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Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

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The NORM and NORM-VET programmes are part of the
Norwegian Government's Action Plan against Antimicrobial Resistance 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 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 usage and resistance in human and veterinary medicine, as well as 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 and Italy. 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.

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 sixth annual joint report from NORM and NORM-VET, presents data for 2005. 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.

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Tromsø / Oslo, September 2006

II. SAMMENDRAG

Dette er den sjette felles rapporten fra Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM) og Norsk overvåkingsprogram for antibiotikaresistens hos fôr, dyr og næringsmidler (NORM-VET). Rapporten presenterer data over forekomst av antibiotikaresistens og forbruk av antibiotika til mennesker og dyr i 2005. Data fra relevante prosjekter som ikke er en del av de kontinuerlige overvåkingsprogrammene er også presentert. Både NORM og NORM-VET programmene er en del av regjeringens tiltaksplan mot antibiotikaresistens som ble offentliggjort i 2000. NORM koordineres av Mikrobiologisk avdeling, Universitetssykehuset i Tromsø og NORM-VET koordineres av Zoonosesenteret ved Veterinærinstituttet, Oslo. De to 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 antibiotika til terapeutisk bruk på landdyr i 2005 var 6 034 kg. Fra 1995 til 2001 ble salget av veterinære antibiotika til landdyr redusert med 40%. Etter dette har forbruket holdt seg konstant på noenlunde samme nivå. Forbruksmønsteret har i denne perioden utviklet seg mer og mer i gunstig retning, det vil si at andelen penicillinbruk har økt. Penicilliner utgjorde 43% av salget av veterinære antibiotika til landdyr i 2005, og av dette var 89% beta-laktamase følsomme penicilliner. Forbruket av tetracykliner utgjorde kun 4%. 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 samt kampanjer for riktig bruk av antibiotika.

Totalsalget av veterinære antibiotika til terapeutisk bruk til oppdrettsfisk i Norge var i 2005 på 1 215 kg aktiv substans, hvorav 32% ble brukt til laks og regnbueørret og 68% til andre (nyere) fiskearter. Kinoloner utgjorde 83% av salget i 2005. Forbruket av antibiotika i oppdrettsnæringen har blitt redusert med 98% siden 1987. Denne betydelige reduksjonen kan tilskrives innføringen av effektive vaksiner til laks og ørret samt sykdomsforebyggende tiltak, herunder bedrede miljøforhold.

Avoparcin ble brukt som antibakteriell vekstfremmer i norsk broiler- og kalkunproduksjon fra 1986 inntil det ble forbudt i 1995. Samme år innførte husdyrnæringene et selvpålagt forbud mot bruk av alle antibakterielle vekstfremmere. Koksidiostatika som fôrtilsetningsstoff brukes fremdeles i norsk fjørfeproduksjon. Salgstallene, i kg aktiv substans, er noe høyere enn før 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, som nå utgjør hovedparten av forbruket av de ionofore koksidiostatika.

Forbruk av antibiotika hos mennesker

Totalsalget av antibiotika til systemisk bruk hos mennesker var i 2005 18,2 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. Salget av penicilliner er stabilt, salget av makrolider og kinoloner øker, mens salget av sulfonamider og trimetoprim er synkende.

I 2005 utgjorde penicilliner 41% av det totale antibiotikaforbruket i Norge. Det har skjedd en forskyvning mot bredspektrede penicilliner, men samtidig var forbruket av penicillinase følsomme penicilliner høyere i 2005 enn i de foregående år. Tetracykliner utgjorde 17% av totalforbruket. Salget av denne medikamentgruppen har sunket gradvis siden 1993, men økte igjen med 5% i 2005. Makrolider, linkosamider og streptograminer utgjorde 12% av totalforbruket i 2005. Forbruket var forholdsvis stabilt gjennom 1990-tallet, men har økt siden 2000 og nådde en foreløpig topp i 2005. Erytromycin utgjorde 55% av salget i denne gruppen. Salget av kefalosporiner, monobaktamer og karbapenemer har økt over de siste år men er fortsatt på et relativt lavt nivå. Etter ytterligere økning utgjorde denne medikamentgruppen 3,1% av totalsalget i 2005. Kinoloner utgjorde kun 3% av totalforbruket, men salget har økt med 73% siden 1999. Det urinveisantiseptiske middelet metenamin utgjorde 14% av totalforbruket, og salget har økt med 36% siden 1999.

Bruken av antibakterielle midler varierer mellom de ulike fylkene, og fordelingen av områder med høyt og lavt forbruk er stabil over tid. Salget av antibakterielle midler til sykehus og almenpraksis utgjorde henholdsvis 7% og 93%. Penicilliner sto for 48% av salget i sykehus og 42% i almenpraksis. Andre viktige medikamentgrupper utenfor sykehus var tetracykliner (18%) og makrolider/linkosamider (12%). På sykehus var kefalosporiner (19%), metronidazol (7%) og kinoloner (7%) mest brukt etter penicilliner.

Resistens hos kliniske isolater fra dyr

De kliniske isolatene inkludert i 2005 var fra diagnostiske prøver fra mastitt hos storfe og sau.

Forekomsten av resistens blant *S. aureus* har vært på omtrent samme nivå siden monitoreringen startet i 2001. Sammenlignet med tidligere publiseringer har resistens forekomsten blant *S. aureus* fra mastitt hos storfe og sau vært på samme nivå siden 1990-tallet.

Beta-laktamaseproduksjon ble observert i hhv. 7,3% og 2% av *S. aureus* isolatene fra storfe og sau. Resistens blant koagulase-negative stafylokokker (KNS) var betydelig mer utbredt enn blant *S. aureus*. Kun 32,7% av KNS isolatene var følsomme for alle antibiotika som inngikk. Beta-laktamaseproduksjon ble observert hos 36,4% av KNS isolatene.

Resistens hos indikatorbakterier

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 2005 ble indikatorbakterier fra storfe (feces og kjøtt) og sau (feces) inkludert.

Forekomsten av resistens blant *E. coli* og *Enterococcus* spp. i 2005 var i et internasjonalt perspektiv relativt lavt. Henholdsvis 92,3% og 69,1% av isolatene var følsomme

for alle antibiotika som var inkludert. Kinolonresistens ble ikke observert. Bruken av fluorokinoloner til matproduserende dyr i Norge er meget begrenset. Resistens mot ceftiofur eller gentamicin ble heller ikke observert.
Forekomsten av resistens mot ulike antibiotika blant *E. coli* hos storfe fra 2001 til 2005 indikerer en relativt stabil og lav resistensforekomst. Streptomycinresistens er redusert signifikant (p <0,05%). Forekomsten av resistens blant *Enterococcus* spp. isolert fra storfe kjøtt var moderat og *E. faecalis* og *E. faecium* hadde noenlunde samme resistensmønster.

Resistens hos zoonosebakterier og andre enteropatogene bakterier

Salmonella spp., med unntak av *S. enterica* subsp. *diarizonae* fra sau, påvises sjelden hos matproduserende dyr i Norge. Kun tre tilfeller av *S*. Typhimurium-infeksjon (to storfe og et svin), ett isolat av *S*. Senftenberg og ett isolat av S. Montevideo ble påvist i det nasjonale overvåkingsprogrammet i 2005. De andre *Salmonella*-isolatene som ble resistenstestet (n=39) var fra diagnostiske innsendelser fra sau, fjørfe, kjæledyr, ville fugler og reptiler. Kun ett av alle isolatene (fra en hund) var multiresistent (*Salmonella* Typhimurium DT104). Bortsett fra ett isolat (*S*. Pullorum fra fjørfe), som var resistent mot sulfonamider, var alle øvrige isolater følsomme mot alle inkluderte antibiotika.
Resultatene indikerer at resistens ikke er særlig utbredt blant *Salmonella* som av og til blir isolert fra norske dyr.

Av de humane salmonellose-tilfellene som ble rapportert i 2005, var 78,2% oppgitt å ha blitt smittet i utlandet. Andelen *S.* Typhimurium isolater som var følsomme for alle antibiotika, var høyere for kategorien "smittet i Norge" (49,5%) enn for kategorien "smittet i utlandet" (33,3%). Sammenlignet med 2004 var denne forskjellen mindre, hvilket sannsynligvis er forårsaket av en høyere andel av infeksjoner av DT104 blant de innenlandsmittede i 2005. Multiresistens (resistens mot mer enn to antibiotika) ble hyppigere påvist i de utenlandsmittede (40,5%) enn de innenlandssmittede (33,6%), men også her mindre forskjell sammenlignet med tidligere år.
Forekomsten av resistens i 2001-2005 mot ulike antibiotika blant *S.* Typhimurium fra både innenlands og utenlandsmittede pasienter indikerer att det kan være en økende forekomst av resistens mot tetracykliner og ampicillin.
Andelen resistente *S*. Enteritidis isolater mot de ulike antibiotika som inngikk var med unntak av nalidiksinsyre betydelig lavere enn for *S*. Typhimurium. Totalt var 24,6% av *S.* Enteritidis isolatene resistente mot nalidiksinsyre. Forekomsten av resistens blant *S.* Enteritidis i 2005 var på samme nivå som i tidligere NORM/NORM-VET rapporter.
Resultatene fra 2005 viser at forekomsten av resistens hos *Campylobacter jejuni* fra norske broilere fremdeles er lav og stabil. Totalt 91,4% av isolatene var følsomme for alle inkluderte antibiotika. Totalt var 6,7% resistente mot kun ett antibiotikum, ampicillin, og 1,9% mot både nalidiksinsyre og enrofloxacin.
Nivået av resistens og resistensmønstrene for *C. jejuni* fra norske broilere samsvarer med *C. jejuni* fra mennesker smittet i Norge med unntak av en høyere forekomst av kinolonresistens blant humanisolatene. Dette forholdet ble også påvist i tidligere rapporter. Resistens var betydelig mer utbredt blant *C. jejuni* fra pasienter smittet i utlandet (89% resistente mot minst ett antibiotikum) enn pasienter smittet i Norge (29%). Fluorokinolonresistens var mer vanlig blant isolater fra pasienter smittet utenlands enn fra innenlands smittede; 61,6% mot 6,0%. Forekomsten av resistens hos *C. jejuni* fra pasienter smittede i Norge såvel som utenlandssmittede var stabilt for perioden 2001-2005.
De aller fleste *Shigella*-isolatene var fra pasienter smittet utenlands. I likhet med hva som rapporteres fra andre land, var resistens utbredt.

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistens i kliniske isolater fra mennesker i Norge var fortsatt meget lav i 2005. Det ble ikke påvist ett eneste isolat av meticillinresistente *Staphylococcus aureus* (MRSA) blant de 741 stammene som ble formelt inkludert i NORM-protokollen, og kun 3 av 1193 (0,25%) av *S. aureus* isolatene i laboratorienes datasystemer ble rapportert som MRSA. Det norske Meldesystemet for infeksjonssykdommer (MSIS) registrerte 257 tilfeller av MRSA-infeksjon i 2005 hvilket er en økning fra 219 i 2004, men det store flertall av disse tilfellene var pasienter behandlet i almenpraksis med mindre alvorlige infeksjoner. Dette indikerer at økt testing av pasienter utenfor sykehus delvis kan forklare økningen i MRSA-insidens. I MSIS-tallene for 2005 har man imidlertid også registrert 201 tilfeller av kolonisering med MRSA, og totalantallet på 458 MRSA-meldinger viser klart ved vedvarende risikoen for MRSA-spredning i Norge.
Blodkulturisolater av *E. coli* og *Klebsiella* spp. var som tidligere generelt følsomme for bredspektrede antibiotika. Det ble imidlertid påvist fortsatt økning av nedsatt gentamicinfølsomhet fra 0,7% (2003) til 1,6% (2004) og nå videre til 2,5% (2005). Forekomsten av nedsatt følsomhet for fluorokinoloner økte tilsvarende fra 3,3% i 2004 til 5,0% i 2005. Forekomsten av resistens mot aminoglykosider og fluorokinoloner var lavere blant *Klebsiella* spp. isolater enn hos *E. coli*. Produksjon av bredspektrede beta-laktamaser (ESBL) er blitt et utbredt problem i mange land, og enkelttilfeller er også blitt rapportert fra Norge. Kun 5/993 (0,5%) av *E. coli* og 2/359 (0,6%) av *Klebsiell*a spp. fremviste denne fenotypen.
Det ble ikke påvist klinisk signifikant vankomycin-resistens i enterokokker i 2005. Forekomsten av nedsatt følsomhet for ampicillin i *Enterococcus faecium* økte fra 74,5% til 82,5%, og høygradig gentamicin-resistens ble påvist i 24,3% av *E. faecalis* og 36,8% av *E. faecium*. Alle isolater av *E. faecium* med høyradig gentamicin-resistens hadde samtidig nedsatt følsomhet for ampicillin, men alle var følsomme for det nye oxazolidinonet linezolid.
Streptococcus pneumoniae fra blodkulturer var generelt følsomme for alle relevante antibiotika. Femten av 704 isolater (2,1%) hadde nedsatt følsomhet for penicillin G, og tre av disse isolatene hadde også nedsatt følsomhet for cefotaxim. Forekomsten av makrolidresistens fortsatte å øke fra 9,7% i 2004 til 10,8% i 2005. Forekomsten av nedsatt antibiotikafølsomhet i luftveisisolater av *S. pneumoniae* økte for penicillin G (3,4%), erytromycin (6,6%) og trimetorpim-sulfa (6,4%).
Pseudomonas aeruginosa blodkulturisolater fra 2002 og 2003 ble inkludert i NORM 2005, og de fleste isolatene var følsomme for tradisjonelle "pseudomonas-midler" så som ceftazidim, piperacillin/tazobactam og tobramycin.

Det ble imidlertid påvist et betydelig antall isolater med nedsatt følsomhet for eller resistens mot ciprofloxacin og meropenem. Dette kan være en følge av den økende bruken av disse midlene.

Totalt 25,6% av alle *Neisseria gonorrhoeae* isolater fra 2003 produserte beta-laktamase. Videre hadde 40,1% av isolatene nedsatt følsomhet for ciprofloxacin , og 18,6% hadde kombinert beta-laktamaseproduksjon og nedsatt ciprofloxacin-følsomhet. *N. gonorrhoeae* av serogruppe 1 var signifikant mer resistent enn serogruoppe 2/3.

Forekomsten av resistens i *E. coli* fra urin var i det vesentlige uendret fra tidligere år. Det ble kun påvist 5/1127 (0,4%) ESBL-positive isolater. Forekomsten av ciprofloxacinresistens var høyere blant sykehuspasienter enn blant pasienter utenfor sykehus, og isolater fra kvinner var noe mindre følsomme for trimetoprim (19,5%) enn isolater fra menn (17,9%). *Enterobacter* spp. fra urin var generelt mer følsomme enn *E. coli* for alle antibiotikagrupper bortsett fra beta-laktamer.

I alt 290 tilfeller av tuberkulose ble meldt til MSIS i 2005. Det ble utført resistensundersøkelse av 206 *Mycobacterium tuberculosis* isolater fra 274 pasienter. Kun tre isolater fra Afrika (2) og Asia (1) ble klassifisert som multiresistente. Det ble også gjort resistens-undersøkelse av åtte isolater fra pasienter som tidligere var blitt behandlet for tuberkulose. Ett isolat fra en afrikansk pasient var resistent mot pyrazinamid.

Det ble utført resistensbestemmelse av 145 blodkulturisolater av *Candida albicans* (103), *C. glabrata* (32) og *C. tropicals* (10). Alle *C. albicans* og *C. tropicalis* isolater var følsomme for azolene mens flertallet av *C. glabrata* hadde redusert følsomhet for fluconazol. Kun et enkelt *C. tropicalis* isolat hadde nedsatt følsomhet for amfotericin B og alle isolatene var følsomme for caspofungin. Resultatene er i overensstemmelse med tidligere studier fra Norge.

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 sixth 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 2005. The NORM and NORM-VET programmes are a 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 2005, the total sales of antimicrobial drugs approved for therapeutic use in animals (excluding fish) in Norway were 6,034 kg. The annual usage of veterinary antimicrobial drugs decreased gradually by 40% from 1995 to 2001, and has thereafter remained 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 25% in 1995 to 43% in 2005. Altogether, 89% of the veterinary penicillin preparations sold in 2005 were beta-lactamase sensitive penicillins. The sales of sulfonamides decreased from 14% in 1995 to 0.4% in 2005. The proportion accounted for by tetracyclines declined from 5% to 4% during the same period. The reduced antimicrobial use as well as the favourable prescribing patterns is 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 2005, the total sale of antimicrobial drugs for therapeutic use in farmed fish was 1,215 kg of active substance. Quinolones accounted for 83% 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 as well as improved health management. In 2000, 98% of the prescribed amounts of antimicrobial agents were for Atlantic salmon and rainbow trout and 2% for other (new) fish species. These figures were 32% and 68% in 2005, respectively. The increased usage in "new" fish species is correlating reasonably well to the increased production of such species.

In 2005, the total sales of coccidiostatic feed additives, in kilograms of active substance, were slightly higher than before the use of antimicrobial growth promoters was abandoned 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 is now dominated by narasin.

Usage of antimicrobial agents in humans

In 2005, the overall sales of antibacterials for systemic use in humans were 18.2 DDD/1,000 inhabitants/day. Total sales of antibacterials have remained relatively unchanged for many years. However, usage trends within subgroups have changed over the years with the penicillin group relatively stable, the macrolides and quinolones steadily increasing, and the sulfonamides and trimethoprim decreasing.

Penicillins represented 41% of total antimicrobial sales in 2005. There has been a shift towards more extended-spectrum compounds, but the use of beta-lactamase sensitive penicillins was higher in 2005 than in earlier years. Tetracyclines represented 17% of total use. The sales have gradually decreased since 1993, but a small increase of 5% was registered in 2005. Macrolides, lincosamides and streptogramins represented 12% of total use in 2005. The sales were fairly stable throughout the nineties, but an increase has been registered since 2000 with the highest use ever seen in 2005. Erythromycin accounts for 55% of total sales within this group. Sales of cephalosporins, monobactams and carbapenems, although limited, have been increasing over the last years. However, a slight decrease was noted in 2005 and the group presently represents 3.1% of the total sales of antibacterials. Quinolones use has been steadily increasing. Although it accounts for only a minor fraction (3%) of total antibacterial sales, this is still a 73% increase since 1999. Finally, the urinary prophylactic agent methenamine represents 14% of total antibacterial use and the sales have increased by 36% since 1999.

The usage of antibacterials varies between counties, and the pattern has been stable with the same high- and low-use counties. Antibacterial sales to hospitals and ambulatory care represented 7% and 93% of total sales, respectively. Penicillins accounted for around 48% in hospitals and 42% in ambulatory care. The other important groups in ambulatory care were tetracyclins (18%) and macrolides/lincosamides (12%) whereas cephalosporins (19%) metronidazole (7%) and quinolones (7%) were most widely used in hospitals after penicillins.

Resistance in animal clinical isolates

The clinical isolates included in 2005 were from diagnostic samples from mastitis in cattle and sheep. The occurrence of resistance among *Staphylococcus aureus* isolates has remained at approximately the same low level from 2001 to 2005. This corresponds well with the level of resistance in *S. aureus* from mastitis in cattle and sheep identified during the 1990s. In 2005, beta-lactamase production was observed in 7.3% and 2% of the *S. aureus* isolates from cattle and sheep, respectively. Resistance in coagulase negative staphylococci (CoNS) from mastitis in cattle was considerably more abundant than in isolates of *S. aureus*. Only 32.7% of CoNS isolates were susceptible to all antimicrobial agents included. Beta-lactamase production was observed in 36.4% of CoNS isolates.

Resistance in indicator bacteria

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 2005, *Escherichia coli* and *Enterococcus* spp. from cattle (faeces and meat) and sheep (faeces) were included as indicator bacteria. The occurrences of resistances were in an international perspective relatively low. In total, 92.3% and 69.1% of the isolates, respectively, were susceptible to all antimicrobial agents included. No quinolone resistance was observed. The usage of fluoroquinolones in food producing animals in Norway is very limited. No resistance to ceftiofur or gentamicin was observed. The prevalence of resistance to various antimicrobials in *E. coli* from cattle in 2001-2005 indicates that the occurrence of resistance has remained stable and low, except resistance to streptomycin, which has declined significantly ($p<0.05\%$). The occurrence of resistance among *Enterococcus* spp. isolated from bovine meat was moderate. The resistance patterns in *E. faecalis* and *E. faecium* were similar.

Resistance in zoonotic and non-zoonotic enteropathogenic bacteria

Salmonella spp., apart from *S*. *enterica* subsp. *diarizonae* in sheep, is rarely isolated from food producing animals in Norway. Only three isolates of *S.* Typhimurium, two from cattle and one from swine, one isolate of *S*. Senftenberg from poultry and one isolate of *S.* Montevideo from poultry were detected in the national surveillance programme. The other *Salmonella* isolates (n=39) were from the surveillance programme or from diagnostic submission from sheep, poultry, pets, wild birds and reptiles. Only one of the isolates, from a dog, was multiresistant (*Salmonella* Typhimurium DT104). All the other isolates except from one isolate, *S.* Pullorum from poultry, which was resistant to sulphonamides, were susceptible to all antimicrobial agents included.

The data, although very limited, indicate that antimicrobial resistance is not very widespread among those *Salmonella* that sometimes are isolated from Norwegian animals.

In 2005, 78.2% 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" (49.5%) than for the "infected abroad" category (33.3%). Compared to 2004, this difference was smaller, which most probably is a result of more infections with DT104 among the domestically acquired infections in 2005. Multiresistance (resistance to more than two antimicrobial agents) was slightly more common in the category "infected abroad" (40.5%) as compared to the category "infected in Norway" (33.6%), but less so than observed in earlier years. The prevalence of resistance in 2001-2005 to various antimicrobials in *S.* Typhimurium indicates that the occurrence of resistance to tetracycline and ampicillin might be increasing.

The proportion of *S.* Enteritidis isolates resistant to the different antimicrobial agents included, except for nalidixid acid, was considerably lower than for *S.* Typhimurium. In total, 24.6% of the isolates of *S.* Enteritidis were resistant to nalidixid acid. The resistance frequencies observed for *S.* Enteritidis in 2005 are quite similar to those reported in previous NORM/NORM-VET reports.

The results obtained in 2005 show that the prevalence of resistance in *Campylobacter jejuni* from Norwegian broilers is still low and stable. A total of 91.4% of the isolates were susceptible to all antimicrobials included. Altogether 6.7% were resistant to one antimicrobial agent (ampicillin) and 1.9% to both nalidixid acid and enrofloxacin. The level 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 within Norway, except for a higher prevalence of resistance to quinolones among the human isolates. This relationship was also observed in previous reports. Resistance was significantly more widespread in the *C. jejuni* isolates derived from patients infected abroad (89% resistant to at least one antimicrobial) than patients infected in Norway (29%). Fluoroquinolone resistance was more common in isolates from infections acquired abroad than from domestic cases; 61.6% versus 6.0%. The occurrence of resistance in *C. jejuni* from both humans infected in Norway and those infected abroad in 2001-2005 has remained at a stable level.

The vast majority of the *Shigella* isolates tested originated from patients infected abroad. As is the case in reports from other countries, resistance was widespread.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still very low in Norway in 2005. Not a single methicillin resistant *Staphylococcus aureus* (MRSA) strain was detected among 741 isolates formally included in the NORM protocol, and only 3 out of 1,193 (0.25%) *S. aureus* isolates were reported as MRSA from the laboratories´ information systems. The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 257 cases of MRSA infections in 2005 which is an increase from 219 cases in 2004, but the vast majority of these cases were non-hospitalised patients with minor infections. This indicates that increased testing of patients outside hospitals may partly explain the increase in overall MRSA incidence. However, the 2005 MSIS data also include 201 cases of MRSA colonization giving a total of 458 MRSA notifications thus demonstrating the continuing threat of MRSA dissemination in Norway.

E. coli and *Klebsiella* spp. blood culture isolates were generally susceptible to broad-spectrum antimicrobials. However, the slow increase in gentamicin non-susceptibility in *E. coli* noted from 2003 (0.7%) to 2004 (1.6%) continued in 2005 (2.5%). Similarly, non-suscpetibility to fluoroquinolones in *E. coli* continued to increase from 3.3% in 2004 to 5.0% in 2005. 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. Only 5/993 (0.5%) *E. coli* and 2/359 (0.6%) *Klebsiella* spp. displayed this phenotype.

Clinically significant vancomcyin resistance was not detected in enterococci in 2005. The prevalence of non-susceptibility to ampicillin in *E. faecium* increased from 74.5% to 82.5% and high-level gentamicin resistance

(HLGR) reached 24.3% in *E. faecalis* and 36.8% in *E. faecium*. All HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin but suscpetible to the novel oxazolidinone linezolid.

Streptococcus pneumoniae from blood cultures were generally susceptible to all relevant antimicrobials. Fifteen of 704 isolates (2.1%) displayed reduced susceptibility to penicillin G, and three isolates were also non-susceptible to cefotaxime. Macrolide resistance continued to increase from 9.7% in 2004 to 10.8% in 2005. The prevalences of non-susceptibility in respiratory tract isolates increased for penicillin G (3.4%), erythromycin (6.6%) and trimethoprim/sulfamethoxazole (6.4%).

Pseudomonas aeruginosa blood culture isolates recovered in 2002 and 2003 were included in NORM 2005, and most isolates were susceptible to commonly used "antipseudomonal" antimicrobials such as ceftazidime, piperacillin/tazobactam and tobramycin. However, a significant number of isolates were intermediately susceptible or resistant to ciprofloxacin and meropenem which may reflect increasing usage of these agent.

A total of 25.6% of all *Neisseria gonorrhoeae* isolates recovered in 2003 were beta-lactamase positive. Furthermore, 40.1% were ciprofloxacin non-susceptible, and 18.6% displayed combined ciprofloxacin resistance and beta-lactamase production. Serogroup 1 isolates were significantly more resistant than serogroup 2/3 strains.

The results for *E. coli* isolates from the urinary tract remained essentially unchanged from previous years. Only 5/1,127 (0.4%) ESBL positive isolates were identified. The prevalence of ciprofloxacin resistance was higher in hospital patients than in outpatients, and non-suscpetibility to trimethoprim was slightly more common among isolates from women (19.5%) than in isolates from men (17.9%). *Enterobacter* spp. urinary tract isolates were generally more susceptible than *E. coli* to non beta-lactam antimicrobials.

A total of 290 cases of tuberculosis were reported to MSIS in 2005. Susceptibility tests were performed on 206 *Mycobacterium tuberculosis* primary isolates from 274 patients. Only three isolates were classified as multidrug resistant originating in Africa (2) and Asia (1). Susceptibility tests were also performed on *Mycobacterium tuberculosis* isolates from eight previously treated patients. One isolate from an African patient was monoresistant to pyrazinamid.

Susceptibility testing was performed on 145 blood culture isolates of *Candida albicans* (103), *C. glabrata* (32) and *C. tropicals* (10). All *C. albicans* and *C. tropicalis* isolates were susceptible to azoles, whereas the majority of *C. glabrata* isolates displayed reduced susceptibility to fluconazole. Only one *C. tropicalis* strain had reduced susceptibility to amphotericin B and all isolates were susceptible to caspofungin. The results are in accordance with previous studies from Norway.

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 use of antimicrobial agents in Norway increases or if 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.

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 1, 2006.
(Data provided by Statistics Norway).

Age group	All	Males	Females
0 to 4 years	287,383	146,674	140,709
5 to 14 years	619,428	318,110	301,318
15 to 24 years	574,183	293,022	281,161
25 to 44 years	1 315,615	667,308	648,307
45 to 64 years	1 161,141	588,089	573,052
65 years and older	682,469	288,778	393,691
All age groups	4 640,219	2 301,981	2 338,238

TABLE 2. Livestock population in Norway and the number of slaughtered animals in 2005.

Animal category	Herds*	Number of Animals*	Slaughtered animals*
Cattle	21,500[1]	930,100[1]	331,800[2]
Dairy cow**	14,700[1]	242,300[1]	-
Suckling cow**	3,900[1]	46,900[1]	-
Combined production (cow)**	1,200[1]	30,700[1]	-
Goat	1,300[1]	72,700[1]	19,200[2]
Dairy goat**	550[1]	44,400[1]	-
Sheep	16,700[1]	2,393,200[1]	1,248,600[2]
Breeding sheep > 1 year**	16,500[1]	927,400[1]	-
Swine	3,300[1]	802,800[1]	1,473,700[2]
Breeding animal > 6 months**	2,000[1]	61,400[1]	-
Fattening pigs for slaughter	2,900[1]	432,500[1]	-
Poultry			-
Egg laying hen (> 20 weeks of age)	2,400[1]	3,318,500[1]	2,195,700[2]
Flocks > 250 birds**	820[1]	3,285,500[1]	-
Broiler	500[2]	-	44,327,600[2]
Turkey, ducks and geese for slaughter	170[1]	328,200[1]	1,040,300[2]
Flocks > 25 birds**	81[1]	327,500	-
Ostrich	12[1]	120[1]	-

Data from: [1)] Register of Production Subsidies as of July 31, 2005; [2)] Register of Slaughtered Animals.
* Numbers > 100 rounded to the nearest ten, numbers > 1000 rounded to the nearest hundred.
** Included in above total.

TABLE 3. Animals (excluding fish) imported to Norway in 2005. *(Data provided by KOORIMP).*

Animal species	Live animals* Individuals	Live animals* Consignments	Semen Doses	Embryos
Cattle			39,265	63
Swine			394	
Goat	53	2		
Sheep	39	2	750	
Reindeer live animals for slaughter	2	1		
Fur animals	4,631	38		
Poultry – day old chicks	133,155	18		
Turkey – day old chicks	8,757	4		
Ducks and geese	1,505	3		

TABLE 4. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2005. *Data provided by The 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	157	498	451	662	67.1	40.6
2000	440,861	48,778	169	129	548	851	37.6	7.6
2001	436,103	71,764	864	318	377	920	22.3	2.5
2002	462,495	83,560	1,258	319	424	2,557	5.0	1.7
2003	509,544	68,931	2,185	272	426	1,829	1.2	1.6
2004	563,815	63,401	3,165	350	649	3,747	45.5	3.3
2005	582,043	58,781	7,410	350	1,173	4,311	3.3	1.2

[1] From the wild population

V. USAGE OF ANTIMICROBIAL AGENTS

A. 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 (see Appendix 1), of veterinary antimicrobial agents for therapeutic use 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. Such drugs are primarily used in small animal practices.

Table 5 summarizes the sales (in kg of active substance) in 2005 of veterinary antimicrobials agents for therapeutic use in domestic animals in Norway. The data are organized according to the main therapeutic substance groups (ATCvet groups) and show the total usage for the various routes of administration. The total sale of veterinary antimicrobial agents is given in Figure 1. Figure 2 illustrates the proportion of the total sale of the various groups of antimicrobial substances. Both figures present annual sales data for the period 1995–2005. In 2005, the sales of veterinary antimicrobial agents approved for therapeutic use in animals in Norway amounted to 6,034 kg of active substance (Table 5). The annual usage of veterinary antimicrobial agents decreased gradually by 40% from 1995 to 2001. Since then, the annual usage has remained on a relatively constant level.

TABLE 5. Sales in 2005, 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 2005 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.

Groups of substances	ATCvet code	Active substance or combinations of substances	Gastro-intestinal (QA07)	Uterine (QG01)	Systemic indiv. (QJ01)	Systemic herds (QJ01)	Intra-mammary (QJ51)
Tetracyclines	QG01AA07	Oxytetracycline		3			
	QJ01AA02	Doxycycline			< 0.1		
	QJ01AA06	Oxytetracycline			109	114	
Beta-lactams	QJ01CA04	Amoxicillin			121	135	
	QJ01CE09/QJ51CE09	Benzylpenicillinprocain[1,2]			2,091		4
	QJ01CE90	Penethamate hydroiodide[1]			4		
	QJ01CR02/QJ51RV01	Amoxicillin+clavulanic acid			235		8
Sulfonamides	QJ01EQ06	Sulfanilamid[3]			22		
Sulfonamides and	QJ01EQ10	Sulfadiazine+trimethoprim[4]			1,194		
trimethoprim[3]	QJ01EQ13	Sulfadoxine+trimethoprim			101		
Lincosamides	QJ01FF01	Clindamycin			14		
	QJ01FF02	Lincomycin			4		
Aminoglycosides	QA07AA01	Neomycin	24				
	QA07AA90	Dihydrostreptomycin (DHS)	132				
Quinolones	QJ01MA90	Enrofloxacin			29		
	QJ01MA96	Ibafloxacin			1		
Others	QJ01XX92	Tiamulin			12	128	
Combinations	QG01AE99	Sulfadimidine+procaine penicillin[1]+DHS		203			
	QJ01RA01/QJ51RC23	Benzylpenicillinprocain[1] +DHS			553		774
	QJ51RC25	Penethamate hydroiodide[1] + DHS					19
Total per route of administration			**156**	**206**	**4,490**	**377**	**805**
Total (kg)							**6,034**

[1]Calculated as benzylpenicillin; [2]Includes one preparation used on exemption from market authorization; [3]Represents an *extemporaneously* prepared preparation; [4]Includes small amounts of baquiloprim.

The proportion accounted for by pure penicillin preparations rose from 25% in 1995 to 43% in 2005. Altogether 89% of the veterinary penicillin preparations sold in 2005 were beta-lactamase sensitive penicillins. From 1995 to 2002, the sale of sulfonamides in combination with trimethoprim or baquiloprim increased from 11% to 24% of the total sales, while this figure decreased gradually to 22% from 2002 to 2005. The proportion of sale of the combination preparations of penicillins and aminoglycosides decreased from 35% to 22% from 1995 to 2005. The corresponding figure for sulfonamides were 14% in 1995 and 0.4% in 2005. The proportion accounted for by tetracyclines declined from 5% to 4% during the same period. The reduced use as well as the favourable prescribing patterns is mainly explained by a successful campaign on prudent use of antimicrobials conducted by the Norwegian husbandry organizations during the second part of the 1990s.

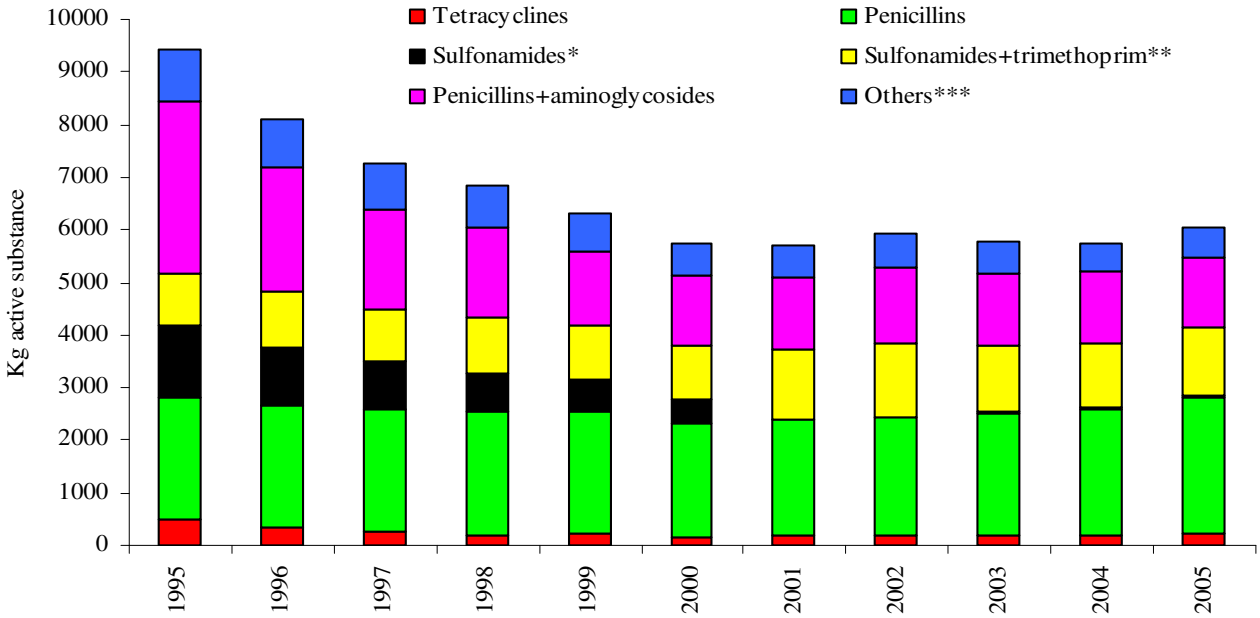

FIGURE 1. Sales (in kilograms of active substance) of veterinary antimicrobial agents (QA07AA, QG01AA, QG01AE, QJ01, QJ51) for therapeutic use in Norway 1995–2005, fish not included. Number of sold items in 2005 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies.
*Sulfonamides not sold in 2001-2003; **Includes small amounts of baquiloprim. ***Includes ATCvet codes: QAA7AA01; QA07AA90;QG01AE99; QJ01EQ06;QJ01FA01;QJ01FF01;QJ01FF02;QJO1MA90;QJ01XX92.

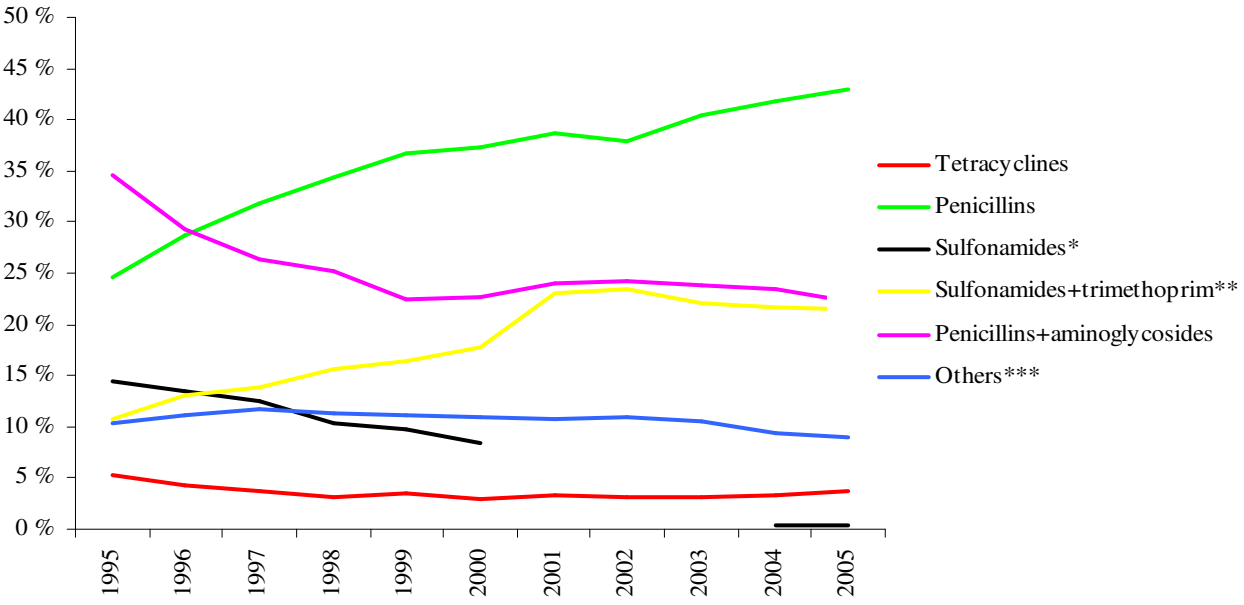

FIGURE 2. Sales (as percentage of total sales) of veterinary antimicrobial agents (QA07AA, QG01AA, QG01AE, QJ01, QJ51) in Norway 1995–2005, fish not included. Number of sold items in 2005 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies.
*Sulfonamides not sold in 2001-2003; **Includes small amounts of baquiloprim. ***Includes ATCvet codes: QAA7AA01; QA07AA90;QG01AE99; QJ01EQ06;QJ01FA01;QJ01FF01;QJ01FF02;QJO1MA90;QJ01XX92.

TABLE 6. Total sales (in kilograms of active substance) of veterinary antimicrobial agents for therapeutic use in farmed fish in Norway in the period 1995-2005. 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
Tetracyclines												
Oxytetracycline	QJ01AA06	70	27	42	55	25	15	12	11	45	9	8
Amphenicols												
Florfenicol	QJ01BA90	64	64	123	135	65	148	109	205	154	111	202
Quinolones												
Flumequine	QJ01MB07	182	105	74	53	7	52	7	5	60	4	28
Oxolinic acid	QJ01MB91	2,800	841	507	436	494	470	517	998	546	1,035	977
Total		**3,116**	**1,037**	**746**	**679**	**591**	**685**	**645**	**1,219**	**805**	**1,159**	**1,215**

In 2005, the sales of veterinary antimicrobial agents for use in farmed fish were 1,215 kg active substance of which 83% were quinolones. 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 (Table 6) and has thereafter remained relatively constant. In the same period, the total production of farmed fish increased more than ten 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 as well as to improved health management.

In 2000, 98% of the prescribed amounts of antimicrobial agents were for Atlantic salmon and rainbow trout and 2 % for other (new) fish species (Fig. 3). In 2005, the latter figures were 32% and 68%, respectively. The increased usage in "new" fish species is correlating reasonably well with the increased production of such species (Table 4).

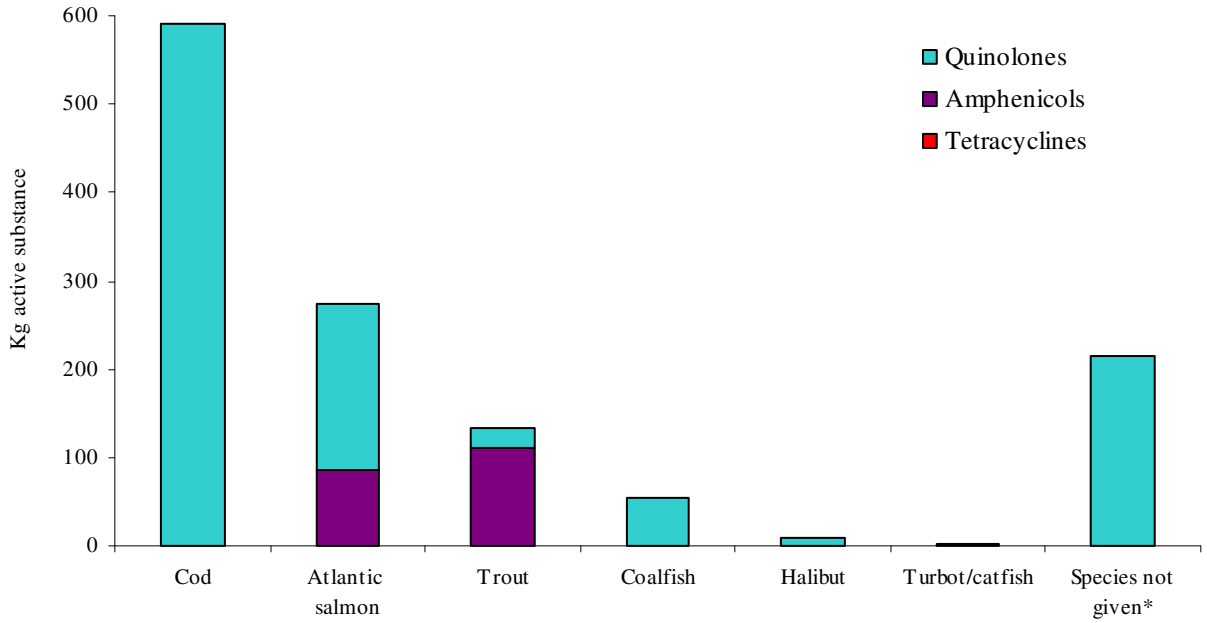

FIGURE 3. Prescribed amounts (in kilograms of active substance) of veterinary antimicrobial agents in Norwegian aquaculture in 2005 split into various fish species. Prescription data were obtained from the Norwegian Food Safety Authority (Reidun Agathe Medhus, data on file). Usage of tetracyclines is very limited and does thus not appear in the figure.
*Prescribed for use in fish farms cultivating Atlantic cod and/or coalfish (6 prescriptions) and salmon (1 prescription).

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 (2003-2005). Table 7 summarizes total sales of antimicrobial growth promoters and coccidiostat feed additives in Norway in the period 1995–2005.

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 (Table 7). 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 1998.

Coccidiostats as feed additives are still used in Norwegian poultry production. The total sales of coccidiostats, in kilograms of active substance, are slightly higher than before 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 is now 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 1995-2005. Data were obtained through annual reports from the Norwegian Agricultural Inspection Service (1996-2002) and the Norwegian Food Safety Authority (2003-2005) (http://www.mattilsynet.no/mattilsynet/multimedia/archive/00020/F_rstatistikk_2005_20296a.pdf, accessed March 22, 2006).

	Total sales in kg active substance										
Active substance	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Avoparcin[1]	419	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.
Zincbacitracin	129	64	27	0	0	0	0	0	0	0	0
Virginiamycin	0	0	0	0	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.	Prohib.
Total antimicrobial growth promoters	**548**	**64**	**27**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Lasalocid	996	480	471	193	208	80	96	514	108	173	37
Monensin	3,422	891	561	485	557	776	629	521	717	817	852
Salinomycin	214	27	0	0	27	233	12	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
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**
Amprolium/etopabat	156	116	582	174	201	135	159	74	42	0.8	0
Total other Coccidiostats	**156**	**116**	**582**	**174**	**201**	**135**	**159**	**74**	**42**	**0.8**	**0**

[1]Prohibited since May 31, 1995.

B. USAGE IN HUMANS

Hege Salvesen Blix

In 2005, the overall sales of antibacterials for systemic use in humans represented 18.2 DDD/1000 inhabitants/day. Total sales of antibacterials have remained relatively unchanged for many years. However, within subgroups of antibacterials, usage trends have changed over the years. The penicillin group is stable, the subgroups of macrolides and quinolones are steadily increasing, while the subgroup of sulfonamides and trimethoprim is decreasing (Table 8, Figure 4).

TABLE 8. Human usage of antibacterial agents in Norway 1999-2005 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change from 2004 to 2005. Collection of data on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	1999	2000	2001	2002	2003	2004	2005	Change (%) 2004-2005
J01A	Tetracyclines	3.19	3.17	3.11	3.13	3.03	2.97	3.11	+ 5
J01B	Amphenicols	0.005	0.004	0.003	0.002	0.002	0.001	0.001	
J01CA	Penicillins with extended spectrum	1.96	2.01	2.1	2.23	2.29	2.37	2.53	+ 7
J01CE	β-lactamase sensitive penicillins	5.01	4.66	4.68	4.48	4.38	4.23	4.55	+ 8
J01CF	β-lactamase resistant penicillins	0.32	0.35	0.41	0.50	0.59	0.63	0.56	- 11
J01CR	Combination of penicillins	0.01	0.01	0.01	0.01	0.01	0.01	0.01	
J01D	Cephalosporins, monobactams, carbapenems	0.47	0.52	0.55	0.58	0.62	0.61	0.57	- 7
J01E	Sulfonamides and trimethoprim	1.26	1.17	1.16	1.15	1.08	1.09	1.06	- 3
J01F	Macrolides, lincosamides and streptogramins	1.59	1.59	1.8	1.98	1.92	1.89	2.12	+ 12
J01G	Aminoglycosides	0.05	0.04	0.06	0.06	0.07	0.06	0.07	
J01M	Quinolones	0.33	0.35	0.40	0.44	0.48	0.52	0.57	+ 10
J01X	Other antibacterials	2.34	2.39	2.55	2.57	2.63	2.83	3.05	+ 8
	Total	**16.6**	**16.3**	**16.8**	**17.1**	**17.1**	**17.2**	**18.2**	**+ 6**

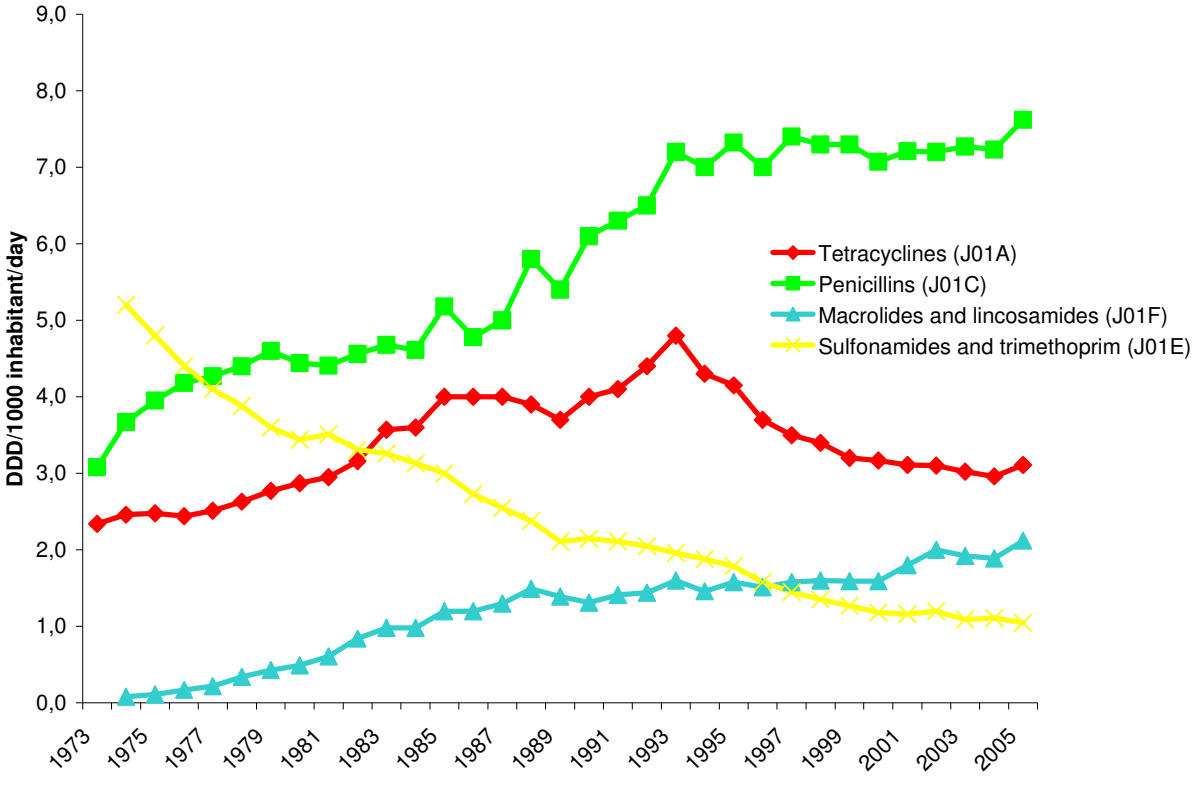

FIGURE 4. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F) and sulfonamides and trimethoprim (J01E) in Norway 1973-2005.

In 2005, the penicillins (ATC group J01C) represented 41% of the total antimicrobial use in Norway (Figure 5). The sales of penicillins have been stable over years. It has, however, looking at ATC 4th levels, been a shift towards more penicillins with extended spectre (Figure 6). In the latest years beta-lactamase sensitive penicillins (J01CE) have been decreasing, but the use in 2005 was higher than earlier years. The subgroup of beta-lactamase-resistant penicillins decreased in 2005.
The tetracyclines (J01A) represent 17% of total use. The sales have been decreasing since 1993, when the highest sale ever was registered; however, in 2005 a small increase of 5% was registered.
The macrolides, lincosamides and streptogramins (J01F) represented 12% of total use in 2005. The sales were fairly stable in the nineties. However, we have registered an increase since 2000. The highest use ever was registered in 2005. The internal pattern of group J01F has remained relatively unchanged over the years. Erythromycin is most frequently used, representing 55% of the subgroup (Figure 7).
In the last years, sales of cephalosporins, monobactams and carbapenems, although limited, have been increasing. However, in 2005 we saw a slight decrease. This group is now representing 3.1% 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 53% of ATC group J01D.
The use of quinolones has also been increasing. Still, it represents only a minor fraction (3%) of total antibacterial sales, but the increase has been 73% since 1999.
The increase of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, representing 14% of total antibacterial use. The sales have increased by 36% since 1999.

The usage of antibacterials varies between the 19 Norwegian counties, and the usage trends has been stable over the years, i.e. a trend of the same high-use and low-use counties (Figure 9)

The antibacterial sales in DDDs to hospitals represented, in 2005, seven percent of total sale in the country. The therapy pattern of antibacterials in hospitals differs to ambulatory care (Figure 10).
Penicillins (J01C) represent around 48% and 42% of the use in hospitals and in ambulatory care, respectively. The most important other groups in ambulatory care are tetracyclins, J01A (18%) and macrolides and lincosamides, J01F (12%). In hospitals cephalosporins, J01D (19%) is the most used group after the penicillins, followed by metronidazole - oral and parenteral (7%) and the quinolones, J01M (7%).

The use of antibacterials outside hospital represents 93% of the total human sale of antimicrobials. The use in nursing homes represents approximately 6%. Due to the amount of antibacterials used, therapy traditions in ambulatory care therefore have much greater impact on the total burden of antimicrobials and furthermore on the development of bacterial resistance. Also, changes towards more broadspectered antibacterials seem to be more distinct in ambulatory care. Hence, more focus should be given to surveillance of antimicrobial use and also to guidance of appropriate use of antibacterials in ambulatory care.

For overall use, the slow, but steady shift towards use of more "broadspectered" antibacterials in Norway is of concern and deserves close surveillance.

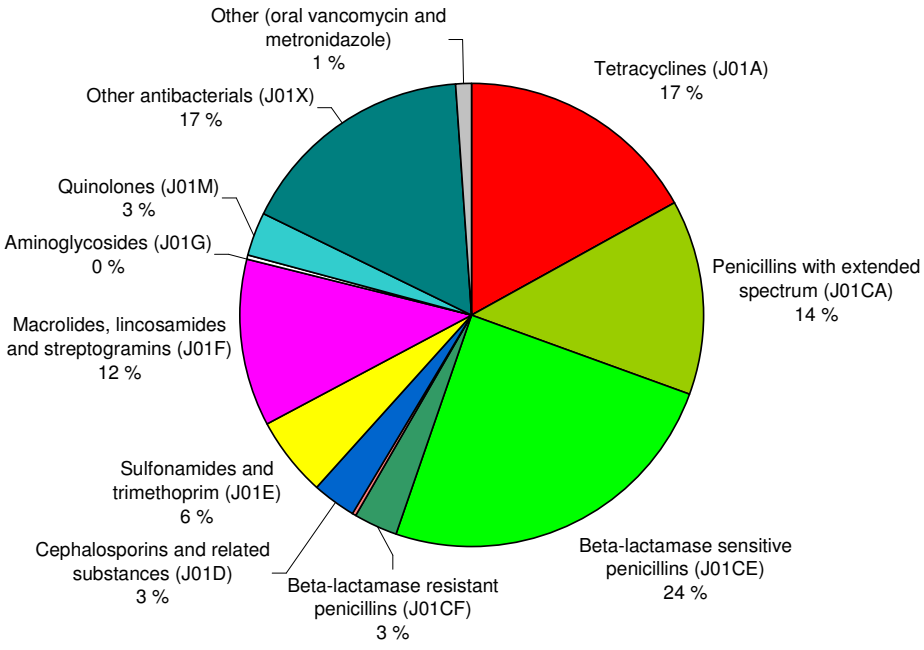

FIGURE 5. Relative amount of antimicrobial agents for systemic use in 2005 in Defined Daily Doses (DDD) (total sale in the country).

TABLE 9. Human usage of single antimicrobial agents for systemic use in Norway (ATC group J01) 1998-2005. Sales given in DDD/1,000 inhabitants/day. Collection of data on human consumption of antimicrobial agents is presented in Appendix 2.

ATC	Substance	1998	1999	2000	2001	2002	2003	2004	2005
A07AA09	Vancomycin	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
J01A A02	Doxycycline	2.34	2.20	2.10	2.1	2.03	1.93	1.80	1.89
J01A A04	Lymecycline	0.09	0.09	0.14	0.19	0.26	0.30	0.34	0.39
J01A A06	Oxytetracycline	0.27	0.25	0.24	0.22	0.21	0.19	0.20	0.20
J01A A07	Tetracycline	0.67	0.65	0.69	0.64	0.62	0.60	0.62	0.64
J01A A07	Minocycline								0.0003
J01B A01	Chloramphenicol	0.004	0.005	0.004	0.003	0.002	0.002	0.001	0.002
J01C A01	Ampicillin	0,09	0.09	0.09	0.08	0.09	0.1	0.1	0.1
J01C A02	Pivampicillin	0.15	0.14	0.13	0.11	0.11	0.09	0.08	0.07
J01C A04	Amoxicillin	0.85	0.87	0.83	0.89	0.94	0.95	0.94	1.06
J01C A08	Pivmecillinam	0.81	0.86	0.96	1	1.09	1.14	1.25	1.29
J01C A11	Mecillinam	0.003	0.004	0.004	0.005	0.005	0.005	0.005	0.006
J01C E01	Benzylpenicillin	0.21	0.23	0.21	0.23	0.24	0.25	0.24	0.26
J01C E02	Phenoxymethylpenicillin	4.91	4.78	4.45	4.45	4.24	4.13	3.99	4.29
J01CE08*	Benzathine benzylpenicillin	<0.0001	<0.0001	0.0001	<0.0001	0.0001	0.0001	0.0002	0.0001
J01C F01	Dicloxacillin	0.19	0.22	0.25	0.31	0.39	0.48	0.51	0.41
J01C F02	Cloxacillin	0.08	0.10	0.10	0.09	0.11	0.11	0.11	0.15
J01C F05*	Flucloxacillin					0.0001	0.0002	0.0002	0.0001
J01C R02	Amoxicillin and enzyme inhibitor	0.01	0.01	0.01	0.01	0.01	0.01	0.0003	0.00
J01C R05	Piperacillin and enzyme inhibitor			0.0001	0.0006	0.0014	0.0024	0.005	0.01
J01D B01	Cefalexin	0.22	0.22	0.26	0.27	0.29	0.3	0.29	0.24
J01D B03	Cefalotin	0.04	0.05	0.05	0.05	0.05	0.06	0.06	0.06
J01D B04	Cefazolin								0.002
J01D C01	Cefoxitin	0.0004	0.0004	0.0004	0.0003	0.0002	0.0001		
J01D C02	Cefuroxim	0.12	0.13	0.13	0.14	0.15	0.15	0.14	0.13
J01D D01	Cefotaxim	0.03	0.04	0.04	0.05	0.05	0.07	0.07	0.08
J01D D02	Ceftazidim	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01D D04	Ceftriaxone	0.007	0.008	0.011	0.01	0.01	0.01	0.02	0.02
J01D D54	Ceftriaxone, combinations	0.0001	0.0001						
J01D F01	Aztreonam	0.0005	0.0008	0.001	0.001	0.001	0.001	0.001	0.0005
J01D H02	Meropenem	0.004	0.008	0.012	0.014	0.017	0.02	0.02	0.026
J01D H51	Imipenem and enzyme inhibitor	0.007	0.006	0.006	0.005	0.005	0.006	0.005	0.005
J01E A01	Trimethoprim	0.87	0.84	0.79	0.8	0.8	0.74	0.76	0.73
J01E B02	Sulfamethizole	0.0002	0.001	0.002	0.002	0.0001			
J01E C20	Sulfonamides, combinations	0.003	0.0004						
J01E E01	Sulfamethoxazol and trimethoprim	0.47	0.42	0.38	0.36	0.36	0.34	0.34	0.33
J01F A01	Erythromycin	1.06	1.01	1.00	1.13	1.2	1.09	1.03	1.16
J01F A02	Spiramycin	0.04	0.03	0.02	0.02	0.02	0.02	0.01	0.01
J01F A09	Clarithromycin	0.24	0.26	0.26	0.3	0.36	0.37	0.37	0.39
J01F A10	Azithromycin	0.17	0.18	0.19	0.21	0.24	0.26	0.28	0.32
J01FA15	Telithromycin					0.0001	0.0003	0.0003	
J01F F01	Clindamycin	0.11	0.11	0.12	0.14	0.16	0.19	0.20	0.23
J01GA01*	Streptomycin					0.0015	0.0004	0.0004	0.0002
J01G B01	Tobramycin	0.03	0.03	0.02	0.03	0.04	0.04	0.03	0.03
J01G B03	Gentamicin	0.006	0.006	0.006	0.008	0.02	0.03	0.03	0.03
J01G B06*	Amikacin					0.0009	0.0008	0.0003	0.0004
J01G B07	Netilmicin	0.02	0.02	0.02	0.02	0.007			

ATC	Substance	1998	1999	2000	2001	2002	2003	2004	2005
J01M A01	Ofloxacin	0.06	0.06	0.05	0.05	0.05	0.05	0.05	0.05
J01M A02	Ciprofloxacin	0.23	0.26	0.29	0.34	0.38	0.42	0.47	0.52
J01MA12*	Levofloxacin					0.001	0.0003		0.0003
J01M B02	Nalidixic acid	0.01	0.01	0.01	0.01				
J01X A01	Vancomycin	0.005	0.004	0.005	0.005	0.006	0.006	0.007	0.007
J01X A02	Teicoplanin	0.001	0.0007	0.0012	0.0013	0.0013	0.0009	0.0007	0.0008
J01X B01	Colistin	0.003	0.003	0.003	0.003	0.003	0.002	0.002	0.002
J01X C01	Fusidic acid	0.003	0.003	0.003	0.01	0.01	0.007	0.008	0.006
J01X D01	Metronidazole	0.06	0.06	0.06	0.07	0.07	0.07	0.08	0.08
J01X E01	Nitrofurantoin	0.38	0.37	0.37	0.36	0.35	0.35	0.36	0.36
J01X X05	Methenamin	1.75	1.91	1.95	2.08	2.13	2.18	2.37	2.59
J01XX08	Linezolid					0.002	0.004	0.006	0.007
P01AB01	Metronidazole	0.18	0.18	0.18	0.18	0.19	0.19	0.20	0.20
J04AB**	Rifampicin	-	0.052	0.046	0.054	0.043	0.049	0.068	0,077

* Drugs not licensed at the Norwegian marked
** Given as the amount of Rifampicin in plain and combination products. Data for 1998 are not available.

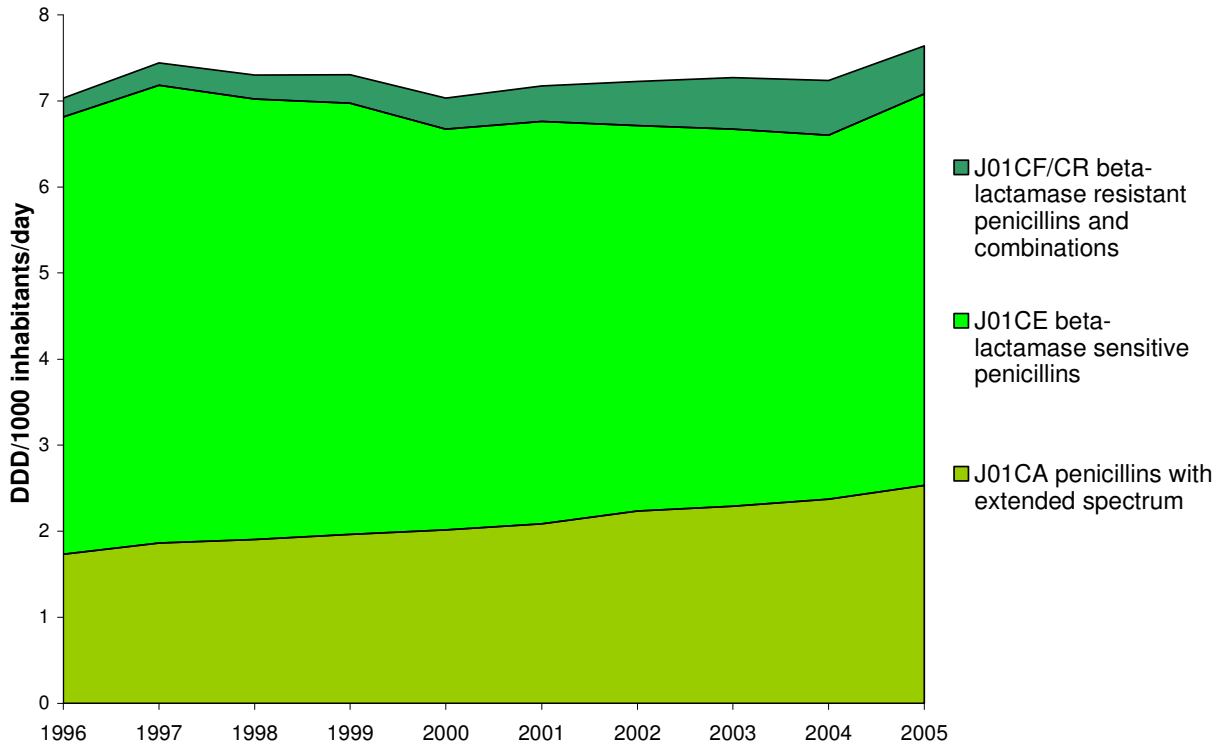

FIGURE 6. Sales of penicillins (J01C) in Norway 1996-2005 and changes within groups of penicillins.

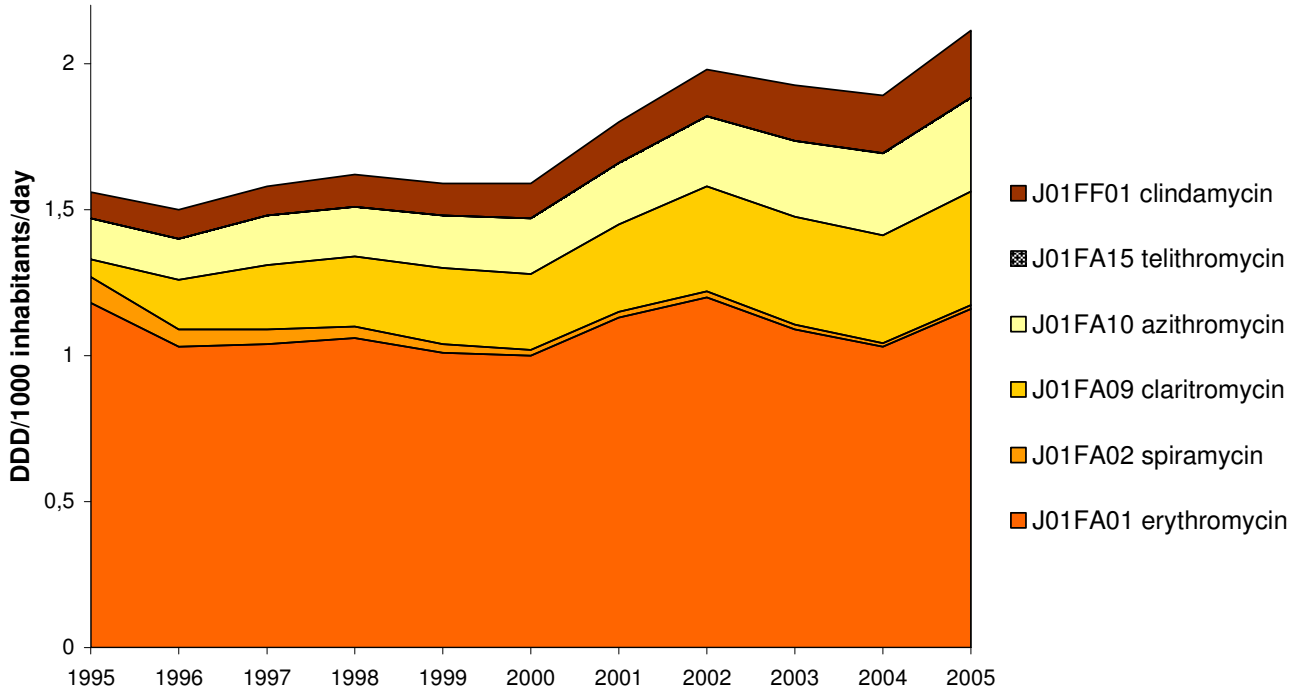

FIGURE 7. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1996-2005.

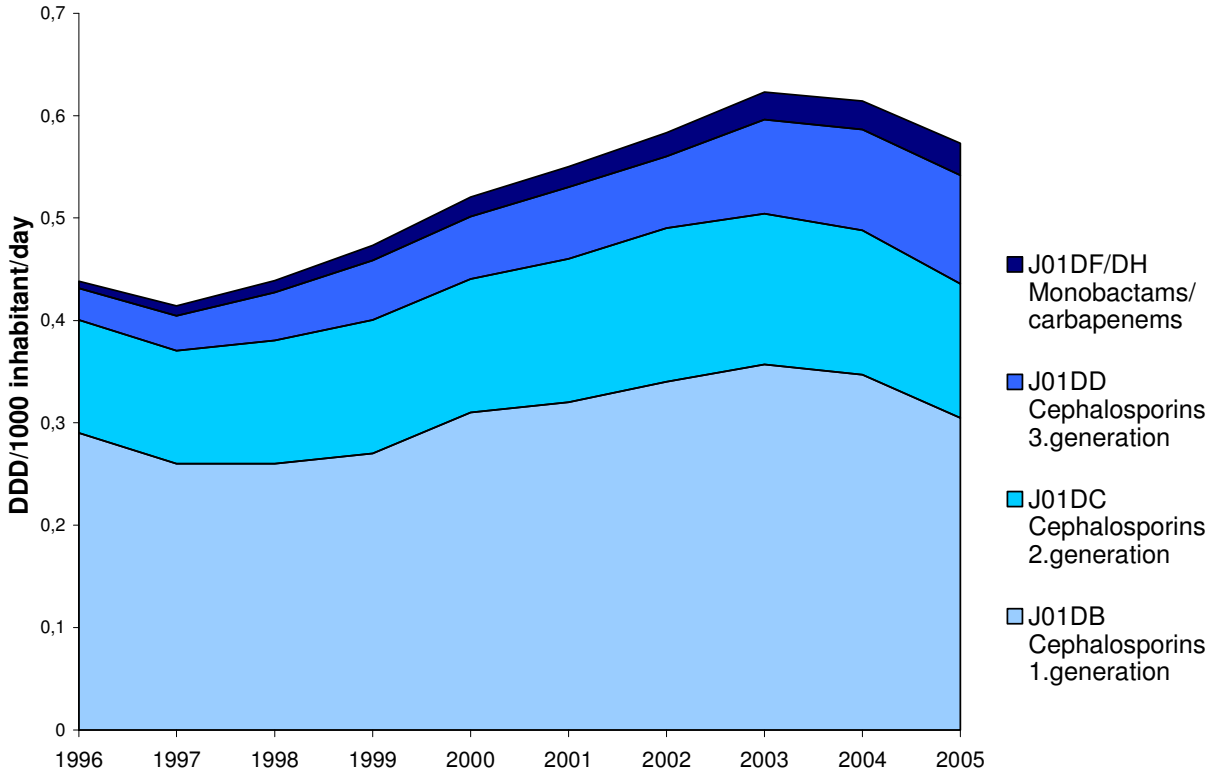

FIGURE 8. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2005 and changes between generations of cephalosporins and monobactams/carbapenems.

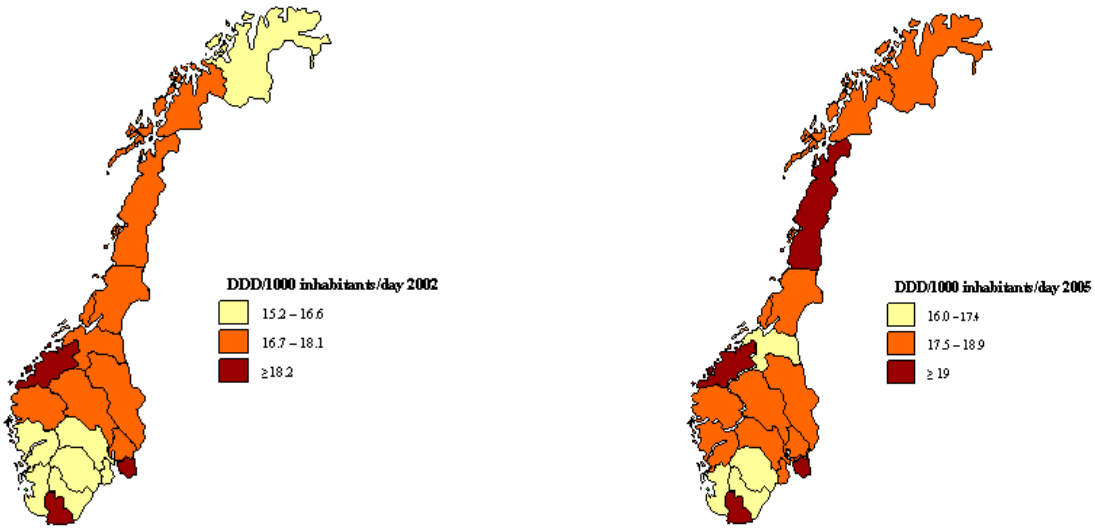

FIGURE 9. Sales of antibacterial agents for systemic use (ATC group J01) in the different counties of Norway in 2002 and 2005.

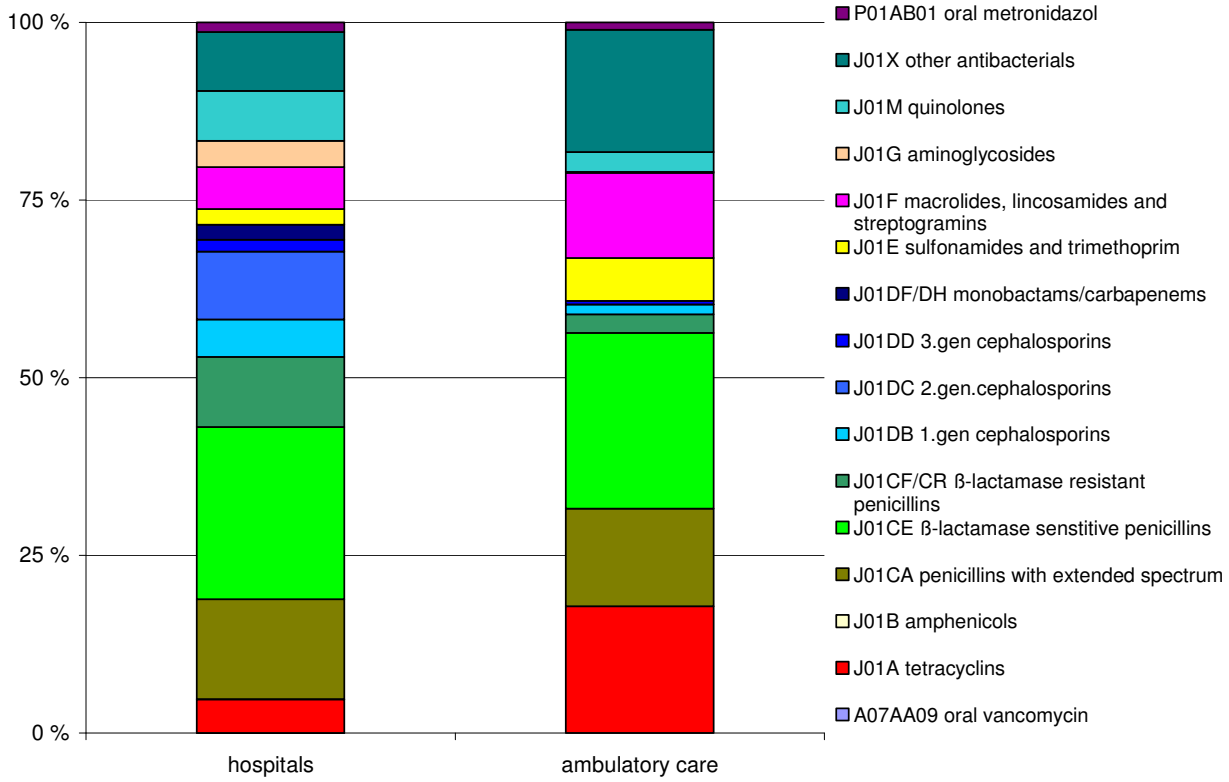

FIGURE 10. Proportions of antibacterial agents for systemic use in Norway 2005 measured in DDD shown for hospitals and ambulatory care.

VI. OCCURRENCE OF ANTIMICROBIAL RESISTANCE

A. ANIMAL CLINICAL ISOLATES

Madelaine Norström, Hilde Kruse, Marianne Sunde

According to the NORM-VET plan, the clinical isolates included in 2005 were *Staphylococcus aureus* and coagulase negative staphylococci (CoNS) from mastitis in cattle and *S. aureus* from mastitis in sheep. Sampling, laboratory methods and data processing are described in Appendix 3.

Staphylococcus spp. from cattle and sheep

A total of 124 and 102 isolates of *Staphylococcus aureus* from mastitis in cattle and sheep, respectively, and 107 isolates of CoNS from mastitis in cattle were susceptibility tested. The results are presented in Tables 10-12, in Figures 11-12 and in the text.

TABLE 10. Antimicrobial resistance in *Staphylococcus aureus* from mastitis in cattle (n=124) and sheep (n=102).

	Animal	Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	species	[95% CI*]		0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Oxytetracycline	Cattle	<1	[0.0-5.1]					98.4	0.8						0.8			
	Sheep	0	[0.0-4.5]					100.0										
Chloramphenicol	Cattle	0	[0.0-3.7]								15.3	83.1	1.6					
	Sheep	0	[0.0-4.5]								7.8	92.2						
Penicillin G**	Cattle	7.3	[3.6-13.8]	7.3	75.8	10.5				0.8		5.6						
	Sheep	2.0	[0.4-7.6]	19.6	71.6	6.9						2.0						
Oxacillin***	Cattle	0	[0.0-5.1]			0.8	21.0	34.7	33.9	8.9	0.8							
	Sheep	0	[0.0-4.5]				41.2	21.6	32.4	4.9								
Cephalothin	Cattle	0	[0.0-3.7]			6.5	73.4	19.4	0.8									
	Sheep	0	[0.0-4.5]			12.7	83.3	3.9										
Trimethoprim	Cattle	0	[0.0-3.7]						4.8	44.4	50.0	0.8						
	Sheep	0	[0.0-4.5]							27.5	69.6	2.9						
Erythromycin	Cattle	0	[0.0-3.7]				21.8	72.6	5.6									
	Sheep	0	[0.0-4.5]					91.2	8.8									
Clindamycin	Cattle	0	[0.0-3.7]				99.2	0.8										
	Sheep	0	[0.0-4.5]				100.0											
Streptomycin	Cattle	4.8	[2.0-10.6]								33.9	52.4	8.1	0.8	0.8			4.0
	Sheep	0	[0.0-3.7]								36.3	52.9	9.8	1.0				
Gentamicin	Cattle	0	[0.0-3.7]					61.3	36.3	2.4								
	Sheep	0	[0.0-4.5]					69.6	30.4									
Neomycin	Cattle	<1	[0.0-5.1]						88.7	10.5	0.8							
	Sheep	0	[0.0-4.5]						90.2	9.8								
Enrofloxacin	Cattle	0	[0.0-3.7]			76.6	23.4											
	Sheep	0	[0.0-4.5]			91.2	8.8											
Vancomycin	Cattle	0	[0.0-3.7]						93.5	6.5								
	Sheep	0	[0.0-4.5]						93.1	4.9	2.0							
Fusidic acid	Cattle	<1	[0.0-5.1]			8.1	86.3	4.8					0.8					
	Sheep	0	[0.0-4.5]			19.6	79.4	1.0										
Avilamycin	Cattle	0	[0.0-3.7]							2.4	40.3	52.4	4.8					
	Sheep	0	[0.0-4.5]							2.0	55.9	41.2	1.0					
Virginiamycin	Cattle	0	[0.0-3.7]					16.9	80.6	2.4								
	Sheep	0	[0.0-4.5]					6.9	89.2	3.9								

Bold vertical lines denote microbiological cut-off values for resistance. White fields denote range of dilutions tested for each antimicrobial agent. MIC-values higher than the highest concentration tested for are given as the lowest MIC-value above the range. MIC-values equal to or lower than the lowest concentration tested are given as the lowest concentration tested. *CI = Confidence interval. ** Classification of resistance to penicillin G was based on β-lactamase production. All but one isolate with a positive β-lactamase test had a MIC-value > 0.125 mg/L, and all β-lactamase negative isolates had a MIC-value ≤ 0.125 mg/L. *** Final classification of resistance to oxacillin was based on *mecA* detection (isolates with MIC>2mg/L). One isolate had an MIC-value over the breakpoint, but *mecA*-PCR was negative.

TABLE 11. Antimicrobial resistance in coagulase negative staphylococci (CoNS) from mastitis in cattle (n=107).

	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
Oxytetracycline	2.8	[0.7-8.6]					87.9	8.4	0.9						2.8		
Chloramphenicol	0.0	[0.0-4.3]						0.9	5.6	62.6	30.8						
Penicillin G**	36.4	[27.5-46.3]	18.7	39.3	5.6	4.7	7.5	4.7	2.8	8.4	8.4						
Oxacillin***	0.0	[0.0-4.3]			5.6	31.8	28.0	17.8	13.1	3.7							
Cephalothin	0.0	[0.0-4.3]			8.4	53.3	33.6	4.7									
Trimethoprim	17.8	[11.3-26.6]					8.4	19.6	14.0	14.0	26.2	14.0	1.9	1.9			
Erythromycin	5.6	[2.3-12.3]				65.4	28.0		0.9	0.9	1.9			2.8			
Clindamycin	0.0	[0.0-4.3]				94.4	4.7		0.9								
Streptomycin	19.6	[12.8-28.6]							32.7	26.2	15.0	3.7	2.8	2.8	10.3	5.6	0.9
Gentamicin	0.0	[0.0-4.3]					95.3	4.7									
Neomycin	<1	[0.0-5.8]						95.3	3.7	0.9							
Enrofloxacin	0.0	[0.0-4.3]			62.6	33.6	3.7										
Vancomycin	0.0	[0.0-4.3]						70.1	29.0	0.9							
Fusidic acid	13.1	[7.6-21.3]		1.9	18.7	28.0	38.3		1.9	3.7	2.8	4.7					
Avilamycin	1.9	[0.3-7.3]						2.8	12.1	34.6	29.0	19.6	1.9				
Virginiamycin	0.0	[0.0-4.3]				1.9	36.4	51.4	9.3	0.9							

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

*CI = Confidence interval.

** Classification of resistance to penicillin G was based on β-lactamase production. All isolates with a positive β-lactamase test had a MIC-value > 0.125 mg/L, and all β-lactamase negative isolates had a MIC-value ≤ 0.125 mg/L.

*** All isolates of CoNS with an MIC- value >0.5 for oxacillin were subjected to PCR for detection of the *mecA* determinant for oxacillin resistance. None of the isolates tested harboured the *mecA* determinant.

TABLE 12. Number of isolates per species of coagulase negative staphylococci (CoNS) from bovine milk samples (n=107).

Species	Number of isolates
Staphylococcus auricularis	1
Staphylococcus capitis ss. *capitis*	3
Staphylococcus caprae	1
Staphylococcus chromogenes	9
Staphylococcus cohnii	2
Staphylococcus epidermidis	12
Staphylococcus haemolyticus	5
Staphylococcus hominis	1
Staphylococcus hyicus	7
Staphylococcus saphrophyticus	1
Staphylococcus sciuri	1
Staphylococcus simulans	45
Staphylococcus warneri	4
Staphylococcus xylosus	5
Other CoNS	10

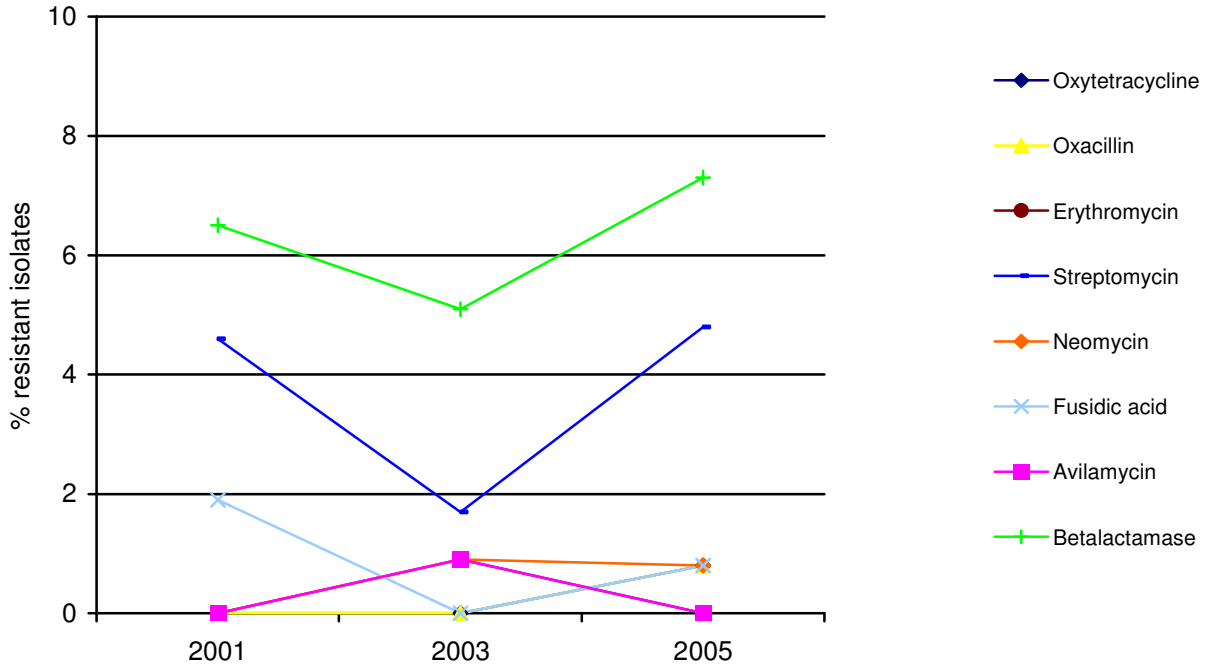

FIGURE 11. Prevalence of resistance to various antimicrobials in *S. aureus* from bovine clinical mastitis isolates, 2001-2005. The breakpoints in NORM-VET 2005 were applied.

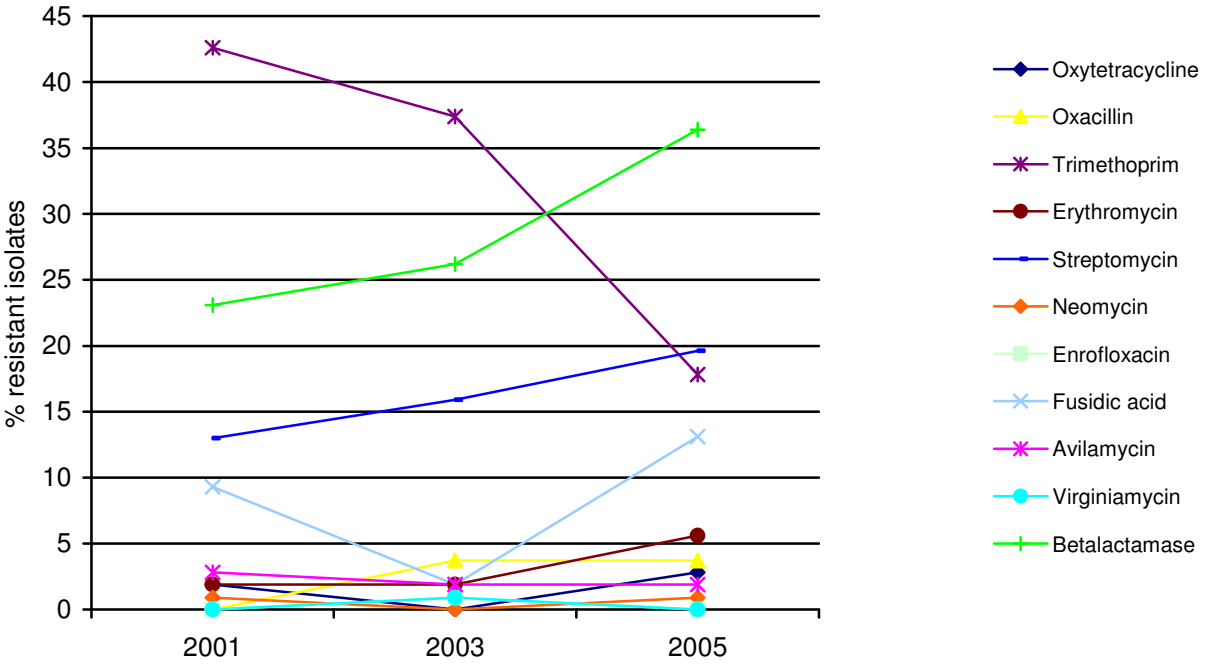

FIGURE 12. Prevalence of resistance to various antimicrobials in CoNS from bovine mastitis isolates, 2001-2005. The breakpoints in NORM-VET 2005 were applied.

RESULTS AND COMMENTS

In 2005, the occurrence of resistance among *S. aureus* from mastitis in cattle was low; 87.9% of the isolates were susceptible to all antimicrobial agents included. In total, 10.5% were resistant to one antimicrobial agent (penicillin, streptomycin or neomycin), 0.8% to two (penicillin and streptomycin), and 0.8% to three antimicrobial agents (penicillin, oxytetracycline and fusidic acid). Also the occurrence of resistance among *S. aureus* from mastitis in sheep was low; 98% of the isolates were susceptible to all antimicrobial agents included. Two isolates from sheep were resistant to one antimicrobial agent (penicillin). The occurrence of resistance to the various antimicrobial agents reflects their usage. Penicillin and streptomycin are among the most commonly used antimicrobial agents for clinical purposes in cattle and sheep.

The occurrence of resistance among *S. aureus* isolates has remained at approximately the same low level from 2001 to 2005 (Figure 11). This corresponds well with the level of resistance from mastitis in cattle and sheep identified during the 1990s. That is the case although the inclusion criteria for isolates applied in NORM-VET differ from those applied before NORM-VET´s establishment in 2000. Before 2000, the prevalence of antimicrobial resistance in staphylococci isolated from cases of mastitis was estimated using all isolates submitted to the diagnostic laboratories. Since 2000, only one isolate per herd has been included to avoid the effect of clustering at herd level due to frequent submission of samples from "problem herds".

In 2005, beta-lactamase production was observed in 7.3% and 2% of the *S. aureus* isolates from cattle and sheep, respectively, and in 36.4% of the CoNS isolates. All but one *S. aureus* isolate with a positive beta-lactamase test had a MIC-value > 0.125 mg/L for penicillin G, and all beta-lactamase negative isolates had a MIC-value ≤ 0.125 mg/L.

Resistance in CoNS from mastitis in cattle was considerably more abundant than in isolates of *S. aureus*. Only 32.7% of the CoNS isolates were susceptible to all antimicrobial agents included. Altogether, 46.7% of the isolates were resistant to one, 12.2% to two and 8.4% to three or more antimicrobial agents. The prevalence of resistance to trimethoprim in CoNS seems to have declined from 2001 to 2005, whereas the prevalence of resistance to penicillin and streptomycin seem to have increased (Figure 12). There are no indications of changes in the antimicrobial usage pattern that can explain this.

The use of fluoroquinolones in veterinary practice in Norway has so far been limited, and no cephalosporins are approved for use in animals in Norway. This is reflected by the high prevalence of susceptibility to these classes of antimicrobial agents in the data presented.

B. INDICATOR BACTERIA FROM ANIMALS AND FOOD

Madelaine Norström, Hilde Kruse, Marianne Sunde

The prevalence of acquired antimicrobial resistance among certain bacteria of the normal enteric microflora can serve 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 in order to get a better understanding of the resistance situation, to detect trends, and to evaluate the effects of interventions.

In NORM-VET, *E. coli* and *Enterococcus* spp. serve as indicator bacteria. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from cattle and sheep

A total of 114 faecal and 141 meat samples from cattle and 78 faecal samples from sheep were collected. For cattle, *E. coli* was isolated from 98 (86%) of the faecal samples and 90 (63.8%) of the meat samples. For sheep, *E. coli* was isolated from 73 (93.6%) of the faecal samples. One isolate per sample positive for *E. coli* was susceptibility tested. The results are presented in Table 13 and Figure 13.

TABLE 13. Antimicrobial resistance in *Escherichia coli* from faecal (n=98) and (n=90) meat samples from cattle and from faecal samples (n=73) from sheep.

		Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	Sample*	[95% CI**]		0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Oxytetracycline	Cattle^{M}	2.2	[0.4-8.5]					1.1	71.1	24.4	1.1					2.2		
	Cattle^{F}	1.0	[0.0-6.3]					1.0	57.1	40.8						1.0		
	Sheep^{F}	0.0	[0.0-6.2]						43.8	56.2								
Chloramphenicol	Cattle^{M}	0.0	[0.0-5.1]							6.7	71.1	21.1	1.1					
	Cattle^{F}	0.0	[0.0-4.7]						1.0	10.2	64.3	24.5						
	Sheep^{F}	0.0	[0.0-6.2]						2.7	13.7	74.0	9.6						
Florfenicol	Cattle^{M}	0.0	[0.0-5.2]								42.7	55.1	2.2					
	Cattle^{F}	0.0	[0.0-5.1]								42.2	55.6	2.2					
	Sheep^{F}	0.0	[0.0-6.2]								47.9	52.1						
Ampicillin	Cattle^{M}	3.3	[0.8-10.1]						12.2	61.1	23.3				3.3			
	Cattle^{F}	2.0	[0.3-7.8]					1.0	12.2	49.0	34.7	1.0			2.0			
	Sheep^{F}	0.0	[0.0-6.2]						6.8	67.1	26.0							
Ceftiofur	Cattle^{M}	0.0	[0.0-5.1]			1.1	40.0	53.3	5.6									
	Cattle^{F}	0.0	[0.0-4.7]			2.0	23.5	69.4	5.1									
	Sheep^{F}	0.0	[0.0-6.2]				11.0	84.9	4.1									
Trimethoprim	Cattle^{M}	3.3	[0.8-10.1]				33.3	51.1	10.0	2.2					3.3			
	Cattle^{F}	0.0	[0.0-4.7]				41.8	49.0	7.1	1.0	1.0							
	Sheep^{F}	1.4	[0.1-8.5]				74.0	24.7							1.4			
Sulfamethoxazole	Cattle^{M}	3.3	[0.8-10.1]										78.9	17.8				3.3
	Cattle^{F}	1.0	[0.0-6.3]										80.6	16.3	2.0			1.0
	Sheep^{F}	0.0	[0.0-6.2]										93.2	6.8				
Streptomycin	Cattle^{M}	10.0	[5.0-18.6]							1.1	53.3	35.6	2.2	1.1	3.3	2.2		1.1
	Cattle^{F}	9.2	[4.6-17.2]							10.2	46.9	33.7	2.0		5.1	1.0	1.0	
	Sheep^{F}	1.4	[0.1-8.5]							16.4	74.0	8.2		1.4				
Gentamicin	Cattle^{M}	0.0	[0.0-5.1]					42.2	54.4	3.3								
	Cattle^{F}	0.0	[0.0-4.7]					53.1	42.9	4.1								
	Sheep^{F}	0.0	[0.0-6.2]					75.3	24.7									
Neomycin	Cattle^{M}	0.0	[0.0-5.1]							97.8	2.2							
	Cattle^{F}	0.0	[0.0-4.7]							99.0	1.0							
	Sheep^{F}	0.0	[0.0-6.2]							100.0								
Enrofloxacin	Cattle^{M}	0.0	[0.0-5.1]	21.1	74.4	3.3	1.1											
	Cattle^{F}	0.0	[0.0-4.7]	19.4	78.6	2.0												
	Sheep^{F}	0.0	[0.0-6.2]	5.5	79.5	12.3	2.7											
Nalidixic acid	Cattle^{M}	0.0	[0.0-5.1]						1.1	44.4	54.4							
	Cattle^{F}	0.0	[0.0-4.7]						2.0	52.0	44.9	1.0						
	Sheep^{F}	0.0	[0.0-6.2]						1.4	57.5	41.1							

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.

*F=faeces, M=meat.

** CI= Confidence interval.

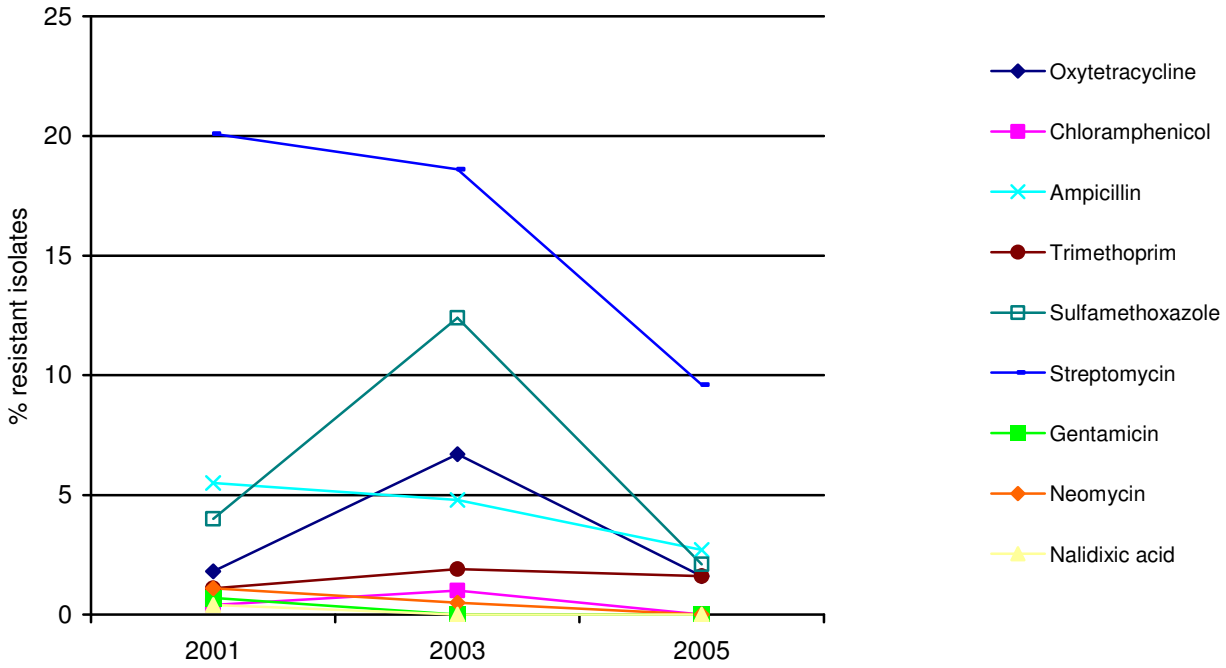

FIGURE 13. Prevalence of resistance to various antimicrobials in *E. coli* from bovine isolates (meat and fecal samples) 2001-2005. The breakpoints in NORM-VET 2005 were applied.

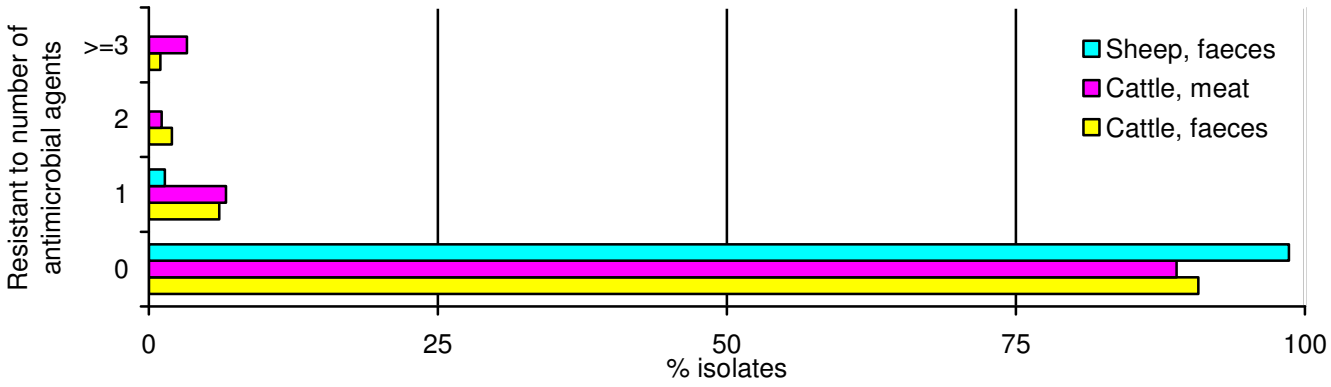

FIGURE 14. Antimicrobial resistance profile for *E. coli* from faecal and meat samples from cattle (98 faecal and 90 meat isolates) and sheep (73 faecal isolates). Proportion of isolates susceptible to all antimicrobial agents included and resistant to one, two, and three or more antimicrobial agents.

RESULTS AND COMMENTS

CATTLE

The data indicate a low occurrence of resistance among *E. coli* from faecal and meat samples from Norwegian cattle. In total, 90.8% and 88.9% of the isolates, respectively, were susceptible to all antimicrobial agents included. Altogether, 6.1% and 6.7% of the faecal and meat isolates, respectively, were resistant to one antimicrobial agent (predominantly streptomycin), 2.0% and 1.1%, respectively, to two antimicrobial agents and 1.0% and 3.3%, respectively, to three or more antimicrobial agents (Figure 14). Resistance to streptomycin was most frequent in both categories (faeces and meat), followed by resistance to ampicillin and sulfamethoxazole. These antimicrobial agents are commonly used for clinical purposes in cattle (sulfonamides in combination with trimethoprim).

No resistance to the fluoroquinolone enrofloxacin or to the quinolone nalidixic acid was observed. The usage of quinolones in terrestric animals in Norway is very limited. No resistance to ceftiofur or gentamicin was observed. No preparations containing cephalosporins or the aminoglycoside gentamicin have been approved for veterinary use in Norway.

The prevalence of resistance to various antimicrobials in *E. coli* for the years 2001-2005 (Figure 13) indicates that the occurrence of resistance in *E. coli* from cattle has remained stable and low, with exception of resistance to streptomycin, which has declined significantly ($p<0.05\%$). This might be due to the changed usage pattern. Ten years ago, a combination of penicillin and streptomycin was commonly used, whereas today penicillin alone is typically used for the treatment of mastitis.

SHEEP

The occurrence of resistance among *E. coli* from faecal samples was low. In total, 98.6% of the isolates were susceptible to all antimicrobial agents included. One isolate was resistant to two antimicrobial agents (trimethoprim and streptomycin). These antimicrobial agents may be used for clinical purposes in sheep production. 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 2005. Lamb production in Norway is very extensive and the lambs spend a large 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.

Enterococcus spp. from cattle

A total of 141 meat samples from cattle were collected. *E. faecalis* or *E. faecium* was isolated from 110 (78%) of the samples. One isolate per positive sample was susceptibility tested. The results are presented in Tables 14-15, Figure 15 and in the text.

TABLE 14. Antimicrobial resistance in *Enterococcus faecalis* from meat (n=84) samples from cattle.

		Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	Sample		[95% CI**]	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Oxytetracycline	Cattle	22.6	[14.5-33.3]			2.4	56.0	17.9	1.2		1.2	2.4	19.0					
Chloramphenicol	Cattle	0.0	[0.0-5.4]				1.2	1.2	14.3	83.3								
Ampicillin	Cattle	0.0	[0.0-5.4]			7.1	60.7	32.1										
Erythromycin	Cattle	4.8	[1.6-12.5]			7.1	17.9	41.7	28.6	4.8								
Streptomycin	Cattle	15.5	[8.8-25.4]												83.3	1.2		15.5
Gentamicin	Cattle	0.0	[0.0-5.4]												100.0			
Neomycin	Cattle	4.8	[1.6-12.5]								11.9	25.0	40.5	16.7	1.2		4.8	
Vancomycin	Cattle	0.0	[0.0-5.4]				6.0	53.6	40.5									
Bacitracin#	Cattle	6.0	[2.2-14.0]						7.1	17.9	53.6	15.5	6.0					
Avilamycin	Cattle	0.0	[0.0-5.4]				8.3	69.0	19.0	2.4	1.2							
Virginiamycin##	Cattle	NR##	NR##						2.4	1.2	58.3	38.1						
Flavomycin	Cattle	0.0	[0.0-5.4]					4.8	15.5	64.3	10.7	4.8						
Narasin	Cattle	0.0	[0.0-5.4]	19.0	54.8	26.2												

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.

* CI = Confidence interval.

Measured in U/ml.

Not relevant as *E. faecalis* is inherently resistant to virginiamycin.

TABLE 15. Antimicrobial resistance in *Enterococcus faecium* from meat (n=26) samples from cattle.

		Resistance (%)		Distribution (%) of MIC values (mg/L)														
Substance	Sample		[95% CI*]	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Oxytetracycline	Cattle	3.8	[0.2-21.5]				92.3		3.8				3.8					
Chloramphenicol	Cattle	0.0	[0.0-16.0]						26.9	73.1								
Ampicillin	Cattle	0.0	[0.0-16.0]		3.8	11.5	11.5	57.7	11.5	3.8								
Erythromycin	Cattle	0.0	[0.0-16.0]			19.2	7.7	30.8	42.3									
Streptomycin	Cattle	7.7	[1.3-26.6]												88.5	3.8		7.7
Gentamicin	Cattle	0.0	[0.0-16.0]												100.0			
Neomycin	Cattle	0.0	[0.0-16.0]								61.5	30.8	7.7					
Vancomycin	Cattle	0.0	[0.0-16.0]				42.3	46.2	11.5									
Bacitracin#	Cattle	19.2	[7.3-40.0]							3.8	15.4	61.5	19.2					
Avilamycin	Cattle	0.0	[0.0-16.0]				3.8	34.6	42.3	19.2								
Virginiamycin	Cattle	0.0	[0.0-16.0]			7.7	53.8		26.9	11.5								
Flavomycin##	Cattle	NR##	NR##												100.0			
Narasin	Cattle	0.0	[0.0-16.0]		7.7	73.1	19.2											

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.

* CI = Confidence interval.

Measured in U/ml.

Not relevant as *E. faecium* is inherently resistant to flavomycin.

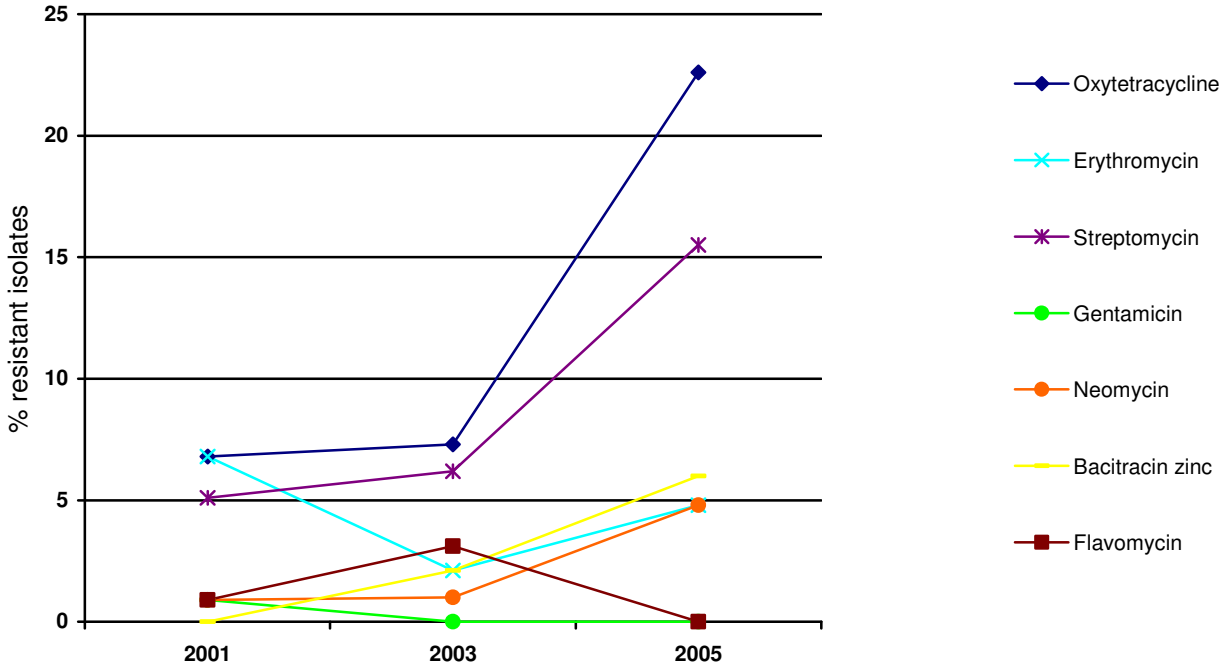

FIGURE 15. Prevalence of resistance to various antimicrobials in *E. faecalis* from bovine isolates (meat and faecal samples), 2001-2005. The breakpoints in NORM-VET 2005 were applied.

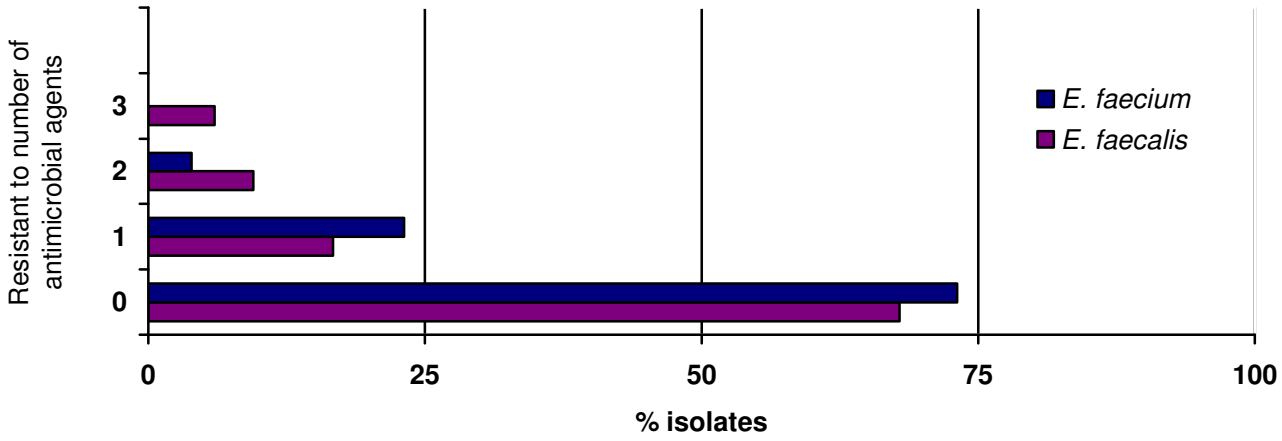

FIGURE 16. Antimicrobial resistance profile for *Enterococcus* spp. from bovine meat samples; 84 isolates of *E. faecalis* and 26 isolates of *E. faecium*. Proportion of isolates susceptible to all antimicrobial agents included and resistant to one, two, and three antimicrobial agents.

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. The situation is reversed for flavomycin. The use of virginiamycin in animal production in Norway has been negligible, and the substance was banned in 1998. Flavomycin has never been approved in Norway. Resistance to virginiamycin and flavomycin is not included in the following comments.

The occurrence of resistance among *Enterococcus* spp. isolated from bovine meat was moderate. The resistance patterns in *E. faecalis* and *E. faecium* were similar. Altogether, 69.1% of the isolates were susceptible to all the antimicrobial agents included. In total, twenty isolates (18.2%) were resistant to one antimicrobial agent (oxytetracycline, bacitracin, erythromycin or streptomycin (high-level)), nine isolates (8.2%) were resistant to two antimicrobial agents (oxytetracycline and streptomycin) and five isolates (4.6%) (*E. faecalis*) were resistant to three antimicrobial agents (oxytetracycline, streptomycin (high-level) and either neomycin (high-level) (four isolates) or erythromycin (one isolate)), see Figure 16. Some tetracycline and streptomycin is used for clinical purposes in Norwegian cattle.

From 2001 to 2005, the prevalence of resistance to oxytetracycline and to streptomycin among *E. faecalis* increased significantly, from 6.8% to 22.6% ($p<0.001$) and from 5.1% to 15.5% ($p<0.05$), respectively, whereas the occurrence of resistance to the other antimicrobial agents included has remained below 10% (Figure 15).

Vancomycin resistant enterococci (VRE) in poultry after the avoparcin ban

The glycopeptide avoparcin was introduced as a growth-promoting feed additive in the Norwegian poultry industry in 1986. During the 1990s, several studies showed an association between the use of avoparcin and the occurrence of vancomycin-resistant enterococci (VRE) in farm animals. To reduce human exposure to VRE, avoparcin was banned as a growth promoter in Denmark and Norway in 1995, in Germany the following year, and in all European Union countries in 1997. It was anticipated that VRE would revert to vancomycin susceptibility in the absence of antimicrobial selection, due to the cost imposed by the resistance determinant on the fitness of the bacteria.

Studies from Denmark, Germany, Italy, and The Netherlands reported a decrease in the occurrence of VRE in animal production following the avoparcin ban. However, in a study performed 3 years after the avoparcin ban, VRE were detected in 99% of poultry fecal samples and in 18% of samples from farmers on Norwegian poultry farms previously exposed to avoparcin. Thus, although the concentration of VRE seemed to have been reduced, no significant reduction in the prevalence of VRE-positive flocks following the avoparcin ban was observed. Another Norwegian study demonstrated that VRE persist in the farm environment even after depopulation and cleaning of the broiler houses. Interestingly, similar results have been reported from Denmark when comparable VRE isolation procedures have been applied. The reservoir of VRE was assumed to be created in the poultry houses that previously used avoparcin. A study was made to determine the prevalence of VRE at farms that had started poultry production after the avoparcin ban. Surprisingly, a large proportion of these farms were also found to have reservoirs of VRE, although the concentration of VRE was shown to be lower than on farms previously exposed to avoparcin. The origin of these VRE has not been determined.

In order to follow the development of vancomycin resistance after the avoparcin ban, the prevalence of fecal VRE in poultry and poultry farmers was examined 3 to 8 years after the Norwegian avoparcin ban. Fecal samples from poultry farmers and their flocks on 29 previously avoparcin-exposed farms were collected on five occasions during the study period (1998 to 2003). All flocks (100%) were VRE positive in 1998. The prevalence of VRE in poultry declined significantly during the study period, but the prevalence of VRE in the farmer samples did not decline. However, the farmers seemed to be only intermittently colonised with VRE. Molecular analyses showed that the VRE isolated from poultry farmers were most likely of poultry origin, which strongly suggests that the farmers are intermittently colonised by VRE originating from their poultry.

In 1998, VRE were isolated from 81% of poultry meat sampled, and even though the concentration was not as high as in faecal samples from later studies, it illustrates that poultry meat can represent a public health risk for foodborne zoonotic transfer of VRE and vancomycin resistance genes. As a part of the Norwegian monitoring program for antimicrobial resistance in the veterinary sector (NORM-VET), VRE were detected in 10% of the poultry meat samples in 2004 using the same method. But since the sample material was not comparable, it is not possible to determine any change in prevalence.

The avoparcin ban has given us the unique opportunity to monitor the population dynamics of VRE and the fate of antimicrobial resistance elements when the selective pressure of an antimicrobial agent is discontinued. One possible explanation for the persistence of vancomycin resistance may be a putative post-segregational killing (PSK) system (“bacterial suicide system”) residing on a plasmid also containing vancomycin resistance genes. With a PSK system, the bacterial cell is killed if the plasmid is lost. The PSK system was detected in the majority of both poultry and farmer isolates, indicating a possible important role in the persistence of vancomycin resistance on Norwegian poultry farms.

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C. ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

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Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum.

In Norway, all *Salmonella* isolates from feed, animals and food, as well as a representative number of *Campylobacter* isolates from broiler and broiler meat are monitored for antimicrobial resistance. Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are monitored, 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 *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 (cattle, pigs, sheep and poultry). The *Salmonella* isolates examined in NORM-VET include those that are detected in this programme, in addition to isolates from other relevant projects as well as clinical submissions to the National Veterinary Institute. The data are presented in Table 16 and in the text.

TABLE 16. Antimicrobial resistance in *Salmonella* spp. (n=41) from animals; *S.* Typhimurium (n=15) and other *Salmonella* spp. (n=26).

	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
Oxytetracycline	2.4	[0.1-14.4]					2.4	43.9	51.2					2.4			
Chloramphenicol	2.4	[0.1-14.4]						2.4	34.1	53.7	7.3					2.4	
Florfenicol	2.4	[0.1-14.4]								78	19.5			2.4			
Ampicillin	2.4	[0.1-14.4]					14.6	80.5	2.4					2.4			
Ceftiofur	0.0	[0.0-10.7]			2.4	7.3	29.3	61.0									
Trimethoprim	0.0	[0.0-10.7]				31.7	68.3										
Sulfamethoxazole	4.9	[0.9-17.8]										19.5	41.5	26.8	2.4	4.9	4.9
Streptomycin	2.4	[0.1-14.4]								7.3	39.0	48.8	2.4	2.4			
Gentamicin	0.0	[0.0-10.7]					70.7	29.3									
Neomycin	0.0	[0.0-10.7]							100.0								
Enrofloxacin	0.0	[0.0-10.7]	12.2	29.3	48.8	9.8											
Nalidixic acid	0.0	[0.0-10.7]							12.2	70.7	17.1						

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.

*CI = Confidence interval.

RESULTS AND COMMENTS

In 2005, a total of 41 isolates of *Salmonella* spp. were susceptibility tested. Only three isolates of *S.* Typhimurium, two from cattle and one from swine, one isolate of *S.* Senftenberg from poultry and one isolate of *S.* Montevideo from poultry were detected in the national surveillance programme. The other *Salmonella* isolates tested were from diagnostic submissions: twelve isolates of *S.* Typhimurium from one dog, two cats and nine wild birds, and eleven isolates of *S. enterica* ss. *diarizonae* from sheep. The other 13 *Salmonella* spp. were from four poultry, one dog, one cat and seven reptiles. Only one of all the isolates, from a dog, was multiresistant (*Salmonella* Typhimurium DT104). All the other isolates except from one isolate, *S.* Pullorum from poultry, which was resistant to sulfonamides, were susceptible to all antimicrobial agents included.

The data, although very limited, indicate that antimicrobial resistance is not very widespread among those *Salmonella* that sometimes are isolated from Norwegian animals.

Salmonella from human clinical specimens

In 2005, 1,484 human cases of salmonellosis, excluding typhoid and paratyphoid fever, were reported in Norway (incidence rate 32.2 per 100,000). In 78.2% of these cases, the infection was reported as having been acquired abroad, whereas for 17.6% the infection was classified as domestically acquired. For the remaining cases, the place of acquisition was unknown.

For *S.* Enteritidis (52.2% of the cases), the proportion of cases reported as imported was particularly high (86.7%). *S.* Enteritidis has never been detected in Norwegian poultry. For *S.* Typhimurium (15.4% of the cases), 47.8% of the infections were acquired in Norway, which 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 infection in these cases are wildlife (mainly 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 infections among the *S.* Typhimurium infections acquired domestically was 22.2%. This represents a significant increase in comparison with earlier years, especially in comparison with the last two years, 2003 and 2004, with a proportion of 3.8% and 0%, respectively.

The proportion of multiresistant *S.* Typhimurium DT104 infections among the *S.* Typhimurium infections acquired abroad was 21.8%.

In total, 229 isolates of *S.* Typhimurium, 728 isolates of *S.* Enteritidis, 19 isolates of *S.* Typhi, 15 isolates of *S.* Paratyhi A, two isolates of *S.* Paratyphi B, and 457 isolates of other *Salmonella* spp. were susceptibility tested. The results are presented in Tables 17-24, Figures 17-21, and in the text.

TABLE 17. *Salmonella* Typhimurium isolates (n=107), including multiresistant DT104 (n=29), from patients infected in Norway. Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)	
	S	R	S	I	R		
Tetracycline	≥ 19	≤ 14	53.3	0.0	46.7	6	29
Chloramphenicol	≥ 21	≤ 20	68.2	0.0	31.8	6	31
Ampicillin	≥ 30	≤ 13	2.8	56.1	41.1	6	31
TMS**	≥ 18	≤ 13	90.7	0.0	9.3	6	≥ 36
Ciprofloxacin	≥ 27	≤ 20	99.1	0.0	0.9	12	≥ 36
Nalidixic acid	≥ 19	≤ 18	89.7	0.0	10.3	6	29

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.

TABLE 18. *Salmonella* Typhimurium isolates (n=107), including multiresistant DT104 (n=29), from patients infected in Norway. Distribution (%) of zone diameters (mm).

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	17.8	2.8			0.9	14.0	9.3		1.9							
Chloramph.	30.8	0.9														
Ampicillin	41.1															
TMS*	9.3															
Ciprofloxacin							0.9									
Nalidixic acid	10.3															

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline		0.9	12.1	18.7	14.0	6.5		0.9							
Chloramph.				0.9	1.9	20.6	17.8	14.0	10.3	2.8					
Ampicillin					0.9	15.9	26.2	13.1	1.9	0.9					
TMS*					0.9	0.9	6.5	9.3	11.2	3.7	8.4	12.1	14.0	15.0	8.4
Ciprofloxacin									0.9	0.9	3.7	1.9	2.8	1.9	86.9
Nalidixic acid		0.9	9.3	7.5	24.3	29.9	15.9	1.9							

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
*TMS=Trimethoprim/sulfamethoxazole.

TABLE 19. *Salmonella* Typhimurium isolates (n=111), including multiresistant DT104 (n=24), from patients infected outside Norway. Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)		
	S	R	S	I	R			
Tetracycline	≥ 19	≤ 14	35.1	1.8	63.1	6	-	30
Chloramphenicol	≥ 21	≤ 20	63.1	0.0	36.9	6	-	32
Ampicillin	≥ 30	≤ 13	4.5	45.9	49.5	6	-	30
TMS**	≥ 18	≤ 13	90.1	0.0	9.9	6	-	≥ 36
Ciprofloxacin	≥ 27	≤ 20	96.4	2.7	0.9	13	-	≥ 36
Nalidixic acid	≥ 19	≤ 18	83.8	0.0	16.2	6	-	30

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.

TABLE 20. *Salmonella* Typhimurium isolates (n=111), including multiresistent DT104 (n=24), from patients infected outside Norway. Distribution (%) of zone diameters (mm).

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	29.7	2.7	1.8		4.5	11.7	10.8	0.9	0.9	1.8					1.8	0.9
Chloramph.	32.4		0.9	0.9	1.8								0.9			
Ampicillin	49.5															0.9
TMS*	9.9															
Ciprofloxacin								0.9								
Nalidixic acid	15.3												0.9	1.8		0.9

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline			7.2	9.0	7.2	7.2		0.9	0.9						
Chloramph.					2.7	15.3	21.6	9.9	10.8	1.8	0.9				
Ampicillin	0.9				1.8	9.9	27.0	5.4	4.5						
TMS*					0.9	6.3	8.1	14.4	13.5	3.6	5.4	5.4	14.4	13.5	4.5
Ciprofloxacin				0.9	1.8		2.7	0.9		2.7	5.4	3.6	0.9	0.9	79.3
Nalidixic acid	0.9	0.9	7.2	7.2	19.8	26.1	14.4	2.7	1.8						

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
*TMS=Trimethoprim/sulfamethoxazole.

TABLE 21. *Salmonella* Enteritidis isolates from patients (n=728[#]). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)		
	S	R	S	I	R			
Tetracycline	≥ 19	≤ 14	95.5	0.3	4.3	6	-	≥ 36
Chloramphenicol	≥ 21	≤ 20	99.5	0.0	0.5	6	-	≥ 36
Ampicillin	≥ 30	≤ 13	3.7	89.3	7.0	6	-	35
TMS**	≥ 18	≤ 13	98.1	0.0	1.9	6	-	≥ 36
Ciprofloxacin	≥ 27	≤ 20	99.7	0.3	0.0	21	-	≥ 36
Nalidixic acid	≥ 19	≤ 18	75.4	0.0	24.6	6	-	33

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.
Place of infection; Norway (n=64), abroad (n=635), unknown (n=29).

TABLE 22. *Salmonella* Enteritidis isolates from patients (n=728[#]). Distribution (%) of zone diameters (mm).*

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	1.2	1.6	1.2	0.1									0.3	0.1	0.3	0.3
Chloramph.	0.4										0.1					
Ampicillin	7.0										0.1					0.1
TMS*	1.9															
Ciprofloxacin																0.1
Nalidixic acid	24.2											0.1	0.3			

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline	0.7	1.5	7.1	20.5	30.1	21.6	10.2	1.6	1.1	0.1					0.3
Chloramph.		0.7	0.3	0.5	1.6	13.0	38.7	25.8	14.8	2.1	0.3	0.3	0.1		1.1
Ampicillin	0.3		0.4	0.3	2.7	20.2	50.8	14.3	3.0	0.1	0.3		0.1	0.1	
TMS*		0.1		0.1	0.1	0.8	0.7	0.1	1.4	2.9	8.9	23.4	34.3	20.5	4.7
Ciprofloxacin				0.1		0.1	1.4	1.6	3.7	3.4	5.4	5.2	3.2	2.5	73.2
Nalidixic acid		0.4	2.9	9.2	25.3	25.1	10.4	1.2		0.3	0.3	0.3			

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
*TMS=Trimethoprim/sulfamethoxazole. # Place of infection; Norway (n=64), abroad (n=635), unknown (n=29).

TABLE 23. *Salmonella* spp. (excluding *S*. Typhimurium, *S*. Enteritidis, *S*. Typhi and *S*. Paratyphi) (n=457[#]). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)
	S	R	S	I	R	
Tetracycline	≥ 19	≤ 14	69.1	0.4	30.4	6 - ≥ 36
Chloramphenicol	≥ 21	≤ 20	93.7	0.0	6.3	6 - 35
Ampicillin	≥ 30	≤ 13	9.4	78.8	11.8	6 - 32
TMS**	≥ 18	≤ 13	86.9	0.0	13.1	6 - ≥ 36
Ciprofloxacin	≥ 27	≤ 20	97.4	1.5	1.1	13 - ≥ 36
Nalidixic acid	≥ 19	≤ 18	75.1	0.0	24.9	6 - 35

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.
Place of infection; Norway (n=73), abroad (n=363), unknown (n=21).

TABLE 24. *Salmonella* spp. (excluding *S*. Typhimurium, *S*. Enteritidis, *S*. Typhi and *S*. Paratyphi) (n=457[#]). Distribution (%) of zone diameters (mm).

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	13.3	7.0	7.7	1.8	0.7					0.2			0.2		0.4	0.7
Chloramph.	3.3	0.4	0.4	0.7	0.7	0.4	0.2			0.2						0.7
Ampicillin	11.8											0.2	0.4			
TMS*	13.1														0.2	0.4
Ciprofloxacin								0.2	0.4		0.4					
Nalidixic acid	22.8	0.2		0.2					0.2	0.4		0.4	0.7	0.7	0.2	0.4

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline	1.3	5.0	12.7	23.9	16.4	5.7	2.0	0.4	0.2						0.4
Chloramph.	0.7	0.2	0.9	3.7	9.4	20.6	28.2	12.3	13.3	2.0	1.3				0.4
Ampicillin		0.2	1.1	0.9	0.9	16.4	36.1	22.5	8.1	0.9	0.4				
TMS*					1.1	0.7	3.3	1.8	2.4	2.2	5.7	14.9	32.6	15.3	6.3
Ciprofloxacin		0.2		0.7	0.7	1.3	1.5	2.4	5.9	3.1	4.4	2.6	4.2	3.9	68.1
Nalidixic acid	1.3	1.1	2.2	8.1	22.3	22.8	11.8	2.4	1.3	0.2				0.2	

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
*TMS=Trimethoprim/sulfamethoxazole. # Place of infection; Norway (n=73), abroad (n=363), unknown (n=21).

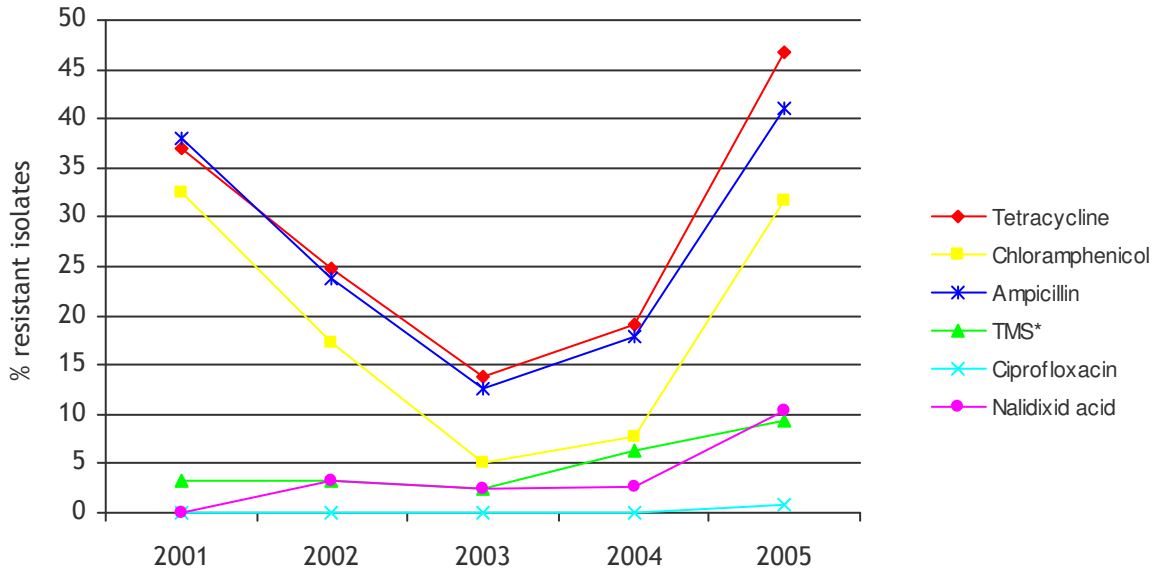

FIGURE 17. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium, including multiresistant DT104, from humans infected in Norway, 2001-2005. The breakpoints in NORM 2005 were applied.
*TMS=Trimethoprim/sulfamethoxazole

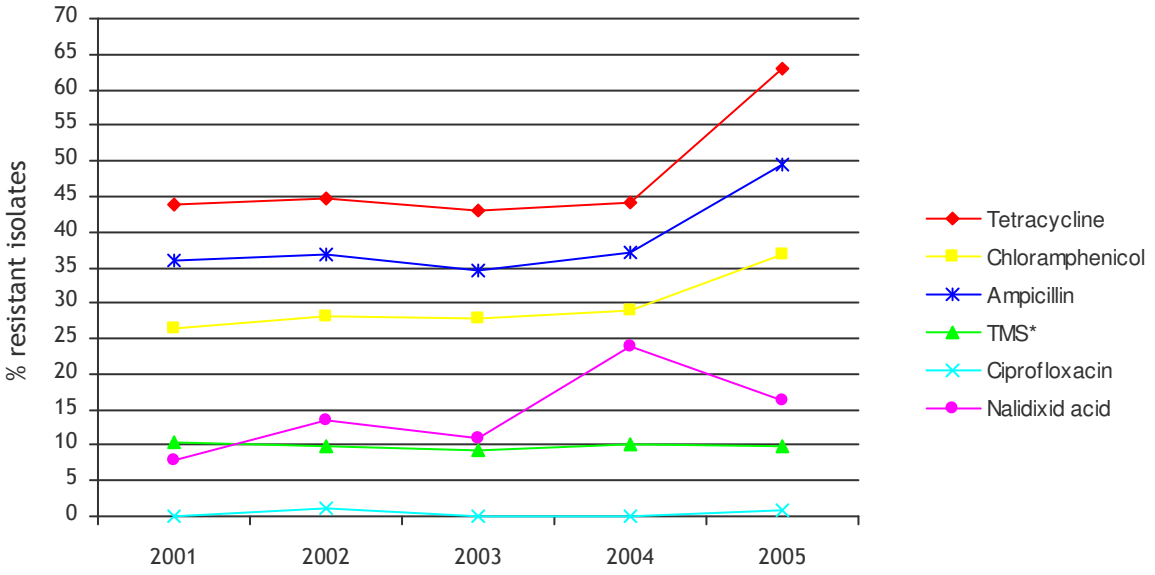

FIGURE 18. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium, including multiresistant DT104, from humans infected outside Norway, 2001-2005. The breakpoints in NORM 2005 were applied. *TMS=Trimethoprim/sulfamethoxazole.

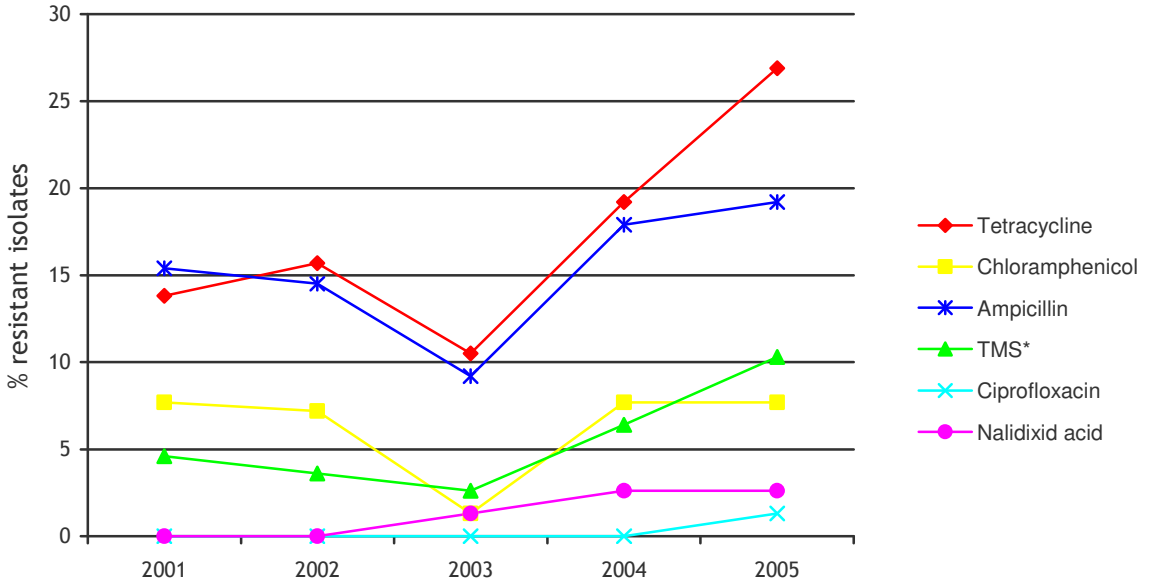

FIGURE 19. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium, excluding multiresistant DT104, from humans infected in Norway, 2001-2005. The breakpoints in NORM 2005 were applied. *TMS=Trimethoprim/sulfamethoxazole.

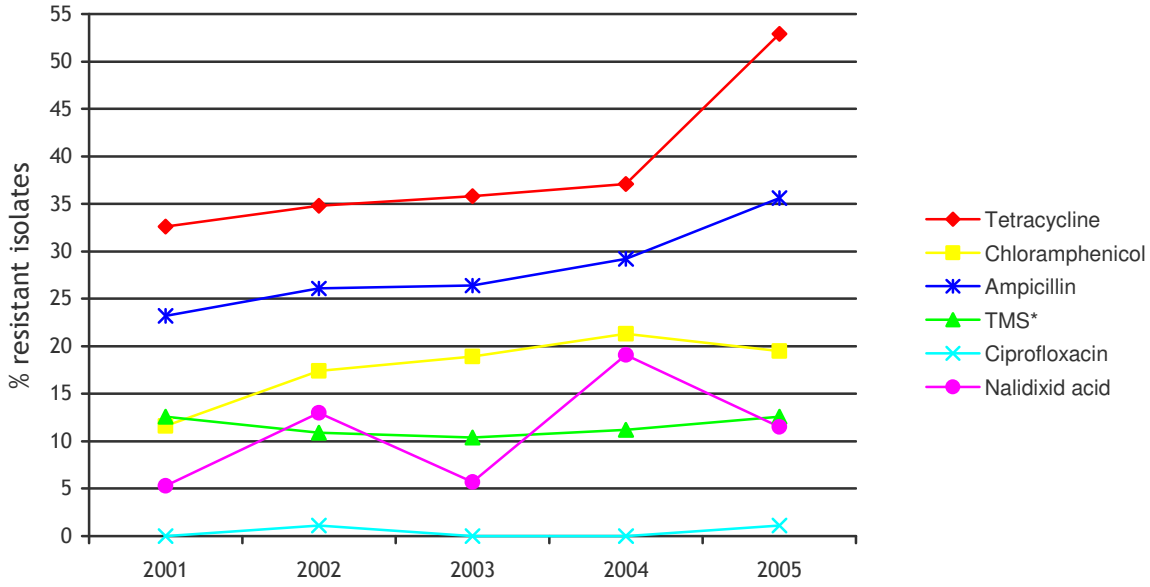

FIGURE 20. Prevalence of resistance to various antimicrobials in *Salmonella* Typhimurium, excluding multiresistant DT104, from humans infected outside Norway, 2001-2005. The breakpoints in NORM 2005 were applied. *TMS=Trimethoprim/sulfamethoxazole.

RESULTS AND COMMENTS

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

The proportion of *S.* Typhimurium isolates susceptible to all antimicrobial agents was higher for the category "infected in Norway" (49.5%) than for the "infected abroad" category (33.3%) (Figure 21). But compared to 2004, this difference was smaller, which most probably is a result of more infections with DT104 among the domestically acquired infections in 2005. Multiresistance (resistance to more than two antimicrobial agents) was slightly more common in the category "infected abroad" (40.5%) as compared to the category "infected in Norway" (33.6%), but less so than observed in earlier years. The prevalence of resistance for the years 2001-2005 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. The proportion of *S.* Enteritidis isolates resistant to the different antimicrobial agents included, except for nalidixid acid, was considerably lower than for *S.* Typhimurium (Figure 21). In total, 24.6% of the isolates of *S.* Enteritidis were resistant to nalidixid acid. There was no resistance to ciprofloxacin, whereas intermediate susceptibility to ciprofloxacin was observed in 0.3% of the isolates. One of the isolates intermediately susceptible to ciprofloxacin was also resistant to nalidixic acid. The resistance frequencies observed for *S.* Enteritidis in NORM/NORM- VET 2005 are quite similar to those reported in previous reports.

With regard to isolates of *Salmonella* spp. other than *S.* Typhimurium, the vast majority of infections had been acquired abroad. Resistance was quite widespread. Resistance to tetracycline was most common followed by resistance to nalidixic acid, trimethoprim-sulfamethoxazole, ampicillin and chloramphenicol. The prevalence of resistance to nalidixic acid was relatively high (24.9%). Similar to what was observed for *S.* Enteritidis isolates, ciprofloxacin resistance was observed in 1.1%, while 1.5% showed reduced susceptibility to ciprofloxacin. It is emphasized that the use of fluoroquinolones in Norway is limited in both human and veterinary medicine.

The few isolates of *S.* Typhi (n=19), *S.* Paratyphi A (n=15) and *S.* Paratyhi B (n=2) detected and susceptibility tested in 2005 indicate that multiresistance is common in *S.* Typhi and *S.* Paratyphi A, and that these isolates are commonly resistant to nalidixic acid. With one exception, all of these infections had been acquired abroad. Thirteen and nine isolates of *S.* Paratyphi A and *S.* Typhi, respectively, were resistant to one or more of the antimicrobial agents included. Fourteen out of all the 36 isolates of *S.* Paratyphi A and *S.* Typhi were resistant to only nalidixid acid and eight isolates to ampicillin, oxytetracycline, chloramphenicol and trimethoprim/ sulfamethoxazole. Out of the latter isolates, two isolates were in addition resistant to nalidixid acid. Among the two isolates of *S.* Paratyphi B, no resistance was observed.

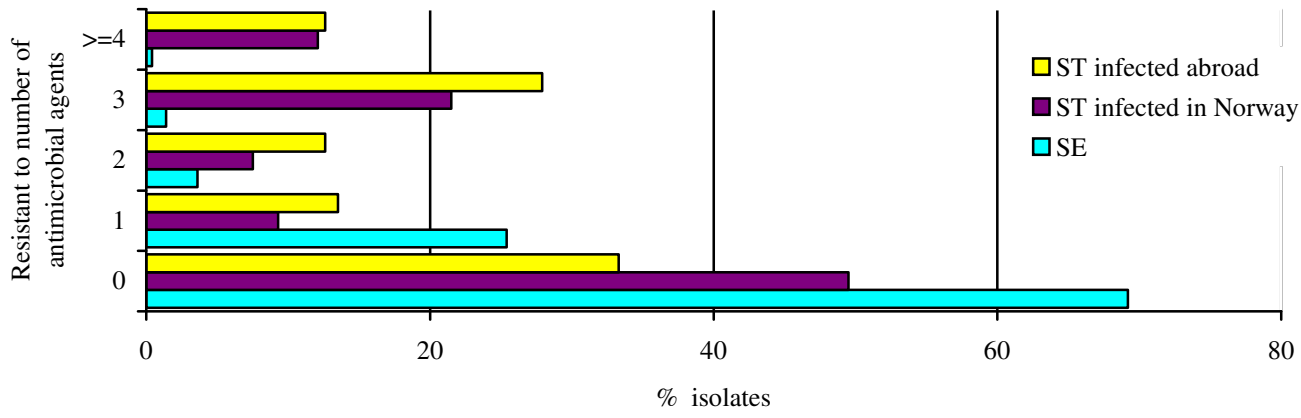

FIGURE 21. Antimicrobial resistance profiles for all *Salmonella* Enteritidis (SE) from humans (n=728) and for *Salmonella* Typhimurium (ST) from humans infected in Norway (n=107) and abroad (n=111), respectively. Proportion of isolates susceptible to all antimicrobial agents included and resistant to one, two, three, or four or more antimicrobial agents.

Genetic and Epidemiological Studies on Equine and Ruminant Staphylococci Resistant to Quaternary Ammonium Compounds

Biocides based on quaternary ammonium compounds (QACs) are widely used in domestic households, in hospitals, in the food industry and in animal health care. Staphylococci resistant to QACs has been described previously, based on isolates from human infections and food products. Recently, such staphylococci have also been found to cause infection in animals.
The aim of this work has been to study the occurrence of QAC-resistant staphylococci associated with disease in horses and dairy ruminants, including the genetic characterization and molecular epidemiology of such staphylococci. Staphylococcal isolates were obtained from lesions in horses and from bulk milk and quarter milk samples from 127 dairy cattle and 70 goat herds in Norway. Methods used included screening for QAC resistance of staphylococci on selective media, plasmid isolation and analysis, PCR, species determination by sequencing of the *sodA* and 16S rRNA genes, cloning and sequencing of QAC resistance plasmids and genes, Southern blot and hybridization studies, and pulsed-field gel electrophoresis typing.
Plasmid-borne *smr* gene was detected in three bovine isolates of *Staphylococcus aureus* that were also resistant to penicillin and tetracycline. A novel gene, *qacJ*, was identified and characterized in equine *S. aureus*, *S. intermedius* and *S. simulans* as well as in bovine *S. delphini* and *S. hominis*. QAC resistance genes were identified in 21% of cattle herds (*qacA/B*, *smr*, *qacG*, and *qacJ*) and in 10% of goat herds (*qacA/B* and *smr*). Genetic linkage between QAC resistance and penicillin resistance was detected: *qacA/B* and the beta-lactamase gene *blaZ* resided on a common plasmid in nine out of eleven *qacA/B*-containing strains. A novel *smr*-containing plasmid pSP187 (5550 bp) was identified in bovine *S. pasteuri*; pSP187 contains seven open reading frames and is the first member of the rolling circle replication group VI observed in a *Staphylococcus* sp.. Recombinant events such as temporal plasmid fusion between a QAC resistance plasmid and a partial tetracycline resistance plasmid (pT181-like) were observed in a long-term persistent bovine *S. warneri* strain.

In conclusion, it seems that the widespread distribution of staphylococci carrying QAC resistance genes in Norwegian dairy cattle and goat herds, as well as in the horse population, is the result of both intra- and interspecies spread of QAC resistance plasmids, the acquisition of QAC resistance genes by novel plasmids, and clonal spread of QAC-resistant strains.

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CAMPYLOBACTER SPP.

Campylobacter jejuni from broilers

The isolates of *Campylobacter jejuni* in broiler originate from the Norwegian action plan against *Campylobacter* spp. in broiler. All broiler flocks slaughtered before 50 days of age are tested for the presence of *Campylobacter* spp. In addition, 100 samples of broiler meat products from retail level are tested monthly. In 2005, one isolate per positive farm as well as one isolate from each batch of positive broiler meat products were submitted for susceptibility testing. A total of 104 isolates, 69 from broiler flocks (faecal or cloacal samples) and 35 from broiler meat were susceptibility tested. The results are presented in Table 25, Figure 22 and in the text.

TABLE 25. Antimicrobial resistance in *Campylobacter jejuni* (n=104) from broiler flocks (n=69) and from broiler meat products (n=35).

	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
Oxytetracycline	0.0	[0.0-4.4]				91.3	7.7	1.0									
Ampicillin	6.7	[3.0-13.8]					1.0	5.8	13.5	51.9	19.2	1.9	3.8	1.9	1.0		
Erythromycin	0.0	[0.0-4.4]				11.5	59.6	25.0	3.8								
Gentamicin	0.0	[0.0-4.4]				9.6	76.0	12.5	1.9								
Enrofloxacin	1.9	[0.3-7.4]	1.9	7.7	73.1	15.4				1.9							
Nalidixic acid	1.9	[0.3-7.4]							5.8	47.1	41.3	3.8			1.0	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.

RESULTS AND COMMENTS

The results show that the occurrence of resistance among *C. jejuni* isolates from Norwegian broilers is low. A total of 91.4% of the isolates tested were susceptible to all antimicrobial agents included. Altogether 6.7% were resistant to one antimicrobial agent (ampicillin) and 1.9% to both nalidixid acid and enrofloxacin. The results reflect the usage of antimicrobial agents in poultry production. Antimicrobial agents (except coccidiostats) are rarely used, and only for therapeutical purposes. If used, amoxicillin (cross-resistance with ampicillin) and tetracycline are the drugs of choice.

The results are similar to those presented in previous NORM/NORM-VET reports (2001, 2002, 2003 and 2004) as presented in Figure 22. However, the data indicate an increasing trend of resistance to ampicillin.

The level of resistance and the resistance patterns for *C. jejuni* isolated from Norwegian broilers are quite 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 human isolates. This relationship was also observed in previous NORM/NORM-VET reports (2001, 2002, 2003 and 2004).

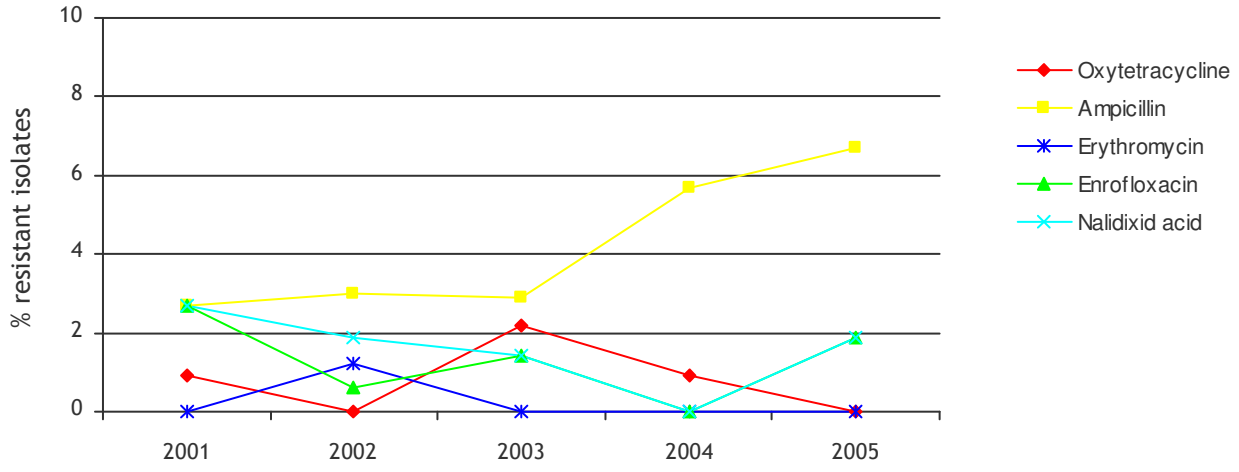

FIGURE 22. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from Norwegian broilers, 2001-2005. The breakpoints for resistance defined in NORM 2005 were applied.

Campylobacter spp. from human clinical specimens

Of the 2,627 cases of human campylobacteriosis recorded in Norway in 2005 (incidence rate 57.0 per 100,000), 47% were reported as acquired abroad. The vast majority of cases were sporadic. Norwegian case-control studies have revealed that consumption of broiler meat purchased fresh and drinking untreated water are important risk factors for domestically acquired campylobacteriosis.

A total of 258 isolates of *C. jejuni*, 100 from patients infected in Norway and 151 from patients infected abroad and seven from patients where the source of infection were unknown, as well as nine isolates of *C. coli* were susceptibility tested. The results are presented in Tables 26-29, Figures 23-24, and in the text.

TABLE 26. *Campylobacter jejuni* isolates from patients infected in Norway (n=100). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Doxycycline	≤ 2	≥ 4	97.0	0.0	3.0	0.047 - 32	19	5
Erythromycin	≤ 0.5	≥ 8	4.0	95.0	1.0	0.094 - 8	15	3
Gentamicin	≤ 4	≥ 8	98.0	0.0	2.0	0.125 - 12	75	2
Ciprofloxacin	≤ 1	≥ 4	94.0	0.0	6.0	0.064 - 32	19	38
Nalidixic acid	≤ 16	≥ 32	89.0	0.0	11.0	1.5 - 256	3	24

*S=Susceptible, I=Intermediately susceptible, R=Resistant.

TABLE 27. *Campylobacter jejuni* isolates from patients infected in Norway (n=100). Distribution (%) of MICs (mg/L).

Substance	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Doxycycline		3.0	27.0	54.0	7.0	4.0	2.0			2.0	1.0			
Erythromycin			1.0	1.0	2.0	23.0	62.0	10.0	1.0					
Gentamicin			1.0	11.0	26.0	38.0	18.0	4.0	1.0	1.0				
Ciprofloxacin		1.0	32.0	52.0	9.0						6.0			
Nalidixic acid							26.0	45.0	14.0	4.0	4.0			7.0

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

TABLE 28. *Campylobacter jejuni* isolates from patients infected outside Norway (n=151). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Doxycycline	≤ 2	≥ 4	52.3	0.0	47.7	0.064 - 256	1	256
Erythromycin	≤ 0.5	≥ 8	3.3	91.4	5.3	0.38 - 256	15	4
Gentamicin	≤ 4	≥ 8	94.0	0.0	6.0	0.125 - 256	1	2
Ciprofloxacin	≤ 1	≥ 4	37.7	0.7	61.6	0.064 - 32	32	32
Nalidixic acid	≤ 16	≥ 32	36.4	0.0	63.6	1.5 - 256	256	256

*S=Susceptible, I=Intermediately susceptible, R=Resistant.

TABLE 29. *Campylobacter jejuni* isolates from patients infected outside Norway (n=151). Distribution (%) of MICs (mg/L).

Substance	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Doxycycline		1.3	17.0	19.0	11.3	3.3	0.7	2.0	3.9	2.6	11.3	7.2	5.3	15.3
Erythromycin					3.3	33.7	45.7	12.0	0.7	2.0	2.0			0.7
Gentamicin			0.7	13.0	17.9	41.7	17.9	3.3	3.3	1.4				1.3
Ciprofloxacin		0.7	15.0	17.0	3.3	1.4	0.7		0.7	4.0	57.0			
Nalidixic acid							10.5	20.0	3.3	2.7		0.7	0.7	62.3

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

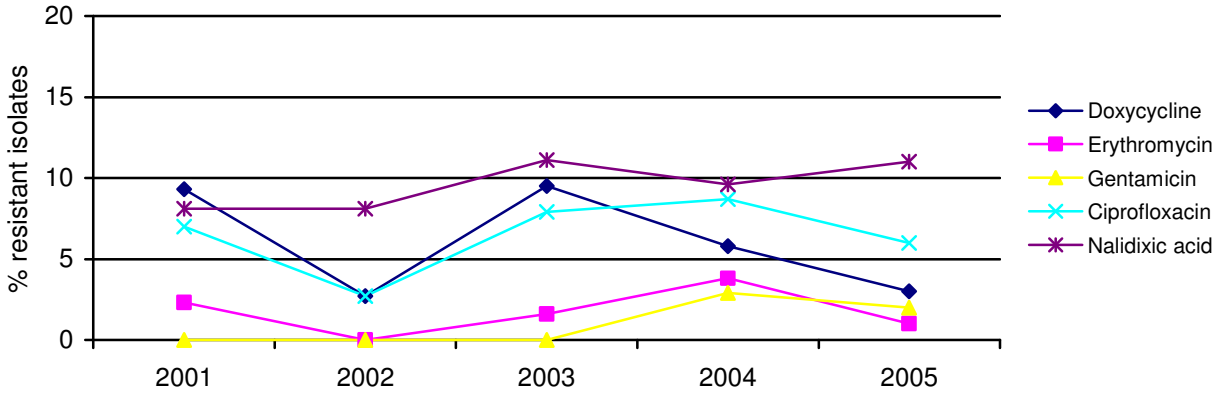

FIGURE 23. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from humans infected in Norway, 2001-2005. The breakpoints in NORM 2005 were applied.

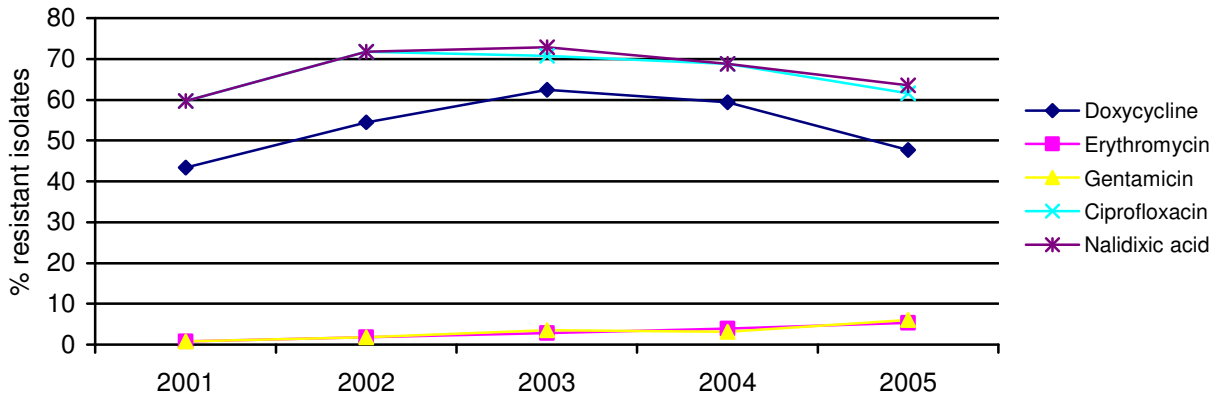

FIGURE 24. Prevalence of resistance to various antimicrobials in *Campylobacter jejuni* from humans infected outside Norway, 2001-2005. The breakpoints in NORM 2005 were applied

RESULTS AND COMMENTS

The data show that resistance was significantly more widespread among *C. jejuni* isolates derived from patients infected abroad as opposed to patients infected in Norway. Only 29.8% of the isolates in the first category were susceptible to all antimicrobial agents included as opposed to 89% of the isolates from patients infected in Norway (Figure 25). These discrepancies are explained by the widespread occurrence among isolates acquired abroad as opposed to patients infected in Norway of resistance to ciprofloxacin/nalidixic acid (61.6%/63.6% versus 6.0%/ 11.0%) and to tetracycline (47.7% versus 3.0%) (Tables 26 and 28 and Figure 25).

The prevalences of resistance and the resistance patterns for *C. jejuni* isolated from humans infected within Norway correspond quite 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 the human isolates. This relationship was also observed in NORM/NORM-VET 2001, 2002, 2003 and 2004. The prevalences of resistance to various antimicrobials in *C. jejuni* from both humans infected in Norway (Figure 23) and abroad (Figure 24) for the period 2001-2005 indicate that the occurrence of resistance is stable.

All nine isolates of *C. coli* were acquired abroad. Five of these isolates were resistant to at least one of the antimicrobial agents included (mainly quinolones and tetracycline). *C. coli* is typically associated with pigs and pork.

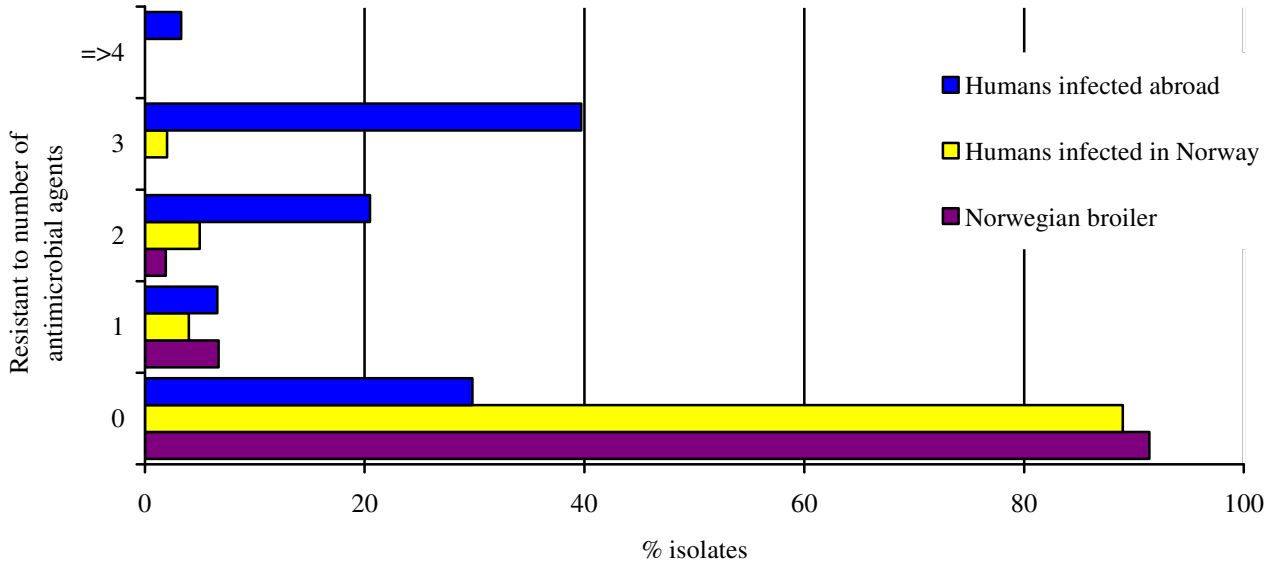

FIGURE 25. Antimicrobial resistance profiles for *Campylobacter jejuni* from Norwegian broiler (n=104) (cloacal/faecal samples (n=69) and meat products (n=35)), humans infected in Norway (n=100) and humans infected abroad (n=151). Proportion of isolates susceptible to all antimicrobial agents included or resistant to one, two, three, or four or more antimicrobial agents. The isolates from humans were tested for susceptibility to doxycycline, erythromycin, gentamicin, ciprofloxacin and nalidixic acid, whereas the sheep and sheep meat isolates in addition were tested for susceptibility to ampicillin (and to oxytetracycline rather than doxycycline).

Yersinia enterocolitica from human clinical specimens

Most cases of *Yersinia enterocolitica* infections in Norway are domestically acquired. In 2005, a total of 125 cases of yersiniosis were reported (incidence rate 2.7 per 100,000 population). A total of 77 (62%) cases were indigenous. In 2005, a total of 113 isolates of *Y. enterocolitica* were susceptibility tested. The results are presented in Tables 30 and 31.

TABLE 30. *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 isolates from human clinical cases (n=113[#]). Distribution (%) of antimicrobial susceptibility groups.

	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)		
Substance	S	R	S	I	R			
Tetracycline	≥ 19	≤ 14	98.2	0.0	1.8	6	-	≥ 36
Chloramphenicol	≥ 21	≤ 20	90.3	0.0	9.7	6	-	35
Ampicillin	≥ 30	≤ 13	0.9	1.8	97.3	6	-	32
TMS**	≥ 18	≤ 13	98.2	1.8	0.0	15	-	35
Ciprofloxacin	≥ 27	≤ 20	92.0	4.4	3.5	6	-	≥ 36
Nalidixic acid	≥ 19	≤ 18	92.9	0.0	7.1	6	-	35

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.
[#] Place of infection; Norway (n=72), Abroad (n=25), Unknown (n=8).

TABLE 31. *Yersinia enterocolitica* serogroup O:3 and O:9 isolates (n=113[#]) from human clinical cases. Distribution (%) of zone diameters (mm).*

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	0.9	0.9												0.9	0.9	2.7
Chloramph.	8.8	0.9														
Ampicillin	34.5	31	9.7	15.9	4.4	1.8			0.9	0.9						
TMS*										0.9	0.9		1.8	1.8	0.9	0.9
Ciprofloxacin	0.9			0.9		0.9									0.9	0.9
Nalidixic acid	7.1															

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline	2.7	1.8	14.2	15.9	22.1	9.7	17.7	2.7	2.7	0.9	0.9		0.9	0.9	0.9
Chloramph.		1.8		1.8	2.7	6.2	15	16.8	18.6	10.6	7.1	6.2	2.7	0.9	
Ampicillin											0.9				
TMS*	1.8	0.9	0.9	0.9	1.8	4.4	2.7	7.1	24.8	11.5	16.8	8	9.7	1.8	
Ciprofloxacin			0.9	0.9	1.8		3.5	0.9	7.1	3.5	4.4	8.8	18.6	13.3	31.9
Nalidixic acid				1.8	1.8	9.7	14.2	13.3	23	15.9	4.4	4.4	1.8	2.7	

*Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark). **TMS=Trimethoprim/sulfamethoxazole.
[#] Place of infection; Norway (n=72), Abroad (n=25), Unknown (n=8).

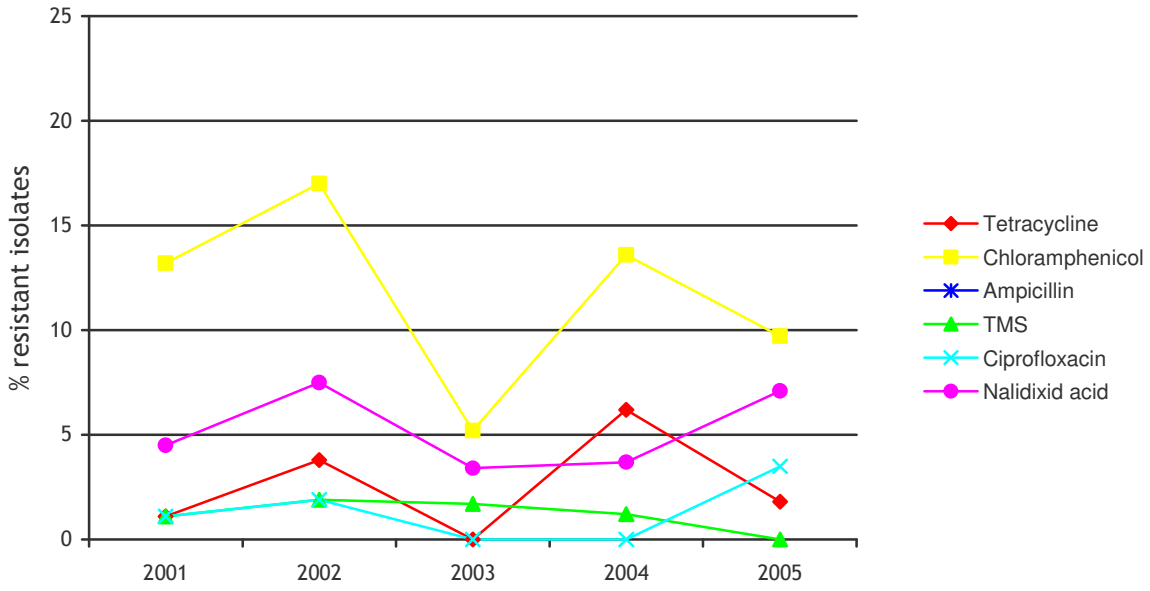

FIGURE 26. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in 2001-2005. The breakpoints in NORM 2005 were applied.

RESULTS AND COMMENTS

The infections in 2005 were mainly domestically acquired thus indicating an increasing problem of quinolone resistance (two of the three isolates resistant to ciprofloxacin derived from domestically acquired cases, whereas the place of infection for the last one was unknown).

In total, 97.3% of the isolates expressed reduced susceptibility to ampicillin, an intrinsic resistance trait in strains of serogroup O:3 and O:9.

Compared to earlier years, the level of resistance seems to be stable (Figure 26).

Shigella spp. from human clinical specimens

It is emphasized that almost all the reported *Shigella* infections in Norway were acquired abroad. In 2005, 5.7% of the 159 reported cases were classified as domestically acquired. Thus, the resistance prevalences reported here predominantly relate to isolates originating in other countries. The distribution of the *Shigella* species was as follows: *S. sonnei* 85 (53.4%), *S. flexneri* 56 (35.2%), *S. boydii* 11 (6.9%), and *S. dysenteriae* 7 (4.4%). The results for *S. sonnei* and *S. flexneri* are presented in Tables 32-35 and in the text.

TABLE 32. *Shigella sonnei* isolates from human clinical cases (n=85). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)
	S	R	S	I	R	
Tetracycline	≥ 19	≤ 14	15.3	1.2	83.5	6 - 30
Chloramphenicol	≥ 21	≤ 20	94.1	0.0	5.9	6 - ≥ 36
Ampicillin	≥ 30	≤ 13	2.4	78.0	20.0	6 - 30
TMS**	≥ 18	≤ 13	4.7	1.2	94.1	6 - ≥ 36
Ciprofloxacin	≥ 27	≤ 20	100	0.0	0.0	27 - ≥ 36
Nalidixic acid	≥ 19	≤ 18	78.8	0.0	21.2	6 - 34

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.

TABLE 33. *Shigella sonnei* isolates from human clinical cases (n=85). Distribution (%) of zone diameters (mm).*

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	69.4	10.6	1.2					1.2	1.2	1.2						
Chloramph.	3.5		1.2									1.2				
Ampicillin	17.6		2.4												1.2	1.2
TMS*	91.8				1.2			1.2	1.2							
Ciprofloxacin																
Nalidixic acid	2.4	2.4	4.7	3.5	2.4	2.4	1.2	1.2	1.2							

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline			1.2	1.2	5.9	1.2	3.5	1.2	1.2						
Chloramph.				3.5	7.1	21.2	31.8	9.4	15.3	2.4	1.2	1.2			1.2
Ampicillin			3.5	9.4	23.5	24.7	10.6	3.5	2.4						
TMS*			2.4	1.2											1.2
Ciprofloxacin						1.2	2.4	3.5	3.5	7.1	3.5		4.7		74.1
Nalidixic acid			1.2		1.2		2.4	2.4	17.6	22.4	14.1	14.1	3.5		

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
**TMS=Trimethoprim/sulfamethoxazole.

TABLE 34. *Shigella flexneri* isolates from human clinical cases (n=56). Distribution (%) of antimicrobial susceptibility groups.

Substance	Breakpoints (mm)		Proportion of isolates (%)*			Range (mm)
	S	R	S	I	R	
Tetracycline	≥ 19	≤ 14	10.7	0.0	89.3	6 - 32
Chloramphenicol	≥ 21	≤ 20	33.9	0.0	66.1	6 - ≥ 36
Ampicillin	≥ 30	≤ 13	14.3	14.3	71.4	6 - 34
TMS**	≥ 18	≤ 13	32.1	0.0	67.9	6 - ≥ 36
Ciprofloxacin	≥ 27	≤ 20	96.4	1.8	1.8	12 - ≥ 36
Nalidixic acid	≥ 19	≤ 18	98.2	0.0	1.8	6 - 35

*S=Susceptible, I=Intermediately susceptible, R=Resistant. **TMS=Trimethoprim/sulfamethoxazole.

TABLE 35. *Shigella flexneri* isolates from human clinical cases (n=56). Distribution (%) of zone diameters (mm).*

Substance	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Tetracycline	78.6	5.4		1.8	3.6											
Chloramph.	17.9		1.8	3.6	7.1	3.6	8.9	14.3	7.1	1.8						1.8
Ampicillin	66.1	1.8	1.8			1.8									1.8	
TMS*	67.9															
Ciprofloxacin							1.8									
Nalidixic acid	1.8															

Substance	22	23	24	25	26	27	28	29	30	31	32	33	34	35	≥ 36
Tetracycline						1.8		3.6		3.6	1.8				
Chloramph.										5.4	1.8	1.8	3.6	3.6	16.1
Ampicillin						1.8	3.6	7.1	8.9	3.6			1.8		
TMS*			1.8				1.8		1.8	1.8		1.8		3.6	19.6
Ciprofloxacin					1.8									1.8	94.6
Nalidixic acid								1.8	8.9	14.3	25.0	28.6	12.5	7.1	

Shaded areas in each row indicate susceptibility (light), intermediate susceptibility (medium) and resistance (dark).
**TMS=Trimethoprim/sulfamethoxazole.

RESULTS AND COMMENTS

As is the case in reports from other countries, resistance was widespread among *Shigella* isolates, regardless of the species. The resistance frequencies were particularly high for trimethoprim/sulfamethoxazole and tetracycline, followed by ampicillin and chloramphenicol. These drugs are commonly used for various clinical purposes within human medicine in many parts of the world. For ampicillin and chloramphenicol there were species differences, as resistance was highly prevalent among *S. flexneri* and less prevalent among *S. sonnei*. Resistance to nalidixic acid was relatively common among *S. sonnei.* Resistance to fluoroquinolones was rarely observed, but the detection of *Shigella* isolates intermediately susceptible to ciprofloxacin and resistant to nalidixic acid indicate that fluoroquinolone resistance may be developing. The few isolates *of S. dysenteriae* (n=7) and *S. boydii* (n=11) detected and susceptibility tested in 2005 indicate that multiresistance is also common in *S. dysenteriae* and *S. boydii*; four and six of the isolates, respectively, were resistant to two or more antimicrobial agents. Only two isolates of both *S. dysenteriae* and *S. boydii*, respectively, were susceptible to all antimicrobial agents included.

D. HUMAN CLINICAL ISOLATES

Gunnar Skov Simonsen, Turid Mannsåker, Per Sandven, Petter Gaustad

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 transition from susceptible bacterial species to inherently more resistant ones will represent de facto emergence of resistance which is not detected. In order to complement the surveillance of individual species, registration of all positive blood cultures in the laboratory information systems of the participants were included in NORM in 2004 and continued in 2005. A patient with a given microbial isolate was excluded from registration with a new isolate of the same identity within a month from the first entry. This rule was applied irrespective of changes in resistance pattern. There were no restrictions concerning registration with a different pathogen. It proved difficult to systematically evaluate the clinical significance of isolates from the skin flora. In Table 36, proportions are therefore estimated from all isolates and from all isolates excluding common skin contaminants such as coagulase negative staphylococci, *Micrococcus* spp., *Corynebacterium* spp., *Bacillus* spp. and *Propionibacterium* spp. This does not imply that such isolates should be disregarded in all instances, 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 the laboratories. Again, limitations of the data extraction procedure prohobited in-depth analysis of these parameters.

TABLE 36. Number of blood culture isolates in 2005, 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 and 2005.

Species	No. of isolates 2005	% of all isolates		% of isolates excluding skin flora	
		2004	2005	2004	2005
Staphylococcus aureus	1,128	12.3	10.3	14.0	13.3
Coagulase negative staphylococci	2,230	11.3	20.3	-	-
Streptococcus pneumoniae	1,027	11.6	9.4	13.2	12.1
Streptococcus pyogenes	239	2.3	2.2	2.6	2.8
Streptococcus agalactiae	177	2.0	1.6	2.3	2.1
Betahaemolytic streptococci group C and G	93	0.7	0.8	0.9	1.1
Viridans- and non-haemolytic streptococci	419	4.6	3.8	5.3	5.0
Enterococcus faecalis	444	4.6	4.0	5.2	5.2
Enterococcus faecium	123	1.1	1.1	1.2	1.5
Other Gram positive bacteria	335	1.8	3.1	1.0	1.3
Escherichia coli	2,456	26.2	22.4	29.9	29.0
Klebsiella spp.	596	6.2	5.4	7.2	7.0
Enterobacter spp.	171	1.5	1.6	1.6	2.0
Proteus spp.	206	2.7	1.9	3.0	2.4
Other Enterobacteriaceae	197	1.8	1.8	2.0	2.3
Pseudomonas spp.	229	1.9	2.1	2.2	2.8
Other Gram negatives aerobic bacteria	236	1.7	2.2	2.0	2.8
Bacteroides spp.	202	2.1	1.8	2.4	2.4
Other anaerobic bacteria	238	1.9	2.2	2.0	2.3
Yeasts	218	1.8	2.0	2.0	2.6
Total	**10,964**	**100**	**100**	**100**	**100**

As seen in Table 36 and Figure 27, Gram positive and Gram negative bacteria represented 56.6% and 37.4% of all isolates, respectively. The predominance of Gram positives among all isolates was an increase from 2004 when the distriubution was 52.3% Gram positives and 42.0% Gram negatives. The increase was mainly due to an 80% increase in the prevalence of coagulase negative staphylococci from 11.3% in 2004 to 20.3% in 2005, but similar trends were also noted for *Bacillus* spp. and *Corynebacterium* spp. It is an open question whether these differences represent true changes in the bacteriology of bloodstream infections or result from a higher proportion of skin contaminants being reported in 2005. 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 44.4% Gram positives and 48.3% Gram negatives.

Among the aerobic Gram negatives, *E. coli* and other Enterobacteriaceae accounted for the vast majority of isolates. However, *Pseudomonas* spp. (2.1% of all, 2.8% excluding skin flora) and the miscellaneous group of "other" Gram negatives excluding Enterobacteriaceae and *Pseudomonas* spp. (2.2% of all, 2.8% excluding skin flora) both increased from 2004 by 19% of all isolates and 33% excluding skin flora. This trend will be closely monitored as non-Enterobacteriaceae Gram negatives may harbor clinically important intrinsic and acquired resistance determinants.

Anaerobic bacteria and yeasts were less common with 4.0% anaerobes (4.7% excluding skin flora) and 2.0% yeasts (2.6% excluding skin flora). The major pathogens in these groups were members of the *Bacteroides fragilis* group (1.4% / 1.8%) and *Candida albicans* (1.2% / 1.6%), but a multitude of other species were also represented.

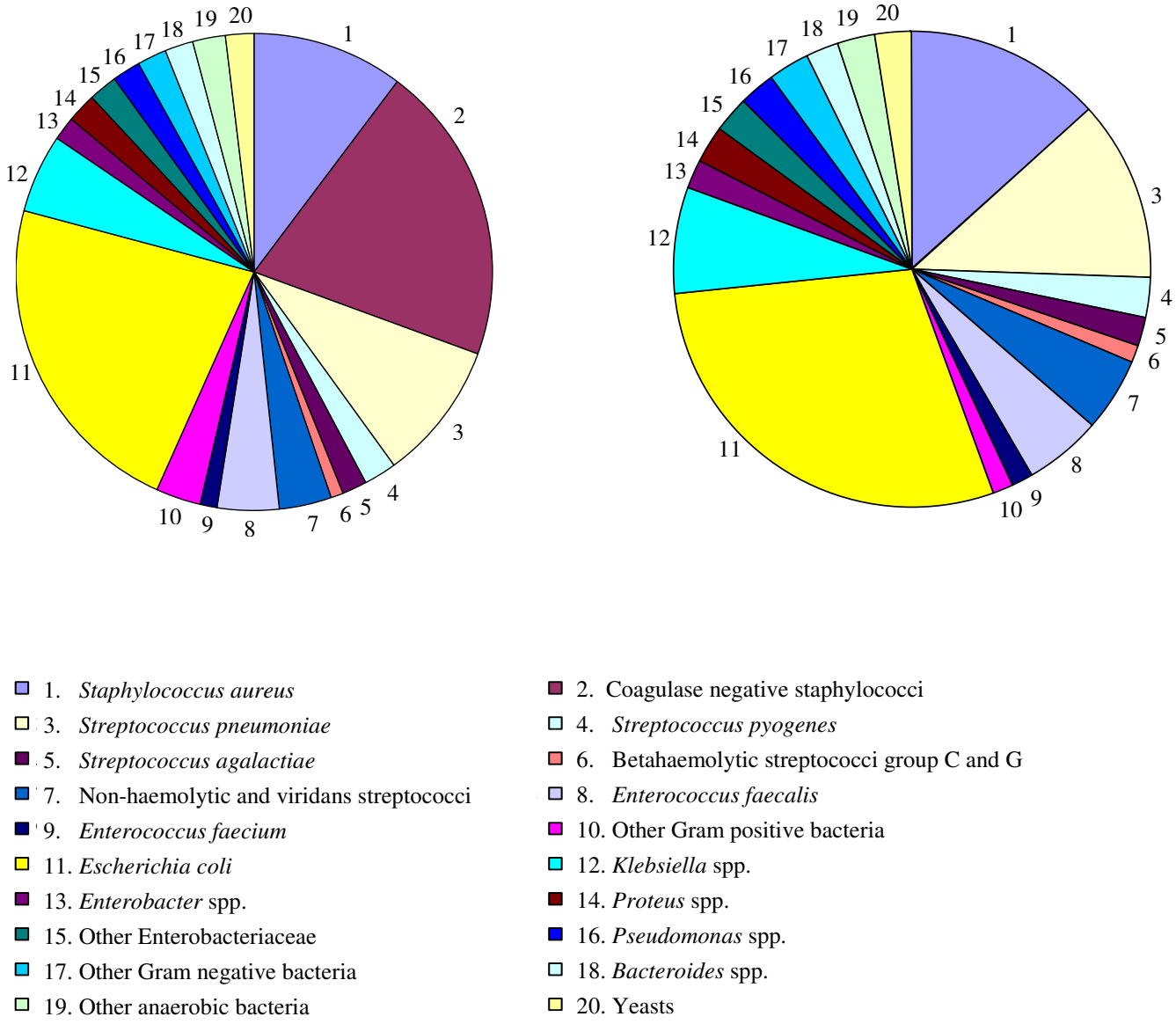

FIGURE 27. Distribution of all blood culture isolates (left, n=10,964) and blood culture isolates excluding coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. (right, n=8,463) in Norway in 2005. The figure is based on data from the information systems of the participating laboratories.

Escherichia coli in blood cultures

TABLE 37. *Escherichia coli* blood culture isolates (n=993). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Ampicillin	≤ 0.5	≥ 16	0.4	67.0	32.6	0.25 - ≥ 256	4	≥ 256
Cefuroxime	≤ 0.5	≥ 16	0.8	95.2	4.0	0.125 - ≥ 256	4	8
Cefotaxime	≤ 1	≥ 8	99.3	0.3	0.4	0.016 - ≥ 256	0.064	0.125
Ceftazidime	≤ 1	≥ 16	98.5	1.1	0.4	0.032 - ≥ 256	0.25	0.5
Cefpirome	≤ 1	≥ 16	99.5	0.1	0.4	0.016 - ≥ 256	0.064	0.125
Ciprofloxacin	≤ 0.5	≥ 2	95.0	0.4	4.6	0.002 - ≥ 32	0.016	0.032
Gentamicin	≤ 2	≥ 8	97.5	0.5	2.0	0.016 - ≥ 256	0.5	1
Meropenem	≤ 0.5	≥ 4	100.0	0.0	0.0	0.004 - 0.5	0.032	0.032
Pip/Tazo**	≤ 8	≥ 32	98.9	0.2	0.9	0.032 - ≥ 256	2	4
TMS***	≤ 2	≥ 16	81.6	0.3	18.1	0.008 - ≥ 32	0.125	≥ 32
Nalidixic acid	≥ 19 mm	≤ 18 mm	90.7	-	9.3			
ESBL			99.5	-	0.5			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Pip/Tazo=Piperacillin/tazobactam
***TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 38. *Escherichia coli* blood culture isolates (n=993). Distribution (%) of MICs (mg/L).*

	≤0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampicillin						0.1	0.3	1.9	10.6	42.7	11.8	1.5	0.3	0.6	0.6	29.6
Cefuroxime					0.1	0.1	0.6	2.2	33.1	50.1	9.8	2.6	0.5	0.3		0.6
Cefotaxime		1.8	9.8	56.2	25.3	4.3	1.2	0.7	0.1	0.2			0.1			0.3
Ceftazidime			0.5	4.8	37.5	42.8	11.1	1.8	0.8	0.2	0.1	0.1	0.1	0.1		0.1
Cefpirome		2.1	29.8	51.7	13.0	2.1	0.4	0.4		0.1			0.1		0.1	0.2
Ciprofloxacin	35.1	49.3	5.8	0.9	1.2	2.1	0.4	0.4	0.1	0.5	0.2	0.2	3.6			
Gentamicin		0.1		0.1	3.1	29.7	45.6	16.8	2.0	0.5	0.3	0.1	0.1	0.8	0.5	0.2
Meropenem	2.4	37.3	58.3	1.7	0.1	0.1	0.1									
Pip/Tazo**			0.2	0.2	0.3	0.7	4.0	39.1	45.4	8.1	0.9	0.2	0.5			0.4
TMS***	0.2	0.8	5.5	39.8	24.5	5.5	4.1	0.8	0.3	0.2	0.1		18.1			

	≤ 18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	≥ 33
Nalidixic acid	9.3	0.4	0.5	1.2	1.9	3.4	5.7	7.2	9.0	12.1	14.3	10.6	12.5	5.5	3.3	3.1

*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.
**Pip/Tazo=Piperacillin/tazobactam
***TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS 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 breakpoints for resistance for Enterobacteriaceae remained unchanged from 2005 to 2006, and the resistance rates from 2004 and 2005 are therefore directly comparable. Amoxicillin/calvulanic acid was removed from the surveillance scheme in 2005 as it was felt that piperacillin/clavulanic acid may serve as a class representative of beta-lactam/beta-lactamases inhibitor combinations. Conversely, cefuroxime was reintroduced after being omitted in 2004.

The vast majority of isolates remained fully susceptible to broad-spectrum antimicrobials such as cefotaxime, ceftazidime, cefpirome, meropenem, gentamicin and piperacillin/tazobactam, see Tables 37 and 38. However, the slow increase in gentamicin non-susceptibility noted in 2004 continued in 2005 and reached 0.5% I (0.1% in 2003 and 0.3% in 2004) and 2.0% R (0.6% in 2003 and 1.3% in 2004) as seen in Figure 28. This trend will be closely watched as it may threaten the traditional aminoglycoside-based empirical regimens often used for treatment of septicaemia in Norway. Similarly, the prevalence of non-suscpetibility to fluoroquinolones continued to increase from a total of 3.3% in 2004 to 5.0% in 2005. The increase was most pronounced among fully resistant isolates from 3.2% in 2004 to 4.6% in 2005. The trend for ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 29. In 2005, the diagnostic quality of fluoro-quinolone test results was verified by introduction of the nalidixic acid screening disk. The results confirmed the usefulnes of this screening strategy as all ciprofloxacin

non-susceptible isolates (n=50) were resistant to nalidixic acid whereas all ciprofloxacin susceptible isolates were susceptible to nalidixic acid (Figure 30). A number of strains (n=42) were suscpetible to ciprofloxacin and resistant to nalidixic acid and thus appeared as false positives, but their MIC values of 0.064 – 0.5 mg/L were clearly above the normal distribution of the wilde-type population and may thus indicate the presence of first-step gyrase and/or topoisomerase mutations in this population. There were no significant changes in the SIR distributions of trimetho-prim/sulfamethoxazole, ampicillin and cefuroxime from 2004 to 2005. These substances are sometimes used for treatment of less severe infections, but antibiotic treatment regimens should be adjusted according to susceptibility test results as significant proportions of isolates are non-susceptible to these agents.

In 2005, the detection of extended spectrum beta-lactamases (ESBL) was based on MIC values of cefotaxime, ceftazidim and cefpirome in addition to visual inspection of a disk approximation test. All isolates with a positive disk approximation test and/or reduced susceptibility to ceftazidime (MIC ≥ 1 mg/L) and/or cefotaxime (MIC ≥ 1 mg/L) and/or cefpirome (MIC ≥ 1 mg/L) were further characterized by combination Etests and/or molecular examinations. A total of six isolates were registered as ESBL producers, but only five were verified by Etest (0.5%). All these five isolates were non-susceptible to ampicillin (MIC ≥ 256 mg/L), cefuroxime (MIC 64 – 256 mg/L), cefotaxime (MIC 4 – 256 mg/L), and ceftazidime (MIC 8 – 256 mg/L), and four of them were non-susceptible to cefpirome (MIC 32 – 256 mg/L). Three of the isolates were in addition high-level resistant to ciprofloxacin, but all remained susceptible to meropenem. The ESBL prevalence of 0.5% is in accordance with NORM surveillance data from previous years (0.3% in 2003 and 0.7% in 2004). The MIC profiles with cefotaxime MICs above ceftazidime MICs may indicate that CTX-M enzymes continue to predominate in Norway as recently reported from the Reference Centre for Antibiotic Resistance Determination. Etests for cefotaxime and cefpirome revealed a limited number of non-ESBL strains with moderately elevated MIC values for cefotaxime and cefpirome (two and one, respectively), but in accordance with disk diffusion results from NORM 2004 a number of strains were non-susceptible to ceftazidime (MIC 2 mg/L: n=7; MIC 4 mg/L: n=2).

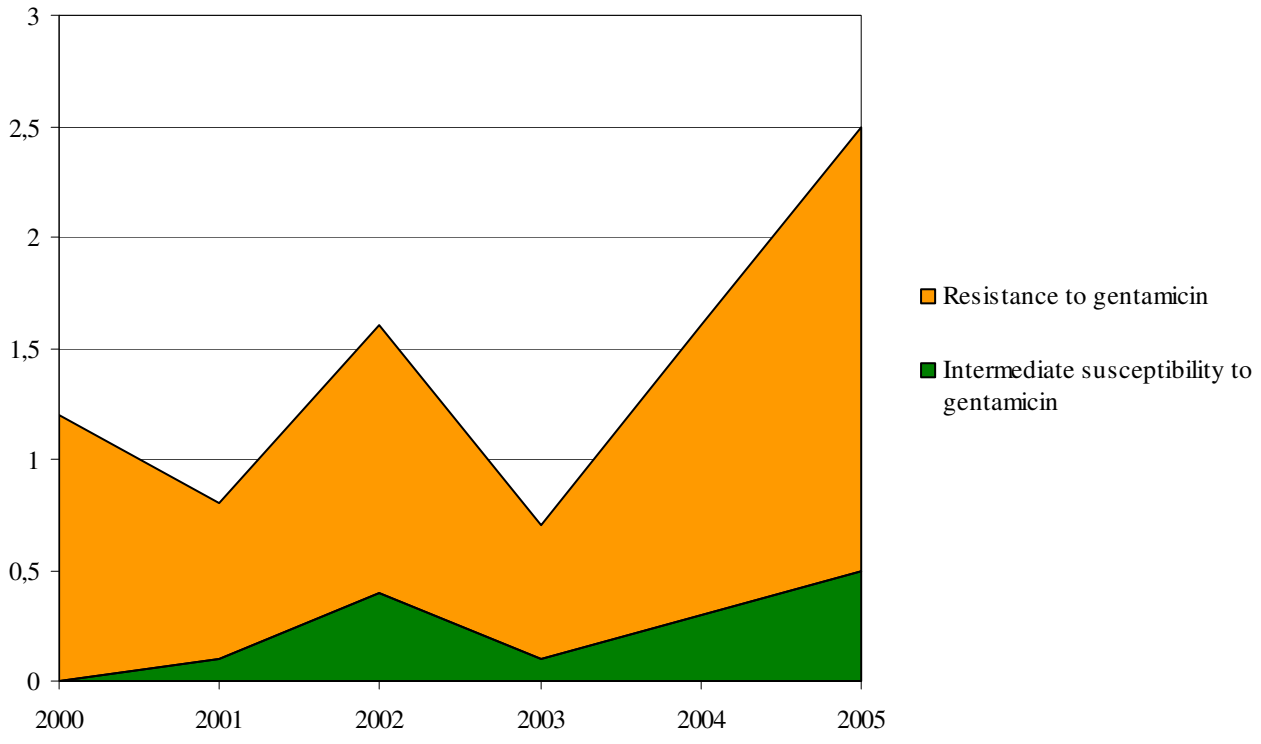

FIGURE 28. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000 – 2005.

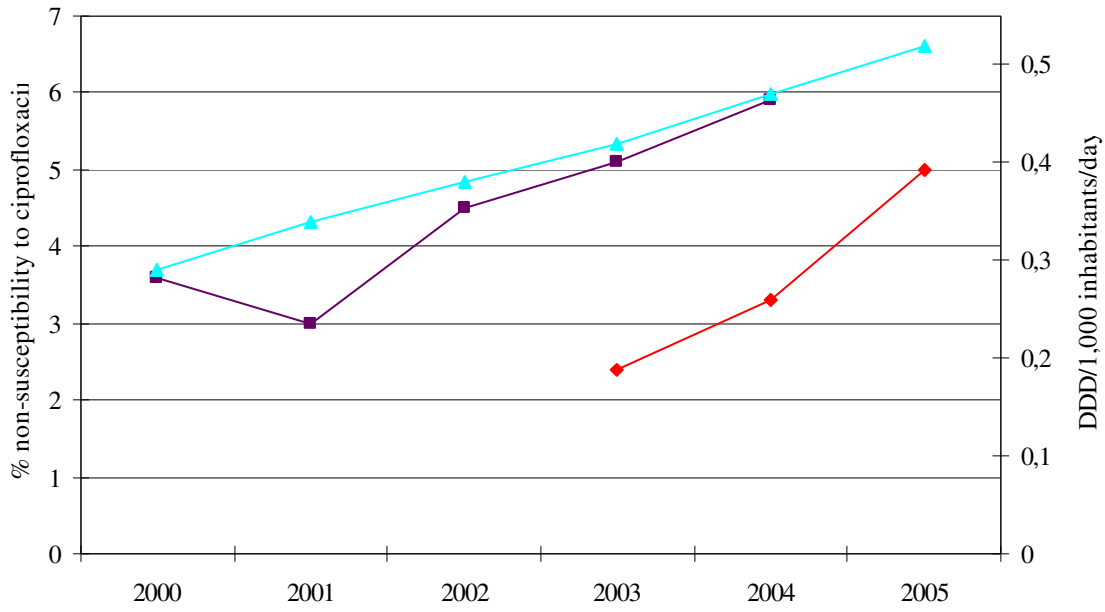

FIGURE 29. Prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the former (magenta) and present (red) breakpoint protocol versus usage of ciprofloxacin (turquoise) 2000 – 2005.

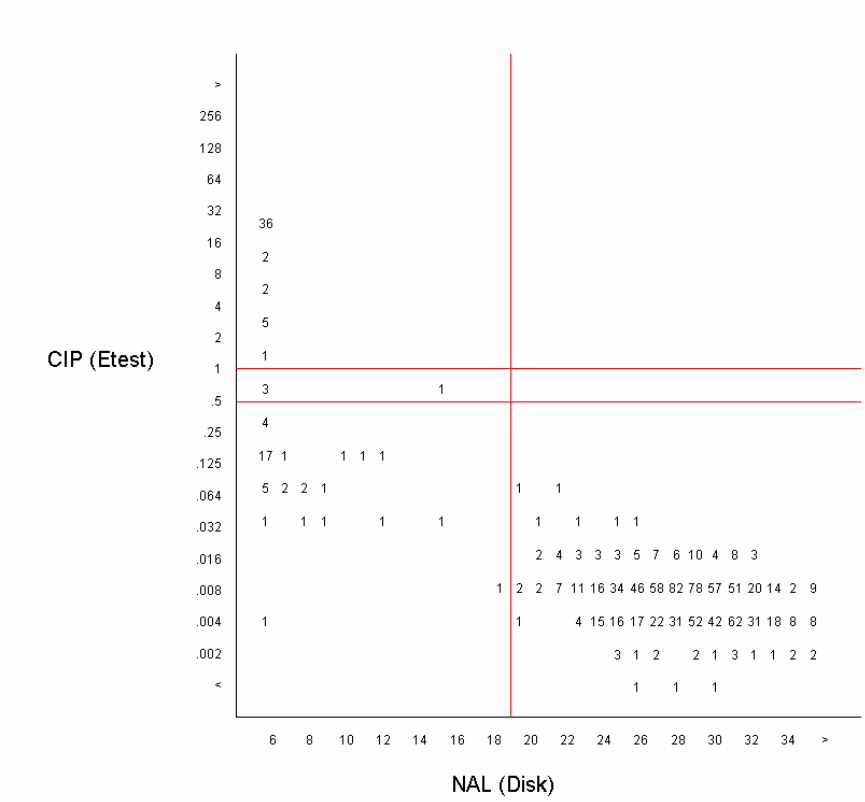

FIGURE 30. Correlation between nalidixic acid zone diameters and MICs of ciprofloxacin among 993 *E. coli* blood culture isolates from 2005. The figures indicate number of strains. Red lines represent breakpoints for the nalidixic acid screening disk (S ≥ 19 mm, R ≤ 18 mm) and ciprofloxacin (S ≤ 0.5 mg/L, R ≥ 2 mg/L).

Klebsiella spp. in blood cultures

TABLE 39. *Klebsiella* spp. blood culture isolates (n=359). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Cefuroxime	≤ 0.5	≥ 16	2.8	88.3	8.9	0.064 - ≥ 256	2	8
Cefotaxime	≤ 1	≥ 8	98.3	1.1	0.6	0.016 - 8	0.064	0.25
Ceftazidime	≤ 1	≥ 16	95.3	3.9	0.8	0.032 - 128	0.25	1
Cefpirome	≤ 1	≥ 16	98.6	1.1	0.3	0.016 - 16	0.064	0.25
Ciprofloxacin	≤ 0.5	≥ 2	98.3	0.8	0.8	0.004 - ≥ 32	0.032	0.125
Gentamicin	≤ 2	≥ 8	98.9	0.3	0.8	0.064 - ≥ 256	0.5	1
Meropenem	≤ 0.5	≥ 4	100.0	0.0	0.0	0.016 - 0.25	0.032	0.064
Pip/Tazo**	≤ 8	≥ 32	92.8	5.3	1.9	0.064 - ≥ 256	2	8
TMS***	≤ 2	≥ 16	95.5	0.6	3.9	0.016 - ≥ 32	0.125	0.5
Nalidixic acid	≥ 19 mm	≤ 18 mm	88.6	-	11.4			
ESBL			99.4	-	0.6			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Pip/Tazo=Piperacillin/tazobactam
***TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 40. *Klebsiella* spp. blood culture isolates (n=359). 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
Ceforoxime					0.6		1.7	0.6	7.2	46.0	29.2	5.8	5.3	2.2	0.8		0.6
Cefotaxime			3.0	18.9	51.3	15.3	3.6	5.0	1.1	0.8	0.3	0.6					
Ceftazidime				1.1	4.7	29.2	40.7	13.6	5.8	3.6		0.3		0.3	0.3	0.3	
Cefpirome			1.9	14.8	54.3	15.6	5.6	4.7	1.7	0.6	0.3	0.3	0.3				
Ciprofloxacin	0.3	3.9	19.4	51.5	11.1	4.5	4.7	2.8	0.8	0.3	0.3			0.3			
Gentamicin					0.3	2.5	27.0	58.8	9.7	0.6	0.3			0.3	0.3		0.3
Meropenem			5.3	73.0	20.9	0.6	0.3										
Pip/Tazo**					0.3	0.3	0.8	1.7	8.6	42.1	33.7	5.3	5.3	0.3			1.7
TMS***			0.3	1.7	14.2	46.0	25.1	5.0	2.5	0.8	0.6			3.9			

	≤ 18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Nalidixic acid	11.4	1.1	4.2	3.3	6.4	12.8	13.4	16.2	12.0	7.8	7.0	1.9	1.4	0.8	0.3		

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

RESULTS AND COMMENTS

The surveillance of *Klebsiella* spp. in blood cultures included 257 *K. pneumoniae* (71.6%), 46 *K. oxytoca* (12.8%) and 56 (15.6%) isolates not identified to the species level giving a total of 359 *Klebsiella* spp. isolates (Tables 39 and 40). As for *E. coli* there were no changes in breakpoints from the NORM/NORM-VET 2004 report. Ampicillin and amoxicillin/clavulanic acid were removed from the surveillance scheme whereas cefuroxime was reintroduced.

There were no significant changes in the overall prevalences of resistance to cephalosporins, fluoroquinolones, aminoglycosides, carbapenems and trimethoprim/sulfamethoxazole from 2004 to 2005 (Figure 31). The vast majority of isolates were fully susceptible to these agents, and *Klebsiella* spp. were even more suscpetible to gentamicin, ciprofloxacin and TMS than *E. coli* blood culture isolates were (prevalences of non-susceptibility: 2.5%, 5.0% and 18.4% in *E. coli*; and 1.1%, 1.6% and 4.5% in *Klebsiella* spp., respectively). The exception to this rule was piperacillin/tazobactam with 1.1% non-susceptibility in *E. coli* and 7.2% in *Klebsiella* spp.

The nalidixic acid screening test for reduced susceptibility to fluoroquinolones also proved useful in *Klebsiella* spp. All isolates non-susceptible to ciprofloxacin (intermediately susceptible n=3 and resistant n=3) were resistant to nalidixic acid, and none of the nalidixic acid susceptible isolates displayed reduced susceptibility to ciprofloxacin. A total of 35 isolates were resistant to nalidixic acid and susceptible to ciprofloxacin. This population had higher ciprofloxacin MIC values than the nalidixic acid susceptible isolates, but the two populations were less well separated than in *E. coli*.

As for *E. coli*, the detection of extended spectrum beta-lactamases (ESBL) was based on MIC values of cefotaxime, ceftazidim and cefpirome in addition to visual inspection of a disk approximation test. All isolates with a positive disk approximation test and/or reduced susceptibility to ceftazidime (MIC ≥ 1 mg/L) and/or cefotaxime (MIC ≥ 1 mg/L) and/or cefpirome (MIC ≥ 1 mg/L) were further characterized by combination Etests and/or molecular examinations. Only two isolates were reported as positive, giving an overall ESBL prevalence of 0.6% which is the same figure as in 2004. One isolate was a *K. pneumoniae* while the other was unspeciated, and both displayed MIC profiles indicative of SHV-mediated resistance to oxyimino-cephalosporins (ceftazidime MICs of 64 and 128 mg/L and cefotaxime MICs of 4 and 8 mg/L). In addition to the confirmed ESBL producers, a total of 16 isolates (4.5%) were suspected as being ESBL-producers on the basis of borderline susceptible or non-suscepetible to cefpirome (n=3) and/or cefotaxime (n=4) and/or ceftazidime (n=14).

There were only minor differences in SIR distributions and MIC_{50}/MIC_{90} values between *K. pneumoniae*, *K. oxytoca* and unspeciated *Klebsiella* spp.. *K. oxytoca* isolates were slightly less susceptible to cephalosporins than other *Klebsiella* spp., and the prevalence of non-susceptibility to piperacillin/tazobactam in *K. oxytoca* was 8.6% (4.3% I and 4.3% R) as compared to 7.0% (5.1% I and 1.9% R) in *K. pneumoniae*. These differences are most likely due to differences in regulation and enzymatic profiles of the chromosomal beta-lactamases K1 in *K. oxytoca* and SHV1 in *K. pneumoniae*. As previously noted in the NORM surveillance data, there was a marked difference between *K. pneumoniae* and *K. oxytoca* in terms of resistance to non beta-lactam antimicrobials with *K. pneumoniae* being significantly more resistant to ciprofloxacin (4.1% non-susceptibility) and trimethoprim/sulfamethoxazole (6.9% non-susceptibility). Not a single *K. oxytoca* isolate was non-susceptible to these substances.

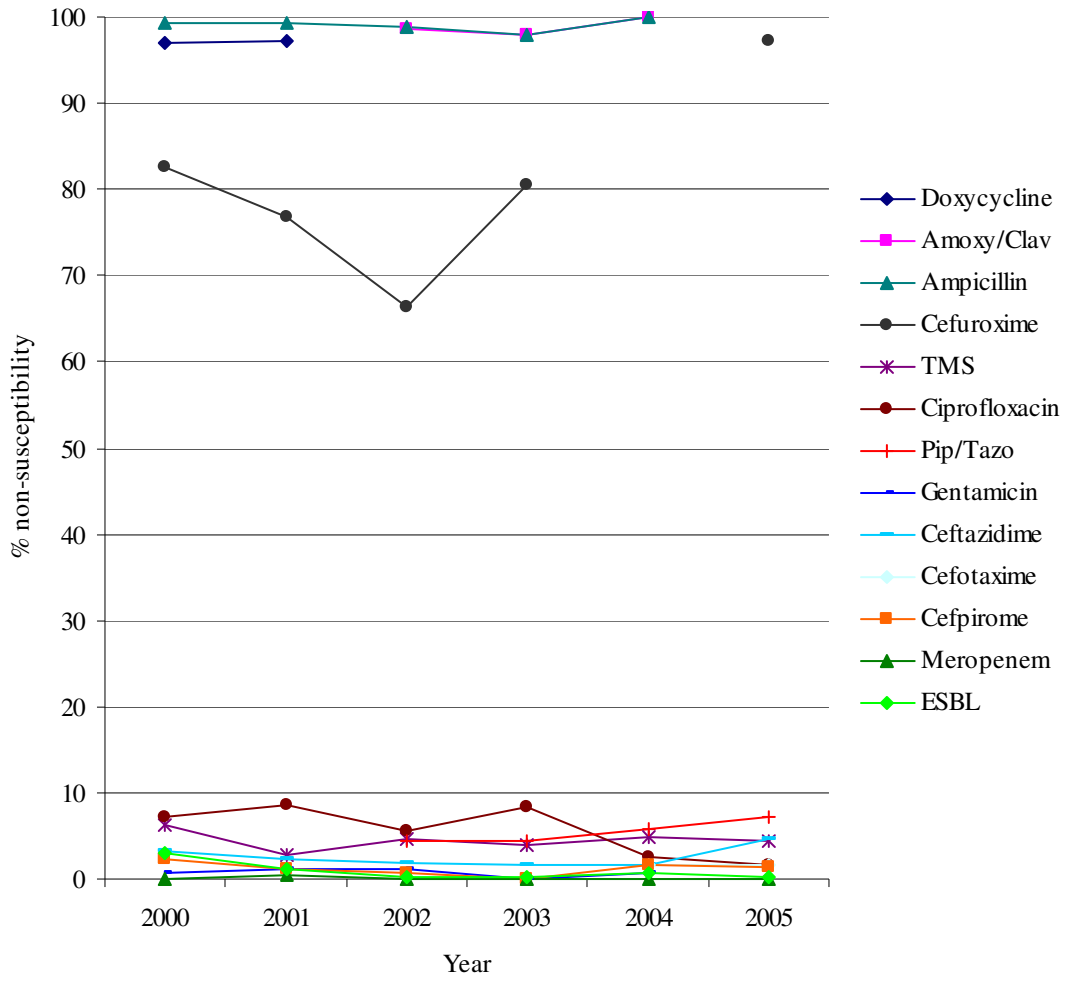

FIGURE 31. Prevalence of non-susceptibility to various antimicrobials in *Klebsiella* spp. blood culture isolates 2000-2005.

Enterococcus spp. in blood cultures

TABLE 41. *Enterococcus* spp. blood culture isolates (n=325). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints mg/L		Proportion of isolates (%)*			MIC range	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Ampicillin	≤ 2	≥ 16	84.0	1.5	14.5	0.064 - ≥ 256	1	≥ 256
Gentamicin	≤ 128	≥ 256	73.8	-	26.2	2 - ≥ 1024	16	≥ 1024
Penicillin G	≤ 4	≥ 16	65.5	10.2	24.3	0.064 - ≥ 256	4	≥ 256
Streptomycin	≤ 256	≥ 512	68.0	-	32.0	8 - ≥ 1024	256	≥ 1024
Quinu/Dalfo**	≤ 1	≥ 4	17.2	4.0	78.8	0.125 - ≥ 32	16	32
Linezolid	≤ 4	≥ 8	100.0	-	0.0	0.125 - 4	2	2
Vancomycin Screen			99.7	-	0.3			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Quinu/Dalfo=Quinupristin/Dalfopristin

TABLE 42. *Enterococcus* spp. blood culture isolates (n=325). Distribution (%) of MICs (mg/L).*

	≤ 0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥ 1024
Ampicillin			0.3	1.2	3.1	11.1	41.8	26.5	1.2	0.3			1.5	1.5	11.4		
Gentamicin								2.5	8.6	19.7	35.4	7.1	0.3	0.3	4.0		22.2
Penicillin G			0.6	0.6	0.6	1.2	4.6	30.8	27.1	10.2	5.2	7.4			11.7		
Streptomycin										1.2	1.2	6.8	8.9	24.3	25.5		32.0
Quinu/Dalfo**				0.3	1.5	9.5	5.8	4.0	7.7	19.7	28.3	23.1					
Linezolid				0.3	0.3	3.4	43.7	48.3	4.0								

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

TABLE 43. *Enterococcus faecalis* blood culture isolates (n=239). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints mg/L		Proportion of isolates (%)*			MIC range	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Ampicillin	≤ 2	≥ 16	100.0	0.0	0.0	0.125 - 2	1	2
Gentamicin	≤ 128	≥ 256	75.7	-	24.3	2 - ≥ 1024	16	≥ 1024
Penicillin G	≤ 4	≥ 16	75.7	11.1	12.1	0.064 - ≥ 256	4	16
Streptomycin	≤ 256	≥ 512	69.5	-	30.5	8 - ≥ 1024	256	≥ 1024
Quinu/Dalfo**	≤ 1	≥ 4	3.3	0.8	95.8	0.125 - ≥ 32	16	32
Linezolid	≤ 4	≥ 8	100.0	-	0.0	0.125 - 4	2	2
Vancomycin Screen			100.0	-	0.0			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Quinu/Dalfo=Quinupristin/Dalfopristin

TABLE 44. *Enterococcus faecalis* blood culture isolates (n=239). Distribution (%) of MICs (mg/L).*

	≤ 0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥ 1024
Ampicillin				0.4	1.7	9.4	55.3	33.2									
Gentamicin								0.4	2.1	17.6	45.6	9.2	0.4	0.4	2.1		22.2
Penicillin G			0.4			0.4	4.6	34.7	35.6	12.1	6.3	5.0			0.8		
Streptomycin										0.4	0.4	2.5	3.7	28.9	33.5		30.5
Quinu/Dalfo**				0.4	0.4	2.1	0.4	0.8	7.5	25.1	35.6	27.6					
Linezolid				0.4	0.4	1.7	42.3	52.7	2.5								

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

TABLE 45. *Enterococcus faecium* blood culture isolates (n=53). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints mg/L		Proportion of isolates (%)*			MIC range	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Ampicillin	≤ 2	≥ 16	14.0	8.8	77.1	0.5 - ≥ 256	≥ 256	≥ 256
Gentamicin	≤ 128	≥ 256	64.2	-	35.8	2 - ≥ 1024	8	≥ 1024
Penicillin G	≤ 4	≥ 16	5.7	7.5	86.8	2 - ≥ 256	≥ 256	≥ 256
Streptomycin	≤ 256	≥ 512	52.8	-	47.2	8 - ≥ 1024	256	≥ 1024
Quinu/Dalfo**	≤ 1	≥ 4	81.1	11.3	7.5	0.25 - 8	1	2
Linezolid	≤ 4	≥ 8	100.0	-	0.0	0.5 - 4	1	2
Vancomycin Screen			100.0	-	0.0			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Quinu/Dalfo=Quinupristin/Dalfopristin

TABLE 46. *Enterococcus faecium* blood culture isolates (n=53). Distribution (%) of MICs (mg/L).*

	≤ 0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	≥ 1024
Ampicillin						1.8	1.8	10.5	7.0	1.8			7.0	8.8	61.4		
Gentamicin								3.8	17.0	34.0	7.5	1.9			5.7		30.2
Penicillin G								1.9	3.8	7.5	1.8	17.0			67.9		
Streptomycin										1.9	3.8	15.1	22.6	5.7	3.8		47.2
Quinu/Dalfo**					7.5	41.5	32.1	11.3	5.7	1.9							
Linezolid						13.2	52.8	32.1	1.9								

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

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a genus and as separate species. 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 Tables 41 and 42. The *Enterococcus* spp. surveillance in NORM 2005 included 239 (73.5%) *E. faecalis* isolates, 53 (16.3%) *E. faecium* isolates and 33 (10.1%) unspeciated enterococcal isolates.

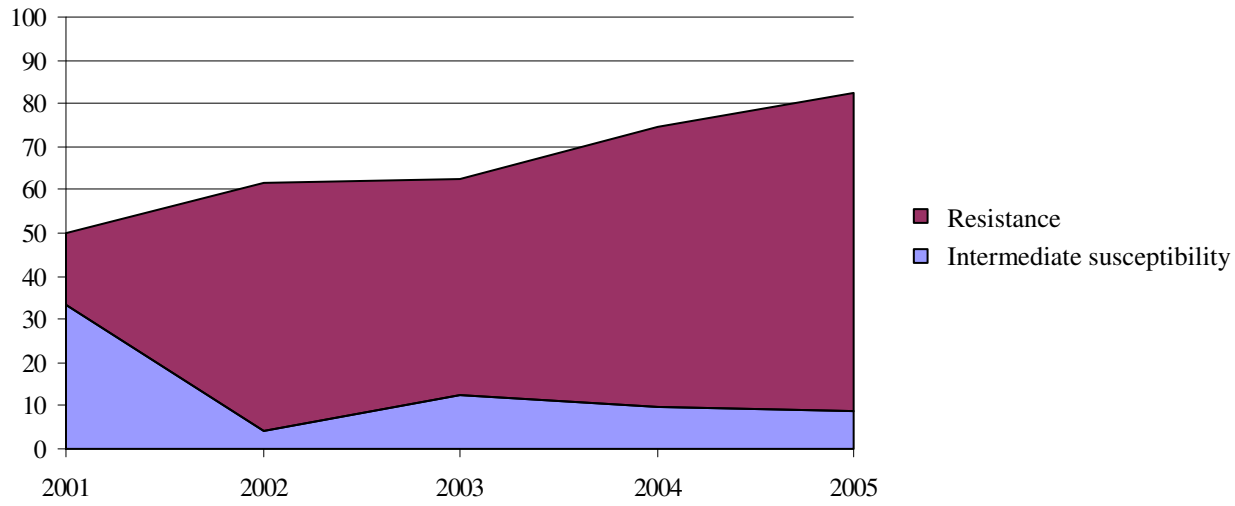

FIGURE 32. Prevalence of intermediate susceptibility and resistance to ampicillin in *E. facium* blood culture isolates. The breakpoints applied were S ≤ 1 mg/L and R ≥ 32 mg/L in 2001 and 2002, and S ≤ 2 mg/L and R ≥ 16 mg/L in 2003-2005.

E. faecalis was still uniformly susceptible to ampicillin (Tables 43 and 44) whereas the prevalence of non-susceptibility to this agent continued to increase in *E. faecium* from 74.5% in 2004 to 82.5% in 2005 (Tables 45 and 46, Figure 32). The data indicate continuing spread 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. This hypothesis is supported by the observed increase in high-level resistance to gentamicin in *E. faecium* from 2.5% in 2003 to 19.6% in 2004 and now 35.8% in 2005 (Figure 33). A total of 42.9% of ampicillin non-susceptible *E. faecium* isolates were high-level resistant to gentamicin, whereas all gentamicin resistant isolates were non-susceptible to ampicillin thus giving an overall prevalence of 36.8% for combined ampicillin non-susceptibility/high-level gentamicin resistance. The prevalence of high-level resistance to gentamicin in *E. faecalis* may have stabilised at 24.3% in 2005 compared to 22.0% in 2004.

Fortunately, vancomycin resistant enterococci (VRE) have not yet been established in Norway. Only a single VRE isolate was registered in NORM 2005, and this turned out to be an *E. casseliflavus* strain with chromosomally encoded VanC resistance. The streptogramin combination quinupristin/dalfopristin (QD) and the oxazolidinone linezolid were included for the first time in NORM in 2005. As expected, most *E. faecium* isolates were susceptible to QD with only 7.5% of isolates displaying an MIC ≥ 4 mg/L. *E. faecalis* is inherently resistant to QD, presumably due to the chromosomal *lsa* gene which encodes a putative ABC transporter. All enterococcal isolates were fully susceptible to linezolid.

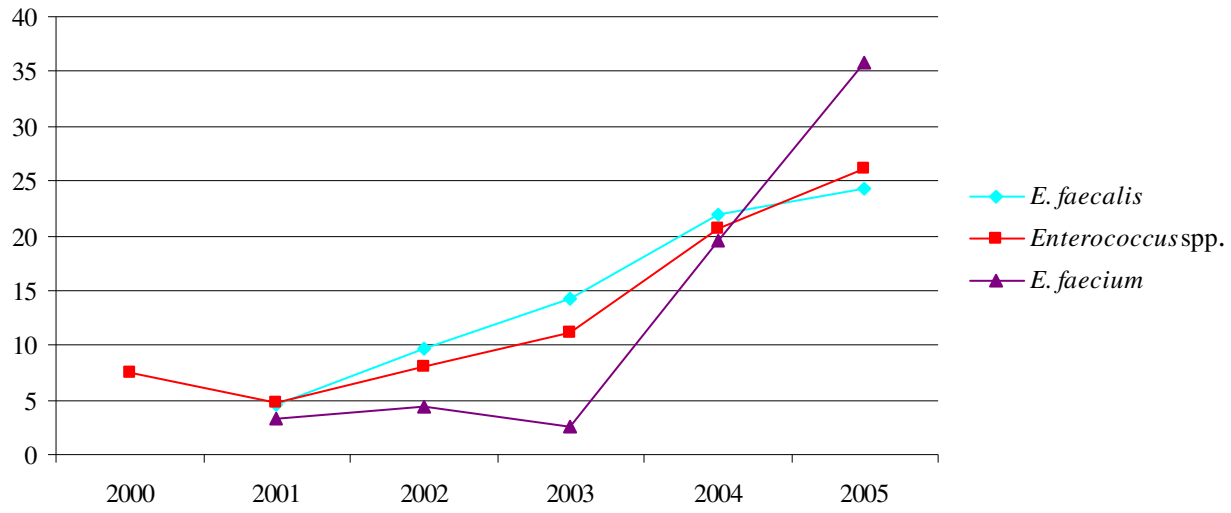

FIGURE 33. Prevalence of high-level resistance to gentamicin in blood culture isolates of *E. faecalis*, *E. faecium* and all enterococci combined 2000-2005. The breakpoint for high-level resistance was decreased from R ≥ 1024 mg/L to R ≥ 256 mg/L in 2004.

Streptococcus pneumoniae in blood cultures

TABLE 47. *Streptococcus pneumoniae* blood culture isolates (n=704). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Cefotaxime	≤ 0.5	≥ 4	99.6	0.4	0.0	0.002 - 1	0.016	0.032
Chloramph.	≤ 4	≥ 8	99.1	-	0.9	0.25 - 16	2	4
Erythromycin	≤ 0.5	≥ 1	89.2	-	10.8	0.032 - ≥ 256	0.125	8
Norfloxacin						1 - ≥ 32	4	8
Pen G**	≤ 0.064	≥ 2	97.9	1.7	0.4	0.004 - 4	0.016	0.032
Tetracycline	≤ 2	≥ 4	96.7	-	3.3	- 64	0.125	0.25
TMS***	≤ 0.5	≥ 4	96.7	2.0	1.3	0.016 - ≥ 32	0.25	0.5
Oxacillin screen	≥ 20 mm	≤ 19 mm	96.6	-	3.4			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Pen G=Benzylpenicillin.
***TMS= Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 48. *Streptococcus pneumoniae* blood culture isolates (n=704). 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
Cefotaxime	0.4	6.5	71.3	18.9	0.7	0.4	0.7	0.6	0.4							
Chloramph.							0.1		8.7	70.6	19.7	0.3	0.6			
Erythromycin				0.9	8.5	61.9	17.9			0.1	0.6	1.3	3.6	2.4	0.9	2.0
Norfloxacin									1.4	8.2	40.8	42.6	6.7	0.3		
Pen G**	2.8	7.2	56.1	30.0	1.7	0.4	0.6	0.3	0.4	0.3	0.1					
Tetracycline				0.4	9.5	67.9	17.8	0.9		0.3	0.7	0.4	0.7	1.3	0.1	
TMS***				0.1	0.1	11.6	73.0	11.8	1.3	0.7	0.3	0.3	0.1	0.6		

	≤ 19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	3.4	0.6	1.0	2.4	3.1	9.5	20.0	13.4	13.5	11.9	4.7	8.1	1.8	3.3	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.
**Pen G=Benzylpenicillin.
***TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

The results are summarised in Tables 47-48 and Figures 34-36. A total of 15 *S. pneumoniae* isolates were non-susceptible to penicillin G comprising 2.1% of the sample. This is comparable to 2.0% non-susceptibility in 2004. Twelve isolates (1.7%) were defined as intermediately susceptible (MIC 0.125-1 mg/L) whereas three isolates were resistant (MIC 2-4 mg/L). Three of the penicillin G non-susceptible isolates were also the only strains non-susceptible to cefotaxime. These three isolates had cefotaxime MICs of 1 mg/L and penicillin G MICs of 2, 2 and 4 mg/L, respectively. They were also all resistant to macrolides.

The oxacillin disk screen for penicillin non-susceptibility performed well as it recognized all 15 non-susceptible isolates. Only six penicillin G susceptible isolates were falsely identified as penicillin G non-susceptible while 683 isolates were correctly classified as negatives. The correlation between the oxacillin disk screen and penicillin G MICs is displayed in Figure 34.

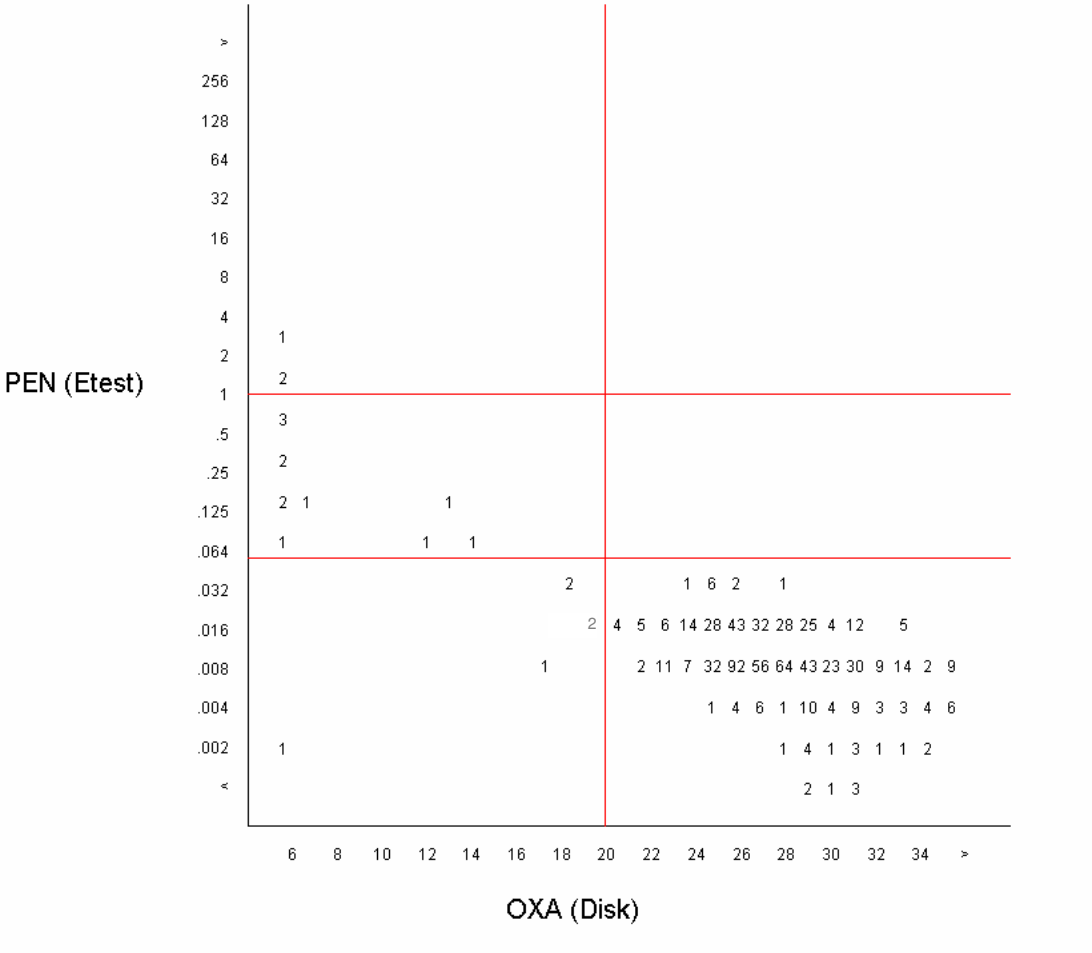

FIGURE 34. Correlation between oxacillin disk zone diameters and MICs of penicillin G among 704 *S. pneumoniae* blood culture isolates from 2005. The figures indicate number of strains. Red lines represent breakpoints for the oxacillin screening disk (S ≥ 20 mm, R ≤ 19 mm) and penicillin G (S ≤ 0.064 mg/L, R ≥ 2 mg/L).

The prevalence of macrolide resistance increased from 9.7% in 2004 to 10.8% in 2005, see Figure 35. 74 out of 76 erythromycin non-susceptible islolates were further subjected to double disk diffusion (DDD) tests for characterization of MLS phenotype. A majority of isolates (9.1% of all isolates, 83.8% of erythromycin non-susceptible isolates) displayed a phenotype compatible with efflux-based M-type resistance to erythromycin only. However, 1.7% of all isolates (16.2% of erythromycin non-susceptible isolates) were either inducibly (n=1) or constitutively (n=11) resistant to clindamycin thus indicating the presence of *erm*-encoded MLS resistance to both macrolides and lincosamides. The increase in macrolide resistance from 2004 to 2005 was entirely attributable to the MLS_B phenotype. There were no significant changes for chloramphenicol, tetracyclines or trimethoprim/ sulfamethoxazole (Figure 36). In the 2005 protocol, ciprofloxacin was replaced by norfloxacin and doxycycline was replaced by tetracycline.

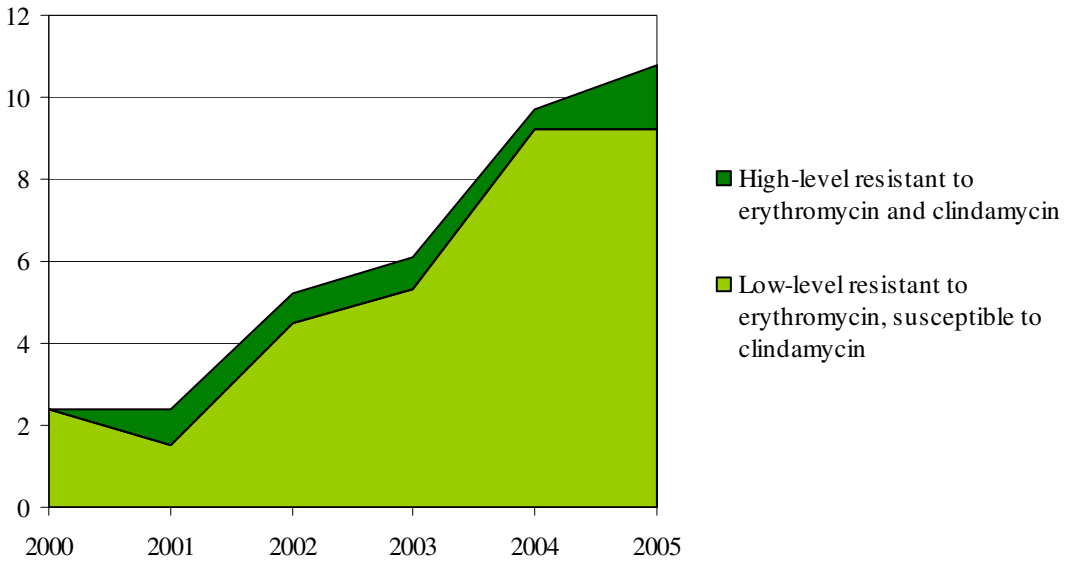

FIGURE 35. Prevalences (%) of macrolide resistant *Streptococcus pneumoniae* blood culture isolates with consitutive or inducible MLS_B phenotype (high-level resistance to ertythromycin and clindamycin) and M phenotype resistance (low-level resistance to erythromycin, susceptibility to clindamycin) 2000-2005.

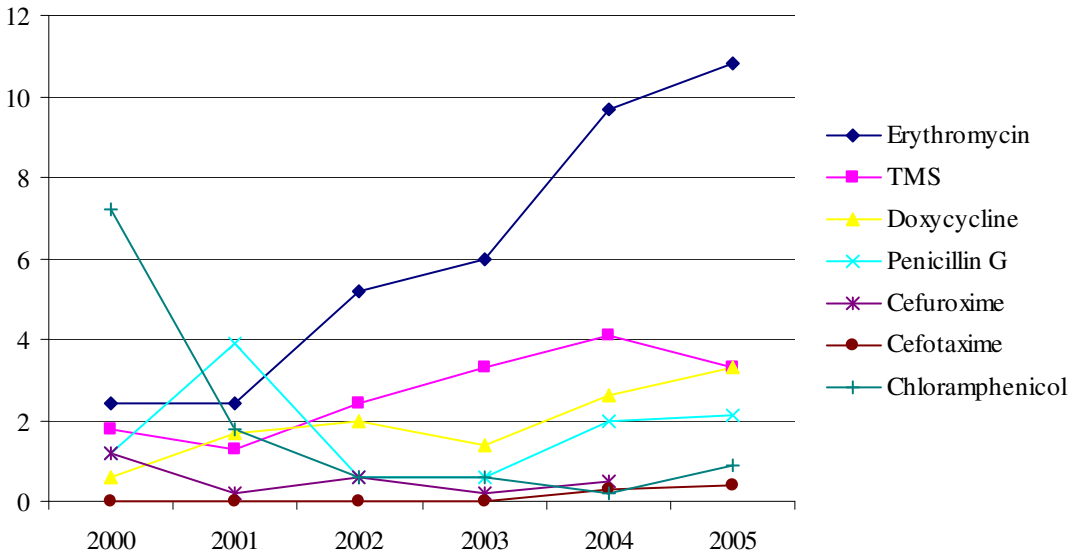

FIGURE 36. Prevalences (%) of non-susceptibility to various antimicrobials in *Streptococcus pneumoniae* blood culture isolates 2000 – 2005. The following breakpoints were adjusted in 2002: Chloramphenicol: S ≤ 2 mg/L and R ≥ 8 mg/L changed to S ≤ 4 mg/L and R ≥ 8 mg/L in 2002; cefuroxime and cefotaxime: S ≤ 1 mg/L and R ≥ 32 mg/L changed to S ≤ 0.5 mg/L and R ≥ 4 mg/L in 2002; trimethoprom/sulfamethoxazole (TMS): S ≤ 2 mg/L and R ≥ 16 mg/L changed to S ≤ 0.5 mg/L and R ≥ 4 mg/L; erythromycin: S ≤ 1 mg/L and R ≥ 4 mg/L changed to S ≤ 0.5 mg/L and R ≥ 1 mg/L.

Staphylococcus aureus in blood cultures

TABLE 49. *Staphylococcus aureus* blood culture isolates (n=741). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Erythromycin	≤ 1	≥ 4	98.1	0.0	1.9	0.032 - ≥ 256	0.25	0.25
Fusidic acid	≤ 0.5	≥ 1	92.3	-	7.7	0.016 - ≥ 256	0.125	0.25
Gentamicin	≤ 1	≥ 2	99.3	-	0.7	0.032 - 4	0.5	0.5
Linezolid	≤ 4	≥ 8	100.0	-	0.0	0.25 - 4	1	2
Oxacillin	≤ 2	≥ 4	99.9	-	0.1	0.064 - 8	0.5	1
Oxacillin screen			100.0	-	0.0			
Cefoxitin screen	≥ 22	≤ 21	100.0	-	0.0			
Penicillin G**	≤ 0.064	≥ 0.25	6.3	24.4	69.2	0.016 - ≥ 256	1	2
Beta-lactamase			29.1	-	70.9			
Vancomycin screen			100.0	-	0.0			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Penicillin G=Benzylpenicillin.

TABLE 50. *Staphylococcus aureus* blood culture isolates (n=741). Distribution (%) of MICs (mg/L).*

	≤0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Erythromycin			1.2	5.7	42.0	45.5	3.6	0.1		0.4	0.3	0.1	0.3			0.8
Fusidic acid		0.4	6.7	35.1	37.2	10.8	2.0	1.2	0.8	3.1	1.2	1.2				0.1
Gentamicin			0.1	0.4	2.3	34.8	57.2	4.5	0.3	0.4						
Linezolid						0.5	20.0	50.1	22.5	6.9						
Oxacillin				0.3	3.1	27.5	51.0	16.3	1.6		0.1					
Penicillin G**		1.5	4.9	19.7	4.7	5.0	6.1	25.1	24.8	4.9	1.3	0.7	0.7	0.3	0.1	0.3

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

RESULTS AND COMMENTS

Not a single methicillin resistant *S. aureus* (MRSA) isolate was detected in the NORM surveillance system in 2005 (Tables 49 and 50). This is in accordance with reports from the laboratory databases of the participating institutions where three out of 1,193 (0.25%) *S. aureus* blood culture isolates were MRSA. None of the twelve *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant. The Norwegian Surveillance System for Communicable Diseases (MSIS) reported an increase in the total number of MRSA infections in Norway from 219 in 2004 to 257 in 2005. However, the cases reported to MSIS are predominantly skin and soft tissue infections and only four were notified as systemic infections. The discrepancy between a very low prevalence of systemic infections and an increasing prevalence of non-systemic infections was thus continued in 2005. There was a remarkable concordance between the results of oxacillin Etests, the oxacillin agar screen and the cefoxitin disk screen.

The surveillance of MRSA in Norway was further strengthened in 2005 by the inclusion of MRSA colonization in MSIS (see below). The results of the Norwegian case-based surveillance system are thus directly comparable to data from the other Nordic countires. In addition, St. Olavs University Hospital in Trondheim has been designated as the Norwegian Reference Centre for MRSA with responsibility for coordination of clonal surveillance and molecular typing. Hopefully, these tools will enable Norway to maintain the presently favourable MRSA situation.

A total of 14 isolates (1.9%) were resistant to erythromycin which is a slight reduction from 2004 (I: 0.3% and R: 2.4%). The macrolide resistance phenotype was determined by double disk diffusion (DDD) tests in all 14 isolates of which 2 (14%) were constitutively MLS_B resistant, 10 (71%) were inducibly MLS_B resistant and 2 (14%) displayed efflux mediated M type resistance. The prevalences of resistance to gentamicin and fusidic acid increased from 0.2% to 0.7% and from 5.8% to 7.7%, respectively. No isolates displayed growth on the vancomycin agar screen and all were fully susceptible to linezolid which was included for the first time in 2005. Figure 37 shows the prevalences of non-susceptibility to various non beta-lactam antimicrobials.

70.9% of the isolates were beta-lactamase positive and 69.2% displayed penicillin G MIC values above the breakpoint for resistance. These figures are essentially unchanged from 2004 (68.1% and 66.9%, respectively). A subgroup analysis revealed that the prevalence of fusidic acid resistance was higher (8.8%) among the 525 beta-lactamase positive isolates compared to the 216 beta-lactamase negative ones (5.1%). There were no significant differences between the two groups for the other non beta-lactam antimicrobials.

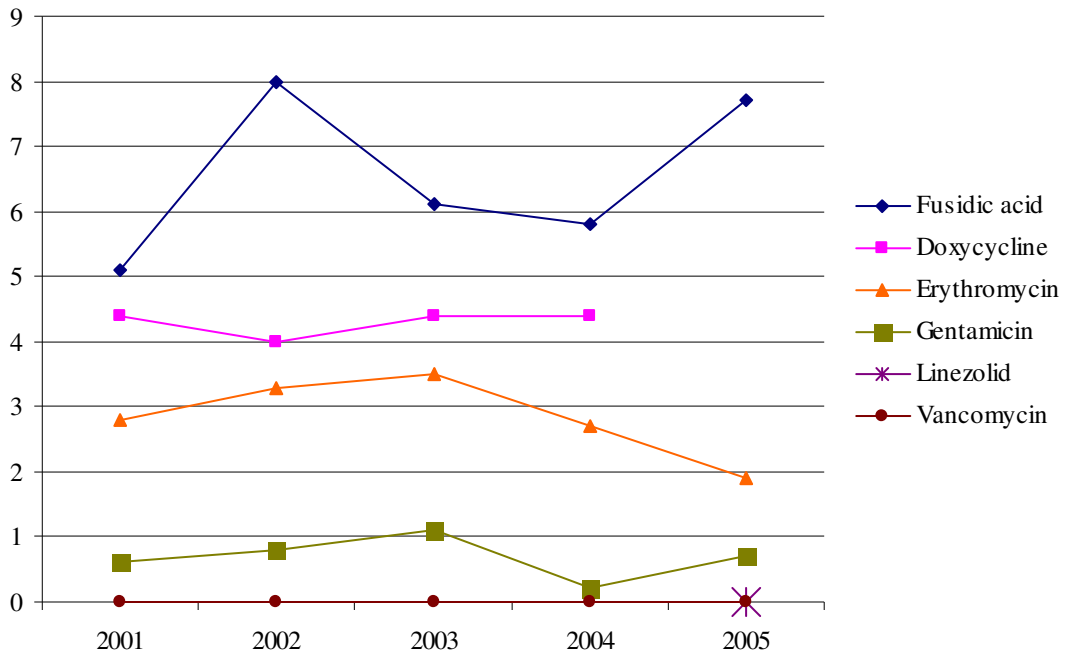

FIGURE 37. Prevalences of non-susceptibility to selected non beta-lactam antimicrobials among *Staphyloccus aureus* blood culture isolates 2000 – 2005. The breakpoint for susceptibility to gentamicin was decreased from S ≤ 2 mg/L to S ≤ 1 mg/L in 2006.

MRSA infections in Norway

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 458 cases of MRSA were notified in 2005. 257cases were reported as infections which is an increase from previous years with 219 in 2004 and 216 in 2003. 201 (44 %) of the cases in 2005 were reported as colonisations, see Figure 38.
Two hundred and forty-two (53 %) were females. 39 % of the patients were either hospitalised (106) or in nursing homes (71) at the time of diagnosis. The mean age of the patients in health care institutions was 65 years (range 0-97 years) while the mean age of patients diagnosed outside hospitals was 38 years (range 0-96 years).

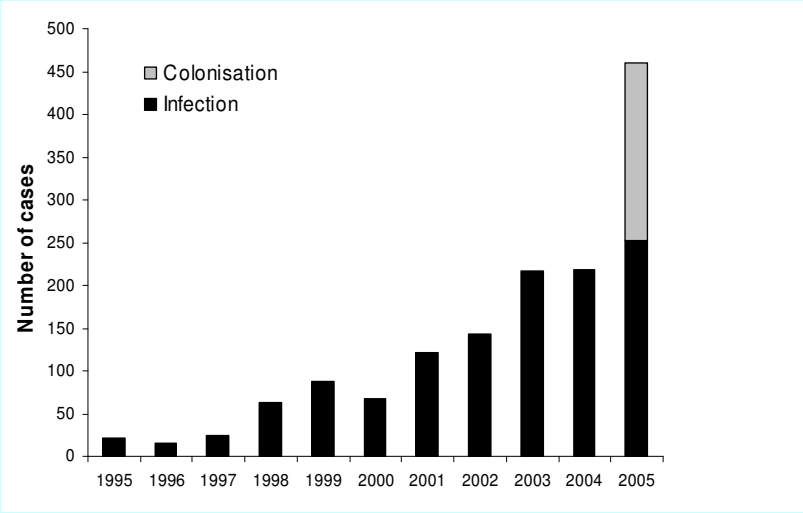

FIGURE 38. Reported cases of MRSA infection 1995–2005 and reported cases of colonisation in 2005.

TABLE 51. Clinical picture of reported cases of MRSA infection in Norway 1995–2005.

Clinical picture	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	Total
Septicaemia	1		3	3	4	2	6	4	5	10	4	42
Septicaemia and meningitis				1						1		2
Meningitis				1								1
Osteomyelitis	2	1		2			2	2	2	4	1	16
RTI*, incl. otitis media	1	1	1	14	8	5	8	13	7	10	8	76
Urinary tract infection		1		4	3	3	2	9	12	13	15	62
Wound infection, abscess	17	14	19	36	71	54	97	115	189	176	215	1003
Other, unknown			2	2	2	3	6		1	5	14	35
Total	21	17	25	63	88	67	121	143	216	219	257	1237

* RTI = Respiratory tract infection

MRSA was found in blood cultures in four patients in 2005 compared to nine in 2004 and seven in 2003 and only a total of 42 for all eleven years reported. The clinical picture shows a majority of wound infections or abscesses (Table 51). The number of reported cases of MRSA infection has increased steadily over the past eleven years. The overwhelming majority consists of wound infections. The number of serious infections is still very low. How large the true increase in the total number of infections is, has to be interpreted with caution. The increase is mainly seen in non-hospitalised patients with minor infections and who have contracted the disease in Norway. This may indicate increased testing of patients outside hospitals.

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Pseudomonas aeruginosa in blood cultures

TABLE 52. *Pseudomonas aeruginosa* blood culture isolates (n=303). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Amikacin						0.5 - 128	4	8
Aztreonam	≤ 8	≥ 16	93.4	-	6.6	0.5 - 128	4	8
Cefepime						0.5 - 32	2	16
Cefpirome						0.5 - 64	2	8
Ceftazidime	≤ 8	≥ 16	98.0	-	2.0	0.5 - 64	2	4
Ciprofloxacin	≤ 0.5	≥ 2	91.7	3.6	4.6	0.032 - ≥ 32	0.125	0.5
Colistin	≤ 4	≥ 8	100.0	-	0.0	0.125 - 4	1	2
Gentamicin						0.125 - 16	2	2
Imipenem	≤ 4	≥ 16	91.1	3.3	5.6	0.125 - ≥ 32	2	4
Meropenem	≤ 2	≥ 16	94.4	4.6	1.0	0.064 - ≥ 32	0.25	1
Piperacillin						1 - ≥ 256	4	16
Pip/Tazo**	≤ 16	≥ 32	96.4	-	3.6	1 - ≥ 256	4	16
Tobramycin	≤ 4	≥ 8	100.0	-	0.0	0.125 - 4	1	2

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Pip/Tazo=Piperacillin/tazobactam

TABLE 53. *Pseudomonas aeruginosa* blood culture isolates (n=303). Distribution (%) of MICs (mg/L).*

	≤ 0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Amikacin						1.3	2.6	15.5	57.8	18.2	3.0	1.3		0.3	
Aztreonam						0.3	5.0	37.3	39.9	10.9	4.0	1.3	1.0	0.3	
Cefepime						1.7	13.2	46.2	20.1	8.6	5.3	5.0			
Cefpirome						1.0	10.6	51.8	24.1	6.6	4.3	1.0	0.7		
Ceftazidime						1.3	34.3	47.5	11.6	3.3	0.3	1.3	0.3		
Ciprofloxacin		0.3	4.6	55.8	24.4	6.6	3.6	1.0	1.3	0.7	0.3	1.3			
Colistin				0.3		8.9	49.5	38.9	2.3						
Gentamicin				0.3	1.3	4.3	12.2	72.6	7.6	1.0	0.7				
Imipenem				0.3		1.3	25.4	50.8	13.2	3.3	2.6	3.0			
Meropenem			5.0	22.8	31.4	20.5	10.6	4.3	3.3	1.3	0.3	0.7			
Piperacillin							0.3	13.2	54.5	19.8	8.6	1.7	1.3		0.7
Pip/Tazo**							0.3	12.9	56.8	18.2	8.3	1.7	1.3		0.7
Tobramycin				1.0	4.3	39.3	41.9	12.5	1.0						

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

RESULTS AND COMMENTS

Pseudomonas aeruginosa has not previously been surveyed in NORM. The present sample included all *P. aeruginosa* blood culture isolates from Norway in 2002 and 2003. Only the first isolate from each patient was included. A nationwide outbreak of nosocomial *P. aeruginosa* infections occurred during the winter of 2001-2002 due to contaminated mouth swabs. A total of 40 patients had the outbreak strain recovered from blood or cerebrospinal fluid. It was not feasible to identify these isolates at the participating laboratories, and the present survey consequently includes the outbreak strain from each of the affected patients.

As seen in Tables 52-53 and Figures 39-40, the vast majority of isolates were fully susceptible to so-called "pseudomonas-specific" antimicrobials. The prevalence of suscpetibility was above 90% for all the eight compounds which at present have species-specific breakpoints defined by the Norwegian Working Group for Antibiotics (NWGA). A subgroup analysis of 50 isolates from intensive care units did not reveal any differences in the prevalences of susceptibility. For some of the beta-lactams it was not easy to delineate the limits of the MIC wildtype distribution, and some of the non-susceptible isolates may have been wrongly categorized due to methodological difficulties. This problem was even more pronounced when looking at the corresponding results from disk diffusion assays, and from the present data one may question the utility of this method for susceptibility testing of *P. aeruginosa* for both aminoglycosides and beta-lactams.

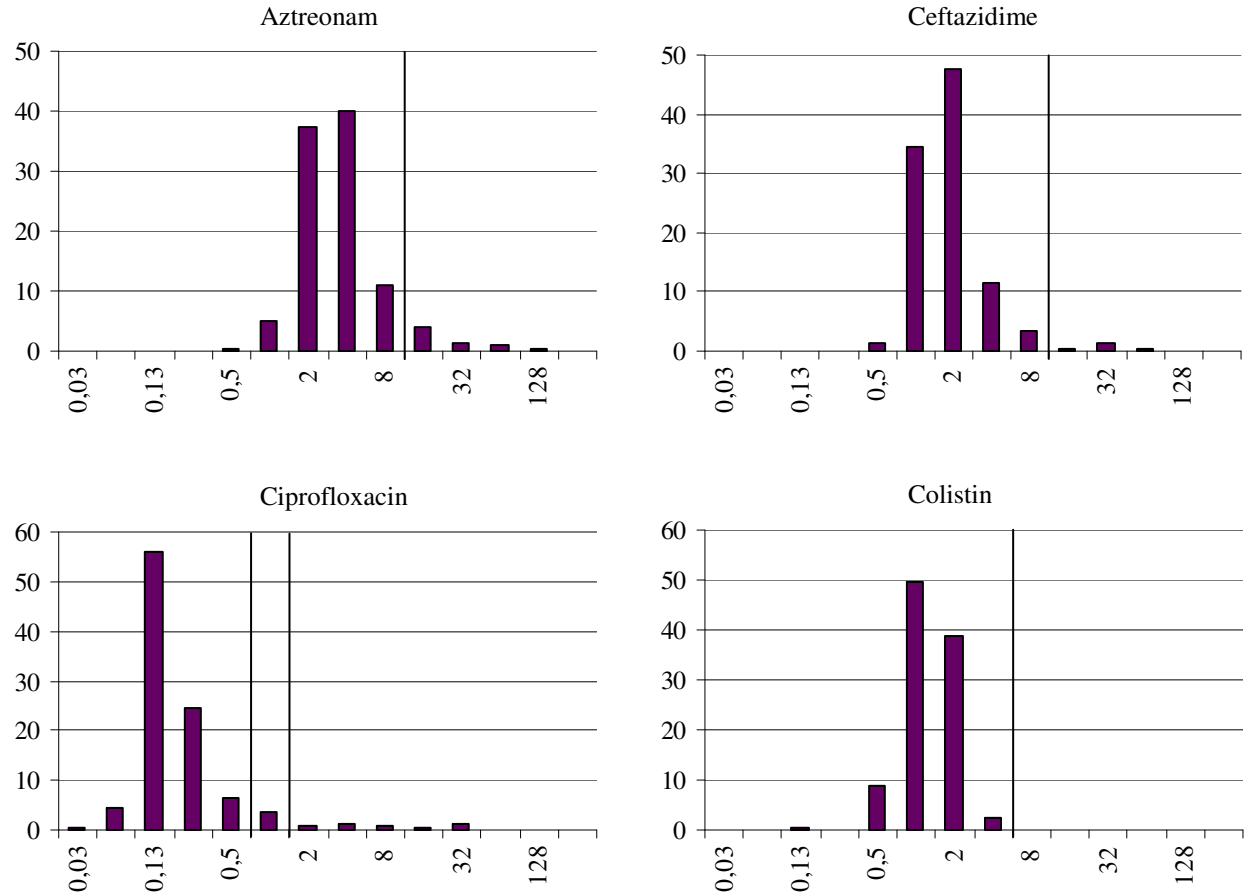

FIGURE 39. Distribution (%) of minimum inhibitory concentrations (mg/L) in 303 *P. aeruginosa* blood culture isolates to aztreonam, ceftazidime, ciprofloxacin and colistin. Species-specific breakpoints according to the Norwegian Working Group for Antibiotics are shown as vertical bars.

Carbapenems are often relied upon for coverage of *P. aeruginosa* in a clinical setting. A total of 17 isolates (5.6%) were either intermediately susceptible (4.6%) or resistant (1%) to meropenem whereas the corresponding figures for imipenem were 5.6% and 3.3%, respectively. Among the 17 meropenem non-susceptible isolates, 12 were non-susceptible to imipenem (3 intermediately susceptible and nine resistant), two were resistant to ceftazidime and four were non-susceptible to ciprofloxacin (two intermediately susceptible and two resistant). All isolates were fully susceptible to tobramycin and colistin.

The differences in susceptibility to different aminoglycosides were nicely demonstrated as shown in Figure 41. Tobramycin is considered the most effective anti-pseudomonal aminoglycoside against wild-type strains, but tobramycin is one of the first aminoglycosides to lose its efficacy when aminoglycoside resistance emerges in *P. aeruginosa*. Gentamicin was included in the study as gentamicin is the most commonly used aminoglycoside in Norway. In most clinical settings, *P. aeruginosa* wildtype strains will respond adequately to this agent. Finally, amikacin is the least effective of the three but the most resistant to emergence of resistance. Amikacin is rarely used in Norway along with colistin for treatment of especially resistant isolates.

It is important to realize that the present data are based on primary isolates and that they should not interpreted as representative of *P. aeruginosa* populations found in patients after prolonged exposure to antimicrobial treatment. Such cases should always be evaluated on the basis of detailed microbiological examinations of the strain in question, preferably by MIC methods.

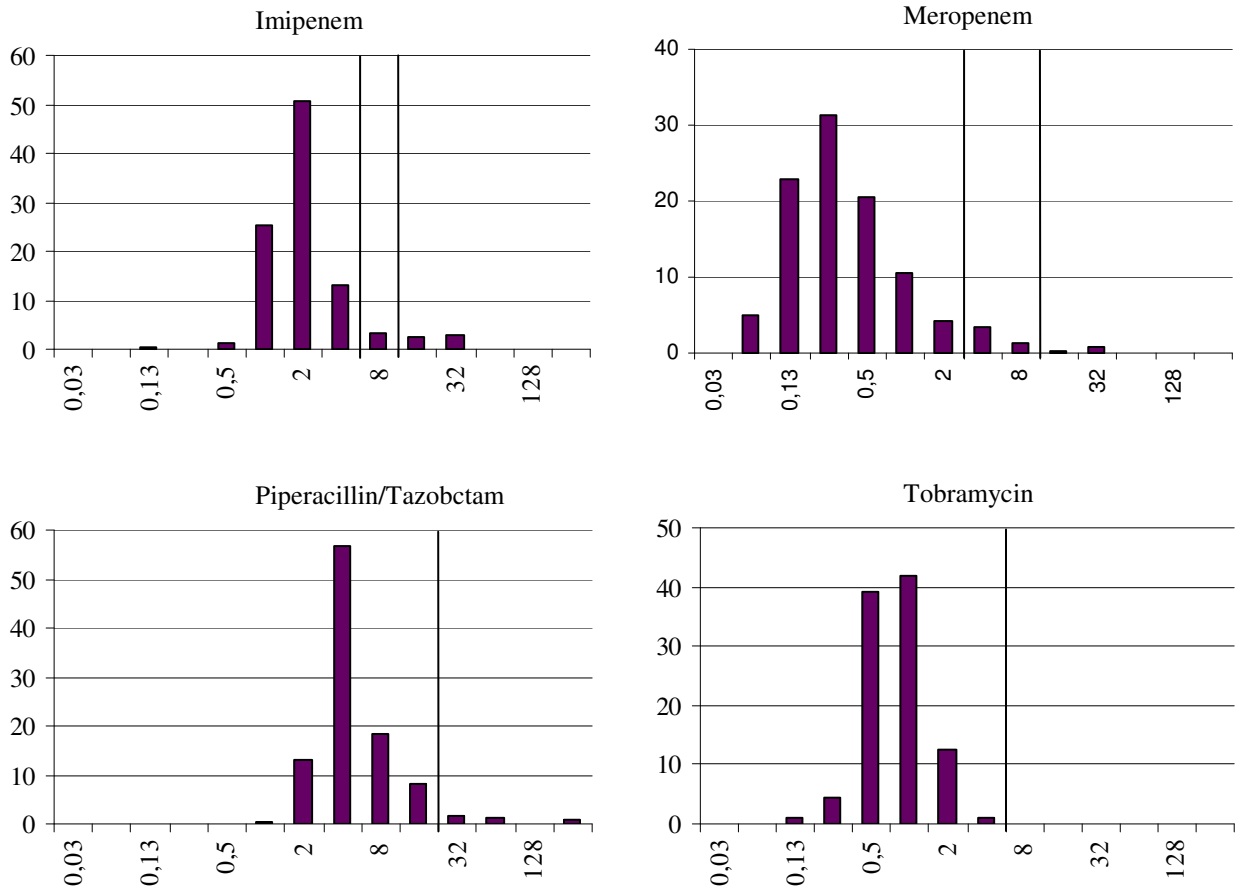

FIGURE 40. Distribution (%) of minimum inhibitory concentrations (mg/L) in 303 *P. aeruginosa* blood culture isolates to imipenem, meropenem, piperacillin/tazobactam and tobramycin. Species-specific breakpoints according to the Norwegian Working Group for Antibiotics are shown as vertical bars.

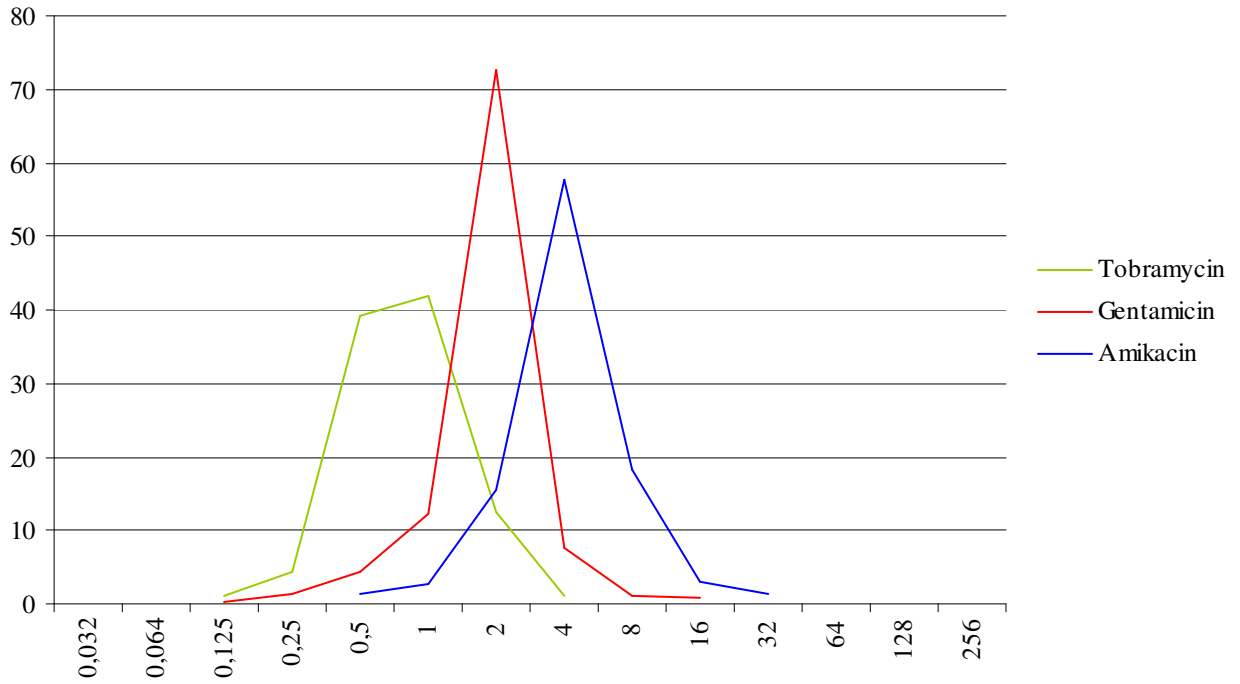

FIGURE 41. Distribution (%) of minimum inhibitory concentrations (mg/L) in 303 *P. aeruginosa* blood culture isolates to tobramycin, gentamicin and amikacins.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 54. *Streptococcus pneumoniae* respiratory tract isolates (n=861). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Cefotaxime	≤ 0.5	≥ 4	99.2	0.8	0.0	0.002 - 2	0.016	0.032
Chloramph.	≤ 4	≥ 8	99.1	-	0.9	0.032 - 32	2	4
Erythromycin	≤ 0.5	≥ 1	93.4	-	6.6	0.032 - ≥ 256	0.125	0.25
Norfloxacin						0.125 - ≥ 32	4	8
Pen G**	≤ 0.064	≥ 2	96.6	2.6	0.8	0.002 - 2	0.016	0.032
Tetracycline	≤ 2	≥ 4	93.8	-	6.2	0.016 - 64	0.125	0.25
TMS***	≤ 0.5	≥ 4	93.6	2.3	4.1	0.032 - ≥ 32	0.25	0.5
Oxacillin screen			95.8	-	4.2			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Pen G=Benzylpenicillin.
***TMS= Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 55. *Streptococcus pneumoniae* respiratory tract isolates (n=861). 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
Cefotaxime	1.5	7.7	71.0	15.3	2.2	0.3	0.5	0.7	0.7	0.1						
Chloramph.				0.1	0.1			0.8	9.3	69.8	18.9	0.5	0.3	0.1		
Erythromycin				0.2	5.3	57.3	29.4	1.2		0.2	0.1	0.2	1.5	1.3	0.2	3.0
Norfloxacin						0.1		0.1	1.3	13.1	41.2	38.4	5.2	0.5		
Pen G**	1.3	7.5	52.8	32.6	2.3	1.3	0.3	0.6	0.3	0.8						
Tetracycline			0.1	0.1	11.4	69.8	10.1	1.2	0.5	0.7	1.5	0.6	1.2	2.3	0.6	
TMS***				0.2	0.7	14.3	68.6	9.8	1.3	1.0	0.8	1.0	0.1	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.
**Pen G=Benzylpenicillin.
***TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS 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 and 2003. However, the selection of antimicrobials has been adjusted with the addition of cefotaxime, chloramphenicol and norfloxacin, and the removal of clindamycin. Erythromycin non-suscpetible isolates were subjected to the DDD (double disk diffusion test), and norfloxacin has been introduced as a screening agent for non-susceptibility to fluoroquinolones although formal breakpoints have not yet been established. Finally, the oxacillin disk screen for non-susceptibility to penicillin was performed on two different agars with different breakpoints, and the distribution of zone diameters has therefore been omitted in this presentation.

The prevalences of non-susceptibility to various antimicrobials are shown in Tables 54-55 and Figure 42. There is a clear increase in non-susceptibility to penicillin G (2001: 2.6%; 2003: 2.8%; 2005: 3.4%), erythromycin (2001: 3.3%; 2003: 5.7%; 2005:6.6%) and trimethoprim/sulfamethoxazole (2001: 1.9%; 2003: 4.4%; 2005: 6.4%) even when changes in breakpoints are taken into account. The conclusion is less obvious for tetracyclines as the test substance was changed from doxycycline to tetracycline in 2005.

A total of 29/861 isolates (3.4%) were non-susceptible to penicillin G. Seven of these isolates were penicillin G resistant (MIC = 2 mg/L) while the remaining 22 were intermediately susceptible (MIC 0.125-1 mg/L). Six of the seven penicillin G resistant isolates and 16 of the 22 intermediately susceptible ones were detected by the oxacillin screening disk. Thus, a total of seven penicillin non-susceptible isolates (one resistant and six intermediately susceptible) were not detected by the oxacillin screening test. Conversely, 14 penicillin G susceptible isolates were identified as oxacillin resistant. Furthemore, seven isolates were non-susceptible to cefotaxime. One of the isolates was negative in the oxacillin screening test and had a penicillin G MIC = 0.125 mg/L and may represent an error, but the remaining six (cefotaxime MIC = 1 mg/L) showed consistent results with positive oxacillin screening tests and penicillin MICs of 1-2 mg/L. The correlation between MICs for penicillin G and cefotaxime is shown in Figure 43. Four of the six isolates were concomitantly high-level resistant to erythromycin.

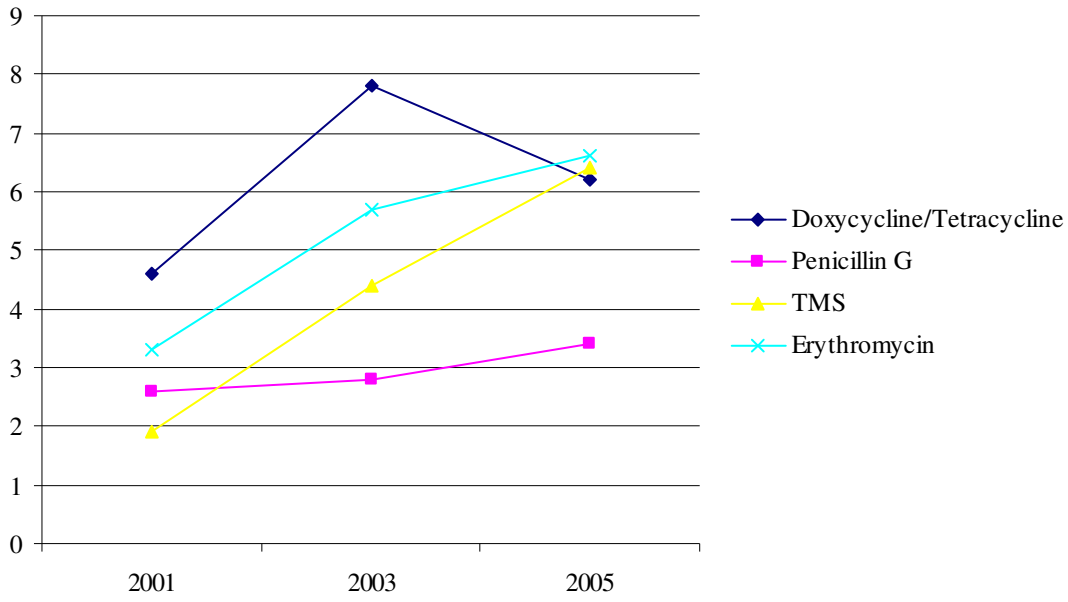

FIGURE 42. Prevalences of non-susceptibility to various antimicrobials in *S. pneumoniae* from respiratory tract samples in 2005. The breakpoints for erythromycin were adjusted in 2003 from S ≤ 1 mg/L and R ≥ 4 mg/L to S ≤ 0.5 mg/L and R ≥ 1 mg/L. The breakpoints for trimethoprim/sulfamethoxazole (TMS) were adjusted in 2003 from S ≤ 2 mg/L and R ≥ 16 mg/L to S ≤ 0.5 mg/L and R ≥ 4 mg/L. Doxycycline with the breakpoints S ≤ 1 mg/L and R ≥ 4 mg/L was replaced by tetracycline with the breakpoints S ≤ 2 mg/L and R ≥ 4 mg/L in 2005. The breakpoints for penicillin G have remained unaltered at S ≤ 0.064 and R ≥ 2 mg/L throughout the period.

The prevalence of macrolide resistance in *S. pneumoniae* blood culture isolates has steadily increased and reached 10.8% in 2005. This tendency has been less pronounced in respiratory tract isolates with 6.6% erythromycin resistance in 2005. However, there was an interesting difference in resistance phenotypes between the two specimen types. Whereas the majority of erythromycin resistant blood culture isolates displayed the M-phenotype (9.1% of all isolates; 83.8% of erythromycin resistant isolates), a major proportion of respiratory tract isolates (3.6% of all; 47.2% of erythromycin resistant isolates) displayed the MLS_B-phenotype either constitutively (3.0% of all; 45.3% of erythromycin resistant isolates) or inducibly (0.1% of all; 1.9% of erythromycin resistant isolates). This may indicate that there are different pneumococcal clones causing systemic and localized infections. Moreover, there was a clear correlation between macrolide resistance phenotype and co-resistance to other antimicrobial classes. For all relevant alternative therapies, the prevalence of non-susceptibility was significantly higher in MLS_B strains that in M strains (penicillin G: MLS_B 16%, M 0%; tetracycline: MLS_B 84%, M 11%; trimethoprim/sulfamethoxazole: MLS_B 28%, M 11%). Overall, linked selection of resistance determinants is still a limited problem in Norway as seen by the 1.1% prevalence of combined non-susceptibility to penicillin G and erythromycin.

Norfloxacin has been suggested as the most suitable agent when screening for reduced susceptibility to fluoroquinolones in Gram positive cocci including *S. pneumoniae*. Fluroquinolones are not used for the treatment of respiratory tract infections in Norway and ciprofloxacin and ofloxacin are the only substances of this class on the market. Norfloxacin was introduced in NORM in 2005 in order to define the normal MIC distribution and detect possible outliers suggesting emergence of resistance. As seen in Figure 44, there were apparently no isolates seperated from the wild-type distribution.

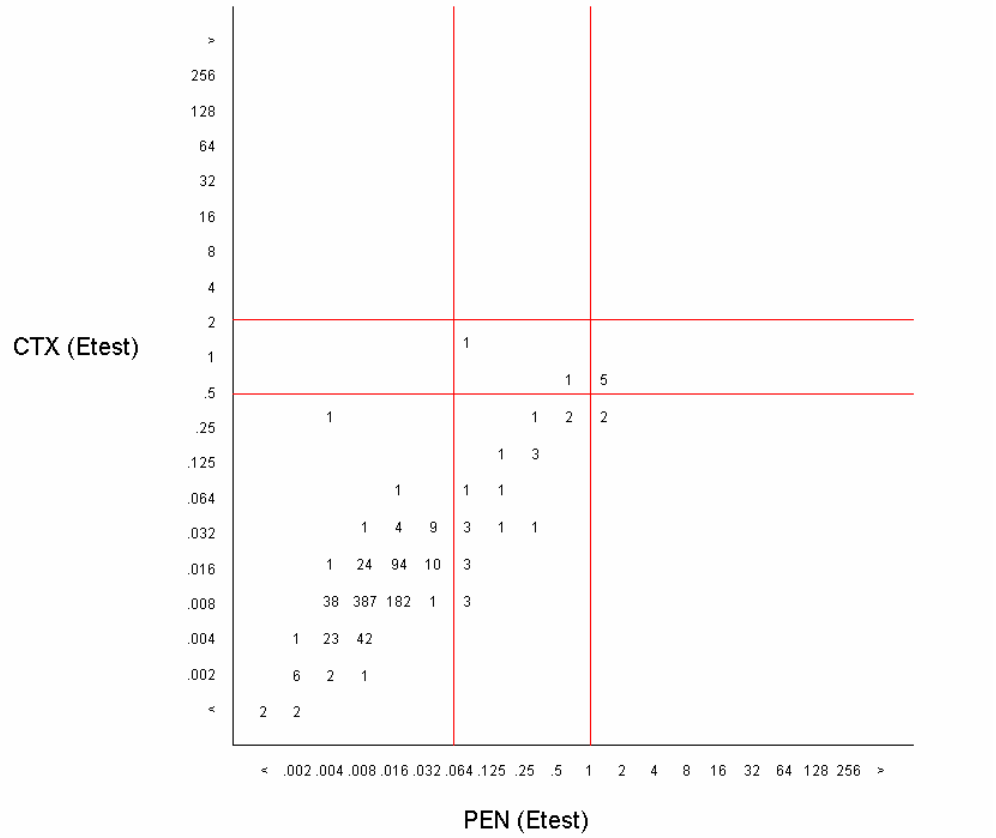

FIGURE 43. Correlation between MICs of penicillin G (x-axis) and cefotaxime (y-axis) among 861 *Streptococcus pneumoniae* respiratory tract isolates from 2005. The figures indicate number of strains. Red lines represent breakpoints for penicillin G (S ≤ 0.064 mg/L, R ≥ 2 mg/L) and cefotaxime (S ≤ 0.5 mg/L, R ≥ 4 mg/L).

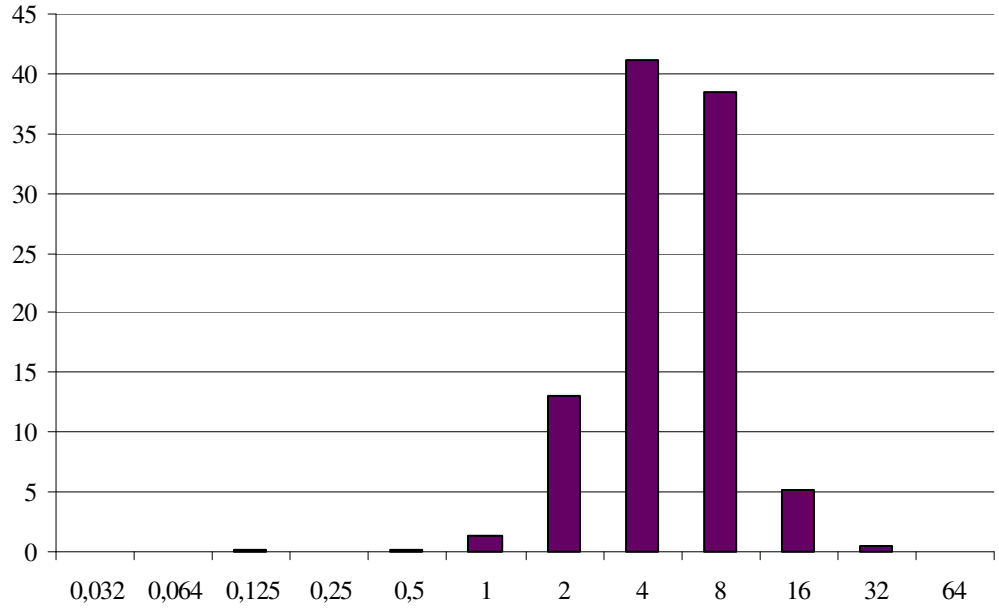

FIGURE 44. Distribution (%) of minimum inhibitory concentrations (mg/L) of norfloxacin in 861 *S. pneumoniae* respiratory tract isolates from 2005.

Escherichia coli in urine

TABLE 56. *Escherichia coli* urinary tract isolates (n=1,127). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*		
	S	R	S	I	R
Ampicillin	≤ 0.5	≥ 16	0.6	72.7	26.7
Ciprofloxacin	≤ 0.5	≥ 2	95.6	1.0	3.4
Mecillinam	≤ 2	≥ 16	85.2	12.6	2.2
Nalidixic acid	≤ 16	≥ 32	93.7	-	6.3
Nitrofurantoin	≤ 32	≥ 64	97.6	-	2.4
Sulfadiazine	≤ 64	≥ 256	76.0	0.5	23.5
Trimethoprim	≤ 2	≥ 8	80.7	-	19.3
TMS**	≤ 2	≥ 16	82.8	0.5	16.7
ESBL			99.6	-	0.4

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 57. *Escherichia coli* urinary tract isolates from patients treated by general practitioners (n=638). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*		
	S	R	S	I	R
Ampicillin	≤ 0.5	≥ 16	0.6	74.3	25.1
Ciprofloxacin	≤ 0.5	≥ 2	97.0	0.5	2.5
Mecillinam	≤ 2	≥ 16	87.1	12.4	0.5
Nalidixic acid	≤ 16	≥ 32	94.7	-	5.3
Nitrofurantoin	≤ 32	≥ 64	98.0	-	2.0
Sulfadiazine	≤ 64	≥ 256	77.1	0.3	22.6
Trimethoprim	≤ 2	≥ 8	81.5	0.0	18.5
TMS**	≤ 2	≥ 16	83.7	0.8	15.5

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 58. *Escherichia coli* urinary tract isolates from patients admitted to hospital (n=287). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*		
	S	R	S	I	R
Ampicillin	≤ 0.5	≥ 16	0.3	71.1	28.6
Ciprofloxacin	≤ 0.5	≥ 2	93.4	2.1	4.5
Mecillinam	≤ 2	≥ 16	79.1	15.3	5.6
Nalidixic acid	≤ 16	≥ 32	91.6	-	8.4
Nitrofurantoin	≤ 32	≥ 64	96.5	-	3.5
Sulfadiazine	≤ 64	≥ 256	72.8	1.4	25.8
Trimethoprim	≤ 2	≥ 8	79.4	0.0	20.6
TMS**	≤ 2	≥ 16	80.5	0.3	19.2

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 59. *Escherichia coli* urinary tract isolates from patients at long-term healthcare facilities (n=53). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*		
	S	R	S	I	R
Ampicillin	≤ 0.5	≥ 16	1.9	67.9	30.2
Ciprofloxacin	≤ 0.5	≥ 2	94.3	0.0	5.7
Mecillinam	≤ 2	≥ 16	86.8	11.3	1.9
Nalidixic acid	≤ 16	≥ 32	94.3	-	5.7
Nitrofurantoin	≤ 32	≥ 64	100.0	-	0.0
Sulfadiazine	≤ 64	≥ 256	83.0	0.0	17.0
Trimethoprim	≤ 2	≥ 8	75.5	1.9	22.6
TMS**	≤ 2	≥ 16	83.0	0.0	17.0

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Urinary tract isolates of *E. coli* and *Enterobacter* spp. were analysed by disk diffusion in NORM 2005. This approach was used to obtain the dual aims of conducting surveillance and of improving the quality of routine susceptibility testing in Norwegian diagnostic laboratories. Two different disk systems were used, and the data reported here are therefore the combined results for all laboratories categorized according to the SIR breakpoints for the respective systems.

There were only minor changes in prevalences of resistance for urinary tract *E. coli* isolates from 2004 to 2005 (Table 56). Resistance to trimethoprim and sulfadiazine were approximately 80%, and the prevalence of susceptibility to the most active agent (in this case sulfadiazine) was perfectly mirrored by the prevalence of susceptibility to the combination compound trimethoprim/ sulfamethoxazole. Similarly, there was excellent concordance between non-susceptibility to nalidixic acid and ciprofloxacin with 6.3% and 4.4%, respectively. This is an increase from 2.3% in 2003 and 3.7% in 2004, but due to the changes in surveillance protocol it is premature to conclude about possible emergence of fluoroquinolone resistance. It is difficult to delineate the limits of the wild-type zone distribution for mecillinam, and it is therefore not surprising that the prevalence of resistance may fluctuate from one year to the next

As shown in Tables 57-59, the data were further analysed for possible differences in resistance rates according to inpatient or outpatient status of patients. There were only minor differences between isolates from patients admitted to hospital, patients treated in the community and patient living in long-term healthcare facilities. The most notable difference was the prevalence of non-susceptibility to fluoroquinolones which was 3.0% in isolates from the community and approximately 5-6% in all the other groups. One may hypothesize that the higher antimicrobial selection pressure in institutions may favour more resistance in these settings, but differences in sampling practices should also be taken into account.

In general there were no significant differences in prevalences of resistance between isolates from female (85.5%) and male (14.5%) patients. However, non-susceptibility to trimethoprim was slightly more common in isolates from women (19.5%) than in isolates from men (17.9%). Such a difference may be explained by a higher proportion of recurrent urinary tract infections in women and consequently a higher proportion of isolates originating from patients recently treated with antimicrobials. Trimethoprim has been the recommended primary treatment for uncomplicated UTI in Norway for many years. It is generally accepted that cystitis in adult women should be treated without susceptibility testing whereas all men with UTI should have samples taken for bacteriological examination. There is thus a selection bias in favour of higher prevalences of resistance among women for this condition.

Extended-spectrum beta-lactamase positive *E. coli* isolates are occasionally recovered from routine urinary samples, and emergence of CTX-M type ESBL production has been reported from many countries including Norway. ESBL production was specifically examined by a disk approximation assay using a disk containing amoxicillin/ clavulanic acid surrounded by cefotaxime, ceftazidime, cefpodoxime, aztreonam and cefpirome. Only 5/1,127 (0.4%) ESBL positive isolates were identified. Three of these isolates were isolated from urinary samples submitted by general practitioners, whereas the remaining two were recovered from hospital patients. Two of the three outpatient isolates originated from the Stavanger area in the south-western part of Norway which has recently experienced an outbreak of both nosocomial and community acquired ESBL-positive *E. coli* strains. All five isolates were resistant to sulfadiazine, four were in addition resistant to trimethoprim and trimethoprim/ sulphamethoxazole, and three were also resistant to ciprofloxacin.

Enterobacter spp. in urine

TABLE 60. *Enterobacter* spp. urinary tract isolates (n=411). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*		
	S	R	S	I	R
Ampicillin	≤ 0.5	≥ 16	0.5	31.4	68.1
Ciprofloxacin	≤ 0.5	≥ 2	96.6	1.9	1.5
Mecillinam	≤ 2	≥ 16	86.1	10.0	3.9
Nalidixic acid	≤ 16	≥ 32	90.3	-	9.7
Sulfadiazine	≤ 64	≥ 256	91.5	0.7	7.8
Trimethoprim	≤ 2	≥ 8	90.3	2.7	7.1
TMS**	≤ 2	≥ 16	94.2	1.7	4.1

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**TMS=Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

Enterobacter spp. urinary tract isolates were included in NORM for the first time in 2005. As for *E. coli*, the surveillance was performed using two different disk diffusion systems and the data presented are the combined results after SIR categorization according to the two systems. The *Enterobacter* spp. isolates were generally more susceptible to sulfadiazine, trimethoprim and trimethoprim/sulfamethoxazole than the *E. coli* isolates (Table 60). The prevalence of non-susceptibility to ciprofloxacin was comparable to *E. coli*, but a considerable number of ciprofloxacin susceptible/nalidixic acid resistant isolates were detected. This may indicate a bacterial reservoir with first step mutation which can evolve to ciprofloxacin resistance when exposed to this agent. Beta-lactams such as mecillinam and ampicillin should be used with caution due to the chromosomal AmpC enzyme present in the genus *Enterobacter*, and nitrofurantoin is not considered appropriate for treatment of *Enterobacter* urinary tract infections.

Neisseria gonorrhoeae

TABLE 61. *Neisseria gonorrhoeae* from all specimen types (n=167). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Ampicillin	≤ 0.25	≥ 4	62.3	13.8	24.0	0.016 - ≥ 256	0.25	32
Amoxi/Clav**						0.016 - 2	0.5	1
Azithromycin						0.016 - 4	0.125	0.5
Ceftriaxone	≤ 0.25		100.0	-	-	0.002 - 0.25	0.008	0.032
Chloramph.						0.064 - 8	0.5	4
Ciprofloxacin	≤ 0.032	≥ 0.125	58.1	1.8	40.1	0.002 - ≥ 32	0.004	8
Erythromycin	≤ 0.5	≥ 8	56.3	42.5	1.2	0.016 - 64	0.5	2
Gentamicin						2 - 32	8	16
Pen. G***	≤ 0.064	≥ 2	10.8	56.9	32.3	0.004 - ≥ 32	0.25	32
Spectinomycin	≤ 32	≥ 64	100.0	-	0.0	0.064 - 32	16	32
Tetracycline	≤ 0.125	≥ 2	12.6	46.1	41.3	0.016 - ≥ 256	1	32
TMS****						0.016 - ≥ 32	4	8
Beta-lactamase			74.4	-	25.6			

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Amoxicillin/Clavulanic acid
***Pen G=Benzylpenicillin.
****TMS= Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

TABLE 62. *Neisseria gonorrhoeae* from all specimen types (n=167). 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
Ampicillin			2.4	5.4	3.6	24.0	26.9	7.8	3.6	2.4	6.6	4.2	1.8	2.4	0.6	8.4
Amoxi/Clav**			3.0	0.6	3.6	9.0	26.3	38.9	17.4	1.2						
Azithromycin			2.4	12.6	13.2	28.7	28.7	11.4	2.4		0.6					
Ceftriaxone	49.7	25.1	15.0	6.6	2.4		1.2									
Chloramph.								1.3	34.3	47.5	11.6	3.3	0.3	1.3	0.3	
Ciprofloxacin	51.5	4.8		1.8	1.8	3.6	3.6	5.4	3.0	6.0	5.4	4.2	1.8	7.2		
Erythromycin			1.2	3.6	4.2	6.0	15.6	25.7	28.7	11.4	2.4	0.6			0.6	
Gentamicin										0.6	15.0	48.5	35.3	0.6		
Pen. G***	0.6	1.2	2.4	2.4	4.2	12.0	28.1	7.2	9.6	6.6	5.4	3.6	3.0	13.8		
Spectinomycin					0.6						1.2	22.2	64.7	11.4		
Tetracycline			0.6	1.2	2.4	8.4	6.6	29.3	10.2	10.8	1.2	3.0	11.4	7.8	3.0	4.2
TMS****			0.6			1.2	1.2	10.2	14.4	18.0	29.3	16.2	4.8	4.2		

*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.
**Amoxicillin/Clavulanic acid
***Pen G=Benzylpenicillin.
****TMS= Trimethoprim/sulfamethoxazole. Breakpoints for the TMS combination are given for the trimethoprim component only.

RESULTS AND COMMENTS

The present report is based on all *Neisseria gonorrhoeae* isolates recovered in Norway in 2003. A total of 173 strains were available for analysis, but six isolates failed to grow on the GC agar used for susceptibility testing and the material thus consisted of 167 strains. Most isolates were recovered from urethra (70.7%) while the others were found in specimens from cervix uteri (7.8%), anus (7.8%), throat (1.2%) or others/unknown (12.5%). Only the first isolate from each patient was included. Epidemiological information about geographical origin of strains or mode of transmission was not collected as this was not available to the participating laboratories. Results are presented in Tables 61-62 and Figure 45.

The majority of isolates were non-susceptible to penicillin G and ampicillin according to the breakpoints of the Norwegian Working Group for Antibiotics, but this was in contrast to the prevalence of only 25.6% containing a beta-lactamase. Almost all beta-lactamase positive isolates (n=42) were resistant to penicillin G (n=40, 95.2%) and ampicillin (n=38, 90.5%), and all ampicillin and penicillin G susceptible isolates were beta-lactamase negative (n=104 and n=17, respectively). However, when looking at the ampicillin non-susceptible isolates it appeared that almost all the resistant isolates were beta-lactamase positive (38/39, 97.4%) while only a few of the intermediately susceptible isolates had this property (4/23, 17.4%). The same trend was seen for penicillin G where 40/52 (76.9%) of resistant isolates were beta-lactamase positive whereas only 2/95 (2.1%) of intermediately susceptible isolates had this property. The conclusion was thus that high-level resistance to ampicillin and penicillin G was strongly linked to beta-lactamase production, but that a significant number of strains were either miscategorized as intermediately susceptible or non-susceptible due to other mechanisms. The significance of beta-lactamases was further demonstrated by the elimination of high-level resistance by addition of clavulanic acid as seen in Table 62.
It is interesting to note that the Norwegian Surveillance System for Communicable Diseases (MSIS) reported a total of 241 cases of gonorrhoeae in 2003. The discrepancy between 241 cases and 173 strains may be due to cases reported on clinical criteria alone and/or failure of growth after two years of storage at the laboratories. It is more difficult to explain that 17.0% of cases were reported to be infected with beta-lactamase positive strains to MSIS when the NORM sample contained 25.6% beta-lactamase positive isolates.

Non-susceptibility to fluoroquinolones was detected in 41.9% of isolates with 40.1% beeing fully resistant (MIC ≥ 0.125 mg/L). Again, these figures are higher than the 10.4% prevalence of resistance reported to MSIS. 73.8% of beta-lactamase positive isolates were resistant to ciprofloxacin wile 47.0% of ciprofloxacin resistant isolates were beta-lactamanse positive. In total, 31/167 (18.6%) of the isolates displayed combined ciprofloxacin resistance and beta-lactamase production which is significantly higher than the prevalence of 10.4% reported through MSIS. The breakpoints for ciprofloxacin have been reduced by one dilution step since 2003, but this has only a marginal effect on the percentages above (S=59.9%, I=3.6% and R=36.5% by the former breakpoints).

All isolates were fully susceptible to the second-line antibiotics ceftriaxone and spectinomycin. Similarly, all isolates had azithromycin MIC values ≤ 4 mg/L *in vitro* which is interesting as this compound is often used for empirical treatment of urethritis. The data for erythromycin, tetracycline, chloramphenicol and trimethoprim/sulfamethoxazole were collected for academic purposes and do not imply that these agents should be used for treatment of suspected gonorrhoeae.

15.6% (n=26) belonged to serogroup 1, 83.2% (n=139) belonged to serogroup 2/3 and two isolates could not be satisfactorily classified by agglutination. The serogroup 1 isolates were significantly more resistant than serogroup 2/3 isolates to both beta-lactams (69.2% versus 17.5% betalactamase) and fluoroquinolones (80.8% R versus 33.1% R).

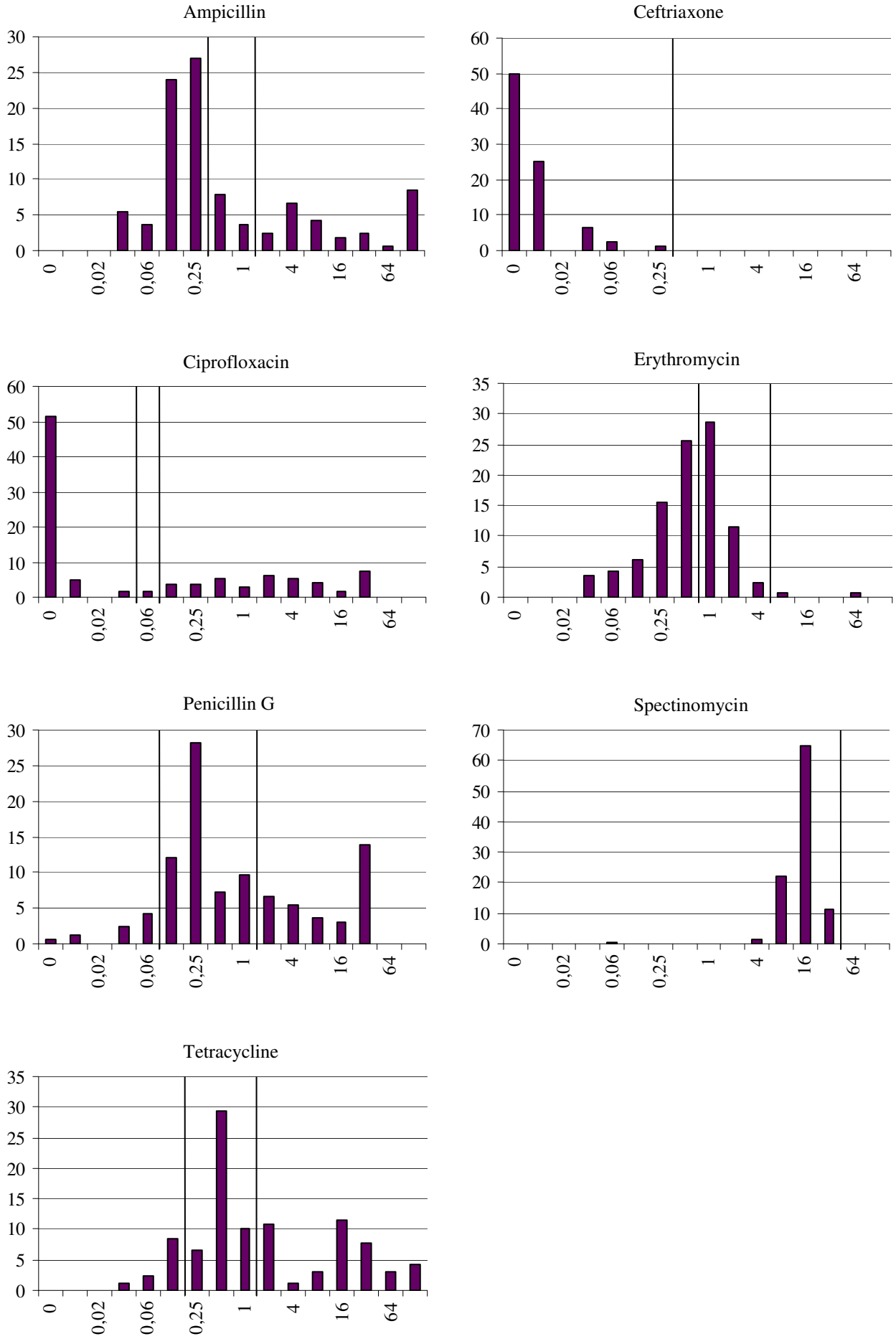

FIGURE 45. Distribution (%) of minimum inhibitory concentrations (mg/L) in 167 *N. gonorrhoeae* isolates to ampicillin, ceftriaxone, ciprofloxacin, erythromycin, penicillin G, spectinomycin and tetracycline. Species-specific breakpoints according to the Norwegian Working Group for Antibiotics are shown as vertical bars.

Mycobacterium tuberculosis

A total of 290 cases of tuberculosis were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2005. 274 of these patients had not previously been treated with antituberculosis drugs, and *Mycobacterium tuberculosis* was isolated from 206 cases. All these isolates were tested for susceptibility, see Table 63.

TABLE 63. Antimicrobial susceptibility of 206 isolates of *M. tuberculosis* complex isolated in 2005 from patients not previously treated for tuberculosis.

Geographical origin of patient	No. of isolates	Resistance to antimicrobial agents (isolates)					
		Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDRTB*
Norway	44	2		1	2		
Europe outside Norway	16	3		1	4		
Asia	57	6	1	1	9	7	1
Africa	88	10	2	1	16	6	2
America	1						
Total	206	21	3	4	31	13	3
Proportion of resistant isolates		10.2	1.5	1.9	15.0	6.3	1.5

*MDRTB: Multi drug resistant tuberculosis, resistant to at lealeast rifampicin and isoniazid.

RESULTS AND COMMENTS

Susceptibility tests were also performed on *M. tuberculosis* isolates from 8 patients who had previously received antituberculosis drug treatment. Out of these one isolate from an African patient was monoresistant to pyrazinamid. The rest of the isolates were susceptible to the first line drugs.

Candida spp. in blood cultures

TABLE 64. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=103). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Amphotericin B**	≤ 1	≥ 2	100.0	-	0.0	0.032 - 1	0.25	0.5
Fluconazole**	≤ 4	≥ 64	100.0	0.0	0.0	0.125 - 1	0.25	0.5
Voriconazole***	≤ 1	≥ 4	100.0	0.0	0.0	0.004 - 1	0.008	0.016
Caspofungin****						0.032 - 0.5	0.125	0.25

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Breakpoints from the the Norwegian Reference Group on Antibiotic Susceptibility Testing – AFA.
*** Proposed breakpoints (Pfaller, M. A., et al. 2006. J Clin.Microbiol 44:819-826).
****There are no recommended breakpoints. Strains with MIC ≤ 1mg/L are presumably susceptible.

TABLE 65. *Candida albicans* blood culture isolates (n=103). 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				1.0	4.9	16.5	40.8	32.0	4.9								
Fluconazole						5.8	49.5	41.7	2.9								
Voriconazole	10.7	46.6	39.8	1.9			1.0										
Caspofungin				4.9	30.1	47.6	16.5	1.0									

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

TABLE 66. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=32). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Amphotericin B**	≤ 1	≥ 2	100.0	-	0.0	0.064 - 0.5	0.5	0.5
Fluconazole**	≤ 4	≥ 64	34.4	56.3	9.4	1 - ≥ 256	8	16
Voriconazole***	≤ 1	≥ 4	90.6	6.3	3.1	0.032 - 8	0.25	1
Caspofungin****						0.064 - 0.25	0.25	0.25

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Breakpoints from the the Norwegian Reference Group on Antibiotic Susceptibility Testing – AFA.
*** Proposed breakpoints (Pfaller, M. A., et al. 2006. J Clin.Microbiol 44:819-826).
****There are no recommended breakpoints. Strains with MIC ≤ 1mg/L are presumably susceptible.

TABLE 67. *Candida glabrata* blood culture isolates (n=32). 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					3.1		6.3	87.5	3.1								
Fluconazole									3.1	6.3	25.0	37.5	18.8		3.1	3.1	3.1
Voriconazole				3.1	12.5	31.3	25.0	12.5	6.3	6.3		3.1					
Caspofungin					3.1	34.4	62.5										

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

TABLE 68. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates (n=10). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)*			MIC range (mg/L)	MIC_{50}	MIC_{90}
	S	R	S	I	R			
Amphotericin B**	≤ 1	≥ 2	90.0	-	10.0	0.125 - 2	0.5	1
Fluconazole**	≤ 4	≥ 64	100.0	0.0	0.0	0.25 - 1	0.5	1
Voriconazole***	≤ 1	≥ 4	100.0	0.0	0.0	0.016 - 0.125	0.064	0.125
Caspofungin****						0.125 - 0.25	0.125	0.25

*S=Susceptible, I=Intermediately susceptible, R=Resistant.
**Breakpoints from the the Norwegian Reference Group on Antibiotic Susceptibility Testing – AFA.
*** Proposed breakpoints (Pfaller, M. A., et al. 2006. J Clin.Microbiol 44:819-826).
****There are no recommended breakpoints. Strains with MIC ≤ 1mg/L are presumably susceptible.

TABLE 69. *Candida tropicalis* blood culture isolates (n=10). 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						10.0	10.0	30.0	40.0	10.0							
Fluconazole							10.0	70.0	20.0								
Voriconazole			10.0	20.0	50.0	20.0											
Caspofungin						80.0	20.0										

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

RESULTS AND COMMENTS

In 2005, 171 strains of 13 different yeast species isolated from patients with bloodstream infection were received at the national mycology reference laboratory.

All isolates were tested for susceptibility to amphotericin B, fluconazole, voriconazole and caspofungin. The results for the three most common species (*Candida albicans* (n=103), *C. glabrata* (n=32) and *C. tropicalis* (n=10)) are shown in the Tables 64-69. These three species accounted for 87% of the candidemia isolates.

All isolates, except one *C. tropicalis* strain with a MIC of 2 mg/L, were susceptible to amphotericin B. The majority of the *C. glabrata* isolates had decreased susceptibility to fluconazole (9.4% resistant and 56.3% intermediately susceptible). All *C. albicans* and *C. tropicalis* strains were susceptible to fluconazole. Three of the *C. glabrata* strains with a high fluconazole also had decreased voriconazole susceptibily (MIC ≥2 mg/L). The remaining isolates were susceptible to this drug. All the strains were susceptible to caspofungin and all the *C. albicans* and *C. tropicalis* strains were susceptible to voriconazole.

Compared to an earlier study on susceptibility of Norwegian blood stream yeasts isolates (J Clin Microbiol 2006: 44; 1977-81) there has been no increase in resistance.

Antimicrobial resistance and susceptibility testing in yeasts

Opportunistic fungal infections and especially *Candida* infections have emerged as important causes of morbidity and mortality in many patient groups. Advances in therapeutic technology, the use of increasingly aggressive regimens of chemotherapy, and the insertion of intravascular devices, account for a dramatic rise in invasive fungal infections in many countries. The importance of fungal infections in cancer and transplant patients has been documented in numerous studies. Other important factors associated with candidemia are surgery, intensive care treatment and the use of central venous catheters.

The mortality of invasive fungal infections remains high. The crude mortality of nosocomial candidemia is, for instance, approximately 60% with an attributable mortality of 49% (1).

For many years amphotericin B, which is known to cause significant nephrotoxicity, was the only drug available for the treatment of systemic fungal infections. Flucytosine became available in the 1970s. This drug could, however, not be used as monotherapy because of rapid development of resistance. The development of the azoles in the late 1980s and 1990s was therefore a major advance. Some of these drugs had significant side-effects in a few patients, but four azoles, itraconazole, fluconazole, voriconazole and posaconazole, are used today for the treatment of systemic fungal infections. Recently a new class of drugs, the echinocandins, has been developed.

Fluconazole is the most commonly used agent in the azoles family and much of the scientific literature focuses on this drug. Resistance to fluconazole was described in the early 1990s and since then a lot of research has been performed to elucidate the mechanisms for resistance (10,11). It is recognised that *Candida* species may acquire resistance to azole antifungal drugs as the result of genetic mutations (10). In the early reports on resistance development this was discovered in patients with chronic mucocutaneous candidiasis undergoing prolonged ketoconazole therapy. In the last decade, many reports have described the development of fluconazole resistant *C. albicans* isolates and other *Candida* species (e.g. *C. glabrata*, *C. dubliniensis* and *C. tropicalis*) in AIDS patients with oral thrush and oesophageal candidiasis who have been given prolonged fluconazole therapy (9). Development of resistance has also been found in animals given fluconazole.

At the molecular level, distinct mechanisms for the acquisition of azole resistance have been described, including decreased accumulation of the drug from enhanced efflux, interference of their action on the target enzyme lanosterol 14a-demethylase, alterations in other enzymes of the biosynthetic pathway of ergosterol, and decreased permeability of the fungal membrane to the drug (10).

It seems that azole resistance develops gradually as a result of sequential alterations due to the continuous pressure exerted by the drug. It is likely that several mechanisms will contribute simultaneously to the final resistant phenotype, especially in the case of a high degree of resistance. In a recent study on *C. albicans* strains displaying high-level fluconazole resistance (MICs, >64 µg/ml) confirmed the multifactorial nature of azole resistance with different mechanisms acting simultaneously in 75% of the resistant isolates. In general, overexpression of the genes encoding for the efflux pumps was detected in 85% of the cases, mutations in the gene encoding for the enzyme lanosterol 14a-demethylase in 65%, and overexpression of this gene in 35% (3).

It has been shown that one of the important mechanisms of resistance in *Candida* is upregulation of multidrug efflux transporter genes, often the ATP-binding cassette (ABC) transporter genes. Since the ABC-transporters accept as substrates almost the entire spectrum of azole antifungals used in medicine, it is no surprise that cross-resistance between azoles occurs quite frequently.

The emergence of drug resistance in all pathogenic microorganisms, including fungi, is an evolutionary process initiated by exposure to antimicrobial agents. Increased use of antifungals will exert a selective pressure on the growth of the least-susceptible members of a fungal population. Whether the isolates exhibiting reduced susceptibility result from a mixed population or whether they emerge as the result of genetic mutation, the result is similar: a population of fungi with higher MIC than the pre-treatment isolates. As the use of antifungal azoles in medicine, agriculture and animal health becomes more widespread, the selection and nosocomial spread of azole-resistant *Candida* spp. appears inevitable.

It is true that the problem of antifungal resistance has so far not reached the magnitude of antibacterial drug resistance. Nevertheless, it is of utmost importance to limit the development of resistance as much as possible. To achieve this, the lessons from antibacterial drug resistance should be applied: Appropriate use of antifungal agents should be promoted to reduce selecting pressure.

Antifungal susceptibility testing

It is understandable that little interest was taken in antifungal susceptibility tests for many years because serious fungal infections were considered to be rare and treatment options for the management of systemic fungal infections were limited primarily to amphotericin B. Antifungal susceptibility testing did also prove to be quite problematic, since the results can vary quite a lot depending on the test conditions. The most important factors found to influence results are: media used, inoculum preparation, inoculum size, incubation time, incubation temperature and endpoint determinations. Therefore, it was apparent that standardization of test methodology was necessary and a considerable amount of work was done in the United States by the NCCLS Subcommittee on Antifungal Susceptibility Tests towards this goal. On the basis of results from several studies conducted by the NCCLS, a reference standard for susceptibility testing of yeasts was proposed in 1992 and finally accepted in 1997 (2).

The NCCLS reference method is a broth dilution method that can be performed either in tubes or in microtiter plates. Based on comparative studies of in vitro susceptibility testing and clinical treatment results interpretative breakpoints for susceptibility testing of yeasts to fluconazole, itraconazole and voriconazole have been proposed (4-6).

Commercial methods for susceptibility testing of yeasts have been developed. A number of studies have been done to compare Etest (AB BIODISK, Solna, Sweden) with the NCCLS method. Many of these studies conclude that the Etest is a reliable alternative to the NCCLS method.

Results of in vitro susceptibility testing of Norwegian yeast isolates

The monitoring of yeast susceptibility to antifungal drugs was started in Norway in 1991. All the medical microbiological laboratories agreed to cooperate in a long-term, nationwide prospective candidemia study. The study has been ongoing until now and is the most extensive prospective population-based candidemia study ever performed. The specific objectives of the study have been threefold: (a) to define the incidence of fungal bloodstream infections in Norway; (b) to identify the spectrum of pathogens causing yeast bloodstream infections; and (c) to obtain antifungal susceptibility data for Norwegian bloodstream isolates. Results for the years 1991-96 and 1991-2003 have been published (7,8).

During the period 1991-2003 a total of 1393 episodes of candidemia occurred in 1348 patients. The majority of the strains (95.3%) were tested for susceptibility to amphotericin B and fluconazole and 75% were tested for susceptibility to flucytosine. Nearly all strains (99.5%) were susceptible to amphotericin B (MIC $\leq$ 1 µg/ml). Most strains (95.8%) were also susceptible to flucytosine. Only 16 (2.2%) *C. albicans*, 4 (2.9%) *C. glabrata*, 2 (2.5%) *C. tropicalis* isolates had decreased flucytosine susceptibility with MICs $\geq$ 8 mg/L.

All 934 *C. albicans* strains and nearly all *C. tropicalis* and *C. parapsilosis* isolates were susceptible to fluconazole. Only one (1.3%) *C. parapsilosis* and three (3.2%) *C. tropicalis* strains had decreased susceptibility with MICs $\geq$ 16 mg/L. All *C. krusei* strains had MIC $\geq$ 32 mg/L and the majority of *C. glabrata* strains (68.7%) had MICs $\geq$ 16 mg/L. The percentage of yeast isolates with decreased susceptibility to fluconazole (MICs $\geq$ 16 mg/L) was 10.7% during the first period of this study (1991-1996) and 11.7% during the second period (1997-2003).

The results of this study provide important information regarding overall long-term candidemia trends and antifungal resistance in Norway. These data should be helpful to physicians and antimicrobial use committees in establishing guidelines for the appropriate use of antifungal agents in Norwegian hospitals.

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

Data sources

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

Antimicrobial agents for therapeutic use
In Norway, veterinary 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 2005 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 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
All veterinary antimicrobial specialities included in this report belong to the following ATCvet groups: gastrointestinal infections (QA07AA), uterine infections (QG01AA+AE), and antimicrobial agents for systemic use (QJ), including intramammary dose applicators (QJ51). The QJ-group also includes medicated feeds and premixes for farmed fish that are approved by the drug authorities and classified as pharmaceutical specialities (QJ01). Dermatological preparations (QD) and preparations intended for sensory organs (QS) are not included in the material. In small animal practice human antimicrobial preparations are used. However, data on the use of such antimicrobial drugs in animals are not included in this report as such usage cannot be separated from sales 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 by pharmacies. This data covers total sales of antibacterials for humans 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 with 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 has been collected since the beginning of the seventies.
Data on antibacterial use in hospitals are retrieved from drug wholesalers by permission of LIS (Legemiddel Innkjøp Samarbeid), who are responsible of the public procurement of drugs to all hospitals in Norway.
Data on the use in ambulatory care are estimated from the use in hospitals and total use of antibacterials for humans. The use in ambulatory care includes the use of antibacterials in nursing homes. From 1 January 2004, a national prescription database has been established. These data will give exact population prevalence of antibacterials in ambulatory care. Data from this register will be available in 2006.

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 2006 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 antiinfectives are as a main rule based on the use in infections of moderate severity. Some antiinfectives 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 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

Clinical isolates from animals in 2005 were collected from diagnostic submissions: *Staphylococcus aureus* and coagulase negative *Staphylococcus* spp. (CoNS) from cattle with mastitis and *Staphylococcus aureus* from sheep with mastitis. The samples from sheep were collected from diagnostic submissions during the period 2003-2004. Milk samples were collected by veterinary practitioners. Only one isolate per herd was tested for antimicrobial susceptibility.

Indicator bacteria *Escherichia coli* and *Enterococcus* spp. (*E. faecalis* and *E. faecium*) included in the NORM-VET monitoring programme 2005 were collected from cattle and sheep. Faecal samples (from caecum or colon) were collected at slaughterhouses and samples of minced cattle meat were collected at cutting plants. The sampling period was from January to December. Personnel from the Norwegian Food Safety Authority collected the faecal samples from cattle and sheep at slaughterhouses. To obtain a representative random sample from cattle and sheep, the number of samples collected at each slaughterhouse were determined by the proportion of animals slaughtered there, relative to the total number of animals slaughtered in Norway in 2004. Abattoirs that slaughtered >1% of the total delivered slaughter in 2004 were included. The meat samples from cattle were collected from 15 cutting plants (10 samples at each facility equally distributed over the year).

Isolation and identification of bacteria

***Staphylococcus* spp.**

The staphylococcal isolates included in NORM-VET 2005 were isolated at the National Veterinary Institute or at the Mastitis Laboratory in Molde. Secretions (0.01 ml) were plated on blood agar (Heart infusion agar (Difco) containing 5% washed bovine erythrocytes). The plates were incubated at 37°C for 24 and 48 h. If no growth was detected after incubation for 24 h, the original secretion sample was preincubated for 4 h at 37°C, and a larger inoculum (0.05 ml) was cultivated on another blood agar as described above. Identification of the *S. aureus* was performed at the National Veterinary Institute and was based on the occurrence of haemolytic zones, Gram stain, production of catalase and coagulase, growth on peptone agar with acriflavine and anaerobic fermentation of mannitol. The Staph-Zym® biochemical test kit (Rosco) was used for species identification of CoNS.

Escherichia coli

The *E. coli* isolates included in NORM-VET 2005 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: Intestinal content was gathered on swabs and 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 isolates included in NORM-VET 2005 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: Intestinal content was gathered on swabs and plated directly onto the surface of Slanetz & Bartley agar (Oxoid) without broth enrichment.

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

Susceptibility testing

Only one isolate per herd or product were tested for antimicrobial susceptibility. Bacterial isolates were tested for antimicrobial susceptibility at the National Veterinary Institute. The VetMIC™ microdilution method (Dept. of Antibiotics, National Veterinary Institute, Sweden) was used for the susceptibility testing of all isolates. *S. aureus* was tested for production of beta-lactamase using the cloverleaf method. All *S. aureus* and CoNS isolates with a MIC-value>2 mg/L and 0.5 mg/L, respectively, were subjected to *mecA* PCR.

Microbiological cut-off values were used to classify the isolates as resistant or susceptible (Appendix 6). The microbiological cut-off value is defined as the highest MIC-value of isolates that belong to the original genetically unchanged population (wild-type). It classifies the isolates with a MIC-value greater than the microbiological cut-off value as resistant.

Quality assurance systems

The following bacteria were included as quality controls on a weekly basis, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213. The following resistant bacteria were tested on a regular basis: *E. faecium* CCUG 33829, CCUG 36804 and *S. aureus* CCUG 35603. The results were approved according to reference values given by CLSI when available.

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 for antimicrobial resistance in bacteria of animal origin ARBAO-II http://www.dfvf.dk/Default.asp?ID=9753).

Data processing

Susceptibility test results were recorded and processed in WHONET 5.3, a program developed by WHO.

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.zoonose.no), samples from chickens were collected at slaughter plants (caecal samples), and samples from fresh broiler products were collected at retail level. One isolate per positive farm or batch of products was included for susceptibility testing.

Sampling strategy - humans

Salmonella, Yersinia enterocolitica* and *Shigella

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

Campylobacter

A total of 250 human isolates were obtained from clinical specimens. Five regional laboratories submitted the first five isolates each month to the National Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health. One isolate per patient was included for susceptibility testing.

Isolation and identification of bacteria

Isolation and identification of *Salmonella* from animals was carried out by the National Veterinary Institute according to the Nordic Committee on Food Analyses (NMKL) method number 71. Isolation of *Campylobacter* spp. from broiler and broiler products was carried out by the local food control laboratories according to the Nordic Committee on Food Analyses (NMKL) method number 119, with minor modifications. Identification of *C. jejuni* was carried out by the Norwegian Institute of Public Health.

Isolation and identification of bacteria from humans were performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th ed.ition 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 were verified at the National Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

Susceptibility testing

The 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).

The *Salmonella*, *Yersinia* and *Shigella* isolates from humans were tested for antimicrobial susceptibility at the Norwegian Institute of Public Health by an agar disk diffusion test using BD Sensi-Disc on Mueller-Hinton II-medium. The *Campylobacter* isolates from humans were tested for antimicrobial susceptibility at the Norwegian Institute of Public Health by using Etest (AB Biodisk).

For animal isolates, microbiological cut-off values were used to classify the isolates as resistant or susceptible (Appendix 6). The microbiological cut-off value is defined as the highest MIC-value of isolates that belong to the original genetically unchanged population (wild-type). It classifies the isolates with a MIC-value greater than the microbiological cut-off value as resistant. 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 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 participates also in the external quality assurance programmes organized by ARBAO-II http://www.dfvf.dk/Default.asp?ID=9753. 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 WHONET5.3, 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 values (MIC).

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

General considerations
NORM is based upon periodic sampling and local testing 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. 2005 was the sixth year of surveillance, and all twenty-four laboratories in Norway participated in the surveillance system in addition to the Norwegian Institute of Public Health. All laboratories follow 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 up to a defined maximum of isolates for each surveillance category. The surveillance categories in 2005 were: *E. coli*, *Klebsiella* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Enterococcus* spp. and yeasts from blood cultures; *Streptococcus pneumoniae* from respiratory tract infections, and *E. coli* and *Enterobacter* spp. from urinary tract infections. In addition, all blood culture isolates of *Pseudomonas aeruginosa* from 2002 and 2003 and all *Neisseria gonorrhoeae* isolates recovered in 2003 are included in the 2005 report. Blood culture isolates, respiratory tract isolates and *N. gonorrhoeae* isolates were tested using Etest, while isolates from urinary tract infections were examined by a disk diffusion method in accordance with the Norwegian Reference Group on Antibiotic Susceptibility Testing (AFA). All resistance values were recorded either as MICs or mm inhibition zone sizes in order to monitor trends in the occurrence of resistance. Suspected MRSA (*S. aureus* with oxacillin MIC $\geq$ 4 mg/L) were examined by *mecA* PCR, and suspected VRE (enterococci growing on BHI with 6 mg/L vancomycin) were examined by PCRs for *van* genes. The eNORM computer program was used for the registration of patient data, sample data and resistance data. Data were analyzed by WHONET5 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.

Blood culture isolates
Consecutive isolates of up to 50 each of *E. coli*, *S. aureus*, and *S. pneumoniae*, up to 25 isolates of *Klebsiella* spp., and up to 20 isolates of *Enterococcus* spp. were included in the surveillance from January until testing in October. All isolates were tested using Etest (AB Biodisk, Solna, Sweden). A total of 993 *E. coli* isolates, 359 *Klebsiella* spp. isolates, 741 *S. aureus* isolates, 325 *Enterococcus* spp. isolates and 303 *P. aeruginosa* isolates were tested on BBL MH II agar (BD) at 35ºC in ambient air, while 704 *S. pneumoniae* isolates were tested on MH II agar with 5% lysed horse blood at 35ºC in 5% CO_2. All *E. coli* and *Klebsiella* spp. isolates were tested for ESBL production using disk approximation including amoxicillin/clavulanic acid, aztreonam, ceftazidime, cefotaxime, cefpodoxime and cefpirome. All *S. aureus* isolates were tested for beta-lactamase production by nitrocefin disk, acidometric agar plate (3.6 mg/L penicillin G and phenol red) or the clover leaf test. All *S. aureus* isolates were screened for methicillin resistance using MH II agar with 4% NaCl and oxacillin 4 mg/L and a spot inoculum of 10^6 cfu/spot. All enterococci were screened for vancomycin resistance using BHI agar (Difco) and vancomycin 6 mg/L. The following strains were used for quality control: *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 (ESBL positive), *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, *S. aureus* ATCC 43300 (heterogeneous MRSA), and *S. aureus* CCUG 35600 (homogeneous MRSA).

Respiratory tract isolates
Up to 50 consecutive isolates of *S. pneumonia* from patients with respiratory tract infections were collected in each laboratory from January to March. All isolates were kept in a freezer and tested in batch using Etest on MH II agar supplemented with 5% lysed horse blood followed by incubation at 35°C in 5% CO_2. A total of 861 *S. pneumoniae* isolates were included. *S. pneumoniae* ATCC 49619 was used for quality control.

Urinary tract isolates
Up to 50 consecutive isolates each of *E. coli* and *Enterobacter* spp. from patients with urinary tract infections were collected in each lab during January and February. All isolates were either kept on bench or in a freezer until tested in batch by disk diffusion with either MH II (BD) or ISA (Oxoid) agar and paper disks from BD or Oxoid, respectively, at 35ºC in ambient air. ESBL production was examined by the disk approximation test described for blood culture isolates. The study included 1,127 *E. coli* isolates and 411 *Enerobacter* spp. isolates, and *E. coli* ATCC 25922 was used for quality control.

Neisseria gonorrhoeae
All 167 *N. gonorrhoeae* isolates recovered in 2003 were examined by Etest on GC agar (Oxoid) incubated for 24 h at 35°C in 5% CO_2. *N. gonorrhoeae* ATCC 49226 was used for quality control.

Mycobacterium tuberculosis
Susceptibility testing (DST) was performed at the Norwegian Institute of Public Health, Ullevål University Hospital and National Hospital. 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* to detect resistance to rifampicin.

Yeasts
Susceptibility testing of yeasts was peformed by Etests according to the instructions of the manufacturer.

Appendix 6: Breakpoints NORM-VET

For classification as resistant or susceptible, the following microbiological cut-off values were applied in this report. A microbiological cut-off value is defined as the highest MIC-value of isolates that belong to the original genetically unchanged population (wild-type). It classifies the isolates with a MIC-value greater than the microbiological cut-off value as resistant. For details regarding bacteria and antimicrobial panels, see the tables in the text.

Antimicrobials	Resistant (MIC values, mg/L)	*Campylobacter*	*E. coli* / *Salmonella*	*S. aureus*** / *CoNS****	*Enterococcus*
Oxytetracycline	> 2	■		■	
	> 4				■
	> 8		■		
Chloramphenicol	> 16		■	■	■
Florfenicol	> 16		■		
Ampicillin	> 8		■		■
	> 16	■			
Penicillins	Based upon beta-lactamase production			■	
Oxacillin	> 2			■	
Cephalothin	> 1			■	
Ceftiofur	> 2		■		
Trimethoprim	> 4		■		
	> 8			■	
Sulfonamides	> 256		■		
Erythromycin	> 2			■	
	> 4				■
	> 8	■			
Clindamycin	> 2			■	
Streptomycin	> 8		■*		
	> 32		■*	■	
	> 1024				■
Gentamicin	> 2			■	
	> 4	■	■		
	> 512				■
Neomycin	> 2			■	
	> 4		■		
	> 512				■
Enrofloxacin	> 0.25		■		
	> 0.5	■		■	
Nalidixic acid	> 16	■	■		
Vancomycin	> 4			■	■
Fusidic acid	> 0.5			■	
Avilamycin	> 16			■	■
Bacitracin	> 32				■
Flavomycin	> 32				■
Virginiamycin	> 4			■	
	> 8				■
Narasin	> 2				■

*> 8 for *Escherichia coli*, > 32 for *Salmonella* spp.

***Final classification of resistance to oxacillin was based on mecA detection (isolates with MIC>2mg/L).*

**** AllCoNS isolates with oxacillin MIC >0.5mg/L were subjected to mecA PCR for detection of the determinant for oxacillin resistance.*

Appendix 7: Breakpoints NORM

Breakpoints for antimicrobial resistance used in this report. NORM data are categorized according to the breakpoints of the Norwegian Reference Group on Antibiotic Susceptibility Testing – AFA (isolates from humans). Breakpoints for *Campylobacter* are preliminary and based on MIC-distributions. For details regarding bacteria and antimicrobial panels, see tables in text.

	MIC values mg/L														
Antimicrobials	S	R	*E. coli*	*Klebsiella* spp.	*Enterobacter* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Enterococcus* spp.	*S. aureus*	*S. pneumoniae*	*P. aeruginosa*	*N. gonorrhoeae*	*Campylobacter* spp.	*M. tuberculosis*	Yeasts
Ampicillin	≤ 0.25	≥ 4											■			
	≤ 0.5	≥ 16			■											
	≤ 2	≥ 16							■							
Aztreonam	≤ 8	≥ 16										■				
Cefotaxime	≤ 0.5	≥ 4									■					
	≤ 1	≥ 8			■											
Cefpirome	≤ 1	≥ 16			■											
Ceftazidime	≤ 1	≥ 16			■											
	≤ 8	≥ 16										■				
Ceftriaxone	≤ 0.25												■			
Cefuroxime	≤ 0.5	≥ 16			■											
Chloramphenicol	≤ 4	≥ 8									■					
Ciprofloxacin	≤ 0.032	≥ 0.125											■			
	≤ 0.5	≥ 2			■							■				
	≤ 1	≥ 4												■		
Colistin	≤ 4	≥ 8										■				
Doxycycline	≤ 2	≥ 4												■		
Erythromycin	≤ 0.5	≥ 1									■					
	≤ 0.5	≥ 8											■	■		
	≤ 1	≥ 4								■						
Fusidic acid	≤ 0.5	≥ 1								■						

Antimicrobials	MIC values mg/L S	R	*E. coli*	*Klebsiella*	*Enterobacter* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Enterococcus* spp.	*S. aureus*	*S. pneumoniae*	*P. aeruginosa*	*N. gonorrhoeae*	*Campylobacter* spp.	*M. tuberculosis*	Yeasts
Gentamicin	≤ 1	≥ 2								■						
	≤ 2	≥ 8			■											
	≤ 4	≥ 8												■		
	≤ 128	≥ 256							■							
Imipenem	≤ 4	≥ 16										■				
Linezolid	≤ 4	≥ 8							■	■						
Mecillinam	≤ 2	≥ 16			■											
Meropenem	≤ 0.5	≥ 4			■											
	≤ 2	≥ 16										■				
Nalidixid acid	≤ 16	≥ 32			■									■		
Nitrofurantoin	≤ 32	≥ 64			■											
Oxacillin	≤ 2	≥ 4								■						
Penicillin G	≤ 0.064	≥ 0.25								■						
	≤ 0.064	≥ 2									■		■			
	≤ 4	≥ 16							■							
Pip./Tazo.	≤ 8	≥ 32			■											
	≤ 16	≥ 32										■				
Quinu./Dalfo.	≤ 1	≥ 4							■							
Spectinomycin	≤ 32	≥ 64											■			
Streptomycin	≤ 256	≥ 512							■							
Sulfa	≤ 64	≥ 256			■											
Tobramycin	≤ 4	≥ 8										■				
Tetracycline	≤ 0.125	≥ 2											■			
	≤ 2	≥ 4									■					
Trimethoprim	≤ 2	≥ 8			■											
TMS	≤ 0.5	≥ 4									■					
	≤ 2	≥ 16			■											