2007

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ISSN: 1502-2307

Suggested citation: ***NORM/NORM-VET 2007. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. Tromsø / Oslo 2008. ISSN:1502-2307.***

This report is available at www.vetinst.no and www.antibiotikaresistens.no

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The NORM and NORM-VET programmes are part of the
Norwegian Government's Action Plan against Antimicrobial Resistance issued in 2000.

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 by antimicrobial usage 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 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 antimicrobial usage 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 in Sweden, Belgium, Luxembourg, Italy and Slovenia. 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 usage and resistance in both human and veterinary medicine and have 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 emphasized. 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 surveillance of both resistance and drug usage was again emphasized. A combined action plan for antimicrobial resistance and infection control will be issued later in 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 National 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, including antimicrobial and coccidiostatic growth promoters, are collated at the Norwegian Food Safety Authority.

This report, which is the eighth annual joint report from NORM and NORM-VET, presents data for 2007. 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 antimicrobial usage 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 2008

II. SAMMENDRAG

Dette er den åttende 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 2007. 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 2007 var 6 364 kg. Fra 1995 til 2001 ble salget av veterinære antibiotika til landdyr redusert med ca 40 %. Etter dette har forbruket holdt seg relativt konstant. Forbruksmønsteret har utviklet seg mer og mer i gunstig retning siden 1995; det vil si at andelen penicillinbruk har økt. Rene penicillinpreparater utgjorde 43 % av salget av veterinære antibiotika til landdyr i 2007, og av dette var 76 % beta-laktamase følsomme penicilliner. Forbruket av tetracykliner utgjorde kun 5 %. Nedgangen i antibiotikaforbruket 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 og for riktig bruk av antibiotika.
Totalsalget av veterinære antibiotika til terapeutisk bruk til oppdrettsfisk i Norge var i 2007 på 649 kg aktiv substans, hvorav 65 % var kinoloner. Forbruket av antibiotika i oppdrettsnæringen er redusert med 98 % siden 1987. Denne betydelige reduksjonen kan tilskrives innføringen av effektive vaksiner til laks og ørret samt andre infeksjonsforebyggende tiltak, herunder bedrede miljøforhold. Av all antibiotika rekvirert til oppdrettsfisk i 2007 ble 50 % brukt til torsk, 20 % til laks, 8 % til kveite og de resterende 22 % hovedsakelig til nye oppdrettsarter.
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. Salgstallene, i kg aktiv substans, er nesten fordoblet siden forbudet mot bruk av antibakterielle vekstfremmere, noe som kan forklares ved økt produksjon av broilere. Forbruksmønstret for koksidiostatika er vesentlig endret siden 1996, fra monensin til narasin, og har siden da utgjort hovedparten av forbruket av de ionofore koksidiostatika.

Forbruk av antibiotika hos mennesker

Totalsalget av antibiotika til systemisk bruk hos mennesker i var 2007 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 undergruppene. Fra 2004 har totalforbruket av antibiotika økt. Salget av penicilliner, tetracykliner, makrolider og kinoloner øker, mens salg av sulfonamider og trimetoprim synker.
I 2007 utgjorde penicilliner 42 % av det totale antibiotika-forbruket i Norge. Det har skjedd en forskyvning mot bredspektrede penicilliner. I 2007 så vi en økning i alle undergruppene av penicilliner. Smalspektrede, bredspektrede og penicillinase stabile penicilliner økte med henholdsvis 2 %, 7 % og 9 %. Tetracykliner utgjorde 17 % av totalforbruket i 2007, og makrolider og linkosamider utgjorde 12 %. Salget av cefalosporiner, monobaktamer og karbapenemer utgjør bare 3 % av totalsalget. Det har vært en markant økning i forbruket av fluorokinoloner. Denne gruppen utgjorde kun 3 % av totalforbruket i 2007, men har hatt en økning på 91 % siden 2000. Det urinveisantiseptiske middelet metenamin økte også i 2007. Salget utgjorde 14 % av totalt salg.
Bruken av antibakterielle midler varierer avhengig av kjønn, alder og bosted. Salget til sykehus og allmennpraksis utgjorde i 2007 henholdsvis 8 % og 92 %. Penicilliner sto for 46 % av antibiotikasalget målt i DDD til sykehus og 42 % i allmennpraksis. Andre viktige grupper på sykehus var cefalosporiner (22 %), kinoloner (7 %) og metronidazol (6 %), mens det i allmennpraksis var tetracykliner (18 %) og makrolider (13 %).

Resistens hos indikatorbakterier fra dyr og mat

Forekomsten av ervervet antibiotikaresistens blant bakterier som utgjør den normale tarmfloraen, kan tjene som en indikator på selektivt antibiotikapress i ulike populasjoner. I NORM-VET benyttes *Escherichia coli* og *Enterococcus* spp. som indikatorbakterier. I 2007 ble indikatorbakterier fra sau og svin (faeces) og kalkun (faeces og kjøtt) inkludert. Forekomsten av resistens hos henholdsvis. *E.coli* og *Enterococcus* spp. var lav til moderat, og i et internasjonalt perspektiv lav.
Totalt var 71,7 % (kalkun, faeces), 76,3 % (kalkun, kjøtt), 71,2 % (svin) og 98 % (sau) av alle *E. coli* isolatene følsomme for alle antibiotika som det ble undersøkt for. Hyppigst ble resistens mot ampicillin, tetracyklin og streptomycin påvist. Forekomsten av fluorokinolonresistens var meget lav.
Totalt var 21,4 % (kalkun, faeces), 26,4 % (kalkun, kjøtt), og 38,4 % (svin) av enterokokkisolatene følsomme for alle antibiotika som det ble undersøkt for. *E. faecium* utgjorde flertallet av isolatene. *E. faecium* fra kalkun var hyppigst resistent mot narasin, mens resistens mot tetracyklin og erytromycin var vanligst blant isolatene fra svin. Vancomycinresistens blant enterokokker fra kalkun kunne bare påvises i 3,9 % av prøvene ved bruk av selektiv metode. Alle disse isolatene var *E. faecium.*

Resistens hos zoonosebakterier og andre enteropatogene bakterier

I 2007 ble det gjort resistensbestemmelse av 25 *Salmonella* spp. isolater fra norske dyr. Atten av isolatene var *S*. Typhimurium fra storfe (5), svin (4), hest (4), hund (3) og katt (2). De øvrige syv isolatene var *S*. Dublin fra storfe, *S*. Heidelberg, *S*. Gallinarum og *S*. Enteritidis fra fjørfe, og *S*. Montevideo, *S*. Minnesota og *S*. Infantis fra hunder. Resistensforekomsten var lav blant disse isolatene. Resultatene indikerer at resistens ikke er utbredt blant *Salmonella* som av og til blir isolert fra norske dyr.

Av de humane salmonellose-tilfellene som ble rapportert i 2007, var 72,2 % oppgitt å ha blitt smittet i utlandet. Andelen *S*. Typhimurium isolater som var følsomme for alle antibiotika, var høyere for kategorien "smittet i Norge" (69,2 %) enn for kategorien "smittet i utlandet" (23,5 %). Multiresistens definert som resistens mot to eller flere antibiotika, ble hyppigere påvist hos de utenlandssmittede (54,9 %) enn hos de innenlandssmittede (26,1 %). Resultatene for *S*. Typhimurium 2001-2007 indikerer en økende forekomst av resistens mot tetracykliner og ampicillin. Forekomsten av antibiotikaresistens var betydelig lavere blant *S*. Enteritidis enn blant *S*. Typhimurium med unntak av nalidixinsyre. Til sammen 22,5 % av *S*. Enteritidis isolatene var resistente mot nalidixinsyre. Forekomsten av resistens blant *S*. Enteritidis var på samme nivå i 2007 som i tidligere rapporter fra NORM/NORM-VET.

Resultatene fra 2007 viser at forekomsten av resistens hos *Campylobacter jejuni* fra norske broilere fremdeles er lav og stabil. Hele 96,9 % av isolatene var følsomme for alle undersøkte antibiotika. Forekomsten av resistens og resistensmønstrene hos *C. jejuni* fra norske broilere samsvarer med *C. jejuni* fra mennesker smittet i Norge med unntak av høyere forekomst av kinolonresistens blant isolatene fra mennesker. Dette forholdet ble også påvist i tidligere rapporter. Resistens var betydelig mer utbredt blant *C. jejuni* fra pasienter smittet i utlandet (72,1 % resistente mot minst ett antibiotikum) enn hos pasienter smittet i Norge (11,2 %). Forskjellen kan forklares med høyere forekomst av resistens mot ciprofloxacin/nalidixinsyre (57,4 % / 58,1 % versus 5,1 % / 7,1 % og mot tetracyklin 49,3 % versus 5,1 %), for henholdsvis utenlandssmittede og innenlandssmittede. Forekomsten av resistens hos *C. jejuni* fra pasienter smittet i Norge, så vel som utenlandssmittede, var stabil for perioden 2001-2007.

De aller fleste *Shigella*-isolatene var fra pasienter smittet utenfor Norge. Antibiotikaresistens var utbredt i *Shigella* slik det også rapporteres fra andre land.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterieisolater fra mennesker var, som i de foregående år, meget lav i 2007. Det ble påvist to tilfeller av meticillinresistente *Staphylococcus aureus* (MRSA) blant 832 blodkulturisolater (0,2 %) som ble inkludert i NORM-protokollen, og kun 5 av 1273 (0,4 %) *S. aureus* blodkulturisolater i laboratorienes datasystemer ble rapportert som MRSA. I 2007 var fem av 1293 (0,4 %) *S. aureus* fra blodkultur og spinalvæske MRSA. Denne andelen er stabil sammenlignet med tidligere år. Meldesystemet for infeksjonssykdommer (MSIS) registrerte 342 tilfeller av MRSA-infeksjon i 2007 hvilket er uendret fra 2006 da det ble registrert 333 tilfeller. Hele 292 (85 %) av disse tilfellene var pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus*-isolater fra sårprøver (12/1800, 0,7 %). MSIS registrerte videre 252 tilfeller av MRSA-kolonisering i 2007. Det totale antallet MRSA-meldinger på 594 var på nivå med 2006 da tilsvarende antall meldinger var 603. Fortsatt overvåking vil vise om den mangeårige økningen av antall MRSA-tilfeller i Norge nå har flatet ut. Blant *S. aureus* isolater fra sårprøver fortsatte nedgangen i andelen med fucidinresistens fra 14,5 % i 2006 til 11,1 % i 2007.

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 disse isolatene var 3,9 %. Dette er en økning fra 2,3 % i 2006. Det er observert en økning av resistens og nedsatt følsomhet for ciprofloxacin fra 3,3 % i 2004, 5,0 % i 2005 og 6,4 % i 2006 til 8,9 % i 2007. 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 enkelttilfeller er også blitt rapportert fra Norge. Til sammen 14/1169 *E. coli* (1,2 %) og 5/493 (1,0 %) av *Klebsiella* spp. fra blodkulturer hadde denne fenotypen. For *E. coli* var forekomsten av ESBL på samme nivå som i 2006 (1,1 %), mens forekomsten hos *Klebsiella* spp. økte fra 0,5 % i 2006. Andelen ESBL positive isolater var fortsatt litt høyere blant *E. coli* fra blodkulturer (1,2 %) enn fra urinprøver (0,8 %).

Det ble ikke påvist klinisk signifikant vankomycinresistens i enterokokker i 2007. Forekomsten av nedsatt følsomhet for ampicillin i *Enterococcus faecium* ligger fortsatt stabilt over 80 %, og høygradig gentamicinresistens ble påvist i 30,4 % av *E. faecalis* og 55,1 % av *E. faecium*. De aller fleste (56 av 59) *E. faecium*-isolater med høygradig gentamicinresistens hadde samtidig nedsatt følsomhet for ampicillin. Alle enterokokkisolater var følsomme for linezolid.

Streptococcus pneumoniae fra blodkulturer var generelt følsomme for alle relevante antibiotika. Tyve av 609 isolater (3,3 %) hadde nedsatt følsomhet for penicillin G, og ni av disse hadde også redusert følsomhet for cefalosporiner. Dette er en økning fra perioden 2004 – 2006 (ca 2,0 %), og andelen av pneumokokker med nedsatt følsomhet for penicillin G er nå den samme blant blodkulturisolater og isolater fra luftveisprøver (3,3 %). Forekomsten av makrolidresistens blant pneumokokker i blodkultur ble for første gang siden registreringen startet redusert - fra 12,4 % i 2006 til 9,9 % i 2007. Nedgangen kan skyldes innføringen av den konjugerte pneumokokkvaksinen i barnevaksinasjonsprogrammet i juli 2006, men dette må analyseres nærmere med undersøkelse av sirkulerende serotyper. *Haemophilus influenzae* fra luftveisprøver viste økende forekomst av betalaktamaseproduksjon - fra 7,0 % i 2001 og 8,8 % i 2004 til 10,5 % i 2007. Også andelen av isolater med kromosomal betalaktamresistens økte fra tidligere år.

I alt 307 tilfeller av tuberkulose ble meldt til MSIS i 2007. Det ble utført resistensbestemmelse av 225 *Mycobacterium tuberculosis* isolater fra pasienter som ikke hadde blitt behandlet for tuberkulose tidligere. To isolater fra pasienter smittet i henholdsvis Afrika og Asia ble klassifisert som multiresistente. Det ble også gjort

resistensbestemmelse av 17 isolater fra pasienter som tidligere var blitt behandlet for tuberkulose. Åtte av disse isolatene var resistente mot ulike tuberkulostatika, og ett oppfylte definisjonen av ekstensiv antibiotikaresistens (XDR-TB).

Det ble utført resistensbestemmelse av 189 blodkulturisolater av *Candida albicans* (155), *C. glabrata* (22) og *C. tropicals* (12). Alle *C. albicans* isolater var følsomme for amphotericin B, fluconazole og voriconazole, men et caspofunginresistent isolat ble for første gang påvist i Norge. Det ble påvist økende forekomst av resistens mot fluconazol og voriconazol blant *C. glabrata* og *C. tropicalis*. Resultatene er i overensstemmelse med tidligere studier fra Norge.

Overvåking av resistens hos influensavirus ble for første gang rapportert i NORM/NORM-VETi 2007. Det ble overraskede påvist en svært høy forekomst av resistens (76 %) mot neuraminidasehemmeren oseltamivir blant influensavirus A(H1N1). Funnene har senere vist seg å være del av et globalt mønster, og de blir nå nærmere undersøkt.

Konklusjon

Antibiotikaresistens er fortsatt et begrenset problem i Norge både når det gjelder 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 resistens fra andre land. Det er derfor nødvendig med fortsatt aktiv innsats for å sikre at vi også i fremtiden kan gi tilfredsstillende 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 eighth joint report from the NORM surveillance programme for antimicrobial resistance in human pathogens and the NORM-VET monitoring programme for antimicrobial resistance in the veterinary and 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 2007. 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, National 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 antimicrobials in Norwegian animal production and aquaculture is low. In 2007, the total sales of antimicrobial drugs approved for therapeutic use in animals in Norway were 6,364 kg (fish not included). The annual usage of veterinary antimicrobial drugs decreased gradually by approximately 40% from 1995 to 2001, and has thereafter remained relatively stable. The patterns of use have gradually been more favourable as the proportion of penicillin-use has increased. The proportion accounted for by pure penicillin preparations rose from 24% in 1995 to 43% in 2007. Altogether, 76% of the veterinary penicillin preparations sold in 2007 were beta-lactamase sensitive penicillins. The sales of sulfonamides decreased from 14% in 1995 to 0.3% in 2007. The proportion accounted for by tetracyclines varied between 3-5% in the period 1995-2007. The reduced antimicrobial drug use as well as the favourable prescribing patterns are mainly explained by a successful campaign on prudent use of antimicrobials conducted by the Norwegian husbandry organizations during the second part of the 1990s.

In 2007, the total sale of antimicrobial drugs for therapeutic use in farmed fish was 649 kg of active substance. Quinolones accounted for 65% of this amount. The usage of antimicrobials in Norwegian aquaculture declined by approximately 98% from 1987 to 1996 and has thereafter remained relatively constant. This reduction is mainly attributed to the introduction of effective vaccines in salmonids as well as to improved health management. In 2007, 50% of the prescribed amounts of antimicrobial agents used in aquaculture were for Atlantic cod, 20% for Atlantic salmon, 8% for Atlantic halibut and 22 % were almost exclusively for "new" species.

In 2007, the total sales of coccidiostatic feed additives, in kilograms of active substance, was close to twice the amounts used prior to the ban of 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 2007, the overall sales of antibacterials for systemic use in humans represented 19.7 DDD/1000 inhabitants/day. Total sales of antibacterials have remained relatively unchanged for many years although within subgroups of antibacterials, usage trends have changed. Since 2004 an increase has been observed. Sales of penicillins, tetracyclines, macrolides and quinolones are increasing, while the subgroup of sulphonamides and trimethoprim is decreasing.

Penicillins represented 42% of the total antimicrobial sales in 2007. Within the penicillins the subgroup of beta-lactamase sensitive penicillins is most commonly used. All three subgroups of penicillins were increasing in 2007, beta-lactamase sensitive penicillins by 2%, penicillins with extended specter by 7%, and beta-lactamase resistant penicillins by 9%. Tetracyclines represented 17% of the total use in 2007, and macrolides and lincosamides represented 12%. The sales of cephalosporins, monobactams and carbapenems represented 3% of the total sales of antibacterials. There has been a marked increase in quinolone use. Quinolones represented only 3% of total antibacterial sales in 2007, but since 2000 an increase of 91% is observed. Finally, the use of methenamine, an urinary antiseptic agent, is increasing, by 46% since 2000. The use now represents 14% of total DDDs of antibacterials.

The use of antibacterials varies according to age, gender and place of residency. Antibacterial sales to hospitals and ambulatory care represented 8% and 92% of the total human sales in 2007, respectively. Penicillins accounted for around 46% of the sales to hospital and for 42% in ambulatory care. The most important other groups in hospitals were the cephalosporins (22%), followed by the quinolones (7%) and metronidazole (6%) and in ambulatory care the tetracyclines (18%), while macrolides and lincosamides (13%) were the most important other groups.

Resistance in indicator bacteria from animals and food

The prevalence of antimicrobial resistance among certain bacteria of the normal enteric microflora can serve as an indicator of the selective antimicrobial pressure in the various populations. In NORM-VET 2007, *Escherichia coli* and *Enterococcus* spp. from sheep and swine (faeces) and turkey (faeces and meat) were included as indicator bacteria. The occurrences of resistance in *E. coli* and *Enterococcus* spp. in 2007 were low to moderate, and relatively low in an international perspective.

In total, 71.7% (turkey, faeces) 76.3% (turkey, meat), 71.2% (swine) and 98% (sheep) of *E. coli* isolates were susceptible to all antimicrobial agents included. Resistance to ampicillin, tetracycline and streptomycin was most commonly observed. In total, 21.4% (turkey, faeces), 26.4% (turkey, meat), and 38.4% (swine) of the *Enterococcus* isolates were susceptible to all antimicrobial agents included. The *E. faecium* strains from turkey were frequently resistant to narasin while the most commonly observed resistance in the isolates from swine were towards tetracycline and erythromycin. By using a selective isolation method, vancomycin resistance was observed among 3.9% of the samples from turkey. All these isolates were *E. faecium.*

Resistance in zoonotic and non-zoonotic enteropathogenic bacteria

In 2007, a total of 25 *Salmonella* spp. isolates were susceptibility tested. Eighteen of the isolates were *S*. Typhimurium from cattle (5), swine (4), horse (4), dog (3), and cat (2). The remaining seven *Salmonella* spp. isolates were *S*. Dublin from cattle, *S*. Heidelberg, *S*. Gallinarum and *S*. Enteritidis from poultry and *S*. Montevideo, *S*. Minnesota and *S*. Infantis from dogs. The occurrence of resistance among these isolates was low. The data, although very limited, indicate that antimicrobial resistance is not widespread among *Salmonella* occasionally isolated from animals in Norway.

In 2007, 72.2% of the human cases of salmonellosis were reported as being infected abroad. The proportion of *S*. Typhimurium isolates susceptible to all antimicrobial agents was higher for the category "infected in Norway" (69.2%) than for the "infected abroad" category (23.5%). Multiresistant strains defined as resistant to two or more antimicrobial agents, were more common in the category "infected abroad" (54.9%) than in the category "infected in Norway" (26.1%). The data from 2001-2007 indicate that the prevalence of resistance to tetracyclines and ampicillin in *S*. Typhimurium may be increasing.

The prevalence of resistance was considerably lower in *S*. Enteritidis isolates than in *S*. Typhimurium except for nalidixic acid. In total, 22.5% of *S*. Enteritidis isolates were resistant to nalidixic acid. The resistance frequencies observed for *S*. Enteritidis in 2007 are similar to those reported in previous reports from NORM/NORM-VET.

The results obtained in 2007 show that the prevalence of resistance in *Campylobacter jejuni* from Norwegian broilers is still low and stable. A total of 96.9% of the isolates were susceptible to all antimicrobial agents. The prevalence of resistance and the resistance patterns for *C. jejuni* isolated from Norwegian broilers correspond quite well with what was observed for *C. jejuni* isolated from humans infected in Norway, except for a higher prevalence of resistance to quinolones among isolates of human origin. This relationship was also observed in previous reports.

Resistance was significantly more widespread in *C. jejuni* isolates derived from patients infected abroad (72.1% resistant to at least one antimicrobial) than patients infected in Norway (11.2%). The discrepancies are explained by the widespread occurrence of resistance to ciprofloxacin/nalidixic acid (57.4% / 58.1% versus 5.1% / 7.1%) and to tetracycline (49.3% versus 5.1%) in isolates acquired abroad as opposed to isolates from patients infected in Norway, respectively. The occurrence of resistance in *C. jejuni* from both humans infected in Norway and those infected abroad was relatively stable during the period 2001-2007.

The vast majority of the *Shigella* isolates tested originated from patients infected abroad. Resistance was widespread in this species as previously reported from other countries.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still very low in Norway in 2007. Only two methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among 832 strains included in the NORM protocol (0.2%), and five out of 1,273 (0.4%) *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 1,293 including five MRSA strains (0.4%). This prevalence has remained stable over the last years. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 342 cases of MRSA infections in 2007 which is similar to the 333 cases registered in 2006. A majority of the MRSA cases (292, 85%) were reported to be wound infections and/or abscesses. Conversely, the prevalence of MRSA among non-invasive *S. aureus* isolates is still very low (0.7%). Furthermore, MSIS registered 252 cases of MRSA colonization giving a total of 594 MRSA notifications in 2007. This is on the same level as the 603 notifications registered in 2006. Continued surveillance is needed to ascertain whether the increasing trend of MRSA has now come to an end. The prevalence of resistance to fusidic acid among *S. aureus* wound isolates continued to decrease from 14.5% in 2006 to 11.1% in 2007.

E. coli and *Klebsiella* spp. blood culture isolates were generally susceptible to broad-spectrum antimicrobials. The prevalence of gentamicin non-susceptibility in *E. coli* increased from 2.3% in 2006 to 3.9% in 2007. *E. coli* non-susceptibility to fluoroquinolones continued to increase from 3.3% in 2004, 5.0% in 2005 and 6.4% in 2006 to 8.9% in 2007. 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 14/1,169 (1.2%) *E. coli* and 5/493 (1.0%) *Klebsiella* spp. blood culture isolates displayed this phenotype. For *E. coli*, this is unchanged from 2006 (1.1%), while the prevalence in *Klebsiella* spp. has increased from 0.5% in 2006. The proportion of ESBL positive isolates is still higher among *E. coli* from blood cultures (1.2%) than among urinary tract isolates (0.8%).

Clinically significant vancomcyin resistance was not detected in enterococci in 2007. The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilized around 80%, and high-level gentamicin resistance (HLGR) was detected in 30.4% of *E. faecalis* and 55.1% of *E. faecium*. Virtually all (56 out of 59) HLGR *E. faecium* isolates were also non-susceptible to ampicillin. All enterococcal isolates were suscpetible to linezolid.

Streptococcus pneumoniae from blood cultures were generally susceptible to all relevant antimicrobials. Twenty out of 688 isolates (3.3%) displayed reduced susceptibility to penicillin G, and nine of these isolates were also non-susceptible to cefalosporins. This is an increase compared to the period 2000-2004 (≈2.0%), and the proportion of isolates with reduced susceptibility to penicillin G is now approximately the same from blood cultures and respiratory tract specimens. The prevalence of macrolide resistance among pneumococcal blood culture isolates decreased for the first time from 12.4% in 2006 to 9.9% in 2007. This reduction may be due to the conjucated pneumococcal vaccine which was introduced into the childhood vaccination programme in July 2006, but this hypothesis will need further investigation including serotyping. The prevalence of beta-lactamase production in *Haemophilus influenzae* from respiratory tract specimens increased from 7.0% in 2001 and 8.8% in 2004 to 10.5% in 2007. The prevalence of chromosomal

betalactam resistance has also increased from previous years.

A total of 307 cases of tuberculosis were reported to MSIS in 2007. Susceptibility tests were performed on 225 *Mycobacterium tuberculosis* primary isolates. Only two isolates, originating from Africa and Asia were classified as multidrug resistant (MDR). Susceptibility tests were also performed on *Mycobacterium tuberculosis* isolates from 17 previously treated patients. Eight of these isolates were resistant to one or more tuberculostatic agents and a single isolate fullfilled the definition of extensive drug resistance (XDR-TB).

Susceptibility testing was performed on 189 blood culture isolates of *Candida albicans* (155), *C. glabrata* (22) and *C. tropicals* (12). All *C. albicans* isolates were susceptible to amphotericin B, fluconazole and voriconazole, but a caspofungin resistant isolate was detected for the first time in Norway. Increased prevalences of resistance were detected for fluconazole and voriconazole among *C. glabrata* and *C. tropicalis*. The results are in accordance with previous studies from Norway.

Surveillance data on resistance in influenza virus was included in the NORM/NORM-VET report for the first time in 2007. An unprecedented proportion of high-level resistance to the neuraminidae inhibitor oseltamivir was found. It was subsequently found that this was part of an emerging global pattern which is now subjected to further studies.

Conclusion

Antimicrobial resistance is still a limited problem in Norway. The relatively low usage of antimicrobial agents as well as the advantageous 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 healthcare have succeeded. However, the situation may rapidly change if the uses 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, 2008.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	293,803	150,230	143,573
5 to 14 years	613,574	314,397	299,177
15 to 24 years	600,144	307,454	292,690
25 to 44 years	1 331,279	678,420	652,859
45 to 64 years	1 205,063	612,266	592,797
65 years and older	693,308	296,923	396,385
All age groups	4 737,171	2 359,690	2 377,481

TABLE 2. Livestock population in Norway and the number of slaughtered animals in 2007.

		Number of *	
Animal category	Herds	Animals	Slaughtered animals
Cattle	29,300[1]	902,000[1]	319,000[2]
Dairy cows only**	12,600[1]	229,700[1]	-
Suckling cow only**	4,100[1]	53,100[1]	-
Combined production (cow)**	1,100[1]	30,800[1]	-
Goat	1,300[1]	71,500[1]	29,500[2]
Dairy goat**	490[1]	41,000[1]	-
Sheep	15,400[1]	2 243,400[1]	1 379,700[2]
Breeding sheep > 1 year**	15,100[1]	854,000[1]	-
Swine	2,800[1]	815,400[1]	1 470,100[2]
Breeding animal > 6 months**	1,700[1]	59,300[1]	-
Fattening pigs for slaughter	2,500[1]	449,000[1]	-
Poultry			-
Egg laying hen (> 20 weeks of age)	1,800[1]	3 436,200[1]	907,900[2]
Flocks > 250 birds**	710[1]	3 412,700[1]	-
Broiler	550[2]	-	54 423,900[2]
Turkey, ducks and geese for slaughter	100[1]	334,200[1]	1 125,100[2]
Flocks > 25 birds**	46[1]	333,800[1]	-
Ostrich	5[1]	50[1]	-

Data from: [1)] Register of Production Subsidies as of July 31st , 2007; [2)] Register of Slaughtered Animals.
* Numbers > 100 rounded to the nearest ten, numbers > 1,000 rounded to the nearest hundred.
** Included in above total.

TABLE 3. Import of live animals and animal products (excluding fish) to Norway in 2007.

Species	Imported product	No. of consignments	No. of animals or products
Cattle	Live animals	3	31[1]
	Semen (doses)	C	45,000[1]
	Embryos	NA	22[1]
Swine	Live animals	0	0[1]
	Semen (doses)	NA	520[1]
Sheep	Live animals	1	4[1]
	Embryos	-	0[1]
	Semen (doses)	NA	200[1]
Goat	Live animals	1	5[1]
	Semen (doses)	-	0[1]
Reindeer	Live animals for	NA	600[1]
Fur animal	Live animals	18	22,025[2]
Poultry	Day-old chicks	20*	148,881*[1]
	Fertilised eggs	67*	3 058,090*[1]
Turkey	Day-old chicks	8*	20,490*[1]
Duck and goose	Live birds	1*	400*[1]

[1]Data from Norwegian Livestock Industry's Biosecurity Unit (KOORIMP)
[2]Data from Statistics Norway
*Only commercial imports, hobby imports are not registered. C=Continuous import, not possible to differentiate consignments. NA= Not available.

TABLE 4. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2007. *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	291	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[2]	736,168	77,578	9,611	391	397	2,473	6	4

[1] From the wild population.
[2] Preliminary figures.

V. USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

Kari Grave

Therapeutic usage of veterinary antimicrobials

The data are based on sales from drug wholesalers to Norwegian pharmacies and from feed mills to fish farmers (see Appendix 1) of veterinary antimicrobial agents for therapeutic usage and includes pharmaceutical formulations approved for food animals, including horses, and/or dogs and cats. Thus, the figures represent national sales data for veterinary antimicrobial agents. Antimicrobial agents authorized for human use, but prescribed for animals, are not included (see Appendix 1 for inclusion criteria).

Table 5 summarizes the sales of veterinary antimicrobial agents for therapeutic use in domestic animals in Norway in 2007. The data are organized according to therapeutic substance groups (ATCvet groups) and show the total usage for the various routes of administration. The total annual sale of veterinary antimicrobial agents for terrestrial animals for the period 1995-2007 is given in Figure 1. Figure 2 illustrates the proportion of the total sale of the various groups of antimicrobial substances. In 2007, the sales of veterinary antimicrobial agents approved for therapeutic use in animals in Norway amounted to 6,364 kg of active substance (Table 5). The annual usage of veterinary antimicrobial agents decreased gradually by 40% from 1995 to 2001; thereafter this usage has remained on a relatively constant level although a slight increase was observed for 2005-2007 (Figure 1).

TABLE 5. Sales in 2007, calculated as kilograms of active substance, of veterinary antimicrobial agents approved in Norway for therapeutic use in animals (farmed fish not included, see Table 6). Number of sold items in 2007 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to the Norwegian pharmacies.

Groups of substances	ATCvet code	Active substance or combinations of substances	Gastro-intestinal (QA07)	Uterine (QG01)	Systemic indiv. (QJ01)	Intra-mammary (QJ51	Herds (QJ01)
Tetracyclines	QG01AA07/QJ01AA06	Oxytetracycline		2	207		110
	QJ01AA02	Doxycycline			0.3		
Betalactams	QJ01CA04	Amoxicillin			128		235
	QJ01CE09/QJ51CE09	Procaine penicillin[1,2]			2,018	22	
	QJ01CE90	Penethamate hydroiodide[1]			1		
	QJ01CR02/QJ51RV01	Amoxicillin-clavulanic acid			317	8	
Sulfonamides	QJ01EQ06	Sulfanilamid[3]			17		
Sulfonamides and	QJ01EW10	Sulfadiazine+trimethoprim[4]			1,247		268
Trimethoprim	QJ01EW13	Sulfadoxine+trimethoprim			102		
Lincosamides	QJ01FF01	Clindamycin			19		
	QJ01FF02	Lincomycin			0.3		
Aminoglycosides	QA07AA01	Neomycin	34				
	QA07AA90	Dihydrostreptomycin (DHS)	122				
	QJ01GB03	Gentamicin[5]			12		
Quinolones	QJ01MA90	Enrofloxacin[2]			29		
	QJ01MA96	Ibafloxacin			1		
Others	QJ01XX92	Tiamulin[2]			8		190
Combinations	QJ01RA01/QJ51RC23	Procaine penicillin[1] +DHS			473	612	
	QJ51RC24	Benzylpenicillinbenzatine[1]+ DHS[5]				11	
	QJ51RC25	Penethamate hydroiodide[1] + DHS				2	
	QG01AE99	Sulfadimidine+procaine penicillin[1]+DHS		167			
Total per route of administration			**156**	**169**	**4,580**	**656**	**803**
Total (kg)							**6,364**

[1]Calculated as benzylpenicillin; [2]Includes also one preparation used on exemption from market authorization; [3]Represents an extemporaneously prepared preparation; [4]Includes a premix approved for farmed fish that are used solely in terrestrial animals such as pigs and calves (Kari Grave, unpublished data); [5]Represents a preparation used on exemption from market authorization.

The proportion accounted for by pure penicillin preparations rose from 24% in 1995 to 43% in 2007. Altogether 76% of the pure penicillin preparations sold in 2007 was beta-lactamase sensitive penicillins. From 1995 to 2007, the sale of sulfonamides in combination with trimethoprim (or baquiloprim 1995-2000) increased from 11% to 25% of the total sales. The proportion of sale of the combination preparations of penicillins and aminoglycosides decreased from 34% to 17% from 1995 to 2007. The corresponding figures for the sulfonamides were 14% in 1995 and 0.3% in 2007. The proportion accounted for by tetracyclines varied between 3-5% in the same period. The reduced use as well as the favourable prescribing patterns are mainly explained by a successful campaign on prudent use of antimicrobials conducted by the Norwegian husbandry organizations during the second part of the 1990s.

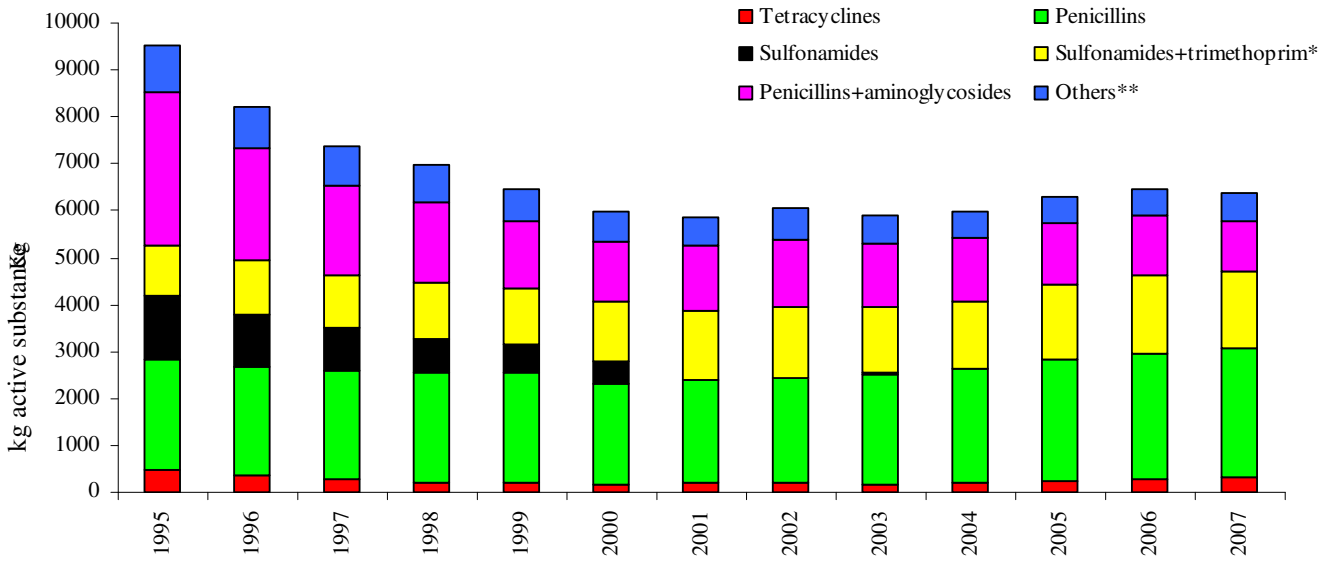

FIGURE 1. Sales (in kilograms of active substance) of veterinary antimicrobial agents (QA07AA, QG01AA, QG01AE, QJ01, QJ51) for therapeutic use in Norway 1995–2007, fish not included. Number of sold items in 2007 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies. Sulfonamides were not sold during 2001-2003.
*Includes small amounts of baquiloprim (1995-2000); includes a premix approved for farmed fish used solely in terrestrial animals such as pigs, horses and calves (Kari Grave, unpublished data). **Includes ATCvet codes: QAA7AA01; QA07AA90; QG01AE99; QJ01FA01; QJ01FF01; QJ01FF02; QJ01GB06; QJO1MA90; QJO1MA96; QJ01XX92; QJ51RC26.

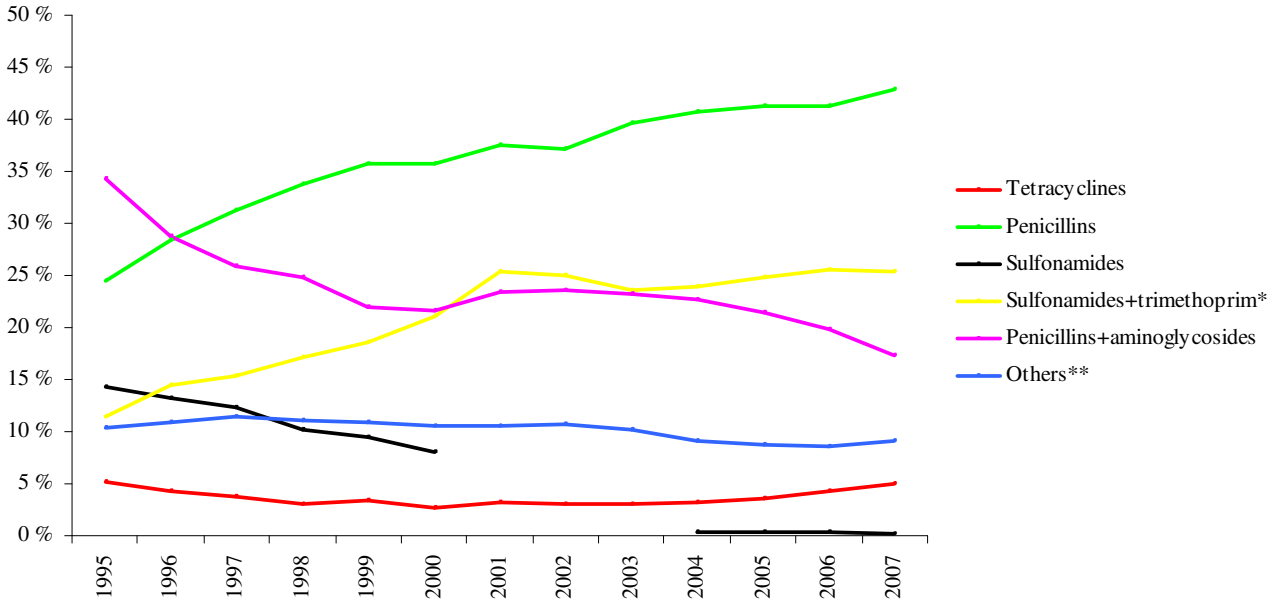

FIGURE 2. Sales (as percentage of total sales) of veterinary antimicrobial agents (QA07AA, QG01AA, QG01AE, QJ01, QJ51) in Norway 1995–2007, fish not included. Number of sold items in 2007 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies. Sulfonamides were not sold during 2001-2003.
*Includes small amounts of baquiloprim (1995-2000); includes a premix approved for farmed fish used solely in terrestrial animals such as pigs, horses and calves (Kari Grave, unpublished data). **Includes ATCvet codes: QAA7AA01; QA07AA90; QG01AE99; QJ01FA01; QJ01FF01; QJ01FF02; QJ01GB06; QJO1MA90; QJO1MA96; QJ01XX92; QJ51RC26.

TABLE 6. Total sales (in kilograms of active substance) of veterinary antimicrobial agents for therapeutic use in farmed fish in Norway in the period 1995-2007. The data were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies and sales by feed mills.

Groups of substances/active substance	ATCvet code	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Tetracyclines														
Oxytetracycline	QJ01AA06	70	27	42	55	25	15	12	11	45	9	8	0	19
Amphenicols														
Florfenicol	QJ01BA90	64	64	123	135	65	148	109	205	154	111	202	302	139
Quinolones														
Flumequine	QJ01MB07	182	105	74	53	7	52	7	5	60	4	28	7	18
Oxolinic acid	QJ01MB91	2,800	841	507	436	494	470	517	998	546	1,035	977	1,119	406
Combinations														
Spectinomycin · lincomycin (2+1)	QJ01RA												50	67
Total		**3,116**	**1,037**	**746**	**679**	**591**	**685**	**645**	**1,219**	**805**	**1,159**	**1,215**	**1,428**	**649**

In 2007, the sales of veterinary antimicrobial agents for use in farmed fish were 649 kg active substance, of which 65% were quinolones (Table 6). The annual usage of antimicrobial agents in Norwegian fish farming peaked in 1987 when the reported sales figures amounted to approximately 48 tonnes. This implies that the usage of antimicrobials in Norwegian aquaculture declined by approximately 98% from 1987 to 1996. From 1987 the total production of farmed fish increased more than sixty times. This significant decrease in the usage of antimicrobial agents in Norwegian aquaculture in the period 1987 to 1996 was 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.

In 2007, 50% of the prescribed amounts of antimicrobial agents in aquaculture were for Atlantic cod, 20% for Atlantic salmon and 8% for Atlantic halibut (Figure 3).

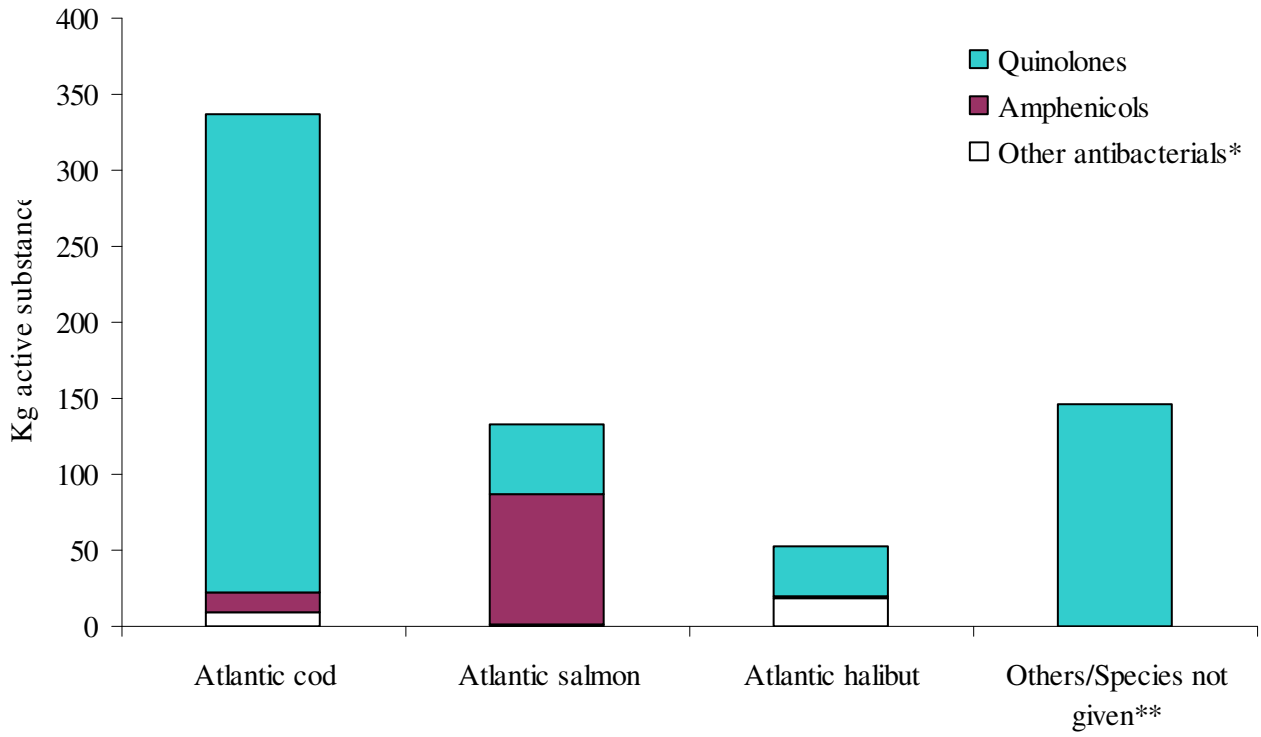

FIGURE 3. Prescribed amounts (in kilograms of active substance) of veterinary antimicrobial agents in Norwegian aquaculture in 2007 split into various fish species. Prescription data were obtained from the Norwegian Food Safety Authority (Trygve Helle, data on file).

*Includes: 10 kg oxytetracycline (for Atlantic cod), 33 kg spectinomycin+lincomycin (for Atlantic halibut) and 1.1 kg procaine penicillin + dihydrostreptomycin (for Atlantic salmon). ** Others: 0.2 kg for rainbow trout; Species not given: 29.1 kg prescribed fish farms cultivating coalfish.

Antimicrobial and coccidiostatic feed additives

Data on the usage of various substances and categories of feed additives were obtained through annual reports from the Norwegian Agricultural Inspection Service (1995-2002) and the Norwegian Food Safety Authority (2003-2007). Table 7 summarizes total sales of antimicrobial growth promoters and coccidiostat feed additives in Norway in the period 1995–2007.

The glycopeptide avoparcin was licensed for the Norwegian market as a growth promoter in broilers and turkeys in 1986. It was prohibited in 1995 due to a reported association between its use and the occurrence of vancomycin resistant enterococci in animal husbandry. The same year, the Norwegian food animal production industry voluntarily abandoned the use of all antimicrobial growth promoters. These measures resulted in an immediate reduction in the usage of these substances. In 1998, the streptogramin virginiamycin was officially prohibited due to reports from other countries of an association between its use and the occurrence of enterococci that were resistant to quinupristin-dalfopristin, a streptogramin combination preparation used in human medicine. No antimicrobial growth promoters have been used in animals in Norway since 1997.

Coccidiostats as feed additives are still used in Norwegian poultry production. The total sales of coccidiostats, in kilograms of active substance, have been close to doubled since the ban on antimicrobial growth promoters. During the same time the production of broilers has increased. However, the pattern of usage has changed (Table 7). While monensin was the most frequently used ionophore in the poultry industry in 1995, the usage of coccidiostats has since then been almost totally dominated by narasin.

TABLE 7. Total sales, in kilograms of active substance, of antimicrobial growth promoters and of coccidiostats as feed additives in Norway 1995-2007. Data were obtained through annual reports from the Norwegian Agricultural Inspection Service (1995-2002) and the Norwegian Food Safety Authority (2003-2007).

Active substance	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Avoparcin[1]	419	P	P	P	P	P	P	P	P	P	P	P	P
Zincbacitracin	129	64	27	0	0	0	0	0	0	0	0	P	P
Virginiamycin[2]	0	0	0	0	P	P	P	P	P	P	P	P	P
Total antimicrobial growth promoters	**548**	**64**	**27**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Lasalocid	996	480	471	193	208	80	96	514	108	173	37	13	17
Monensin	3,422	891	561	485	557	776	629	521	717	817	852	889	919
Salinomycin	214	27	0	0	27	233	12	0	0	0	0	0	0
Narasin	24	3,508	3,343	3,530	4,062	4,486	4,195	4,470	5,067	5,270	5,318	5,615	7,065
Total ionophore coccidiostats	**4,656**	**4,906**	**4,375**	**4,208**	**4,854**	**5,575**	**4,932**	**5,505**	**5,892**	**6,260**	**6,207**	**6,517**	**8,001**
Amprolium/etopabat	156	116	582	174	201	135	159	74	42	0.8	0	0	0
Total other	**156**	**116**	**582**	**174**	**201**	**135**	**159**	**74**	**42**	**0.8**	**0**	**0**	**0**

[1]Prohibited since May 31st, 1995. [2]Prohibited since 1999.

USAGE IN HUMANS

Hege Salvesen Blix

In 2007, the overall sales of antibacterials for systemic use in humans was 19.7 DDD/1,000 inhabitants/day. Total sales of antibacterials have remained relatively unchanged for many years. However, since 2004 an increase has been observed. This change is mainly due to the penicillin group and to increased use of methenamine. Furthermore, the subgroups of tetracyclines, macrolides and quinolones are increasing, while the subgroup of sulfonamides and trimethoprim is decreasing (Tables 8-9, Figure 4).

TABLE 8. Human usage of antibacterial agents in Norway 2000-2007 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and percent change 2006 - 2007. Collection of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2000	2001	2002	2003	2004	2005	2006	2007	Change (%) 2006-2007
J01A	Tetracyclines	3.17	3.11	3.13	3.03	2.97	3.11	3.24	3.32	+ 2
J01B	Amphenicols	0.004	0.003	0.002	0.002	0.001	0.001	0.002	0.001	
J01CA	Penicillins with extended spectrum	2.01	2.1	2.23	2.29	2.37	2.53	2.74	2.93	+ 7
J01CE	Beta-lactamase sensitive penicillins	4.66	4.68	4.48	4.38	4.23	4.55	4.63	4.70	+ 2
J01CF	Beta-lactamase resistant penicillins	0.35	0.41	0.50	0.59	0.63	0.56	0.66	0.72	+ 9
J01CR	Combination of penicillins	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	
J01D	Cephalosporins, monobactams, carbapenems	0.52	0.55	0.58	0.62	0.61	0.57	0.60	0.60	
J01E	Sulfonamides and trimethoprim	1.17	1.16	1.15	1.08	1.09	1.06	1.04	1.02	- 2
J01F	Macrolides, lincosamides and streptogramins	1.59	1.8	1.98	1.92	1.89	2.12	2.24	2.30	+ 3
J01G	Aminoglycosides	0.04	0.06	0.06	0.07	0.06	0.07	0.07	0.07	
J01M	Quinolones	0.35	0.40	0.44	0.48	0.52	0.57	0.62	0.67	+ 8
J01X	Other antibacterials	2.39	2.55	2.57	2.63	2.83	3.05	3.18	3.30	+ 4
	Total exclusive of methenamine	**14.3**	**14.7**	**15.0**	**14.9**	**14.8**	**15.6**	**16.3**	**16.9**	**+ 4**
	Total all antibacterials	**16.3**	**16.8**	**17.1**	**17.1**	**17.2**	**18.2**	**19.0**	**19.7**	**+ 4**

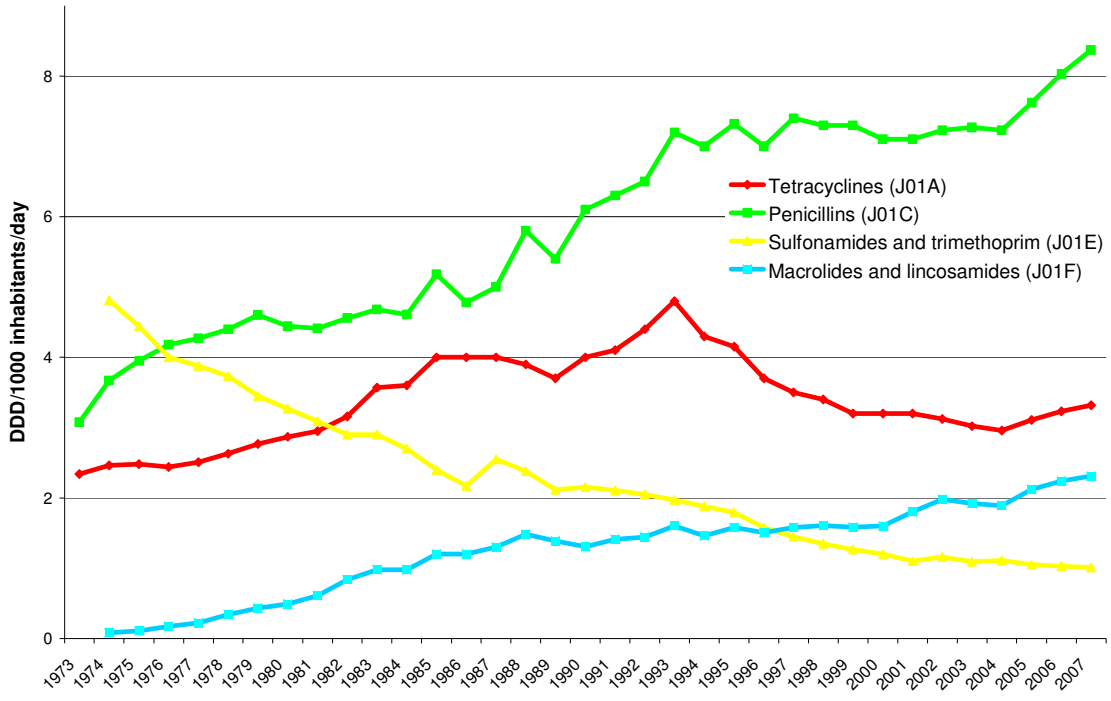

FIGURE 4. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F) and sulfonamides and trimethoprim (J01E) in Norway 1973-2007.

In 2007, the penicillins (ATC group J01C) represented 42% of the total antimicrobial use in Norway (Figure 5). Within the penicillins the beta-lactamase sensitive penicillins (J01CE) is the largest subgroup. It has been so over years. It has, however, been a shift towards use of more broadspectered penicillins. Penicillins with extended spectrum (J01CA) now represent 35% of the penicillin group compared to 25% in 1996, and the subgroup of beta-lactamase resistant penicillins represents 9% today compared to 5% in 1996 (Figure 6). Beta-lactamase sensitive penicillins (J01CE) was decreasing in the years 2002-2004, but now the use is back at the same level as in the beginning of this decade.

The tetracyclines (J01A) represent 17% of the total use. The sales have increased since 2004, but the proportion of the total sales is the same. The macrolides, lincosamides and streptogramins (J01F) represented 12% of total use in 2007. The sales were fairly stable in the nineties. However, since 2000 the use has steadily increased. The internal pattern of group J01F has remained relatively unchanged over the years. Erythromycin is most frequently used, representing 53% of the subgroup (Figure 7). In the latest years, sales of cephalosporins, monobactams and carbapenems, although little, have been increasing. This group is representing 3% of the total sales of antibacterials. The internal subgroup pattern has changed since 1996 (Figure 8). 1st generation cephalosporins i.e. cefalexin and cefalotin, represent 52% of ATC group J01D. The use of quinolones has also been increasing. Still, it represents only a minor fraction (3%) of the total antibacterial sales, but the increase has been 91% since 2000. The increase of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, representing 14% of total antibacterial use. The sales of methenamine have increased by 46% since 2000.

The usage of antibacterials varies between the 19 Norwegian counties, the county using the least is using 75% (in DDDs) of the county using the most. There is a trend of the same high-use and low-use counties over the years (Figure 9).

The use of antibacterials outside hospital represents 92% of the total human sale of antimicrobials. This includes the use in nursing homes. Antibacterials are prescription-only drugs in Norway. Physicians are of course the main prescribers to humans, but dentists prescribe 4-5 % (measured in DDDs) of antibiotics (J01) to humans in ambulatory care in Norway. The most important antibiotic groups in ambulatory care are penicillins (J01C: 42% of DDDs). tetracyclins (J01A: 18%) and macrolides and lincosamides (J01F: 13%). Females use more antibiotics than males. 30% of females purchased at least one antibiotic course in 2007 compared to 22% of the males. This pattern accounts to all regions in the country (Figure 10). The highest use is found among young children, young adults and the elderly (Figure 11).

The antibacterial sales in DDDs to hospitals represented eight percent of the total sale in the country in 2007. The therapy pattern of antibacterials in hospitals does not change much from 2006 to 2007 (Figure 12). Penicillins (J01C) represent around 46% of the use in hospitals followed by cephalosporins (J01D: 22%), quinolones (J01M: 7%), and metronidazole - oral and parenteral (6%). Due to the amount of antibacterials used, therapy traditions in ambulatory care have much greater impact on the total burden of antimicrobials and furthermore to the development of bacterial resistance. For overall use, the slow, but steady shift towards use of more "broadspectered" antibacterials in Norway is of concern and deserves close follow-up and further surveillance.

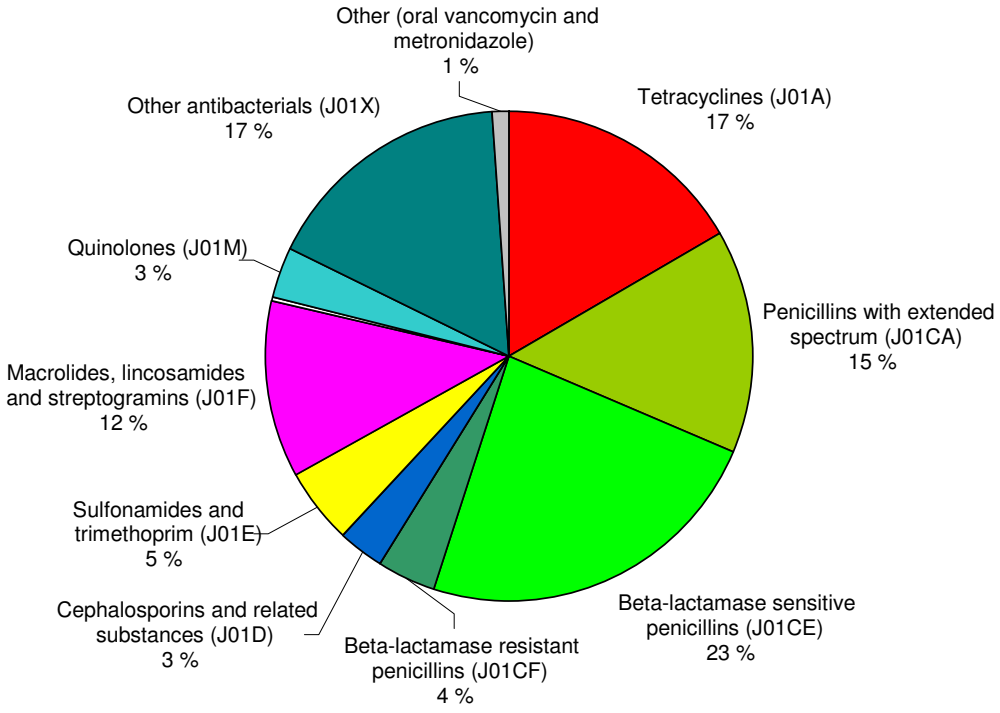

FIGURE 5. Relative amount of antibacterial agents for systemic use in 2007 in Defined Daily Doses (DDD) (total sale in the country).

TABLE 9. Human usage of single antibacterial 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	2000	2001	2002	2003	2004	2005	2006	2007
A07A A09	Vancomycin	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
J01A A02	Doxycycline	2.10	2.1	2.03	1.93	1.80	1.89	1.97	2.0
J01A A04	Lymecycline	0.14	0.19	0.26	0.30	0.34	0.39	0.45	0.51
J01A A06	Oxytetracycline	0.24	0.22	0.21	0.19	0.20	0.20	0.19	0.18
J01A A07	Tetracycline	0.69	0.64	0.62	0.60	0.62	0.64	0.63	0.63
J01AA07*	Minocycline						0.0003	0.0003	0.0001
J01AA12	Tigecycline							0.0001	0.0002
J01B A01	Chloramphenicol	0.004	0.003	0.002	0.002	0.001	0.002	0.002	0.001
J01C A01	Ampicillin	0.09	0.08	0.09	0.1	0.1	0.1	0.1	0.1
J01C A02	Pivampicillin	0.13	0.11	0.11	0.09	0.08	0.07	0.06	0.01
J01C A04	Amoxicillin	0.83	0.89	0.94	0.95	0.94	1.06	1.11	1.26
J01C A08	Pivmecillinam	0.96	1	1.09	1.14	1.25	1.29	1.46	1.55
J01C A11	Mecillinam	0.004	0.005	0.005	0.005	0.005	0.006	0.006	0.006
J01C E01	Benzylpenicillin	0.21	0.23	0.24	0.25	0.24	0.26	0.26	0.25
J01C E02	Phenoxymethylpenicillin	4.45	4.45	4.24	4.13	3.99	4.29	4.37	4.45
J01C E08*	Benzathine benzylpenicillin	0.0001	<0.0001	0.0001	0.0001	0.0002	0.0001	0.0002	0.0001
J01C F01	Dicloxacillin	0.25	0.31	0.39	0.48	0.51	0.41	0.54	0.61
J01C F02	Cloxacillin	0.10	0.09	0.11	0.11	0.11	0.15	0.12	0.12
J01C F05*	Flucloxacillin			0.0001	0.0002	0.0002	0.0001	0.0001	0.0003
J01C R02*	Amoxicillin and enzyme inhibitor	0.01	0.01	0.01	0.01	0.0003	0.0000	0.0001	0.0001
J01C R05	Piperacillin and enzyme inhibitor	0.0001	0.0006	0.0014	0.0024	0.005	0.01	0.01	0.02
J01D B01	Cefalexin	0.26	0.27	0.29	0.3	0.29	0.24	0.26	0.25
J01D B03	Cefalotin	0.05	0.05	0.05	0.06	0.06	0.06	0.06	0.07
J01D B04*	Cefazolin						0.002	0.002	0.001
J01D C01	Cefoxitin	0.0004	0.0003	0.0002	0.0001				
J01D C02	Cefuroxim	0.13	0.14	0.15	0.15	0.14	0.13	0.12	0.12
J01D D01	Cefotaxim	0.04	0.05	0.05	0.07	0.07	0.08	0.09	0.09
J01D D02	Ceftazidim	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01D D04	Ceftriaxone	0.011	0.01	0.01	0.01	0.02	0.02	0.02	0.02
J01D F01	Aztreonam	0.001	0.001	0.001	0.001	0.001	0.0005	0.0008	0.0008
J01D H02	Meropenem	0.012	0.014	0.017	0.02	0.02	0.026	0.031	0.035
J01D H03	Ertapenem							0.000	0.001
J01D H51	Imipenem and enzyme inhibitor	0.006	0.005	0.005	0.006	0.005	0.005	0.004	0.004
J01E A01	Trimethoprim	0.79	0.8	0.8	0.74	0.76	0.73	0.70	0.68
J01E E01	Sulfamethoxazol and trimethoprim	0.38	0.36	0.36	0.34	0.34	0.33	0.34	0.34
J01F A01	Erythromycin	1.00	1.13	1.2	1.09	1.03	1.16	1.24	1.21
J01F A02	Spiramycin	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01
J01F A09	Clarithromycin	0.26	0.3	0.36	0.37	0.37	0.39	0.40	0.43
J01F A10	Azithromycin	0.19	0.21	0.24	0.26	0.28	0.32	0.34	0.39
J01FA15	Telithromycin			0.0001	0.0003	0.0003			
J01F F01	Clindamycin	0.12	0.14	0.16	0.19	0.20	0.23	0.25	0.26
J01GA01*	Streptomycin			0.0015	0.0004	0.0004	0.0002	0.0003	0.0002
J01G B01	Tobramycin	0.02	0.03	0.04	0.04	0.03	0.03	0.03	0.03
J01G B03	Gentamicin	0.006	0.008	0.02	0.03	0.03	0.03	0.04	0.04
J01G B06*	Amikacin			0.0009	0.0008	0.0003	0.0004	0.0009	0.0003
J01G B07	Netilmicin	0.02	0.02	0.007				0.0001	
J01M A01	Ofloxacin	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.04

ATC	Substance	2000	2001	2002	2003	2004	2005	2006	2007
J01M A02	Ciprofloxacin	0.29	0.34	0.38	0.42	0.47	0.52	0.57	0.62
J01MA12*	Levofloxacin			0.001	0.0003		0.0003	0.0003	0.0008
J01MA14	Moxifloxacin								0.007
J01X A01	Vancomycin	0.005	0.005	0.006	0.006	0.007	0.007	0.008	0.01
J01X A02	Teicoplanin	0.0012	0.0013	0.0013	0.0009	0.0007	0.0008	0.0008	0.0007
J01X B01	Colistin	0.003	0.003	0.003	0.002	0.002	0.002	0.002	0.001
J01X C01	Fusidic acid	0.003	0.01	0.01	0.007	0.008	0.006	0.006	0.006
J01X D01	Metronidazole	0.06	0.07	0.07	0.07	0.08	0.08	0.07	0.07
J01X E01	Nitrofurantoin	0.37	0.36	0.35	0.35	0.36	0.36	0.37	0.36
J01X X05	Methenamin	1.95	2.08	2.13	2.18	2.37	2.59	2.71	2.84
J01XX08	Linezolid			0.002	0.004	0.006	0.007	0.006	0.006
P01AB01	Metronidazole	0.18	0.18	0.19	0.19	0.20	0.20	0.20	0.21
J04AB**	Rifampicin	0.046	0.054	0.043	0.049	0.068	0.077	0.082	0.092

* Drugs not licensed for the Norwegian marked but prescribed off-licence.
** Given as the amount of rifampicin in plain and combination products.

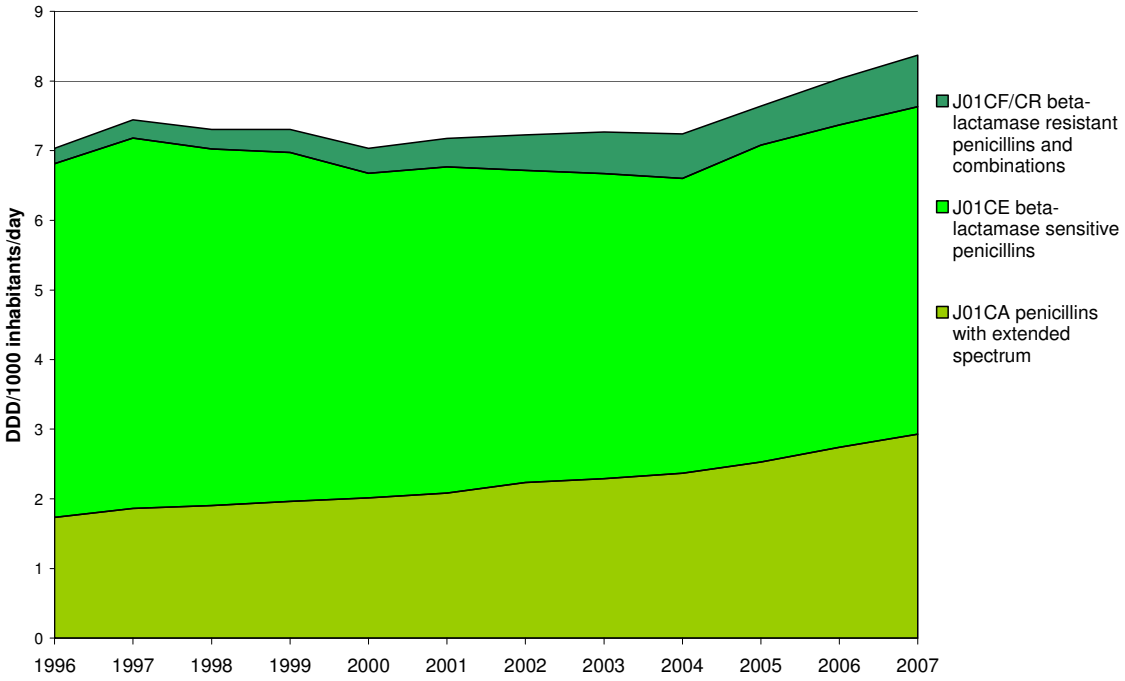

FIGURE 6. Sales of penicillins (J01C) in Norway 1996-2007 and changes between groups of penicillins.

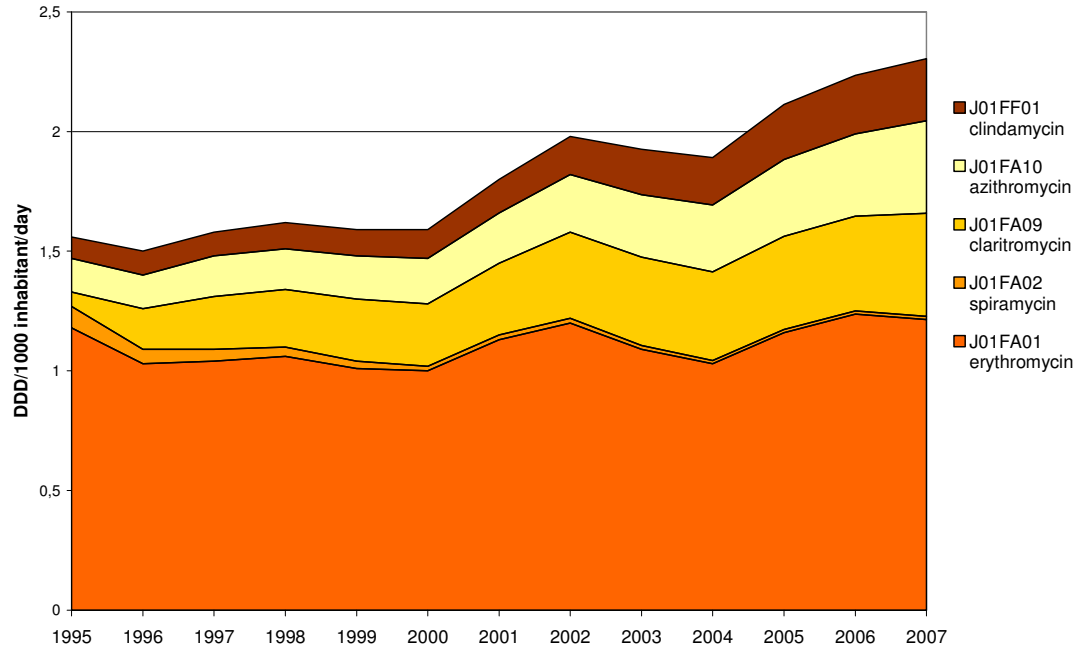

FIGURE 7. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1996-2007.

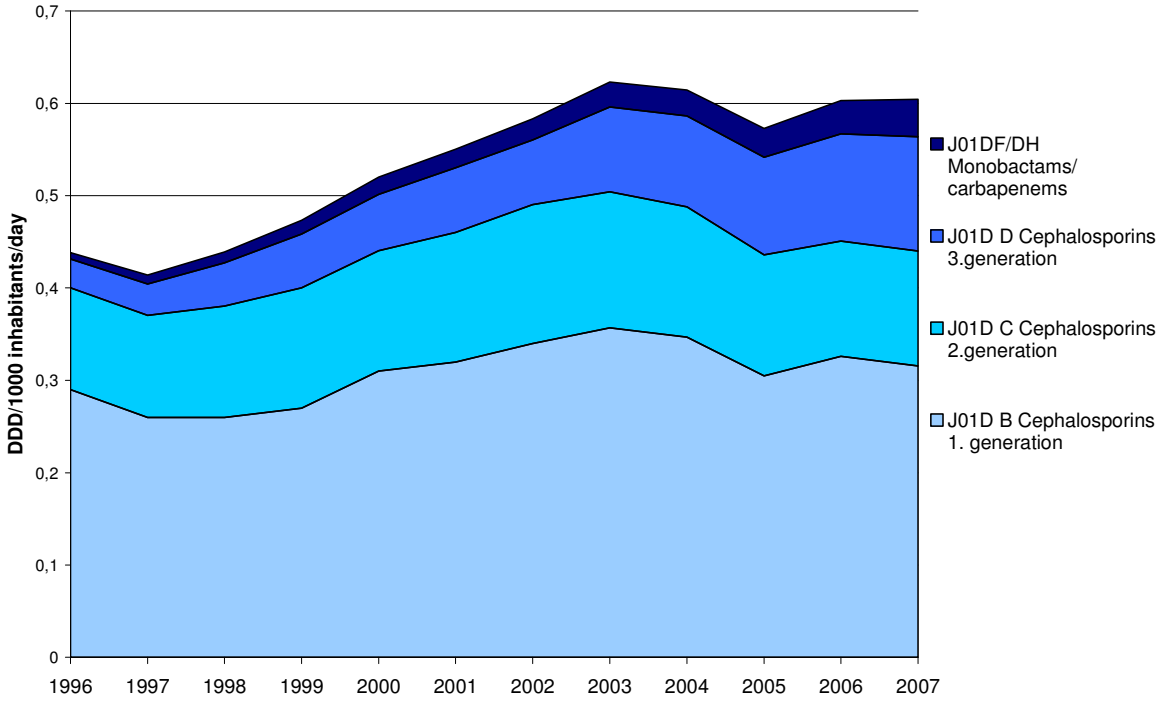

FIGURE 8. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2007 and changes between generations of cephalosporins and monobactams/carbapenems.

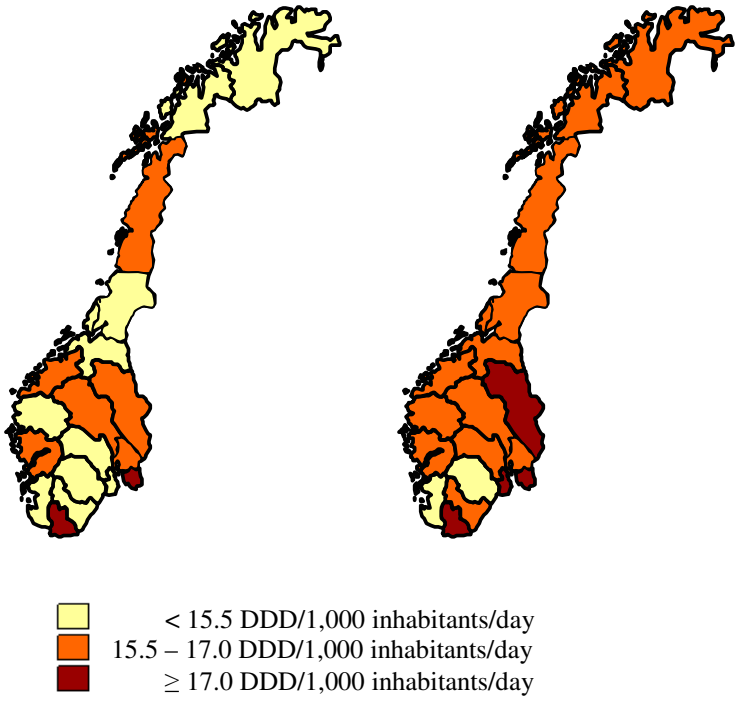

FIGURE 9. Sales of antibacterial agents for systemic use (ATC group J01 minus methenamine J01XX05) in the different counties of Norway in 2005 (left) and 2007 (right).

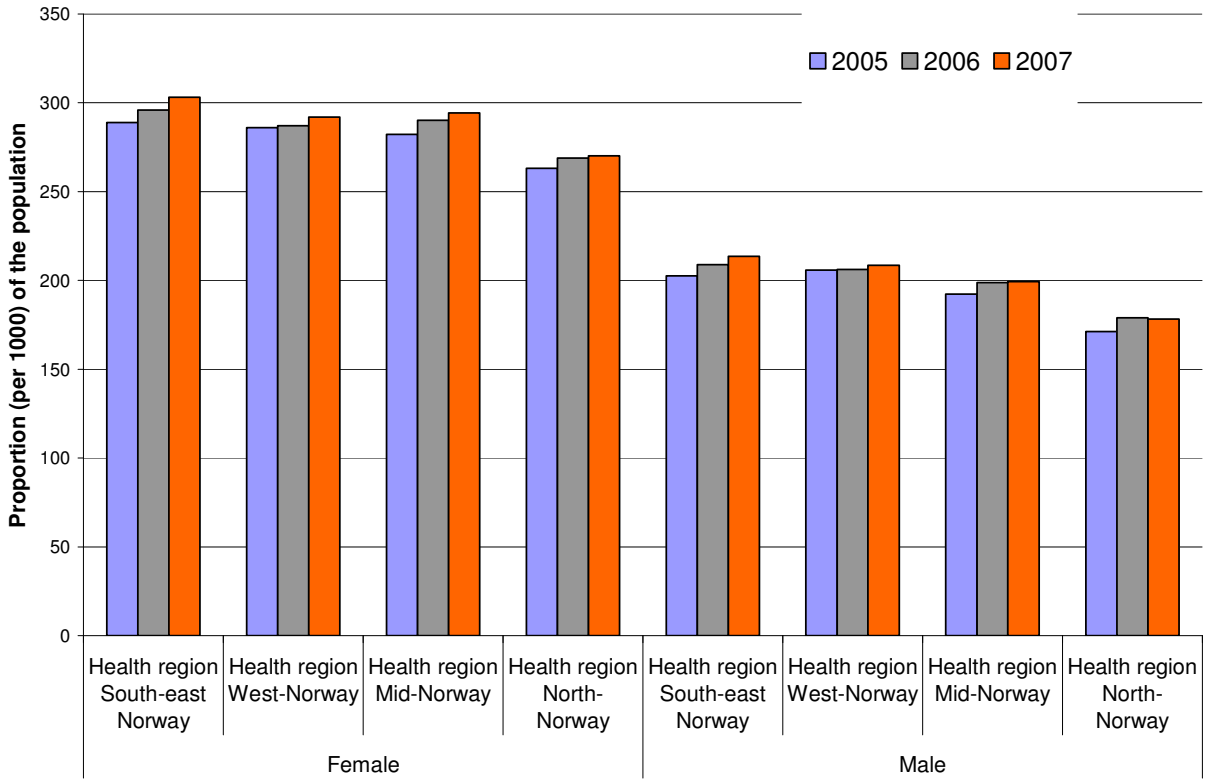

FIGURE 10. One year prevalence (%) of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2005, 2006 and 2007. Antibacterials for systemic use include ATC group J01, vancomycin (A07AA09) and metronidazole (P01AB01).

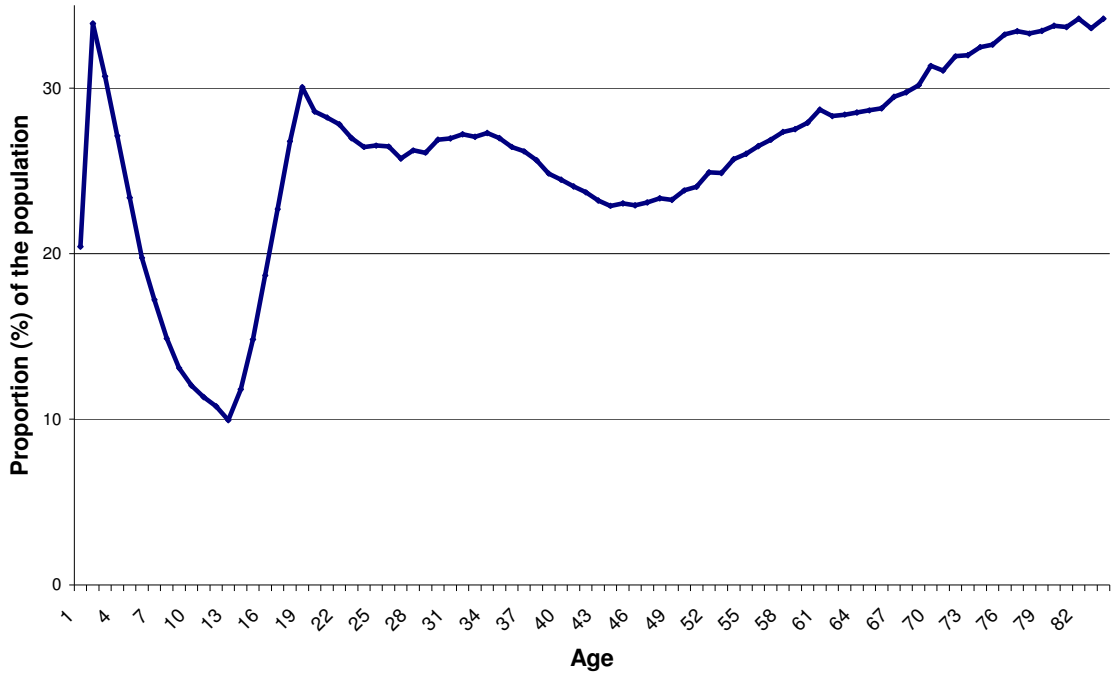

FIGURE 11. One year prevalence (%) of systemic antibacterial use in ambulatory care by age (from 1-85 year) in Norway 2007. Antibacterials for systemic use include ATC group J01, vancomycin (A07AA09) and metronidazole (P01AB01).

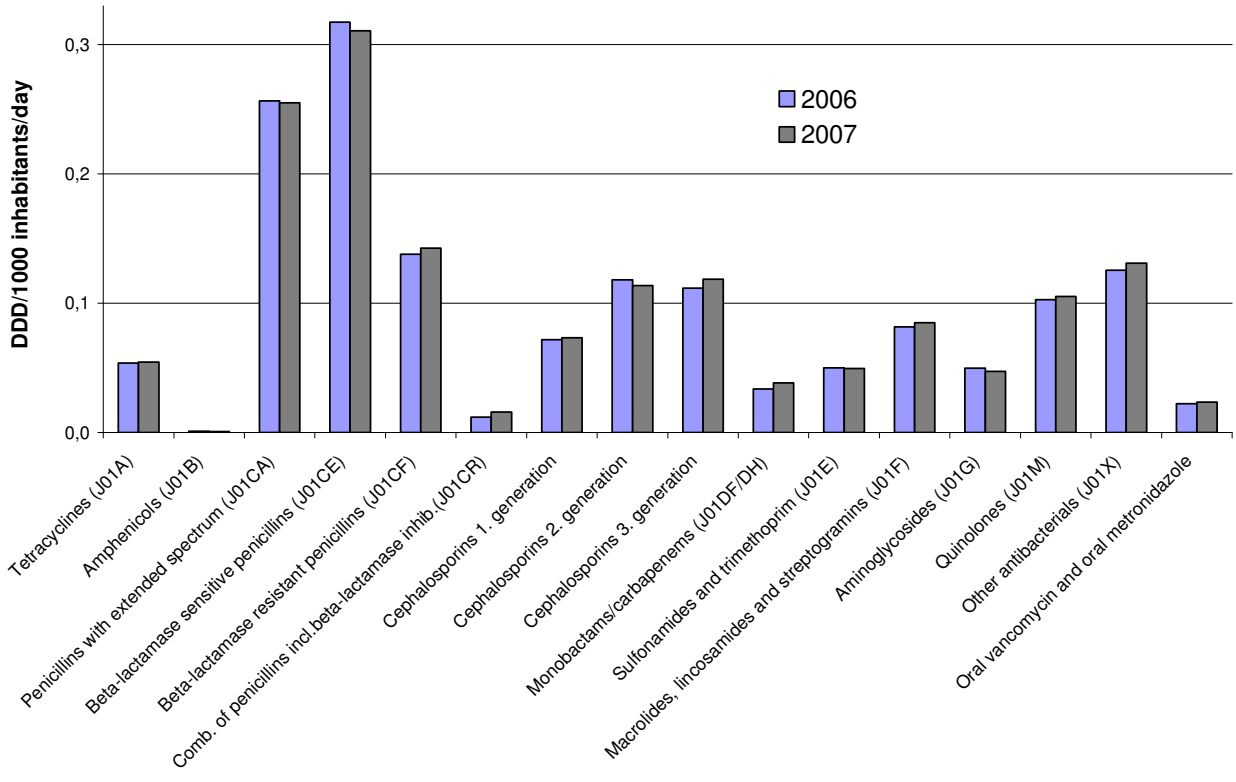

FIGURE 12. Proportions of antibacterial agents for systemic use in Norwegian hospitals 2006 and 2007 measured in DDD/1,000 inhabitants/day.

New guidelines for use of antibiotics in Norwegian primary health care

The first national guidelines for use of antibiotics in general practice came in 1999. It was one of the initiatives from the governmental plan against antibiotic resistance of the same year. Another initiative was the establishment of The National Centre for Antibiotic Use in Primary Care, ASP. The centre was officially opened in Oslo, November 2006. It has been given governmental funding for 5 years as a starting period, but in the new governmental plan against antibiotic resistance, it has been proposed that it should be established as a permanent centre. Located at the Institute of General Practice and Community Medicine, University of Oslo, it is central for research in the field for all of the four medical faculties in Norway. More than 90 % of antibiotics are prescribed in primary care in Norway. As the guidelines from 1999 needed revision, the Norwegian Directorate of Health asked ASP to take the task.

The revision began in February 2007, and in May, the 30 co-authors were gathered in Oslo. As in the work with the previous guidelines, there have been 2 authors for every therapeutic chapter, one GP and one hospital specialist in the field. Thus consensus in the therapy recommendations between primary health care and specialist care has been secured.

The new guidelines are evidence based and graded as such. Cooperation with the Norwegian Knowledge Centre for Health Services has made this possible. New from the last guidelines is overview chapters on antibiotic resistance, delayed prescription, better use of diagnostic tools, use of antibiotics for pregnant and nursing women, and the special efforts needed to be taken in nursing homes.

In May and June the recommendations have been out on hearing to all the medical specialists associations, and governmental organisations with interests in the field, as the Norwegian Institute for Public health and the Norwegian Medicines Agency. The new guidelines are planned to be published in September 2008. They will be published both as a handbook and sent out to all the GPs, nursing homes and medical students in Norway. Foreign physicians getting a Norwegian authorization will also receive the guidelines. They will also be published on the ASP web page www.*antibiotikasenteret.no*, as well as in the national electronic handbook for physicians, NEL, www.*legehandboka.no*.

As implementation efforts, several courses and material for small group sessions will be made. As the electronic prescription project, eResept, is established, the guidelines will be made interactive as a prescription support for the GPs. As resistance development goes fast, it will not be 9 years for the next revision. There is funding for revision every 2nd year, and all of the co-authors have said they would like to follow up their work.

Knut Eirik Eliassen, National Centre for Antibiotic Use in Primary Care, ASP

Changing habits of antibiotic prescription in general practice. The Rx-PAD study

The aim of this study was to test a model for improving GPs' antibiotic prescribing practice with an intervention comprised by peer-based, industry-independent drug education, targeting the existing continous medical education peer groups. In Norway, participation in a peer group is compulsory for a general practitioner (GP) to re-certificate the speciality every 5th year. Approximately 500 GP peer groups are registered by the Norwegian Medical Association, representing the vast majority of GP specialists.

The evaluation of this model was conducted as an intervention trial based on cluster randomisation (a peer group representing a cluster). A group of GP specialists, the peer academic detailers (PADs), was trained in the intervention topic, and in communication and pedagogic skills. Each PAD served three peer groups. 40 groups were randomized to intervention for assessing use of antibiotic drugs in respiratory tract infections. 39 groups completed the study. 41 groups were randomized as controls.

Outcome data from each participant's electronic record system and from the Norwegian Prescription Database (NorPD) were extracted and partly fed back to the individual prescriber. The peer group work was based on discussing the individual reports in relation to National Guidelines from 2000, and on news from research. Each peer group had two sessions devoted to the intervention followed by a one day regional workshop after some months. After one year, a second extraction of outcome data was made to reflect intended changes in prescription practice.

Main topics of the intervention:

- Use antibiotics according to the National Guidelines from 2000
- Reduce overall use of antibiotics in self limiting respiratory tract infections
- When prescription is needed, use penicillinV on account of broad-spectrum antibiotics, especially macrolides.
- When in doubt, use delayed prescription where the patient is asked to wait a number of days before fetching the antibiotic drug from the pharmacy.

Data from the study are now merged into a research database, and evaluation of the results is in progress as part of a PhD thesis. The final analyses will be based on multilevel modelling to compensate for the cluster effects of doctors and intervention groups. Preliminary results based on simple analyses, indicate significant effects of the intervention.

Prescription rates at visits with respiratory tract infections (including otitis media) increased from year 2005 to 2006 in both groups, but significantly less in the intervention group. The proportion of penicillinV prescriptions was reduced in the control group and increased in the intervention group, mainly on account of macrolides and to a smaller extent teracyclines. These effects are considered clinically significant.

The project has so far proved this kind of pedagogic intervention to be both effective and feasible, and it may become a permanent offer to general practitioners' Continuing medical education (CME) in Norway. The main study results will be published in international medical journals.

The protocol for this study is published, and is available as a freely accessible full text article at
http://www.ncbi.nlm.nih.gov/pubmed/16776824

Gjelstad, Svein, et al. "Can antibiotic prescriptions in respiratory tract infections be improved? A cluster-randomized educational intervention in general practice - The Prescription Peer Academic Detailing (Rx-PAD) Study [NCT00272155]." BMC Health Services Research 6.1 (2006): 75.

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VI. OCCURRENCE OF ANTIMICROBIAL RESISTANCE

INDICATOR BACTERIA FROM ANIMALS AND FOOD

Madelaine Norström, Kari Grave, Marianne Sunde

The prevalence of acquired antimicrobial resistance among certain bacteria of the normal enteric microflora can be used as an indicator of the selective antimicrobial pressure in the 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 2007, indicator bacteria from turkey, swine and sheep were included in the monitoring. The substances included in the test panels might not always be substances used in the veterinary medicine, but are included because of their importance for human health. Some of the cut-off values defining resistance (breakpoints) applied in NORM-VET have been changed over the years. To facilitate comparisons, data on prevalence of resistance from earlier reports have been recalculated using the cut-off values applied in 2007. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from turkey, swine and sheep

A total of 58 faecal and 107 meat samples from turkey, and 203 and 209 faecal samples from swine and sheep, respectively were collected. For turkey, *E. coli* was isolated from 53 (91.4%) of the faecal samples and from 97 (90.7%) of the meat samples. For swine, *E. coli* was isolated from 198 (97.5%) of the faecal samples and for sheep, *E. coli* was isolated from 207 (99%) of the faecal samples. One isolate per sample positive for *E. coli* was susceptibility tested. The results are presented in Table 10, Figures 13-14, and in the text.

TABLE 10. Antimicrobial resistance in *Escherichia coli* from faecal (n=53) and meat (n=97) samples from turkey and faecal samples from swine (n=198) and sheep (n=207) in 2007.

		Resistance (%)		Distribution (%) of MIC-values (mg/L)												
Substance	Sample		[95% CI]	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Turkey^{F}	13.2	[5.9-25.9]					39.6	47.2				5.7	1.9	5.7		
	Turkey^{M}	10.3	[5.3-18.6]					43.3	46.4				3.0	4.1	3.1		
	Swine	9.1	[5.6-14.2]				1.0	46.5	42.9	0.5			3.5	5.1	0.5		
	Sheep	0.0	[0.0-2.3]					62.3	37.2	0.5							
Chloramphenicol	Turkey^{F}	1.9	[0.1-11.4]						9.4	73.6	15.1				1.9		
	Turkey^{M}	1.0	[0.0-6.4]						5.2	83.5	10.0				1.0		
	Swine	0.0	[0.0-2.4]					0.5	15.2	71.2	13.1						
	Sheep	0.0	[0.0-2.3]						8.2	73.9	17.9						
Florfenicol	Turkey^{F}	0.0	[0.0-8.4]							60.4	39.6						
	Turkey^{M}	0.0	[0.0-4.7]							59.8	39.0	1.0					
	Swine	0.0	[0.0-2.4							64.1	35.4	0.5					
	Sheep	0.0	[0.0-2.3]							52.7	47.3						
Ampicillin	Turkey^{F}	15.1	[7.2-28.2]				1.9	9.4	45.3	20.8	7.5			15.1			
	Turkey^{M}	13.4	[7.6-22.2]				1.0	8.2	36.1	32.0	9.3			13.4			
	Swine	10.1	[6.4-15.4]				0.5	17.7	31.8	28.8	11.1		0.5	9.6			
	Sheep	1.0	[0.2-3.9]					9.7	45.9	33.8	9.7			1.0			
Ceftiofur	Turkey^{F}	0.0	[0.0-8.4]			17.0	79.2	3.8									
	Turkey^{M}	0.0	[0.0-4.7]		1.0	32.0	64.9	2.1									
	Swine	0.5	[0.0-3.2		2.5	47.0	48.0	2.0	0.5								
	Sheep	0.0	[0.0-2.3]		1.0	37.7	59.9	1.4									
Cefotaxime	Turkey^{F}	0.0	[0.0-8.4]	47.2	45.3	7.5											
	Turkey^{M}	0.0	[0.0-4.7]	46.4	48.5	5.2											
	Swine	0.5	[0.0-3.2	53.5	36.4	9.6	0.5										
	Sheep	0.0	[0.0-2.3]	50.2	42.0	7.7											
Trimethoprim	Turkey^{F}	0.0	[0.0-8.4]			39.6	54.7	5.7									
	Turkey^{M}	0.0	[0.0-4.7]			40.2	51.5	8.2									
	Swine	7.1	[4.1-11.9]			44.4	44.9	3.5						7.1			
	Sheep	0.5	[0.0-3.1]			71.5	27.1	1.0						0.5			
Sulfamethoxazole	Turkey^{F}	5.7	[1.5-16.7]									77.4	15.1	1.9			5.7
	Turkey^{M}	3.1	[0.8-9.4]									83.0	12.0	2.1			3.1
	Swine	12.6	[8.5-18.2]									72.2	13.6	1.5			12.6
	Sheep	1.0	[0.2-3.9]									96.0	2.9				1.0
Streptomycin	Turkey^{F}	9.4	[3.5-21.4]							60.4	30.2		1.9	1.9	3.8		1.9
	Turkey^{M}	6.2	[2.5-13.5]						2.1	45.4	44.0	2.1		1.0	2.1	3.1	
	Swine	24.2	[18.5-30.9]						3.5	46.5	25.8		4.0	7.6	8.1	3.5	1.0
	Sheep	1.0	[0.2-3.9]						2.9	53.0	41.0	2.4			1.0		

Substance	Sample	Resistance (%) [95% CI]		Distribution (%) of MIC-values (mg/L) 0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Gentamicin	Turkey[F]	0.0	[0.0-8.4]				43.4	54.7	1.9								
	Turkey[M]	1.0	[0.0-6.4]				26.8	67.0	5.2	1.0							
	Swine	0.0	[0.0-2.4				51.0	46.0	3.0								
	Sheep	0.0	[0.0-2.3]				43.0	52.7	4.3								
Kanamycin	Turkey[F]	3.8	[0.7-14.1]						41.5	52.8	1.9		3.8				
	Turkey[M]	0.0	[0.0-4.7]						29.9	63.9	5.2	1.0					
	Swine	1.0	[0.2-4.0]						54.0	42.4	2.5		1.0				
	Sheep	0.0	[0.0-2.3]						31.9	64.0	2.9	1.0					
Nalidixic acid	Turkey[F]	1.9	[0.1-11.4]					1.9	50.9	45.3					1.9		
	Turkey[M]	0.0	[0.0-4.7]					4.1	59.8	36.1							
	Swine	0.5	[0.0-3.2					4.0	60.6	33.8	1.0					0.5	
	Sheep	0.0	[0.0-2.3]					0.5	72.5	27.0							

Substance	Sample	Resistance (%) [95% CI*]		Distribution (%) of MIC values (mg/L) 0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64
Ciprofloxacin*	Turkey[F]	1.9	[0.1-11.4]		13.2	35.8	49.1		1.9								
	Turkey[M]	0.0	[0.0-4.7]		10.3	39.2	50.5										
	Swine	0.5	[0.0-3.2]		18.2	47.0	34.3			0.5							
	Sheep	0.0	[0.0-2.3]		1.9	33.3	64.7										

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for are given as the lowest MIC-value above the range. MIC-values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.
[F]=faecal samples. [M]=meat samples. CI= Confidence interval. *The Cut-off value from NORM-VET 2006 was used as the distribution of the MIC values probably are one or two dilution steps higher than the EUCAST distribution

RESULTS AND COMMENTS

The cut-off value for ciprofloxacin applied in NORM-VET 2006 was used instead of the cut-off value recommended by the European Food Safety Authority (EFSA) as the distribution of MIC values obtaines were one or two dilution steps higher than the European Committee on Antimicrobial Susceptibility Testing (EUCAST) distribution.

TURKEY

The occurrence of resistance among *E. coli* from faecal and meat samples from turkey was low in an international perspective. The prevalence of resistance in the isolates obtained from faecal samples and those obtained from meat samples were similar.

In total, 71.7% and 76.3% of the faecal and meat isolates, respectively, were susceptible to all antimicrobial agents included, 17.0% and 16.5% were resistant to one antimicrobial agent (predominantly ampicillin), 1.9% and 4.1% to two (mainly ampicillin and tetracycline), and 9.4% and 3.1% to three or more antimicrobial agents (Figure 13).

Resistance to ampicillin was most commonly observed, followed by resistance to tetracycline. Amoxicillin (cross-resistance with ampicillin) but also some oxytetracycline is used for clinical purposes in poultry, while streptomycines and trimethoprim are not used in Norwegian poultry production. The occurrence of fluoroquinolone resistance was low (1.9% of the faecal isolates) and on the same level as previously reported in broilers. There is no formulation of fluoroquinolone for poultry on the Norwegian market. However, in the period 2000-2007 minor amounts of such preparations were used in poultry on exemption from market authorization, and this may explain the occurrence of fluoroquinolone resistance. Compared with the prevalence of resistance to various antimicrobials in *E. coli* from broilers for the years 2000-2006, the occurrence of resistance in *E. coli* from turkey in 2007 is similar to what was observed for broilers in 2006 as shown in Figure 16.

The resistance to sulfonamides was even lower (5.7% and 3.1% from faecal and meat samples, respectively) than observed in *E. coli* from broilers in 2006 (8.1%). Formerly, sulfonamides were the most commonly used antimicrobials to poultry in Norway. Since the early 1990s antimicrobials belonging to this drug group have not been used in poultry. This may explain why resistance towards the sulfonamides has declined significantly since 2000.

SWINE

The occurrence of resistance among *E. coli* from faecal samples from swine was in an international perspective low. In total, 71.2% were susceptible to all antimicrobial agents included, 11.6% were resistant to one antimicrobial drug (predominantly streptomycin), 7.6% to two (mainly streptomycin and sulfamehoxazole) and 9.6% to three or more antimicrobial agents (Figure 13). In addition to penicillin, tetracyclines and dihydrostreptomycin are among the most commonly used antimicrobial agents for therapy in swine production. One isolate was resistant to fluoroquinolones. However, the usage of fluoroquinolones to food producing animals in Norway is very limited and there are no preparations containing cephalosporins licensed for usage in food producing animals in Norway. One isolate was resistant to the cephalosporines ceftiofur and cefotaxime with MICs only one step above the cut-off values. This isolate was subjected to further investigations, but was considered negative to extended-spectrum-beta lactamase (ESBL) production.

SHEEP

The occurrence of resistance in *E. coli* isolated from faecal samples from sheep is almost absent. In total, 98% were susceptible to all antimicrobial agents included (Figure 13). Only two isolates were multiresistant (resistant to ampicillin, sulfonamides and streptomycin) and one isolate was additionally resistant to trimethoprim. Ampicillin, sulfonamides in combination with trimethoprim and dihydrostreptomycin in combination with procaine penicillin are used for clinical purposes in sheep. Lambs slaughtered at an age of about six months account for approximately 70% of the group of slaughtered sheep, and thus dominate the material included in NORM-VET 2007. Lamb production in Norway is very extensive, and in Norway lambs spend a major part of their lives roaming freely on rough, upland grazing. Consequently, the antimicrobial use in lambs is very limited, which is also reflected in the resistance prevalences observed.

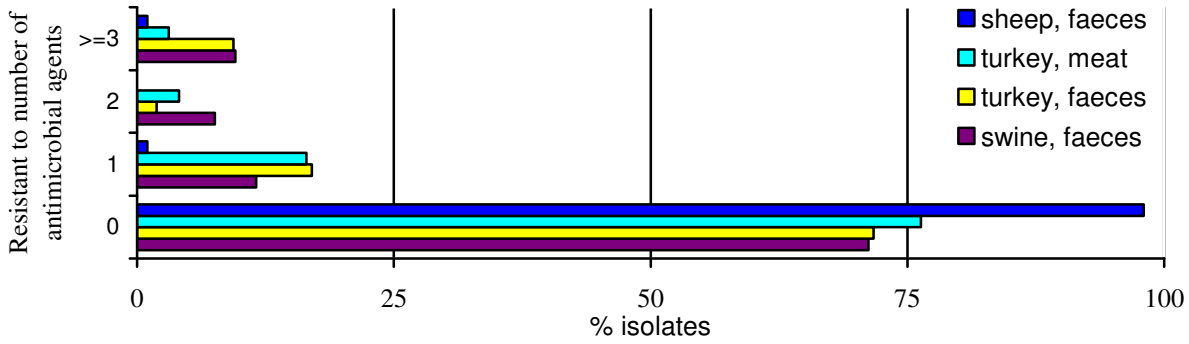

FIGURE 13. Antimicrobial resistance profile for *E. coli* from faecal (n=53) and meat (n=97) isolates from turkey and faecal isolates from swine (n=198) and sheep (n=207) in 2007. Proportions of isolates susceptible to all or resistant to one, two and three or more antimicrobial agents are illustrated.

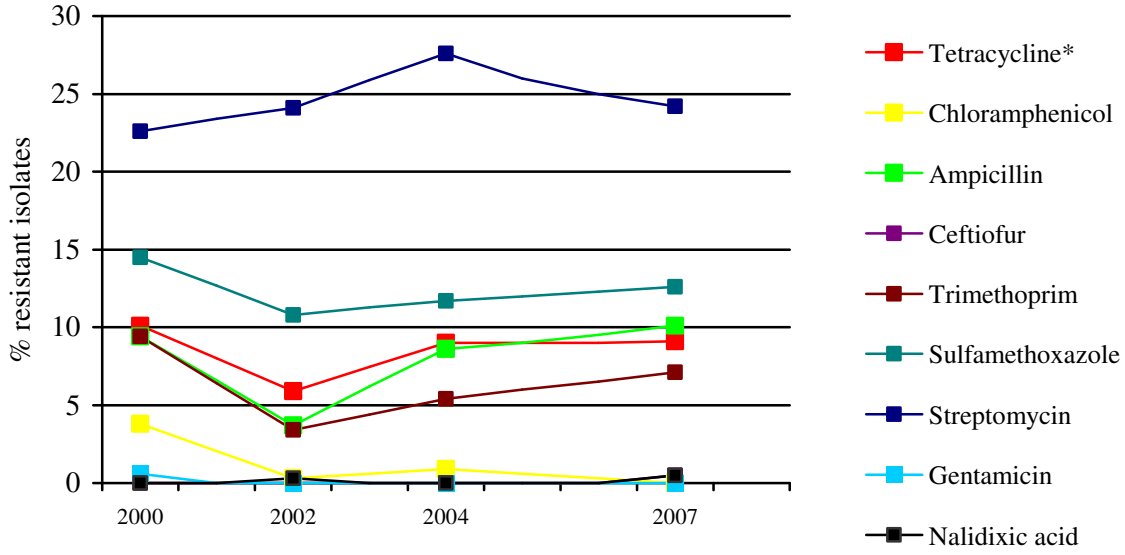

FIGURE 14. Prevalence of resistance to various antimicrobials in *E. coli* from swine isolates (faecal samples) 2000-2007. The breakpoints used in NORM-VET 2007 were applied.
*Oxytetracycline instead of tetracycline in 2002 and 2004.

Enterococcus spp. from turkey and swine

A total of 58 fecal and 107 meat samples from turkey and 203 faecal samples from swine were collected. For turkey, *E. faecium* or *E. faecalis* was isolated from 56 (96.6%) of the faecal samples and 72 (67.3%) of the meat samples. For swine, *E. faecium* or *E. faecalis* was isolated from 86 (42.4%) of the faecal samples. One isolate per sample positive for *Enterococcus* spp. was susceptibility tested. The results are presented in Tables 11-12, Figures 15-16, and in the text.

TABLE 11. Antimicrobial resistance in *Enterococcus faecalis* from meat samples from turkey (n=25) and fecal samples from swine (n=19) in 2007.

		Resistant	Distribution (n) of MIC values (mg/L)														
Substance	Sample	(n)	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	Turkey	13			10	2					10	3					
	Swine	15			2	2		1			4	10					
Chloramphenicol	Turkey	0						13	12								
	Swine	1						2	16				1				
Ampicillin	Turkey	0			1	21	1	2									
	Swine	0			1	15	3										
Erythromycin	Turkey	6			4	4	7	4			2	1	3				
	Swine	2			3	7	5	2					2				
Streptomycin	Turkey	1										7	16	1			1
	Swine	4								1		3	11			4	
Gentamicin	Turkey	0							10	15							
	Swine	1						1	3	14					1		
Kanamycin	Turkey	0									4	17	3	1			
	Swine	2									2	15					2
Vancomycin	Turkey	0					2	17	6								
	Swine	0						16	3								
Bacitracin#	Turkey	4					1	2	13	5				4			
	Swine	0							12	16	1						
Linezolide	Turkey	0				8	17										
	Swine	0				3	16										
Virginiamycin	Turkey	NR						3	**1**	17	4						
	Swine	NR							1	12	6						
Narasin	Turkey	1			13	3	1	3									
	Swine	0	12	7					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. # Measured in U/ml.
NR=Not relevant as *E. faecalis* is known to be inherently resistant to the streptogramin virginiamycin.

Enterococcus faecium isolates with MIC 16 mg/L and 32 mg/L to chloramphenicol

Susceptibility testing of *Enterococcus* spp. against chloramphenicol usually gives a typical gradual fading of growth, both with the agar diffusion method and with the broth dilution method. Due to our findings of sharp growth endpoints with MIC 16 mg/L and 32 mg/L, we suspected possible production of chloramphenicol modifying enzymes. A chloramphenicol "clover-leaf"-test was performed, and the test was found to be positive for all these isolates.
Further investigations are necessary to detect the presence of resistance genes. If resistance genes are demonstrated, these isolates should be considered resistant and the epidemiological cut-off values reconsidered. The recommended cut-off value is > 32 mg/L.

TABLE 12. Antimicrobial resistance in *Enterococcus faecium* from faecal (n=55) and meat (n=47) samples from turkey and fecal samples from swine (n=67) in 2007.

		Resistance (%)		Distribution (%) of MIC values (mg/L)													
Substance	Sample		[95%CI*]	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	Turkey[F]	23.6	[13.6-37.3]		69.1	7.3					1.8	20.0	1.8				
	Turkey[M]	17.0	[8.1-31.3]		78.7	4.3			2.1	2.1		12.8					
	Swine	19.4	[11.1-31.2]		61.2	19.4					3.0	14.9	1.5				
Chloramph.[##]	Turkey[F]	0.0	[0.0-8.1]				9.1	43.6	34.5	5.5	7.3						
	Turkey[M]	0.0	[0.0-9.4]				4.3	44.7	36.2	14.9							
	Swine	0.0	[0.0-6.8]					53.7	43.3		3.0						
Ampicillin	Turkey[F]	10.9	[4.5-22.9]	5.5	7.3	27.3	27.3	21.8	9.1		1.8						
	Turkey[M]	4.3	[0.8-9.4]	2.1	17.0	40.4	21.3	14.9	4.3								
	Swine	1.5	[0.1-9.2]		14.9	34.3	37.3	11.9	1.5								
Erythromycin	Turkey[F]	20.0	[10.9-33.4]		21.8	30.9	25.5	1.8	3.6	1.8	5.5		9.1				
	Turkey[M]	38.3	[24.9-53.6]		14.9	17.0	19.1	10.6	14.9	8.5	6.4		8.5				
	Swine	29.9	[19.6-42.5]		13.4	4.5	19.4	32.8	19.4	6.0	1.5		3.0				
Streptomycin	Turkey[F]	1.8	[0.1-11.0]								38.2	56.4	3.6		1.8		
	Turkey[M]	0.0	[0.0-9.4]							2.1	17.0	63.8	17.0				
	Swine	13.4	[6.7-24.4]								23.9	61.2	1.5		1.5	7.5	4.5
Gentamicin	Turkey[F]	0.0	[0.0-8.1]					18.2	67.3	14.5							
	Turkey[M]	0.0	[0.0-9.4]				2.1	12.8	55.3	29.8							
	Swine	0.0	[0.0-6.8]				1.5	16.4	59.7	19.4	3.0						
Kanamycin	Turkey[F]	0.0	[0.0-8.1]									10.9	32.7	47.3	9.1		
	Turkey[M]	0.0	[0.0-9.4]								4.3	12.8	36.2	27.7	19.1		
	Swine	4.5	[1.2-13.4]								1.5	7.5	38.8	35.8	10.4	1.5	4.5
Vancomycin	Turkey[F]	0.0	[0.0-8.1]			76.4	18.2	5.5									
	Turkey[M]	0.0	[0.0-9.4]			61.7	29.8	8.5									
	Swine	0.0	[0.0-6.8]			68.7	17.9	13.4									
Bacitracin[#]	Turkey[F]	23.6	[13.6-37.3]			27.3	12.7	1.8	5.5	21.8	7.3	5.5	5.5	12.7			
	Turkey[M]	27.7	[16.1-42.9]			31.9	4.3	4.3	4.3	14.9	12.8	4.3	2.1	21.3			
	Swine	10.4	[4.6-20.9]			1.5		4.5	9.0	44.8	29.9			10.4			
Linezolide	Turkey[F]	0.0	[0.0-8.1]			18.2	80.0	1.8									
	Turkey[M]	0.0	[0.0-9.4]			17.0	78.7	4.3									
	Swine	0.0	[0.0-6.8]			14.9	82.1	3.0									
Virginiamycin	Turkey[F]	3.6	[0.6-13.6]		3.6	32.7	23.6	36.4	3.6								
	Turkey[M]	2.1	[0.1-12.7]		10.6	38.3	12.8	36.2		2.1							
	Swine	1.5	[0.1-9.2]		11.9	32.8	13.4	40.3	1.5								
Narasin	Turkey[F]	63.6	[49.5-75.8]	10.9	18.2	5.5	1.8	21.8	32.7	9.1							
	Turkey[M]	51.1	[36.3-65.7]	12.8	34.0	2.1		27.7	23.4								
	Swine	6.0	[1.9-15.4]	6.0	70.1	17.9		4.5	1.5								

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for are given as the lowest MIC-value above the range. MIC-values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.
[F]=faecal samples. [M]=meat samples.
* CI= Confidence interval. [#] Measured in U/ml. [##] See comments in textbox "*Enterococcus faecium* isolates with MIC 16 mg/L and 32 mg/L to chloramphenicol" page 32.

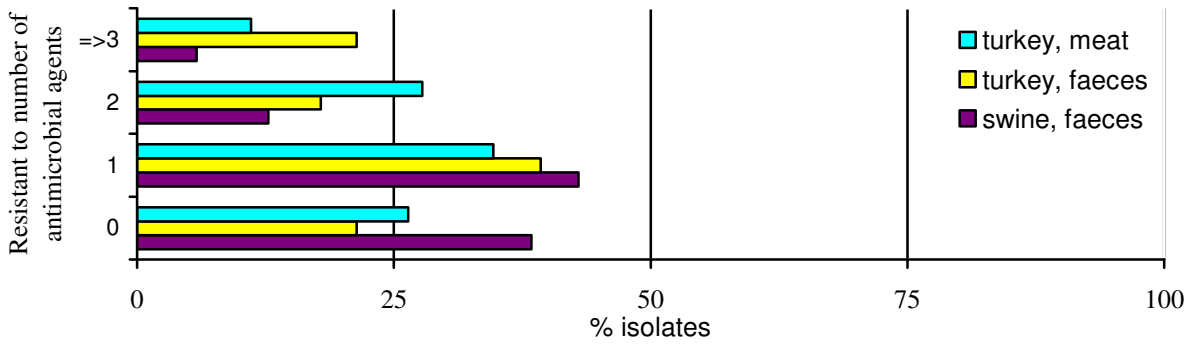

FIGURE 15. Antimicrobial resistance profile for *Enterococcus* spp. in 2007. Proportions of isolates susceptible to all or resistant to one, two, and three or more antimicrobial agents are illustrated.

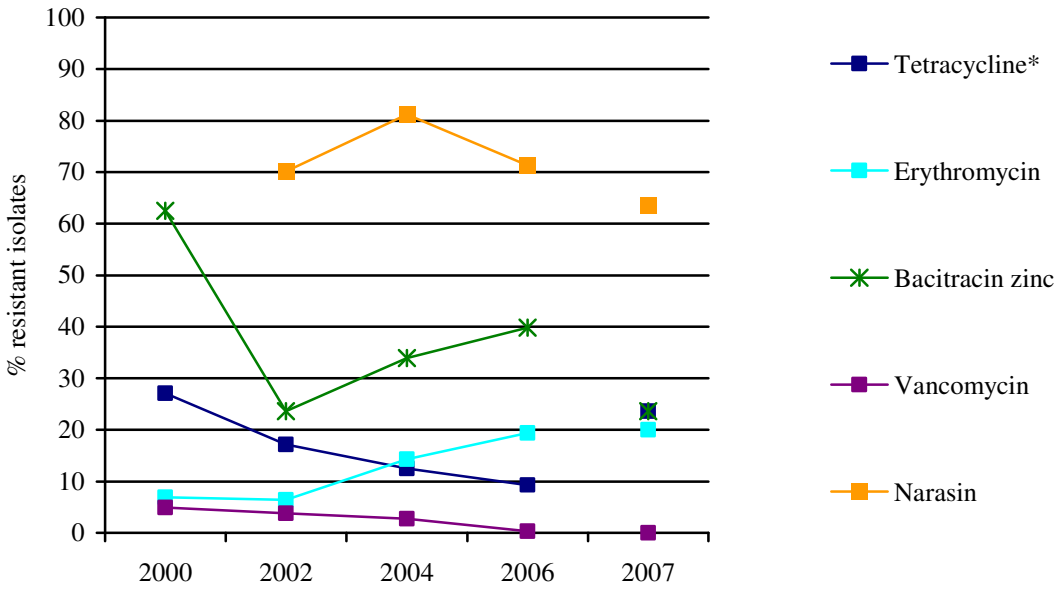

FIGURE 16. Prevalence of resistance to various antimicrobials in *E. faecium* from broiler (meat and faecal samples; 2000-2006)) and from turkey in 2007. The breakpoints used in NORM-VET 2007 were applied.
* Oxytetracycline in 2002 and 2004.

RESULTS AND COMMENTS

E. faecalis is known to be inherently resistant to the streptogramin virginiamycin, while *E. faecium* is known to be susceptible to this antimicrobial agent. Resistance to virginiamycin is therefore excluded from the interpretation of the data. In 2007, a low number of *E. faecalis* isolates was obtained both from faecal and meat samples. Therefore no statistical comparisons or conclusions could be made for this species alone. However, a high number of *E. faecium* isolates were obtained from the collected samples.

TURKEY

This is the first time indicator bacteria from turkey are included in NORM-VET. The prevalence of resistance to narasin was high. However, this cannot be explained by the usage of this substance. The dominating coccidiostat used in turkey production is monensin, and there are to our knowledge no cross resistance between monensin and narasin.

The prevalence of resistance to the other antimicrobial agents among *E. faecalis* and *E. faecium* from healthy turkeys was moderate. The resistance profiles of the isolates from turkey presented in Figure 15 include all the *Enterococcus* spp. isolated in 2007 divided by origin of sample; faeces or meat. The occurrence of resistance in faecal and meat samples was similar.

In total 21.4% and 26.4% of the faecal and meat isolates, respectively, were susceptible to all antimicrobial agents included, 39.3% and 34.7 % were resistant to one antimicrobial agent, 17.9% and 27.8% were resistant to two, and 21.4% and 11.1% to three or more antimicrobial agents (Figure 15).

Compared to the occurrence of resistance in *Enterococcus* spp. from broilers the occurrences were similar to what was observed in 2006 (Figure 16).

No vancomycin resistance was observed in the isolates obtained by a random selection. Five (3.9 %) strains were obtained by a selective isolation procedure and were *vanA* positive with MIC-values >128mg/L. All of these isolates were *E. faecium* from faecal samples.

SWINE

The occurrence of resistance among *E. faecalis* and *E. faecium* from healthy swine was moderate. The prevalences of resistance were similar to what has been observed in previous years.

In total 38.4% of the isolates were susceptible to all antimicrobial agents included, 43% were resistant to one antimicrobial agent, 12.8% were resistant to two, and 5.8% to three or more antimicrobial agents (Figure 15). Resistance to erythromycin and tetracycline was most common, followed by resistance to streptomycin.

gyrA and *parC* mutations and associated quinolone resistance in *Vibrio anguillarum* serotype O2b isolated from Norwegian farmed Atlantic cod (*Gadus morhua*)

Farmed cod are susceptible to a range of bacterial diseases, the most significant of which are associated with *Vibrio anguillarum* infection, particularly serotypes O2a and O2b. Despite vaccination, infection with *V. anguillarum* remains problematical at all stages of the cod culture cycle, and oxolinic acid (OA) is presently the antibiotic of choice for treatment of this disease. In the present study, strains isolated in 2004, from clinically diseased, farmed Atlantic cod (*Gadus morhua*), displaying three different degrees of susceptibility to quinolone antibiotics were investigated.

The Quinolone Resistance Determining Regions (QRDR) of *gyrA*, *parC* and *gyrB* genes were sequenced and compared with disc diffusion zones and MIC values for enrofloxacin, nalidixic acid and OA (Table 13).

Single serine- isoleucine substitutions at position 83 (in relation to *V. anguillarum* AB201277) were identified in *gyrA* of both intermediately susceptible and resistant strains, and a single serine → leucine substitution at position 85 (relating to *V. anguillarum* BAF33487) in *parC* of the resistant strain. Identical *gyrB* QRDR sequences were obtained from all studied isolates, indicating non-involvement of this locus in the observed quinolone resistance.

Although not functionally tested, the *gyrA* and *parC* substitutions correlate directly with incremental increases in quinolone resistance. It is therefore concluded, given the evidence from similar studies in other bacteria, that these mutations are probably responsible for the increased quinolone resistance in the studied isolates, although additional mutations in other genes, such as *parE* or the presence of plasmid bound Qnr-like elements (Poirel 2005) cannot be discounted.

MIC (OA) values for both sensitive isolates and those harbouring *gyrA* position 83 Ser → Ile substitutions in the present study appear to be lower than equivalent strains from Japan (Okuda 2006). However, the Ser → Leu mutation at position 85 in *parC* identified in the present study appears to award a significantly higher MIC value than the Glu → Gly substitution at position 90 (*V. anguillarum* BAF33487) of Japanese field isolates. Higher MIC values in laboratory induced strains (Okuda 2006), with the same *gyrA* and *parC* sequences as field strains, suggests that mutations outside the investigated areas can also be involved in quinolone resistance.

Some of the fish from which the studied isolates were recovered had been treated eight times with oxolinic acid during the two preceding years, and since conducting the original study, quinolone resistant *V. anguillaurum* continue to be steadily encountered during diagnostic investigations. There is however some evidence that following cessation of quinolone treatment, resistant isolates may be relatively quickly replaced by sensitive strains. Development of quinolone resistance in one of the major pathogens of cod at this early stage of the industry's development indicates a requirement for both a conservative approach to antibiotic use and further development/use of effective vaccines.

Table 13. Summary of MIC values and disc diffusion zones for the studied isolates

Strain designation	Date of isolation	Mutation	MIC values (μg ml^{-1})			Disc diffusion zone (mm)	
			Enrofloxacin	Nalidixic acid	Oxolinic acid	Oxolinic acid	Flume-quine
04/09/363-5036	30/7-2004	"wild-type"	≤ 0.03	≤ 1	≤ 0.0001	47	52
04/09/363-5034	30/7-2004	"wild-type"	≤ 0.03	≤ 1	n.d.	49	54
04/09/422-5063	10/9-2004	*gyrA*	0.5	16	0.06	30	37
04/09/367-5042	12/8-2004	*gyrA*	0.25	16	0.06	27	36
04/09/367-5043	12/8-2004	*gyrA*	0.25	8	0.06	28	37
04/09/494-5106	11/10-2004	*gyrA*/*parC*	1	>128	16	0	17

References

1. Okuda J., Kanamaru S., Yuasa A., Nakaoka N., Kawakami H. and Nakai T. (2006) A possible mechanism of quinolone resistance in *Vibrio anguillarum*. Fish Pathology 41 (2): 73 – 75.
2. Poirel L., Liard A., Rodriguez-Martinez J.M. and Nordmann Patrice (2005) Vibrionaceae as a possible source of Qnr-like quinolone resistance determinants. J Antimicrob Chemother 56: 1118-1121.

Duncan J Colquhoun, Section for Fish Health, National Veterinary Institute

ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

Madelaine Norström, Jørgen Lassen, Trine-Lise Stavnes

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, all *Salmonella* isolates from control programmes concerning feed samples, animals and food products, as well as a representative number of *Campylobacter* isolates from broiler and broiler meat samples are monitored for antimicrobial resistance. Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates. Sampling, laboratory methods and data processing are described in Appendix 4.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food producing animals in Norway is very good. Such animals are virtually free from *Salmonella* spp. except for the endemic occurrence of *S. enterica* subsp. *diarizonae* in sheep. To document this favourable situation, Norway runs an extensive surveillance programme that covers both live animals (cattle, pigs and poultry) and meat samples (cattle, pigs, sheep and poultry). 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 clinical submissions to the National Veterinary Institute. The data are presented in Table 14 and in the text.

TABLE 14. Antimicrobial resistance in *S.* Typhimurium (n=18) and other *Salmonella* spp. (n=7) isolates from animals. Distribution (n) of MICs (mg/L).

		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	2							23				2					
Chloramphenicol	2								10	11	2				1	1	
Florfenicol	2									21	2		1	1			
Ampicillin	2						7	16						2			
Ceftiofur	0					1	7	17									
Cefotaxime	0			15	10												
Trimethoprim	1					16	8							1			
Sulfamethoxazole	3											9	11	2			3
Streptomycin	2									1	14	7	1	2			
Gentamicin	0						20	5									
Kanamycin	0								4	21							
Ciprofloxacin	0			1	24												
Nalidixic acid	0								3	20	2						

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

RESULTS AND COMMENTS

In 2007, a total of 25 isolates of *Salmonella* spp. were susceptibility tested. Of the 18 *S.* Typhimurium, five isolates were from cattle, four isolates each from swine and horses, three isolates from dogs and two isolates from cats. Two of the *S.* Typhimurium isolates belonged to phagetype DT104 and were both resistant to ampicillin, streptomycin, florfenicol, chloramphenicol and sulfamethoxazole. The other seven *Salmonella* spp. were *S.* Dublin from a cow, one isolate each of *S.* Heidelberg, *S.* Gallinarum and *S.* Enteritidis from poultry, and one isolate each of *S.* Montevideo, *S.* Infantis and *S.* Minnesota from dogs.

The data, although very limited, indicate that antimicrobial resistance is not very widespread among those *Salmonella* spp. that occasionally are isolated from animals in Norway.

Salmonella from human clinical specimens

In 2007, a total of 1,649 cases of human salmonellosis were reported of which 391 (24%) were infected in Norway. The incidence rate was 35.2 per 100,000 inhabitants. Altogether 719 (44%) of the cases were due to *S.* Enteritidis of which 84 (12%) were infected in Norway, while 339 (21%) of the cases were due to *S.* Typhimurium of which 176 (52%) were infected in Norway. The latter is partly explained by the endemic occurrence of specific clones of this serovar in Norwegian wildlife.

Data from surveillance programmes show that domestically produced food is not an important source of human salmonellosis acquired in Norway. The most likely sources of salmonellosis acquired in Norway are wild birds and hedgehogs, imported food products and patients infected abroad. Thus, the isolates categorized as "infected in Norway" also partly reflect the *Salmonella* situation outside Norway.

The proportion of multiresistant *S.* Typhimurium DT104 from domestically acquired cases of *S.* Typhimurium infections was 6.2%. This is lower than in 2006 (13.3 %) but still higher than in 2003 and 2004, with a proportion of 3.8% and 0%, respectively. The proportion of multi-resistant *S.* Typhimurium DT104 from *S.* Typhimurium infections acquired abroad was 5.5%. This is lower than in previous years. In total, 293 isolates of *S.* Typhimurium, 701 isolates of *S.* Enteritidis, 23 isolates of *S.* Typhi, ten isolates of *S.* Paratyphi A, five isolates of *S.* Paratyphi B and 556 isolates of other *Salmonella* spp. were susceptibility tested. The results are presented in Tables 15-18, Figures 17-21, and in the text.

TABLE 15. *Salmonella* Typhimurium isolates (n=130), including multiresistant DT104 (n=8), from patients infected in Norway. Distribution (%) of antimicrobial susceptibility groups. 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	73.1	26.9
Chloramphenicol	≤ 8	> 8	89.2	0.0	10.8
Tetracycline*	≤ 4	> 8	73.1	0.0	26.9
Nalidixic acid	≤ 16	> 16	96.2	0.0	3.8
Ciprofloxacin	≤ 0.5	> 1	95.4	4.6	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	91.5	1.5	6.9

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

TABLE 16. *Salmonella* Typhimurium isolates (n=146), including multiresistant DT104 (n=8), from patients infected outside Norway. Distribution (%) of antimicrobial susceptibility groups. 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	43.2	56.8
Chloramphenicol	≤ 8	> 8	82.2	0.0	17.8
Tetracycline*	≤ 4	> 8	35.6	1.4	63.0
Nalidixic acid	≤ 16	> 16	85.6	0.0	14.4
Ciprofloxacin	≤ 0.5	> 1	89.0	9.7	1.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	84.9	0.0	15.1

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

TABLE 17. *Salmonella* Enteritidis isolates from patients (n=701[#]). Distribution (%) of antimicrobial susceptibility groups. 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	0.1	93.4	6.4
Chloramphenicol	≤ 8	> 8	98.9	0.0	1.1
Tetracycline*	≤ 4	> 8	97.0	0.0	3.0
Nalidixic acid	≤ 16	> 16	77.5	0.0	22.5
Ciprofloxacin	≤ 0.5	> 1	86.4	13.4	0.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	98.7	0.3	1.0

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defiend by AFA 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=71), abroad (n=610), unknown (n=20).

TABLE 18. *Salmonella* spp. (excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi) (n=556[#]). Distribution (%) of antimicrobial susceptibility groups. 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	0.4	85.3	14.4
Chloramphenicol	≤ 8	> 8	91.9	0.0	8.1
Tetracycline*	≤ 4	> 8	79.3	0.0	20.7
Nalidixic acid	≤ 16	> 16	83.8	0.0	16.2
Ciprofloxacin	≤ 0.5	> 1	87.9	11.4	0.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	89.9	0.7	9.4

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defiend by AFA 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=98), abroad (n=424), unknown (n=34).

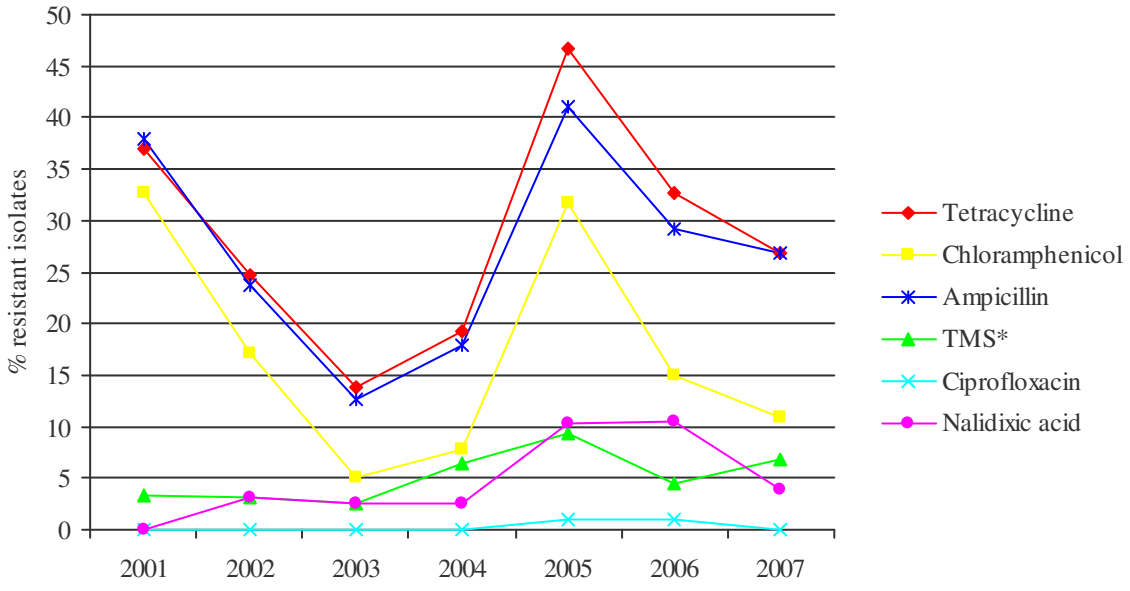

FIGURE 17. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium including multiresistant DT104. from humans infected in Norway 2001-2007. The breakpoints in NORM 2007 were applied.
*TMS=Trimethoprim-sulfamethoxazole.

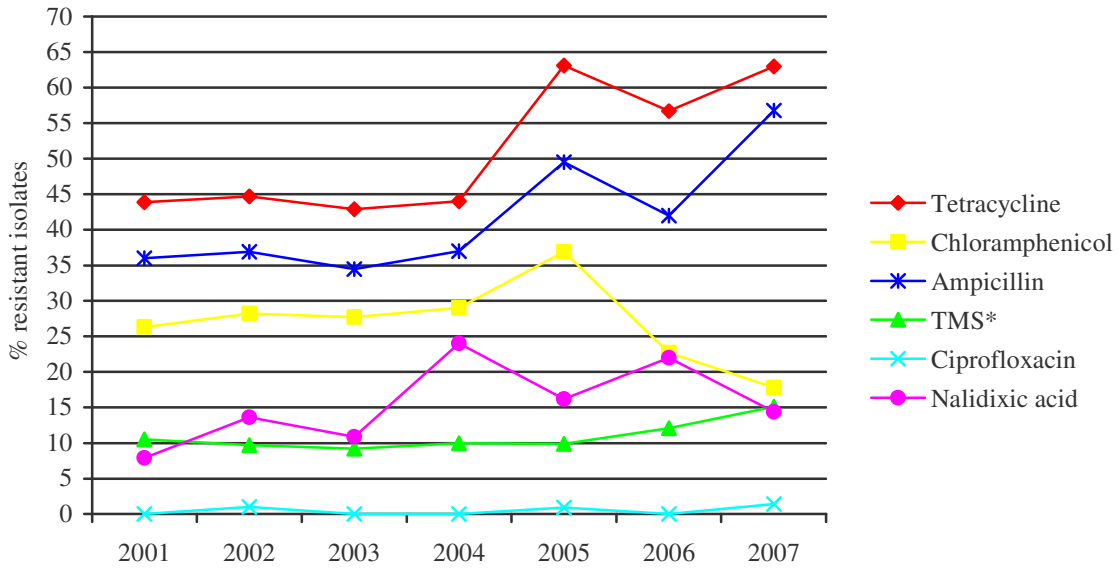

FIGURE 18. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium including multiresistant DT104. from humans infected outside Norway 2001-2007. The breakpoints in NORM 2007 were applied.
*TMS=Trimethoprim-sulfamethoxazole.

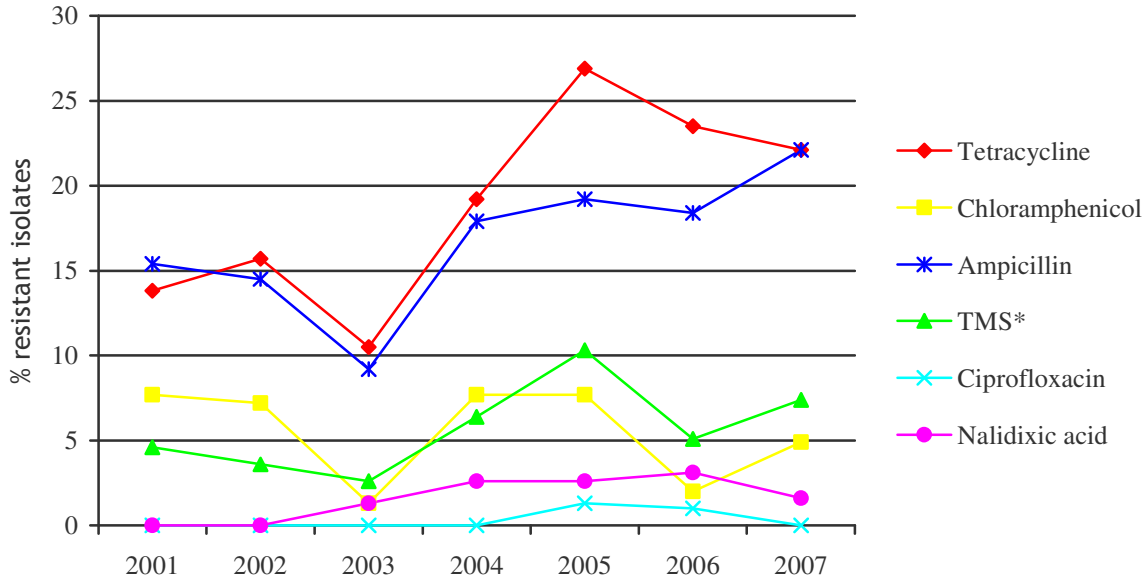

FIGURE 19. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium excluding multiresistant DT104. from humans infected in Norway 2001-2007. The breakpoints in NORM 2007 were applied.
*TMS=Trimethoprim-sulfamethoxazole.

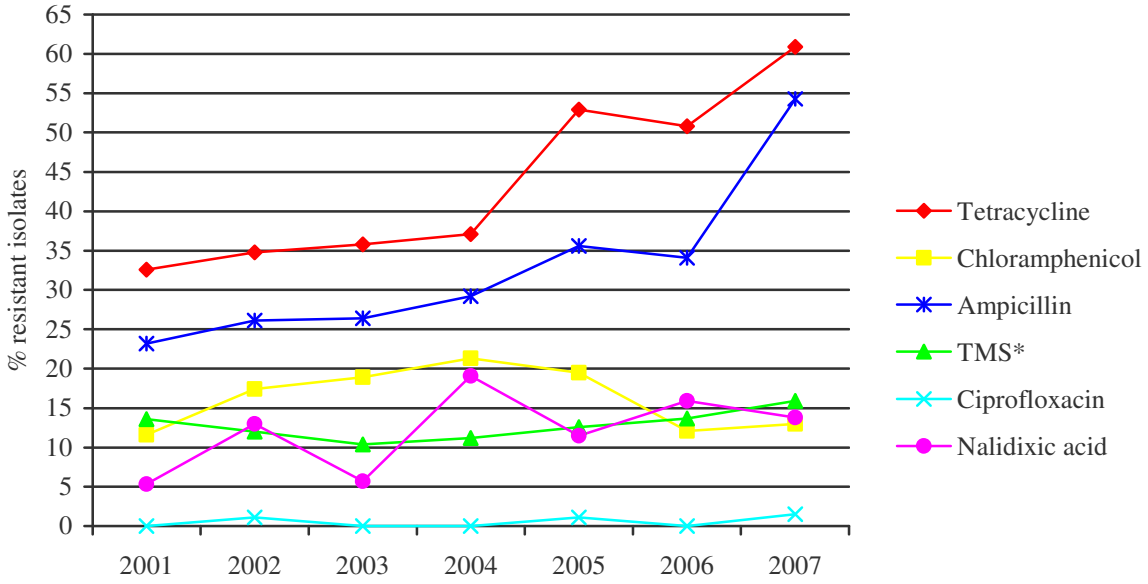

FIGURE 20. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium excluding multiresistant DT104. from humans infected outside Norway 2001-2007. The breakpoints in NORM 2007 were applied.
*TMS=Trimethoprim-sulfamethoxazole.

RESULTS AND COMMENTS

For *S.* Typhimurium, resistance to tetracycline was most commonly observed followed by resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and nalidixic acid.

The proportion of *S.* Typhimurium isolates susceptible to all antimicrobial agents tested was higher for the category "infected in Norway" (69.2%) than for the "infected abroad" category (25.3%) (Figure 21). Multiresistant strains defined as resistant to two or more antimicrobial agents, were more common in the category "infected abroad" (54.9%) than in the category "infected in Norway" (26.1%). The prevalence of resistance for the years 2001-2007 to various antimicrobials in *S.* Typhimurium from both humans infected in Norway (Figures 17 and 19) and abroad (Figures 18 and 20) indicates that the occurrence of resistance to tetracycline and ampicillin might be increasing.

The vast majority of *S.* Enteritidis isolates had been acquired abroad (Table 17). The proportion of *S.* Enteritidis isolates resistant to the different antimicrobial agents included, except for nalidixic acid, was considerably lower than for *S.* Typhimurium. In total, 22.5% of the isolates of *S.* Enteritidis were resistant to nalidixic acid. Resistance to ciprofloxacin was found in 0.1%, and as much as 13.4% of the isolates were intermediately susceptible. This is a significant increase compared to previous years. With the exception of this observation the resistance frequencies observed for *S.* Enteritidis in NORM/NORM-VET 2007 are similar to those reported for previous years.

With regard to *Salmonella* spp. isolates other than *S.* Typhimurium and *S.* Enteritidis, most infections had been acquired abroad, and antimicrobial resistance was frequently detected (Table 18). Resistance to tetracycline was most common, followed by resistance to nalidixic acid and ampicillin. Similar to what was observed for *S.* Enteritidis isolates, ciprofloxacin resistance was observed in 0.7%, while 11.4% showed reduced susceptibility to ciprofloxacin. It is emphasized that the use of fluoroquinolones in Norway is very limited in both human and veterinary medicine.

The susceptibility testing of the few isolates of *S.* Typhi (n=23), *S.* Paratyphi A (n=10) and *S.* Paratyphi B (n=5) (results not shown) in 2007 indicate that multiresistance, including resistance to nalidixic acid, is common in these serovars. With the exception of one case of unknown origin, all the infections were aquired abroad. Eleven, seven and two isolates of *S.* Typhi, *S.* Paratyphi A and *S.* Paratyphi B, respectively, were resistant to one or more of the antimicrobial agents included in the survey.

In 2007, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefpodoxime. All isolates with reduced susceptibility to cefpodoxime were further characterized by combination Etests and molecular examination. A total of eleven isolates displayed reduced susceptibility to cefpodoxime. One isolate of *S.* Typhi and six isolates in the group *Salmonella* spp. were identified as ESBL producers.

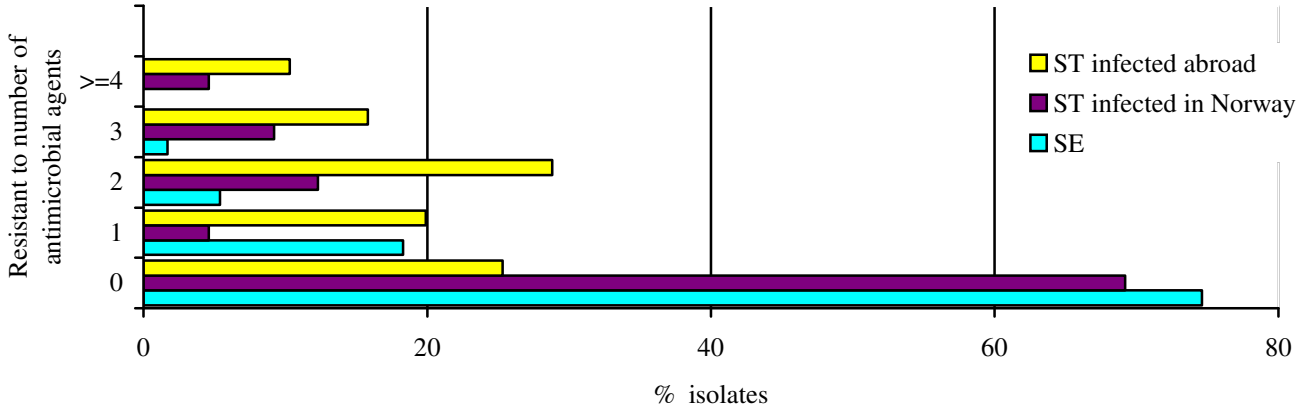

FIGURE 21. Antimicrobial resistance profiles for all *Salmonella* Enteritidis (SE) from humans (n=701) and for *Salmonella* Typhimurium (ST) from humans infected in Norway (n=130) and abroad (n=146), respectively. Proportion of isolates susceptible to all or resistant to one, two, three, or four or more antimicrobial agents are illustrated.

CAMPYLOBACTER SPP.

Campylobacter jejuni from from broilers and turkey

The isolates of *Campylobacter jejuni* in broilers presented in Table 19 and Figure 22 originate from the Norwegian action plan against *Campylobacter* spp. in broiler meat production. All broiler flocks slaughtered before 50 days of age are tested for the presence of *Campylobacter* spp. In 2007, one isolate per positive farm identified was submitted for susceptibility testing. A total of 99 isolates from broiler flocks (caecal samples) were susceptibility tested. Additonally, isolates of both broiler meat and turkey meat and turkey flocks were obtained from another study and susceptibility tested. The results of this study are presented in table 20. All results are commented in the text.

TABLE 19. Antimicrobial resistance in *Campylobacter jejuni* (n=99) from broiler flocks. Distribution (%) of MICs (mg/L).

	Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance		[95% CI*]	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	1.0	[0.1-6.3]			82.8	16.2				1.0							
Erythromycin	0.0	[0.0-4.7]					70.7	27.3	2.0								
Streptomycin	2.0	[0.3-7.8]					8.1	66.7	23.2					1.0	1.0		
Gentamicin	0.0	[0.0-4.7]			1.0	13.1	81.8	4.0									
Ciprofloxacin	1.0	[0.1-6.3]		3.0	32.3	58.6	3.0	2.0				1.0					
Nalidixic acid	1.0	[0.1-6.3]							2.0	42.4	51.5	3.0			1.0		

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 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.

TABLE 20. Antimicrobial resistance in *Campylobacter jejuni* from turkey flocks (n=14) and from turkey meat (n=7) and broiler meat (n=29) meat. Distribution (n) of MICs (mg/L).

			Distribution (n) of MIC values (mg/L)														
Substance	Sample	Resistance (n)	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Turkey^{F}	1			10	3						1					
	Turkey^{M}	1			5	1							1				
	Broiler	0			28		1										
Erythromycin	Turkey^{F}	0					8	5	1								
	Turkey^{M}	0					4	3									
	Broiler	0					24	5									
Streptomycin	Turkey^{F}	0						10	4								
	Turkey^{M}	0						4	3								
	Broiler	0					3	23	3								
Gentamicin	Turkey^{F}	0				1	12	1									
	Turkey^{M}	0				2	5										
	Broiler	0				5	22	2									
Ciprofloxacin	Turkey^{F}	1			3	9	1					1					
	Turkey^{M}	1			3	1	2					1					
	Broiler	0			10	17	2										
Nalidixic acid	Turkey^{F}	1								3	10				1		
	Turkey^{M}	1							1	2	2	1			1		
	Broiler	0								14	14	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 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

The results show that the occurrence of antimicrobial resistance among *C. jejuni* isolates from Norwegian broilers is low. A total of 96.9 % of the included isolates were susceptible to all antimicrobial agents tested. Altogether, one isolate was resistant to both nalidixic acid and ciprofloxacin, one isolate to both streptomycin and tetracycline, and one isolate only to streptomycin. The results reflect the usage of antimicrobial agents in poultry production. Antimicrobials except coccidiostatic agents are rarely used, and only for therapeutic purposes. If used, the aminopenicillin amoxicillin or the tetracycline oxytetracycline are the drugs of choice. Nalidixic acid is not used in poultry, but a minor amount of enrofloxacin has been used on exemption from marked authorization in recent years (K. Grave. unpublished data).

The results are similar to those presented in previous NORM/NORM-VET reports as seen in Figure 22.

The prevalence of resistance and the resistance patterns for *C. jejuni* isolated from Norwegian broilers are similar to what was observed for *C. jejuni* isolated from humans infected within Norway, except for a higher prevalence of resistance to quinolones (nalidixic acid and ciprofloxacin) among the isolates of human origin. This relationship was also observed in previous NORM/NORM-VET reports.

Two of the isolates from turkey (one from meat and one from flocks) were resistant to tetracyclines, nalidixic acid and ciprofloxacin, whereas all of the isolates from broiler meat were susceptible to all the antimicrobial agents included.

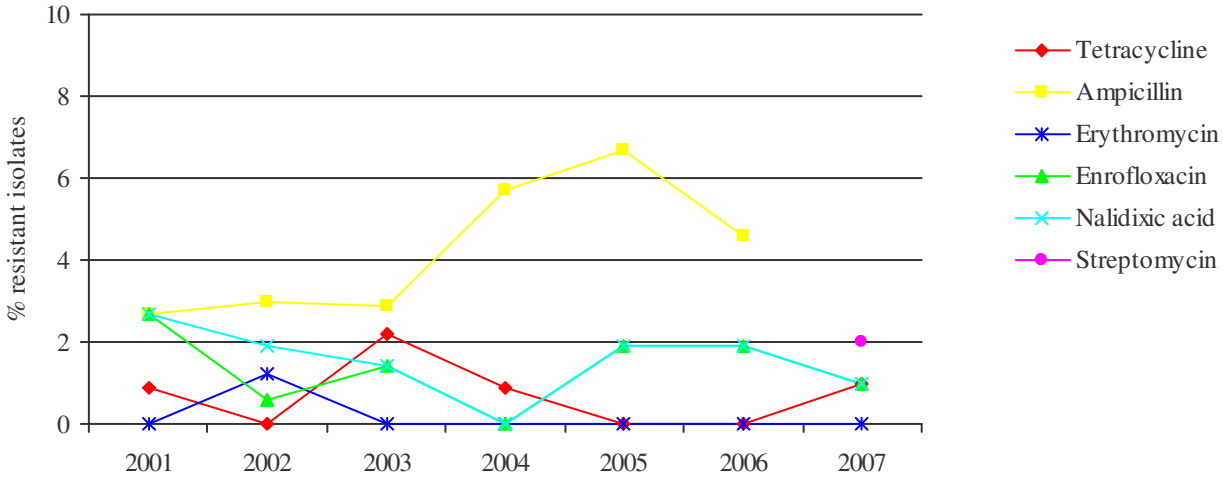

FIGURE 22. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers 2001-2007. The breakpoints for resistance defined in NORM-VET 2006 were applied for the data generated before 2007.

Campylobacter spp. from human clinical specimens

Among the 2,834 cases of human campylobacteriosis recorded in Norway in 2007, 51% were reported as acquired abroad. The incidence rate was 59.8 per 100,000. The vast majority of cases were sporadic. Case-control studies in Norway have revealed that consumption of broiler meat purchased fresh and drinking of untreated water are important risk factors for domestically acquired campylobacteriosis. A total of 264 isolates of *C. jejuni*, 98 from patients infected in Norway, 136 from patients infected abroad and 30 from patients where the origin of infection was unknown, as well as fourteen isolates of *C. coli*, three isolates of *C. lari,* one isolate of *C. upsaliensis* and two other isolates of *Campylobacter* (unspecified genus) were susceptibility tested. The results are presented in Tables 21-24, Figures 23-25, and in the text.

TABLE 21. *Campylobacter jejuni* isolates from patients infected in Norway (n=98). Distribution (%) of antimicrobial susceptibility groups.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 1	> 2	94.9	0.0	5.1
Erythromycin	≤ 2	> 2	99.0	0.0	1.0
Gentamicin	≤ 2	> 4	98.0	1.0	1.0
Nalidixic acid	≤ 16	> 16	92.9	0.0	7.1
Ciprofloxacin	≤ 0.5	> 1	94.9	0.0	5.1

TABLE 22. *Campylobacter jejuni* isolates from patients infected in Norway (n=98). Distribution (%) of MICs (mg/L).

	<=0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Tetracycline		6.1	56.2	25.5	7.2					1.0	1.0	1.0		2.0
Erythromycin			1.0	3.0	15.3	55.1	24.5							1.0
Gentamicin			1.0	8.1	25.5	49.0	14.3	1.0	1.0					
Nalidixic acid				1.0	1.0	1.0	20.4	50.0	16.0	3.0	1.0	1.0		5.1
Ciprofloxacin	1.0	7.1	54.1	31.6	1.0						5.1			

*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.

TABLE 23. *Campylobacter jejuni* isolates from patients infected outside Norway (n=119). Distribution (%) of antimicrobial susceptibility groups.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 1	> 2	50.7	0.0	49.3
Erythromycin	≤ 2	> 2	91.9	0.0	8.1
Gentamicin	≤ 2	> 4	98.5	0.7	0.7
Nalidixic acid	≤ 16	> 16	41.9	0.0	58.1
Ciprofloxacin	≤ 0.5	> 1	41.9	0.7	57.4

TABLE 24. *Campylobacter jejuni* isolates from patients infected outside Norway (n=119). 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		7.3	27.2	11.0	4.4	0.7	0.7		3.7	3.6	13.2	11.8	4.4	11.8
Erythromycin			0.7	1.5	20.6	48.6	20.5	2.2						5.9
Gentamicin		0.7	0.7	13.3	30.9	52.2	0.7	0.7						0.7
Nalidixic acid						1.4	12.5	22.8	4.4	0.7	0.7			57.4
Ciprofloxacin	0.7	3.7	26.5	9.6	1.5	0.7					57.3			

*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.

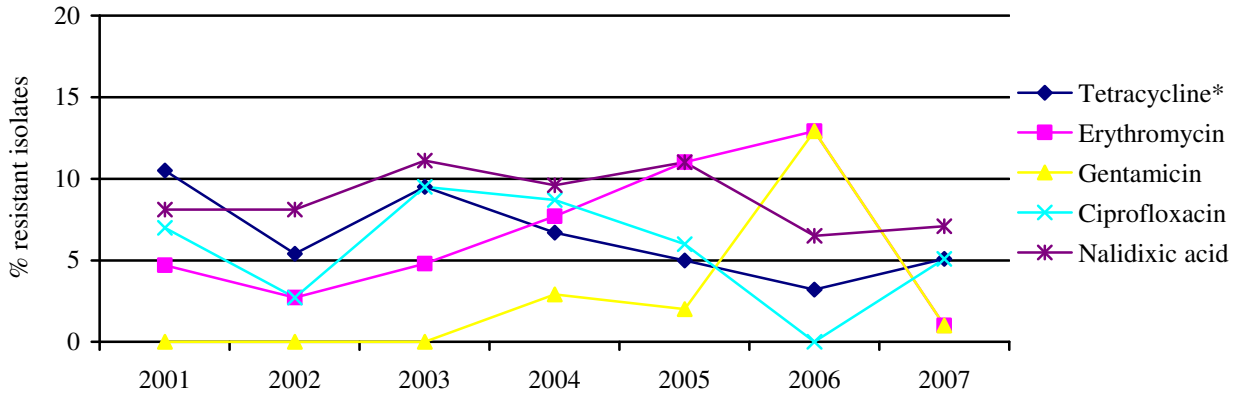

FIGURE 23. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from humans infected in Norway 2001-2007. The breakpoints in NORM 2007 were applied. * Doxocycline before 2006.

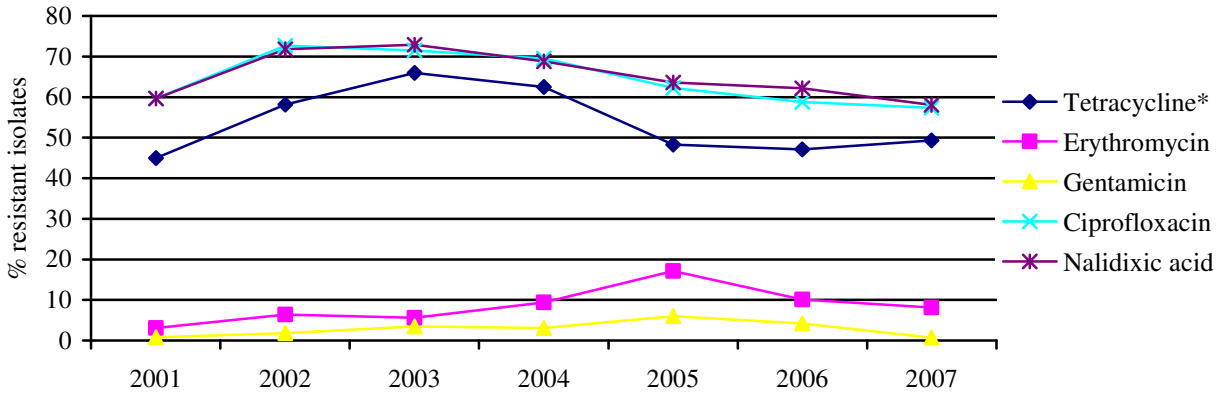

FIGURE 24. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from humans infected outside Norway 2001-2007. The breakpoints in NORM 2007 were applied. * Doxocycline before 2006.

RESULTS AND COMMENTS

The data show that resistance was significantly more widespread among *C. jejuni* isolates recovered from patients infected abroad than in patients infected in Norway. Only 27.9% of isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 88.8% of the isolates from patients infected in Norway (Figures 25). The main differences between the two groups were seen for ciprofloxacin/nalidixic acid (57.4%/58.1% resistance in isolates from infections acquired abroad versus 5.1%/7.1% resistance in isolates from infections acquired in Norway) and tetracycline (49.3% resistance in isolates from infections acquired abroad versus 5.1% resistance in isolates from infections acquired in Norway), see Tables 21-24 and Figures 23-24.

The prevalence of resistance and the resistance patterns for *C. jejuni* isolated from humans infected within Norway correspond well with what was observed for *C. jejuni* isolated from Norwegian broilers, except for a higher prevalence of resistance to quinolones (nalidixic acid and ciprofloxacin) among isolates of human origin. This relationship has also beeen observed in previous NORM/NORM-VET reports. The prevalence of resistance to various antimicrobials in *C. jejuni* from both humans infected in Norway (Figure 23) and abroad (Figure 24) for the period 2001-2007 indicate that the occurrence of resistance is relatively stable.

Eleven *C. coli* isolates were acquired abroad, one was acquired in Norway, whereas the origins of the remaining two isolates were unknown. Ten of these isolates were resistant to at least one of the antimicrobial agents included, mainly quinolones or tetracycline. *C. coli* is typically associated with pigs and pork.

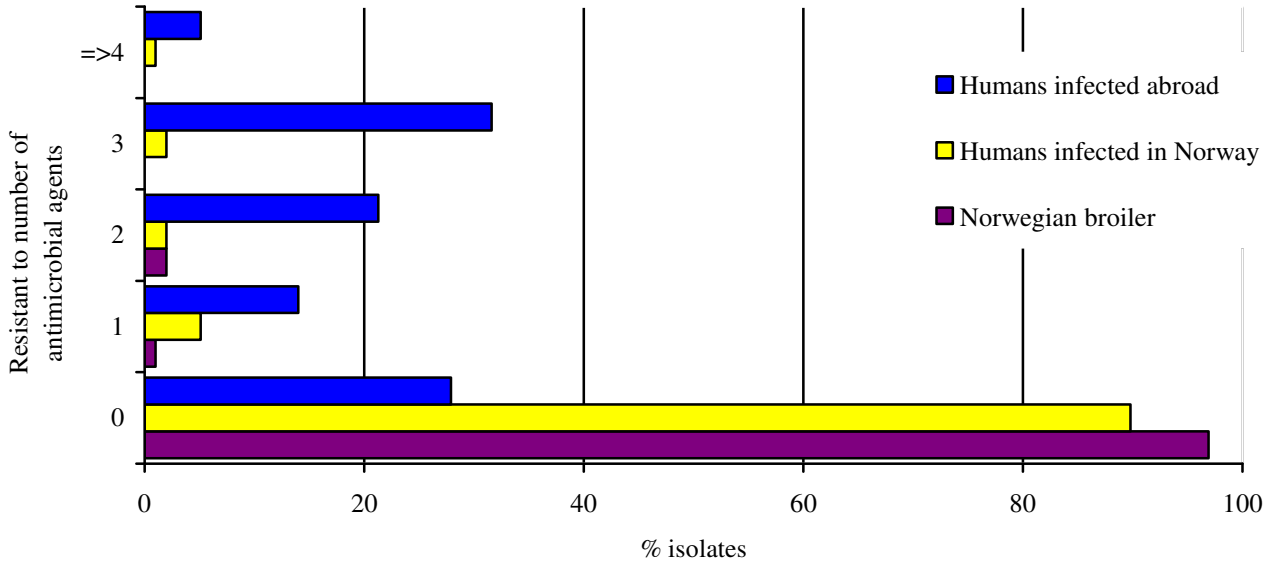

FIGURE 25. Antimicrobial resistance profiles for *Campylobacter jejuni* from Norwegian broiler (n=99), humans infected in Norway (n=98) and humans infected abroad (n=119). Proportion of isolates susceptible to all or resistant to one, two, three, or four or more antimicrobial agents are illustrated. The isolates from humans were tested for susceptibility to tetracycline, erythromycin, gentamicin, ciprofloxacin and nalidixic acid, whereas the broiler isolates in addition were tested for susceptibility to streptomycin.

Yersinia enterocolitica from human clinical specimens

Most cases of *Yersinia enterocolitica* infections in Norway are domestically acquired. A total of 71 cases of yersiniosis were reported in 2007 giving an incidence rate of 1.5 per 100,000. Fourty-four of these cases (62%) were registered as acquired in Norway. A total of 65 *Y. enterocolitica* isolates were susceptibility tested. The results are presented in Table 25 and Figure 26.

TABLE 25. *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 isolates from human clinical cases (n=64[#]). Distribution (%) of antimicrobial susceptibility groups. 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	1.6	98.4
Chloramphenicol	≤ 8	> 8	85.9	0.0	14.1
Tetracycline*	≤ 4	> 8	100	0.0	0.0
Nalidixic acid	≤ 16	> 16	92.2	0.0	7.8
Ciprofloxacin	≤ 0.5	> 1	78.1	21.9	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	84.4	3.1	12.5

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defiend by AFA 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=44), Abroad (n=14), Unknown (n=6).

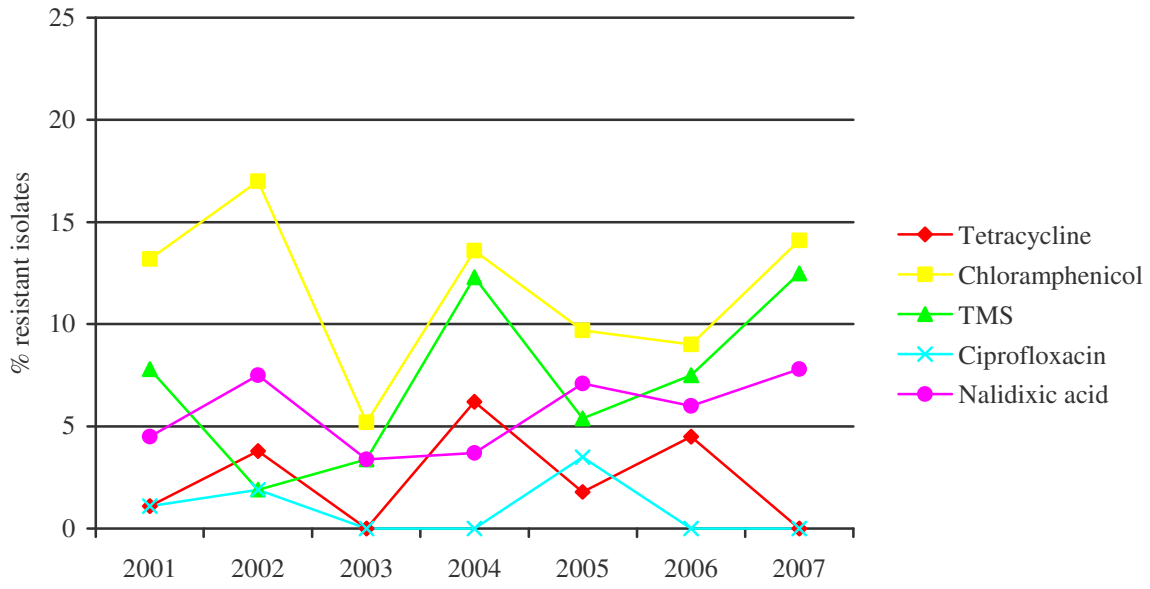

FIGURE 26. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2006. The breakpoints in NORM 2007 were applied.

RESULTS AND COMMENTS

The infections in 2007 were mainly domestically acquired. All serogroup O:3 and O:9 isolates expressed intrinsic resistance to ampicillin. The prevalence of resistance to other antimicrobials was stable compared to earlier years (Figure 26).

In 2007, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefpodoxime. All isolates with reduced susceptibility to cefpodoxime were further characterized by combination Etests and molecular examination. A total of three isolates displayed reduced susceptibility to cefpodoxime, but none were identified as ESBL producers.

Shigella spp. from human clinical specimens

It should be emphasized that almost all reported *Shigella* infections in Norway are acquired abroad. In 2007, 9.5% of the 148 reported cases were classified as domestically acquired. Thus, the prevalence of resistance in this report predominantly relates to isolates originating in other countries. The species distribution of the 140 *Shigella* isolates that were susceptibility tested was as follows: *S. sonnei* 80 (57.1%), *S. flexneri* 47 (33.6%), *S. boydii* 9 (6.4%), and *S. dysenteriae* four (2.9%). The results for *S. sonnei* and *S. flexneri* are presented in Tables 26-27 and in the text.

TABLE 26. *Shigella sonnei* isolates from human clinical cases (n=80). Distribution (%) of antimicrobial susceptibility groups. 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	83.8	16.2
Chloramphenicol	≤ 8	> 8	97.5	0.0	2.5
Tetracycline*	≤ 4	> 8	20.0	1.2	78.8
Nalidixic acid	≤ 16	> 16	73.8	0.0	26.2
Ciprofloxacin	≤ 0.5	> 1	87.5	12.5	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	5.0	1.2	93.8

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

TABLE 27. *Shigella flexneri* isolates from human clinical cases (n=47). Distribution (%) of antimicrobial susceptibility groups. 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	36.2	63.8
Chloramphenicol	≤ 8	> 8	40.4	0.0	59.6
Tetracycline*	≤ 4	> 8	10.6	0.0	89.4
Nalidixic acid	≤ 16	> 16	83.0	0.0	17.0
Ciprofloxacin	≤ 0.5	> 1	87.2	8.5	4.3
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	36.2	2.1	61.7

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

RESULTS AND COMMENTS

As reported from other countries, resistance was widespread among *Shigella* isolates, regardless of the bacterial species.

The resistance frequencies observed were particularly high for tetracycline, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole. These drugs are commonly used for various clinical purposes within human medicine in many parts of the world. For ampicillin and chloramphenicol we found differences between *Shigella* species. Resistance was most prevalent among *S. flexneri* and least prevalent among *S. sonnei* isolates. In addition, resistance to nalidixic acid was relatively common. Clinical resistance to fluoroquinolones was rarely observed, but the detection of *Shigella* isolates intermediately susceptible to ciprofloxacin and resistant to nalidixic acid indicates that high-level fluoroquinolone resistance may be developing. The few isolates *of S. dysenteriae* (n=4) and *S. boydii* (n=9) recovered and susceptibility tested in 2007 indicate that multiresistance is also common in these species; three and seven of the isolates, respectively, were resistant to two or more antimicrobial agents. Only one isolate (*S. dysenteriae*) was susceptible to all antimicrobial agents included in the survey.

In 2007, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefpodoxime. All isolates with reduced susceptibility to cefpodoxime were further characterized by combination Etests and/or molecular examination. Four isolates displayed reduced susceptibility to cefpodoxime, and three of them were verified as ESBL producers.

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 collect 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. All new 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 28, proportions are therefore estimated from all isolates and from all isolates excluding species considered to be common skin contaminants such as coagulase negative staphylococci, *Micrococcus* spp., *Corynebacterium* spp., *Bacillus* spp. and *Propionibacterium* spp. This does not imply that such isolates cannot cause infections, but only that it was not possible to enforce a standardised protocol for inclusion of the clinically significant isolates. Similarly, all isolates were registered as individual findings although polymicrobial bloodstream infections are regularly detected in some patients. Limitations in the data extraction procedure prohibited in-depth analysis of these parameters.

TABLE 28. Number of blood culture isolates in 2007, and proportion of all isolates and proportion of isolates excluding possible skin contaminants (Coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) in 2004, 2005, 2006 and 2007.

Species	No. of isolates 2007	% of all isolates				% of isolates excluding skin flora			
		2004	2005	2006	2007	2004	2005	2006	2007
Staphylococcus aureus	1,273	12.3	10.3	10.3	10.1	14.0	13.3	13.7	13.3
Coagulase negative staphylococci	2,714	11.3	20.3	22.7	21.6	-	-	-	-
Streptococcus pneumoniae	976	11.6	9.4	7.9	7.8	13.2	12.1	10.6	10.2
Streptococcus pyogenes	144	2.3	2.2	1.3	1.1	2.6	2.8	1.7	1.5
Streptococcus agalactiae	214	2.0	1.6	1.7	1.7	2.3	2.1	2.2	2.2
Betahaemolytic streptococci group C and G	110	0.7	0.8	1.2	0.9	0.9	1.1	1.5	1.1
Viridans- and non-haemolytic streptococci	459	4.6	3.8	3.7	3.7	5.3	5.0	5.0	4.8
Enterococcus faecalis	542	4.6	4.0	4.3	4.3	5.2	5.2	5.7	5.7
Enterococcus faecium	171	1.1	1.1	1.1	1.4	1.2	1.5	1.5	1.8
Other Gram positive bacteria	427	1.8	3.1	3.4	3.4	1.0	1.3	1.8	2.1
Escherichia coli	2,795	26.2	22.4	21.6	22.3	29.9	29.0	28.9	29.2
Klebsiella spp.	757	6.2	5.4	5.4	6.0	7.2	7.0	7.2	7.9
Enterobacter spp.	222	1.5	1.6	1.7	1.8	1.6	2.0	2.3	2.3
Proteus spp.	211	2.7	1.9	1.8	1.7	3.0	2.4	2.4	2.2
Other *Enterobacteriaceae*	280	1.8	1.8	1.9	2.2	2.0	2.3	2.5	2.9
Pseudomonas spp.	197	1.9	2.1	1.7	1.6	2.2	2.8	2.3	2.1
Other Gram negative aerobic bacteria	258	1.7	2.2	2.3	2.1	2.0	2.8	3.1	2.7
Bacteroides spp.	274	2.1	1.8	1.9	2.2	2.4	2.4	2.5	2.9
Other anaerobic bacteria	309	1.9	2.2	2.4	2.5	2.0	2.3	2.8	2.9
Yeasts	218	1.8	2.0	1.9	1.7	2.0	2.6	2.5	2.3
Total	**12,551**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

As seen in Table 28 and Figure 27, aerobic Gram positive and Gram negative bacteria represented 56.0% and 37.6% of all isolates, respectively. The predominance of Gram positives among all isolates was at the same level as in previous years. The most common Gram positive species were coagulase negative staphylococci which represented 21.6% of all isolates. The difference between 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 42.7% Gram positives and 49.3% Gram negatives.

Among the aerobic Gram positives, the prevalences of *S. pneumoniae* declined even when skin contaminants were excluded (13.2% in 2004, 12.1% in 2005, 10.6% in 2006 and 10.2% in 2007). A similar trend was seen for *S. pyogenes* (group A streptococci). The increase previously noted for the combined group C and G streptococci did not continue in 2007 (0.9% in 2004, 1.1% in 2005, 1.5% in 2006 and 1.1% in 2007).

Among the aerobic Gram negatives, *E. coli* (29.2%) and other *Enterobacteriaceae* (15.3%) accounted for the vast majority of isolates. *Pseudomonas* spp. (2.1%) decreased to the same level as in 2004 (2.2%) after a peak in 2005 (2.8%), all excluding skin flora.

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 4.7% (5.8% excluding skin flora) and yeasts accounted for 1.7% (2.3% excluding skin flora). The major pathogens among anaerobes were members of the *Bacteroides fragilis* group (2.2%/2.9%) and among yeasts *Candida albicans* (1.3%/1.7%). However, a multitude of other species was also represented.

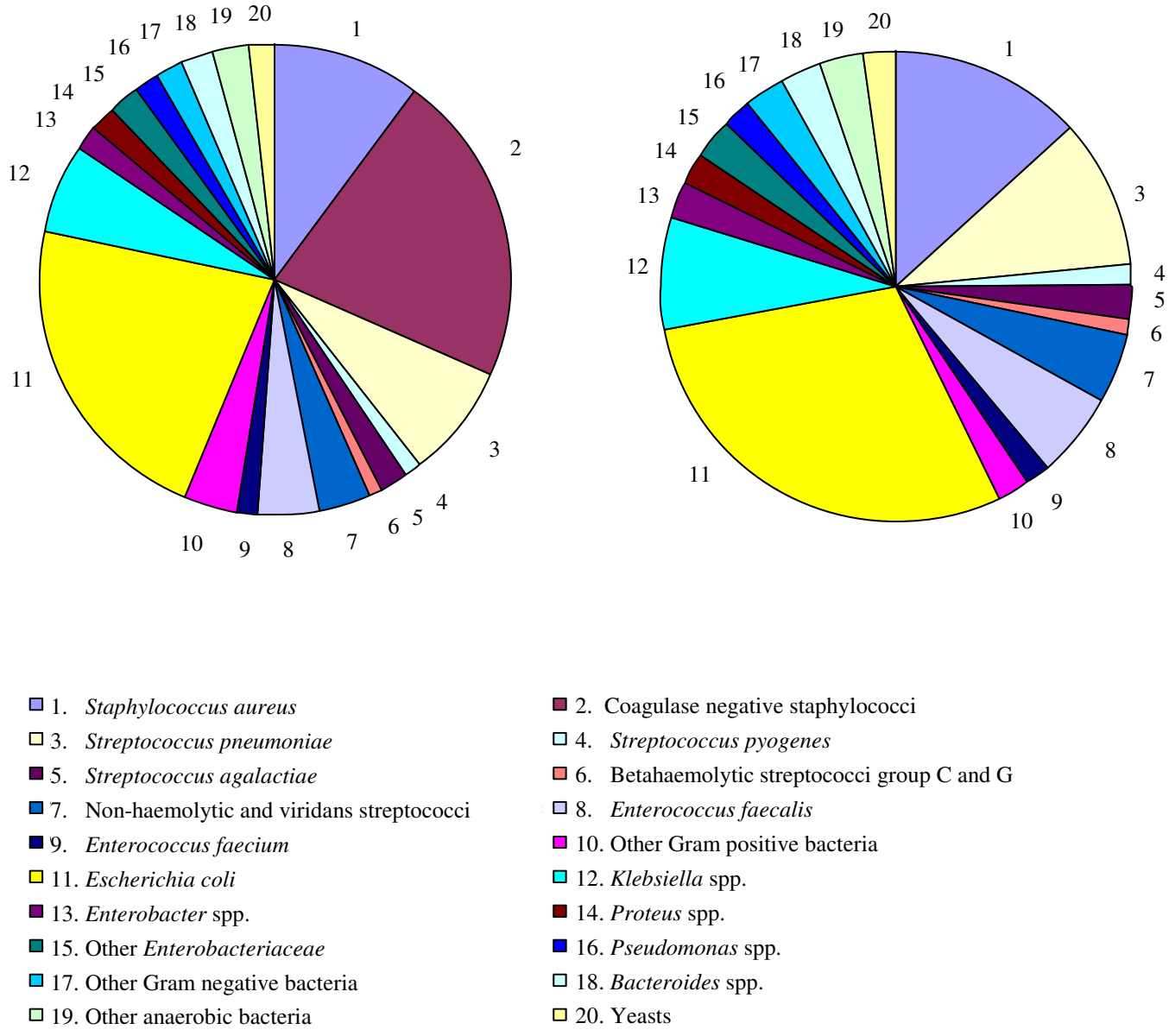

FIGURE 27. Distribution of all blood culture isolates (left, n=12,551) and blood culture isolates excluding common skin contaminants (right, n=9,578) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. The figure is based on data from the information systems of all Norwegian laboratories in 2007.

Escherichia coli in blood cultures

TABLE 29. *Escherichia coli* blood culture isolates (n=1,169). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin*	≤ 0.5	> 8	0.0	61.8	38.2
Piperacillin-tazobactam	≤ 8	> 16	94.0	3.5	2.5
Cefuroxime*	≤ 0.5	> 8	0.0	95.1	4.9
Cefotaxime	≤ 1	> 2	97.8	0.4	1.8
Ceftazidime	≤ 1	> 8	97.8	1.7	0.5
Aztreonam	≤ 1	> 8	97.5	0.8	1.7
Meropenem	≤ 2	> 8	99.8	0.2	0.0
Gentamicin	≤ 2	> 4	96.2	0.2	3.7
Nalidixic acid	≤ 16	> 16	87.2	-	12.8
Ciprofloxacin	≤ 0.5	> 1	91.1	2.1	6.8
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	75.0	1.2	23.8
ESBL	Negative	Positive	98.8	-	1.2

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

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, and the Norwegian breakpoints will therefore correspond to common EUCAST breakpoints when these have been established. The breakpoints for Enterobacteriaecea towards betalactams remained unchanged from 2006 and are given in Table 29. The SIR distribution for cefpirome is not given as one of the disk suppliers has not defined breakpoints for this substance. The trimethoprim-sulfamethoxazole breakpoint for resistance was reduced from R > 8/152 to R > 4/76. The breakpoint for susceptibility remained unchanged at S ≤ 2 mg/L.

The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobials such as cefotaxime, ceftazidime, meropenem, gentamicin and piperacillin-tazobactam, see Table 29. The increase in gentamicin non-susceptibility noted in 2004 and 2005 resumed in 2007 with 0.2% I (0.5% in 2005) and 3.7% R (1.8% in 2005) as seen in Figure 28. The prevalence of non-suscpetibility to ciprofloxacin continued to increase from a total of 3.3% in 2004, 5.0% in 2005 and 6.4% in 2006 to 8.9% in 2007. The prevalences of both intermediate susceptibility and resistance increased from 2006 to 2007 (I from 1.2% to 2.1% and R from 5.2% to 6.8%). The trend for ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 29. The prevalence of resistance to the indicator antibiotic nalidixic acid increased correspondingly from 9.3% in 2006 to 12.8% in 2007. The prevalence of resistance to ampicillin increased from 31.0% in 2006 to 38.2% in 2007. Similarly, the prevalence of susceptibility to trimethoprim-sulfamethoxazole decreased from 81.0% to 75.0%, but this may be related to changes in breakpoints.

In 2007, 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 characterized by combination Etests and/or molecular examination. A total of 32 isolates displayed reduced susceptibility to one or both of the test substrates, but only fourteen were verified as true ESBL producers by Etest (1.2%). This is an increase from 0.3% in 2003, 0.7% in 2004 and 0.5% in 2005, but unchanged from 1.1% in 2006. The ESBL strains were recovered from nine different laboratories, and there were no indications of local outbreaks.

All the fourteen isolates were resistant to ampicillin. Thirteen isolates were non-susceptible to cefotaxime (twelve resistant and one intermediately susceptible) and twelve were non-suscpetible to ceftazidime (five resistant and seven intermediately susceptible). When looking at the specificity of individual test substrates, cefotaxime identified thirteen non-ESBL producers (nine resistant and four intermediately susceptible) whereas ceftazidime identified fourteen non-ESBL producers (two resistant and twelve intermediately susceptible). Overall, the two test substances performed equally well with regard to sensitivity and specificity for ESBL detection. There was a tendency for ESBL strains to be categorized as resistant to cefotaxime and intermediately susceptible to ceftazidime, which is in accordance with previous studies documenting CTX-M enzymes as the predominant ESBL genotype in Norway. However, non-ESBL strains were also more often scored as fully resistant to cefotaxime. Among the fourteen ESBL strains, twelve were resistant to cirpofloxacin, six were non-susceptible to gentamicin (five resistant and one intermediately susceptible), and six were non-susceptible to piperacillin/tazobactam (two resistant and four intermediately susceptible). All ESBL strains were fully susceptible to meropenem.

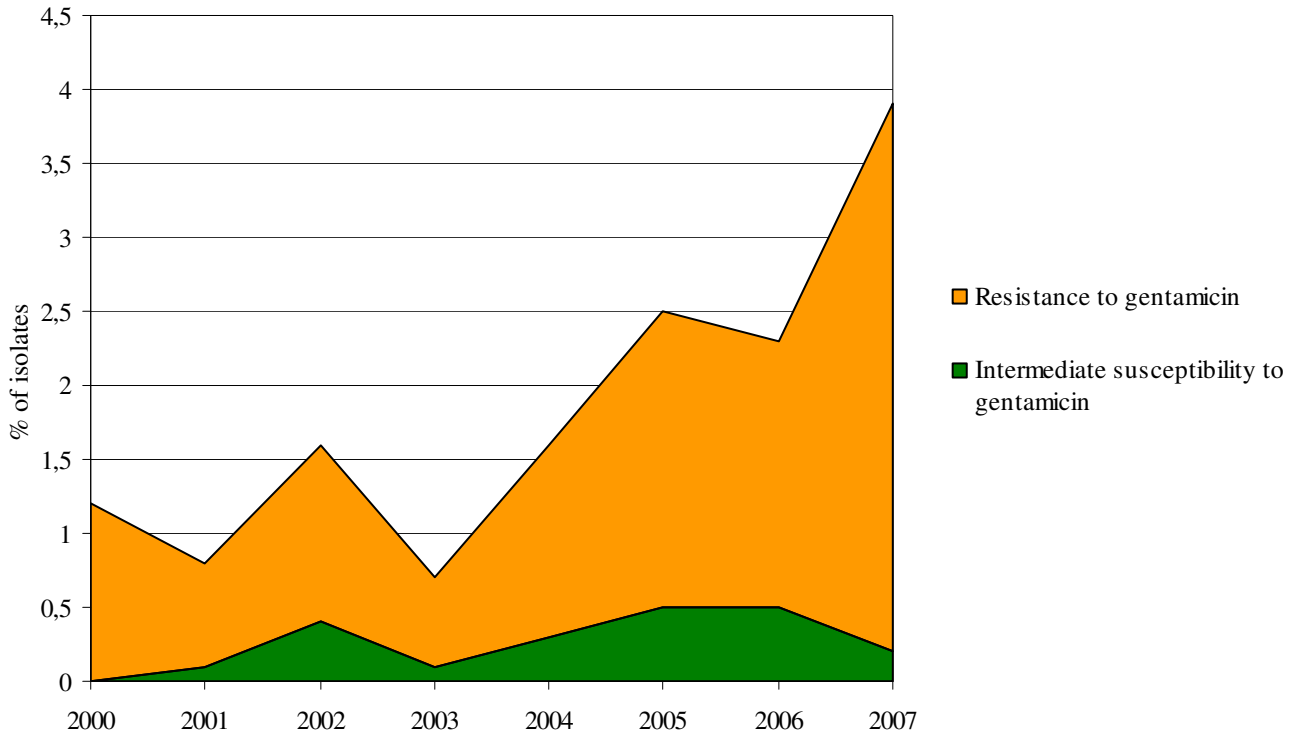

FIGURE 28. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000 – 2007.

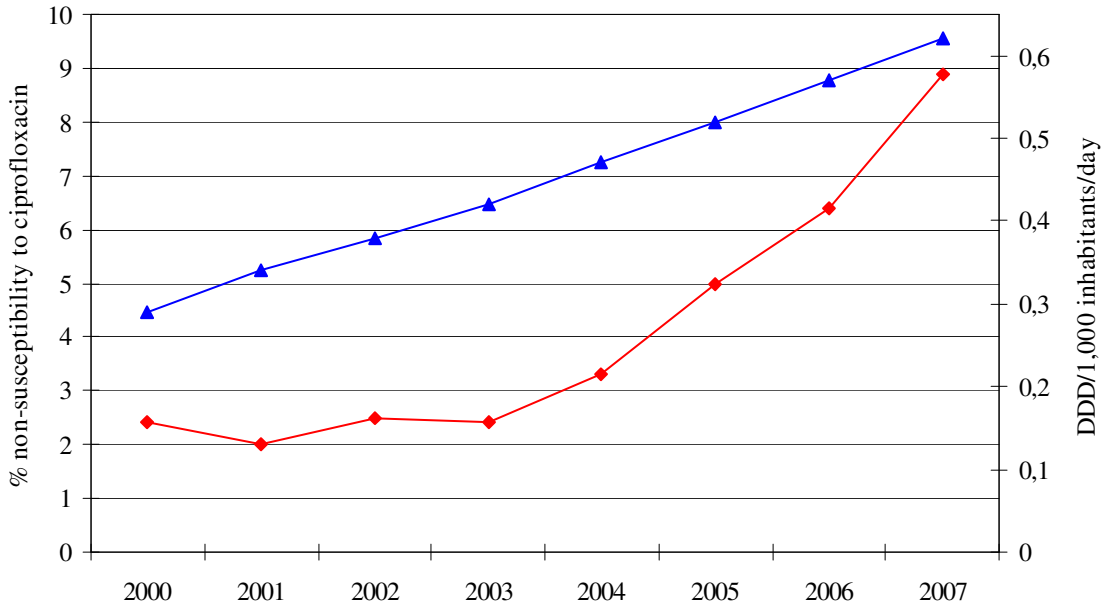

FIGURE 29. Prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2008 breakpoint protocol (red) versus usage of ciprofloxacin (blue) 2000 – 2007.

Escherichia coli in urine

TABLE 30. *Escherichia coli* urinary tract isolates (n=2,793). 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	70.0	29.8
Mecillinam	≤ 2	> 8	90.9	7.4	1.7
Cefuroxime*	≤ 0.5	> 8	1.0	96.7	2.3
Cefotaxime	≤ 1	> 2	99.0	0.1	0.9
Ceftazidime	≤ 1	> 8	99.2	0.4	0.4
Meropenem	≤ 2	> 8	99.8	0.1	0.1
Gentamicin	≤ 2	> 4	97.9	0.1	2.0
Nalidixic acid	≤ 16	> 16	93.0	-	7.0
Ciprofloxacin	≤ 0.5	> 1	95.3	1.2	3.5
Nitrofurantoin	≤ 32	> 32	97.7	0.0	2.3
Trimethoprim	≤ 2	> 4	80.5	0.6	18.9
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	80.8	1.4	17.8
ESBL	Negative	Positive	99.2	-	0.8

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

RESULTS AND COMMENTS

Urinary tract isolates of *E. coli* have been included in the surveillance programme every year since NORM was established in 2000. The prevalences of resistance for 2007 are shown in Table 30 and the results 2000 – 2007 are shown in Figure 30. There were no changes in the protocol for examination of urinary tract isolates in 2007. Most of the samples were submitted from general practice (72.4%).

The resistance rates have remained remarkably stable over the last seven years. Approximately 30% of *E. coli* isolates are resistant to ampicillin, while the remaining 70% belong to the wild type which in Norway is categorized as intermediately susceptible. Close to 20% of *E. coli* isolates are resistant to trimethoprim and trimethoprim-sulfamethoxazole. Susceptibility testing to mecillinam is technically challenging, and the rates of resistance have fluctuated. The prevalence of non-susceptibility was 9.1% in 2007 which is a slight increase compared to 6.5 – 8.3% in the years 2002 – 2006.

Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. The prevalence of non-susceptibility has remained relatively stable and was 4.7% in 2007 (1.2% intermediately susceptible and 3.5% resistant). The corresponding rates for blood culture isolates were 2.1% intermediate susceptibility and 6.8% resistance. The same difference was seen for nalidixic acid with 7.0% resistance in urinary tract isolates and 12.8% 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. A total of 119 out of 196 nalidixic acid resistant isolates were non-susceptible to ciprofloxacin (96 resistant and 23 intermediately susceptible). Conversely, 119/131 (90.8%) of ciprofloxacin non-susceptible isolates were resistant to nalidixic acid. The failure to detect twelve (9.2%) ciprofloxacin non-susceptible isolates by the screening test indicate a potential for further quality improvement in the laboratories and/or a possible need for adjustment of zone breakpoints.

In total, 22 isolates (0.8%) were confirmed as ESBL producers. The majority of these strains were non-susceptible to both cefotaxime (twenty resistant, one intermediately susceptible and one susceptible) and ceftazidime (ten resistant, eight intermediately susceptible and four susceptible). In addition, the screening procedure identified eight non-ESBL strains by cefotaxime and five by ceftazidime. The prevalence of ESBL increased from 0.4% in 2005 and 0.3% in 2006. Most ESBL strains were resistant to ciprofloxacin (16/22) and trimethoprim (16/22), but many remained susceptible to nitrofurantoin (20/22) and mecillinam (13/22 susceptible and 9/22 intermediately susceptible). ESBL strains were recovered from samples submitted from general practice (n=11), hospital wards (n=4), outpatient clinics (n=4) and nursing homes (n=3).

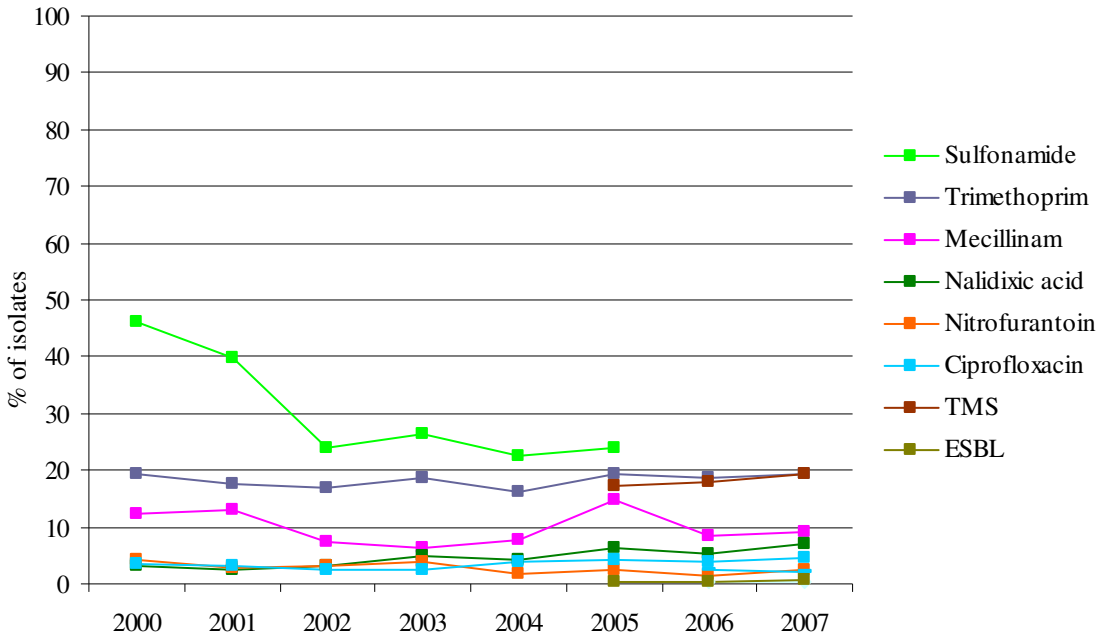

FIGURE 30. Prevalences of non-susceptibility to various antimicrobial agents in urinary tract *E. coli* isolates 2000 – 2007.

Klebsiella spp. in blood cultures

TABLE 31. *Klebsiella* spp. blood culture isolates (n=493). 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	94.5	3.4	2.0
Cefuroxime*	≤ 0.5	> 8	1.2	91.9	6.9
Cefotaxime	≤ 1	> 2	98.8	0.2	1.0
Ceftazidime	≤ 1	> 8	98.2	1.2	0.6
Aztreonam	≤ 1	> 8	97.0	0.4	2.6
Meropenem	≤ 2	> 8	99.4	0.6	0.0
Gentamicin	≤ 2	> 4	99.8	0.0	0.2
Nalidixic acid	≤ 16	> 16	88.2	-	11.8
Ciprofloxacin	≤ 0.5	> 1	90.5	7.5	2.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	86.4	2.0	11.6
ESBL	Negative	Positive	99.0	-	1.0

*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.

TABLE 32. *Klebsiella pneumoniae* blood culture isolates (n=361). 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	94.7	3.9	1.4
Cefuroxime*	≤ 0.5	> 8	1.4	92.0	6.6
Cefotaxime	≤ 1	> 2	98.9	0.3	0.8
Ceftazidime	≤ 1	> 8	98.1	1.4	0.6
Aztreonam	≤ 1	> 8	98.3	0.3	1.4
Meropenem	≤ 2	> 8	99.4	0.6	0.0
Gentamicin	≤ 2	> 4	99.7	0.0	0.3
Nalidixic acid	≤ 16	> 16	87.0	-	13.0
Ciprofloxacin	≤ 0.5	> 1	89.5	8.3	2.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.6	1.9	12.5
ESBL	Negative	Positive	98.9	-	1.1

*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.

TABLE 33. *Klebsiella oxytoca* blood culture isolates (n=84). 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	94.0	1.2	4.8
Cefuroxime*	≤ 0.5	> 8	1.2	92.9	6.0
Cefotaxime	≤ 1	> 2	100.0	0.0	0.0
Ceftazidime	≤ 1	> 8	100.0	0.0	0.0
Aztreonam	≤ 1	> 8	90.5	1.2	8.3
Meropenem	≤ 2	> 8	98.8	1.2	0.0
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Nalidixic acid	≤ 16	> 16	96.4	-	3.6
Ciprofloxacin	≤ 0.5	> 1	97.6	1.2	1.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.2	1.2	4.8
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 361 *K. pneumoniae* (73.2%), 84 *K. oxytoca* (17.0%) and 48 (9.7%) isolates not identified to the species level, giving a total of 493 *Klebsiella* spp. isolates (Tables 31-33). As for *E. coli*, the breakpoints for towards betalactams remained unchanged from 2006 and are given in the tables. The SIR distribution for cefpirome is not given as one of the disk suppliers has not defined breakpoints for this substance. The trimethoprim-sulfamethoxazole breakpoint for resistance was reduced from R > 8/152 mg/L to R > 4/76 mg/L. The breakpoint for susceptibility remained unchanged at S ≤ 2 mg/L.

There were no significant changes in the overall prevalences of resistance to cephalosporins, aminoglycosides or carbapenems from 2006 to 2007 (Figure 31). The prevalence of resistance to trimethoprim-sulfamethoxazole continued to increase from 7.8% to 11.6% in addition to 2.0% intermediate susceptibility. As the lower breakpoint was not changed, the increase of non-susceptibility from 8.1% to 13.6% may represent a significant trend.

The results for *K. pneumoniae* and *K. oxytoca* isolates identified to the species level are displayed in Tables 32 and 33. The low number of *K. oxytoca* strains precludes any firm conclusions, but the prevalences of non-susceptibility to ciprofloxacin and trimethoprim-sulfamethoxazole are still remarkably higher in *K. pneumoniae* (10.5% and 14.4%, respectively) than in *K. oxytoca* (2.4% and 6.0%, respectively).

The nalidixic acid disk was used as a screening test for detection of quinolone resistance mechanisms. A total of 10 isolates were resistant to ciprofloxacin, and 37 were

intermediately susceptible to this agent. The screening test identified 27 of these 47 strains, thus missing 20 (42.6%) of ciprofloxacin non-susceptible strains. Conversely, a total of 31 ciprofloxacin susceptible strains were resistant to nalidixic acid. These 31 isolates may represent a subpopulation with first-step mutations in the DNA gyrase responsible for quinolone resistance, but this was not further investigated.

As for *E. coli*, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidim disks. Isolates with reduced zone diameters were further characterized by combination Etests and/or molecular examination. Only five isolates were confirmed as ESBL positive including four *K. pneumoniae* and one unspeciated strain. This gives an overall ESBL prevalence of 1.0% among all *Klebsiella* isolates and 1.1% among speciated *K. pneumoniae* isolates. This is an increase from 2006 (0.5% and 0.7%, respectively). Three of the isolates were resistant to both cefotaxime and ceftazidime, whereas the remaining two were susceptible to cefotaxime and intermediately susceptible to ceftazidime. Two of the five isolates were resistant to ciprofloxacin, while all five were fully susceptible to gentamicin and meropenem. None of them were categorized as susceptible to piperacillin/tazobactam. The four *K. pneumoniae* isolates all originated from a single hospital in Oslo. It will be further investigated whether this may represent an outbreak as well as possible links to nosocomial epidemics of ESBL *K. pneumoniae* in Sweden and Denmark.

A total of seven *Klebsiella* isolates were non-susceptible to one or both test substrates used for ESBL detection without being confirmed as ESBL producers. The specificity of the screening strategy (1.4% false positive ESBL producers) was thus considerably better than in 2006 when 6.1% of *Klebsiella* isolates were non-susceptible to cefotaxime and/or ceftazidime and/or cefpirome without being ESBL producers.

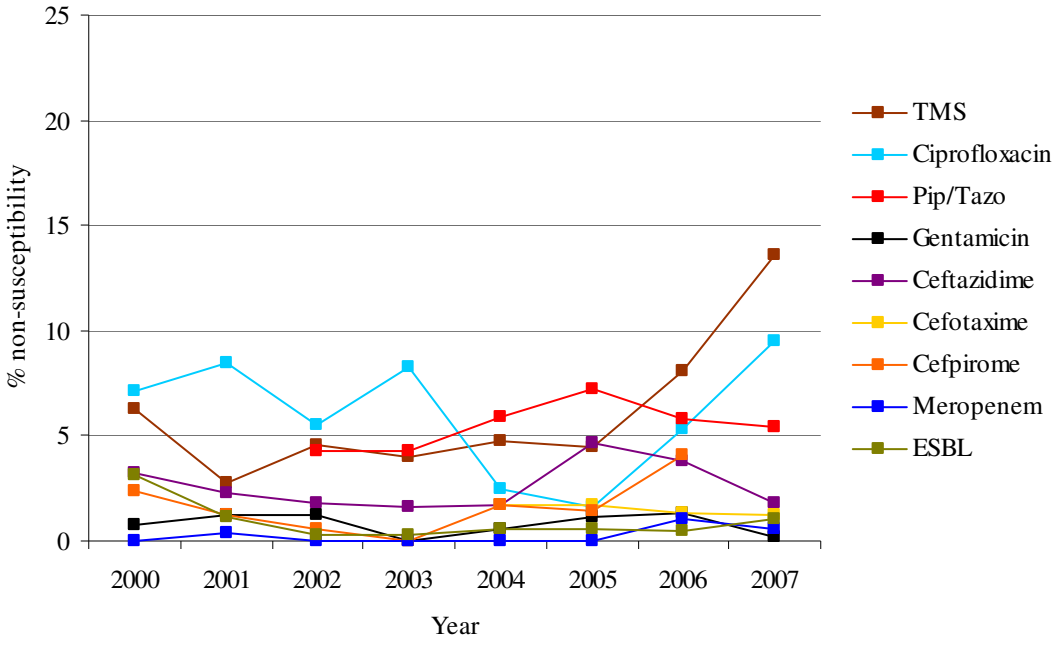

FIGURE 31. Prevalence of non-susceptibility to various antimicrobials in *Klebsiella* spp. blood culture isolates 2000-2007.

Metallo-beta-lactamases (MBLs) and *Klebsiella pneumoniae* carbapenemases (KPCs); two new mobile beta-lactamases emerging in Gram-negative bacteria – A problem in Norway or just a curiosity?

Carbapenems (imipenem, meropenem and ertapenem) are the latest betalactam antibiotics. They show good activity towards Gram-negative isolates harbouring beta-lactamases such as ESBLs and AmpCs. However, in response, Gram-negative bacteria have acquired beta-lactamases that are able to hydrolyse carbapenems (carbapenemases). Several clinically important carbapenemases have now been identified in Gram-negative bacteria (7). These include among others the MBLs, KPCs, OXA-, and GES-enzymes. Two of these carbapenemases (MBLs and KPCs) have now been identified in Norwegian clinical isolates of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.

Metallo-beta-lactamases (MBLs) are class B beta-lactamases that differs from serine beta-lactamases in that the mechanism of hydrolysis requires zinc ions in the active site (14). Several bacterial species of relatively low clinical importance, with the possible exception of *Bacillus cereus* and *Stenotrophomonas maltophilia*, harbour MBL genes that are chromosomally encoded (14). However, it is the dissemination of transferable MBLs in clinically significant Gram-negative bacteria such as *P. aeruginosa*, *Acinetobacter baumannii* and various *Enterobacteriaceae* that is causing concern (2,14). So far six types of transferable MBLs have been discovered namely the IMP-, VIM-, SPM-, GIM-, SIM- and AIM-types (2,3,14,16). Within the IPM- and the VIM-types several variants have been discovered (www.lahey.org/Studies). MBLs have a broad spectrum of hydrolysis and inactivate virtually all betalactams with the exception of the monobactam aztreonam (14). In addition they are not inhibited by the clinically available beta-lactamase inhibitors such as clavulanic acid, tazobactam and sulbactam (14). Most of the transferable MBLs with the exception of the SPM-type are localised in integrons that also harbour other resistance genes (i.e. aminoglycoside resistance genes) resulting in isolates that are multi-resistant limiting therapeutic options (2,14). Integrons with MBLs are often found in association with mobile genetic elements such as transposons and plasmids increasing the possibility for spread among bacteria (14). MBLs now show a worldwide dissemination. In some countries like Greece they have become endemic in the hospital setting (13). In Europe the VIM-type is most prevalent while in Asia and South-America the IMP- and SPM-types dominate, respectively (14).

KPCs enzymes are class A serine beta-lactamases that have predominately been identified in *K. pneumoniae*, but have now been reported in *P. aeruginosa*, *Enterobacter* spp. and *Salmonella* spp. (7,15). KPCs were initially discovered in the United States and have been associated with several outbreaks in hospitals in the New York area. KPCs have now been identified in several countries (Greece, Colombia, China, France and Scotland), and outbreaks have also occurred in Israel (8). In Sweden the first KPC isolate was identified in 2007 in a patient that had been hospitalised in Greece (11). To date seven KPC variants have been detected (www.lahey.org/Studies), and the hydrolysis spectrum covers betalactams of all classes (7). KPC-enzymes are reported to be inhibited by the serine beta-lactamase inhibitors. However, this inhibition is not always observed in clinical isolates. The dissemination of these enzymes is caused by the localization of KPC-genes on various plasmids with different sizes. Further, analysis of the genetic context surrounding KPC-genes show that they are localised in transposon related structures which are likely to contribute to the dissemination (5).

In Norway, seven MBL-producers and two KPC-producers have been identified at the Reference Centre for Detection of Antimicrobial Resistance (K-res) in clinical isolates from various laboratories. Five *P. aeruginosa* and two *K. pneumoniae* isolates have been shown to harbour MBL-genes (9,10, unpublished results) while two *K. pneumoniae* isolates have been identified to harbour KPC-genes (unpublished results). These isolates have in common that they are multi-drug resistant including resistance to aminoglycosides and ciprofloxacin. Some *P. aeruginosa* isolates were only susceptible to colistin. The VIM-type is the dominating MBL being identified in six isolates while IMP has been identified in one isolate. Both KPC-producers harboured the KPC-2 variant. Investigation of the epidemiological data show that all isolates except two have been imported with patients that have been hospitalised abroad (Denmark, Ghana, Turkey, Philippines, Thailand, Greece and Cyprus).

Unfortunately there are no standardised phenotypic detection methods for either MBLs or KPCs. For MBLs, detection methods are based on the utilization of metal chelators that remove the zinc ions from the active site thus inactivating the enzyme (14). Spectrophotometric measurement of carbapenem hydrolysis by crude cell extracts with subsequent inhibition with a metal chelator such as EDTA is considered the reference method. However, this method requires specialized equipment and is labour intensive, thus not suitable in a clinical laboratory. Several simple phenotypic tests such as the MBL Etest, combined disc and double disc synergy test have been developed and evaluated with variable results (6). These tests are based on synergy with an MBL inhibitor and an oximino-cephalosporin or carbapenem. One of the problems is that the best combination of inhibitor and substrate varies between various Gram-negative bacteria making it difficult to standardise the methods. Some of these tests have been evaluated on Norwegian clinical isolates of *P. aeruginosa* showing that the MBL Etest and a combined disc diffusion test works well but shows problems with a relative high number of false positive results giving a low positive predicative value of these tests in a low prevalence country (9). It should be noted that the current MBL Etest strip is not suitable for detection of MBLs in *Enterobacteriaceae*. Detection of KPC-enzymes is also a challenge for diagnostic laboratories primarily due to low MIC values (often in the intermediate or borderline susceptible range) that can be observed to carbapenems. Studies suggest that ertapenem might be the most suitable carbapenem for detection of KPC-production (1). Carbapenem resistance can also be overlooked in automated systems thus the isolates may therefore not be further analysed

(12). Confirmatory tests for ESBL-production have also been shown to be positive, thus KPC-producing isolates can be misdiagnosed as ESBL-producers (4). Carbapenemase activity can be confirmed in KPC-producers by spectrophotometric analysis of carbapenem hydrolysis, but this can not discriminate between a KPC enzyme and another non-MBL carbapenemase. Molecular detection of KPC-genes is thus the only confirmatory test.

The criteria for testing for MBL- and KPC production is difficult due to the high phenotypic diversity observed especially among *Enterobacteriaceae* which often express borderline susceptibility to carbapenems according to clinical breakpoints. For the detection of MBL-producers the following recommendations for criteria have been suggested by the Norwegian Working Group on Antibiotics (AFA) in collaboration with K-res; (i) *P. aeruginosa*: isolates that are resistant to both imipenem and meropenem as well as reduced susceptibility to ceftazidime and piperacillin-tazobactam. (ii) *Enterobacteriaceae*: isolates that are not categorised as susceptible to carbapenems. The latter criterion would also apply for the selection of strains to detect production of KPC. Note that *Protea*-species (*Proteus*-related) might express inherent reduced susceptibility to imipenem.

In summary, MBLs and KPCs have been identified in a limited number of multi-drug resistant isolates in Norway, mostly associated with hospitalization abroad. Diagnostic laboratories and clinicians should be aware of this threat as the prevalence of MBLs and KPCs is increasing worldwide.

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Haemophilus influenzae in respiratory tract specimens

TABLE 34. *Haemophilus influenzae* respiratory tract isolates (n=808). 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	≤ 1	> 4	72.9	10.3	16.8
Penicillin V*	≤ 0.5	> 4	1.0	63.6	35.4
Ampicillin	≤ 1	> 4	86.6	4.2	9.2
Amoxicillin-clavulanic acid	≤ 2	> 4	92.0	4.7	3.3
Cefuroxime	≤ 1	> 2	58.5	25.1	16.3
Cefotaxime	≤ 0.125	> 0.125	99.5	-	0.5
Tetracycline	≤ 2	> 2	97.5	-	2.5
Trimethoprim-sulfamethoxazole**	≤ 0.5	> 2	78.9	3.3	17.8
Ampicillin screen (mm)	≥ 16	< 16	88.5	-	11.5
Cefaclor screen (mm)	≥ 20	< 20	84.0	-	16.0
Beta-lactamase	Negative	Positive	89.5	-	10.5

*The wild type is defined as intermediately susceptible indicating that the clinical efficacy of treatment with phenoxymethyl penicillin is uncertain.
** Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 35. *Haemophilus influenzae* respiratory tract isolates (n=808). Distribution (%) of MICs (mg/L).*

	≤ 0.008	0.016	0.032	0.063	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Penicillin G				0.4	0.9	4.8	40.7	26.1	6.2	4.1	1.1	0.7	15.0			
Penicillin V**						0.4	0.6	2.2	28.6	32.8	9.4	5.8	4.6	3.3	0.6	11.6
Ampicillin			0.2	0.7	5.3	42.6	28.2	9.5	3.1	1.1	1.1	1.1	0.9	0.6	0.5	5.0
Amoxi.-clav.***		0.2	0.2	0.1	0.7	4.6	42.6	36.0	7.4	4.7	1.1	1.2	0.9	0.1		
Cefuroxime			0.1		0.1	1.0	6.1	51.2	25.1	4.3	5.2	6.1	0.5	0.2		
Cefotaxime	3.2	24.6	51.4	12.6	7.8	0.1	0.4									
Tetracycline			0.1	0.1	0.7	6.9	47.0	37.7	4.8	1.7	0.4	0.1	0.2			
TMS****	0.2	1.0	3.3	16.6	33.5	19.1	5.1	2.6	0.7	1.6	0.9	0.7	14.6			
Screening (mm)	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Ampicillin 2 µg	7.4	0.1	0.6	0.2	0.5	0.5	0.7		0.4	1.0	0.9	1.3	3.1	4.2	6.2	5.7
Cefaclor 30 µg	2.1	0.2	0.2	0.4	0.4	1.2	2.0	1.2	2.0	1.5	1.4	0.6	1.1	1.6	2.7	1.6
Penicillin V 10 µg	18.3	0.1	1.0	0.8	1.1	0.4	1.8	1.4	1.5	1.1	2.2	2.5	5.2	4.9	12.7	11.2
Screening (mm)	22	23	24	25	26	27	28	29	30	31	32	33	34	35	> 35	
Ampicillin 2 µg	11.1	15.0	14.4	11.0	7.1	2.6	1.7	1.0	0.6	0.6	1.1		0.4	0.2	0.2	
Cefaclor 30 µg	4.3	4.7	7.9	9.8	12.1	12.0	11.2	5.3	6.1	1.6	2.4	1.0	0.4	0.2	0.6	
Penicillin V 10 µg	13.1	7.1	5.7	3.3	2.0	0.4	0.3	0.3	0.6	0.1	0.6	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. **The wild type is defined as intermediately susceptible indicating that the clinical efficacy of treatment with phenoxymethyl penicillin is uncertain. ***Amoxi.-clav.=Amoxicillin-clavulanic acid. ****TMS=Trimethoprim-sulfamethoxazole. Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Haemophilus influenzae isolates from the respiratory tract have previously been surveyed in 2000, 2001 and 2004. The prevalence of beta-lactamase production has increased from 7.0% in 2001 and 8.8% in 2004 to 10.5% in 2007 (Table 34). Resistance to betalactam antibiotics may also be mediated by chromosomal changes in the penicillin-binding proteins (PBPs), but the optimal strategy for detection of this chromosomal resistance mechanism has not yet been defined. As seen i Tables 34-35 and Figure 32, the prevalence of non-susceptibility to amoxicillin-clavulanic acid has increased from 1.3% in 2001 to 3.1% in 2004 and 8.0% in 2007. However, use of the cefaclor screening disk may indicate a much higher prevalence of PBP-mediated resistance (16.0%) according to the breakpoints provided by the disk manufacturer. In Figure 33, beta-lactamase positive isolates have zone diameters for ampicillin 2 µg below 16 mm and for penicillin 10 µg at 6 mm. The cefaclor 30 µg disk does not delineate a well-defined subpopulation with PBP-mediated chromosomal betalactam resistance.

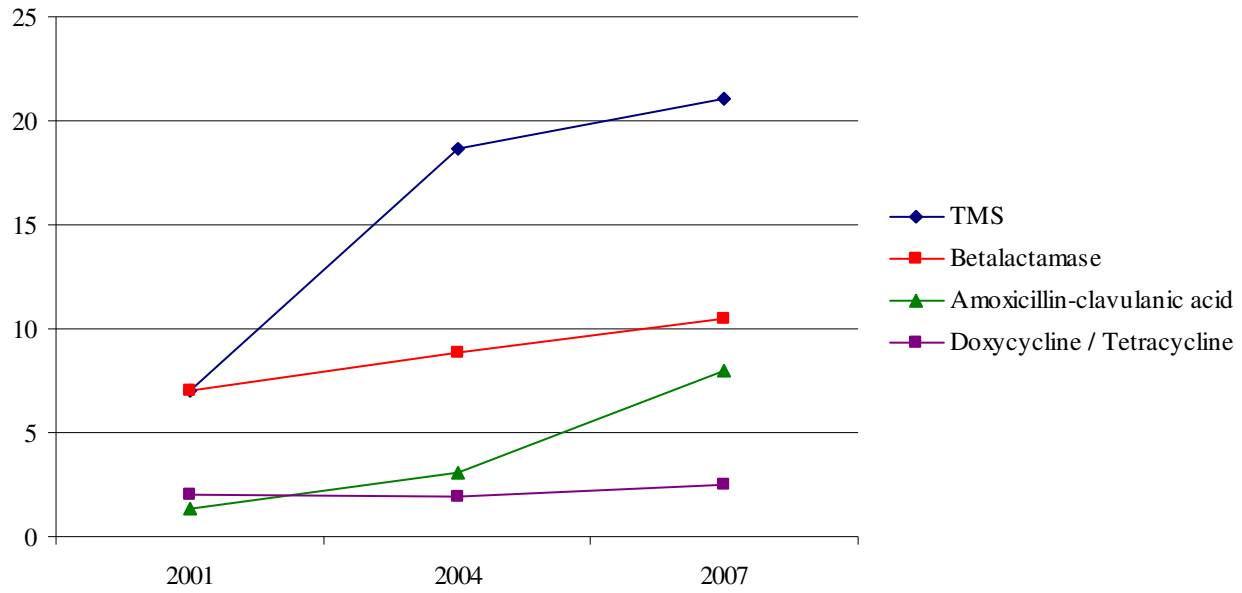

FIGURE 32. Prevalence of non-susceptibility to various antimicrobials in *Haemophilus influenzae* respiratory tract isolates 2001-2007. Susceptibility testing was performed on PDM II agar in 2001 / 2004 and MH II agar in 2007, both supplemented with 1% haemoglobin and 1% IsoVitalex. Doxycycline (S ≤ 4 mg/L and R > 4 mg/L) was substituted by tetracycline (S ≤ 2 mg/L and R > 2 mg/L) in 2007.

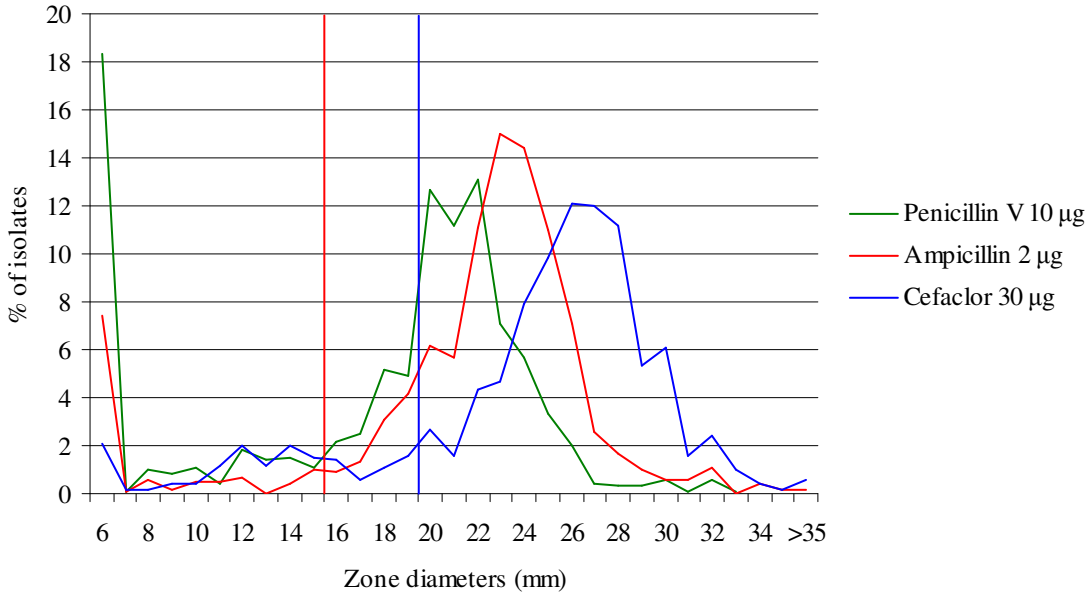

FIGURE 33. Distribution of zone diameters for respiratory tract isolates of *Haemophilus influenzae* using penicillin V 10 µg, ampicillin 2 µg and cefaclor 30 µg disks. The red bar indicates the ampicillin 2 µg screening breakpoint for detection of beta-lactamase production. The blue bar indicates the cefaclor 30 µg screening breakpoint for detection of chromosomal betalactam resistance. The manufacturer of the MH II agar has not provided a screening breakpoint for the penicillin V 10 µg disk.

It has been suggested that the cefuroxime MIC may provide a better criterium for detection of PBP alterations, and the MIC distribution shown in Figures 34-35 indicates that a breakpoint of R > 4 may correspond to a non-susceptible subpopulation. This is the breakpoint presently used by the Clinical Laboratory Standards Institute (CLSI). A similar but less obvious phenomenon is seen for amoxicillin-clavulanic acid. When using the cefuroxime criterium, 0.6% of all isolates harbour both beta-lactamase production and PBP alterations. Only four isolates displayed minimal elevation of the MICs to cefotaxime. This may be due to mutations, technical errors, or the use of MH II agar with 1% haemoglobin and 1% IsoVitalex as opposed to HTM agar for the Etest methodology.

The prevalences of non-susceptibility to tetracyclines and trimethoprim-sulfamethoxozole were not significantly different between beta-lactamase negative and beta-lactamase positive isolates (2.2% and 4.7% for tetracycline, and 21.8% and 16.5% for trimethoprim-sulfamethoxazole, respectively). However, the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole was significantly higher among isolates with cefuroxime MICs > 4 mg/L (41.2%) than among isolates with cefuroxime MICs ≤ 4 mg/L (18.5%). The comparability to previous years is limited due to changes in breakpoints, agar and test substance.

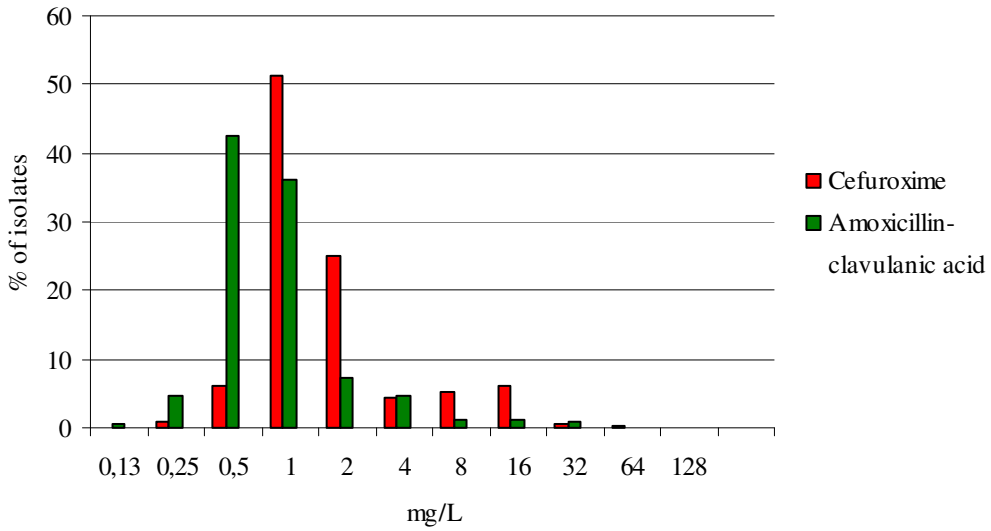

FIGURE 34. Distribution (%) of minimum inhibitory concentrations (mg/L) of cefuroxime and amoxicillin-clavulanic acid in *Haemophilus influenzae* from respiratory tract samples. The NWGA breakpoints for cefuroxime are S ≤ 1 mg/L and R > 2 mg/L. The NWGA breakpoints for amoxicillin-clavulanic acid are S ≤ 2 mg/L and R > 4 mg/L.

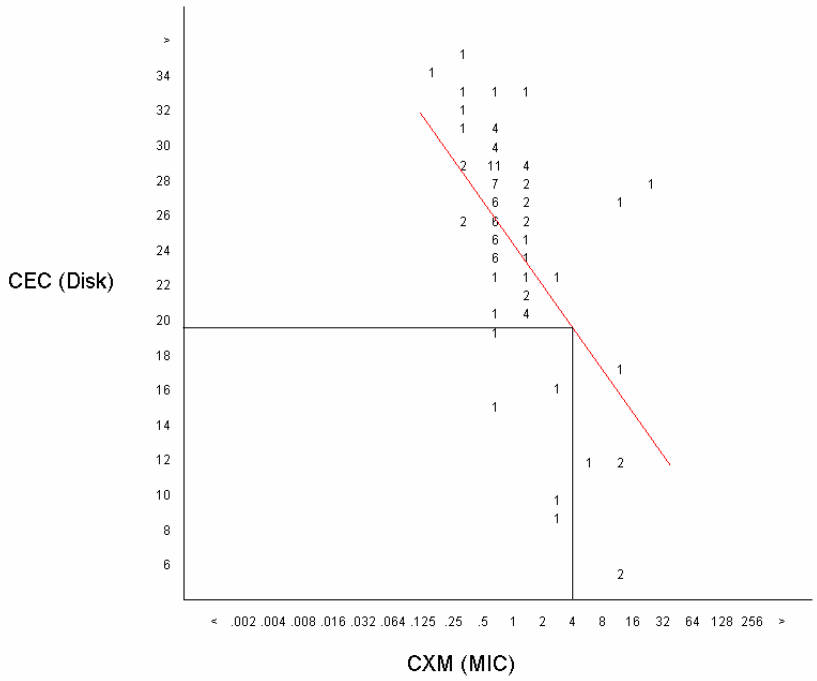

FIGURE 35. Scatter plot of minimum inhibitory concentrations (mg/L) of cefuroxime (CXM) versus zone diameters (mm) of cefaclor (CEC) 30 µg disk on MH II agar with 1% haemoglobin and 1% IsoVitalex. The regression line suggests a breakpoint of approximately S ≥ 20 mm for cefaclor corresponding to the suggested breakpoint of S ≤ 4 mg/L for cefuroxime.

Staphylococcus aureus in blood cultures

TABLE 36. *Staphylococcus aureus* blood culture isolates (n=832). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	96.0	0.0	4.0
Clindamycin	≤ 0.25	> 0.5	98.3	0.1	1.6
Fusidic acid	≤ 0.5	> 0.5	95.8	-	4.2
Ciprofloxacin	≤ 1	> 1	96.4	-	3.6
Gentamicin	≤ 1	> 1	99.6	-	0.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 1	> 1	99.8	-	0.2
Tetracycline	≤ 1	> 2	95.7	0.0	4.3
Trimethoprim-sulfamethoxazole*	≤ 2	> 8	99.2	0.6	0.2
Beta-lactamase	Negative	Positive	27.9	-	72.1
Cefoxitin screen	Negative	Positive	97.5	-	2.5
MRSA (*mecA*)	Negative	Positive	99.8	-	0.2
Vancomycin screen	Negative	Positive	100.0	-	0.0

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

RESULTS AND COMMENTS

Only two methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2007 (Table 36) corresponding to a prevalence of 0.2%. The resistance phenotype was confirmed by *mecA* PCR in both cases. One MRSA isolate was resistant to ciprofloxacin, erythromycin and clindamycin, while the other was fully susceptible to all non betalactam antibiotics tested. The findings are in accordance with reports from the laboratory databases of the participating institutions where 5 out of 1,273 (0.4%) *S. aureus* blood culture isolates were MRSA. None of the 20 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 5/1,293 (0.4%). The Norwegian Surveillance System for Communicable Diseases (MSIS) reported a slight increase in the total number of MRSA infections in Norway from 333 in 2006 to 342 in 2007. However, the cases reported to MSIS are predominantly skin and soft tissue infections (n=292) and colonizations (n=252). The discrepancy between the very low prevalence of systemic MRSA infections and an increasing prevalence of non-systemic infections was thus continued in 2007. A total of 594 cases of MRSA infections and colonizations were reported to MSIS in 2007. This is practically unchanged from 603 in 2006, the only previous year with registration of MRSA colonization. Further information about MRSA cases in MSIS is presented on page 67.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. The two MRSA blood culture isolates had cefoxitin zone diameters below the screening breakpoints for the respective test systems. In addition, 19 out of 830 (2.3%) isolates displayed reduced cefoxitin zone diameters but were not confirmed as MRSA by genotypic analysis. The false positive MSSA isolates had cefoxitin zone diameters within 2 mm of the screening breakpoints.

A total of 33 isolates (4.0%) were non-susceptible to erythromycin. This is a minor increase from 2006 (3.3%) and 2005 (1.9%). The macrolide resistance phenotypes were determined by the double disk diffusion (DDD) test. Nine (27%) were constitutively MLS_B resistant, 18 (55%) were inducibly MLS_B resistant and six (18%) displayed efflux mediated M type resistance. These figures represent 1.1%, 2.2% and 0.7% of all *S. aureus* isolates from blood cultures, respectively. The distribution of macrolide resistance phenotypes is similar to the results from previous years.

The prevalence of resistance to fusidic acid continued to decrease from 6.0% in 2006 to 4.2% in 2007. 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 36 shows the prevalences of non-susceptibility to various antimicrobials.

72.1% of the isolates were beta-lactamase positive which is unchanged from previous years. A subgroup analysis revealed that beta-lactamase positive isolates were more often resistant to fusidic acid (5.0%) and tetracycline (4.7%) than beta-lactamase negative isolates (2.2% and 3.4%, respectively).

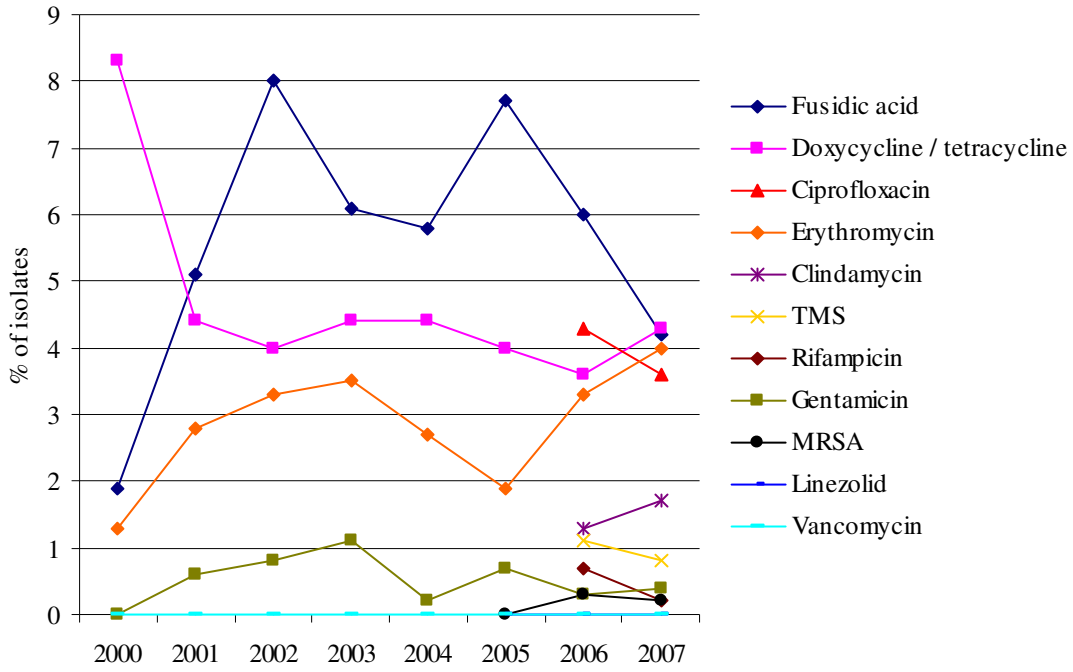

FIGURE 36. Prevalences of non-susceptibility to various antimicrobials among *Staphyloccus aureus* blood culture isolates 2000 – 2007. The breakpoint for susceptibility to gentamicin was decreased from S ≤ 2 mg/L to S ≤ 1 mg/L in 2006. Doxycycline was replaced by tetracycline in 2006. The breakpoints for clindamycin were reduced from S ≤ 1 mg/L and R > 2 mg/L to S ≤ 0.25 mg/L and R > 0.5 mg/L in 2007.

Staphylococcus aureus in wound specimens

TABLE 37. *Staphylococcus aureus* isolates from wound specimens (n=1,800). 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	95.8	0.1	4.1
Clindamycin	≤ 0.25	> 0.5	98.6	0.2	1.2
Fusidic acid	≤ 0.5	> 0.5	88.9	-	11.1
Ciprofloxacin	≤ 1	> 1	97.1	-	2.9
Gentamicin	≤ 1	> 1	99.2	-	0.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 1	> 1	99.9	-	0.1
Tetracycline	≤ 1	> 2	95.4	0.2	4.4
Trimethoprim-sulfamethoxazole*	≤ 2	> 8	98.7	1.0	0.3
Beta-lactamase	Negative	Positive	26.3	-	73.7
Cefoxitin screen	Negative	Positive	98.5	-	1.5
MRSA (*mecA*)	Negative	Positive	99.3	-	0.7
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. Twelve out of 1,800 (0.67%) isolates were confirmed as MRSA by *mecA* PCR. The MRSA prevalence in wound specimens is thus consistenly higher than in blood cultures (0.24%) which is in accordance with the high number of MRSA skin and soft tissue infections reported to the Norwegian Surveillance System for Communicable Diseases (MSIS), see page 67. The twelve MRSA isolates all displayed cefoxitin zone diameters at least six mm below the screening breakpoints for the respective test systems. Three of the MRSA isolates were susceptible to all non betalactams tested. The remaining nine isolates displayed various resistance patterns including resistance to tetracycline (n=6), erythromycin (n=3), clindamycin (n=2), ciprofloxacin (n=2), gentamicin (n=1) and trimethoprim-sulfamethoxazole (n=2). A total of 15/1788 MSSA isolates were false positives by the cefoxitin test, but none of these isolates had zone diameters less than two mm below the sceening breakpoint.

The high prevalence of resistance to fusidic acid in *S. aureus* wound isolates continued to decline from 25.0% in 2004 to 14.5% in 2006 and now 11.1% in 2007, see Table 37 and Figure 37. 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 over the last years. The prevalence of resistance to fusidic acid is still much lower in blood culture isolates (4.2%).

For other antibiotics such as tetracyclines and macrolides there were only minor changes from 2006 to 2007, and the prevalences of non-susceptibility were similar for blood culture isolates and isolates from wound specimens. A total of 76 (4.2%) isolates were non-susceptible to erythromycin, and 74 of these were further examined for determination of resistance phenotype. The majority (49/74, 66% 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=14) or low-level resistant to erythromycin (n=11) expressing efflux mediated M type resistance. The findings are in accordance with the results from blood culture isolates.

A total of 73.7% of the isolates were beta-lactamase positive which is a minor reduction from 2006 (77.3%). Resistance to fusidic acid was significantly more common among the 1,326 beta-lactamase positive isolates (13.3%) than among the 474 beta-lactamasenegative ones (3.8%). The prevalence of tetracycline resistance was also slightly higher (5.3%) among beta-lactamase positive isolates compared to beta-lactamase negative isolates (1.9%).

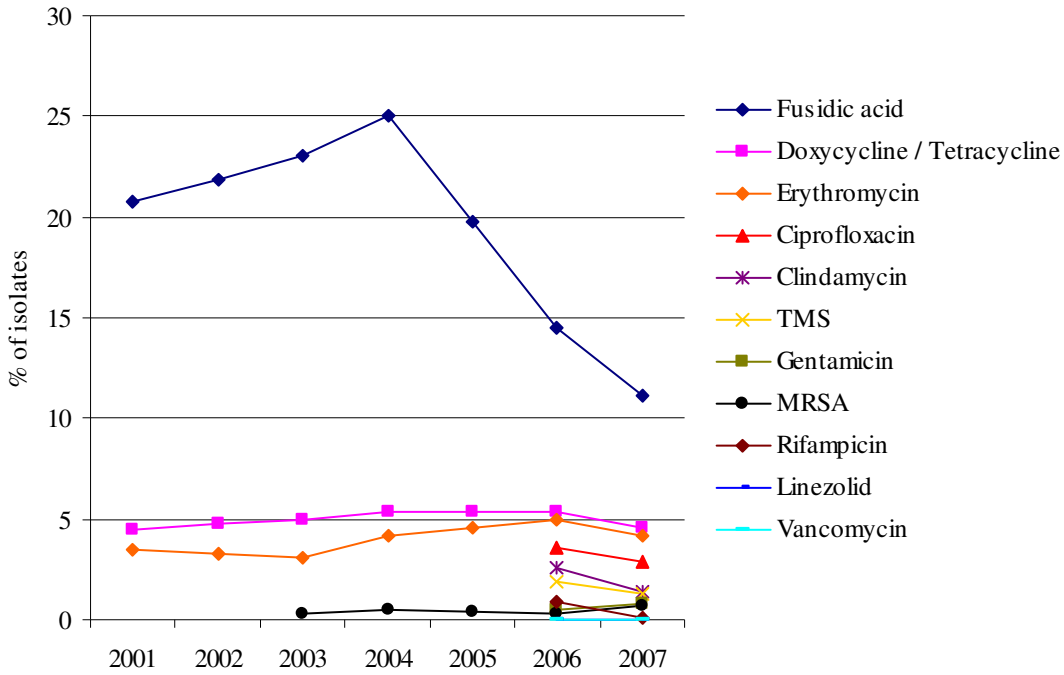

FIGURE 37. Prevalences of non-susceptibility to various antimicrobials among *Staphyloccus aureus* wound isolates 2000 – 2007. The breakpoint for susceptibility to gentamicin was decreased from S ≤ 2 mg/L to S ≤ 1 mg/L in 2006. Doxycycline was replaced by tetracycline in 2006. The breakpoints for clindamycin were reduced from S ≤ 1 mg/L and R > 2 mg/L to S ≤ 0.25 mg/L and R > 0.5 mg/L in 2007.

MRSA infections in Norway 2007

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been notifiable in Norway since 1995, and colonisation without infection was made notifiable in 2005. Consistent discrimination between the two can be difficult. A total number of 594 MRSA cases were notified in 2007; 342 (58 %) of the cases were reported as infections and 252 cases were reported as colonisations (Figure 38).

Three hundred and one patients (51 %) were females. At the time of diagnosis, 141 (24 %) were hospitalized and 79 (13 %) were residents in nursing homes. The number of cases diagnosed outside health care institutions has increased steadily over the past ten years. In 2007 MRSA were diagnosed in 359 (60 %) patients outside health care institutions. Several outbreaks in nursing homes have contributed to a high incidence of MRSA among residents in the past three years (Figure 39).

The total number of reported MRSA infections has increased steadily since surveillance started. The clinical picture shows a majority of wound infections or abscesses (292 infections, 85 % of reported infections in 2007). Although the number of infections is increasing, the number of serious infections is still low. On the basis of the reported information, 16 infections were classified as systemic infections or infections in inner organs: lower respiratory tract infections (5), septicaemia (4), osteomyelitis (2), bursitis (2), arthritis (1), necrotizing fasciitis (1) and peritonitis (1). MRSA was detected in blood cultures from four patients in 2007. The number of MRSA isolates from blood or spinal fluid has been below ten cases per year every year since 1995. The true increase in the total number of MRSA infections has to be interpreted with caution. The increase is mainly seen among non-hospitalised patients with minor infections who have contracted the disease in Norway. This may indicate increased testing of patients outside hospitals.

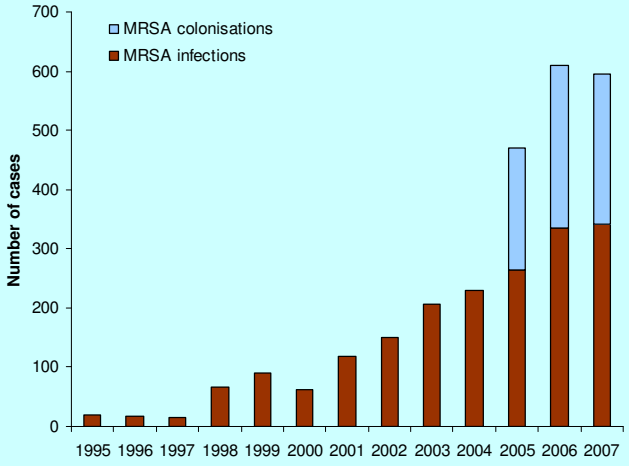

FIGURE 38. Reported cases of MRSA infection 1995 – 2007 and MRSA colonisation 2005 – 2007 in Norway.

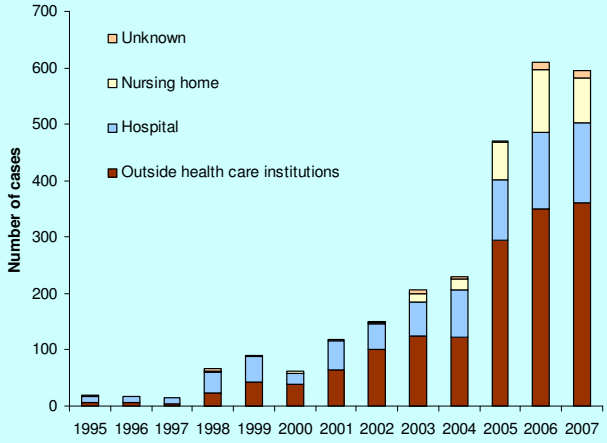

FIGURE 39. Reported cases of MRSA infection 1995 – 2007 and MRSA colonisation 2005 – 2007, by residency when diagnosed.

Petter Elstrøm, Norwegian Institute of Public Health

MRSA strain typing methods in the context of epidemiological analysis

Epidemiological analysis is an assessment of interrelationship. It is of interest to follow the distribution of strains throughout a region over time, and to be able to calculate the risk of spread of certain strains. The choice of typing method depends on the level of discrimination that is required. Suitable methods for differentiating clonal vs. epidemiologically unrelated strains in a specific outbreak would be different from methods used to follow the spread of bacterial clones over centuries or country borders.

Phenotypic methods

- Biotyping
- Antibiogram
- Serotyping
- Bacteriophage typing
- Immunoblot
- Multilocus enzyme electrophoresis

Genotypic methods

- Plasmid profile
- PCR based
  - Ribotyping
  - SCC*mec*
  - AFLP
- Restriction fragment
  - PFGE
- Sequence based
  - MLST
  - VNTR (*spa*-typing)
  - MLVA

Before the introduction of molecular biology, epidemiological analyses microbial organisms were restricted to the phenotypic methods. However, these methods were frequently not able to discriminate outbreak strains from epidemiologically unrelated strains. In the last 25 years, a wealth of information about the bacterial chromosome has become available, and a diversity of typing methods based upon the analysis of the bacterial genome has been developed. Several of these have higher discriminatory strength than phenotypic methods. However, no method is suitable or perfect for every need, and a combination of – or variation among – different methods are sometimes necessary to accomplish a satisfying discrimination of the strains. The following is a short description of the genotypic methods most commonly used for epidemiological characterization of MRSA.

PFGE – Pulsed Field Gel Electrophoresis

PFGE is still regarded as the gold standard method of molecular epidemiologic characterization of outbreaks over a short period of time and in limited geographical areas. The discriminatory power of the method is excellent, but the method is labour intensive, slow (2-4 days) and is dependent on the experience of the technician. The method is based upon the random distribution of restriction endonuclease cleavage sites throughout the bacterial genome. Using a restriction enzyme the genome is cleaved into fragments with different lengths. For *S. aureus* the enzyme *SmaI* is most commonly employed, yielding a pattern of 8-20 fragments ranging from 8 to 800 kb when analyzed by pulsed field gel electrophoresis (Figure 40).

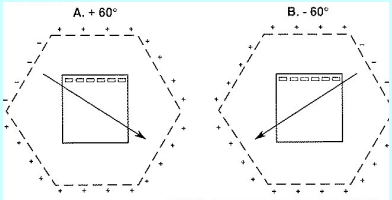

FIGURE 40. Separation of large restriction fragments require the use of pulsed fields of electrical current from 24 electrodes spaced in a hexagonal contour that alternate in direction at a 120° fixed angle over a prolonged electrophoresis time. Figure from CHEF Mapper XA Pulsed Field Electrophoresis System, Instruction Manual and Application Guide.

Strains are differentiated by fragment numbers and sizes as results of different genetic events changing the endonuclease recognition sites. Single point mutations, insertions, deletions, inversions, or transpositions might lead to the loss or gain of one particular restriction site resulting in a three-fragment difference between the strains. The interpretation of fragment patterns between strains may be done manually, based on objective criteria (Tenover 1995) or by standardized computer-assisted analysis. Strains may be classified as indistinguishable, closely related, possibly related or unrelated. It has been suggested that the term "closely related" should be used for one to three-fragment differences between strains most likely representing a single genetic event (Tenover 1995). The classification as "possibly related" has been suggested for a four to six bands difference, while strains differing in seven or more bands most likely are not related. These criteria may be useful in the interpretation of fragment differences, but should be used cautiously and only when comparing epidemiologically related bacterial isolates (Tenover 1995, Figure 41).

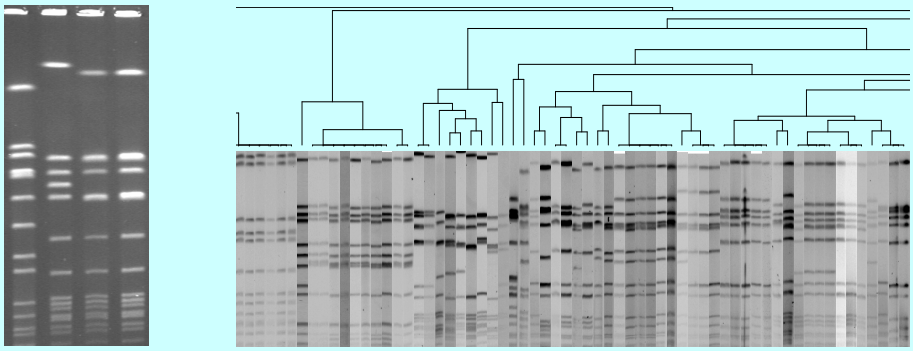

FIGURE 41. Image of PFGE showing fragment patterns of three different MRSA strains (lanes 2-4) with a standard in lane 1 (left), and dendrogram showing genotypic interrelationship between selected MRSA strains based on computer-assisted cluster analysis (right).

AFLP – Amplified Fragment length Polymorphism

The principle of AFLP is based on the selective amplification of genomic DNA restriction fragments by PCR. Whole cellular DNA is first digested by two different restriction endonucleases. The resulting restriction fragments are thereafter ligated with oligonucleotide adaptors and subsequently amplified by primers specific to the adapter sequences. The pattern of amplified fragment is then visualized by capillary electrophoresis. The method is fast, mainly automatic, and has been shown to be highly discriminatory (Melles 2007, Faria 2008).

***Spa*-typing**

The *spa* gene codes for staphylococcal protein A. The 3'-end of the gene has a highly variable repeat region consisting of variable numbers of usually 24 bps repetitions with internal nucleotide differences within each repeat. This X region of *spa* is subject to spontaneous mutations as well as loss and gain of repeats. The sequence based method of *spa*-typing assigns the repeat structure in a numerical code which is unique to every different nucleotide combination, see Table 38. Spa sequences are automatically assigned a spa type by submission to the RIDOM StaphType database (Harmsen 2003). Sequence data are delivered by SeqNet.org. The relatedness between different *spa*-types may be analyzed by BURP analysis.

Spa-typing is a quick and useful tool for characterizing strains, but with somewhat lower discriminatory power in the characterization of localized/local outbreaks compared to PFGE (Faria 2008). However, the method is objective and therefore suitable for comparison of strains between regions or countries as shown in Table 38 (http://www.ridom.de/spaserver/). *Spa*-typing is the method most commonly used to characterize variable number tandem repeats (VNTR) in *Staphylococcus aureus*. Single-locus DNA sequencing of repeat regions of *coa* (coding for coagulase) is regarded as less useful due to the higher clock-frequency of mutations. However, the use of a VNTR-analysis panel of several genes (multilocus VNTR-analysis (MLVA)) is shown to have an excellent discriminatory power making this a quick, objective and easy tool in the epidemiological assessment of stains.

Spa-type	Repeat succession	MLST	Comment
t001	26-30-17-34-17-20-17-12-17-16	ST-5, ST-222, ST-228	CC5, Southern German MRSA (prototype & subclone), Rhine Hesse MRSA (subclone), EMRSA-3, New York clone
t002	26-23-17-34-17-20-17-12-17-16	ST-5, ST-231	CC5, Rhine Hesse MRSA (prototype), EMRSA-3, New York clone, Japan clone, Pediatric, USA100 ORSA II, USA800 ORSA IV, ST 5 ORSA I
t003	26-17-20-17-12-17-17-16	ST-5, ST-225	CC5, Rhine Hesse MRSA (subclone), EMRSA-3, New York clone
t004	09-02-16-13-13-17-34-16-34	ST-45	CC45, Berlin MRSA (prototype), USA600 ORSA II, USA600

TABLE 38. Example from the Ridom website (http://www.ridom.de) showing spa-type and related MLST-types of common MRSA-strains.

MLST – Multilocus Sequence Typing

MLST is based on the comparison of the DNA sequence of conserved housekeeping genes which are characterized by low selection pressure. For *S. aureus*, seven gene fragments each of about 450-500 bp throughout the chromosome have been chosen. These gene loci are amplified by PCR and sequenced. The specific DNA sequence for each gene in a strain is given an allele number through submission to a universal database (http://www.mlst.net/). The sequence type of a *S. aureus* strains is based on the combination of allele numbers of each of the seven genes. By BURST analysis different strains may be grouped into clonal complexes (CC) of closely related strains that share at least five or six alleles in common (Figure 42). The founder of each CC is the genotype with the largest number of single or double locus variants (Enright 2002). MLST distinguishes only major clonal lineages, and its discriminatory power is not sufficient for the separation of strains within a clonal group in the purpose of investigating a local outbreak. However, the method is very useful for describing the evolutionary history of MRSA, but is labouring intensive and expensive.

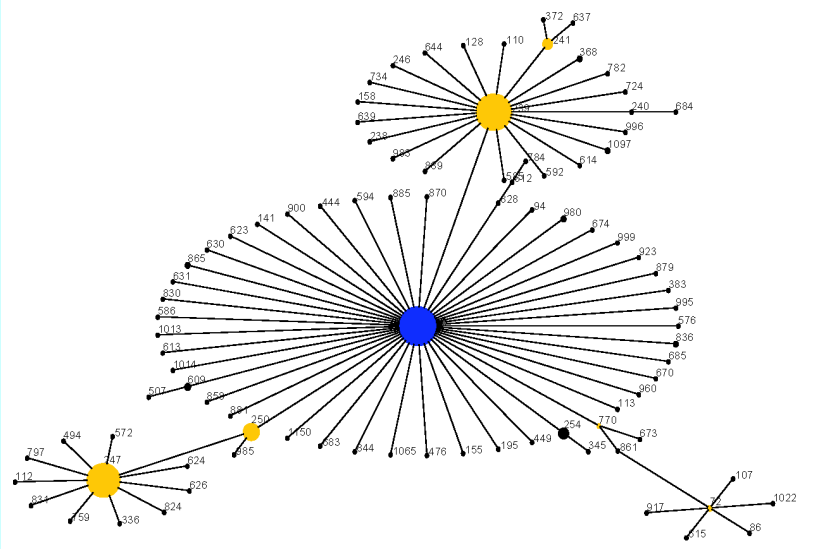

FIGURE 42. Example of eBURST analysis showing CC8 with ST8 as founder and related STs (http://www.mlst.net/).

SCC*mec* – Staphylococcal Cassette Chromosome

SCC*mec* is the genetic element that carries the *mec*A gene encoding methicillin resistance in the staphylococcus species. At least five different types of SCC*mec* (I-V) have been described so far. The nomenclature is subject to debate as various research groups employ different terms (Oliveira 2002, Chongtrakool 2006). Some of the SCC*mec* types often carry genes encoding other resistance mechanisms as well, while the SCC*mec* types IV and V usually have no other resistance elements than *mec*A. These SCC*mec* elements are much smaller than the others and are often associated to community acquired MRSA stains. It appears that *S. aureus* has acquired different SCC*mec* types at different times in evolutionary history. Thus, the PCR method for investigation SCC*mec* give additional knowledge to the ability of identifying and distinguishing between strains with common or unrelated origin.

Characterization of virulence factors

In certain instances the presence or absence of virulence factors may be of relevance for characterizing *S. aureus* strains. In particular, the presence of PVL (Panton-Valentine Leucocidin) has gained considerable attention, but other enzymes, toxins and virulence factors may also represent potential candidates for characterization of epidemiologically related strains. PCR amplification of the gene of interest is the most common method.

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Enterococcus spp. in blood cultures

TABLE 39. *Enterococcus* spp. 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
Ampicillin	≤ 2	> 8	78.9	0.2	20.9
Gentamicin	≤ 128	> 128	63.1	-	36.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Vankomycin	≤ 4	> 8	98.9	1.1	0.0

TABLE 40. *Enterococcus faecalis* blood culture isolates (n=303). 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	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 128	> 128	69.6	-	30.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Vankomycin	≤ 4	> 8	100.0	0.0	0.0

TABLE 41. *Enterococcus faecium* blood culture isolates (n=107). 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	≤ 2	> 8	19.6	0.9	79.5
Gentamicin	≤ 128	> 128	44.9	-	55.1
Linezolid	≤ 4	> 4	100.0	-	0.0
Vankomycin	≤ 4	> 8	100.0	0.0	0.0

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 39. The surveillance in NORM 2007 included 303 (63.9%) *E. faecalis* isolates, 107 (22.6%) *E. faecium* isolates and 64 (13.5%) unspeciated enterococcal isolates. The results display a shift from *E. faecalis* to *E. faecium* which has previously been reported from other countries.

The panel of antibiotics examined was modified in 2007 by removal of penicillin G and quinupristin-dalfopristin. In addition, streptomycin is not included in the printed tables as one of the disk diffusion systems does not provide breakpoints for this substance. Distributions of zone diameters for both systems are available at www.antibiotikaresistens.no.

E. faecalis was universally susceptible to ampicillin. The prevalence of non-susceptibility to ampicillin in *E. faecium* remained relatively stable at 80.4% compared to 85.9% in 2005 and 82.7% in 2006 (Tables 40-41 and Figure 43).

The prevalence of high-level gentamicin resistance (HLGR) continued to increase in *E. faecium* from 35.8% in 2005 to 46.6% in 2006 and now 55.1% in 2007 (Figure 44). Virtually all (56/59, 94.9%) HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin. Conversely, 56 out of 86 (65.1%) ampicillin non-susceptible *E. faecium* also displayed HLGR. The findings are in accordance with the results from previous years.

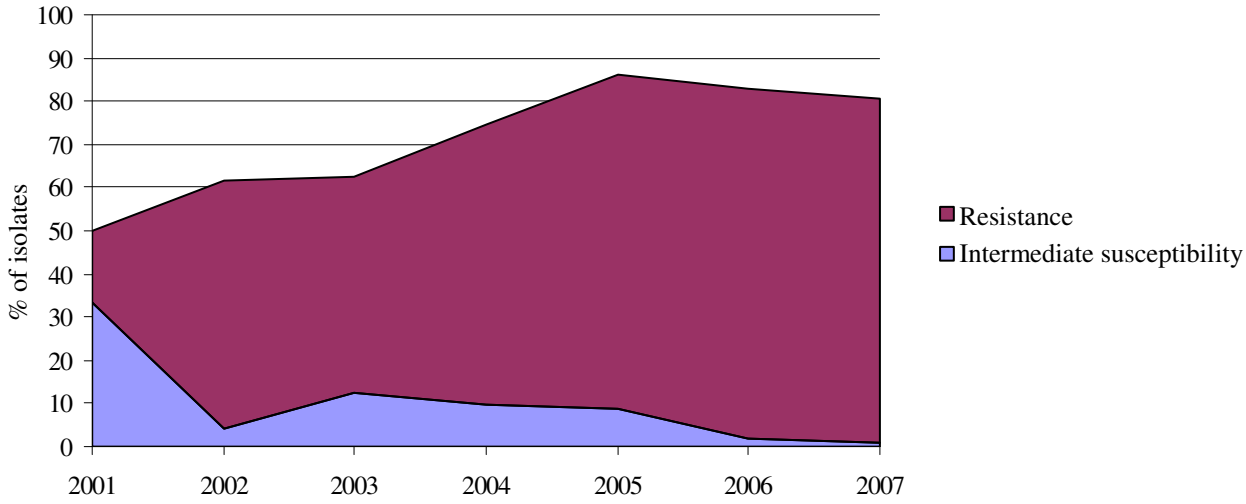

FIGURE 43. Prevalence of intermediate susceptibility and resistance to ampicillin in *E. facium* blood culture isolates. The breakpoints applied were S ≤ 1 mg/L and R > 16 mg/L in 2001-2002, and S ≤ 2 mg/L and R > 8 mg/L in 2003-2007.

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 prevalence of HLGR in *E. faecalis* increased from 24.3% in 2005 and 27.9% in 2006 to 30.4% in 2007. The wide dissemination of high-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and betalactams often used for treatment of severe enterococcal infections.

Transferable vancomycin resistance has not yet been established in clinical enterococcal isolates in Norway. Five isolates were reported as vancomycin resistant (1.1%), but they were all registered as *Enterococcus* spp. One may therefore suspect that they belong to the species *E. gallinarum* or *E. casseliflavus* which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. There were no isolates with transferable high-level vancomycin resistance, and all the five isolates with low-level resistance were fully susceptible to linezolid.

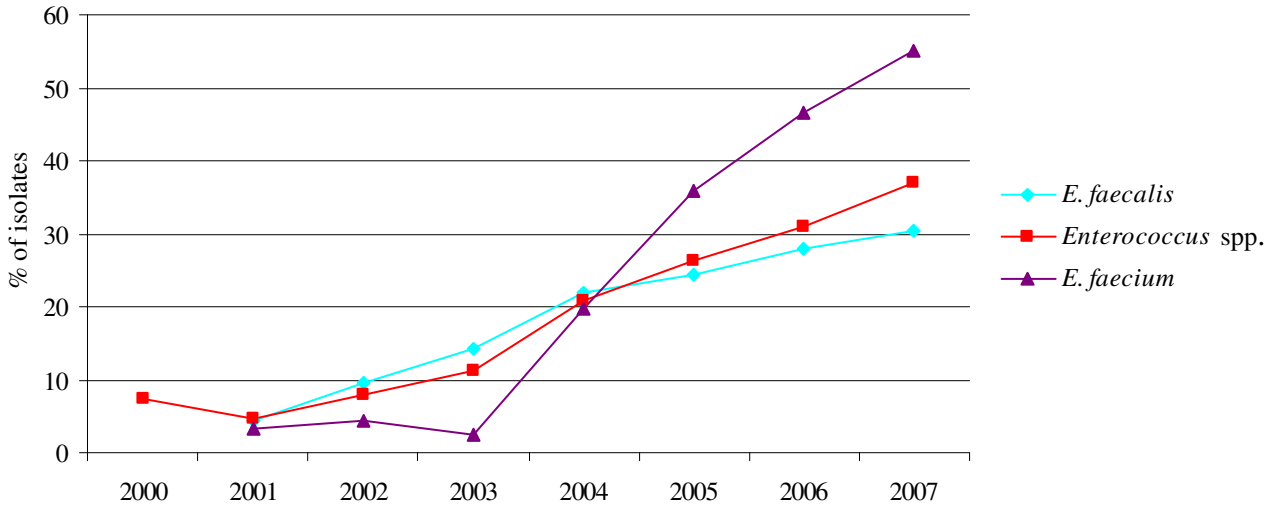

FIGURE 44. Prevalence of high-level resistance to gentamicin in blood culture isolates of *E. faecalis*, *E. faecium* and all enterococci combined during 2000-2007. The breakpoint for high-level resistance was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Streptococcus pneumoniae in blood cultures

TABLE 42. *Streptococcus pneumoniae* blood culture isolates (n=609). 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	96.7	2.5	0.8
Cefuroxime	≤ 0.5	> 1	98.7	0.0	1.3
Cefotaxime	≤ 0.5	> 2	99.0	0.8	0.2
Erythromycin	≤ 0.25	> 0.5	90.1	0.5	9.4
Clindamycin	≤ 0.5	> 0.5	98.2	-	1.8
Tetracycline	≤ 2	> 2	95.9	-	4.1
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 2	88.8	6.9	4.3
Oxacillin screen (mm)	≥ 20	< 20	94.4	-	5.6

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

TABLE 43. *Streptococcus pneumoniae* blood culture isolates (n=609). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G	3.8	5.7	53.4	31.9	2.0	1.0	0.8	0.3	0.3	0.5	0.3					
Cefuroxime			30.4	37.1	25.8	3.4	1.8	0.2		0.5	0.7		0.2			
Cefotaxime	3.9	3.3	35.0	44.5	7.6	3.4	0.7	0.7	0.5	0.3	0.2					
Erythromycin			1.6	2.8	13.3	58.6	13.8	0.5		0.2	1.1	2.1	2.5	1.1	0.8	1.5
Clindamycin			1.1	4.9	21.5	43.7	24.1	2.8	0.2			0.2				1.5
Tetracycline				1.1	11.8	54.2	25.9	1.5	0.2	1.1	0.8	0.5	1.0	1.1	0.7	
TMS**					1.3	10.5	43.2	33.8	4.6	2.3	0.8	1.0		2.5		
Norfloxacin									0.3	7.1	38.9	46.1	6.6	0.7	0.2	0.2

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	5.6	0.7	1.1	3.0	2.8	5.3	7.4	10.7	11.2	14.9	7.9	14.1	7.2	4.9	1.1	2.1

*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 summarised in Tables 42-43 and Figures 45-46. A total of 3.3% (20/609) *S. pneumoniae* isolates were non-susceptible to penicillin G. This is an increase from 2.0% non-susceptibility in 2004, 2.1% in 2005 and 1.9% in 2006. Fifteen isolates (2.5%) were intermediately susceptible (MIC 0.125-1 mg/L) whereas five isolates (0.8%) were resistant (MIC 2-4 mg/L). Five of the penicillin G non-susceptible isolates were resistant to cefuroxime (MIC 2-16 mg/L) and intermediately susceptible or resistant to cefotaxime (MIC 1-4 mg/L). One additional isolates was intermediately susceptible to cefotaxime (MIC 2 mg/L) and resistant to penicillin G (MIC 2 mg/L), but this isolate was fully susceptible to cefuroxime. Three isolates were resistant to cefuroxime and non-susceptible to penicllin G, but displayed borderline MICs of 0.5 mg/L to cefotaxime. The remaining eleven isolates were intermediately susceptible to penicillin G (MIC 0.125 – 0.5 mg/L) and susceptible to cefalosporins.

The oxacillin screening disk is often used to discriminate between penicillin susceptible and non-susceptible isolates. Nineteen of the 20 penicillin G non-susceptible isolates were resistant to oxacillin. Conversely, 15 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test were thus 95.0% and 97.5%, respectively. The oxacillin screening test identified all cephalosporin non-susceptible isolates. Reduced susceptibility to betalactams is often linked to other resistance determinants, and this finding was confirmed in NORM 2007. Among the 20 penicillin G non-susceptible isolates, the majority were resistant to one or more antibiotics such as erythromycin (n=7), clindamycin (n=7), tetracycline (n=9) and trimethoprim-sulfamethoxazole (n=12).

The prevalence of macrolide resistance decreased for the first time since NORM was started in 2000 (Figure 45). A total of 9.4% of the isolates were erythromycin resistant compared to 12.4% in 2006. In addition, 0.5% displayed reduced susceptibility to this agent in 2007. The breakpoint for susceptibility was reduced from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L for the 2007 data, but the breakpoint for resistance remained unaltered at R > 0.5 mg/L. The reduction from 12.4% to 9.4% resistance is consequently not a result of changes in the protocol. There may be several explanations for this phenomenon. NORM 2006 was based on a maximum number of isolates from

each laboratory while NORM 2007 included all consecutive isolates from a given period. Local differences in the distribution of serotypes and resistance determinants may thus have influenced the change from 2006 to 2007. A comparison with data from the National Pneumococcal Reference Laboratory at the Norwegian Institute of Public Health indicates that the figure for 2006 would have been reduced by about 1% if all systemic isolates had been included. However, the most likely reason for the change in epidemiology is the introduction of the 7-valent conjugated pneumococcal vaccine (PCV-7) in the childhood vaccination programme in July 2006. The majority of erythromycin resistant isolates belong to serotypes included in PCV-7, and one may therefore expect a decline in the overall rate of macrolide resistance. Among the 60 erythromycin non-susceptible isolates, 59 were subjected to double disk diffusion (DDD) tests for characterization of MLS phenotypes. A majority of isolates (n=41, 69.5% of erythromycin non-susceptible isolates, 6.9% of all isolates) displayed a phenotype compatible with efflux-based M-type resistance to erythromycin only. The remaining isolates were either inducibly (n=11, 18.6% of erythromycin non-susceptible isolates, 1.8% of all isolates) or constitutively (n=7, 11.9% of erythromycin non-susceptible isolates, 1.2% of all isolates) resistant to clindamycin, thus indicating the presence of *erm*-encoded MLS resistance to both macrolides and lincosamides. The proportion of M-type resistance is a decline from 85.0% in 2006. Furthermore, a subgroup analysis made a distinction between isolates from adults born before 1992 (91.3%) and children born in 1992 or thereafter (8.7%). As in previous years, the prevalence of macrolide resistance was higher among children (8/53, 15.1%) than among adults (49/556, 8.8%), and the reduction in macrolide resistance was possibly larger among children (19.8% and 11.1% in 2006, respectively). Taken together, one may suspect that PCV-7 has reduced the distribution of the *mefA*-encoding serotype-14 clone which has spread in Norway over the last years. Further analysis including serotype data are needed to explore these issues.

There was a further increase in the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole from 9.9% in 2006 to 11.2% in 2007. Although susceptibility testing to this agent is technically demanding, the results for 2007 indicate that there is a significant change to higher prevalences of resistance. Similarly, the prevalence of resistance to tetracycline increased from 2.2% in 2006 to 4.1% in 2007 (Figure 46). The low prevalence of high-level norfloxacin resistance (Table 43) is in accordance with the absence of levofloxacin and other "respiratory fluoroquinolones" from the Norwegian market.

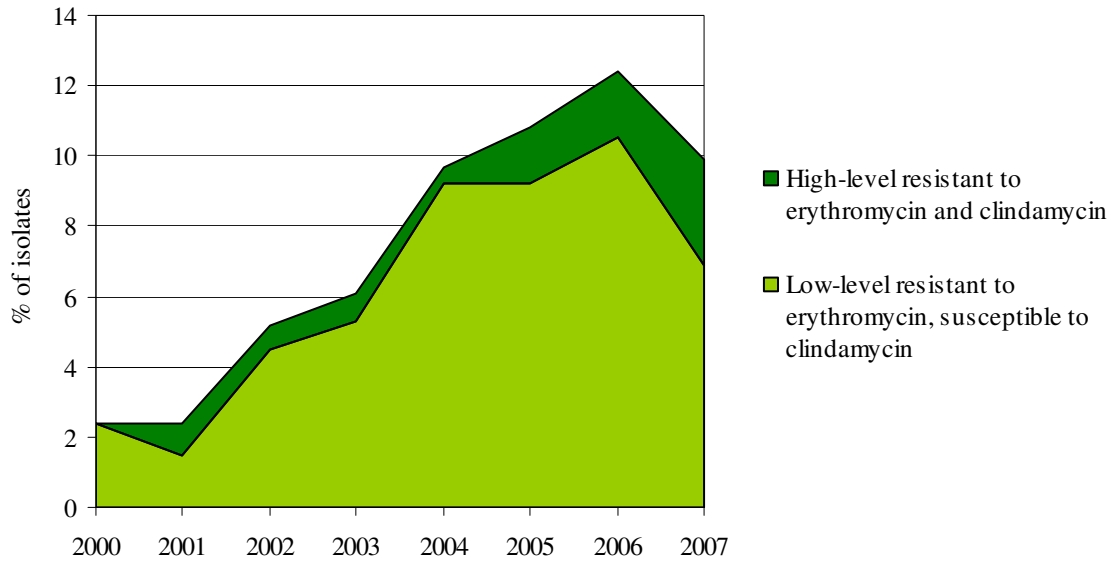

FIGURE 45. Prevalence (%) of macrolide resistant *Streptococcus pneumoniae* blood culture isolates with constitutive or inducible MLS_B phenotype (high-level resistance to erythromycin and clindamycin) and M phenotype resistance (low-level resistance to erythromycin, susceptibility to clindamycin) 2000-2007. The breakpoint for susceptibility was reduced from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L for the 2007 data. The breakpoint for resistance has remained unaltered at R > 0.5 mg/L.

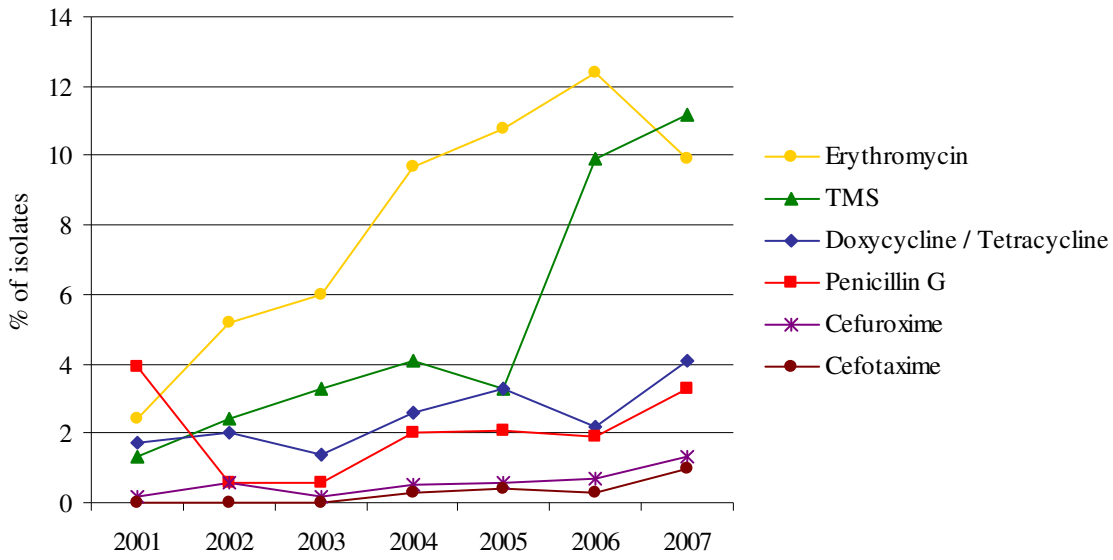

FIGURE 46. Prevalences (%) of non-susceptibility to various antimicrobials in *Streptococcus pneumoniae* blood culture isolates during 2000 – 2007. Doxycycline was substituted by tetracycline in 2005. The breakpoints for erythromycin were changed from S ≤ 0.5 mg/L and R > 0.5 mg/L to S ≤ 0.25 mg/L and R > 0.5 mg/L in 2007.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 44. *Streptococcus pneumoniae* respiratory tract isolates (n=538). 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	96.7	2.6	0.7
Cefuroxime	≤ 0.5	> 1	98.7	0.4	0.9
Cefotaxime	≤ 0.5	> 2	99.4	0.6	0.0
Erythromycin	≤ 0.25	> 0.5	92.0	0.6	7.4
Clindamycin	≤ 0.5	> 0.5	97.0	-	3.0
Tetracycline	≤ 2	> 2	94.4	-	5.6
Trimethoprim-sulfamethoxazole*	≤ 0.5	> 2	86.1	10.4	3.5
Oxacillin screen (mm)	≥ 20	< 20	95.2	-	4.8

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

TABLE 45. *Streptococcus pneumoniae* respiratory tract isolates (n=538). 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	2.2	8.4	51.3	32.0	2.8	0.7	1.1	0.7		0.6	0.2					
Cefuroxime			13.8	48.7	29.4	3.7	2.2	0.9	0.4	0.2	0.6	0.2				
Cefotaxime	1.9	11.5	41.6	36.2	5.0	1.5	1.1	0.6	0.6							
Erythromycin			1.3	2.8	19.9	55.2	12.8	0.6		0.6	0.6	0.4	2.0	0.9	0.2	2.8
Clindamycin			0.6	2.0	12.6	42.9	31.4	7.4	0.2							2.8
Tetracycline			0.2	2.2	22.7	61.7	6.1	0.4	0.6	0.6	0.9	0.9	1.3	1.7	0.6	0.2
TMS**				0.4	0.9	9.1	40.7	34.9	8.2	2.2	1.3	0.7		1.5		
Norfloxacin								0.4	1.9	9.7	39.4	39.0	7.8	0.7	0.9	0.2
	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	4.8	1.3	0.2	3.2	2.4	5.8	6.7	9.9	8.0	9.9	8.4	12.5	3.9	7.1	3.0	13.2

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

RESULTS AND COMMENTS

S. pneumoniae isolates from respiratory tract specimens have previously been surveyed in NORM in 2000, 2001, 2003 and 2005. The prevalences of non-susceptibility to various antimicrobials are shown in Tables 44-45 and Figure 47. There is a clear increase in non-susceptibility to erythromycin (2001: 3.3%; 2003: 5.7%; 2005:6.6%; 2007: 8.0%) and trimethoprim-sulfamethoxazole (2001: 1.9%; 2003: 4.4%; 2005: 6.4%; 2007: 13.9%) even when changes in breakpoints are taken into account. The situation is apparently more stable for penicillin G (2001: 2.6%; 2003: 2.8%; 2005: 3.4%; 2007: 3.3%) and tetracyclines (2001: 4.6%; 2003: 7.8%; 2005: 6.2%; 2007: 5.6%) even though the conclusion is less obvious for tetracyclines as the test substance was changed from doxycycline to tetracycline in 2005.

A total of 18/538 isolates (3.3%) were non-susceptible to penicillin G. Four of these isolates were penicillin G resistant (MIC 2-4 mg/L) while the remaining 14 were intermediately susceptible (MIC 0.125-1 mg/L). All the penicillin G resistant isolates and 13 of the 14 intermediately susceptible ones were detected by the oxacillin screening disk. Conversely, nine penicillin G susceptible isolates were identified as oxacillin resistant. Three isolates were intermediately susceptible to cefotaxime. They were all resistant to cefuroxime, penicillin G and oxacillin. Four additional isolates were either resistant (n=2) or intermediately susceptible (n=2) to cefuroxime, resistant to oxacillin (n=4) and resistant (n=1) or intermediately susceptible (n=3) to penicillin G. The betalactam resistant isolates were often non-susceptible to one or more alternative antibiotics such as tetracycline, erythromycin or trimethoprim-sulfamethoxazole.

The prevalence of macrolide resistance in *S. pneumoniae* blood culture isolates increased steadily 2000 – 2006 but decreased to 9.4% in 2007. The epidemic spread of macrolide resistant pneumococcal clones has been been less pronounced in respiratory tract isolates with 7.4% erythromycin resistance in 2007. However, there is still an interesting difference in resistance phenotypes between the two specimen types. Whereas the majority of erythromycin resistant blood culture isolates displayed the M-phenotype (41/56, 73.2%), a major proportion of respiratory tract isolates (3.5% of all; 47.5% of erythromycin resistant isolates) displayed the MLS_B-phenotype either constitutively (2.4% of all; 32.5% of erythromycin resistant isolates) or inducibly (1.1% of all; 15.0% of erythromycin resistant isolates). This may indicate that there are different pneumococcal clones causing systemic and localized infections. A total of ten isolates (1.9%) were concomitantly non-susceptible to penicillin G and erythromycin.

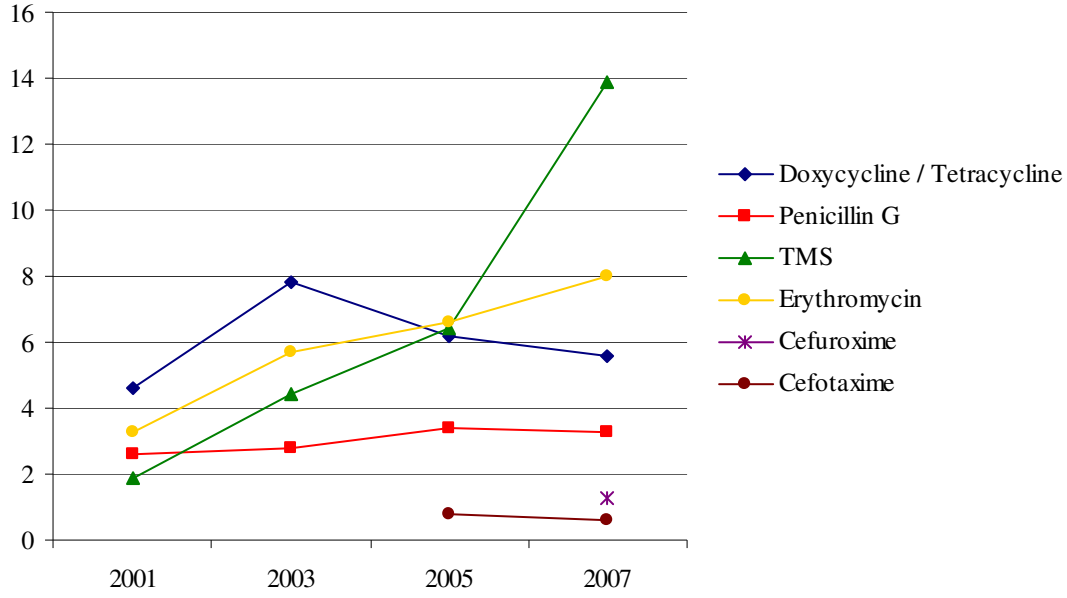

FIGURE 47. Prevalences of non-susceptibility to various antimicrobials in *S. pneumoniae* from respiratory tract samples 2001-2007. The breakpoints for erythromycin were adjusted in 2003 from S ≤ 1 mg/L and R > 2 mg/L to S ≤ 0.5 mg/L and R > 0.5 mg/L and then finally to S ≤ 0.25 mg/L and R > 0.5 mg/L in 2007. The breakpoints for trimethoprim-sulfamethoxazole (TMS) were adjusted in 2003 from S ≤ 2 mg/L and R > 8 mg/L to S ≤ 0.5 mg/L and R > 2 mg/L. Doxycycline with the breakpoints S ≤ 1 mg/L and R > 2 mg/L was replaced by tetracycline with the breakpoints S ≤ 2 mg/L and R > 2 mg/L in 2005. The breakpoints for penicillin G have remained unaltered at S ≤ 0.064 and R > 1 mg/L throughout the period.

Mycobacterium tuberculosis

A total of 307 cases of tuberculosis were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2007. Of these, 282 individuals had not previously been treated with antituberculosis drugs. Among these individuals 227 were confirmed by culture, and *Mycobacterium tuberculosis* was isolated from 225 of these individuals. All isolates were susceptibility tested. The results are presented in Table 46.

TABLE 46. Antimicrobial susceptibility of 225 isolates of *M. tuberculosis* complex isolated in 2007 from patients not previously treated for tuberculosis.

Geographical origin of patient	No. of isolates		Resistance to antimicrobial agents (No. of isolates)					
	2007	(2006)	Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDR TB*
Norway	43	(38)	2			2	2	
Europe outside Norway	11	(15)	2			3		
Asia	69	(59)	8	2	2	4	2	1
Africa	100	(104)	7	1		11	5	1
America	2	(1)						
Total	225	(217)	19	3	2	20	9	2
Proportion of resistant isolates (%)			8.4	1.3	0.9	8.9	4.0	0.9

*MDR TB: Multi drug resistant tuberculosis, resistant to at least rifampicin and isoniazid.

RESULTS AND COMMENTS

Susceptibility tests were also performed on *M. tuberculosis* isolates from 17 patients who had previously received antituberculosis drug treatment. Among these, four isolates were monoresistant to isoniazid, two were monoresistant to streptomycin and one was resistant to both isoniazid and streptomycin. In addition one isolate showed resistance to all first line drugs and in addition showed resistance to amikacin, kanamycin, capreomycin, ethionamid, ofloxacin, PAS and rifabutin. It therefore met the current criteria for extensive drug resistant tuberculosis (XDR TB).

Candida spp. in blood cultures

TABLE 47. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=155). 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***	≤ 0.25	> 0.25	100.0	-	0.0
Caspofungin****	≤ 1	> 1	99.4	-	0.6

* Recommended breakpoints by the Norwegian Reference Group on Antibiotics – AFA.
** Recommended breakpoints for fluconazole by the European Committee on Antimicrobial Susceptibility Testing – EUCAST.
*** Breakpoints are pending. Recommendations based on epidemiological cut-off values are made by the Nordic Reference Group on Methods in Medical Mycology – NRMM.
****There are no recommended breakpoints for caspofungin. Strains with MIC ≤ 1mg/L are considered susceptible.

TABLE 48. *Candida albicans* blood culture isolates (n=155). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B				0.6	0.6	3.2	41.3	51.0	3.2								
Fluconazole					1.3	7.1	51.6	38.1	0.6								
Voriconazole	14.8	58.7	21.9	1.9		1.3	1.3										
Caspofungin			1.3	10.3	29.0	37.4	20.6		0.6					0.6			

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

TABLE 49. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=22). 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	18.2	-	81.8
Voriconazole***	≤ 0.25	> 0.25	72.7	-	27.3
Caspofungin****	≤ 1	> 1	100.0	-	0.0

*Recommended breakpoints by the Norwegian Reference Group on Antibiotics – AFA.
** Recommended breakpoints for fluconazole by the European Committee on Antimicrobial Susceptibility Testing – EUCAST.
*** Breakpoints are pending. Recommendations based on epidemiological cut-off values are made by the Nordic Reference Group on Methods in Medical Mycology – NRMM.
****There are no recommended breakpoints for caspofungin. Strains with MIC ≤ 1mg/L are considered susceptible.

TABLE 50. *Candida glabrata* blood culture isolates (n=22). Distribution (%) of MICs (mg/L).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B						4.5	9.1	77.3	9.1								
Fluconazole								4.5		13.6	27.3	22.7	13.6	9.0	4.5	4.5	
Voriconazole			4.5		13.6	22.7	31.8	13.6	4.5		9.1						
Caspofungin					4.5	13.6	81.8										

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

TABLE 51. 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	83.4	-	16.6
Fluconazole**	≤ 2	> 2	83.4	-	16.6
Voriconazole***	≤ 0.25	> 0.25	91.7	-	8.3
Caspofungin****	≤ 1	> 1	100.0	-	0.0

*Recommended breakpoints by the Norwegian Reference Group on Antibiotics – AFA.
** Recommended breakpoints for fluconazole by the European Committee on Antimicrobial Susceptibility Testing – EUCAST.
*** Breakpoints are pending. Recommendations based on epidemiological cut-off values are made by the Nordic Reference Group on Methods in Medical Mycology – NRMM.
****There are no recommended breakpoints for caspofungin. Strains with MIC ≤ 1mg/L are considered susceptible.

TABLE 52. *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						8.3	8.3	16.7	50.0	16.7							
Fluconazole								50.0	25.0	8.3	8.3			8.3			
Voriconazole				25.0	50.0	8.3	8.3	8.3									
Caspofungin					8.3	25.0	66.7										

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

RESULTS AND COMMENTS

In 2007, 207 strains of eight different *Candida* species isolated from patients with blood stream infections were received at the National Mycology Reference Laboratory. In 2006, 183 strains from 11 different yeast species were received. All isolates were tested for susceptibility to amphotericin B, fluconazole, voriconazole and caspofungin by E-tests. The results for the three most common species *Candida albicans* (n=155, 74.9 %), *Candida glabrata* (n=22, 10.6 %) and *Candida tropicalis* (n=12, 5.8 %) are shown in Tables 47-52.

C. albicans isolates were still all susceptible to fluconazole, while 82 % of the *C. glabrata* isolates were resistant. Though a change in breakpoints to fluconazole has been made, there is an actual increase in the percentage of resistant (previously intermediately susceptible and resistant) strains. Two isolates (16.7%) of *C. tropicalis* also had reduced susceptibility to fluconazole.

While 18 strains (82%) of *C. glabrata* were resistant to fluconazole, 6 (27 %) of these isolates were also resistant to voriconazole. One strain (8.3%) of *C. tropicalis* also had reduced susceptibility to voriconzole, but this isolate was susceptible to fluconazole. All *C. albicans* isolates are still susceptible to fluconazole.

Both *C. glabrata* and *C. tropicalis* isolates were all susceptible to caspofungin. However, one isolate of *C. albicans* was resistant (MIC 32 mg/L) – the first such isolate detected in Norway. Two *C. tropicalis* strains were resistant to amphotericin B. All isolates of *C. albicans* and *C. glabrata* were susceptible to this drug.

Compared to earlier data, there is both an increase in fluconazole resistant and voriconazole resistant *C. glabrata*. Patients with *C. glabrata* infections should be treated with other antifungal agents than azoles.

The breakpoints used in yeast susceptibility testing are under consideration. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is expected to introduce breakpoints for voriconazole and caspofungin in 2008. In this report the breakpoints recommended by the Norwegian Reference Group on Antibiotics (AFA) are used for amphotericin B. The EUCAST breakpoint has been introduced for fluconazole with either susceptible or resistant strains. The intermediately susceptible category has been removed. Breakpoints for voriconazole are based on recommendations made by the Nordic Reference group on Methods in Medical Mycology (NSMM) and EUCAST. No breakpoint recommendations have been made for caspofungin, but strains with MICs ≤ 1 mg/l are presumably susceptible.

Influenza virus in respiratory tract specimens

Background

Two classes of antiviral drugs are being used against influenza virus infection. Whereas M2 blockers inhibit replication of influenza type A viruses, the more recently developed neuraminidase inhibitors (NIs) inhibit the replication of both type A and B. In Norway, only the NIs oseltamivir and zanamivir are approved for the prophylaxis and treatment of influenza; however, both the NI oseltamivir and the M2 blocker rimantadin form parts of the government's stockpile for use against pandemic influenza.

Usage of influenza antivirals in Norway is very sparse, but effective treatment is of great importance for individuals who are severely affected by influenza. Since the antiviral treatment must be started early to ensure optimal effect, resistance testing will almost never be done in time to inform the decision to treat. Knowledge on the occurrence of resistance at population level is therefore needed. Furthermore, the close monitoring of antiviral resistance is essential for the management of pandemic influenza.

The Department of Virology at the Norwegian Institute of Public Health (NIPH) serves in the function as a WHO National Influenza Centre (NIC) and has been designated by the Ministry of Health as national reference laboratory for influenza. In the latter function lies also the obligation to monitor and assess the occurrence of resistance.

Historically, resistance has been known to develop against the M2 blockers when used to counter outbreaks in closed settings like nursing homes. The mutant viruses have tended not to suffer reduced ability to spread. Over the last decade, increasing proportions of resistant viruses have been observed, particularly of subtype A(H3N2). Some Asian countries, where there has been widespread use of adamantane drugs, have been leading in this trend. During the first years of use, the more recently developed NIs seemed to be much less affected by resistance development and resistant mutants in general have seemed less viable. Locally, the influenza viruses die out at the end of each winter season, and subsequently are reintroduced at the beginning of the next season through global spread of new variants. Consequently, the monitoring of resistance needs to have a strong international dimension.

Laboratories serving as international reference centres for antiviral resistance are organised globally in the Neuraminidase Inhibitor Susceptibility Network (NISN), as well as regionally in the EU sponsored European Surveillance Network for Vigilance Against Viral Resistance (VIRGIL). A selection of influenza viruses shipped by European NICs to the WHO Collaborating Centre in the United Kingdom are routinely passed on to the VIRGIL laboratory in London for antiviral susceptibility testing. Where desirable, VIRGIL also works actively on national laboratory capacity building. Up to 2007, Norwegian influenza viruses were mainly tested locally in the NIC through genotyping and in the VIRGIL laboratory through both functional (phenotypic) and genotyping methods.

Strengthening of resistance monitoring in Norway

Like in many other countries, stockpiled antivirals form a major part of the Norwegian national preparedness against pandemic influenza. As a consequence of this strategy, the MoH has tasked the NIPH to establish capability to closely monitor resistance during a pandemic. In order to do this, the capability needs to be established beforehand, i.e. operative during seasonal influenza and with sufficient resilience to be sustained during the excessive strain foreseen in a pandemic. Strengthening of staff and implementation of methods is underway, with rapid genotyping through pyrosequencing now in place and phenotypic assays to be in place by the end of the year.

Surveillance findings

Findings from the first years of surveillance are summarised in Table 53. Since the influenza viruses at the end of the year are invariably closer related to viruses occuring early next year than to the viruses from the preceding spring, it is meaningful to summarise according to winter seasons rather than by calendar years. The findings for M2 blocker resistance is largely in accordance with the global pattern, with high and increasing proportion of reistant viruses. These viruses remain sensitive to the NIs oseltamivir and zanamivir.

TABLE 53. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the NI oseltamivir during the influenza seasons 2005/06 to 2007/08.

Season	Adamantane resistance		Oseltamivir resistance		
	A(H1N1)	A(H3N2)	A(H1N1)	A(H3N2)	B
2005/06	nd	75% (n=4)	0% (n=6)	75% (n=4)	0% (n=21)
2006/07	0% (n=6)	90% (n=10)	0% (n=5)	90% (n=10)	nd
2007/08*	0% (n=17)	nd	76% (n=17)	nd	0% (n=7)

*for the 2007/08 season, only viruses from autumn 2007 are included

For NIs, resistant viruses have been very rare in most countries, this is also reflected in the Norwegian data up to 2007. However, when VIRGIL tested the first Norwegian viruses in the 2007-08 season, an unprecedented proportion of high-level resistance to oseltamivir (but not zanamivir) was found. It was subsequently found that this was part of an emerging global pattern, not associated with recorded usage of drug, with Norway reporting the highest proportion of resistance. More data on this novel development is being published elsewhere and will be more extensively treated in the next NORM annual report.

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 antimicrobials 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 only supplied by drug wholesalers. An exemption from the pharmacy/wholesaler monopoly has been granted for medicated feeds (i.e., feeds into which drugs for therapeutic use are mixed prior to sale). 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 antimicrobials from wholesalers and feed mills are thought to roughly equal the use of these drugs. Sales figures for veterinary antimicrobials are therefore used as a synonym of veterinary antimicrobial use. 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 sold items in 2007 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.

Veterinarians has since 1989 been obliged by regulation to submit copies of all prescriptions to farmed fish to the Norwegian Directorate of Fisheries (NDF), and since 2004 to the Norwegian Food Safety Authority (NFSA). NFSA (and formerly NDF) compiles all relevant information from the prescriptions into a prescription database such as the drug substance and the amounts prescribed, fish species to be treated and the date of prescribing. Data on annual usage of antimicrobials per fish species was obtained from this prescription database. These data has since 1996 been regularly validated against overall national sales statistics of drugs sold for use in farmed fish and this validation shows that the data from these two sources are highly correlated.

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 (AM) specialities belonging to the following ATCvet groups: QA07AA (gastrointestinal infections), QG01AA+AX (uterine infections) and, QJ [AM agents for systemic use that includes intramammary dose applicators (QJ51)]. Additionally, a few AMs preparations sold on special exemption from market authorization have been included following a case by case assessment (se footnotes for the various tables and figures). Sales of AMs 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 AMs 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 5 that presents detailed sales figures for AMs for terrestrial animals for the latest year; for Fig. 1 and 2 this premix has been included for the whole period. Consequently, the sales of the AM drugs in terrestrial animals reported for the years 1995-2005 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 AMs 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.

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

Data sources

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

The Wholesales database covers total sales of antibacterials in Norway and is based on sale 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 has been collected since the beginning of the seventies.

Data on antibacterial use in hospitals are retrieved from *Sykehusapotekenes Legemiddelstatistikk* (Hospital Pharmacies´ Drug Statistics): a cooperation of the Norwegian pharmacies delivering drugs to hospitals and LIS (Drug Purchasing Cooperation - Legemiddel Innkjøp Samarbeid). *Sykehusapotekenes Legemiddelstatistikk* collects sales data from each hospital pharmacy. Data are collected as sales to wards/hospitals from the pharmacy.

Data on the use in ambulatory care are retrieved from NorPD, a national prescription database. This database includes all prescriptions being prescribed to out-patients in Norway. These data give us the exact population prevalence of antibacterials in ambulatory care.

Drug Classification

The data is categorized according to the ATC classification system. Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2008 is used.

Unit of measurement

The ATC/DDD system is recommended by the WHO to serve as a tool for drug utilisation research in order to improve quality of drug use. One component of this is the presentation and comparison of drug consumption statistics at international and other levels.

The use of defined daily dose, DDD, as a unit of measurement, simplifies and improves the evaluation of drug consumption over time, nationally and internationally. The DDD is a theoretical unit of measurement, and does not necessarily reflect the recommended or Prescribed Daily Dose.

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

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

Inclusion criteria

The antibacterials for human use included in this report belong to ATC 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 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.

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

Sampling strategy

The isolates of indicator bacteria (*E. coli* and *Enterococcus* spp.) included in the NORM-VET monitoring programme in 2007 were collected from sheep (only *E. coli*), turkey and swine (faecal samples) and turkey meat. The faecal samples from sheep, turkey and swine were collected within the frame of other surveillance programs. Only one sample from each herd or flock was subjected to NORM-VET. The turkey meat was sampled from two slaughter houses within a project studying the occurrence of *Campylobacter* spp. in turkey meat.

Isolation and identification of bacteria

Escherichia coli

The *E. coli* strains included in NORM-VET 2007 were isolated and identified at the National Veterinary Institute. Meat: Five grams of material from each specimen were incubated in 45 ml of MacConkey broth (Oxoid). After incubation at 44°C for 24 h, a small amount (approx. 10 µl) of broth was plated onto the surface of lactose-saccarose-bromthymol blue agar. Faeces: The sample was plated directly onto the surface of lactose-saccarose-bromthymol blue agar without broth enrichment.

After incubation of the agar plates at 37°C for 24 h, a typical colony was plated onto blood agar (Heart infusion agar (Difco) containing 5% bovine blood). Colonies were identified as *E. coli* by typical appearance, lactose and/or saccarose fermentation and a positive indole reaction.

***Enterococcus* spp.**

The enterococcal strains included in NORM-VET 2007 were isolated and identified at the National Veterinary Institute. Meat: Five grams of material from each specimen were incubated in 45 ml of Azide dextrose broth (Oxoid). After incubation at 44°C for 24 h, a small amount (approx. 10µl) of broth was plated onto the surface of Slanetz & Bartley agar (Oxoid). Faeces: The sample was plated directly onto the surface of Slanetz & Bartley agar (Oxoid) without broth enrichment.

After incubation of the agar plates at 44°C for 48h, typical colonies were plated onto blood agar (Heart infusion agar (Difco) with 5% bovine blood). Typical colonies were tested by catalase reaction and *E. faecium* and *E. faecalis* were identified by *ddl*-PCR (Dutka-Malen et al., 1995).

For the selective isolation of vancomycin resistant *Enterococcus* spp. (VRE), the samples were treated as described above, and plated out on additional Slanetz and Bartley's agar plates containing 32 mg/L vancomycin. Colonies from each positive sample were selected, and the isolates confirmed as *Enterococcus* spp. by phenotypic characterization. The isolates were further identified to species level and tested for the presence of the *vanA* gene using PCR (Dutka-Malen et al, 1995, Simonsen et al, 2000).

Susceptibility testing

Only one isolate per herd, flock or product were tested for antimicrobial susceptibility. Bacterial isolates were tested for antimicrobial susceptibility at the National Veterinary Institute. A broth microdilution method; VetMIC™ (Dept. of Antibiotics, National Veterinary Institute, Sweden) was used for susceptibility testing of all isolates.

Epidemiological cut-off values recommended by the European Food Safety Authority (EFSA) were used (www.efsa.europa.eu) for the substances recommended by EFSA with the exception of ciprofloxacin for *E. coli.* For the additional antimicrobial agents, included in our national monitoring programme, a cut-off value was defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also appendix 6).

Quality assurance systems

The following susceptible bacteria were included as quality controls on a weekly basis, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212. The following resistant bacteria were tested on a regular basis: *E. faecium* CCUG 33829, CCUG 36804. The results were approved according to reference values given by CLSI when available. Additional control strains were included when necessary.

The participating laboratories at the National Veterinary Institute are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in external quality assurance programmes for veterinary pathogens (VLQAS Veterinary Laboratories Agency Quality Assurance Unit, Loughborough, England and Community Reference Laboratory, Denmark).

Data processing

Susceptibility data were recorded and processed in WHONET 5.4, a program developed by the World Health Organization (WHO) for analysis of antimicrobial resistance data (http://www.who.int/drugresistance/whonetsoftware/en/index.html). The susceptibility data were stored as continuous MIC-values.

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 National Veterinary Institute. One isolate of each serovar per incident was included for susceptibility testing.

Campylobacter jejuni

As part of the Norwegian action plan against *Campylobacter* in broilers (www.vetinst.no), caecal samples were collected at slaughter plants. One isolate per positive farm was included for susceptibility testing.
In addition, isolates obtained from a research project regarding the occurrence of *Campylobacter* spp. in turkey flocks and broiler and turkey meat were included in the report.

Sampling strategy - humans

Salmonella, Yersinia enterocolitica* and *Shigella

All human isolates were obtained from clinical specimens. One isolate per patient or one isolate per outbreak was included for susceptibility testing.

Campylobacter

A total of 250 human isolates were obtained from clinical specimens. Five regional laboratories submitted the first five independent isolates each month to the National Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Isolation and identification of bacteria

Isolation and identification of *Salmonella* from animals was carried out at the National Veterinary Institute 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 of *Campylobacter* spp. from broiler was carried out by local laboratories. The samples from turkeys and broiler meat were analysed at the National Veterinary Institute. All *Campylobacter* spp. were isolated according to the Nordic Committee on Food Analyses (NMKL) method number 119, with minor modifications. Identification of the isolates was carried out by the National Veterinary Institute.
Isolation and identification of bacteria from humans was performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th edition ASM-Press, Washington 2003 and Ewing WH: Edwards and Ewing's Identification of *Enterobacteriaceae*, 4. edition, Elsevier, New York 1986). The identification of all isolates from animals and humans was verified at the National Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Susceptibility testing

Isolates from animals were tested for antimicrobial susceptibility at the National Veterinary Institute. MIC values were obtained using the VetMIC™ microdilution method (Dept. of Antibiotics, National Veterinary Institute, Sweden).

Salmonella, *Yersinia* and *Shigella* isolates from humans were susceptibility tested at the Norwegian Institute of Public Health 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 at the Norwegian Institute of Public Health using Etest (AB Biodisk).

For animal isolates, epidemiological cut-off values recommended by the European Food Safety Authority (EFSA) were used (www.efsa.europa.eu) for the substances recommended by EFSA. For the additional antimicrobial agents, included in our national monitoring programme, a cut-off value was defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also appendix 6). For human isolates, MIC breakpoints defined by AFA (Norwegian Reference Group on Antibiotic Susceptibility Testing) were applied when available and appropriate. For disk diffusion results, population based breakpoints were used. Breakpoints for *Campylobacter* are preliminary and based on MIC distributions.

Quality assurance systems

The National Veterinary Institute and the Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health have a quality assurance system according to the requirements of NS-EN ISO/IEC 17025.
Campylobacter jejuni subsp. *jejuni* CCUG 33057 and CCUG 11284 were used as quality control strains at the National Veterinary Institute on a weekly basis. The National Veterinary Institute participates in an external quality assurance programme for veterinary pathogens organized by the VLQA (Veterinary Laboratories Agency Quality Assurance Unit, Loughborough, England) and also in the external quality assurance programmes organized by CRL. The Norwegian Institute of Public Health participates in the external quality assessment programme for *Salmonella* organized by Enter-Net.

Data processing

Susceptibility data were recorded and processed in WHONET 5.3, a program developed by the World Health Organization (WHO) for analysis of resistance data (http://www.who.int/drugresistance/whonetsoftware/). The susceptibility data were stored as discrete values (MIC).

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, or septicaemiae. For enteric infections see Appendix 4. 2007 was the eighth year of surveillance, and all 23 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 use identical criteria for the inclusion of microbial strains. Only one isolate per patient and infectious episode was included. 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 2007 were as follows: *E. coli* in blood cultures 6 months; *Klebsiella* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterococcus* in blood cultures 10 months; *Candida* spp. from blood cultures 12 months, *S. pneumoniae* and *Haemophilus influenzae* from respiratory tract specimens 3 weeks; *S. aureus* from wound samples 2 weeks; *E. coli* from urinary tract infections 1 week; and *Mycobacterium tuberculosis* from all samples for 12 months.

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. 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 Reference Group on Antibiotic Susceptibility Testing (AFA). The AFA breakpoints are identical to EUCAST breakpoints where such have been established. 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. *S. pneumoniae* isolates were susceptibility tested using Etest on MH II agar supplemented with 5% lysed sheep blood AB Biodisk (Solna, Sweden). *H. influenzae* isolates were susceptibility tested using Etest on MH II agar supplemented with 1% haemoglobin and 1% IsoVitalex. All resistance values were recorded either as mm inhibition zone sizes or MIC values in order to monitor trends in the occurrence of resistance.

Confirmation of resistance phenotypes
E. coli and *Klebsiella* spp. with reduced susceptibility to 3rd generation cephalosporins were examined for ESBL production using the ESBL Etest according to the instructions of the manufacturer. *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* gene PCRs for confirmation of VRE. Erythromycin resistant *S. pneumoniae* 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), *H. influenzae* ATCC 49247, *E. faecalis* ATCC 29212, *E. faecalis* ATCC 51299, *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *S. aureus* ATCC 25923, *S. aureus* ATCC 43300 (heterogeneous MRSA), *S. aureus* CCUG 35600 (homogeneous MRSA).

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 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 1 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.

Mycobacterium tuberculosis
Susceptibility testing (DST) was performed at the Norwegian Institute of Public Health, Ullevål University Hospital and Rikshospitalet. All isolates were tested using the BACTEC 460 or BACTEC MGIT 960 systems. All three 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.

Yeasts
All systemic yeast isolates in Norway are submitted to Rikshospitalet, Oslo. Susceptibility testing on *Candida* spp. isolates was performed by Etest using RPMI agar containing 2% glucose and MOPS. *C. albicans* ATCC 10231 was used for quality control.

Appendix 6: Breakpoints NORM-VET

European Food Safety Authority (EFSA) recommends certain antimicrobial agents to be included in the monitoring for the zoonotic bacteria (*Salmonella* and *Campylobacter jejuni*) and the indicator bacteria (*E. coli* and *Enterococcus* spp.). These are marked in the table in bold. For these substances, mainly the epidemiological cut-off values recommended by EFSA were applied. For the additional antimicrobial agents included in our national monitoring programme, a cut-off value was defined on the basis of the actual MIC distributions obtained in the NORM-VET programme. The cut-off value recommended by EFSA for ciprofloxacin in *E. coli* was not applicable to the distributions of MICs in our laboratory and it was therefore decided to use the above approach also for this antimicrobial agent and bacteria.

Antimicrobial	Resistant (MIC values, mg/L)	*Campylobacter*	*Salmonella*	*E. coli*	*Enterococcus*
Tetracycline	**> 2**	■			■
	> 8		■	■	
Chloramphenicol	**> 16**		■	■	
	>32				■
Florfenicol	> 16		■	■	
Ampicillin	**>4**		■		■
	> 8			■	
Ceftiofur	> 1		■	■	
Cefotaxime	**>0.25**			■	
	>0.5		■		
Trimethoprim	**> 2**		■	■	
Sulfonamides	**> 256**		■	■	
Erythromycin	**> 4**	■			■
Streptomycin	**>2**	■			
	> 16			■	
	> 32		■		
	>128				■ [a]
	> 512				■ [a]
Gentamicin	**> 1**	■			
	>2		■	■	
	> 32				■
Kanamycin	>16		■	■	
	> 1024				■
Ciprofloxacin	**>1**	■			
	>0.06		■	■#	
Nalidixic acid*	**> 16**	■	■	■	
Vancomycin	> 4				■
Bacitracin**	> 32				■
Linezolid	**> 4**				■
Virginiamycin***	> 4				■
Narasin	> 2				■

In bold: Antimicrobial agents and epidemiological cut-off values recommended by EFSA
[a] >128 mg/L for *E. faecium*, >512 mg/L for *E. faecalis*. * Not included in the recommendation by EFSA for *Campylobacter jejuni*. ** units, *** applies only for *E. faecium*, # for *E. coli* ased on the MIC-distribution, not as recommeded by EFSA for *E. Coli*

Appendix 7: Breakpoints NORM

NORM data are categorized according to the breakpoints of the Norwegian Reference Group on Antibiotic Susceptibility Testing – AFA (isolates from humans) which are harmonized with EUCAST breakpoints when available. Breakpoints for *Campylobacter* are preliminary and based on MIC-distributions. For details regarding bacteria and antimicrobial panels, see tables in text. AFA breakpoints are available at www.antibiotikaresistens.no.

	MIC values mg/L												
Antimicrobials	S	R	*E. coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*S. aureus*	*Enterococcus* spp.	*S. pneumoniae*	*Candida* spp.
Amoxi.-clav.	≤ 2	> 4							■				
Amphotericin B	≤ 1	> 1											■
Ampicillin	≤ 0.5	> 8	■		■	■	■						
	≤ 1	> 4							■				
	≤ 2	> 8									■		
Aztreonam	≤ 1	> 8	■	■									
Caspofungin	≤ 1	> 1											■
Cefotaxime	≤ 0.125	> 0.125							■				
	≤ 0.5	> 2										■	
	≤ 1	> 2	■	■									
Ceftazidime	≤ 1	> 8	■	■									
Cefuroxime	≤ 0.5	> 1										■	
	≤ 0.5	> 8	■	■									
	≤ 1	> 2							■				
Chloramphenicol	≤ 8	> 8			■	■	■						
Ciprofloxacin	≤ 0.5	> 1	■	■	■	■	■	■					
	≤ 1	> 1								■			
Clindamycin	≤ 0.25	> 0.5								■			
	≤ 0.5	> 0.5										■	
Erythromycin	≤ 0.25	> 0.5										■	
	≤ 1	> 2								■			
	≤ 2	> 2						■					
Fluconazole	≤ 2	> 2											■
Fusidic acid	≤ 0.5	> 0.5								■			

Antimicrobials	MIC values mg/L S	R	*E. coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Haemophilus influenzae*	*S. aureus*	*Enterococcus* spp.	*S. pneumoniae*	*Candida* spp.
Gentamicin	≤ 1	> 1								■			
	≤ 2	> 4	■	■				■					
	≤ 128	> 128									■		
Linezolid	≤ 4	> 4								■	■		
Mecillinam	≤ 2	> 8	■										
Meropenem	≤ 2	> 8	■	■									
Nalidixic acid	≤ 16	> 16	■	■	■	■	■	■					
Nitrofurantoin	≤ 32	> 32	■										
Penicillin G	≤ 0.064	> 1										■	
	≤ 1	> 4							■				
Penicillin V	≤ 0.5	> 4							■				
Pip./Tazo.	≤ 8	> 16	■	■									
Rifampicin	≤ 1	> 1								■			
Tetracycline	≤ 1	> 2						■[#]		■			
	≤ 2	> 2							■			■	
	≤ 4	> 8			■[#]	■[#]	■[#]						
Trimethoprim	≤ 2	> 4	■										
TMS*	≤ 0.5	> 2							■			■	
	≤ 2	> 4	■	■	■	■	■						
	≤ 2	> 8								■			
Vancomycin	≤ 4	> 4								■	■		
Voriconazole	≤ 0.25	> 0.25											■

*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.

ISSN 1502-2307

LUNDBLADMEDIA AS, TROMSØ, TLF 77 75 32 50 Design, forside: Ida Skaar