to serogroup 5 biotype 3. All *Y. enterocolitica* isolates were susceptibility tested. The results for *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 are presented in Table 26 and Figure 29.

TABLE 26. *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 isolates from human clinical cases (n=50[#]). 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	2.0	98.0
Chloramphenicol	≤ 8	> 8	90.0	-	10.0
Tetracycline*	≤ 4	> 8	94.0	-	6.0
Nalidixic acid	≤ 16	> 16	94.0	-	6.0
Ciprofloxacin	≤ 0.5	> 1	96.0	4.0	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	92.0	2.0	6.0

The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by NWGA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.
[#] Place of infection; Norway (n=27), abroad (n=11), unknown (n=12).

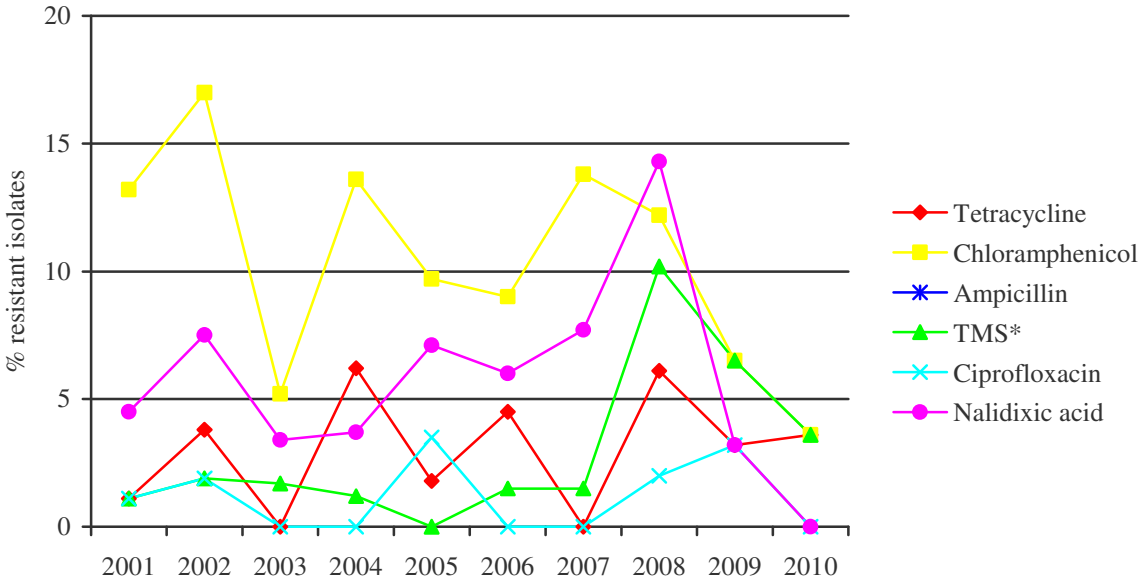

FIGURE 29. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2010 (n=50). *TMS=Trimethoprim-sulfamethoxazole

RESULTS AND COMMENTS

The infections in 2010 were mainly domestically acquired. All serogroup O:3 and O:9 isolates expressed intrinsic resistance to ampicillin. The prevalence of resistance to other antimicrobial agents has been fairly stable during the years 2001-2007, but in 2008 there seemed to be a tendency towards higher prevalences of resistance for all antimicrobial agents except for chloramphenicol (Figure 29). These tendencies seem to be counteracted in 2009 and 2010. More likely these fluctuations may be due to a small absolute number of isolates, and thus, to chance, rather than true epidemiological changes.

Shigella spp. from human clinical specimens

It should be emphasized that almost all reported *Shigella* infections in Norway are acquired abroad. In 2010, 24 (18.2%) of the 132 reported cases were classified as domestically acquired. The majority of these 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 125 *Shigella* isolates that were susceptibility tested was as follows: *S. sonnei* 80 (64.0%); *S. flexneri* 39 (31.2%); *S. boydii* four (3.2%); and *S. dysenteriae* two (1.6%). Multi-resistance was defined as resistance to two or more antimicrobial agents. The results for *S. sonnei* and *S. flexneri* are presented in Table 27 and Figure 30 and in Table 28 and Figure 31, respectively.

TABLE 27. *Shigella sonnei* isolates from human clinical cases (n=80). 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	87.5	12.5
Chloramphenicol	≤ 8	> 8	93.7	-	6.3
Tetracycline*	≤ 4	> 8	15.0	-	85.0
Nalidixic acid	≤ 16	> 16	68.7	-	31.3
Ciprofloxacin	≤ 0.5	> 1	80.0	0.0	20.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	6.3	3.7	90.0

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

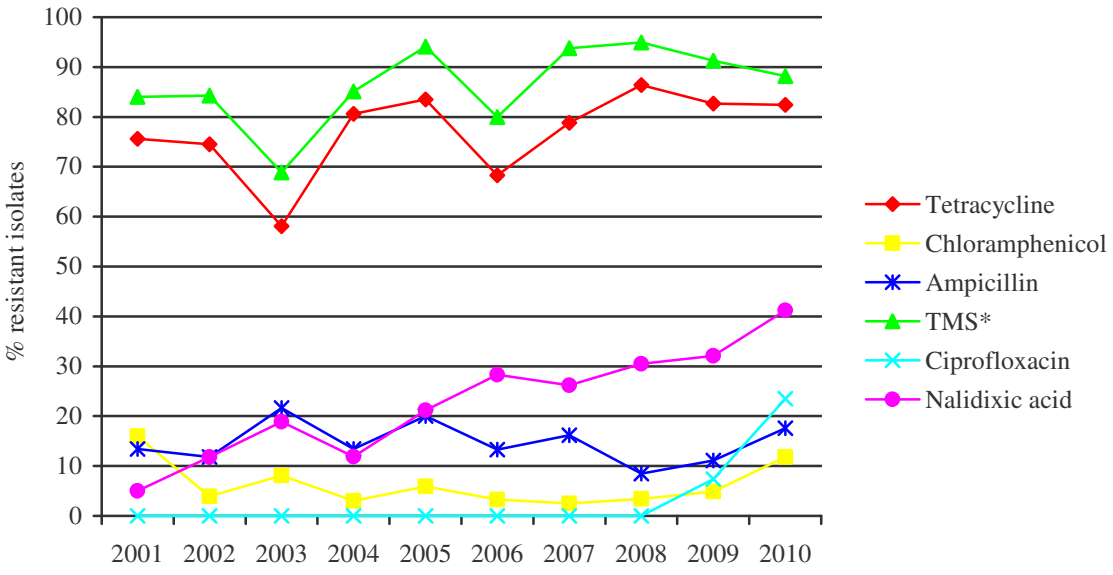

FIGURE 30. Prevalence of resistance to various antimicrobial agents in *Shigella sonnei* from humans in Norway 2001-2010 (n=80). *TMS=Trimethoprim-sulfamethoxazole.

TABLE 28. *Shigella flexneri* isolates from human clinical cases (n=39). 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 (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	38.5	61.5
Chloramphenicol	≤ 8	> 8	41.0	-	59.0
Tetracycline*	≤ 4	> 8	30.8	-	69.2
Nalidixic acid	≤ 16	> 16	76.9	-	23.1
Ciprofloxacin	≤ 0.5	> 1	76.9	0.0	23.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	56.4	0.0	43.6

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

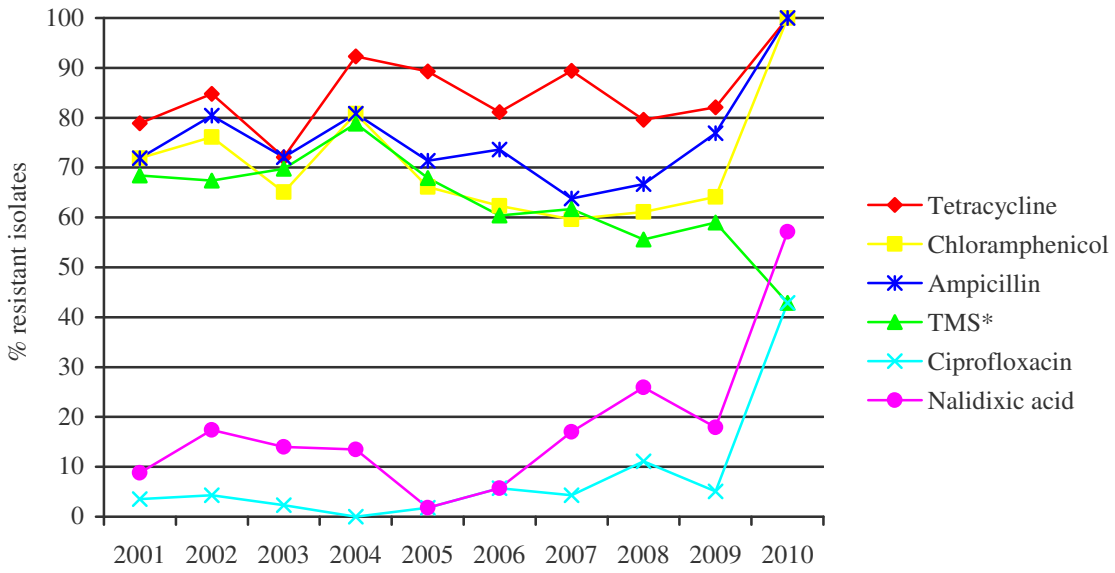

FIGURE 31. Prevalence of resistance to various antimicrobial agents in *Shigella flexneri* from humans in Norway 2001-2010 (n=39). *TMS=Trimethoprim-sulfamethoxazole.

RESULTS AND COMMENTS

The resistance patterns for *S. sonnei* have been fairly stable during the period 2001-2010, but stably high for tetracycline and for trimethoprim-sulfamethoxazole.

Resistance has been very frequent in *S. flexneri* for all the antimicrobial agents tested. From 2009-2010 there is a further increase in resistance to all antibiotics except for trimetoprim-sulphamethoxazole. As for *C. jejuni*, this may be due to small absolute numbers or to unknown methodological problems, but if this is a true tendency, it is, indeed, worrisome.

All the tested antimicrobials are commonly used for various clinical purposes within human medicine in many parts of the world. The few isolates of *S. dysenteriae* (n=2) and *S. boydii* (n=4) recovered and susceptibility tested in 2010 (results not shown) indicate that multi-resistance is fairly frequent in these species as well. The two isolates of *S. dysenteriae* and two out of the four isolates of *S. boydii* were resistant to two or more antimicrobial agents. None of the isolates were susceptible to all antimicrobial agents included in the survey.

D. HUMAN CLINICAL ISOLATES

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Distribution of bacterial species in blood cultures

Surveillance of antimicrobial resistance is usually based on prevalences of reduced susceptibility and resistance to certain combinations of antimicrobials and bacterial species in clinical samples. The NORM surveillance programme generally follows this approach. However, there is a serious limitation to the model because a transition in the distribution from susceptible bacterial species to inherently more resistant ones will represent de facto emergence of resistance which is not easily detected. In order to complement the surveillance of individual species, NORM collects data on all positive blood cultures from the laboratory information systems of the participating institutions. A patient with a given microbial isolate was excluded from registration with a new isolate of the same species within a month from the first entry. This rule was applied irrespectively of changes in the organism´s susceptibility pattern. Isolates of a different species 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 29, 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 29. Number of blood culture isolates in 2010, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) 2006-2010. The table is based on data from the information systems of all laboratories in Norway except one in 2010.

Species	No. of isolates 2010	% of all isolates					% of isolates excluding skin flora				
		2006	2007	2008	2009	2010	2006	2007	2008	2009	2010
Staphylococcus aureus	1,447	10.3	10.1	10.6	10.6	11.4	13.7	13.3	13.9	13.9	14.5
Coagulase negative staphylococci	2,451	22.7	21.6	21.3	22.3	19.3	-	-	-	-	-
Streptococcus pneumoniae	727	7.9	7.8	6.6	6.2	5.7	10.6	10.2	8.7	8.2	7.3
Streptococcus pyogenes	160	1.3	1.1	1.3	1.3	1.3	1.7	1.5	1.7	1.7	1.6
Streptococcus agalactiae	193	1.7	1.7	1.6	1.4	1.5	2.2	2.2	2.0	1.8	1.9
Beta-haemolytic streptococci group C and G	169	1.2	0.9	1.4	1.1	1.3	1.5	1.1	1.9	1.4	1.7
Viridans- and non-haemolytic streptococci	595	3.7	3.7	3.9	3.5	4.7	5.0	4.8	5.1	4.7	5.9
Enterococcus faecalis	586	4.3	4.3	4.0	4.6	4.6	5.7	5.7	5.2	6.0	5.9
Enterococcus faecium	215	1.1	1.4	1.4	1.3	1.7	1.5	1.8	1.9	1.7	2.1
Other Gram positive aerobic bacteria	357	3.4	3.4	3.4	2.7	2.8	1.8	2.1	1.5	1.5	1.4
Escherichia coli	2,961	21.6	22.3	22.8	23.0	23.4	28.9	29.2	29.9	30.2	29.6
Klebsiella spp.	869	5.4	6.0	5.8	6.5	6.8	7.2	7.9	7.6	8.6	8.7
Enterobacter spp.	209	1.7	1.8	1.9	1.9	1.6	2.3	2.3	2.5	2.5	2.1
Proteus spp.	216	1.8	1.7	1.5	1.5	1.7	2.4	2.2	2.0	2.0	2.2
Other *Enterobacteriaceae*	295	1.9	2.2	2.1	1.9	2.3	2.5	2.9	2.8	2.6	2.9
Pseudomonas spp.	225	1.7	1.6	1.8	1.9	1.8	2.3	2.1	2.4	2.5	2.2
Other Gram negative aerobic bacteria	292	2.3	2.1	2.1	1.9	2.3	3.1	2.7	2.8	2.5	2.9
Bacteroides spp.	258	1.9	2.2	2.3	2.2	2.0	2.5	2.9	3.0	2.9	2.6
Other anaerobic bacteria	286	2.4	2.5	2.5	2.3	2.3	2.8	2.9	2.8	2.8	2.6
Yeasts	195	1.9	1.7	1.8	1.9	1.5	2.5	2.3	2.3	2.5	1.9
Total	**12,706**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 29 and Figure 32, aerobic Gram positive and Gram negative bacteria represented 54.3% and 39.9% of all isolates, respectively. The predominance of Gram positives among all isolates was at the same level as in previous years. The most common Gram positive species were coagulase negative staphylococci which represented 19.3% 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 42.3% Gram positives and 50.6% 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 7.3% in 2010. The prevalence of viridans and non-haemolytic streptococci was higher (5.9%) than in previous years. The prevalence of coagulase negative staphylococci was reduced from 22.3% in 2009 to 19.3% in 2010, but this may be due to changes in blood culture practices.

E. coli (29.6%) and other *Enterobacteriaceae* (15.9%) accounted for the vast majority of aerobic Gram negative isolates, but the proportions have remained relatively unchanged since 2005. *Pseudomonas* spp. (2.2%) has been fairly stable after a peak in 2005 (2.8%), all figures excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 4.3% (5.2% excluding skin flora) and yeasts accounted for 1.5% (1.9% excluding skin flora). The major pathogens among anaerobes were members of the *Bacteroides fragilis* group (2.0%/2.6%) and among yeasts *Candida albicans* (1.0%/1.3%). However, a multitude of other species was also represented.

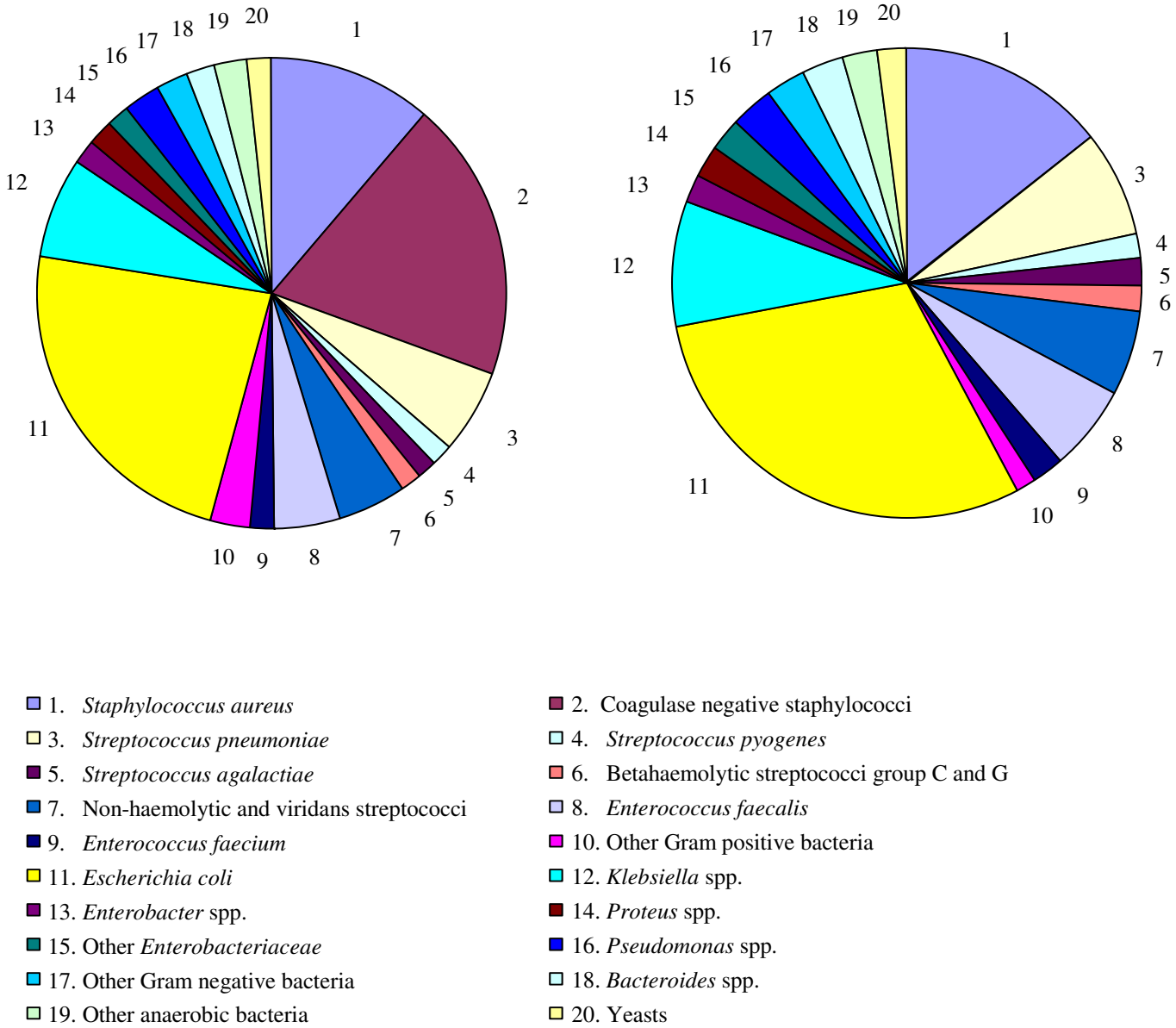

FIGURE 32. Distribution of all blood culture isolates (left, n=12,706) and blood culture isolates excluding common skin contaminants (right, n=10,010) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. The figure is based on data from the information systems of all Norwegian laboratories except one in 2010.

Escherichia coli in blood cultures

TABLE 30. *Escherichia coli* blood culture isolates (n=1,359). 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*	≤ 0.5	> 8	0.3	62.5	37.2
Piperacillin-tazobactam	≤ 8	> 16	94.8	3.0	2.2
Cefuroxime*	≤ 0.5	> 8	0.3	94.5	5.2
Cefotaxime	≤ 1	> 2	96.6	0.1	3.3
Ceftazidime	≤ 1	> 4	96.3	0.4	3.3
Meropenem	≤ 2	> 8	99.9	0.0	0.1
Gentamicin	≤ 2	> 4	94.8	0.4	4.8
Nalidixic acid	≤ 16	> 16	84.8	-	15.2
Ciprofloxacin	≤ 0.5	> 1	92.3	0.5	7.2
Tigecycline	≤ 1	> 2	98.9	0.1	1.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	74.4	1.7	23.9
ESBL	Negative	Positive	97.0	-	3.1

*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. The NWGA participates in the European breakpoint harmonization process. Norwegian breakpoints therefore correspond to common EUCAST breakpoints except for ampicillin and cefuroxime where the wild type is defined as intermediately susceptible by NWGA. In NORM 2010, the surveillance protocol remained unchanged from 2009 except for the omission of tobramycin. Breakpoints are presented in Table 30.

The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobial agents such as cefotaxime (96.6%), ceftazidime (96.3%), gentamicin (94.8%), piperacillin-tazobactam (94.8%) and tigecycline (98.9%) (Table 30). However, for several of these agents there was a reduction in the prevalence of susceptibility by approximately one percentage point. The prevalence of non-susceptibility to gentamicin noted from 2004 to 2009 continued to increase from 2009 (0.4% I and 3.6% R) to 2010 (0.4% I and 4.8% R, Figure 33). This increase is of great concern as aminoglycosides are core components of empirical treatment for severe infections in Norway. A non-susceptibility rate among *E. coli* exceeding 5% may jeopardize this therapeutic approach. The molecular basis for aminoglycoside resistance in Norway is presently being explored.

The prevalence of non-suscpetibility to ciprofloxacin declined for the first time in ten years of surveillance. The decrease from 8.6% in 2009 to 7.7% in 2010 is encouraging but must be confirmed over the coming years. The temporal association between ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 34. A similar association between quinolone use and resistance in systemic *E. coli* isolates is reported from many other European countries. The prevalence of resistance to the indicator antibiotic nalidixic acid (15.2%) as well as ampicillin (37.2%) and trimethoprim-sulfamethoxazole (23.9%) are all at the same level as in 2009.

In 2010, 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 42 isolates (3.1%) were reported as ESBL positive which is an increase from 1.2% in 2007, 1.5% in 2008 and 2.5% in 2009. The 42 isolates originated from 18 different hospitals with up to seven isolates from each institution. The ESBL isolates were all resistant to ampicillin, cefuroxime, cefotaxime and ceftazidime. Many isolates were intermediately (n=4) or even fully susceptible (n=31) to piperacillin/tazobactam and tigecycline (n=40), but the majority were co-resistant to ciprofloxacin (27/42), gentamicin (18/42) and/or trimethoprim-sulfamethoxazole (26/42). The ESBL isolates were molecularly characterised by PCR and DNA sequencing which revealed a predominance of CTX-M groups 1 (n=26) and 9 (n=10). The remaining isolates harboured SHV (n=3), TEM (n=1) and derepressed AmpC (n=1) sequences. The results are in accordance with previous surveys from Norway. A single isolate displayed resistance to meropenem, and molecular analysis revealed the presence of the gene encoding New Dehli beta-lactamase 1 (NDM-1). The isolate was concomitantly resistant to all other antimicrobials in the protocol except tigecycline. This is the first detection of NDM-1 in a clinical isolate in Norway. The patient had been admitted to hospital in India within the last year and presented with bacteremia secondary to a urinary tract infectuion.

It should be noted that classification of ESBLs solely on the basis of non-susceptibility to cefotaxime or ceftazidime would have overestimated the prevalence of ESBL by approximately 23% (3.7% instead of 3.0%).

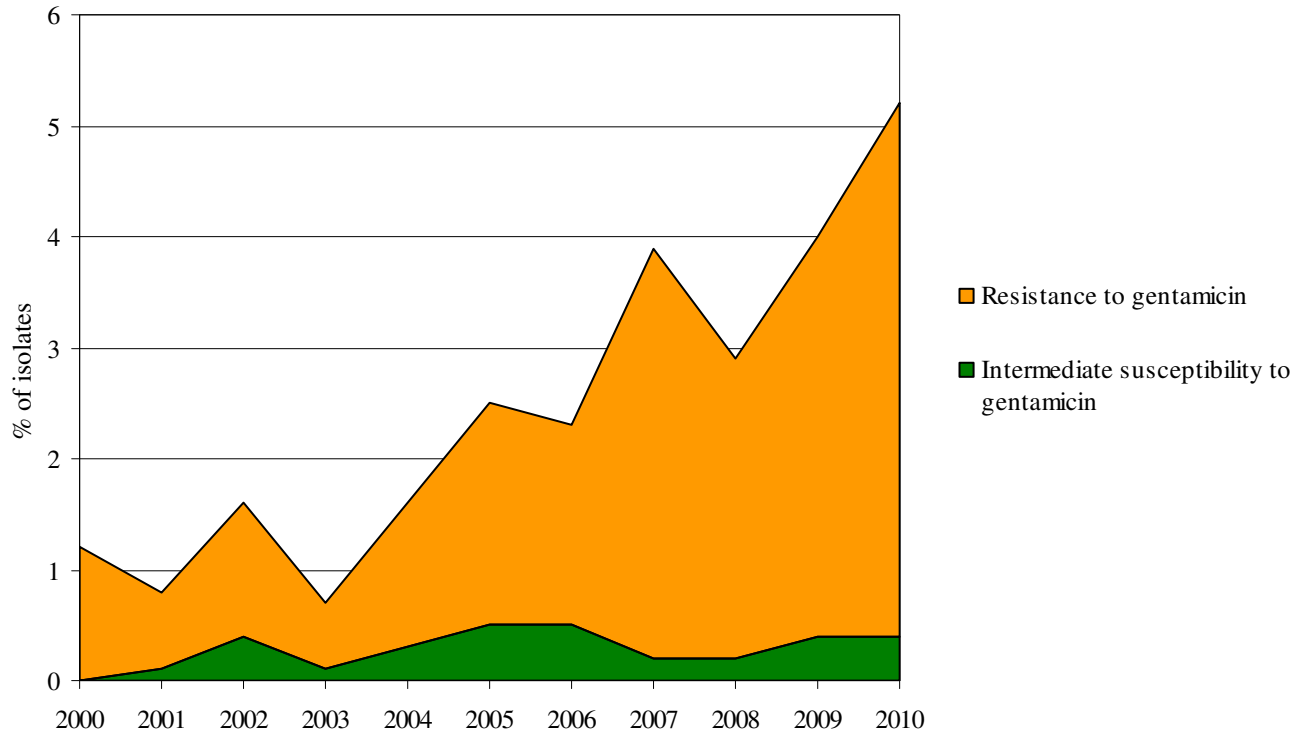

FIGURE 33. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2010.

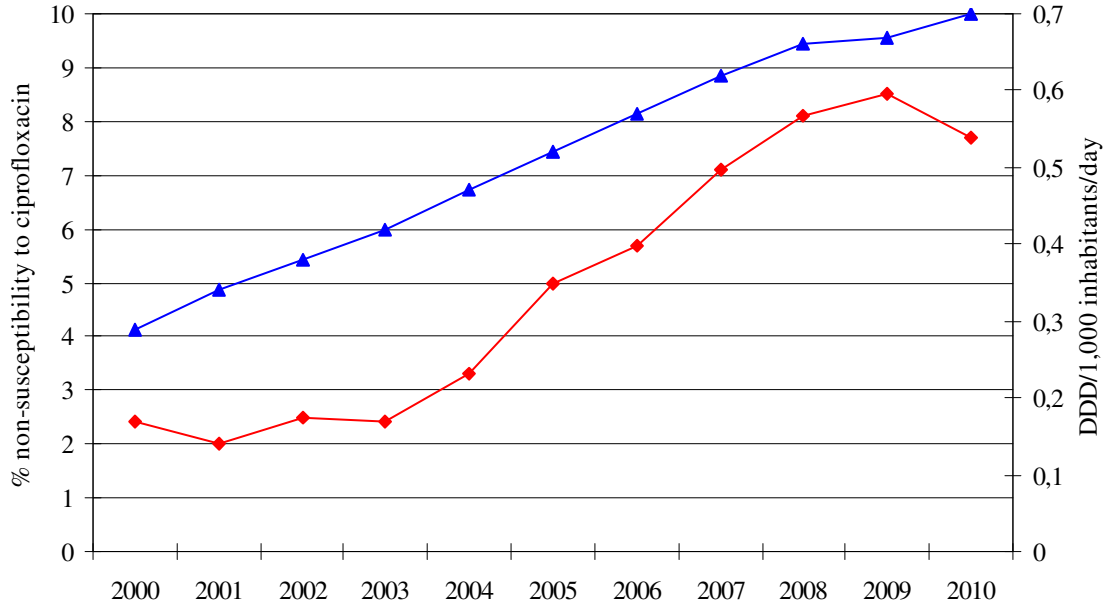

FIGURE 34. Prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2010 breakpoints (red) versus usage of ciprofloxacin (blue) 2000-2010.

Escherichia coli in urine

TABLE 31. *Escherichia coli* urinary tract isolates (n=1,093). 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*	≤ 0.5	> 8	0.1	68.5	31.4
Mecillinam**	≤ 8	> 8	95.6	-	4.4
Cefuroxime*	≤ 0.5	> 8	0.2	96.5	3.3
Cefotaxime	≤ 1	> 2	98.3	0.0	1.7
Ceftazidime	≤ 1	> 4	98.1	0.2	1.7
Gentamicin	≤ 2	> 4	97.3	0.0	2.7
Nalidixic acid	≤ 16	> 16	88.6	-	11.4
Ciprofloxacin	≤ 0.5	> 1	94.2	0.3	5.5
Nitrofurantoin	≤ 64	> 64	97.7	-	2.3
Trimethoprim	≤ 2	> 4	79.2	0.2	20.6
Trimethoprim-sulfamethoxazole***	≤ 2	> 4	77.7	1.9	20.4
ESBL	Negative	Positive	98.6	-	1.4

*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. **The breakpoint for susceptibility to mecillinam was reduced from S ≤ 8 to S ≤ 1 during the transition to the EUCAST disk diffusion method in 2010/2011. However, as the NORM 2010 protocol was performed using two disk diffusion standards with semi-confluent growth, the results are interpreted according to the previous breakpoints as the new breakpoint has not been developed for these methodologies. ***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 2010 are shown in Table 31 and the results 2000-2010 are shown in Figure 35. As for *E. coli* blood culture isolates, tobramycin was omitted from the surveillance scheme in 2010. The breakpoints used did not change from 2009.

The resistance rates among urinary tract isolates have remained remarkably stable over the last ten years. Approximately 30% of *E. coli* isolates are resistant to ampicillin. The remaining 70% belong to the wild type, which in Norway is categorized as intermediately susceptible. A little more than 20% of *E. coli* isolates are resistant to trimethoprim and trimethoprim-sulfamethoxazole. The prevalence of resistance to mecillinam has increased slightly from 2.6% to 4.4%, but 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 3.5-4.5% over the last five years. The result for 2010 was 5.8% with 0.3% intermediate susceptibility and 5.5% resistance. This is an increase from 4.7% non-susceptibility in 2009 (0.6% intermediate susceptibility and 4.1% resistance). The corresponding rates for blood culture isolates in 2010 were 0.5% intermediate susceptibility and 7.2% resistance. The difference between isolates from systemic and localized infections was also seen for nalidixic acid with 11.4% resistance in urinary tract isolates and 15.2% 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 increasing prevalence of first-step mutations in both bloodstream and urinary tract isolates is cause for great concern.

In total, 15 isolates (1.4%) were reported as ESBL producers. This prevalence is an increase from 2009 (0.5%), but still significantly lower than in blood culture isolates (3.0%). The isolates were retrieved from nine different laboratories in all parts of the country. Two isolates were found in hospitalized patients, while the others were detected in samples submitted from outpatient clinics and general practitioners. The ESBL strains were all resistant to ampicillin, cefuroxime, cefotaxime, ceftazidime and mecillinam. Most of the ESBL isolates were non-susceptible to quinolones (n=10) and trimethoprim-sulfamethoxazole (n=12), but remained susceptible to nitrofurantoin (n=14) and gentamicin (n=11). Carbapenems were not included in the 2010 protocol. By molecular characterisation it was found that the 15 isolates harboured CTX-M groups 1 (n=7), 9 (n=5) and 2 (n=1). The two remaining isolates displayed derepressed AmpC (n=1) and wild type phenotypes. This is in accordance with findings in blood culture isolates and previous surveys. As for blood culture isolates, the ESBL rate would have been significantly higher (3.6%) if it had been reported on the basis of non-susceptibility to cefotaxime and/or ceftazidime without further verification.

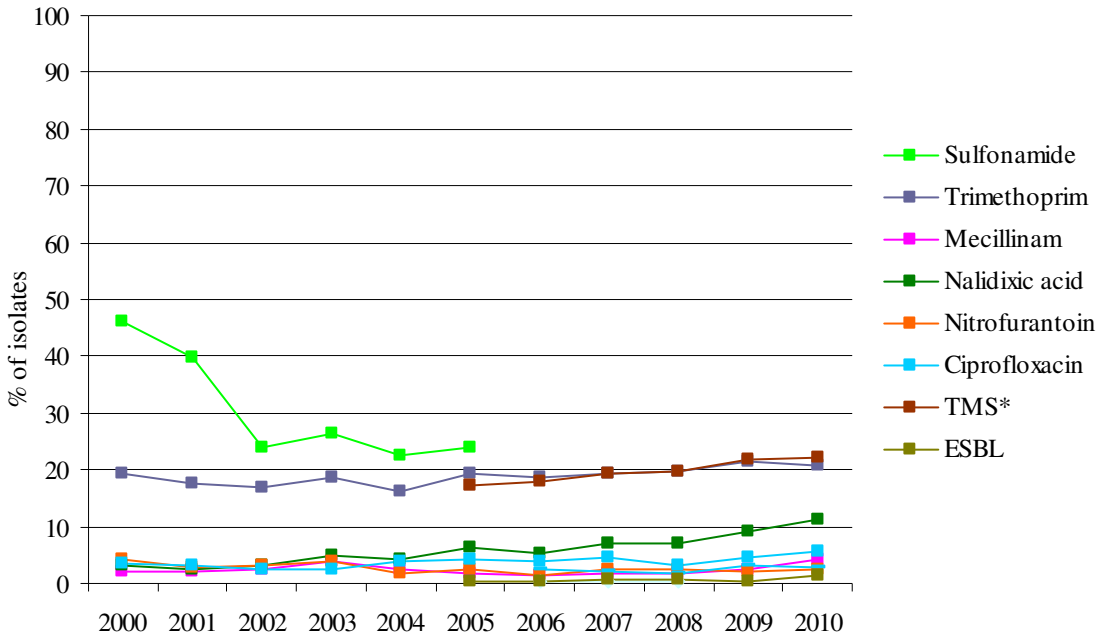

FIGURE 35. Prevalences of non-susceptibility to various antimicrobial agents in urinary tract *E. coli* isolates 2000-2010. The breakpoint for susceptibility to mecillinam was reduced from S ≤ 8 to S ≤ 1 during the transition to the EUCAST disk diffusion method in 2010/2011. However, as the NORM 2010 protocol was performed using two disk diffusion standards with semi-confluent growth, the results are interpreted according to the previous breakpoints as the new breakpoint has not been developed for these methodologies. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in blood cultures

TABLE 32. *Klebsiella* spp. blood culture isolates (n=599). 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	95.0	3.5	1.5
Cefuroxime*	≤ 0.5	> 8	0.0	92.0	8.0
Cefotaxime	≤ 1	> 2	97.2	0.5	2.3
Ceftazidime	≤ 1	> 4	96.7	1.0	2.3
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.8	0.7	1.5
Nalidixic acid	≤ 16	> 16	89.0	-	11.0
Ciprofloxacin	≤ 0.5	> 1	94.8	0.2	5.0
Tigecycline	≤ 1	> 2	80.6	6.7	12.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	82.1	3.5	14.4
ESBL	Negative	Positive	98.5	-	1.5

*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 33. *Klebsiella pneumoniae* blood culture isolates (n=474). 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	95.5	3.4	1.1
Cefuroxime*	≤ 0.5	> 8	0.0	91.6	8.4
Cefotaxime	≤ 1	> 2	96.8	0.2	3.0
Ceftazidime	≤ 1	> 4	96.2	0.8	3.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	97.7	0.8	1.5
Nalidixic acid	≤ 16	> 16	87.8	-	12.2
Ciprofloxacin	≤ 0.5	> 1	93.9	0.2	5.9
Tigecycline	≤ 1	> 2	77.9	7.8	14.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	79.7	3.2	17.1
ESBL	Negative	Positive	98.1	-	1.9

*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 oxytoca* blood culture isolates (n=114). 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	3.5	3.5
Cefuroxime*	≤ 0.5	> 8	0.0	93.9	6.1
Cefotaxime	≤ 1	> 2	98.2	1.8	0.0
Ceftazidime	≤ 1	> 4	98.2	1.9	0.0
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	98.2	0.0	1.8
Nalidixic acid	≤ 16	> 16	93.9	-	6.1
Ciprofloxacin	≤ 0.5	> 1	98.2	0.0	1.8
Tigecycline	≤ 1	> 2	91.3	2.6	6.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	91.2	4.4	4.4
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 474 *K. pneumoniae* (79.2%), 114 *K. oxytoca* (19.0%), and 11 (1.8%) isolates not identified to the species level, giving a total of 599 *Klebsiella* spp. isolates (Tables 32-34). The species distribution was not significantly changed from 2009. 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 is not given as one of the disk suppliers has not defined breakpoints for this agent.

The majority of *Klebsiella* spp. isolates remained fully susceptible to meropenem and aminoglycosides. The prevalence of non-susceptibility to gentamicin continued to increase from 1.0% in 2008 and 1.4% in 2009, to 2.2% in 2010. As opposed to earlier years, aminoglycoside resistance was also detected in 1.8% of *K. oxytoca* isolates. The high prevalence of nonsuscpetibility to tigecycline (19.4%) is not supported by other studies from Scandinavian countries, and the limited clinical use of tigecycline does not explain this phenomenon. The majority of isolates display inhibition zones within a few millimeters of the breakpoints. One may therefore suspect that methodological problems or breakpoints intersecting the wild type population have biased the result. It will be important to reevaluate the situation after the transition to the EUCAST disk diffusion method in 2011.

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 4.2% to 5.2% non-susceptibility to

ciprofloxacin in *Klebsiella* spp. (6.1% in *K. pneumoniae*) from 2009 to 2010 may indicate a gradual increase. Non-susceptibility to trimethoprim-sulfamethoxazole continued to increase from 14.4% in 2009 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*. Only 1.8% of *K. oxytoca* were non-susceptible to ciprofloxacin and 8.8% were non-susceptible to trimethoprim-sulfamethoxazole, compared to 6.1% and 20.3% 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 of *K. oxytoca*.

Most *Klebsiella* spp. isolates were susceptible to cefotaxime (97.2%), ceftazidime (96.7%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (95.0%, Figure 36). The rate of non-susceptibility to cefotaxime decreased from 5.1% in 2009 to 2.8% in 2010, and this was linked to a decreasing rate of reported ESBL isolates from 2.6% in 2009 to 1.5% in 2010. The slowly increasing trend over the last years has thus apparently been reversed, but further surveillance is needed to ascertain whether this change is sustainable. 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 and suspected isolates were confirmed by molecular characterisation of resistance determinants. A total of nine isolates (1.5%) were reported as ESBL producers from the laboratories, all of them speciated as *K. pneumoniae*. The isolates originated from five different laboratories. All ESBL isolates were resistant to cefuroxime, cefotaxime and ceftazidime. Cross-resistance was relatively common to ciprofloxacin (7/9), trimethoprim-sulfamethoxazole (8/95) and gentamicin (7/95), whereas most isolates were susceptible to piperacillin-tazobactam (5/9), tigecycline (6/95) and meropenem (9/9). Molecular characterisation of eight of the isolates at the Reference Centre for Detection of Antimicrobial Resistance (K-Res) confirmed the presence of CTX-M group 1 (n=7) and SHV-11 (n=1) determinants.

The overall prevalence of ESBL was not adjusted in spite of the molecular data due to the very limited number of isolates subjected to these analyses. As for *E. coli* blood culture and urinary tract isolates, the ESBL rate would have been significantly higher (3.8%) if it had been reported only on the basis of non-susceptibility to cefotaxime and/or ceftazidime without further verification.

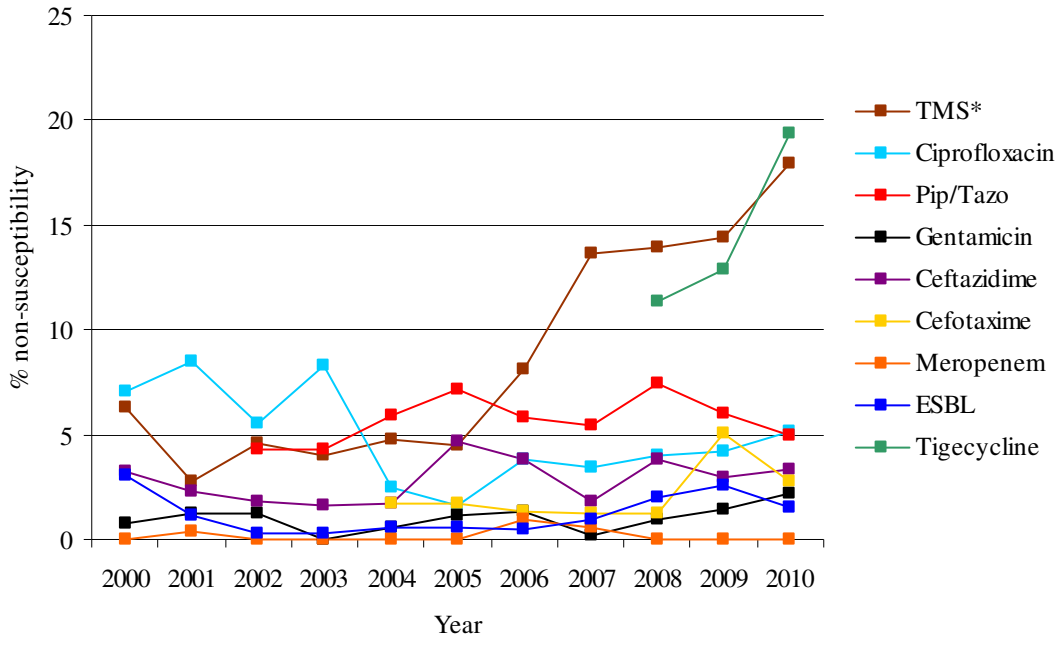

FIGURE 36. Prevalence of non-susceptibility to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2010. *TMS=Trimethoprim-sulfamethoxazole.

Emerging $ESBL_{CARBA}$ (carbapenemases): an update on the Norwegian situation

The global increase in antibiotic resistance among Gram-negative bacteria is mainly caused by the dissemination of beta-lactamases encoded by mobile genetic elements associated with other resistance genes. Beta-lactamases referred to as $ESBL_{CARBA}$ or carbapenemases are now disseminating globally among several clinically important Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (3). There are two dominating classes of $ESBL_{CARBA}$, serine carbapenemases such as KPC and OXA-carbapenemases and metallo-beta-lactamases (MBLs) such as VIM, NDM, and IMP (Table X). $ESBL_{CARBA}$-enzymes have the ability to inactivate virtually all beta-lactam antibiotics, with the exception of $ESBL_{CARBA-B}$ and OXA-48 enzymes which do not inactivate aztreonam and cephalosporins, respectively (1). The level of resistance to carbapenems conferred by $ESBL_{CARBA}$ enzymes depends on the host species and co-existing synergistic resistance mechanisms (efflux, impermeability, or target mutations) (1). Particularly among Enterobacteriaceae $ESBL_{CARBA}$ producers can occur as susceptible to carbapenems using current clinical breakpoints. Thus, detection of $ESBL_{CARBA}$ producers can therefore be a challenge in diagnostic clinical microbiology.

TABLE 35. Dominating $ESBL_{CARBA}$ enzymes and species distribution.

$ESBL_{CARBA}$					
Serine carbapenemases				Metallo-β-lactamases	
$ESBL_{CARBA-A}$	Species	$ESBL_{CARBA-D}$	Species	$ESBL_{CARBA-B}$	Species
KPC	Enterobacteriaceae	OXA-23/-24/-58	*A. baumannii*	VIM	Enterobacteriaceae
	P. aeruginosa	OXA-48	Enterobacteriaceae	NDM	*P. aeruginosa*
	A. baumannii			IMP	*A. baumannii*

Although $ESBL_{CARBA}$ enzymes have disseminated globally there are certain regions or countries that are hot-spots with a prevalence that has reached or is close to reaching an epidemic situation (3). KPC-enzymes have become a serious problem in areas of North-America, Israel and Greece. The global dissemination of KPC can largely be associated with a specific clone (MLST sequence type ST258) or related clones. The hot-spots for VIM-enzymes among Enterobacteriaceae have largely been countries along the Mediterranean basin with a massive dissemination in Greece. Due to an unprecedented global dissemination, the NDM-1 enzyme has recently attracted attention both in the public media and the scientific community (3). Within only a couple of years NDM-1 has disseminated globally, been identified in numerous Gram-negative species, and worryingly also in environmental samples (4). Studies have shown a widespread distribution in the Indian subcontinent and dissemination has often been linked to medical tourism in India (3). Based on isolates submitted to the Reference Centre for Detection of Antimicrobial Resistance (K-res) the number of $ESBL_{CARBA}$-producers in Norway is still low (Figure 37).

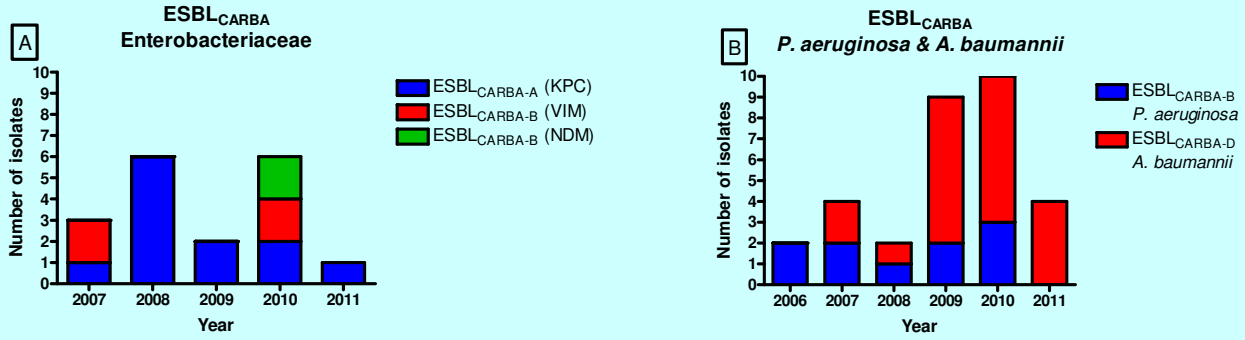

FIGURE 37. Number of $ESBL_{CARBA}$-producers and respective $ESBL_{CARBA}$-enzyme identified in isolates submitted to K-res from 2006 up to June 2011.

The majority of cases in Norway have been linked to recent hospitalisation abroad in countries with a known high prevalence (2). However, cases of intra-hospital spread and in between hospitals, due to patient transfer, have been observed after the import of $ESBL_{CARBA}$-producers. Worryingly, at one Norwegian hospital a small number of clinical clonally related KPC-producing *K. pneumoniae* as well as similar hospital environmental strains were detected over a long-time period, illustrating the epidemic potential also in a Norwegian setting. To maintain a low prevalence of $ESBL_{CARBA}$-producers in Norway it is important to focus on rapid, sensitive detection methods and targeted hygiene control measures. This requires updated knowledge on how to detect $ESBL_{CARBA}$-producers in the laboratory and efficient screening of patients that have been hospitalised abroad.

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4. Walsh, T. R., J. Weeks, D. M. Livermore, et al. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. Lancet Infect. Dis. 2011; 11:355-362.

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Pseudomonas aeruginosa in blood cultures

TABLE 36. *Pseudomonas aeruginosa* blood culture isolates (n=200). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 16	> 16	97.0	-	3.0
Ceftazidime	≤ 8	> 8	97.0	-	3.0
Aztreonam*	≤ 1	> 16	4.5	93.5	2.0
Imipenem	≤ 4	> 8	93.0	2.0	5.0
Meropenem	≤ 2	> 8	96.0	2.5	1.5
Doripenem	≤ 1	> 4	97.0	1.5	1.5
Gentamicin	≤ 4	> 4	97.5	-	2.5
Tobramycin	≤ 4	> 4	99.5	-	0.5
Amikacin	≤ 8	> 16	98.0	1.0	1.0
Ciprofloxacin	≤ 0.5	> 1	92.0	3.5	4.5

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

TABLE 37. *Pseudomonas aeruginosa* blood culture isolates (n=200). Distribution (%) of MICs (mg/L).*

	≤ 0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Pip/Tazo**						1.0	1.0	16.0	61.0	14.5	3.5	1.5			1.5
Ceftazidime						2.5	45.5	42.5	6.5		1.0	0.5	1.0		0.5
Aztreonam						1.0	3.5	43.5	37.5	8.0	4.5	1.0	0.5		0.5
Imipenem					1.5	6.5	34.5	43.0	7.5	2.0	1.5	3.5			
Meropenem	0.5	0.5	7.5	23.0	26.0	17.0	15.5	6.0	1.5	1.0		1.5			
Doripenem	0.5	1.0	16.0	28.0	23.0	19.5	9.0	1.5		1.0		0.5			
Gentamicin					0.5	4.0	8.0	56.5	28.5	1.0	1.0				0.5
Tobramycin					6.0	24.5	55.0	13.5	0.5						0.5
Amikacin						0.5	4.5	21.0	57.5	14.5	1.0			0.5	0.5
Ciprofloxacin		1.0	17.0	50.0	17.0	7.0	3.5	2.0	0.5	0.5	0.5	1.0			

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

RESULTS AND COMMENTS

NORM previously examined *Pseudomonas aeruginosa* blood culture isolates from 2002 and 2003 as reported in NORM/NORM-VET 2005. The present survey included blood culture isolates from 2010. Both protocols were performed by MIC determination, and the results are therefore comparable in spite of breakpoint changes.

The isolates were generally susceptible to all relevant anti-pseudomonal antimicrobials, and there were no significant changes in the rates of resistance compared to 2002/2003. A total of 162 isolates (81%) did not display acquired resistance of any kind, whereas 38 isolates (19%) were non-susceptible to various antimicrobials in different combinations. The most common resistance phenotypes were linked to imipenem (n=14, 7.0%) and ciprofloxacin (n=16, 8.0%). Seven isolates were non-susceptible to one or more aminoglycosides and 17 isolates were non-susceptible to one or more carbapenems. Two of these isolates were multi-resistant and were non-suscpetible to all antimicrobials (n=1) or only susceptible to tobramycin (n=1). The molecular basis for these phenotypes will be further explored.

Neisseria gonorrhoeae

TABLE 38. *Neisseria gonorrhoeae* from all specimen types (n=211). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.064	> 1	2.4	55.0	42.7
Cefotaxime	≤ 0.125	> 0.125	86.3	-	13.7
Ceftriaxone	≤ 0.125	> 0.125	99.1	-	0.9
Cefixime	≤ 0.125	> 0.125	88.2	-	11.8
Azithromycin	≤ 0.25	> 0.5	58.2	20.9	20.9
Tetracycline	≤ 0.5	> 1	18.5	20.4	61.1
Spectinomycin	≤ 64	> 64	100.0	-	0.0
Ciprofloxacin	≤ 0.032	> 0.064	38.4	0.5	61.1
Beta-lactamase	Negative	Positive	71.6	-	28.4

TABLE 39. *Neisseria gonorrhoeae* from all specimen types (n=211). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G**		0.5	0.5	1.4	3.3	14.2	16.1	8.1	13.3	15.6	6.2	4.7	2.4	13.7		
Cefotaxime	5.7	18.5	17.1	18.0	16.1	10.9	5.2	6.6	1.9							
Ceftriaxone	24.2	24.6	19.0	16.6	8.5	6.2	0.5	0.5								
Cefixime			44.1	27.5	10.0	6.6	10.9	0.5	0.5							
Azithromycin				4.7	15.6	16.6	21.3	20.9	8.5	4.3	5.2	1.4	1.4			
Tetracycline	0.5	0.5		0.5	0.5	1.9	3.3	11.4	20.4	16.1	5.7	2.8	12.8	17.1	3.8	2.8
Spectinomycin											5.7	52.6	40.8	0.9		
Ciprofloxacin	32.2	4.7	1.4		0.5		0.5	1.4	3.3	11.4	12.8	5.2	4.3	22.3		

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

RESULTS AND COMMENTS

Neisseria gonorrhoeae was previously surveyed in 2003 and reported in NORM/NORM-VET 2005. In addition to NORM, *N. gonorrhoea* is continously monitored through the Norwegian notification system for communicable diseases (MSIS). However, the clinical and epidemiological data in MSIS could not be linked to the detailed microbiological information in NORM. The present analysis is thus based on the relatively sparse epidemiological information available at the laboratories.

A total of 211 strains were available for analysis. Most isolates were reported to originate from "secretions" (n=173), whereas a few were specified as being recovered from throat (n=9) or eye (n=1) swabs. The clinical samples of twenty-eight isolates were either unknown (n=23) or "others" (n=5). The geographical location where the infection was acquired was in most cases unknown (n=173). The remaning cases originated from Norway (n=11), Europe outside Norway (n=11), Asia (n=18), South-America (n=4) or Africa (n=2). From MSIS it is known that gonococcal infections frequently are acquired abroad with some secondary transmission in sexual networks within Norway. There is an ongoing outbreak among men who have sex with men (MSM), but the strains linked to this outbreak could not be identified within the NORM protocol. A total of 190 isolates originated from men whereas only 21 were recovered from women.

The results of the susceptibility testing are presented in Tables 38-39 and Figure 38. The majority of isolates were non-susceptible to penicillin G according to EUCAST breakpoints. Sixty isolates (28.4%) produced beta-lactamase and were phenotypically resistant (n=56) or intermediately susceptible (n=4) to penicillin G. This is at the same level as in 2003 (25.6%). Most beta-lactamase positive isolates (53/60, 88.3%) were also non-susceptible to ciprofloxacin. In addition, 34 isolates were resistant and 112 were intermediately susceptible to penicillin G in spite of being beta-lactamase negative. This may be caused by alterations in penicillin binding proteins (PBPs) and/or reduced permeability through the outer cell membrane. The MIC distribution for beta-lactamase negative isolates in Figure 38 may indicate the presence of a subpopulation with reduced susceptibility to penicillin G around 1-4 mg/L.

The survey included the three cephalosporins cefotaxime, ceftriaxone and cefixime. A considerable number of isolates were categorised as resistant to cefotaxime (n=29, 13.7%) and/or cefixime (n=25, 11.8%). All isolates except two were categorised as susceptible to ceftriaxone, but many of the ceftriaxone susceptible isolates also appeared to have elevated MIC values compared to the wild type. All cephalosporin resistant (n=32) isolates were non-susceptible to penicilllin G, but only two of them were beta-lactamase positive. The elevated MIC values for

cephalosporins were confirmed by the Neisseria Reference Laboratory in Ørebro, Sweden.

The results indicate the emergence of cephalosporin non-susceptible gonococci in Norway, which is of course extremely alarming from both a clinical and a public health perspective. The two most resistant isolates were recently published (Eurosurveillance 2010, 15 (47), 19721- 11) where it was demonstrated that *in vitro* cefixime resistance corresponded to clinical failure. The two isolates were clonally related and belonged to ST_{1407}. It should be noted that the overall prevalence of gonococcal infections is so low in Norway that individual outbreak strains may significantly influence the overall prevalence of resistance. The recommended dosage of cefalosporins may need to be adjusted as a consequence of the increased MICs.

In Norway, ciprofloxacin is recommended for empirical treatment of gonorrhoeae acquired outside South-East Asia. The present results clearly indicate that these guidelines need to be revised. The majority of isolates are now fully resistant to ciprofloxacin which can no longer be recommended unless susceptibility of the individual isolate has been demonstrated. The clinical efficacy of azithromycin for treatment of gonorrhoeae has been questioned, but the present data do not indicate acquired resistance to be a major problem. The breakpoints seem to intersect the wild type distribution in this survey.

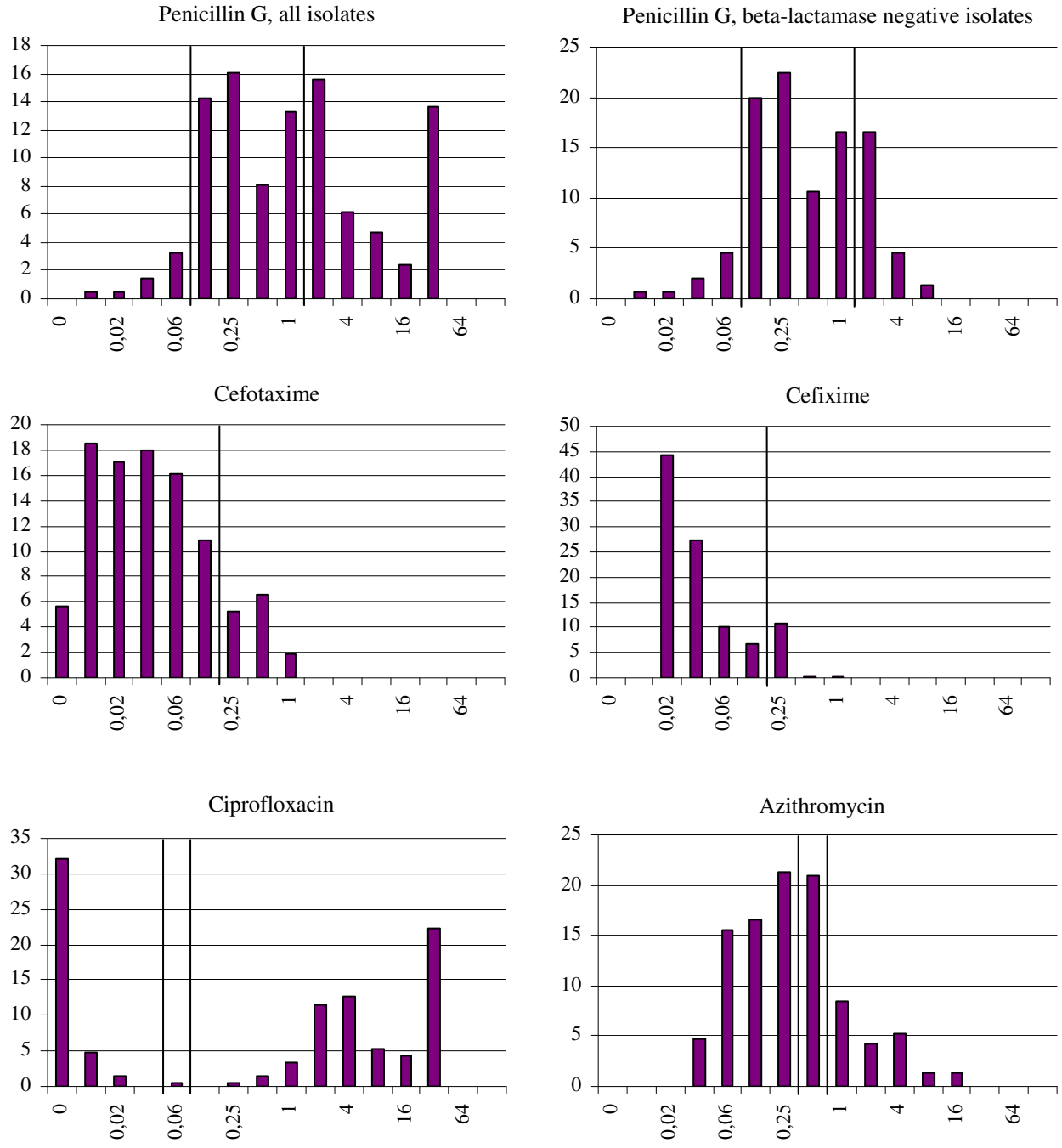

FIGURE 38. Distribution (%) of minimum inhibitory concentrations (mg/L) in 211 *N. gonorrhoeae* isolates to penicillin G (all isolates and beta-lactamase negative isolates), cefotaxime, cefixime, ciprofloxacin and azithromycin. Breakpoints are shown as vertical bars.

Staphylococcus aureus in blood cultures

TABLE 40. *Staphylococcus aureus* blood culture isolates (n=1,005). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	94.6	0.3	5.1
Clindamycin	≤ 0.25	> 0.5	98.0	0.3	1.7
Fusidic acid	≤ 1	> 1	96.6	-	3.4
Ciprofloxacin	≤ 1	> 1	96.1	-	3.9
Gentamicin	≤ 1	> 1	99.5	-	0.5
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.8	0.2	0.0
Tetracycline	≤ 1	> 2	97.1	0.1	2.8
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	99.0	0.4	0.6
Beta-lactamase	Negative	Positive	27.2	-	72.8
Cefoxitin screen	Negative	Positive	97.9	-	2.1
MRSA (*mecA*)	Negative	Positive	99.0	-	1.0
Vancomycin screen	Negative	Positive	100.0	-	0.0

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

RESULTS AND COMMENTS

Ten methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2010 (Table 40) corresponding to a prevalence of 1.0%. This is an increase from 0.4% in 2009 but at the same level as 0.7% in 2008. The resistance phenotype was confirmed by *mecA* PCR in all cases. The isolates originated from six different hospitals and were all isolated from male patients.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. All MRSA isolates had cefoxitin zone diameters below the screening breakpoint. Three MRSA isolates displayed cross-resistance towards ciprofloxacin (n=1), erythromycin and ciprofloxacin (n=1), and tetracycline and fusidic acid (n=1), respectively. All MRSA isolates were fully susceptible to gentamicin, linezolid, rifampicin, vancomycin and trimethoprim-sulfamethoxazole. Eleven methicillin susceptible *S. aureus* (MSSA) isolates (1.1%) displayed reduced cefoxitin zone diameters but were not confirmed as MRSA by genotypic analysis. All these isolates had cefoxitin zone diameters within two millimeters from the screening breakpoint.

The findings are in accordance with reports from the databases of the participating laboratories where 14 out of 1,426 (1.0%) *S. aureus* blood culture isolates were MRSA. None of the 16 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 14/1,442 (1.0%). The Norwegian Surveillance System for Communicable Diseases (MSIS) reported a total number of 912 MRSA cases in 2008. This is a 12% increase from 618 cases in 2009. However, the cases reported to MSIS were predominantly skin and soft tissue infections (82% of infections) and colonisations (n=481). The number of MRSA infections increased to 431 in 2010 compared to 414 in 2009 (+4%) and 348 in 2008, and the number of MRSA colonisations from 304 in 2008 and 402 in 2009 to 481 in 2010 (+20%). Further information about MRSA cases in MSIS is presented on page 62.

A total of 54 *S. aureus* isolates (5.4%) were non-susceptible to erythromycin. This is an increase from 2009 (3.8%). The macrolide resistance phenotypes were determined by the double disk diffusion (DDD) test. Eleven (20%) were constitutively MLS_B resistant, 30 (56%) were inducibly MLS_B resistant and 13 (24%) displayed efflux mediated M type resistance. These figures represent 1.1%, 3.0% and 1.3% 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 slightly reduced in 2010 (3.4%) compared to 2009 (4.5%). This may indicate that the epidemic of fusidic acid resistant *S. aureus* is still receding in Norway. There were no significant changes for ciprofloxacin, gentamicin, rifampicin or trimethoprim-sulfamethoxazole. No isolates displayed growth on the vancomycin agar screen, and all isolates were fully susceptible to linezolid. Figure 39 shows the prevalences of non-susceptibility to various antimicrobials. A total of 72.8% 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 (4.2% vs 2.9%), erythromycin (6.0% vs 2.3%), clindamycin (2.0% vs 0.7%), and tetracycline (3.4% vs 1.1%).

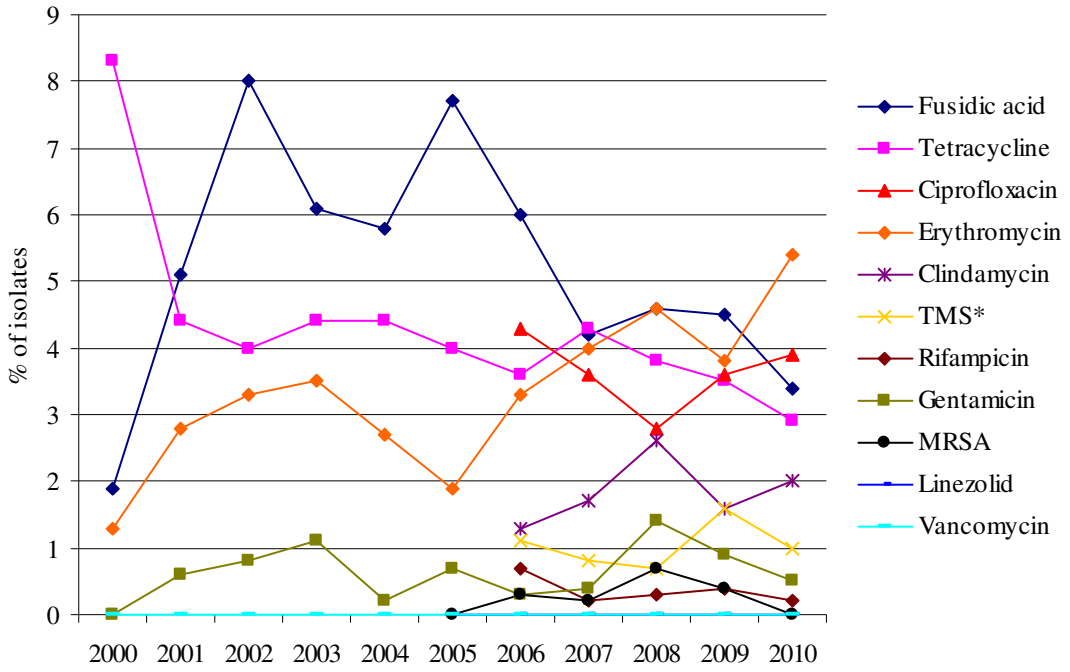

FIGURE 39. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* blood culture isolates 2000-2010. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 41. *Staphylococcus aureus* isolates from wound specimens (n=937). 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	95.1	0.1	4.8
Clindamycin	≤ 0.25	> 0.5	97.8	0.1	2.1
Fusidic acid	≤ 1	> 1	92.3	-	7.7
Ciprofloxacin	≤ 1	> 1	96.2	-	3.8
Gentamicin	≤ 1	> 1	99.3	-	0.7
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.9	0.1	0.0
Tetracycline	≤ 1	> 2	94.9	0.1	5.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	98.7	0.7	0.6
Beta-lactamase	Negative	Positive	25.0	-	75.0
Cefoxitin screen	Negative	Positive	99.0	-	1.0
MRSA (*mecA*)	Negative	Positive	99.4	-	0.6
Vancomycin screen	Negative	Positive	100.0	-	0.0

*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. Six out of 937 (0.6%) isolates were confirmed as MRSA by *mecA* PCR. The prevalence is at the same level as in in 2008 (0.7%) and 2009 (0.8%) and slightly lower than in blood cultures (1.0%, see above). The isolates originated from outpatient clinics (n=4) and general practitioners (n=2) in different parts of the country. The six MRSA isolates all displayed cefoxitin zone diameters below the screening breakpoint. Three of the MRSA isolates were cross-resistant to ciprofloxacin, erythromycin and tetracycline (n=1), fusidic acid and trimethoprim-sulfamethoxazole (n=1), and tetracycline (n=1), respectively. All MRSA isolates were susceptible to rifampicin, linezolid and vancomycin. Only three out of 931 MSSA isolates were false positive by the cefoxitin test (0.3%).

The high prevalence of resistance to fusidic acid in *S. aureus* wound isolates continued to decline from a peak of 25.0% in 2004 to 7.7% in 2010, see Table 41 and Figure 40. One may speculate that this is due to herd immunity to the fusidic acid resistant clone which has caused a high incidence of bullous impetigo in previous years. The prevalence of resistance to fusidic acid is still lower in blood culture isolates (3.4%). For other antimicrobial agents such as tetracycline and erythromycin there were only minor changes from 2009 to 2010, and the prevalences of non-susceptibility were in general similar for blood culture isolates and isolates from wound specimens. A total of 46 (4.9%) isolates were non-susceptible to erythromycin and further examined for determination of resistance phenotype. The majority (31/46, 67% of macrolide resistant isolates) were inducibly resistant to clindamycin, thus representing the $iMLS_B$ phenotype. Only a few isolates were either constitutively resistant to clindamycin (n=7) or low-level resistant to erythromycin (n=8), expressing efflux mediated M type resistance. The findings are in accordance with the results from blood culture isolates.

A total of 75.0% of the isolates were beta-lactamase positive, which is at the same level as in previous years. Resistance to fusidic acid was significantly more common among the 703 beta-lactamase positive isolates (9.1%) than among the 234 beta-lactamase negative ones (3.4%). A similar trend was seen for erythromycin (5.3% vs 3.4%) and tetracycline (5.7% vs 3.0%), but the opposite was the case for ciprofloxacin with 4.7% resistance in beta-lactamase negative isolates and 3.6% resistance in beta-lactamase positive ones.

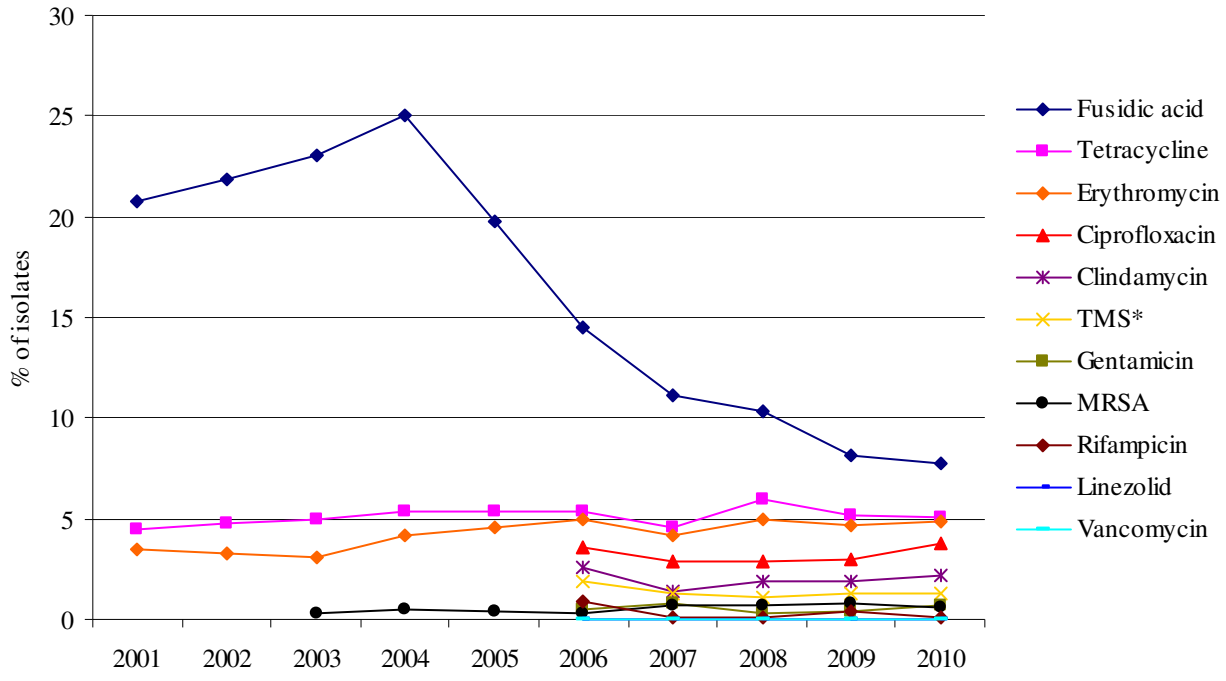

FIGURE 40. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* wound isolates 2000 – 2010. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

MRSA infections in humans in Norway 2010

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been notifiable in Norway since 1995 and colonisation was made notifiable in 2005. A total of 912 cases of MRSA were reported in 2010, giving an incidence rate of 19 per 100,000 population. The incidence rate per county is shown in Figure 43. Four hundred thirty-one (47 %) of the cases had an infection and 481 were colonised (Figure 41). Men and women were equally affected. At the time of diagnosis 192 (21%) were inpatients, 74 (8%) were residents in nursing homes and 617 (67%) were outpatients. Health care workers accounted for 54 of the reported cases (Figure 42). Three hundred fifty-four (82 %) of all MRSA-infections were reported with a clinical picture of skin- or wound infections. Fifty cases were notified with other non-severe infections, while 15 (3%) were reported with systemic infections or infections in inner organs.

The main objective of the Norwegian MRSA guidelines is to prevent MRSA from becoming endemic in health care institutions. In the last five 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. In addition, a stable low number of health care personnel have annually been reported infected or colonised with MRSA.

The low incidence of severe MRSA infections corresponds with the results from the NORM surveillance system where less than 1% of *Staphylococcus aureus* isolates are resistant to methicillin. This may indicate that the increasing number of MRSA colonisations and non-severe infections, mainly among outpatients, to a large extend is a result of more active screening and contact tracing, while the stable low number of severe infections indicates that the incidence of MRSA in the general population still is on a low level.

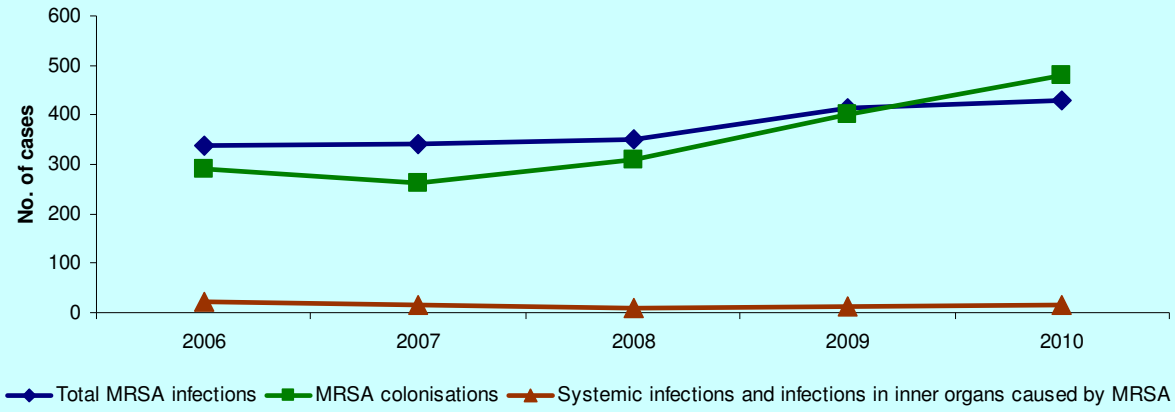

FIGURE 41. Reported cases of MRSA infection and colonisation. 2006 – 2010.

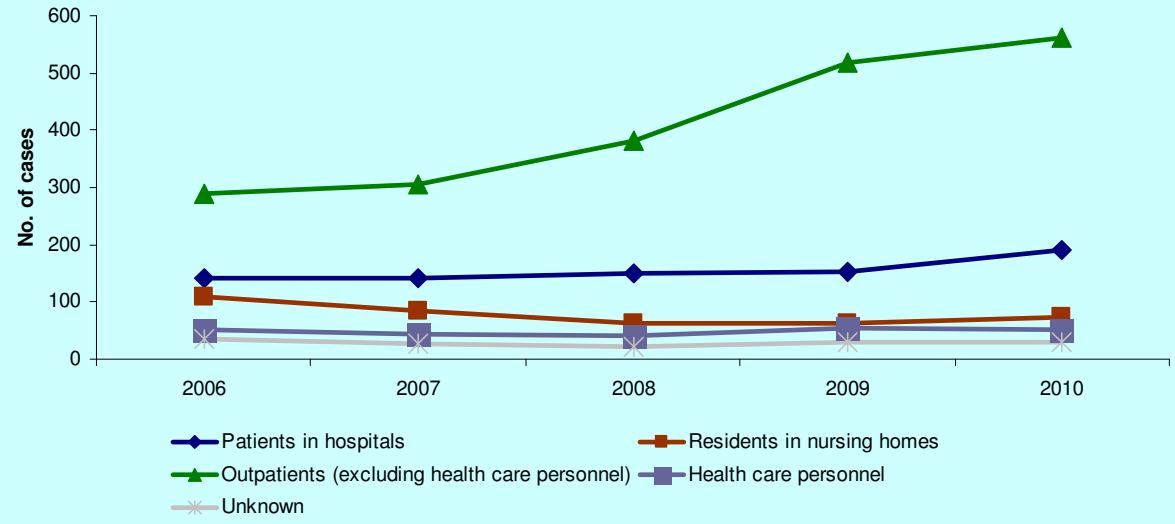

FIGURE 42. Reported cases of MRSA infections and colonisations in Norway 2006 – 2010, distributed by the type of health care contact.

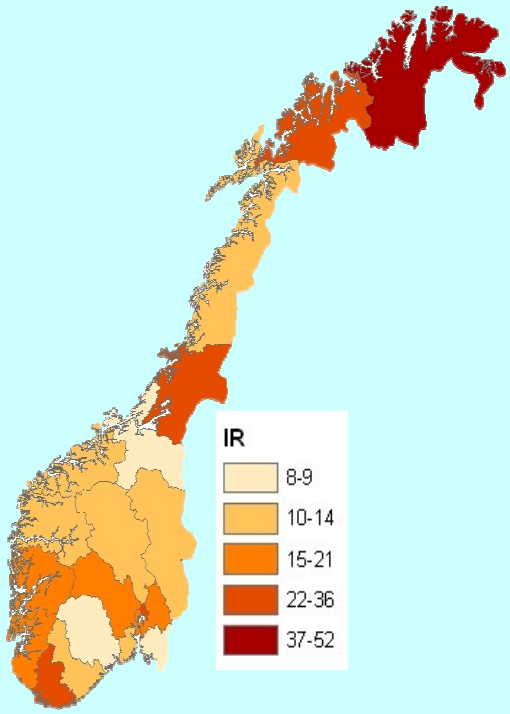

FIGURE 43. Number of MRSA cases per 100,000 inhabitants by county in Norway in 2010.

The Reference Laboratory for MRSA, St. Olav University Hospital, Trondheim, received 918 MRSA isolates in 2010. A total of 183 different spa-types were identified and the six most frequent were (spa-type, n (%)): t002, n=95 (10.3 %), t008, n=81 (8.8 %), t019, n=80 (8.7 %), t044, n=52 (5.7 %), t223, n=37 (4.0 %) and t127, n=35 (3.8 %). Eighty-five spa-types were reported as single events.

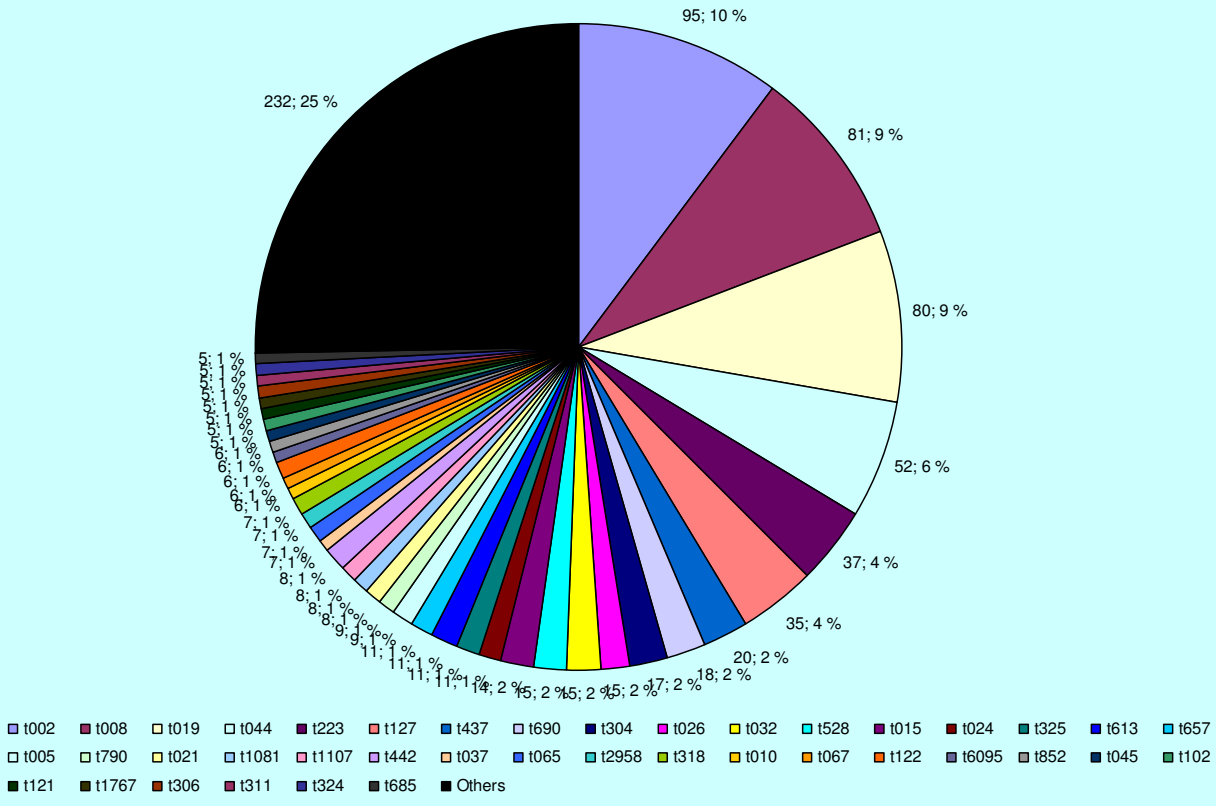

FIGURE 44. Distribution of spa-types in Norwegian MRSA isolates in 2010.

Based on spa-type, all isolates were characterised in MLST clonal complex. Seven hundred and twelve isolates (78 %) occurred in the six most prevalent clusters (CC, n (%)): CC5, n=177 (19.3 %), CC8, n=154 (16.8 %), CC30, n=124 (13.5 %), CC22, n=110 (12.0 %), CC45, n=81 (8.8 %), and CC1, n=66 (7.2%). The increase in CC1 compared to previous years (3% in 2008 and 4% in 2009) is mainly due to spa-type t127 (n=35) and t 657 (n=11).

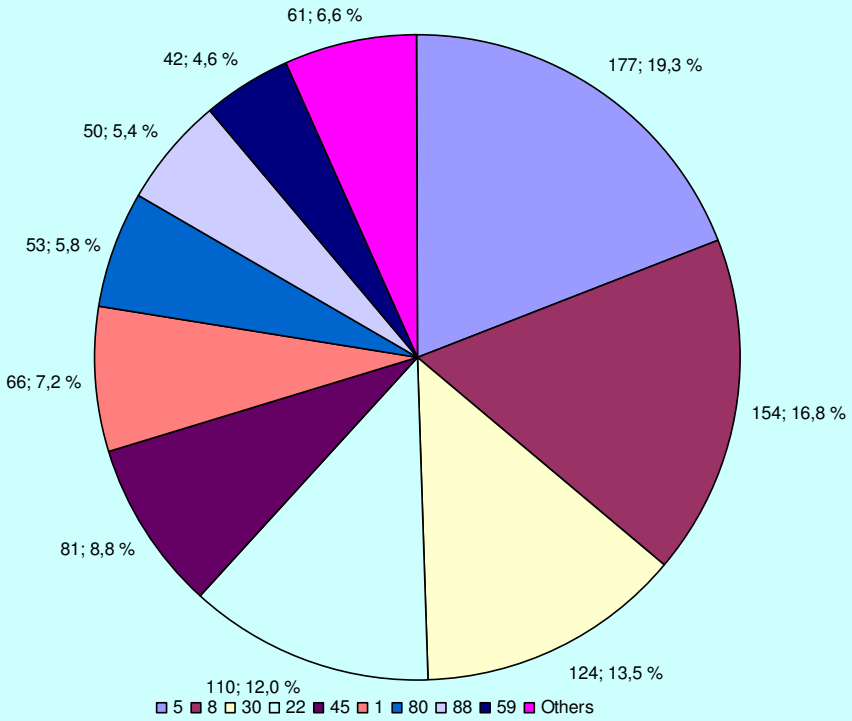

FIGURE 45. Distribution of MLST clonal complex based on spa-type in Norwegian MRSA isolates in 2010.

Susceptibility testing was performed on 794 MRSA isolates collected in 2009 with the EUCAST 2010 agar diffusion method and analysed with breakpoints from AFA 2011. Two hundred seventy-six strains (34.8 %) were sensitive to all antibiotics tested except beta-lactams. The highest proportions of resistance were found for erythromycin (33.2 %) followed by ciprofloxacin (26.1 %). One hundred eighty strains (22.7 %) were resistant to clindamycin, of which 88 strains (49 %) were inducibly resistant. The lowest rates of resistance were found towards mupirocin (1.1%), rifampicin (2.3%), trimethoprim-sulfamethoxazole (5.3%) and chloramphenicol (7.1%). No strains were resistant to linezolid. All isolates were tested for reduced susceptibility to glycopeptides. All were found susceptible except for one isolate. Testing indicates heteroresistance to glycopeptides but further investigations has to be done before concluding.

TABLE 42. Susceptibility characterisation of Methicillin Resistant *Staphylococcus aureus* (MRSA) strains from 2009 (n=794) by the EUCAST 2010 agar diffusion method and breakpoints according to NWGA 2011.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	66.8	0.0	33.2
Clindamycin	≤ 0.25	> 0.5	74.8	2.5	22.7
Fusidic acid	≤ 1	> 1	86.9	-	13.1
Ciprofloxacin	≤ 1	> 1	73.9	-	26.1
Gentamicin	≤ 1	> 1	89.4	-	10.6
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	97.2	0.5	2.3
Tetracycline	≤ 1	> 2	75.9	0.3	23.8
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	93.8	0.9	5.3
Chloramphenicol	≤ 8	> 8	92.9	-	7.1
Mupirocin	≤ 1	> 256	95.1	3.8	1.1

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

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Trond Jacobsen, Lillian Marstein, Anne Kilnes, Hege Snøsen, Frode Width Gran, Norwegian Reference Laboratory forMRSA, St. Olavs University Hospital, Trondheim.

Enterococcus spp. in blood cultures

TABLE 43. *Enterococcus* spp. blood culture isolates (n=561). 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	77.2	0.0	22.8
Gentamicin*	≤ 128	> 128	-	66.1	33.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	98.4	-	1.6

*The wild type is defined as intermediately susceptible.

TABLE 44. *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	-	70.1	29.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	100.0	-	0.0

*The wild type is defined as intermediately susceptible.

TABLE 45. *Enterococcus faecium* blood culture isolates (n=150). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	18.7	0.0	81.3
Gentamicin*	≤ 128	> 128	-	52.7	47.3
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	99.3	-	0.7

*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 43. The surveillance in NORM 2010 included 381 (67.9%) *E. faecalis* isolates, 150 (26.7%) *E. faecium* isolates and 30 (5.3%) unspeciated enterococcal isolates. The proportion of *E. faecalis* isolates has thus been reduced from 73.1% in 2009, whereas the proportion of *E. faecium* has increased from 21.1% last year. 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 2009. Streptomycin is not included in the printed tables as one of the disk diffusion systems does not provide breakpoints for this substance.

E. faecalis was universally susceptible to ampicillin (Table 44). The prevalence of resistance to ampicillin in *E. faecium* remained relatively stable at 81.3% compared to 82.8% in 2009 (Table 45 and Figure 46). The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* was unchanged at 29.9% in 2010 (Figure 47), and the prevalence of HLGR in *E. faecium* has apparently stabilized around 45-50%. Virtually all (70/71, 99%) HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin. Conversely, 70 out of 122 (57%) ampicillin non-susceptible *E. faecium* also displayed HLGR. These findings are similar to the results from previous years.

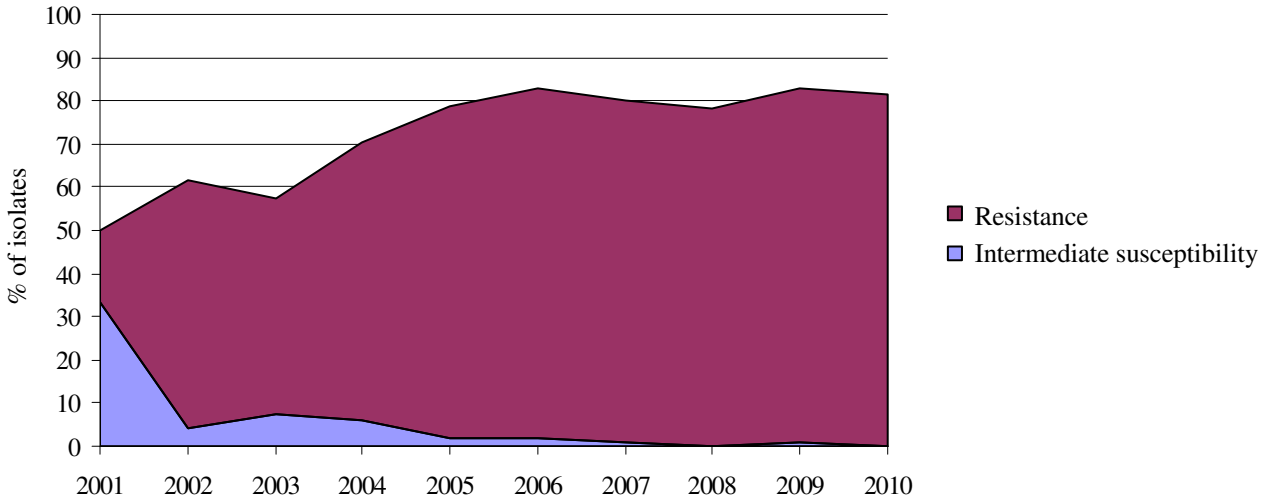

FIGURE 46. Prevalence of intermediate susceptibility and resistance to ampicillin in *E. facium* blood culture isolates 2001-2010. The results are interpreted according to the 2010 breakpoint protocol of S ≤ 4 mg/L and R > 8 mg/L.

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 aminoglycosides and beta-lactams often used for treatment of severe enterococcal infections.

Transferable vancomycin resistance has not yet been established in clinical enterococcal isolates in Norway. Nine isolates were reported as vancomycin resistant (1.6%), but only a single *E. faecium* isolate contained transferable glycopeptide resistance confirmed by positive *vanB* PCR. The remaining vancomycin resistant isolates were all registered as either *E. gallinarum* (n=5), *E. casseliflavus* (n=2) or unspeciated *Enterococcus* sp. which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All the nine isolates were fully susceptible to linezolid.

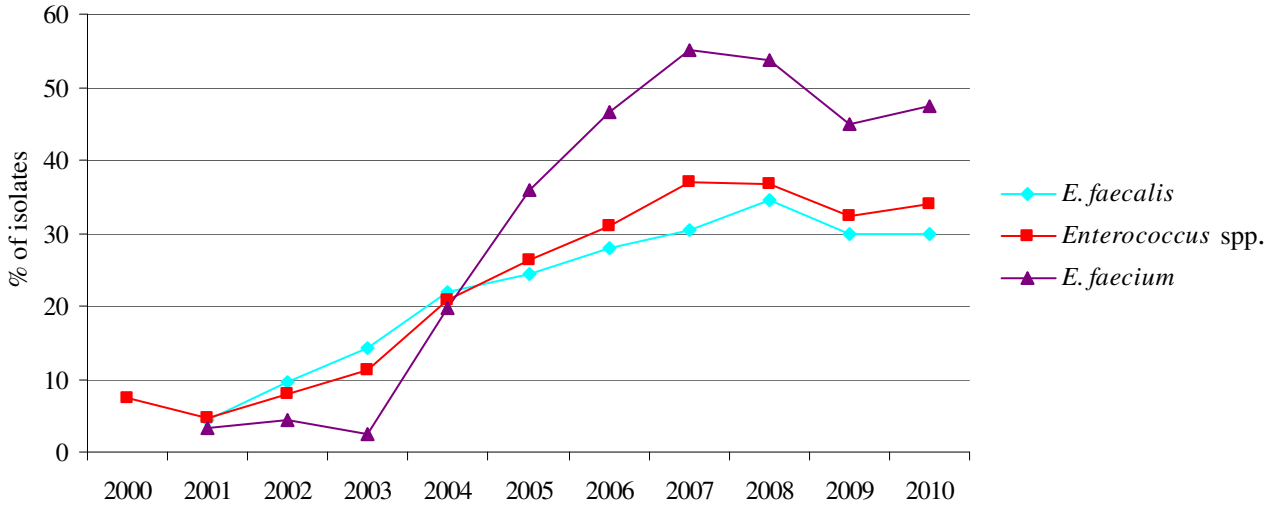

FIGURE 47. Prevalence of high-level resistance to gentamicin in blood culture isolates of *E. faecalis*, *E. faecium* and all enterococci combined during 2000-2010. The breakpoint for high-level resistance was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Enterococcus spp. in urine

TABLE 46. *Enterococcus* spp. urinary tract isolates (n=923). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	94.1	0.0	5.9
Gentamicin*	≤ 128	> 128	-	77.6	22.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	99.9	-	0.1
Trimethoprim*	≤ 0.03	> 1	-	70.1	29.9
Nitrofurantoin	≤ 64	> 64	94.4	-	5.6

*The wild type is defined as intermediately susceptible.

TABLE 47. *Enterococcus faecalis* urinary tract isolates (n=830). 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	-	78.8	21.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	100.0	-	100.0
Trimethoprim*	≤ 0.03	> 1	-	73.4	26.6
Nitrofurantoin	≤ 64	> 64	99.3	-	0.7

*The wild type is defined as intermediately susceptible.

TABLE 48. *Enterococcus faecium* urinary tract isolates (n=49). 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	8.2	0.0	91.8
Gentamicin*	≤ 128	> 128	-	49.0	51.0
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 4	100.0	-	0.0
Trimethoprim*	≤ 0.03	> 1	-	18.4	81.6
Nitrofurantoin	≤ 64	> 64	22.4	-	77.6

*The wild type is defined as intermediately susceptible.

RESULTS AND COMMENTS

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

The proportion of *E. faecalis* was higher (89.9%) among urinary tract isolates than in blood cultures (67.9%). *E. faecalis* isolates from urine were uniformly susceptible to ampicillin, and the prevalence of high-level gentamicin resistance (HLGR) (21.2%) was somewhat lower than in systemic isolates (29.9%). In *E. faecium*, the prevalence of HLGR was similar in urinary tract and blood isolates (approximately 50%), whereas urinary tract isolates were more resistant to ampicillin than blood culture isolates (91.8% versus 81.3%). All isolates were fully susceptible to linezolid, and vancomycin resistance was only detected in a single inherently resistant *E. casseliflavus* strain.

The clinical benefit of trimethoprim in the treatment of enterococcal infections is uncertain, and the substance is only recommended for uncomplicated cystitis. The wild type is classified as intermediately susceptible by EUCAST. As seen in Tables 46-48, the prevalence of *in vitro* resistance was significantly higher in *E. faecium* (81.6%) than in *E. faecalis* (26.6%). A similar situation was seen for nitrofurantoin with 77.6% resistance in *E. faecium* as opposed to 99.3% susceptibility in *E. faecalis*.

Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 49. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=730). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.06	> 2	97.0	3.0	0.0
Cefotaxime	≤ 0.5	> 2	99.6	0.4	0.0
Ceftriaxone	≤ 0.5	> 2	100.0	0.0	0.0
Erythromycin	≤ 0.25	> 0.5	96.0	0.0	4.0
Clindamycin	≤ 0.5	> 0.5	97.9	-	2.1
Tetracycline	≤ 1	> 2	97.3	0.3	2.5
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	95.8	1.0	3.3
Chloramphenicol	≤ 8	> 8	99.7	-	0.3
Oxacillin screen (mm)	≥ 20	< 20	94.4	-	5.6

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

TABLE 50. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=730). 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		5.3	82.2	6.4	3.0	0.7	1.0	0.4	1.0							
Cefotaxime		3.2	83.7	6.8	1.9	2.2	1.2	0.5	0.3	0.1						
Ceftriaxone		12.9	78.2	3.4	2.1	1.9	1.0	0.5								
Erythromycin					10.0	69.7	16.3				0.4	1.0	0.4	0.3		1.9
Clindamycin				0.1	8.4	75.6	13.7			0.3						1.8
Tetracycline					1.4	87.5	8.4			0.3		1.0	1.4	0.1		
TMS**						15.9	74.2	2.5	3.2	1.0	1.1	1.5	0.1	0.5		
Chloramph.							0.1	0.1		57.0	42.3	0.1	0.3			
Norfloxacin										2.3	53.2	43.4	0.7	0.1	0.1	0.1

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	5.6	0.5	1.0	1.4	2.3	7.4	13.4	15.3	14.9	15.3	10.5	8.9	2.3	0.8		0.1

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). Non-shaded cells represent MIC values that are not covered by the standard test method. 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 49-50 and Figure 48. All systemic *S. pneumoniae* isolates submitted to the reference laboratory at the Norwegian Institute of Public Health during 2010 were included in the surveillance protocol. Twenty-five isolates were recovered from cerebrospinal fluids, and four 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 2010. 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 > 0.06, R > 0.5 and R > 0.5 mg/L, respectively).

A total of 3.0% (22/730) *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 on the same level as in 2008 (3.0%) and 2009 (2.9%). Three penicillin G non-susceptible isolates displayed intermediate susceptibility to cefotaxime (MIC values of 1, 1 and 2 mg/L, respectively) but remained susceptible to ceftriaxone. 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 the 22 penicillin G non-susceptible isolates were resistant to oxacillin. Conversely, 19 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test were thus 100.0% and 97.3%, respectively. Many of the penicillin non-susceptible *S. pneumoniae* isolates were also non-susceptible to

erythromycin (6/22), trimethoprim-sulfamethoxazole (11/22) and tetracycline (10/22).

The decrease in the prevalence of macrolide resistance seen in previous years continued in 2010 (Figure 48). A total of 4.0% of the isolates were erythromycin resistant in 2010 compared to 4.6% in 2009, 8.3% in 2008 and 9.4% in 2007. 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). Among the 29 erythromycin non-susceptible isolates, 13 (45% of erythromycin non-susceptible isolates, 1.8% of all isolates) displayed a phenotype compatible with efflux-based M-type resistance to erythromycin only. The remaining isolates were either constitutively (n=14, 48% of erythromycin non-susceptible isolates, 1.9% of all isolates) or inducibly (n=2, 7% of erythromycin non-susceptible isolates, 0.3% 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 2009. The relationship between vaccination, incidence of systemic pneumococcal infections, serotype distribution and burden of resistance in different age groups is further discussed on page 70.

The 4.3% prevalence of non-susceptibility to trimethoprim-sulfamethoxazole was at the same level as 3.8% in 2009. Similarly, the prevalence of non-susceptibility to tetracycline was stable at 2.8% in 2010 compared to 2.9% in 2009 (Figure 48). 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 50) reflects that levofloxacin, moxifloxacin and other "respiratory fluoroquinolones" are not marketed in Norway.

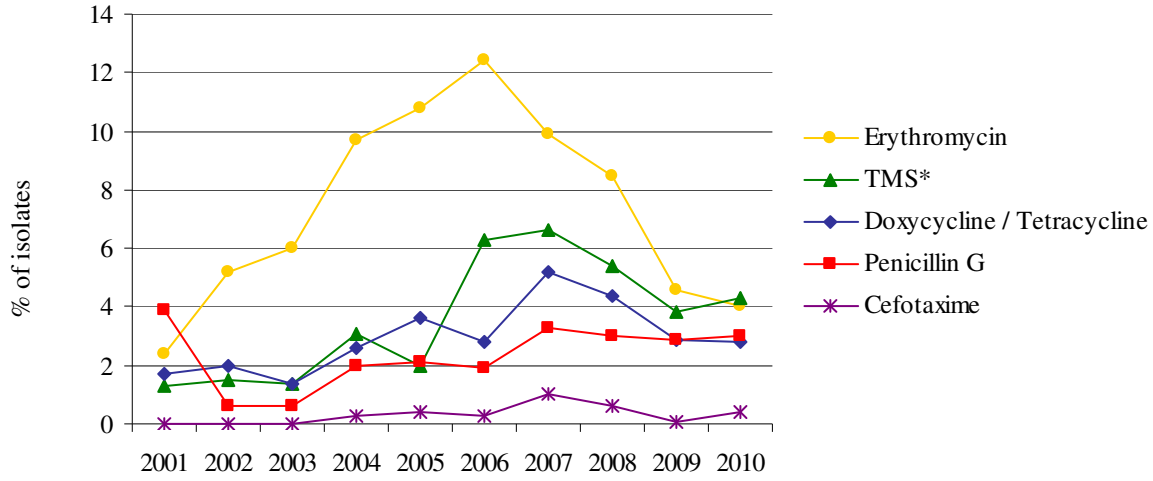

FIGURE 48. Prevalences (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2010. Doxycycline was substituted by tetracycline in 2005. All results are categorised according to the 2010 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

Childhood immunisation against *Streptococcus pneumoniae* in Norway

Streptococcus pneumoniae is a major cause of severe human disease and a commensal of the respiratory tract; colonised young children provide the infectious reservoir. During the last decade, pneumococci have been one of the most frequent etiologies of invasive bacterial disease in Norway, among the most frequently encountered Gram positive bacteria in blood cultures, and the dominating cause of bacterial meningitis.
S. pneumoniae is coated by an immunogenic polysaccharide capsule. At present, 93 antigenically different capsules, defining serotypes, have been identified. These pneumococcal serotypes differ greatly in virulence as seen by their relative prevalence among asymptomatic carriers and the incidence of invasive pneumococcal disease (IPD).

Pneumococcal vaccines
The first trial of a pneumococcal vaccine was conducted one century ago. In currently available pneumococcal vaccines the capsule polysaccharide of selected serotypes is used as vaccine antigen. A polysaccharide vaccine intended for use in older children and adults has been available in Norway since 1978. However, the pure polysaccharide vaccine is not immunogenic in infants and young children, a problem that is overcome by conjugation of the polysaccharide antigen to a carrier protein. The first pneumococcal conjugate vaccine (PCV) indicated for use in children was licensed in the United States in 2000, and has been available in Norway since 2001. It has been part of the Norwegian Childhood Immunisation Programme since 2006. This vaccine offers protection against seven serotypes, i.e. serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, the ones most commonly causing IPD among children, and was thus termed PCV-7. The efficacy of PCV-7 was demonstrated in clinical trials [1], and post-licensure surveillance has confirmed its effectiveness [2,3].

Direct and indirect effect of pneumococcal conjugate vaccines
Although PCV-7 was initially licensed and used in a four-dose immunisation schedule, i.e. 3 doses and 1 booster dose, a three-dose schedule (2+1) was chosen when PCV-7 was introduced into the Norwegian Childhood Immunisation Programme. Reports based on IPD surveillance in Norway have demonstrated that the effectiveness of the three-dose immunisation schedule is comparable to the four-dose schedule [3,4]. The three-dose schedule is now widely used in European national immunisation programmes.
In addition to protection against IPD, the PCVs induce mucosal antibodies that reduce colonisation in the nasopharynx. The effect is reduced transmission of vaccine serotypes between carriers, and thus, a reduced reservoir of these serotypes. Subsequently, IPD caused by vaccine serotypes is reduced in the overall population. This is termed the indirect effect, or herd effect, of PCVs. In Figure 49 incidence rates for IPD caused by PCV-7 serotypes in Norway are shown; both direct and indirect vaccine effects have been observed in Norway.

Serotype replacement
The reduced rate of asymptomatic colonisation by vaccine serotype is countered by an increase of non-vaccine serotypes, with the overall rate of carriage being unchanged [5]. Hence, the reservoir of non-vaccine serotypes is increased, followed by increased numbers of IPD cases due to these serotypes. These phenomena are termed serotype replacement and replacement IPD, respectively. In Figure 50 incidence rates of IPD caused by non-PCV-7 serotypes in Norway are shown. Replacement IPD has mainly occurred among the elderly aged ≥ 65 years.

Pneumococcal conjugate vaccines and antimicrobial non-susceptibility
Antimicrobial non-susceptibility among *S. pneumoniae* has been limited in Norway. Globally, however, non-susceptibility to beta-lactams and macrolides is of major concern. Non-susceptible isolates predominantly belong to PCV-7 serotypes, in addition to serotypes 6A and 19A. Following widespread use of PCV-7 in the United States the incidence rates of drug-resistant *S. pneumoniae* have declined [6].
In Norway the incidence rate of pneumococci non-susceptible to erythromycin increased during the first half of the 2000's; in 2006 approximately 12 % of IPD isolates were non-susceptible. This increase was related to expansion of a serotype 14 clone with efflux mediated macrolide resistance (mef) [7]; this clone is designated sequence type (ST) 9 by multilocus sequence typing and termed England^{14}-ST9 by international nomenclature [8]. Serotype 14 is a PCV-7 serotype, and the incidence rate of erythromycin resistance of the mef-phenotype has declined substantially following vaccine introduction, as is evident from surveillance of antimicrobial susceptibility among pneumococci published elsewhere in the present NORM report.
Increasing incidence rates of the non-PCV-7 serotype 19A are a cause of concern both in Norway and globally. Several clones within this serotype are associated with non-susceptibility to both beta-lactams and macrolides [9]. In 2010, serotype 19A was the most frequent cause of IPD among young children and elderly in Norway. However, susceptible clones still dominate in Norway (unpublished data).

Second generation conjugate vaccines
Recently, newer conjugate vaccines with broader serotype coverage have been licensed; a 10-valent vaccine (PCV-10), in which serotypes 1, 5 and 7F are added, and a 13-valent vaccine, PCV-13, adding serotypes 3, 6A and 19A to the PCV-10 serotypes. PCV-13 is manufactured in the same way as PCV-7, and has replaced the latter on the market. A switch from PCV-7 to PCV-13 was made in the Norwegian Childhood Immunisation Programme in April 2011. In the PCV-10 a conserved protein from *Haemophilus influenzae* is used as carrier protein, and a certain level of protection against mucosal infections due to *H. influenzae*, e.g. otitis media, has been reported [10]. Hence, the two vaccines available at present, PCV-10 and PCV-13, differ somewhat in their serotype coverage and potential for protection against IPD and mucosal infections.

In conclusion, pneumococcal conjugate vaccines have had a major impact on the incidence of IPD, evident as both a direct and an indirect effect. However, as the pool of circulating pneumococci persists among children, replacement may erode the overall effect on prevention of IPD. The second generation vaccines provide broader protection against IPD, and a further potential for controlling the spread of non-susceptible pneumococci in Norway.

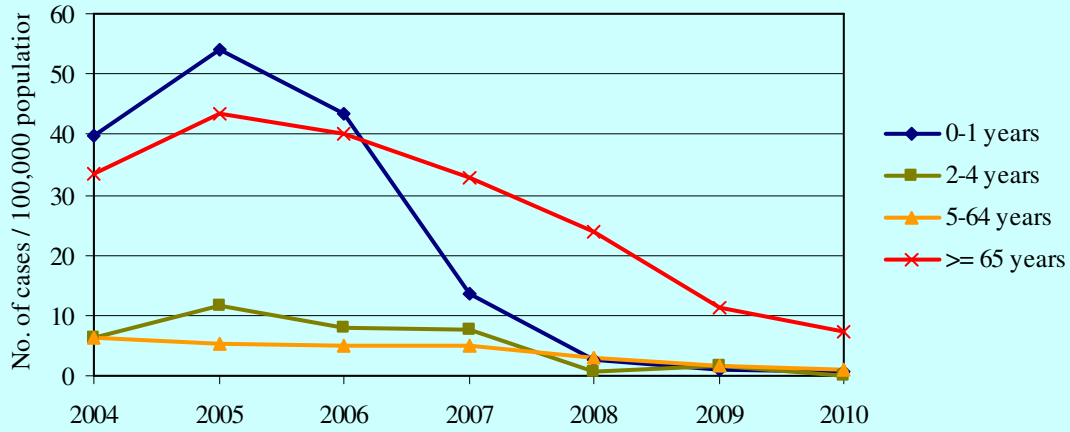

FIGURE 49. Incidence rates of IPD caused by PCV-7. The vaccine was introduced in 2006.

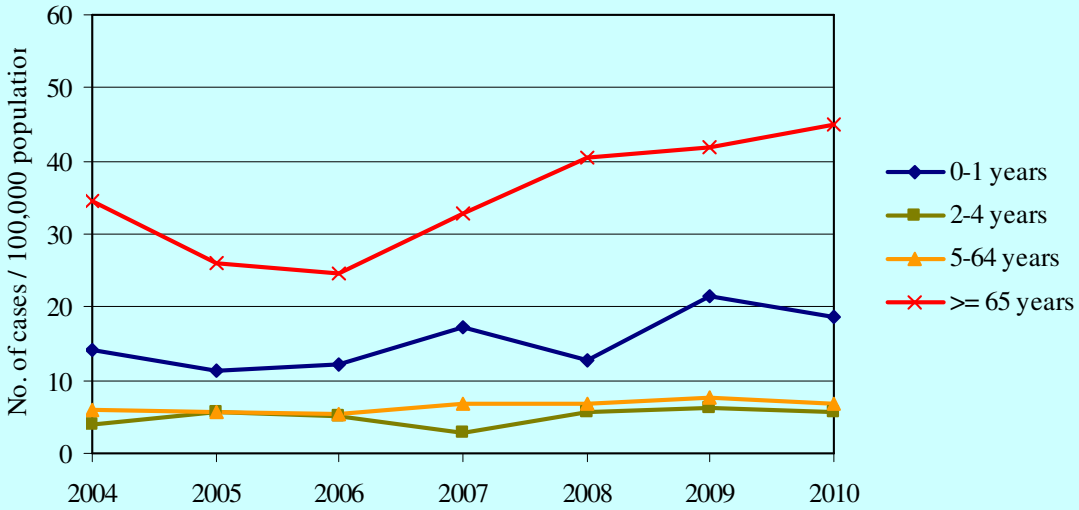

FIGURE 50. Incidence rates of IPD caused by non-PCV-7 serotypes. The vaccine was introduced in 2006.

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Mycobacterium tuberculosis

A total of 342 cases of infection with *M. tuberculosis complex* (not BCG) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2010. Twenty-one of the cases had been treated with anti TB drugs previously. In 52 cases it was not known whether the cases had been previously treated. Two of the nine MDR-TB cases were treated earlier. Six had TB for the first time.

Two hundred seventy-seven cases were confirmed by culture followed by susceptibility testing of the strain isolated. The results are presented in Table 52. Please note that the numbers for 2009 have been adjusted compared to the previous report.

TABLE 51. Antimicrobial susceptibility of 277 isolates of *M. tuberculosis* complex (not *M. bovis (BCG)*) isolated from human infections in 2010 (2009).

Origin of birth	No. of cases	No. of isolates	Resistance to antimicrobial agents (No. of isolates)					
			Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDR TB*
Norway	51 (37)	31 (21)	2 (0)	0 (0)	0 (0)	3 (0)	3 (0)	0 (0)
Europe excl. Norway	23 (21)	16 (18)	6 (2)	4 (1)	1 (0)	5 (2)	4 (2)	4 (1)
Asia	131 (118)	111 (100)	8 (3)	2 (0)	0 (0)	8 (6)	8 (10)	2 (0)
Africa	128 (184)	112 (145)	18 (20)	3 (7)	1 (1)	20 (21)	9 (10)	3 (7)
America	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
No information	8 (0)	6 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	342 (361)	277 (285)	35 (25)	9 (8)	2 (1)	36 (29)	24 (22)	9 (8)
Proportion of resistant isolates (%)			12.6 (8.8)	3.2 (2.8)	0.5 (0.3)	13.0 (10.2)	8.6 (7.7)	3.2 (2.8)

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

Antibiotic susceptibility testing of *Mycobacterium tuberculosis*

Tuberculosis (TB) is one of the most common infectious diseases today, with the second highest mortality rate in the world. Annually, *Mycobacterium tuberculosis* infects 9.2 million and kills approximately two million people (1). It is estimated that every third person in the world is infected with *M. tuberculosis*. Asia accounts for 55% and Africa for 31% of global TB cases (1).

The standard short-course chemotherapy of TB recommended is an initially two months intensive phase of rifampin, isoniazid, pyrazinamide and ethambutol, followed by a four months continuation phase of isoniazid and rifampicin (2). The increasing rate of drug-resistant, included multidrug-resistant (MDR), *M. tuberculosis* strains worldwide challenges the TB treatment. MDR *M. tuberculosis* strains are defined as strains resistant to at least isoniazid and rifampin, the two most important first-line anti-TB drugs. Approximately 0.5 million new MDR-TB cases occur annually. The highest drug resistance incidences are found in some parts of the former Soviet Union, China and India. It takes around two years to treat a person suffering from MDR-TB, compared to the original six months of treatment for persons infected by susceptible *M. tuberculosis* strains. Recently, also extensively drug-resistant (XDR) *M. tuberculosis* strains have been reported globally. XDR-TB is defined as TB caused by MDR *M. tuberculosis* resistant to any fluoroquinolone and to at least one of the three injectable second-line anti-TB drugs amikacin, kanamycin and capreomycin.

M. tuberculosis acquires drug resistance through spontaneous mutations, i.e. nucleotide substitutions, small deletions or insertions. Unlike the situation in most non-mycobacteria, there is no evidence of horizontal gene transfer (plasmids. transposons or other movable elements) in *M. tuberculosis* associated with drug resistance (3). In the absence of antibiotic, the mutations occur with a defined frequency of 10^{-7}-10^{-9}. Exposure to antimicrobial agents provides selective pressure for resistant organisms to become dominant. Approximately 95% of the *M. tuberculosis* strains resistant to rifampicin have a mutation in the *rpoB* gene, encoding the beta-subunit of the RNA polymerase. More than 90% of the rifampin resistant strains are also resistant to isoniazid, thus rifampin resistance is a marker for MDR-TB (4). Resistance to isoniazid is associated with mutations in at least two genes; *katG* (encoding the katalase-peroxidase enzyme of *M. tuberculosis*) and *inhA* (encoding the enzyme enoyl acyl carrier protein reductase). Mutation in *katG* is the main mechanism (50-95%) of isoniazid resistance in *M. tuberculosis* (3). Resistance to ethambutol is associated with mutations in the *embB* gene (encoding arabinosyl transferase) and resistance to pyrazinamide is associated with mutations in the *pncA* gene (encoding the pyrazinamidase enzyme that converts pyrazinamide to its active form).

Antibiotic susceptibility testing (AST) of *M. tuberculosis* is important to optimise individual treatment of TB patients and to limit the spread of drug-resistant *M. tuberculosis* strains. However, few low-income countries have the capacity for high-quality AST and in most high-burden TB countries ASTs may only be performed when treatment fails. Several techniques and cultivation media have been used for AST of *M. tuberculosis*. The Pasteur Institute in Paris was first to perform the proportion method (PM) on solid medium. A strain was considered resistant in the PM if the colonies on the drug-containing medium were more numerous than the colonies on a 1/100 dilution (e.g. 1%) of the inoculum for isoniazid, rifampin and *para*-aminosalycilic acid (10% for the other antibiotics). The critical proportion of resistant cells correlated with the clinical outcome. Indirect AST on solid medium is a time consuming procedure, requiring 2-3 weeks to obtain growth on primary culture and another 3 weeks before the AST result is available.

AST of *M. tuberculosis* in liquid medium reduces the time before test results are available. The first commercially available liquid-based system providing AST of *M. tuberculosis* was the BACTEC 460TB system (Becton Dickinson Biosciences, USA), and this system is considered as the gold-standard for AST of *M. tuberculosis.* AST in the BACTEC 460TB system is based on the principle of the PM. The use of automatic liquid-based systems is limited in high-burden TB countries due to costly reagents and equipment, expensive incubators and the requirement of trained personnel.

Nucleic acid amplification assays (NAATs) are alternative methods for AST of *M. tuberculosis*. NAATs provide test results within one day, but require costly reagents and trained personnel. The NAATs are highly sensitive and specific for the detection of mutations associated with resistance in culture, but have reduced sensitivity when applied directly on sputum samples (6). Recently, direct NAATs with simplified sample processing and amplification steps to make the tests more rapid, robust and applicable in laboratories without substantial technical infrastructure have been developed. The GeneXpert (Cepheid Sunnyvale, USA) is an automated one-step system including sputum processing and real-time PCR using *rpoB* as the amplification target. The GeneXpert system is sensitive and specific, and the test results are available within 2h. Instrumentation costs for the GeneXpert system are similar to that of an automated liquid culture system, and costs per test performed are in the same range as culture. Future challenge is to reduce costs of the NAATs to make the tests affordable in high-burden TB countries.

The costly equipment required for AST of *M. tuberculosis* and the limited resources available for TB diagnostic tests in high-burden TB countries make it difficult to obtain information needed for optimal management of TB patients in many areas in the world. To aid the situation, alternative low-cost tests based on reduction-oxidation reagents or metabolic activity for the AST of *M. tuberculosis* has been developed. One example is the nitrate reductase assay (NRA) performed in nitrate-containing cultures (7). The reduction of nitrate to nitrite by the enzyme nitrate reductase can be detected visually by the addition of specific reagents, with a resulting colour change in the medium. More than 99% of *M. tuberculosis* strains contain the nitrate reductase enzyme and are capable of reducing nitrate to nitrite. It has been shown that the test is comparable to the BACTEC 460TB system in detecting isoniazid and rifampin resistance in *M. tuberculosis* in sensitivity, specificity, and in time before available test result, but is considerably less expensive (7. 8). Recently, these low-cost tests, including the NRA-based susceptibility test, have been selected for endorsement by the WHO as new non-commercial phenotypic tests for AST of *M. tuberculosis*. The tests are rapid, accurate and inexpensive alternatives for AST of *M. tuberculosis* in low-income countries until the costs of the NAATs have been reduced.

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Candida spp. in blood cultures

TABLE 52. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=112). 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	> 2	100.0	-	0.0
Voriconazole*	≤ 0.125	> 0.125	100.0	-	0.0
Caspofungin**	≤ 1	> 1	100.0	-	0.0
Anidulafungin*	≤ 0.03	> 0.03	98.2	-	1.8
Micafungin**	≤ 1	> 1	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 with MICs ≤ 1 mg/l are considered susceptible.

TABLE 53. *Candida albicans* blood culture isolates (n=112). 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							41.1	58.9									
Fluconazole					1.0	24.0	61.0	13.0	1.0								
Voriconazole	3.6	64.2	28.6	2.7	0.9												
Caspofungin			0.9	7.2	36.6	45.5	9.8										
Anidulafungin	53.6	37.5	7.1		0.9	0.9											
Micafungin	3.6	34.8	49.1	12.5													

*Shaded areas in each row indicate susceptibility (light) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 54. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=34). 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	> 2	5.9	-	94.1
Voriconazole**	≤ 0.125	> 0.125	11.7	-	88.3
Caspofungin***	≤ 1	> 1	100.0	-	0.0
Anidulafungin*	≤ 0.06	> 0.06	100.0	-	0.0
Micafungin***	≤ 1	> 1	100.0	-	0.0

* 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 of their use in treating *C. glabrata* infection. 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 with MICs ≤ 1 mg/l are considered susceptible.

TABLE 55. *Candida glabrata* blood culture isolates (n=34). 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						5.9	23.5	70.6									
Fluconazole										5.9	14.7	32.8	8.8	5.9		2.9	29.4
Voriconazole					2.9	8.8	11.9	29.4	8.8		8.8	29.4					
Caspofungin						11.8	88.2										
Anidulafungin	2.9		67.7	29.4													
Micafungin		50.0	32.4	17.6													

*Shaded areas in each row indicate susceptibility (light) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 56. 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	> 2	100.0	-	0.0
Voriconazole*	≤ 0.125	> 0.125	91.7	-	8.3
Caspofungin**	≤ 1	> 1	100.0	-	0.0
Anidulafungin*	≤ 1	> 1	100.0	-	0.0
Micafungin**	≤ 1	> 1	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 with MICs ≤ 1 mg/l are considered susceptible.

TABLE 57. *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							16.6	58.4	25.0								
Fluconazole								66.6	33.4								
Voriconazole				8.3	50.0	33.4	8.3										
Caspofungin					8.3	75.1	8.3	8.3									
Anidulafungin			83.3	16.7													
Micafungin			50.0	50.0													

*Shaded areas in each row indicate susceptibility (light) and resistance (dark). Non-shaded rows indicate that breakpoints have not been defined.

TABLE 58. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates (n=7). 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	> 2	100.0	-	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 applies to other echinocandins (caspofungin and micafungin).

TABLE 59. *Candida parapsilosis* blood culture isolates (n=7)*. 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							14.3	14.3	71.4								
Fluconazole						14.3	42.8	14.3	28.6								
Voriconazole		42.8	28.6	14.3	14.3												
Caspofungin								14.3	85.7								
Anidulafungin									14.3	57.1	14.3			14.3			
Micafungin								28.6	71.4								

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

RESULTS AND COMMENTS

In 2010, 175 isolates of eight different *Candida* species were isolated from blood stream infections in 170 patients and were received at the National Mycology Reference Laboratory. In 2009, 205 isolates of eight different species were received. All isolates were susceptibility tested for amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin by E-test according to the manufacturers` instructions (AB bioMérieux). This year, EUCAST breakpoints have been set for some of the antifungal drugs and *C. albicans*, *C. parapsilosis* and *C. tropicalis*. However, there is still insufficient evidence to recommend treatment of *C. glabrata* with fluconazole or voriconazole. For the echinocandins, breakpoints have only been set for anidulafungin, and the breakpoint differs according to *Candida* species. In this report the breakpoints recommended by EUCAST are used.

Candida albicans is still the most common *Candida* sp. observed (n=112, 65.9%) followed by *C. glabrata* (n=34, 19.4%), *C. tropicalis* (n=12, 6.9%) and *C. parapsilosis* (n=7, 4%).

With the exception of two isolates which had slightly elevated MICs to anidulafungin, all *C. albicans* were susceptible to all antifungal drugs tested, with the lowest MIC values noted for voriconazole and the echinocandins (caspofungin, anidulafungin and micafungin). Although breakpoints have not yet been set for 2 of the echinocandins, the highest MIC levels were 0.25 mg/L and 0.008 mg/L for caspofungin and anidulafungin, respectively.

All *C. glabrata* isolates were susceptible to amphotericin B and anidulafungin. The highest MIC levels for caspofungin and micafungin were 0.25 mg/L and 0.032 mg/L respectively, probably indicating susceptible isolates. Azol resistance continues to increase also in Norwegian *C. glabrata* isolates. When testing for fluconazole susceptibility, only two isolates (5.9%) had MIC of ≤ 2 mg/L, while 10 isolates (29.4%) had MIC ≥ 256 mg/L. In 2009, 9% of the isolates had MIC ≤ 2 mg/L to fluconazole. Four isolates (11.7%) had MIC ≤ 0,125 mg/L when testing for voriconazole susceptibility. This percentage has decreased from 30.2% in 2009.
Heteroresistant *C. glabrata* to both fluconazole and voriconazole were found in 10 isolates (29.4%). This number is fairly stable compared to 2009 (36.5%) and 2008 (21.6%).

EUCAST has still refrained from setting breakpoints for the azoles and *C. glabrata*. Our findings of high MIC values both for fluconazole and voriconazole continue to support the view that azoles should not be recommended when treating serious *C. glabrata* infections.

We still have few *C. parapsilosis* blood stream infections in Norway. They do have higher MIC levels for the echinocandins than what we observe in other Candida sp. However, all seven isolates from 2010 have MIC ≤ 1 mg/L for both caspofungin and micafungin, while six of the seven isolates (85.7%) had MIC ≥ 1 mg/L when testing anidulafungin. EUCAST does not recommend treatment with anidulafungin for *C. parapsilosis* infection. Although the MIC-levels for the two other echinocandins are lower, other treatment options should be sought in *C. parapsilosis* infection.

RAVN (Resistance to Antiviral Drugs in Norway) - a national system for surveillance of resistance to antiviral drugs

Background

Over the years the number of available antiviral drugs has increased considerably with drugs against Human Immunodeficiency Virus type 1 (HIV-1) on the top of the list. However, with access to a broader repertoir of drugs and viral infections that needs therapy for a long time (in some instances life-long), development of resistant viruses is a reality and a cause for concern.
In 2008 the Norwegian Ministry of Health launched "National Strategy for Prevention of Infections in the Health Services and Antibiotic Resistance (2008-2012) in Norway". It was stated that the existing HIV surveillance system should be improved, an influenza surveillance system established and a position taken for establishment of a surveillance system for resistance to antiviral drugs in general. A working group, consisting of experienced clinical virologists, was called upon by the National Institute of Public Health (NIPH) in order to deliver a report by December 1st 2009 (ISBN:978-82-8082-386-1 el 4).

Which viruses to include, organisation of the surveillance system and challenges

In contrast to bacterial resistance testing, which can be performed at most hospital laboratories, virologic resistance testing is more specialised and, up to now, only performed at some regional virus laboratories and at the NIPH. Molecular detection and genotyping are the preferred techniques for the viruses of interest. The following viruses are included in the list of surveillance: HIV-1, Influenza virus, Cytomegalovirus, Hepatitis B and C viruses, and Herpes simplex virus.
The organization and structure of NORM has been successful for Norwegian bacteriologic resistance testing and surveillance. A similar structure is planned for RAVN with a head quarter at the NIPH that works closely with a National Council consisting of virologists and clinicians.
Because antiviral therapy for some infections, i.e. HIV-1, is lifelong, the registers for resistance and drug regimens have to be accumulated for individual patients over several years, which is in sharp contrast to bacterial resistance registration in NORM. Also, a research biobank with identifiable patient data will be established. All this raises particularly challenging legal issues. However, RAVN will become a very important register considering the increase in access to antiviral therapy we are facing and for the proper choice of prophylactic drug in the case of a pandemic influenza.

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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 the Ministry of Health designated 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 is 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 infection. 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, and increasing proportions of resistant viruses have been observed, particularly of subtype A(H3N2) (1). 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 H275Y, 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 exposure to drug.
In early 2009, a novel influenza A(H1N1) virus entered the human population and caused an influenza pandemic. To date the H1N1pdm virus is uniformly resistant to M2 blockers but with very few exceptions they remain fully susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. During the early months of 2011, a variant H1N1pdm virus with mildly reduced oseltamivir and zanamivir sensitivity due to a S247N neuraminidase mutation has been detected in more than 30% of samples from northern Australia. When combined with the H275Y mutation, as detected in an oseltamivir-treated patient, the dual S247N+H275Y mutant shows unusually strong oseltamivir resistance (4).

Surveillance findings

In Norway, Victoria lineage B was the dominating strain in circulation during the 2010/11 season. The circulation of A(H1N1)pdm virus developed at a parallel, but lower level, varying between one-fifth and one-third of the virus detections. A(H3N2) and type B Yamagata-lineage viruses have been encountered only sporadically this season. The uniformly oseltamivir resistant former seasonal A(H1N1) viruses seem to have been displaced during the pandemic; only a very few former seasonal A(H1N1) viruses have been detected globally during the influenza season 2010/11, none of them in Western Europe.
Findings from Norwegian surveillance are summarised in Table 60. So far, the H1N1pdm viruses analysed have been 100% susceptible to the neuramidase inhibitors in the phenotypic assay (MUNANA), but 100% resistant to M2 blockers. Four H1N1pdm viruses had a mixed 275H/Y genotype. The H275Y substitution is commonly associated with oseltamivir resistance. The virus yield in these four samples was however too low to confirm a decrease in sensitivity to oseltamivir with a phenotypic assay. The few recent A(H3N2) viruses that have been analysed remain resistant to the M2 blocker adamantine, but susceptible to the neuramidase inhibitors oseltamivir and zanamivir. All analysed influenza B viruses are susceptible to both oseltamivir and zanamivir. The findings for M2 blocker resistance is largely in accordance with the global patterns, with H3N2 and H1N1pdm viruses generally being resistant. Fortunately, H1N1pdm viruses resistant to NIs are rare and mostly associated with treated, long-term carriers. However, the possibility of community spread of oseltamivir-resistant H1N1pdm virus still remains a concern, particularly given that data from animal studies suggest that the fitness of the H275Y variant may not be significantly compromised.

TABLE 60. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the NIs oseltamivir and zanamivir during the influenza seasons 2005/06 through 2010/11. 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)

* During influenza season 2009/10 and 2010/11all A(H1N1) tested were pdmH1. ** A(H1N1)pdm with the mutation 275Y in mixture commonly associated with oseltamivir resistance. 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 categorize 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 authorization 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). In the present report, the sales of this premix has for the first time been included in Table 4 that presents detailed sales figures for antimicrobial agents for terrestrial animals for the latest year; for Figures 1 and 2 this premix has been included for the whole period. 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 hospitals 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 Legemiddel Innkjøpssamarbeid (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.

Drug Classification
The data are categorised according to the ATC classification system. 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 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) and oral and rectal metronidazole (P01AB01) are also included. Of the antimycobacterials, only rifampicin is included and data are presented as total amount of 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
WHO Collaborating Centre for Drug Statistics Methodology (2010). ATC index with DDDs 2011, WHO Collaborating Centre. Oslo.

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

Sampling strategy

Clinical isolates of *Staphylococcus aureus* were collected from diagnostic submissions of milk samples from cattle with clinical mastitis. Each of the five laboratories of the Norwegian Veterinary Institute (NVI) supplied isolates during four predetermined periods from week number 14 to 41 and only one isolate per herd.

Clinical isolates of *Enterococcus hirae* from broiler were collected at the NVI Sandnes from material obtained at autopsy of animals originating from farms with disease outbreaks in 2010 (NVI project 2010039). In addition, isolates were obtained from diagnostic submissions at NVI, Oslo.

Clinical isolates of *Vibrio anguillarum* were collected from farmed fish, mainly cod and salmon during previous and recent outbreaks of vibriosis. More than one isolate per fish farm was accepted.

Indicator isolates of *Escherichia coli* from cattle were collected from intestinal content of healthy animals. Samples were obtained partly within the frame of a surveillance programme and partly from 20 slaughterhouses (highest slaughter volumes in 2009).

Indicator isolates of *E. coli* from the wild red fox (*Vulpes vulpes*) were collected from intestinal content of animals included in a surveillance programme. Bacterial isolation, species identification and susceptibility testing was performed at NVI, Oslo.

Escherichia coli

The strains were isolated and identified at NVI, Oslo. Sample material was plated directly onto the surface of lactose-bromthymol blue agar without broth enrichment and incubated at 35-37°C for 24 h. Typical colonies were plated onto blood agar (Heart infusion agar (Difco) containing 5% bovine blood) and incubated at 35-37°C for 24 h. Colonies were identified as *E. coli* by typical appearance, lactose fermentation, a positive indole reaction, and negative citrat and oxidase reactions.

Enterococcus hirae

The strains were isolated and identified at NVI in Sandnes and Oslo. Species identification was based on the following criteria: Gram straining, catalase test, growth on lactose-saccarose-bromthymol blue agar, streptococcus grouping and the following biochemical tests: Hippurate, aesculin, mannitol.

Staphylococcus aureus

The strains were isolated and identified at all five NVI laboratories. Species confirmation was based on occurrence of haemolytic zones, Gram stain, katalase test, anaerobic fermentation of mannitol, DNase test and resistance to acriflavine (7mg/l).

Vibrio anguillarum

The strains were obtained from field labs and identified in the NVI in Harstad, Trondheim, Bergen and Oslo. Cultures were generally isolated after direct plating on blood agar with 2% NaCl and incubation at 15°C for 48 hours. Colonies were identified as *V. anguillarum* by typical appearance, growth characteristics, ALO profile, enzymatic profile and carbohydrate utilisation combined with serotyping using slide agglutination.

Susceptibility testing

Only one isolate per production unit was tested for antimicrobial susceptibility except for *V. anguillarum*. The broth microdilution method VetMIC™ (Dept. of Antibiotics. National Veterinary Institute, Sweden) was used for susceptibility testing *S. aureus* was investigated for beta-lactamase production by the clover-leaf method and for methicillin resistance using a cefoxitin disc diffusion test (www.eucast.org).

Epidemiological cut-off values recommended by the European Committes on Antimicrobial Susceptibility Testing (EUCAST, accessed 12.05.2011) 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).

Increased tolerance of *S. aureus* to disinfecting agents (quaternary ammonium compounds, QAC) was investigated using a method described by Bjorland et al (2001 and 2003). In short, 200 µl of diluted culture (10^6 CFU/ml) was spread onto Mueller-Hinton agar plates containing 3.5 mg/L benzalkonium chloride and Mueller Hinton plates containing 5.5 mg/L cetyltrimethyl-ammonium bromide. Isolates showing a semi-confluent or confluent growth (37°C, 20 h) were further grown on Mueller Hinton agar plates containing ethidium bromide (0.5 mg/L) for investigation of efflux mediated resistance to QAC. After incubation (37°C, 20 h) the colonies were inspected under UV light. Colonies accumulating ethidium bromide (red fluorescence) were considered sensitive; colonies that did not accumulate ethidium bromide (white) were considered resistant. As positive controls *Staph. haemolyticus* NVH97A containing *qacA* (Anthonisen et al 2002) and *S. aureus* RN4220(pSK265)qacJ containing *qacJ* (Bjorland et al 2003) were used. *S. aureus* ATCC 29213 was used as negative control.

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. 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 samples were obtained from animals during clinical examinations or necropsies at the Norwegian Veterinary Institute (NVI). One isolate of each serovar per incident was included for susceptibility testing.
Salmonella Typhimurium was isolated from wild birds submitted to the NVI during 2006-2010.

Campylobacter jejuni
Faecal swabs from cattle were obtained within the frame of a surveillance programme and, in addition, from 20 slaughterhouses (with the highest slaughter volume in 2009).

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* spp. from cattle was carried at NVI, Oslo. Sample material was plated onto the surface of selective media (CAT, Oxoid) and incubated at 41°C for 48 hours in microareophilic atmosphere. Suspect isolates were further identified to species level (*C. jejuni*) using standard bacteriological testing.
Isolation and identification of bacteria from humans was performed at the NRL for Enteropathogenic bacteria at the Norwegian Institute of Public Health (NIPH) 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 (Dept. 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 an agar disk diffusion test using BD Sensi-Disc and Mueller-Hinton II-medium. The *Campylobacter* isolates from humans were tested for antimicrobial susceptibility using Etest (AB Biodisk).
For animal isolates, epidemiological cut-off values recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST, accessed 12.05.2011) 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 of *Salmonella, Shigella and Yersinia,* clinical breakpoints defined by the Norwegian Working Group for Antibiotics (NWGA) were applied. Because clinical breakpoints for *Campylobacter* spp. are not yet established by EUACAST, 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. The NRL participated in the external quality assessment programme for *Salmonella* spp. and antimicrobial susceptibility testing, in 2010 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).

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. 2010 was the eleventh year of surveillance, and all 22 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 2010 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. in blood cultures (9 months); *Streptococcus pneumoniae, Pseudomonas aeruginosa* and *Candida* spp. in blood cultures (12 months); *S. aureus* from wound specimens (1 week); *E. coli* from urinary tract infections (2 days); *Enterococcus* spp. from urinary tract infections (2 weeks); *Mycobacterium tuberculosis* and *Neisseria gonorrhoeae* from all samples (12 months). *S. pneumoniae* from blood cultures were further analysed at the the Norwegian Institute of Public Health in Oslo. *P. aeruginosa* from blood cultures were further analysed at Akershus University Hospital, Sørlandet Hospital, Haukeland University Hospital and University Hospital of North Norway. *N. gonorrhoeae* was further analysed at Oslo University Hospital, Ullevål. *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 by disk duffusion using either Oxoid disks on Isosensitest agar, or Beckton Dickinson disks on Mueller Hinton II agar with nutritional additives as specified by the manufacturers. Suitable antibiotics were selected for each bacterial species, and the results were interpreted according to the respective manufacturers´ recommendations using the breakpoints of the Norwegian Working Group on Antibiotics (NWGA). The NWGA breakpoints are harmonized 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 *S. aureus* and *Enterococcus* spp. isolates were screened for glycopeptide resistance using the vancomycin 6 mg/L BHI agar. *P. aeruginosa*, *S. pneumoniae* and *N. gonorrhoeae* were susceptibility tested using MIC gradient tests (AB Biodisk or bioMerieux) on MH II agar (*P. aeruginosa*), MH II agar supplemented with 5% lysed horse blood (*S. pneumoniae*), or GC agar base supplemented with Isovitalex and haemoglobin (*N. gonorrhoeae*). Susceptibility testing of *Candida* spp. isolates was performed by Etest 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 program. 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 the ESBL Etest according to the instructions of the manufacturer. 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), *P. aeruginosa* ATCC 27853, *N. gonorrhoeae* ATCC 49226, *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), *C. albicans* ATCC 10231.

Data processing

The specially designed eNORM computer program was used for the registration of patient data, sample data and resistance data. The results were further analysed by WHONET5.3 with the aid of the NORMlink program, 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 Committe on Antimicrobial Susceptibility Testing (EUCAST, accessed 12.05.2011) were used with the exception of 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.

Antimicrobial	Resistant (MIC values. mg/L)	*Campylobacter jejuni*	*Salmonella* spp.	*Escherichia coli*	*Enterococcus hirae*	*Staphulococcus aureus*	*Vibrio anguilarum*
Ampicillin	>4				●		
	>8		■	■			
	ND						x
Bacitracin*	>32				●		
Cefotaxime	>0.25			■			
	>0.5		■				
	ND						x
Cephalotin	>1					●	
Chloramphenicol	>8				■		
	>16		■	■		■	
	ND						x
Ciprofloxacin	>0.06		■	○			
	>1	■				■	
	ND						x
Clindamycin	>2					○	
Colistin	>2			■			
	ND						x
Erythromycin	>1					■	
	>2				■		
	>4	■					
Florfenicol	>16		■	■			
	ND						x
Fusidic acid	>0.5					■	

Antimicrobial	Resistant (MIC values. mg/L)	*Campylobacter jejuni*	*Salmonella* spp.	*Escherichia coli*	*Enterococcus hirae*	*Staphulococcus aureus*	*Vibrio anguilarum*
Gentamicin	>1	■					
	>2		■	■		■	
	>32				●		
	ND						x
Kanamycin	>8			■		■	
	>16		●				
	>1024				●		
	ND						x
Linezolid	>4				●		
Nalidixic acid	>16	■	■	■			
	ND						x
Narasin	>2				●		
Oxacillin	>2					●	
Sulfamethoxazole	>256		●	●			
	ND						x
Streptomycin	>2	■					
	>16		■	■			
	>128				■		
	ND						x
Tetracycline	>1					■	
	>2	■					
	>4				■		
	>8		■	■			
	ND						x
Trimethoprim	>2		■	■			
	>8					○	
	ND						x
Vancomycin	>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.
Open circles: Cut-off values different than defined by EUCAST - defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.
X: Tested for
ND: Not decided cut-off value
*Units/mL

Appendix 7: Breakpoints NORM

NORM data are categorized according to the breakpoints of the Norwegian Reference Group on Antibiotic Susceptibility Testing (NWGA) which are harmonized with EUCAST breakpoints when available. For details regarding bacteria and antimicrobial panels, see tables in text. 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.	*Pseudomonas aeruginosa*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Candida albicans* ¤
Amphotericin B	≤ 1	> 1												■
Ampicillin	≤ 0.5	> 8	■		■	■	■							
	≤ 4	> 8										■		
Amikacin	≤ 8	> 16							■					
Anidulafungin	≤ 0.03	> 0.03												■
Azithromycin	≤ 0.25	> 0.5								■				
Aztreonam	≤ 1	> 16							■					
Caspofungin	≤ 1	> 1												■
Cefixime	≤ 0.125	> 0.125								■				
Cefotaxime	≤ 0.125	> 0.125								■				
	≤ 0.5	> 2											■	
	≤ 1	> 2	■	■										
Ceftazidime	≤ 1	> 4	■	■										
	≤ 8	> 8							■					
Ceftriaxone	≤ 0.125	> 0.125								■				
	≤ 0.5	> 2											■	
Cefuroxime	≤ 0.5	> 8	■	■										
Chloramphenicol	≤ 8	> 8			■	■	■						■	
Ciprofloxacin	≤ 0.032	> 0.064								■				
	≤ 0.5	> 0.5												
	≤ 0.5	> 1	■	■	■	■	■	■	■					
	≤ 1	> 1									■			
Clindamycin	≤ 0.25	> 0.5									■			
	≤ 0.5	> 0.5											■	
Doripenem	≤ 1	> 4							■					
Erythromycin	≤ 0.25	> 0.5											■	
	≤ 1	> 2									■			
	≤ 4	> 4						■						
Fluconazole	≤ 2	> 2												■
Fusidic acid	≤ 1	> 1									■			

Antimicrobials	MIC values mg/L S	R	*Escherichia coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Pseudomonas aeruginosa*	*Neisseria gonorrhoeae*	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Candida albicans* ¤
Gentamicin	≤ 1	> 1									■			
	≤ 2	> 4	■	■				■						
	≤ 4	> 4							■					
	≤ 128	> 128										■		
Imipenem	≤ 4	> 8							■					
Linezolid	≤ 4	> 4									■	■		
Mecillinam	≤ 8	> 8	■	■										
Meropenem	≤ 2	> 8	■	■					■					
Micafungin	≤ 1	> 1												■
Nalidixic acid	≤ 16	> 16	■	■	■	■	■	■						
Nitrofurantoin	≤ 64	> 64	■	■								■		
Penicillin G	≤ 0.064	> 1								■				
	≤ 0.064	> 2											■	
	≤ 0.25	> 0.25												
Pip./Tazo.*	≤ 8	> 16	■	■										
	≤ 16	> 16							■					
Rifampicin	≤ 0.06	> 0.5									■			
Spectinomycin	≤ 64	> 64								■				
Tetracycline	≤ 0.5	> 1								■				
	≤ 1	> 2									■		■	
	≤ 2	> 2						■#						
	≤ 4	> 8			■#	■#	■#							
Tigecycline	≤ 1	> 2	■	■										
Tobramycin	≤ 4	> 4							■					
Trimethoprim	≤ 0.032	> 1										■		
	≤ 2	> 4	■	■										
TMS*	≤ 1	> 2											■	
	≤ 2	> 4	■	■	■	■	■				■			
Vancomycin	≤ 2	> 2									■			
	≤ 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 the Tables 54-59.
* TMS Trimethoprim-sulfamethoxazole. Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.
# Epidemiological cut-off value based on the wild type distribution by EUCAST.

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