2009

NORM
NORM-VET

Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

ISSN: 1502-2307 (print) / 1890-9965 (electronic)

Suggested citation: ***NORM/NORM-VET 2009. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. Tromsø / Oslo 2010. ISSN:1502-2307 (print) / 1890-9965 (electronic).***

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

CONTRIBUTORS AND PARTICIPANTS

Editors:

Madelaine Norström	NORM-VET, National Veterinary Institute
Gunnar Skov Simonsen	NORM, Univ. Hosp. of North Norway / Norw. Inst. of Pub. Health

Authors:

Hege Salvesen Blix	Usage in humans	hegesbl@ulrik.uio.no	Norw. Inst. of Pub. Health
Kari Grave	Usage in animals	kari.grave@vetinst.no	Nat. Vet. Inst. / Norw. School of Vet. Sc.
Jarle Mikalsen	Animal clinical isolates, indicator and enteropathogenic bacteria	jarle.mikalsen@vetinst.no	NORM-VET, National Veterinary Institute
Ingvild Nordøy	Human clinical isolates	ingvild.nordoy@rikshospitalet.no	Oslo Univ. Hosp., Rikshospitalet
Madelaine Norström	Animal clinical isolates, indicator and enteropathogenic bacteria	madelaine.norstrom@vetinst.no	NORM-VET, National Veterinary Institute
Andreas Radtke	Human clinical isolates	andreas.radtke@stolav.no	St. Olavs Hosp.
Karin Rønning	Human clinical isolates	karin.ronning@fhi.no	Norw. Inst. of Pub. Health
Gunnar Skov Simonsen	Human clinical isolates	gunnar.skov.simonsen@unn.no	NORM, Univ. Hosp. of North Norway
Trine-Lise Stavnes	Enteropathogenic bacteria	trine-lise.stavnes@fhi.no	Norw. Inst. of Pub. Health
Marianne Sunde	Animal clinical isolates and indicator bacteria	marianne.sunde@vetinst.no	National Veterinary Institute
Astrid Louise Wester	Enteropathogenic bacteria	astrid.louise.wester@fhi.no	Norw. Inst. of Pub. Health

Institutions participating in NORM-VET:

Norwegian Food Safety Authority	
National Veterinary Institute, Norwegian Zoonosis Centre	Madelaine Norström / Jarle Mikalsen / Merete Hofshagen
National Veterinary Institute, Section of Bacteriology	Marianne Sunde / Hanne Tharaldsen
Norwegian Institute of Public Health	Astrid Louise Wester / Trine-Lise Stavnes

Institutions participating in NORM:

Akershus University Hospital, Lørenskog, Department of Microbiology	Trond Egil Ranheim / Marit Vattøy
Asker & Bærum Hospital, Bærum, Department of Microbiology	Annette Onken / Merriam Sundberg
Buskerud Hospital, Drammen, Department of Microbiology	Helvi Holm Samdal / Ellen-Margrete Grimstad
Førde Hospital, Department of Microbiology	Reidar Hjetland / Astrid Vedde
Haugesund Hospital, Department of Microbiology	Liv Jorunn Sønsteby / Pirrko-Liisa Kellokumpu
Haukeland Univ. Hospital, Bergen, Dep. of Immunology and Microbiology	Dag Harald Skutlaberg / Torunn Sneide Haukeland
Innlandet Hospital, Lillehammer, Department of Microbiology	Viggo Hasseltvedt / Kari Ødegaard
Levanger Hospital, Department of Microbiology	Angela Kümmel / Anne-Kristine Lorås
Molde Hospital, Department of Microbiology	Einar Vik / Per Gerhard Skotgård
National Reference Laboratory for Enteropathogenic Bacteria, Oslo	Jørgen Lassen / Trine-Lise Stavnes
Nordland Hospital, Bodø, Department of Microbiology	Liisa Mortensen / Hege Elisabeth Larsen
Oslo University Hospital, Aker, Department of Bacteriology	Gorm Hansen / Bitten Rasmussen
Oslo University Hospital, Radiumhospitalet, Laboratory of Microbiology	Truls M. Leegaard / Merete R. Ueland
Oslo University Hospital, Rikshospitalet, Institute of Medical Microbiology	Truls M. Leegaard / Pia Langseth
Oslo University Hospital, Ullevål, Department of Microbiology	Gaute Syversen / Thea Bergheim
Stavanger University Hospital, Department of Microbiology	Paul Naaber / Anita Løvås Brekken
St. Olav University Hospital, Trondheim, Department of Microbiology	Jan Egil Afset / Toril Nordtømme
Sørlandet Hospital, Kristiansand, Department of Microbiology	Ståle Tofteland / Torill S. Larsen
Unilabs Telelab A/S, Skien	Peter Csango / Anne Ragnhild Oseid
University Hospital of North Norway, Tromsø, Department of Microbiology	Gunnar Skov Simonsen / Siv-Heidi Barkhald
Vestfold Hospital, Tønsberg, Department of Microbiology	Dagfinn Skaare / Astrid Lia
Østfold Hospital, Fredrikstad, Department of Microbiology	Eivind Ragnhildstveit / Anne Cathrine Hollekim
Ålesund Hospital, Department of Microbiology	Reidar Hide / Camilla Jensen

NORM reference group in 2009:

Olav Natås	Stavanger University Hospital, Stavanger
Eldbjørg Berg	Levanger Hospital, Levanger
E. Arne Høiby	Norwegian Institute of Public Health, Oslo
Peter Gaustad	Oslo University Hospital, Rikshospitalet, Oslo
Dag Berild	Oslo University Hospital, Aker, Oslo
Ståle Tofteland	Sørlandet Hospital, Kristiansand
Knut Eirik Eliassen	Antibiotic Centre for Primary Care (ASP), University of Oslo.

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

CONTENTS

I. INTRODUCTION

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

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

In response to the growing concern about antimicrobial resistance, the Norwegian Ministry of Health and Social Affairs issued a national action plan against antimicrobial resistance in March 2000. Again, the importance of monitoring both the human and veterinary sectors, including food production, was 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 continued surveillance of both resistance and drug usage was emphasized. An integrated national strategy for prevention of infections in the health service and antibiotic resistance (2008 – 2012) was issued in the summer of 2008.

The NORM surveillance programme for antimicrobial resistance in human pathogens was established in 1999 and is coordinated by the Department of Microbiology and Infection Control at the University Hospital of North Norway in Tromsø. The NORM-VET monitoring programme for antimicrobial resistance in the veterinary and food production sectors was established in 2000 and is coordinated by the Norwegian Zoonosis Centre at the 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, i.e. coccidiostatic growth promoters, are collated at the Norwegian Food Safety Authority.

This report, which is the tenth annual joint report from NORM and NORM-VET, presents data for 2009. In addition to resistance data, the NORM/NORM-VET reports present data on the usage of antimicrobial agents in humans and animals in Norway. The present report, together with earlier reports and reports from the years to come, form a basis for the detection, interpretation and evaluation of trends regarding usage of antimicrobial agents and occurrence of resistance in Norway. The NORM and NORM-VET programmes are valuable tools for setting policies, assessing risks and evaluating interventions.

The editors would like to thank the Reference Center for Detection of Antimicrobial Resistance in Tromsø for fruitful cooperation and all those who contributed to data collection and the writing of this report, for excellent work.

Tromsø / Oslo, September 2010

II. SAMMENDRAG

Dette er den tiende felles rapporten fra Norsk overvåkingssystem for antibiotikaresistens hos mikrober (NORM) og Norsk overvåkingsprogram for antibiotikaresistens i mikrober fra fôr, dyr og næringsmidler (NORM-VET). Rapporten presenterer data over forekomst av antibiotikaresistens og forbruk av antibiotika til mennesker og dyr i 2009. Data fra relevante prosjekter som ikke er med i de kontinuerlige overvåkingsprogrammene, presenteres også.

Både NORM og NORM-VET programmene er deler av Regjeringens tiltaksplan mot antibiotikaresistens som ble offentliggjort i 2000. NORM koordineres av Avdeling for mikrobiologi og smittevern, Universitetssykehuset Nord-Norge i Tromsø. NORM-VET koordineres av Zoonosesenteret ved Veterinærinstituttet i Oslo. Programmene har et godt samarbeid og utgir en felles årsrapport.

Forbruk av antibiotika til dyr

Forbruket av antibiotika i norsk husdyrproduksjon og akvakultur er lavt. Totalsalget av veterinære antibiotika til terapeutisk bruk på landdyr i 2009 var 6137 kg. Fra 1995 til 2001 ble salget av veterinære antibiotika til landdyr redusert med ca 40 %. Etter dette har forbruket holdt seg relativt konstant. Forbruksmønsteret har utviklet seg i gunstig retning siden 1995; det vil si at andelen penicillinbruk har økt. Rene penicillinpreparater utgjorde 47 % av salget av veterinære antibiotika til landdyr i 2009, og av dette var 86 % beta-laktamase følsomme penicilliner. Forbruket av tetracykliner utgjorde kun 3,6 %. Nedgangen i antibiotikaforbruket og endringene i forskrivningsmønsteret skyldes først og fremst at husdyrnæringen i andre halvdel av 1990-tallet gjennomførte systematiske kampanjer for å redusere forbruket av antibiotika til dyr og for riktig bruk av antibiotika.

Totalsalget av veterinære antibiotika til terapeutisk bruk hos oppdrettsfisk i Norge var i 2009 på 1313 kg aktiv substans, hvorav 71 % var kinoloner. Forbruket av antibiotika i oppdrettsnæringen er redusert med 98 % siden 1987. Denne betydelige reduksjonen kan tilskrives innføringen av effektive vaksiner til laks og ørret samt andre infeksjonsforebyggende tiltak, herunder bedrede miljøforhold.

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 mer enn fordoblet siden forbudet mot bruk av antibakterielle vekstfremmere, noe som kan forklares ved økt produksjon av broilere. Forbruksmønstret for koksidiostatika er endret fra monensin til narasin etter 1996. Narasin har de senere årene utgjort hovedparten av forbruket av ionofore koksidiostatika.

Forbruk av antibiotika hos mennesker

I 2009 var humant forbruk av antibiotika til systemisk bruk 19,4 DDD/1000 innbyggere/dag. Det samlede forbruket har vært forholdsvis stabilt gjennom mange år, men det har skjedd en gradvis forskyvning mellom de ulike antibakterielle undergrupper. Fra 2004 har totalforbruket av antibiotika økt jevnt, men i 2009 ble det observert en reduksjon i forhold til 2008. Salget av penicilliner og kinoloner øker fortsatt, mens salg av makrolider, tetracykliner, sulfonamider og trimetoprim synker. Det urinveisantiseptiske middelet metenamin har de seneste årene økt kraftig, og i 2009 utgjorde metenamin 16 % av totalt salg målt i DDD.

I 2009 utgjorde penicillinene 43 % av det totale antibiotikaforbruket i Norge målt i DDD. I 2009 så vi en økning av bredspektrede og penicillinasestabile penicilliner og en nedgang i beta-laktamase følsomme penicilliner. Tetracykliner utgjorde 16 % av totalforbruket i 2009. Forbruket av makrolider og linkosamider utgjorde 10 % av totalt salg i 2009, det ble redusert med 11 % i forhold til 2008. Salget av cefalosporiner, monobaktamer og karbapenemer utgjør kun 3 % av totalsalget. Over år har det vært en markant økning i forbruket av fluorokinoloner. Denne gruppen utgjorde kun 4 % av totalforbruket i 2009, men salget er mer enn doblet på 10 år.

Bruken av antibakterielle midler varierer avhengig av kjønn, alder og bosted. Salget til sykehus og allmennpraksis utgjorde i 2009 henholdsvis 7,5 % og 84 %. Penicilliner utgjør 45 % av antibiotikasalget til sykehus, målt i DDD. Tilsvarende tall for allmennpraksis er 43 %. De største gruppene utenom penicilliner var på sykehus cefalosporiner (23 %) og quinoloner (7 %), og i allmennpraksis tetracykliner (18 %) og makrolider (11 %).

Resistens hos kliniske isolater fra dyr

Kliniske isolater i 2009 inkluderte *E. coli* fra diagnostiske prøver fra kyr med mastitt. Forekomsten av antibiotikaresistens var moderat; 77,1 % av isolatene var følsomme for alle undersøkte antibiotika. Resistens mot streptomycin og ampicillin ble hyppigst identifisert. En relativt stor andel av isolatene (16,7 %) var resistent mot flere enn to antibiotika.

Resistens hos indikatorbakterier fra dyr

Forekomsten av ervervet antibiotikaresistens blant bakterier som utgjør den normale tarmfloraen, kan tjene som en indikator på selektivt antibiotikapress i ulike populasjoner. I 2009 ble *E. coli* isolert fra kumelk (tankmelk) og avføringsprøver fra slaktekylling og hest resistenstestet. I tillegg ble utvalgte *E. coli* isolater fra sau inkludert, hovedsakelig isolater tilhørende serogruppene O26 og O103. Kun et fåtall tankmelkprøver ble funnet positive for *E. coli*, og resistens mot en eller flere substanser ble kun påvist hos to av 15 isolater. Forekomsten av antibiotikaresistens i *E. coli* isolert fra slaktekylling, hest og sau var lav. 76,5 % av *E. coli* fra slaktekylling som var følsomme for alle testede antibiotika, mens andelen fra sau og hest var henholdsvis 86,0 % og 90,6 %. Ampicillinresistens forekom hyppigst

blant *E. coli* fra slaktekylling, mens trimethoprimresistens var mest utbredt i *E. coli* fra hest. Streptomycinresistens var hyppigst observert i *E. coli* fra sau. Forekomsten av kinolonresistens blant *E. coli* fra slaktekylling var relativt høy (8 %) sammenlignet med tidligere år.

I 2009 ble det undersøkt for forekomst av ekstendert spektrum beta-laktamase (ESBL) produserende *E. coli* hos svin, meticillinresistente *Staphylococcus aureus* (MRSA) hos hest, samt vancomycinresistente *Enterococcus* spp. (VRE) hos slaktekylling. Det ble ikke påvist ESBL produserende *E. coli* eller MRSA, noe som indikerer en lav forekomst av henholdsvis ESBL (< 2,3 %) i norske svinebesetninger og MRSA (< 1,6 %) i den norske hestepopulasjonen. Tilstedeværelse av VRE ble påvist i 7,5 % av prøvene fra slaktekylling, og alle ble identifisert som *Enterococcus faecium*. Dette en signifikant økning sammelignet med forrige undersøkelse (NORM-VET 2006). Prøvematerialet er forskjellig i de to studiene (sokkeprøver i 2009 og avføringsprøver i 2006), og dette kan ha hatt betydning for resultatene. VRE bør overvåkes jevnlig for å følge utviklingen over tid.

Resistens hos zoonosebakterier og andre enteropatogene bakterier

I 2009 ble det resistenstestet 13 *Salmonella* spp. isolater fra norske dyr. Elleve av isolatene var *S*. Typhimurium, hvorav åtte ble isolert fra hund. Forekomsten av resistens var moderat, men to av isolater var multiresistente *S*. Typhimurium DT104.

Av de humane salmonellosetilfellene som ble rapportert i 2009, var 79,4 % oppgitt å ha blitt smittet i utlandet. Andelen *S*. Typhimurium isolater som var følsomme for alle antibiotika, var høyere for kategorien "smittet i Norge" (57,3 %) enn for kategorien "smittet i utlandet" (30,8 %). Multiresistens ble hyppigere påvist hos de utenlandssmittede (49,2 %) enn hos de innenlandssmittede (29,3 %). Resultatene for *S*. Typhimurium 2001-2009 indikerer en økende forekomst av resistens mot tetracykliner og ampicillin. Forekomsten av antibiotikaresistens var betydelig lavere hos *S*. Enteritidis enn hos *S*. Typhimurium med unntak av nalidiksinsyre. Til sammen 23,6 % av *S*. Enteritidis isolatene var resistente mot nalidiksinsyre. Andelen av ciprofloxacinresistente *S*. Enteritidis var på samme nivå som i 2008.

Resultatene fra 2009 viser at forekomsten av resistens hos *Campylobacter coli* fra norske svin er moderat. Totalt var 73,1 % av isolatene følsomme for alle undersøkte antibiotika. Resistens mot streptomycin ble hyppigst registret (22,4 %). Det ble ikke påvist resistens mot erythromycin, tetracyklin eller gentamicin.

Bare 17,2 % av *C. jejuni* fra pasienter smittet i utlandet var følsomme for alle undersøkte antibiotika sammenliknet med 85,1 % fra pasienter smittet i Norge. Andelen multiresistente *C. jejuni* isolater fra pasienter smittet i utlandet er betydelig høyere enn det som rapporteres fra "norske" isolater. Omtrent halvparten av *C. jejuni* isolatene var ervervet i utlandet, og av disse var 46,4 % resistente mot tre eller flere antibiotika.

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

Resistens hos kliniske isolater fra mennesker

Forekomsten av antibiotikaresistente kliniske bakterie-isolater fra mennesker var, som i de foregående år, meget lav i 2009. Det ble påvist fire tilfeller av meticillin-resistente *Staphylococcus aureus* (MRSA) blant de 929 blodkulturisolater (0,4 %) som ble inkludert i NORM-protokollen. Dette er i samsvar med at 7 av 1344 (0,5 %) *S. aureus* blodkulturisolater i laboratorienes datasystemer ble rapportert som MRSA. I 2009 var dermed 7 av 1359 (0,5 %) *S. aureus* fra blodkultur og spinalvæske MRSA. Andelen er på samme nivå som tidligere år med 0,7 % i 2008 og 0,4 % i 2007. Meldesystemet for infeksjons-sykdommer (MSIS) registrerte 414 tilfeller av MRSA-infeksjon i 2009. Dette er en klar økning (+19,0 %) fra 2008 da det ble registrert 348 tilfeller. Hele 80 % av tilfellene var pasienter med sårinfeksjoner og abscesser. MRSA utgjør fortsatt en svært liten andel av *S. aureus* isolater fra sårprøver (14/1763, 0,8 %). MSIS registrerte videre 402 tilfeller av MRSA-kolonisering i 2008 mot 304 i 2008. Det totale antallet MRSA-meldinger økte dermed fra 652 meldinger i 2008 til 816 i 2009 (+25,2 %). Resultatene fra overvåkingen viser at det totale antallet personer med påvist infeksjon eller kolonisering med MRSA igjen er sterkt økende, men at antallet med alvorlige infeksjoner fortsatt er stabilt på et lavt nivå. Blant *S. aureus* isolater fra sårprøver fortsatte nedgangen i andelen med fucidinresistens fra 14,5 % i 2006 til 8,1 % i 2009.

Blodkulturisolater av *E. coli* og *Klebsiella* spp. var som tidligere stort sett følsomme for bredspektrede antibiotika. Forekomsten av resistens og nedsatt følsomhet for gentamicin hos *E. coli* var 4,0 %. Dette er en svak økning fra 2,9 % i 2008 men på samme nivå som 3,9 % i 2007. Det er observert en vedvarende økning av resistens og nedsatt følsomhet for ciprofloxacin fra 3,3 % i 2004 til 8,6 % i 2009. Tallene er justert i henhold til nye brytningspunkter. Det er en klar samvariasjon mellom forbruket av fluorokinoloner og nedsatt følsomhet for denne antibiotikagruppen. *Klebsiella* spp. hadde lavere forekomst av resistens mot aminoglykosider og fluorokinoloner enn *E. coli*.

Produksjon av bredspektrede beta-laktamaser (ESBL) er blitt et utbredt problem i mange land, og forekomsten har også vært økende i Norge. Til sammen 34/1379 *E. coli* (2,5 %) og 15/568 (2,6 %) *Klebsiella* spp. fra blodkulturer ble rapportert som ESBL positive. For *E. coli* var forekomsten av ESBL klart høyere enn i 2008 (1,5 %). Forekomsten av ESBL blant *Klebsiella* spp. økte fra 2,0 % i 2008 til 2,6 % i 2009. De fleste av isolatene kunne verifiseres ved molekylære analyser, og det er derfor grunn til å følge utviklingen med spesiell oppmerksomhet. Andelen av ESBL positive isolater var fortsatt høyere blant *E. coli* fra blodkulturer (2,5 %) enn fra urinprøver (0,5 %). Fosfomycin kan tilsynelatende være et aktuelt alternativ for behandling av urinveisinfeksjoner med ESBL positive *E. coli*, men ikke for ESBL positive *K. pneumoniae*.

Det ble bare påvist ett enkelt enterokokkisolat med klinisk signifikant vankomycinresistens i 2009. Forekomsten av nedsatt følsomhet for ampicillin i *Enterococcus faecium* ligger fortsatt rundt 80 %, og høygradig gentamicinresistens ble påvist i 29,9 % av *E. faecalis* og 44,8 % av *E. faecium*. De aller fleste (49 av 52) *E. faecium*-isolater med høygradig gentamicinresistens hadde samtidig nedsatt følsomhet for ampicillin. Alle enterokokkisolatene var følsomme for linezolid.

Streptococcus pneumoniae fra blodkultur og spinalvæske var generelt følsom for alle relevante antibiotika. Tjuetre av 784 isolater (2,9 %) hadde nedsatt følsomhet for penicillin G, og kun ett enkelt isolat hadde samtidig redusert følsomhet for cefalosporiner. Andelen isolater med nedsatt følsomhet for penicillin G var på samnme nivå som i 2008 (3,0 %). Forekomsten av makrolid-resistens blant systemiske pneumokokkisolater fortsatte nedgangen fra toppåret 2006 (12,4%) til 4,6% i 2009. Nedgangen må sees i sammenheng med innføringen av den konjugerte pneumokokkvaksinen i barnevaksinasjons-programmet i juli 2006.

Systemiske isolater av *Streptococcus agalactiae* (beta-hemolytiske streptokokker gruppe B – GBS) var generelt følsomme for beta-laktamantibiotika. Forekomsten av resistens mot andre antibiotikaklasser var uendret fra 2006.

I alt 351 tilfeller av tuberkulose ble meldt til MSIS i 2009. Det ble utført resistensbestemmelse av 283 *Mycobacterium tuberculosis* isolater fra pasienter som ikke hadde blitt behandlet for tuberkulose tidligere. Syv isolater fra pasienter smittet i henholdsvis Afrika (n=6) og Europa utenfor Norge (n=1) ble klassifisert som multiresistente.

Det ble utført resistensbestemmelse av 195 blodkulturisolater av *Candida albicans* (n=139), *C. glabrata* (n=33), *C. tropicals* (n=13) og *C. parapsilosis* (n=10). Alle *C. albicans* isolater var følsomme for amphotericin B, fluconazol, voriconazol, caspofungin, anidulafungin og micafungin. Det ble påvist høy forekomst av resistens mot fluconazol og voriconazol blant *C. glabrata*, mens echinocandinene viste høy aktivitet mot alle de undersøkte soppartene. Resultatene er i samsvar med tidligere studier fra Norge.

Overvåking av resistens mot antivirale midler omfattet i 2009 både influensavirus og HIV, men resultatene for HIV er foreløpig ikke blitt analysert nærmere. Influensa-sesongen 2009/2010 ble dominert av pandemisk influensa A(H1N1) som er fullstedig resistent mot M2 blokkere. Det ble imidlertid ikke påvist resistens mot neuraminidase-hemmerne oseltamivir og zanamivir i Norge. Den tidligere dominerende influensa A(H3N2) med resistens mot oseltamivir synes å ha blitt fullstendig fortrengt under H1N1-pandemien.

Konklusjon

Antibiotikaresistens er fortsatt et begrenset problem i Norge både når det gjelder mennesker og dyr. Det lave forbruket av antibiotika og det fordelaktige forbruks-mønsteret 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 tenth 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 2009. The NORM and NORM-VET programmes are part of the Norwegian Government's Action Plan against Antimicrobial Resistance issued in 2000. NORM is coordinated by the Department of Microbiology and Infection Control, University Hospital of North Norway, Tromsø. NORM-VET is coordinated by the Norwegian Zoonosis Centre, National Veterinary Institute, Oslo. Successful collaboration has been established between NORM and NORM-VET and a joint report is issued annually.

Usage of antimicrobial agents in animals

The usage of antimicrobials in Norwegian animal production and aquaculture is low. In 2009, the total sales of antimicrobial drugs approved for therapeutic use in animals in Norway were 6,137 kg (fish not included). The annual usage of veterinary antimicrobial drugs decreased gradually by approximately 40% from 1995 to 2001, and has thereafter remained relatively stable. The patterns of use have gradually become more favourable as the proportion of penicillin-use has increased. The proportion accounted for by pure penicillin preparations rose from 24% in 1995 to 47% in 2009. Altogether, 86% of the veterinary penicillin preparations sold in 2009 were beta-lactamase sensitive penicillins. The sales of sulfonamides decreased from 14% in 1995 to 0.01% in 2009. The proportion accounted for by tetracyclines varied between 3-5% in the period 1995-2009. The reduced antimicrobial drug 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 2008, the total sale of antimicrobial drugs for therapeutic use in farmed fish was 1,313 kg of active substance. Quinolones accounted for 71% of this amount. The usage of antimicrobials in Norwegian aquaculture declined by approximately 98% from 1987 to 1996 and has thereafter remained relatively constant. This reduction is mainly attributed to the introduction of effective vaccines in salmonids as well as to improved health management.

In 2009, the total sales of coccidiostatic feed additives, in kilograms of active substance, was more than twice the amounts used prior to the ban of antimicrobial growth promoters in 1995. This is explained by increased production of broilers. While monensin was the most frequently used ionophore in poultry in 1995, the usage of coccidiostats has since then been dominated by narasin.

Usage of antimicrobial agents in humans

In 2009, the overall sales of antibacterials for systemic use in humans were 19.4 DDD/1,000 inhabitants/day. The total consumption has been relatively stable over many years, although there has been a gradual shift among the various subgroups. From 2004, the total consumption of antibiotics increased steadily, but in 2009 there was a reduction compared to 2008. Sales of penicillins and quinolones are increasing, while sales of macrolides, tetracyclines, sulfonamides and trimethoprim are decreasing. Use of the urinary antiseptic agent methenamine is still sharply increasing and accounted for 16% of total sales in 2009 when measured in DDDs.

In Norway, 43% of the total antibiotic human use measured in DDDs, was penicillins in 2009. The use of penicillins with extended specter and beta-lactamase resistant penicillins increased, combined with a decrease in the use of beta-lactamase sensitive penicillins. Tetracyclines accounted for 16% of total consumption in 2009. The consumption of macrolides and lincosamides decreased by 11% in 2009 and accounted for 10% of total sales. Sales of cephalosporins, monobactams and carbapenems constitute 3% of total sales. Over the last years, there has been a marked increase in quinolone use. This group accounted for only 4% of total consumption in 2009, but sales have more than doubled in 10 years.

The use of antibacterials varies according to gender, age and residence. Sales to hospitals and general practice accounted for 7.5% and 84% in 2009, respectively. Penicillins accounted for around 45% of the sales to hospitals and 43% in ambulatory care. The main other groups in hospitals were cephalosporins (23%) and quinolones (7%), while in ambulatory care the most important other groups were tetracyclines (18%) and macrolides and lincosamides (11%).

Resistance in animal clinical isolates

The clinical isolates included in 2009 were *E. coli* from diagnostic samples from clinical mastitis in cattle. The prevalence of antimicrobial resistance in *E. coli* was moderate. In total, 77.1% of *E. coli* isolates were susceptible to all antimicrobial agents included. Resistance to streptomycin and ampicillin was most commonly identified. A relatively large part of the isolates (16.7%) was resistant to more than two antimicrobial agents.

Resistance in indicator bacteria from animals

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 2009, *E. coli* isolated from dairy milk (bulk milk) and from faecal samples from broiler and horses were included. In addition, *E. coli* isolates from sheep, primarily isolates belonging to serogroups O26 and O103, were susceptibility tested. Only a few bulk milk samples were positive for *E. coli*. Resistance to one or more of the antimicrobial agents was only identified in two of the 15 isolates. The occurrence of antimicrobial resistance in *E. coli* from faecal swabs was low. In total, 76.5%, 86.0%, and 90.6% of the *E. coli* isolates from broiler, sheep and horse, respectively, were susceptible to all antimicrobial agents tested. The most commonly identified antimicrobial resistance in *E. coli* isolates from broiler and horse were ampicillin and trimethoprim,

respectively. Streptomycin resistance was most commonly identified in *E. coli* from sheep. The occurrence of quinolone resistant *E. coli* among broilers was relatively high (8%).

In 2009, screening for some emerging and important antimicrobial resistance mechanisms was performed; extended spectrum beta-lactamase (ESBL) producing *E. coli* in swine, methicillin resistant *Staphylococcus aureus* (MRSA) in horses and vancomycin resistant *Enterococcus* spp. (VRE) in broilers. No ESBL or MRSA isolates were identified, indicating a low prevalence (<2.3%) of ESBL producing *E. coli* in Norwegian swine and a low prevalence (<1.6%) of MRSA in Norwegian horses. Vancomycin resistant *Enterococcus* spp. was identified in 7.5% of the broiler samples. All isolates were identified as *Enterococcus faecium*. This is a significant increase compared to the previous screening (NORM-VET 2006). However, the sampling material differs in the two studies (boot swabs in 2009 compared with faecal samples in 2006), which might have influenced the results. VRE should be monitored on a regular basis to follow the development over time.

Resistance in zoonotic and non-zoonotic enteropathogenic bacteria

In 2009, a total of 13 *Salmonella* spp. isolates from Norwegian animals were susceptibility tested. Eleven of the isolates were *S*. Typhimurium, eight of them originating from dogs. The occurrence of resistance was moderate; but two of the isolates were multiresistant *S*. Typhimurium DT104.

In 2009, 79.4% 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" (57.3%) than for the category "infected abroad" (30.8%). Multiresistant strains, i.e. resistant to two or more antimicrobial agents, were more common in the category "infected abroad" (49.2%) than in the category "infected in Norway" (29.3%). The data from 2001-2009 indicate that the prevalence of resistance to tetracyclines and ampicillin in *S*. Typhimurium may be increasing. The prevalence of resistance was considerably lower in *S*. Enteritidis isolates than in *S*. Typhimurium except for nalidixic acid. In total, 23.6% of *S*. Enteritidis isolates were resistant to nalidixic acid. The prevalence of resistance to ciprofloxacin was unchanged from 2008 to 2009.

The results obtained in 2009 show that the prevalence of resistance in *Campylobacter coli* from Norwegian swine is moderate. A total of 73.1% of the isolates were susceptible to all antimicrobial agents included. Streptomycin resistance was most common and identified in 22.6% of the isolates. Resistance to erythromycin, tetracycline or gentamicin was not identified.

Only 17.2% of *C. jejuni* isolates from patients infected abroad were susceptible to all antibiotics examined, compared to 85.1% from patients infected in Norway. The proportion of multiresistant *C. jejuni* among patients infected abroad is significantly higher than what is reported from "Norwegian" isolates. Approximately 50% of *C. jejuni* infections were acquired abroad, and 46.4% of these isolates were resistant to three or more antimicrobial agents.

Infections with *Yersinia enterocolitica* are typically obtained domestically, and the most common serotype is O:3. Resistance to chloramphenicol and trimethoprim-sulfamethoxazole was most frequently identified. In 2009, the majority of *Shigella* isolates were acquired out of the country and - as reported by other countries - antimicrobial resistance was commonly identified.

Resistance in human clinical isolates

The prevalence of resistance in human clinical isolates was still very low in Norway in 2009. Only four methicillin resistant *Staphylococcus aureus* (MRSA) blood culture isolates were detected among the 929 strains included in the NORM protocol (0.4%), and seven out of 1,344 (0.5%) *S. aureus* isolates were reported as MRSA from the laboratories´ information systems. The total number of systemic *S. aureus* isolates from blood cultures and cerebrospinal fluids was 1,359 including seven MRSA strains (0.5%). This prevalence is at the same level as in 2008 (0.7%) and 2007 (0.4%). The Norwegian Surveillance System for Communicable Diseases (MSIS) registered 414 cases of MRSA infections in 2009. This is a significant increase (+19.0%) from the 348 cases registered in 2008. A majority of the MRSA cases (80%) were reported to be wound infections and/or abscesses. Conversely, the prevalence of MRSA among non-invasive *S. aureus* isolates is still very low (14/1,763, 0.8%). Furthermore, MSIS registered 402 cases of MRSA colonisation giving a total of 816 MRSA notifications in 2009. This is a 25.1% increase from the 652 notifications registered in 2008. The results may indicate an increasing number of MRSA infections and colonisations, while the prevalence of invasive disease remains stable at a low level. The prevalence of resistance to fusidic acid among *S. aureus* wound isolates continued to decrease from 14.5% in 2006 to 8.1% in 2009.

E. coli and *Klebsiella* spp. blood culture isolates were generally susceptible to broad-spectrum antimicrobials. The prevalence of gentamicin non-susceptibility in *E. coli* was 4.0% in 2009. This is a minor increase from 2.9% in 2008 and on the same level as 3.9% in 2007. *E. coli* non-susceptibility to fluoroquinolones continued to increase from 3.3% in 2004 to 8.6% in 2009. The figures have been adjusted for changes in microbiological breakpoints. There is a clear correlation between the total usage of fluoroquinolones and non-susceptibility to these agents. The prevalence of resistance to aminoglycosides and fluoroquinolones was lower in *Klebsiella* spp. isolates than in *E. coli*.

Extended spectrum beta-lactamases (ESBL) have emerged as a significant clinical problem in many countries, and occasional cases have also been reported from Norway. A total of 34/1,379 (2.5%) *E. coli* and 15/568 (2.6%) *Klebsiella* spp. blood culture isolates were reported with this phenotype. For *E. coli*, this is an increase from 2008 (1.5%). The prevalence of ESBL production in *Klebsiella* spp. increased from 2.0% in 2008 to 2.6% in 2009. As most of these isolates were verified by molecular methods, the trend should be closely monitored. The proportion of ESBL positive isolates is still higher among *E. coli* from

blood cultures (2.5%) than among urinary tract isolates (0.5%). Fosfomycin appears to be an alternative for the treatment of urinary tract infections caused by ESBL positive *E. coli*, but not for ESBL positive *K. pneumoniae*. Only a single isolate with clinically significant vancomycin resistance was detected in enterococci in 2009. The prevalence of non-susceptibility to ampicillin in *E. faecium* has stabilized around 80%, and high-level gentamicin resistance (HLGR) was detected in 29.9% of *E. faecalis* and 44.8% of *E. faecium*. Virtually all (49 out of 52) HLGR *E. faecium* isolates were also non-susceptible to ampicillin. All enterococcal isolates were susceptible to linezolid.

Streptococcus pneumoniae from blood cultures and cerebrospinal fluids were generally susceptible to all relevant antimicrobials. Twenty-three out of 784 isolates (2.9%) displayed reduced susceptibility to penicillin G, and only a single isolate was also non-susceptible to cefalosporins. The proportion of penicillin non-susceptible isolates was on the same level as in 2008 (3.0%). The prevalence of macrolide resistance among pneumococcal blood culture isolates continued to decrease from the peak of 12.4% in 2006 to 4.6% in 2009. This reduction may be due to the conjugated pneumococcal vaccine which was introduced into the childhood vaccination programme in July 2006.

Systemic *Streptococcus agalactiae* isolates (beta-haemolytic streptococci group B - GBS) were in general susceptible to beta-lactam antibiotics. The prevalence of resistance to other antibiotic classes was unchanged since 2006.

A total of 351 cases of tuberculosis were reported to MSIS in 2009. Susceptibility tests were performed on 283 *Mycobacterium tuberculosis* primary isolates. Only seven isolates, originating from Africa (n=6) and Europe outside Norway (n=1), were classified as multidrug resistant (MDR).

Susceptibility testing was performed on 195 blood culture isolates of *Candida albicans* (n=139), *C. glabrata* (n=33), *C. tropicals* (n=13) and *C. parapsilosis* (n=10). All *C. albicans* isolates were susceptible to amphotericin B, fluconazole, voriconazole, caspofungin, anidulafungin and micafungin. A high prevalence of resistance to fluconazole and voriconazole was detected in *C. glabrata*, while the echinocandins were active against all yeast isolates. The results are in accordance with previous studies from Norway.

Surveillance data on resistance to antiviral agents included both influenza virus and HIV in 2009, but the HIV data have as yet not been analysed. The 2009/2010 influenza season was dominated by pandemic influenza A(H1N1) which is completely resistant to M2 blockers. However, reduced susceptibility or resistance to the neuraminidase inhibitors oseltamivir and zanamivir was not detected in Norway. The previously predominant influenza A(H3N2) with resistance to oseltamivir seems to have been displaced during the H1N1 pandemic.

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 health care have succeeded. However, the situation may rapidly change if the use of antimicrobial agents in Norway increases or resistant clones are imported from abroad. A continued effort is needed to prevent the development and spread of antimicrobial resistance and thereby ensure the effectiveness of antimicrobials when such treatment is needed. The NORM/NORM-VET report is a vital component in the work aimed at preventing the development and spread of antimicrobial resistance in Norway.

IV. POPULATION STATISTICS

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

TABLE 1. Human population in Norway as of January 1st, 2010.
Data provided by Statistics Norway.

Age group	All	Males	Females
0 to 4 years	303,928	155,882	148,046
5 to 14 years	613,797	314,371	299,426
15 to 24 years	627,546	321,350	306,196
25 to 44 years	1 350,583	689,757	660,826
45 to 64 years	1 239,672	630,714	608,958
65 years and older	722,673	314,678	407,995
All age groups	4 858,199	2 426,752	2 431,447

TABLE 2. Livestock population in Norway in 2009.
Data provided by the Register of Production Subsidies as of 31 July, 2009.

	Number* of	
Animal category	Herds	Animals
Cattle	17,400	876,300
Dairy cows only**	10,800	216,800
Suckling cow only**	4,100	58,900
Combined production (cow)**	950	30,700
Goat	1,300	67,800
Dairy goat**	450	37,700
Sheep	14,800	2 228,200
Breeding sheep > 1 year**	14,700	877,400
Swine	2,500	828,600
Breeding animal > 6 months**	1,500	58,700
Fattening pigs for slaughter	2,300	442,400
Poultry		
Egg laying hen (> 20 weeks of age)	1,800	3 780,700
Flocks > 250 birds**	650	3 770,400
Broiler	640	-
Turkey, ducks and geese for slaughter	140	494,800
Flocks > 25 birds**	130	494,500

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

TABLE 3. Import of live animals and animal products (excluding fish) to Norway in 2009.
Data provided by the Norwegian Livestock Industry´s Biosecurity Unit (KOORIMP).

Species	Imported product	No. of consignments	No. of animals or products
Cattle	Live animals		
	Semen (doses)		45,000
	Embryos		3
Swine	Live animals		
	Semen (doses)		488
Sheep	Live animals		18
	Embryos		
	Semen (doses)		1,869
Goat	Live animals		
	Semen (doses)		
Reindeer	Live animals for slaughter		
Fur animal	Live animals		
Poultry*	Day-old chicks		28,225
	Fertilised eggs		2 144,520

*Includes turkey and duck

TABLE 4. Production volume of the most important species in Norwegian aquaculture during the time period 1992-2009.
Data provided by the Norwegian Directorate of Fisheries.

Year	Atlantic salmon (ton)	Rainbow trout (ton)	Cod (ton)	Arctic char (ton*)	Halibut (ton*)	Blue mussels (ton)	Scallops[1] (ton)	Oysters (ton)
1992	141,000	-	-	-	-	-	-	-
1993	170,000	-	-	-	-	-	-	-
1994	204,686	14,571	569	262	63	542	-	-
1995	261,522	14,704	284	273	134	388	-	-
1996	297,557	22,966	191	221	138	184	-	-
1997	332,581	33,295	304	350	113	502	-	-
1998	361,879	48,431	203	200	291	309	-	-
1999	425,154	48,692	147	498	451	662	67	41
2000	440,061	48,778	169	129	548	851	38	8
2001	435,119	71,764	864	318	291	920	22	3
2002	462,495	83,560	1,258	665	507	2,557	5	2
2003	509,544	68,931	2,185	1,037	523	1,829	1	2
2004	563,915	63,401	3,165	1,141	565	3,747	46	3
2005	586,512	58,875	7,409	1,012	716	4,885	3	2
2006	629,888	62,702	11,087	1,390	722	3,714	4	1
2007	744,222	77,381	11,104	940	722	2,661	6	4
2008	737,694	85,176	18,052	707	859	2,035	4	3
2009[2]	859,056	76,008	20,683	662	702	1,649	8	2

[1]From the wild population. [2]Preliminary figures. *After 2001 in numbers of 1,000 individuals.

V. USAGE OF ANTIMICROBIAL AGENTS

USAGE IN ANIMALS

Kari Grave

Therapeutic usage of veterinary antimicrobial agents

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

Table 5 summarizes the sales of veterinary antimicrobial agents for therapeutic use in domestic animals in Norway in 2009. The data are organized according to therapeutic substance groups (ATCvet groups) and show the total usage for the various routes of administration. The total annual sale of veterinary antimicrobial agents for terrestrial animals for the period 1995-2009 is given in Figure 1. Figure 2 illustrates the proportion of the total sale of the various groups of antimicrobial agents. In 2009, the sales of veterinary antimicrobial agents approved for therapeutic use in animals in Norway amounted to 6,137 kg of active substance (Table 5). The annual usage of veterinary antimicrobial agents decreased gradually by 40% from 1995 to 2001, from 2001-2006 this usage varied slightly but a 9% increase was observed for this period. From 2007 to 2009 a 4% decrease in the usage was seen (Figure 1).

TABLE 5. Sales in 2009 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 2009 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to the Norwegian pharmacies.

Groups of substances	ATCvet code	Active substance or combinations of substances	Gastro-intestinal (QA07)	Uterine (QG01)	Systemic indiv. (QJ01)	Intra-mammary (QJ51)	Herds (QJ01)
Tetracyclines	QG01AA07/QJ01AA06	Oxytetracycline		3	103		116
	QJ01AA02	Doxycycline			1		
Amphenicols	QJ01BA99	Florfenicol+flunixin[1]			24		
Beta-lactams	QJ01CA04	Amoxicillin			130		142
	QJ01CE09/QJ51CE09	Procaine penicillin[2]			2,179	34	
	QJ01CE90	Penethamate hydroiodide[2]			1		
	QJ01CR02/QJ51RV01	Amoxicillin+clavulanic acid			377	9	
Cephalosporins	QJ01DD91	Cefovecin			1		
Sulfonamides	QJ01EQ06	Sulfanilamid[3]			10		
Sulfonamides +	QJ01EW10	Sulfadiazine+trimethoprim[5]			1,329		258
Trimethoprim	QJ01EW13	Sulfadoxine+trimethoprim			97		
Lincosamides	QJ01FF01	Clindamycin			22		
Aminoglycosides	QA07AA01	Neomycin	3				
	QA07AA90	Dihydrostreptomycin (DHS)	116				
	QJ01GB03	Gentamicin[5]			10		
Quinolones	QJ01MA90	Enrofloxacin[4]			29		
	QJ01MA96	Ibafloxacin			1		
Others	QJ01XX92	Tiamulin[4]			1		103
Combinations	QJ01RA01/QJ51RC23	Procaine penicillin[1] +DHS			445	455	
	QJ51RC24	Benzylpenicillinbenzatine[2]+ DHS[6]				15	
	QJ51RC25	Penethamate hydroiodide[4] + DHS				1	
	QG51AE99	Sulfadimidine+procaine penicillin[2]+DHS		122			
Total per route of administration			**119**	**125**	**4,760**	**514**	**619**
Total (kg)							**6,137**

[1] Flunixin not included in figure; [2] Calculated as benzylpenicillin; [3] Represents extemporaneously prepared preparations; [4] Includes also a preparation used on exemption from market authorization; [5] Includes a premix approved for farmed fish that are used solely in terrestrial animals such as pigs and calves (Kari Grave, unpublished data); [6] Represents two preparations used on exemption from market authorization.

The proportion accounted for by pure penicillin preparations rose from 24% in 1995 to 47% in 2009. Altogether 86% of the pure penicillin preparations sold in 2009 were beta-lactamase sensitive penicillins. From 1995 to 2009, the sale of sulfonamides in combination with trimethoprim (or baquiloprim 1995-2000) increased from 11% to 27% of the total sales. The proportion of sale of the combination preparations of penicillins and amino-glycosides decreased from 34% to 15% from 1995 to 2009. The corresponding figures for the sulfonamides were 14% in 1995 and 0.01% in 2009. The proportion accounted for by tetracyclines varied between 3-5% in 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.

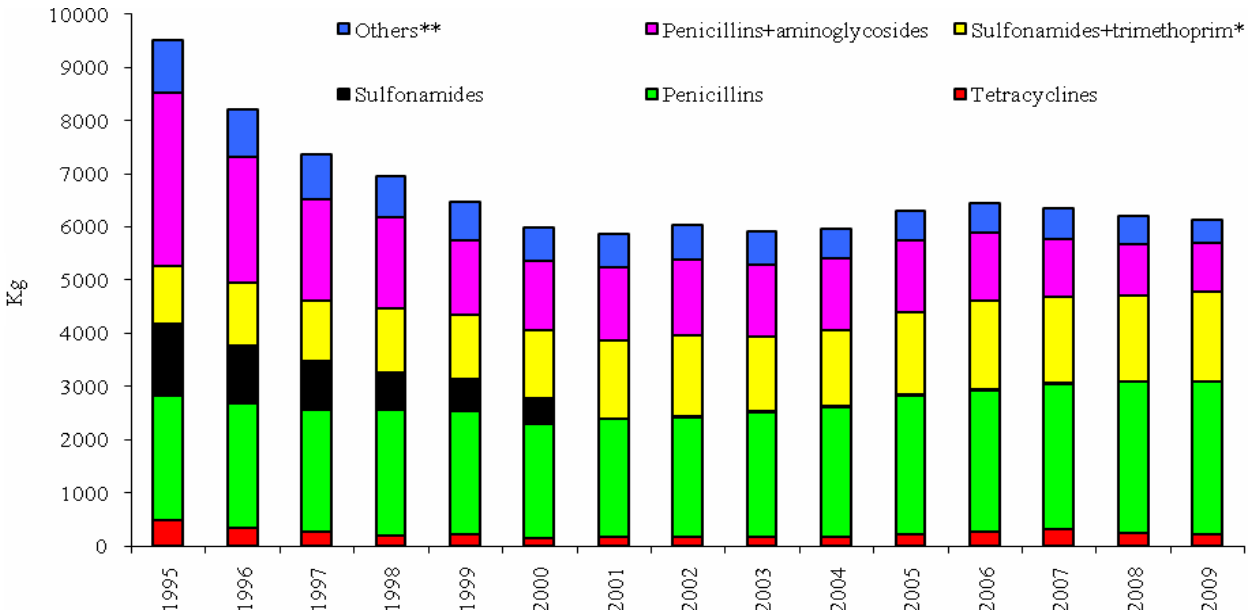


FIGURE 1. Sales (in kilograms of active substance) of veterinary antimicrobial agents (QA07AA, QG51AA, QG51AE, QJ01, QJ51) for therapeutic use in Norway 1995–2009, fish not included. Number of sold items in 2009 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies. Sulfonamides were not sold during 2001-2003. *Includes small amounts of baquiloprim (1995-2000); includes a premix approved for farmed fish used solely in terrestrial animals such as pigs, horses and calves (Kari Grave, unpublished data). **Includes ATCvet codes: QAA7AA01; QA07AA90; QG01AE99; QJ01BA99; QJ01FA01; QJ01FF01; QJ01FF02; QJ01GB06; QJO1MA90; QJO1MA96; QJ01XX92; QJ51RC26.

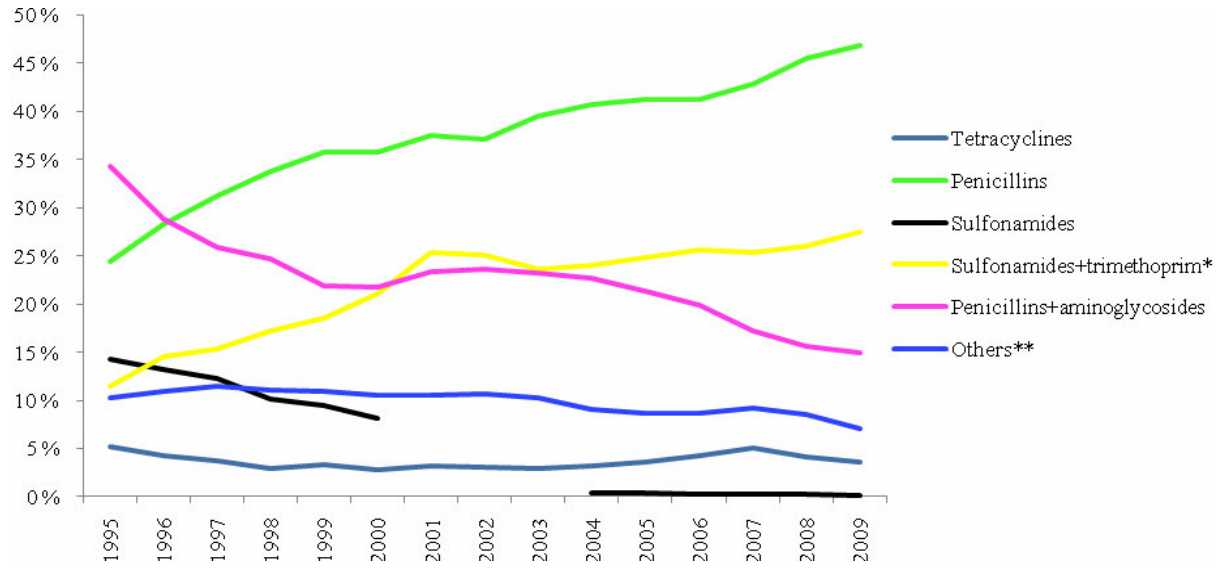


FIGURE 2. Sales (as percentage of total sales) of veterinary antimicrobial agents (QA07AA, QG51AA, QG51AE, QJ01, QJ51) in Norway 1995–2009, fish not included. Number of sold items in 2009 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and represent sales from drug wholesalers to Norwegian pharmacies. Sulfonamides were not sold during 2001-2003. *Includes small amounts of baquiloprim (1995-2000); includes a premix approved for farmed fish used solely in terrestrial animals such as pigs, horses and calves (Kari Grave, unpublished data). **Includes ATCvet codes: QAA7AA01; QA07AA90; QG01AE99; QJ01BA99; QJ01FA01; QJ01FF01; QJ01FF02; QJ01GB06; QJO1MA90; QJO1MA96; QJ01XX92; QJ51RC26.

TABLE 6. Total sales (in kilograms of active substance) of veterinary antimicrobial agents for therapeutic use in farmed fish in Norway in the period 1995-2009. 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 to fish farms.

Group of substances/active substance	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Tetracyclines															
Oxytetracycline	70	27	42	55	25	15	12	11	45	9	8	0	19	23	40
Amphenicols															
Florfenicol	64	64	123	135	65	148	109	205	154	111	202	302	139	166	303
Quinolones															
Flumequine	182	105	74	53	7	52	7	5	60	4	28	7	18	1	1
Oxolinic acid	2,800	841	507	436	494	470	517	998	546	1,035	977	1,119	406	681	926
Combinations															
Spectinomycin + lincomycin (2+1)	0	0	0	0	0	0	0	0	0	0	0	50	66	70	43
Total	**3,116**	**1,037**	**746**	**679**	**591**	**685**	**645**	**1,219**	**805**	**1,159**	**1,215**	**1,478**	**648**	**941**	**1,313**

The annual usage of antimicrobial agents in Norwegian fish farming peaked in 1987 when the reported sales figures amounted to approximately 48 tonnes. In 2009, the sales of veterinary antimicrobial agents for use in farmed fish were 1,313 kg active substance, of which 71% were quinolones (Table 6) which implies that the usage has declined by approximately 98% from 1987. From 1987 the total production of farmed fish increased from approximately 55,100 tons to 940,000 tons (www.ssb.no). The significant decrease in the usage of antimicrobial agents in Norwegian aquaculture in the period 1987 to 1996 was mainly attributed to the introduction of effective vaccines against bacterial diseases in Atlantic salmon and rainbow trout and to some extent also to improved health management.

Antimicrobial and coccidiostatic feed additives

Data on the usage of various substances and categories of feed additives (Table 7) were obtained through annual reports from the Norwegian Agricultural Inspection Service (1995-2002) and the Norwegian Food Safety Authority (2003-2009).

The glycopeptide avoparcin was licensed in Norway as growth promoter in broilers and turkeys in 1986. In 1995 the food animal production industry voluntarily abandoned the use of all antimicrobial growth promoters, including avoparcin. These measures resulted in an immediate reduction in the usage of these substances. In 1998, also the streptogramin virginiamycin was prohibited. No antimicrobial growth promoters have been used in animals in Norway since 1997.

Coccidiostats as feed additives are still used in Norwegian poultry production. The total sales of coccidiostats (kilograms of active substance) have been close to doubled since the ban on antimicrobial growth promoters, but the usage is highly correlated to the number of slaughtered chicken produced in this period. However, the pattern of usage has changed (Table 7). While monensin was the most frequently used ionophore in the poultry industry in 1995, the usage of coccidiostats has since then been almost totally dominated by narasin.

TABLE 7. Total sales, in kilograms of active substance, of antimicrobial growth promoters and of coccidiostats as feed additives in Norway 1995-2009. Data were obtained through annual reports from the Norwegian Agricultural Inspection Service (1995-2002) and the Norwegian Food Safety Authority (2003-2009).

Active substance	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Avoparcin[1]	419	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Zincbacitracin	129	64	27	0	0	0	0	0	0	0	0	P	P	P	P
Virginiamycin[2]	0	0	0	0	P	P	P	P	P	P	P	P	P	P	P
Total antimicrobial growth promoters	**548**	**64**	**27**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Lasalocid	996	480	471	193	208	80	96	514	108	173	37	13	17	16	63
Monensin	3,422	891	561	485	557	776	629	521	717	817	852	889	919	897	885
Salinomycin	214	27	0	0	27	233	12	0	0	0	0	0	0	0	0
Narasin	24	3,508	3,343	3,530	4,062	4,486	4,195	4,470	5,067	5,270	5,318	5,615	7,065	9,212	8,621
Total ionophore coccidiostats	**4,656**	**4,906**	**4,375**	**4,208**	**4,854**	**5,575**	**4,932**	**5,505**	**5,892**	**6,260**	**6,207**	**6,517**	**8,001**	**10,125**	**9,569**
Amprolium/etopabat	156	116	582	174	201	135	159	74	42	0.8	0	0	0	0	0
Total other	**156**	**116**	**582**	**174**	**201**	**135**	**159**	**74**	**42**	**0.8**	**0**	**0**	**0**	**0**	**0**

[1]Prohibited since May 31st, 1995. [2]Prohibited since 1998.

USAGE IN HUMANS

Hege Salvesen Blix

In 2009, the overall sales of antibacterials for systemic use in humans were 19.4 DDD/1,000 inhabitants/day. Since 2004, total sales of antibacterials have been increasing, mainly due to the penicillin group and to increased use of methenamine. In 2009, a decrease in antibiotic use was observed and, when methenamine is excluded, the level of antibiotic use in 2009 was the same as in 2006. The macrolides, which had been steadily increasing over many years, decreased by 7% in 2008 and by 11% in 2009. The use of quinolones is still increasing (Table 8, Figure 3).

TABLE 8. Human usage of antibacterial agents in Norway 2002-2009 by ATC groups. The usage is presented as DDD (Defined Daily Doses)/1,000 inhabitants/day and in % change 2008-2009. Methodology of data collection on human usage of antimicrobial agents is presented in Appendix 2.

ATC	Groups of substances	2002	2003	2004	2005	2006	2007	2008	2009	Change (%) 2008-2009
J01A	Tetracyclines	3.13	3.03	2.97	3.11	3.24	3.32	3.22	3.09	- 4
J01B	Amphenicols	0.002	0.002	0.001	0.001	0.002	0.001	0.001	0.002	-
J01CA	Penicillins with extended spectrum	2.23	2.29	2.37	2.53	2.74	2.93	3.09	3.15	+ 2
J01CE	Beta-lactamase sensitive penicillins	4.48	4.38	4.23	4.55	4.63	4.70	4.71	4.47	- 5
J01CF	Beta-lactamase resistant penicillins	0.50	0.59	0.63	0.56	0.66	0.72	0.77	0.80	+ 4
J01CR	Combination of penicillins	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.02	-
J01D	Cephalosporins, monobactams, carbapenems	0.58	0.62	0.61	0.57	0.60	0.60	0.60	0.58	- 3
J01E	Sulfonamides and trimethoprim	1.15	1.08	1.09	1.06	1.04	1.02	0.98	0.94	- 4
J01F	Macrolides, lincosamides and streptogramins	1.98	1.92	1.89	2.12	2.24	2.30	2.13	1.89	- 11
J01G	Aminoglycosides	0.06	0.07	0.06	0.07	0.07	0.07	0.07	0.07	-
J01M	Quinolones	0.44	0.48	0.52	0.57	0.62	0.67	0.70	0.71	+ 1
J01X	Other antibacterials	2.57	2.63	2.83	3.05	3.18	3.30	3.48	3.65	+ 5
	Total exclusive of methenamine	**15.0**	**14.9**	**14.8**	**15.6**	**16.3**	**16.9**	**16.8**	**16.2**	**- 4**
	Total all antimicrobial agents	**17.1**	**17.1**	**17.2**	**18.2**	**19.0**	**19.7**	**19.8**	**19.4**	**- 2**

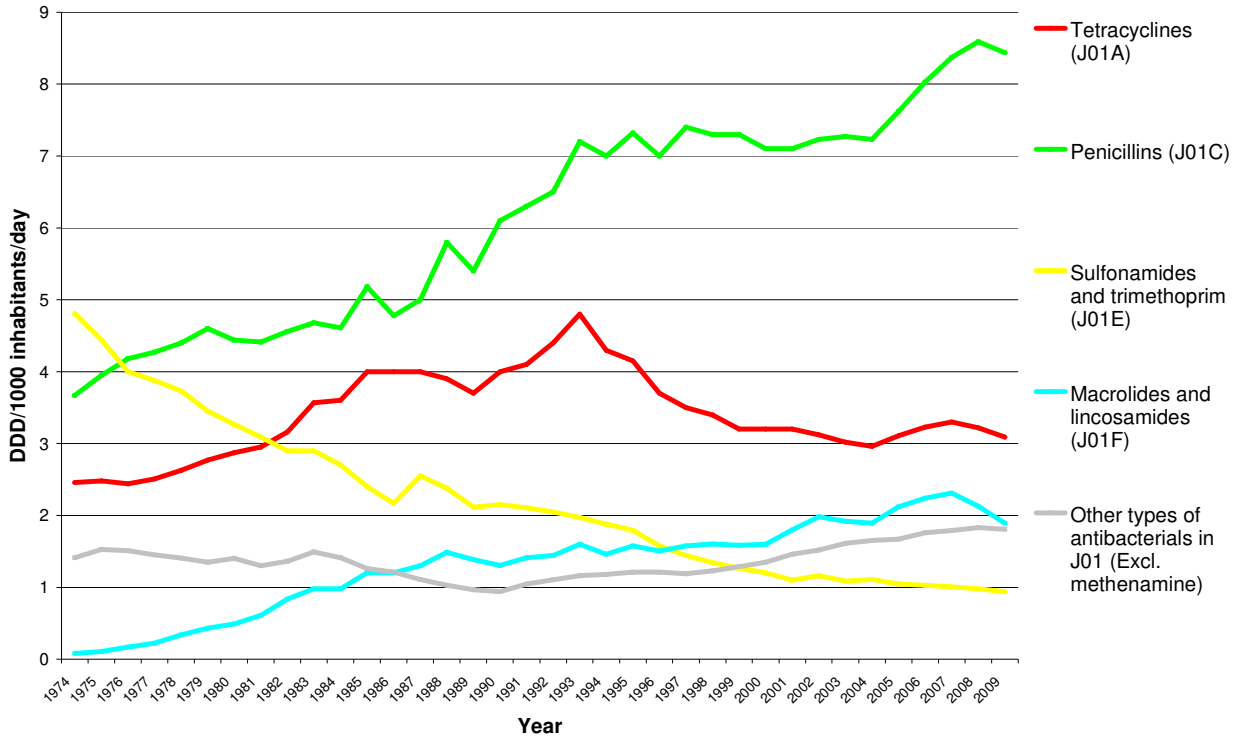


FIGURE 3. Sales of penicillins (J01C), tetracyclines (J01A), macrolides, lincosamides and streptogramines (J01F), sulfonamides and trimethoprim (J01E) and other antibacterials in Norway 1974-2009. Other types of antibacterials include all other antibacterials in ATC group J01, except methenamine (J01XX05).

In 2009, the penicillins (ATC group J01C) accounted for 43% of the total antibacterial use in Norway (Figure 4). Among the penicillins, the beta-lactamase sensitive penicillins (J01CE) are the largest subgroup. Over the years there has been a shift towards use of more broadspectered penicillins. Penicillins with extended spectrum (J01CA) now represent 37% of the penicillin group compared to 29% a decade ago (Figure 5). This is mainly due to increasing use of pivmecillinam, which has become a prominent choice for urinary tract infections at the expense of the subgroup of sulfonamides and trimethoprim. The tetracyclines (J01A) represent 16% of total use. The sales have been relatively stable over time. Macrolides, lincosamides and streptogramins (J01F) accounted for 10% of total use in 2009. The use has decreased by 19% since 2007, when the highest use ever was observed. The internal pattern of group J01F has remained relatively unchanged over the years although erythromycin, which is most frequently used (49% of the subgroup J01F), now seems to be less used (Figure 6). Sales of cephalosporins, monobactams and carbapenems, have been relatively stable over the last years. This group represents 3% of the total sales of antibacterials. The internal subgroup pattern has changed since 1996 (Figure 7). First generation cephalosporins i.e. cefalexin and cefalotin, hold 48% of ATC group J01D. The use of quinolones is increasing. Still, it represents only a minor fraction (4%) of total antibacterial sales, but the sales have more than doubled since 2000. The increase of ATC group J01X is mainly due to the urinary prophylactic agent methenamine, accounting for 16% of total antibacterial use. The sales of methenamine have increased by 64% since 2000.

The usage of antibacterials varies between the 19 Norwegian counties. The county using the least is using 71% (in DDDs) of the county using the most. Moreover, the same counties display high-use or low-use patterns over the years. The use has decreased from 2008-2009 in all counties except for three of the low-use counties (Finnmark, Aust Agder and Telemark) (Figure 8). However, compared to 2005, the use in all counties has increased by 2-14%.

Antibacterials are prescription-only drugs in Norway. Eighty-four percent of the total human sales of antibacterials are used outside institutions (hospitals and nursing homes). Physicians are the main prescribers to humans, but dentists prescribe 5% of antibiotics (J01) to humans in ambulatory care as measured in DDDs. Dentists most often prescribe phenoxymethylpenicillin (78% of all antibiotic-DDDs prescribed by dentists) followed by amoxicillin (9%), see page 26.

In ambulatory care, the most important antibiotic groups are penicillins, J01C (43% of DDDs), tetracyclins, J01A (18%), and macrolides and lincosamides, J01F (11%). Females use more antibiotics than males with 29% of all females purchasing at least one antibiotic course in 2009 compared to 20% of the males. The gender pattern accounts to all regions in the country (Figure 9). The highest use is found among young children, young adults and the elderly (Figure 10).

In 2009, the antibacterial sales (in DDDs) to hospitals represented 7.5% of total sales of antibacterials for human use in the country. The therapy pattern of antibacterials in hospitals does not change much from one year to another (Figure 11). Penicillins (J01C) represent around 45% of the use measured in DDDs in hospitals (J01CE 19%, J01CA 16% and J01CF 9%). The second largest group is the cephalosporins; 23% of all DDDs, the dominant subgroup being third generation cephalosporins (J01DD) (9%). In 2009, three single substances accounted for 28% of all antibacterial use in hospitals; benzylpenicillin (14%), cefotaxime (7%) and ciprofloxacin (7%). Two antibacterial groups have been steadily increasing in hospitals since 2006; the carbapenems (J01DH) and penicillins combined with beta-lactamase inhibitors (J01CR). The carbapenems increased by 30% compared to 2006 and represented 3% of all DDDs used in hospitals in 2009. The ATC group J01CR (mainly piperacillin and tazobactam) has increased by 85% since 2006.

Updated National Guidelines for antibiotic use are available for ambulatory care and nursing homes, but not for hospitals (latest national version 2001). A national center for antibiotic prescription in primary health care was established in 2006, and a similar centre for antibiotic use in hospitals is planned. These centers will be responsible for updating the national treatment guidelines and hopefully have a positive impact on therapy traditions for antibacterial prescribing in Norway.

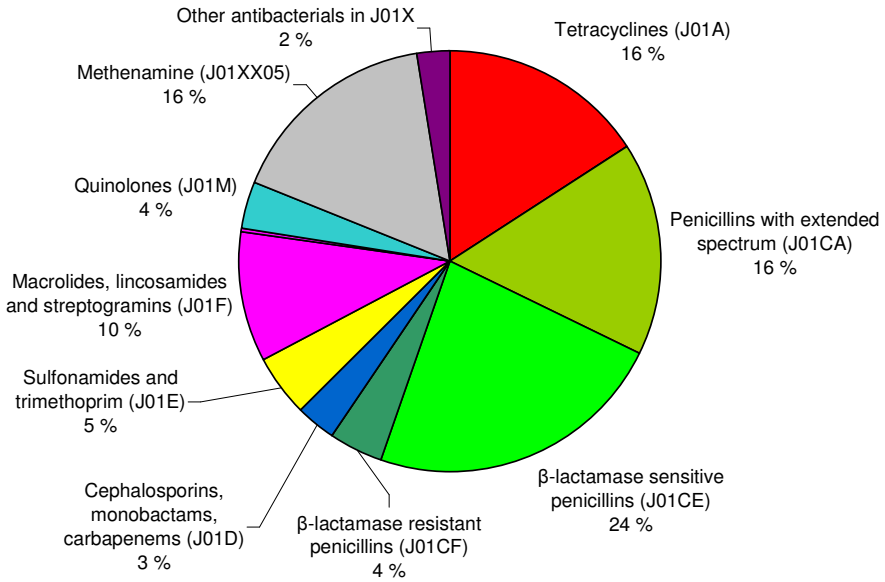


FIGURE 4. Relative amount of antibacterial agents for systemic use in 2009 in Defined Daily Doses (DDD).

TABLE 9. Human usage of single antimicrobial agents for systemic use in Norway. Sales are given in DDD/1,000 inhabitants/day. The methodology for collection of data on human usage of antibacterial agents is presented in Appendix 2.

ATC	Substance	2001	2002	2003	2004	2005	2006	2007	2008	2009
A07A A09	Vancomycin	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
J01A A02	Doxycycline	2.1	2.03	1.93	1.80	1.89	1.97	2.0	1.9	1.78
J01A A04	Lymecycline	0.19	0.26	0.30	0.34	0.39	0.45	0.51	0.52	0.54
J01A A06	Oxytetracycline	0.22	0.21	0.19	0.20	0.20	0.19	0.18	0.17	0.16
J01A A07	Tetracycline	0.64	0.62	0.60	0.62	0.64	0.63	0.63	0.62	0.60
J01AA07*	Minocycline					0.0003	0.0003	0.0001	0.0002	0.0003
J01AA12	Tigecycline						0.0001	0.0002	0.0004	0.0005
J01B A01	Chloramphenicol	0.003	0.002	0.002	0.001	0.002	0.002	0.001	0.001	0.002
J01C A01	Ampicillin	0.08	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.10
J01C A02*	Pivampicillin	0.11	0.11	0.09	0.08	0.07	0.06	0.01		
J01C A04	Amoxicillin	0.89	0.94	0.95	0.94	1.06	1.11	1.26	1.34	1.31
J01C A08	Pivmecillinam	1	1.09	1.14	1.25	1.29	1.46	1.55	1.65	1.72
J01C A11*	Mecillinam	0.005	0.005	0.005	0.005	0.006	0.006	0.006	0.008	0.008
J01C E01	Benzylpenicillin	0.23	0.24	0.25	0.24	0.26	0.26	0.25	0.24	0.28
J01C E02	Phenoxymethylpenicillin	4.45	4.24	4.13	3.99	4.29	4.37	4.45	4.46	4.19
J01C E08*	Benzathine benzylpenicillin	<0.0001	0.0001	0.0001	0.0002	0.0001	0.0002	0.0001	0.0001	0.0002
J01C F01	Dicloxacillin	0.31	0.39	0.48	0.51	0.41	0.54	0.61	0.64	0.67
J01C F02	Cloxacillin	0.09	0.11	0.11	0.11	0.15	0.12	0.12	0.13	0.13
J01C F05*	Flucloxacillin		0.0001	0.0002	0.0002	0.0001	0.0001	0.0003	0.0005	0.0007
J01C R02*	Amoxicillin and enzyme inhibitor	0.01	0.01	0.01	0.0003	0.0000	0.0001	0.0001	0.0012	0.003
J01C R05	Piperacillin and enzyme inhibitor	0.0006	0.0014	0.0024	0.005	0.01	0.01	0.02	0.02	0.02
J01D B01	Cefalexin	0.27	0.29	0.3	0.29	0.24	0.26	0.25	0.23	0.21
J01D B03	Cefalotin	0.05	0.05	0.06	0.06	0.06	0.06	0.07	0.07	0.07
J01D B04*	Cefazolin					0.002	0.002	0.001	0.001	
J01D C01*	Cefoxitin	0.0003	0.0002	0.0001						
J01D C02	Cefuroxim	0.14	0.15	0.15	0.14	0.13	0.12	0.12	0.11	0.10
J01D D01	Cefotaxim	0.05	0.05	0.07	0.07	0.08	0.09	0.09	0.10	0.10
J01D D02	Ceftazidim	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01D D04	Ceftriaxone	0.01	0.01	0.01	0.02	0.02	0.02	0.02	0.02	0.02
J01D F01	Aztreonam	0.001	0.001	0.001	0.001	0.0005	0.0008	0.0008	0.0007	0.0006
J01D H02	Meropenem	0.014	0.017	0.02	0.02	0.026	0.031	0.035	0.037	0.042
J01D H03	Ertapenem						0.000	0.001	0.001	0.002
J01D H51	Imipenem and enzyme inhibitor	0.005	0.005	0.006	0.005	0.005	0.004	0.004	0.003	0.002
J01E A01	Trimethoprim	0.8	0.8	0.74	0.76	0.73	0.70	0.68	0.64	0.60
J01E E01	Sulfamethoxazol and trimethoprim	0.36	0.36	0.34	0.34	0.33	0.34	0.34	0.34	0.33
J01F A01	Erythromycin	1.13	1.2	1.09	1.03	1.16	1.24	1.21	1.08	0.92
J01F A02	Spiramycin	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01
J01F A09	Clarithromycin	0.3	0.36	0.37	0.37	0.39	0.40	0.43	0.37	0.31
J01F A10	Azithromycin	0.21	0.24	0.26	0.28	0.32	0.34	0.39	0.38	0.37
J01FA15*	Telithromycin		0.0001	0.0003	0.0003					
J01F F01	Clindamycin	0.14	0.16	0.19	0.20	0.23	0.25	0.26	0.28	0.28
J01GA01*	Streptomycin		0.0015	0.0004	0.0004	0.0002	0.0003	0.0002	0.0003	0.0002
J01G B01	Tobramycin	0.03	0.04	0.04	0.03	0.03	0.03	0.03	0.03	0.03

ATC	Substance	2001	2002	2003	2004	2005	2006	2007	2008	2009
J01G B03	Gentamicin	0.008	0.02	0.03	0.03	0.03	0.04	0.04	0.04	0.04
J01G B06*	Amikacin		0.0009	0.0008	0.0003	0.0004	0.0009	0.0003	0.0007	0.0008
J01G B07*	Netilmicin	0.02	0.007				0.0001			
J01M A01	Ofloxacin	0.05	0.05	0.05	0.05	0.05	0.04	0.04	0.04	0.03
J01M A02	Ciprofloxacin	0.34	0.38	0.42	0.47	0.52	0.57	0.62	0.66	0.67
J01MA12*	Levofloxacin		0.001	0.0003		0.0003	0.0003	0.0008	0.0008	0.0004
J01MA14*	Moxifloxacin							0.0007	0.001	0.001
J01X A01	Vancomycin	0.005	0.006	0.006	0.007	0.007	0.008	0.01	0.01	0.01
J01X A02	Teicoplanin	0.0013	0.0013	0.0009	0.0007	0.0008	0.0008	0.0007	0.001	0.0007
J01X B01*	Colistin	0.003	0.003	0.002	0.003	0.004	0.005	0.004	0.004	0.005
J01X C01	Fusidic acid	0.01	0.01	0.007	0.008	0.006	0.006	0.006	0.006	0.005
J01X D01	Metronidazole	0.07	0.07	0.07	0.08	0.08	0.07	0.07	0.07	0.07
J01X E01	Nitrofurantoin	0.36	0.35	0.35	0.36	0.36	0.37	0.36	0.36	0.36
J01X X05	Methenamin	2.08	2.13	2.18	2.37	2.59	2.71	2.84	3.02	3.19
J01XX08	Linezolid		0.002	0.004	0.006	0.007	0.006	0.006	0.007	0.008
J01XX09	Daptomycin							0.000	0.000	0.000
D06AX09/ R01AX06*	Mupirocin in kg ointment/cream (2%)	1.0	1.3	3.0	3.0	3.4	4.3	4.0	3.9	5.1
P01AB01	Metronidazole	0.18	0.19	0.19	0.20	0.20	0.20	0.21	0.21	0.22
J04AB**	Rifampicin	0.054	0.043	0.049	0.068	0.077	0.082	0.092	0.092	0.127

* Drugs not licensed for the Norwegian marked but prescribed on exemption from marketing authorization.
** Given as the amount of rifampicin in plain and combination products.

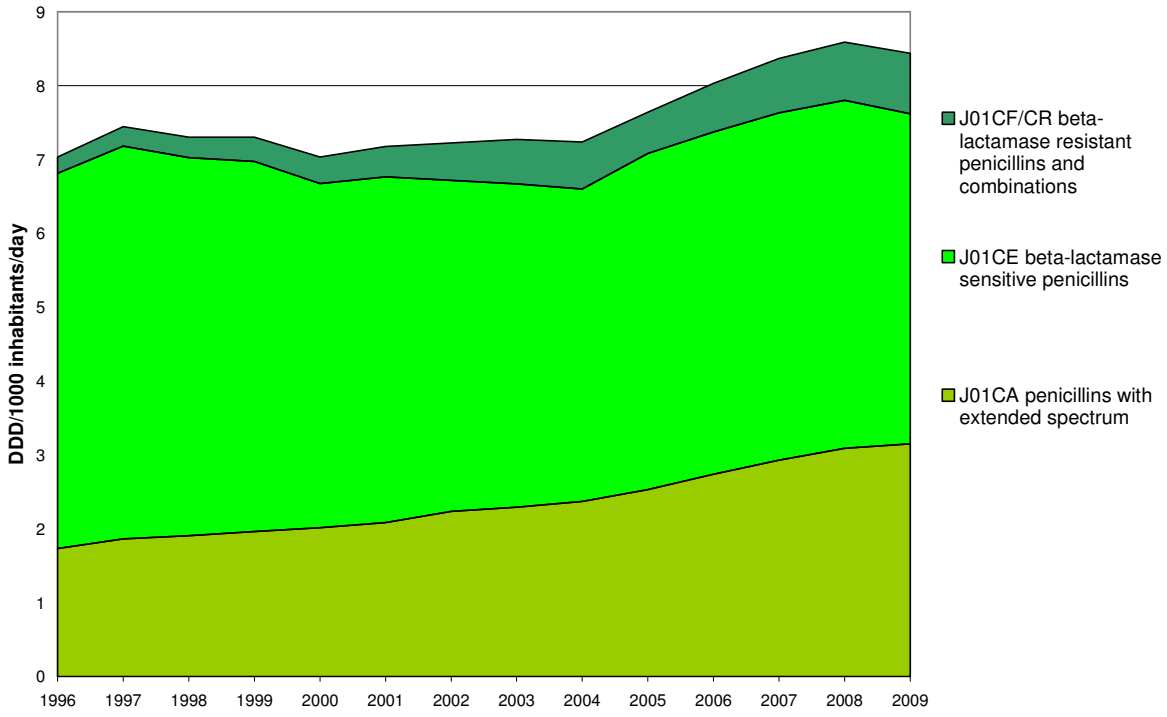


FIGURE 5. Total annual sales of penicillins (J01C) in Norway 1996-2009.

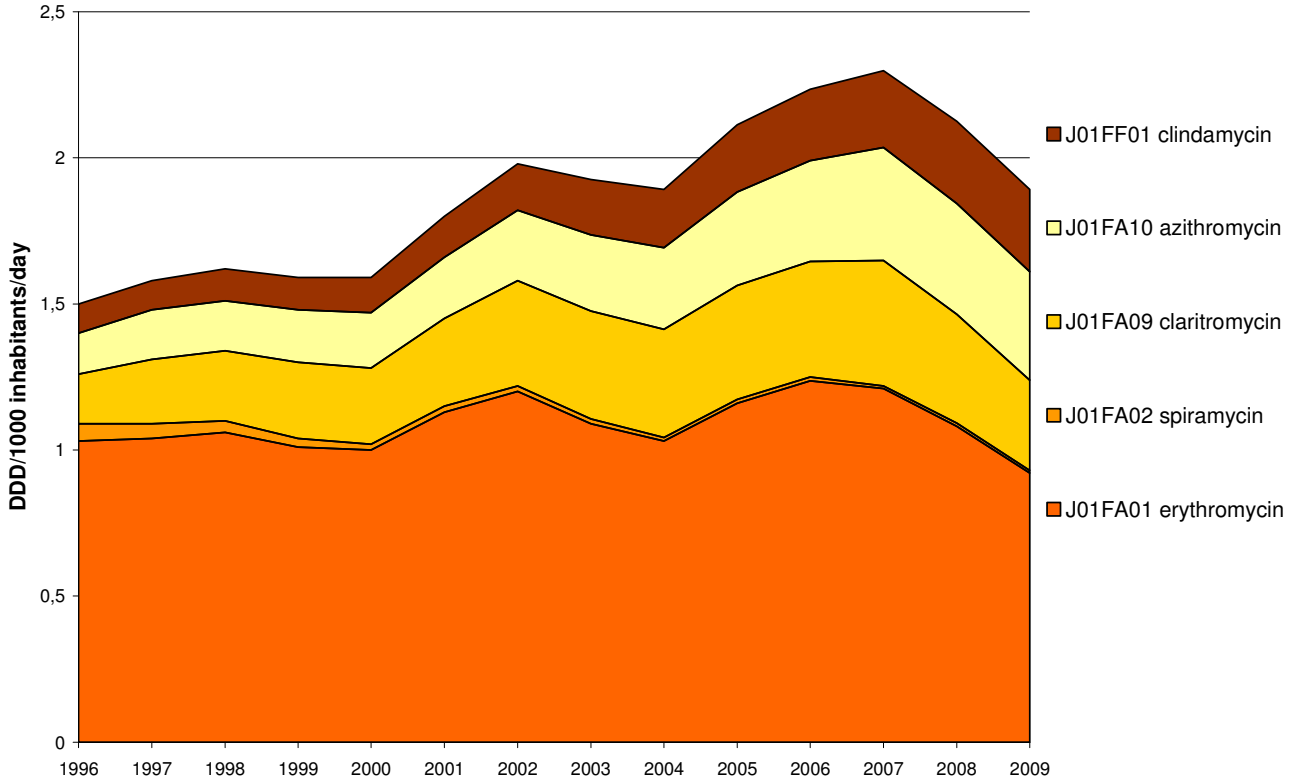


FIGURE 6. Sales of macrolides, lincosamides and streptogramins (J01F) in Norway 1996-2009.

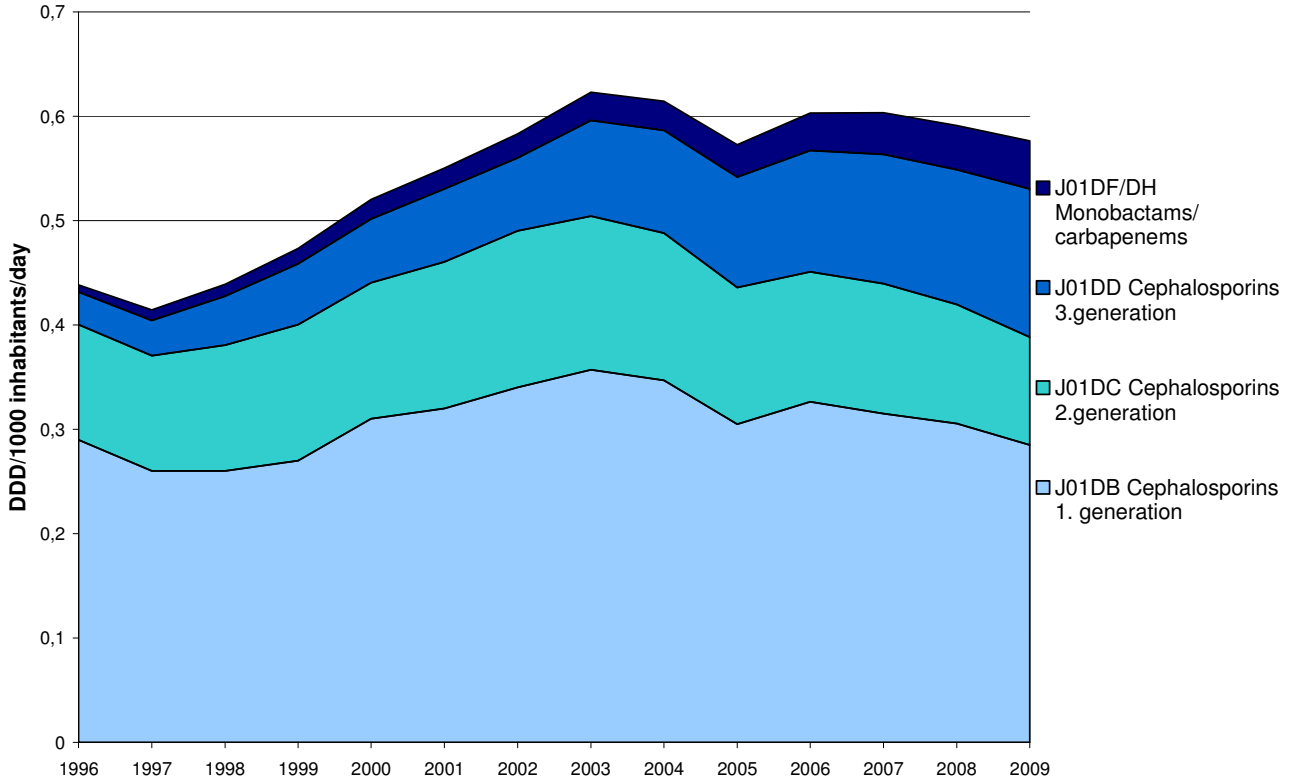


FIGURE 7. Sales of cephalosporins, monobactams and carbapenems (J01D) in Norway 1996-2009.

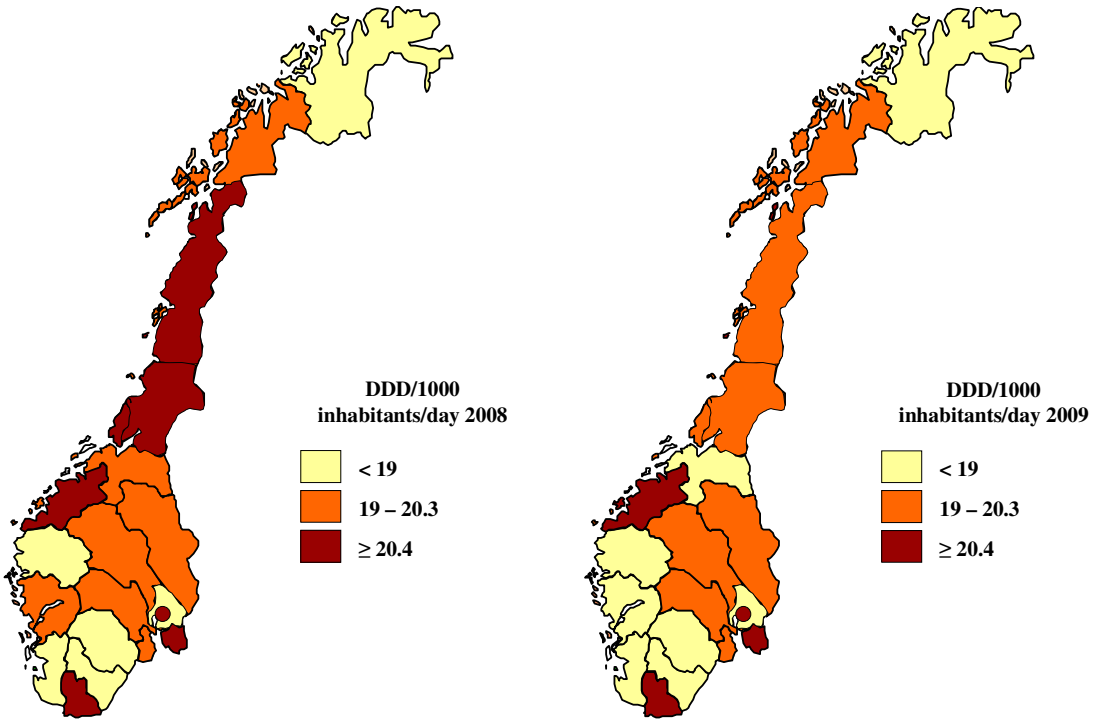


FIGURE 8. Sales of antibacterial agents for systemic use (ATC group J01) in the different counties of Norway in 2008 (left) and 2009 (right).

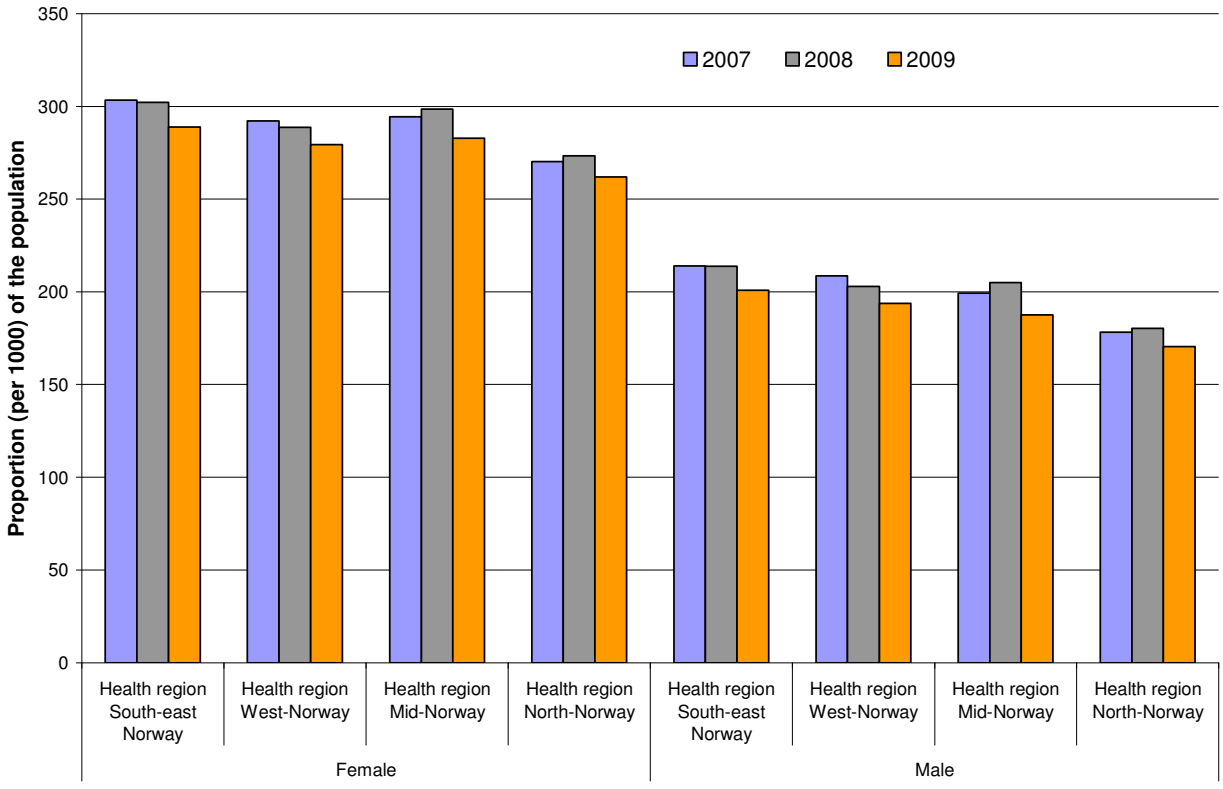


FIGURE 9. One year prevalence of systemic antibacterial use in ambulatory care by gender and health region in Norway for the years 2007, 2008 and 2009. Antibacterials for systemic use include ATC group J01, Vancomycin (A07AA09) and metronidazole (P01AB01).

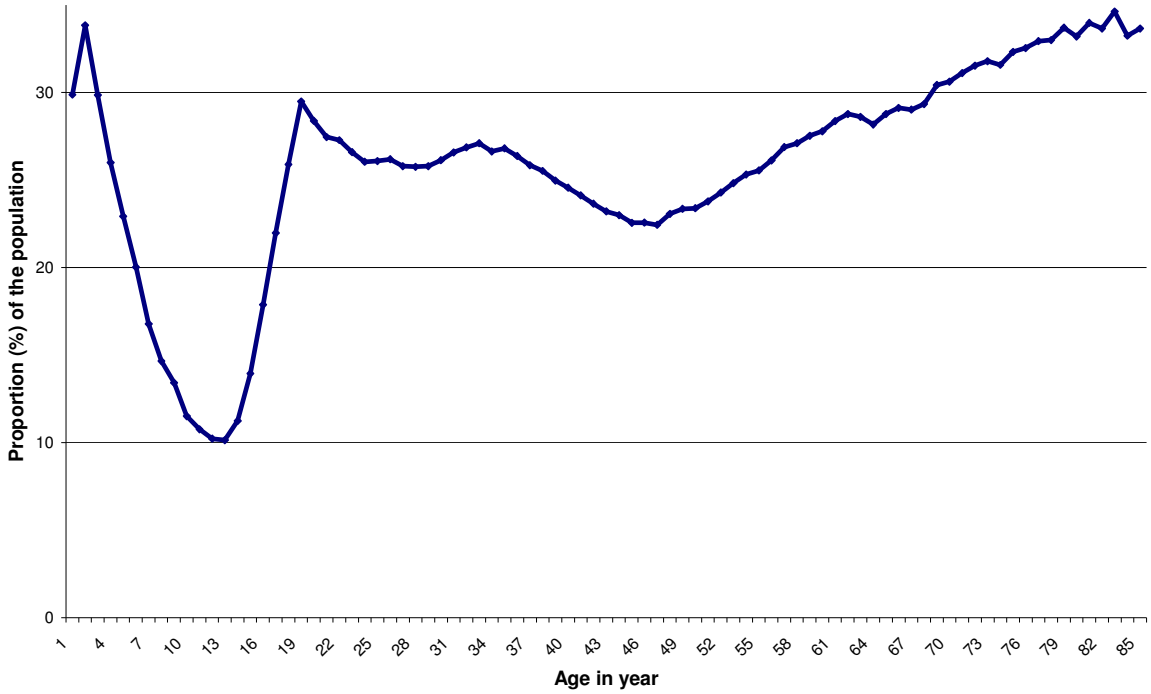


FIGURE 10. One year prevalence (%) of antibacterial use in ambulatory care by age (from 1 year to 85+ years) in Norway, 2009. Antibacterials included are antibacterials for systemic use (ATC group J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01).

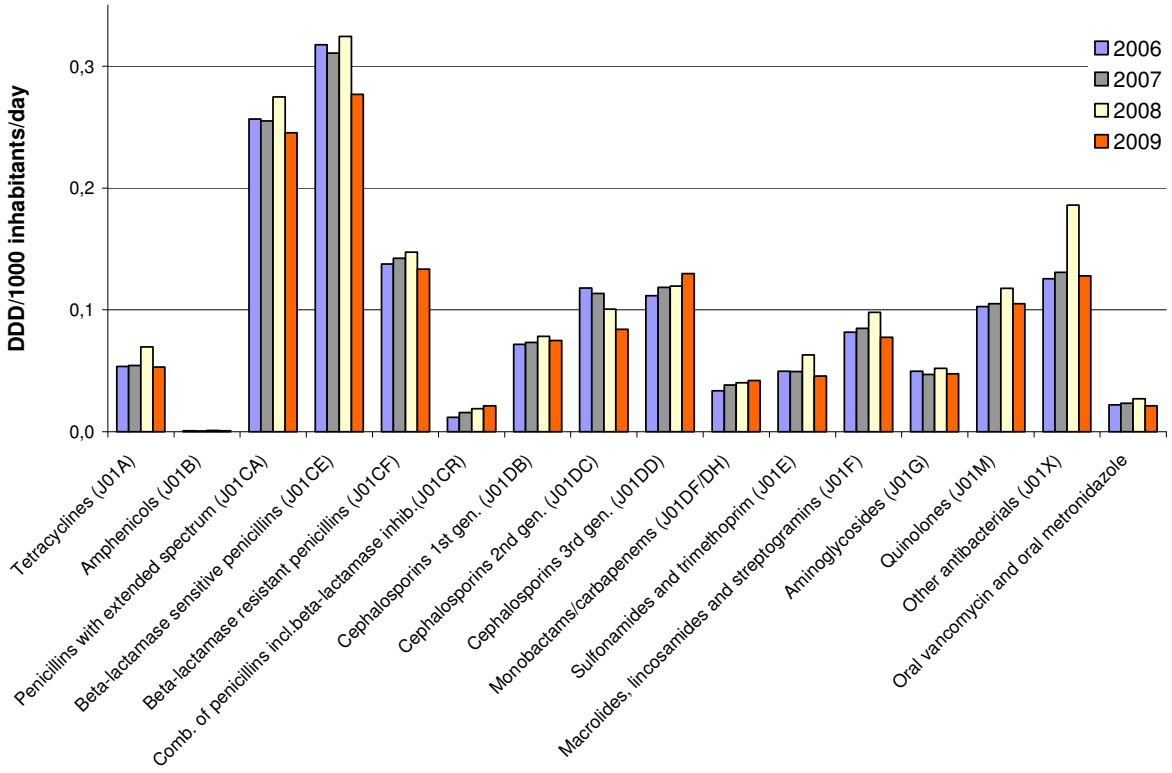


FIGURE 11. Proportions of antibacterial agents for systemic use in Norwegian hospitals 2006 – 2009, measured in DDDs/1,000 inhabitants/day.

Antibiotic resistance in dentistry

Antibiotic resistance in bacteria currently represents one of the greatest challenges to modern medicine throughout the world. There is an annual increase in morbidity and mortality due to health care associated infections. In a recent EU report on the problem of antibiotic resistance it was stated that approximately 25,000 patients die in the EU from an infection with one of a list of only 8 different nosocomial, multidrug-resistant bacteria. Additionally, economic implications for health care providers, in terms of increased patient stay in hospitals, isolation procedures and additional medical intervention are increasingly impinging on the available budgets of health care providers. In the EU this has resulted in extra health care costs and productivity losses of at least €1.5 billion each year.

There is no disagreement that antibiotics select and induce development of resistant bacteria whenever and wherever they are used. Antibiotic resistance mechanisms are continuously evolved by bacteria, and are sometimes ahead of the innovation of new drugs. Therefore, the prudent use of antibiotics is crucial to preserve and prolong the usefulness of the antibiotics that are currently available.

Dental treatment and preventive measures are usually characterized by being population-based. Treatment protocols are usually standardized but non-specific, especially in relation to their microbiological origin [1]. Sub-epithelial oral infections are characterized by mixed bacterial infections where multiple bacterial species can in fact be recovered from oral microbiological specimens [1]. This is mainly because of the complex bacterial composition of the oral ecosystem that probably consists of thousands of bacterial species.

Dentists have the legal right to prescribe a panel of antibiotics in their practice to treat bacterial infections related to the oral cavity. Dental-based prescriptions of some antibiotics could reach considerable figures [2]. In general, their prescriptions contribute up to 7-9% of the total national prescriptions [2, 3]. In Norway, and probably in all Scandinavian countries, antibiotic prescription follows the general trend in these countries, where narrow-spectrum penicillins are profoundly used, amounting to about 70% of all prescriptions by dentists [2]. On the contrary, dentists in the UK prescribe mostly the broad-spectrum penicillins, i.e. amoxicillin [4]. Moreover, in Spain, amoxicillin-clavulanate was the drug most frequently prescribed by dentists during 2005 [5]. Therefore, it is a fact that antibiotic prescribing attitudes among dentists in Europe are not the same. The reasons for the lack of harmony in antibiotic prescription by dentists in Europe need further research.

In light of the current rate of increase in resistance to antimicrobial agents among oral bacteria, the need for regular susceptibility testing of clinical isolates along with antibiotic prescription data becomes evident. Unfortunately, dentists hardly use microbiological services and the use of the first line antibiotics and even the second line once is mostly empirical [6]. The non-involvement of microbiological services by dentists irrespective of the reasons mainly reflects the fact that communication between dentists and oral microbiologists is poor in modern dentistry. There is a demand for collaboration of oral microbiologists and dentists to work out a structured program on antimicrobial resistance surveillance among oral bacteria and to link such a program with the antibiotic prescription data [7]. Although this might seem at first to be a relatively simple undertaking, however, it is rather more complicated in reality.

Antibiotic resistance of oral bacteria in Norway

It is documented that Norwegian dental patients harbour a very few subgingival bacteria resistant to ampicillin and metronidazole [8]. On the other hand, it is found that a high proportion (68%) of the patients with refractory periodontitis in Norway harboured beta-lactamase-producing bacteria in their subgingival plaque [9]. The controversy between the two studies could be explained by the fact that the study subjects in the later study were refractory to standard dental treatment and had been exposed to several courses of antibiotic treatment that may explain the presence of high proportion of beta-lactamase-producing bacteria.

The use of antibiotics by dentists in Norway was recently evaluated [2, 6]. A total of 268,834 prescriptions prescribed by dentists in 2004 and 2005 were evaluated, and the result highlights that the prescription of the narrow-spectrum phenoxy-methylpenicillin prevails among dentists in the country [2]. It is also noted that 35% of a randomly selected sample of Norwegian dentists do not prescribe a single antibiotic in a typical working week [6]. These findings explain and support, at least partially, the low proportion of antibiotic resistance among oral bacteria in Norway [8]. The frequencies of antibiotic prescribed by dentists in Norway are presented in Table 10.

TABLE 10. The prescription frequencies of the 11 antibiotics prescribed by dentists in Norway.

Prescribed antibiotics	Dentists' prescriptions (%)	Prescribed antibiotics	Dentists' prescriptions (%)
Phenoxymethylpenicillin	74.0%	Azithromycin	1.2%
Metronidazole	6.6%	Spiramycin	0.7%
Erythromycin	4.9%	Tetracycline	0.6%
Amoxicillin	4.6%	Oxytetracyline	0.2%
Clindamycin	4.0%	Clarithromycin	0.04%
Doxycycline	2.3%		

References

1. Dahlen, G., *Microbiological diagnostics in oral diseases.* Acta Odontol Scand, 2006. 64(3): p. 164-8.
2. Al-Haroni, M. and N. Skaug, *Incidence of antibiotic prescribing in dental practice in Norway and its contribution to national consumption.* J Antimicrob Chemother, 2007. 59(6): p. 1161-6.
3. Pallasch, T.J., *Antibiotic resistance.* Dent Clin North Am, 2003. 47(4): p. 623-39.
4. Palmer, N.O., et al., *An analysis of antibiotic prescriptions from general dental practitioners in England.* J Antimicrob Chemother, 2000. 46(6): p. 1033-5.
5. Poveda Roda, R., et al., *Antibiotic use in dental practice. A review.* Med Oral Patol Oral Cir Bucal, 2007. 12(3): p. E186-92.
6. Demirbas, F., P.E. Gjermo, and H.R. Preus, *Antibiotic prescribing practices among Norwegian dentists.* Acta Odontol Scand, 2006. 64(6): p. 355-9.
7. Al-Haroni, M., *Bacterial resistance and the dental professionals' role to halt the problem.* J Dent, 2008. 36(2): p. 95-103.
8. Al-Haroni, M.H., N. Skaug, and N.N. Al-Hebshi, *Prevalence of subgingival bacteria resistant to aminopenicillins and metronidazole in dental patients from Yemen and Norway.* Int J Antimicrob Agents, 2006. 27(3): p. 217-23.
9. Handal, T., D.A. Caugant, and I. Olsen, *Antibiotic resistance in bacteria isolated from subgingival plaque in a norwegian population with refractory marginal periodontitis.* Antimicrob Agents Chemother, 2003. 47(4): p. 1443-6.

Mohammed Al-Haroni, Department of Pharmacy, Faculty of Health Sciences, University of Tromsø, Tromsø.

VI. OCCURRENCE OF ANTIMICROBIAL RESISTANCE

A. ANIMAL CLINICAL ISOLATES

Jarle Mikalsen, Madelaine Norström, Marianne Sunde

Escherichia coli from bovine mastitis

A total of 96 isolates of *Escherichia coli* from bovine mastitis samples were tested. Sampling, laboratory methods and data processing are described in Appendix 3. The results are presented in Table 11 and in the text.

TABLE 11. Antimicrobial resistance in *Escherichia coli* from bovine mastitis (n=96) in 2009.

	Resistance %		Distribution (n) of MIC values (mg/L)															
Substance		[95% CI]	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	12.6	[7.3-20.6]						1.0	66.7	18.8					8.3	5.2		
Chloramphenicol	1.0	[0.0-6.4]							1.0	7.3	74.0	16.7					1.0	
Florfenicol	0.0	[0.0-4.8]									44.8	55.2						
Ampicillin	18.8	[11.8-28.3]						3.1	12.5	52.1	13.5		2.1		16.7			
Ceftiofur	0.0	[0.0-4.8]				6.2	44.8	49.0										
Cefotaxime	0.0	[0.0-4.8]			80.2	18.8	1.0				.							
Trimethoprim	8.3	[3.9-16.2]					51.0	37.5	3.1						8.3			
Sulfamethoxazole	13.5	[7.7-22.4]											64.6	17.7	4.2			13.5
Streptomycin	19.8	[11.6-26.7]								1.0	36.5	40.6	2.1	2.1	2.1	7.3	7.3	1.0
Gentamicin	0.0	[0.0-4.8]						42.7	54.2	3.1								
Kanamycin	0.0	[0.0-4.8]								43.8	50.0	6.2						
Ciprofloxacin	0.0	[0.0-4.8]	3.1	63.5	33.3													
Nalidixic acid	0.0	[0.0-4.8]							4.2	45.8	50.0							

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

RESULTS AND COMMENTS

The occurrence of resistance among faecal *E. coli* isolates from bovine mastitis was moderate. In total, 77.1% of the isolates were susceptible to all antimicrobial agents included. Altogether, 5.2% were resistant to one (predominantly streptomycin), 1.0% to two, 5.2% to three and 11.5% to four or more antimicrobial agents (Figure 12). Resistance was predominantly expressed to streptomycin, ampicillin, sulfamethoxazole, tetracycline and trimethoprim. The high prevalence of multiresistant *E. coli* from bovine mastitis samples is worrisome and needs to be carefully monitored in years to come.

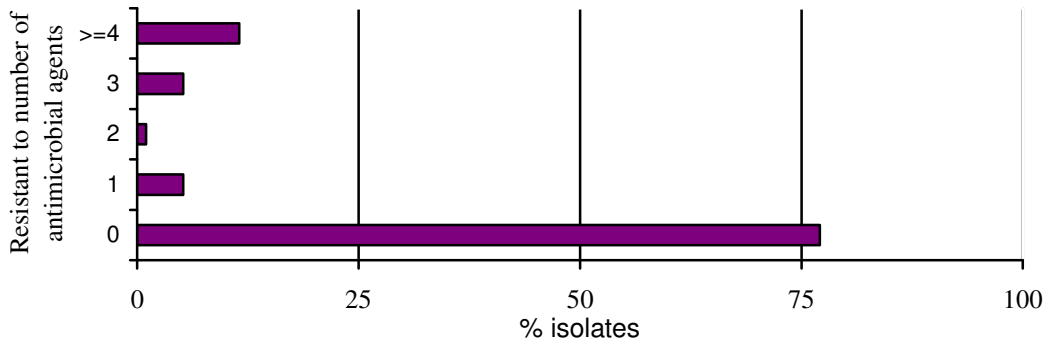


FIGURE 12. Antimicrobial resistance profile for *E. coli* from bovine mastitis (n=96) in 2009. Proportions of isolates susceptible to all or resistant to one, two, three and four or more antimicrobial agents are illustrated.

B. INDICATOR BACTERIA FROM ANIMALS AND FOOD

Jarle Mikalsen, Madelaine Norström, Marianne Sunde

The prevalence of acquired antimicrobial resistance among certain bacteria of the normal enteric microflora can be used as an indicator of the selective pressure from use of antimicrobial agents in various populations. These bacteria may form a reservoir of transferable resistance genes from which antimicrobial resistance can be spread to other bacteria, including those responsible for infections in animals or humans. Thus, monitoring of resistance among so-called indicator bacteria of the normal enteric microflora from healthy animals, as well as indicator bacteria from feed and food, is important to get a better overview of the resistance situation, detect trends and evaluate the effects of interventions.

In NORM-VET, *Escherichia coli* and *Enterococcus* spp. are used as indicator bacteria. In 2009, *E. coli* from bulk milk from dairy cattle and faecal samples from broiler and horses were included. Additionally, a collection of *E. coli* isolates (mainly belonging to serogroups O26 and O103) from sheep was susceptibility tested.

The substances included in the test panels might not always be substances used in veterinary medicine, but are included because of their importance for human health. Some of the cut-off values defining resistance applied in NORM-VET have been changed over the years. To facilitate comparisons in this report, data on prevalence of resistance presented in earlier reports have been recalculated using the cut-off values applied in 2009. Sampling, laboratory methods and data processing are described in Appendix 3.

Escherichia coli from dairy milk

A total of 194 bulk milk samples yielded only 15 (7.3%) samples positive for *Escherichia coli*. One isolate per positive sample was susceptibility tested. The results are presented in Table 12 and in the text.

TABLE 12. Antimicrobial resistance in *Escherichia coli* (n=15) from bulk milk from dairy cattle in 2009.

		Distribution (n) of MIC values (mg/L)															
Substance	Resistance (n)	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	1							7	7				1				
Chloramphenicol	0									9	6						
Florfenicol	0									6	9						
Ampicillin	1						2	3	6	3				1			
Ceftiofur	0				2	7	6										
Cefotaxime	0			12	3												
Trimethoprim	0					9	6										
Sulfamethoxazole	1											9	5				1
Streptomycin	1									7	7				1		
Gentamicin	0						5	8	2								
Kanamycin	0								5	10							
Ciprofloxacin	0	1	13	1													
Nalidixic acid	0							1	6	8							

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

RESULTS AND COMMENTS

The fact that very few bulk milk samples were positive for *E. coli* indicates a high quality of unpasteurized dairy milk in Norway. Among the isolates found, there was one multiresistant isolate (resistant to ampicillin, sulfamethoxazole and streptomycin) and one isolate resistant to tetracycline. These are all substances commonly used for clinical therapy in cattle. The results indicate a low to moderate prevalence of resistance in *E. coli* that occasionally might be present in unpasteurized dairy milk.

Escherichia coli from broiler, horse and sheep

A total of 228 and 186 faecal samples from broiler and horse, respectively, were collected. For broiler, *E. coli* was isolated from 162 (71.1%) samples. For horse, *E. coli* was isolated from 171 (91.9%) samples. One isolate per positive sample was susceptibility tested. In addition, 136 isolates from a collection of *E. coli* isolates (mainly serogroups O26 and O103) from sheep were included. The results are presented in Table 13, Figures 13-14, and in the text.

TABLE 13. Antimicrobial resistance in *Escherichia coli* from faecal samples from broiler (n=162), horse (n=171) and sheep (n=136) in 2009.

		Resistance %		Distribution (%) of MIC-values (mg/L)													
Substance	Sample	[95% CI]		0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	Broiler	8.0	[4.5-13.6]				1.2	52.5	38.3				4.9	2.5	0.6		
	Horse	1.8	[0.5-5.5]				0.6	41.5	55.0	1.2				0.6	1.2		
	Sheep	1.5	[0.3-5.8]					85.3	13.2					0.7	0.7		
Chloramphenicol	Broiler	0.0	[0.0-2.9]					0.6	9.3	63.0	26.5	0.6					
	Horse	0.0	[0.0-2.7]						13.5	57.3	29.2						
	Sheep	0.0	[0.0-3.4]						1.5	71.3	26.5	0.7					
Florfenicol	Broiler	0.0	[0.0-2.9]							33.3	64.2	2.5					
	Horse	0.0	[0.0-2.7]							52.0	45.6	2.3					
	Sheep	0.0	[0.0-3.4]							14.0	85.3	0.7					
Ampicillin	Broiler	11.7	[7.4-17.9]				1.2	16.7	55.6	14.2	0.6			11.7			
	Horse	1.8	[0.5-5.5]				1.8	14.0	51.5	29.2	1.8			1.8			
	Sheep	2.2	[0.6-6.8]					1.5	43.4	46.3	6.6		0.7	1.5			
Ceftiofur	Broiler	0.0	[0.0-2.9]		3.7	40.1	50.0	6.2									
	Horse	0.0	[0.0-2.7]		3.5	32.2	63.7	0.6									
	Sheep	0.0	[0.0-3.4]			16.9	80.1	2.9									
Cefotaxime	Broiler	0.0	[0.0-2.9]	62.3	33.3	4.3											
	Horse	0.0	[0.0-2.7]	70.8	28.7	0.6											
	Sheep	0.0	[0.0-3.4]	38.2	54.4	7.4											
Trimethoprim	Broiler	2.5	[0.8-6.6]			43.2	50.6	6.2									
	Horse	8.8	[5.2-14.3]			48.0	48.5	3.5									
	Sheep	0.0	[0.0-3.4]			26.5	70.6	2.9									
Sulfamethoxazole	Broiler	7.4	[4.1-12.9]									62.3	27.2	3.1			7.4
	Horse	7.6	[4.3-12.9]									73.1	18.1	1.2			7.6
	Sheep	2.9	[0.9-7.8]									31.6	47.1	18.4			2.9
Streptomycin	Broiler	3.1	[1.1-7.5]						1.2	44.4	45.7	5.6	1.9	0.6		0.6	
	Horse	7.6	[4.3-12.9]						4.7	50.3	35.1	2.3	1.2	1.8	2.3	1.2	1.2
	Sheep	14.0	[8.9-21.2]						2.2	37.5	46.3		0.7	3.7	6.6	2.2	0.7
Gentamicin	Broiler	0.0	[0.0-2.9]				43.2	50.6	6.2								
	Horse	0.0	[0.0-2.7]				48.0	48.5	3.5								
	Sheep	0.0	[0.0-3.4]				26.5	70.6	2.9								
Kanamycin	Broiler	0.0	[0.0-2.9]						46.9	45.1	8.0						
	Horse	0.6	[0.0-3.7]						60.8	35.1	3.5		0.6				
	Sheep	0.0	[0.0-3.4]						33.1	62.5	4.4						
Nalidixic acid	Broiler	8.0	[4.5-13.6]					3.7	36.4	49.4	2.5		1.2	0.6	3.1	3.1	
	Horse	0.0	[0.0-2.7]					2.9	53.8	42.1	1.2						
	Sheep	0.0	[0.0-3.4]						27.2	72.1	0.7						

		Resistance (%)		Distribution (%) of MIC values (mg/L)													
Substance	Sample	[95% CI]		0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64
Ciprofloxacin	Broiler	8.0	[4.5-13.6]		2.5	56.8	32.7	0.6	3.1	3.1	0.6	0.6					
	Horse	0.0	[0.0-2.7]		9.9	73.1	17.0										
	Sheep	0.0	[0.0-3.4]			42.6	57.4										

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

RESULTS AND COMMENTS

BROILER

The data indicate moderate occurrence of resistance among *E. coli* from broiler faecal samples. In total, 76.5% of the isolates were susceptible to all antimicrobial agents included. Altogether, 13.0% were resistant to one antimicrobial agent (predominantly ampicillin), 6.2% to two (mainly streptomycin and sulfamethoxazole), 1.9% to three and 2.5% to four antimicrobial agents (Figure 13). Resistance to ampicillin was the most frequently identified resistance determinant, followed by resistance to ciprofloxacin, nalidixic acid and tetracycline.

Resistance to the fluoroquinolone ciprofloxacin and to the quinolone nalidixic acid has increased significantly compared to previous years (Figure 14). A few strains had MIC patters indicative of having plasmid mediated quinolone resistance. However, further investigation showed that the strains were negative for the known genes involved in plasmid mediated quinolone resistance. The usage of fluoroquinolones in food producing animals in Norway is very limited and rising quinolone resistance is worrisome.

HORSE

The data indicate a low occurrence of antimicrobial resistance among *E. coli* from horse faecal samples. In total, 90.6% was susceptible to all antimicrobial agents included. Altogether, 0.6% was resistant to one antimicrobial agent, 2.9% to two, 3.5% to three and 2.3% to four or more antimicrobial agents (Figure 13). Resistance to trimethoprim, sulfamethoxazole and streptomycin was most commonly observed. No quinolone resistance was observed.

SHEEP

Antimicrobial resistance in *E. coli* (mainly belonging to serogroups O26 and O103) from sheep was low. However, 14.0% of the isolates were resistant to streptomycin. This is significantly higher than what has been observed in *E. coli* isolates randomly selected from faeces or meat from sheep in previous years. In total, 86.0% of the included isolates were susceptible to all included antimicrobial agents. Altogether, 9.6% were resistant to one antimicrobial agent (streptomycin), 2.2% to two and 2.2% to three antimicrobial agents (Figure 13).

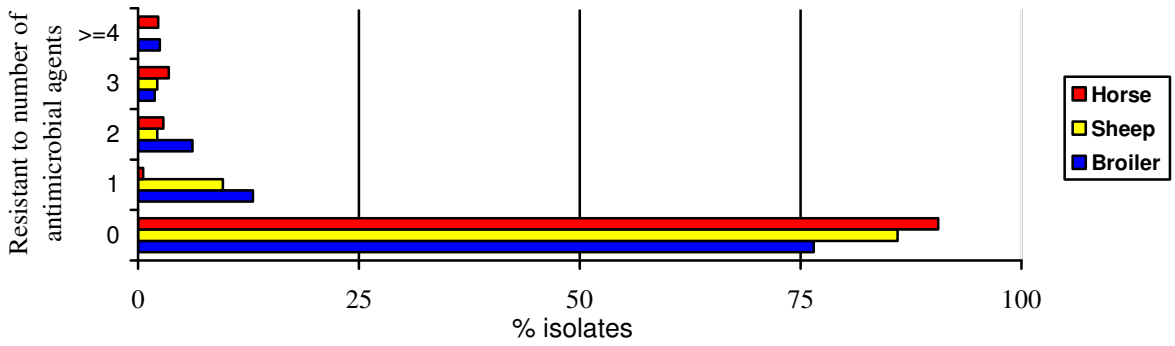


FIGURE 13. Antimicrobial resistance profile for *E. coli* from broiler (n=162), horse (n=171) and sheep (n=136) in 2009. Proportions of isolates susceptible to all or resistant to one, two, three and four or more antimicrobial agents are illustrated.

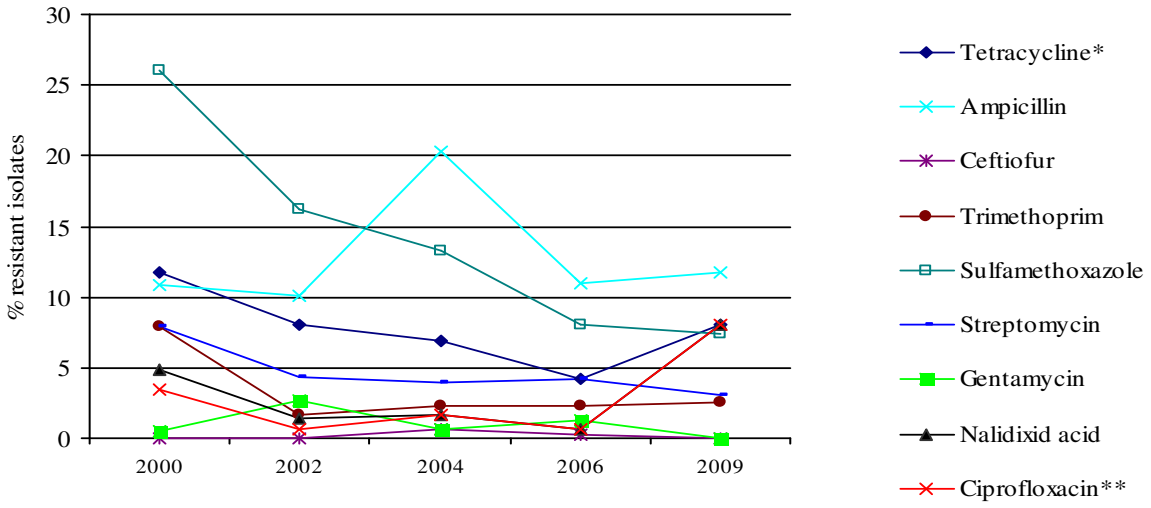


FIGURE 14. Prevalence of resistance to various antimicrobials in *E. coli* from broiler isolates in 2000-2009. The cut-off values used in NORM-VET 2009 were applied. *Oxytetracycline in 2002 and 2004. **Enrofloxacin before 2006.

SCREENING OF IMPORTANT ANTIMICROBIAL RESISTANCE DETERMINANTS

Resistance to critically important antimicrobials represents a significant public health problem. In 2009, screening for extended-spectrum beta-lactamase (ESBL) producing *E. coli* from swine, methicillin resistant *Staphylococcus aureus* (MRSA) from horse and vancomycin resistant *Enterococcus* spp. (VRE) from broiler was performed. Sampling, laboratory methods and data processing are described in Appendix 3.

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

A total of 183 faecal samples from 92 swine herds were screened for the presence of ESBL producing *E. coli.* No positive isolates were identified, indicating a prevalence of ESBL producing *E. coli* in the Norwegian swine population below 2.3%.

Methicillin resistant *Staphylococcus aureus* (MRSA) from horse

Nasal swabs from a total of 186 horses were screened for the presence of MRSA. No positive samples were identified, indicating a prevalence of MRSA in the Norwegian horse population below 1.6%.

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

A total of 228 boot swab samples from broiler were screened for the presence of VRE. The results are presented in Table 14. Seventeen (7.5%, 95% CI: 4.4-11.7) samples were positive for VRE. All *vanA* positive isolates were identified as *E. faecium*. All isolates were also resistant to narasin, indicating a possible co-selection between the two resistance phenotypes. One isolate had additional resistance to ampicillin. Resistance to tetracycline, the most common antimicrobial resistance in vancomycin sensitive *Enterococcus* spp., was not observed.

The previous monitoring of faecal samples from broilers in 2006 indicated a surprising decrease in the prevalence of VRE compared with previous results. The increased prevalence of VRE seen in 2009 might be a result of the sampling method with boot swabs used instead of faecal samples, which might mirror the prevalence in the broiler houses and not necessary the actual prevalence in the live broilers. The results warrant future monitoring of the situation.

TABLE 14. Antimicrobial resistance in vancomycin resistant *Enterococcus faecalis* (n=17) from faecal samples from broiler in 2009.

		Distribution (%) of MIC values (mg/L)													
Substance	Resistance (n)	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	≥ 2048
Tetracycline	0		17												
Chloramphenicol	0				6	8	3								
Ampicillin	1	1	3	3		9	1								
Erythromycin	0		12	1	3	1									
Streptomycin	0								1	14	2				
Gentamicin	0					1	10	5	1						
Kanamycin	0									3	7	5	2		
Vancomycin	17											17			
Bacitracin[#]	0			6	4	1	3	2	1						
Linezolid	0			5	12										
Virginiamycin	0		4	1	9	3									
Narasin	17					6	11								

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

C. ZOONOTIC AND NON-ZOONOTIC ENTEROPATHOGENIC BACTERIA

Astrid Louise Wester, Trine-Lise Stavnes, Jarle Mikalsen and Madelaine Norström

Zoonotic and non-zoonotic enteropathogenic bacteria represent a considerable public health problem. Furthermore, the occurrence of acquired antimicrobial resistance in such bacteria represents a major public health concern. Therefore, it is of great importance to monitor the occurrence of antimicrobial resistance in zoonotic and other enteropathogenic bacteria at relevant stages in the farm-to-fork continuum. In Norway, *Salmonella* isolates from control programmes concerning feed samples, animals and food products, as well as diagnostic samples are monitored for antimicrobial resistance. Additionally in 2009, antimicrobial resistance in *Campylobacter coli* from swine was included. Regarding human isolates, all *Salmonella*, *Shigella* and *Yersinia enterocolitica* isolates are included, as well as a representative number of *Campylobacter* isolates. Sampling, laboratory methods and data processing are described in Appendix 4.

SALMONELLA SPP.

Salmonella from animals

The situation regarding occurrence of *Salmonella* spp. in food producing animals in Norway is very good as such animals are virtually free from *Salmonella* spp. To document and maintain this favourable situation, Norway runs an extensive surveillance programme that covers both live animals (cattle, pigs and poultry) and meat samples (cattle, pigs, sheep and poultry). The *Salmonella* isolates examined in NORM-VET include those that are detected in this programme, in addition to selected isolates from other relevant projects, as well as clinical submissions to the National Veterinary Institute. The data are presented in Table 15 and in the text.

TABLE 15. Antimicrobial resistance in *S.* Typhimurium (n=11) and other *Salmonella* spp. (n=2) isolates from animals 2009.

			Distribution (n) of MIC values (mg/L)														
Substance	Serovar	Resistance (n)	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	*S.* Typhimurium	3						3	5			2	1				
	Salmonella spp.	1							1						1		
Chloramphenicol	*S.* Typhimurium	3							3	4	1					3	
	Salmonella spp.	0								2							
Florfenicol	*S.* Typhimurium	3							2	4	2		2	1			
	Salmonella spp.	0								1	1						
Ampicillin	*S.* Typhimurium	3						8							3		
	Salmonella spp.	1						1							1		
Cefotaxime	*S.* Typhimurium	0			3		8										
	Salmonella spp.	0					2										
Trimethoprim	*S.* Typhimurium	0				10	1										
	Salmonella spp.	0				1	1										
Sulfamethoxazole	*S.* Typhimurium	3											5	3			3
	Salmonella spp.	1											1				1
Streptomycin	*S.* Typhimurium	3									3	4	1	1	2		
	Salmonella spp.	1									1						1
Gentamicin	*S.* Typhimurium	0					5	6									
	Salmonella spp.	0					2										
Kanamycin	*S.* Typhimurium	0							7	4							
	Salmonella spp.	0							1	1							
Ciprofloxacin	*S.* Typhimurium	1	9	1			1										
	Salmonella spp.	0	1	1													
Nalidixic acid	*S.* Typhimurium	1								8	2					1	
	Salmonella spp.	0								2							

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

RESULTS AND COMMENTS

In 2009, a total of 13 isolates of *Salmonella* spp. were susceptibility tested. Two isolates, *S.* Senftenberg and *S. enterica* subsp. *enterica*, were both isolated from dogs. The remaining 11 isolates were all *S.* Typhimurium; eight from dogs and one isolate each from cattle, horse and broiler. Two of the *S.* Typhimurium isolates from dogs were typed as DT104 and exhibited the frequently reported penta-resistant phenotype. In addition, one more isolate from a dog exhibited the penta-resistant phenotype but was not further typed. Furthermore, one of the confirmed DT104 isolates was additionally resistant to fluoroquinolones (ciprofloxacin) and quinolones (nalidixic acid), important classes of antimicrobial agents in both human and veterinary medicine.

Salmonella from human clinical specimens

In 2009 the National Reference Laboratory for Enteropathogenic Bacteria received a total of 1,263 *Salmonella* isolates from human infections of which 16.4% were reported as acquired in Norway, 79.4% acquired abroad, whereas the place of origin was unknown for 4.2%. The incidence rate was 25.7 per 100,000 person years. Altogether 543 (43%) of the isolates were *S.* Enteritidis, of which only 37 (6.8%) were infected in Norway, while 217 (17.2%) of the isolates were *S.* Typhimurium, of which 82 (37.8%) were reported as infected in Norway. The relatively high proportion of domestically acquired *S.* Typhimurium infections is mainly explained by the endemic occurrence of specific clones of this serovar in Norwegian wildlife.

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

In total, 217 isolates of *S.* Typhimurium (of which 15 with unknown place of origin are not included in the following tables), 543 isolates of *S.* Enteritidis, 10 isolates of *S.* Typhi, nine isolates of *S.* Paratyphi A, four isolates of *S.* Paratyphi B and 434 isolates of other *Salmonella* spp. were susceptibility tested. The results are presented in Tables 16-19, Figures 15-19, and in the text. Sampling, laboratory methods, and data handling are described in Appendix 4.

The proportion of multiresistant *S.* Typhimurium DT104 from domestically acquired cases of *S.* Typhimurium infections was 3.7% (against 5.8% in 2008), from infections acquired abroad 5.1% (against 5.5% in 2008).

Several European countries have reported a worrisome increase in multiresistant *S. enterica* serovar 4,[5],12:i:-, which may count as a variant of *S.* Typhimurium. In Norway, when counted as a variant of *S.* Typhimurium, the proportion of *Salmonella enterica* serovar 4,[5],12:i:- was 20.7% (against 20.3% in 2008). Of the total of 45 isolates, 43 were multiresistant (against 43 out of a total of 59 in 2008). 28 isolates were acquired abroad, and 14 were acquired in Norway.

TABLE 16. *Salmonella* Typhimurium isolates (n=82), including multiresistant DT104 (n=8), and *S. enterica* serovar 4,[5],12:i:- from patients infected in Norway. Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	64.6	35.4
Chloramphenicol	≤ 8	> 8	86.6	-	13.4
Tetracycline*			61.0	-	39.0
Nalidixic acid	≤ 16	> 16	91.5	-	8.5
Ciprofloxacin	≤ 0.5	> 1	98.8	1.2	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	95.2	2.4	2.4

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

TABLE 17. *Salmonella* Typhimurium isolates (n=120), including multiresistant DT104 (n=11), and *S. enterica* serovar 4,[5],12:i:- from patients infected outside Norway. Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.8	45.0	54.2
Chloramphenicol	≤ 8	> 8	83.3	-	16.7
Tetracycline*			34.2	-	65.8
Nalidixic acid	≤ 16	> 16	89.2	-	10.8
Ciprofloxacin	≤ 0.5	> 1	98.3	1.7	0.0
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	90.0	7.5	2.5

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

TABLE 18. *Salmonella* Enteritidis isolates from patients (n=543[#]). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.2	94.8	5.0
Chloramphenicol	≤ 8	> 8	98.9	-	1.1
Tetracycline*			96.5	-	3.5
Nalidixic acid	≤ 16	> 16	76.4	-	23.6
Ciprofloxacin	≤ 0.5	> 1	99.8	0.0	0.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	98.5	0.2	1.3

Place of infection; Norway (n=37), abroad (n=493), unknown (n=13). * The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

TABLE 19. *Salmonella* spp. (excluding *S.* Typhimurium, *S.* Enteritidis, *S.* Typhi and *S.* Paratyphi) (n=434[#]). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.2	86.7	13.1
Chloramphenicol	≤ 8	> 8	95.2	-	4.8
Tetracycline*			79.5	-	20.5
Nalidixic acid	≤ 16	> 16	84.6	-	15.4
Ciprofloxacin	≤ 0.5	> 1	97.2	1.4	1.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	88.0	1.2	10.8

Place of infection; Norway (n=71), abroad (n=343), unknown (n=20). * The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this drug is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.

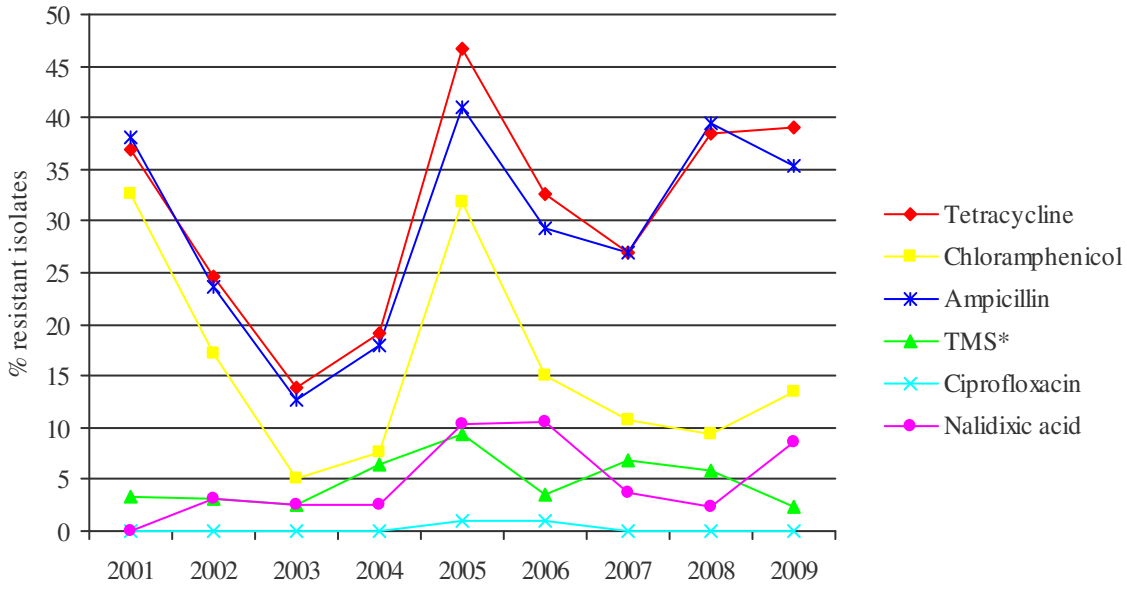


FIGURE 15. Prevalence of resistance to various antimicrobial agents in *Salmonella* Typhimurium (including multiresistant DT104 and *S. enterica* serovar 4,[5],12:i:-) from humans infected in Norway 2001-2009. *TMS=Trimethoprim-sulfamethoxazole.

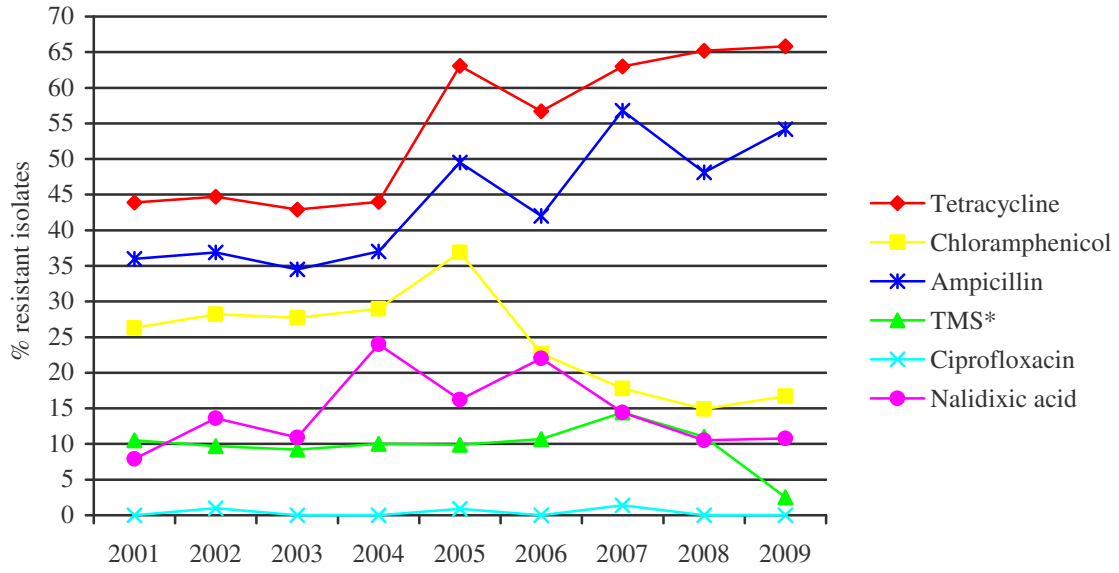


FIGURE 16. Prevalence of resistance to various antimicrobial agents in *Salmonella* Typhimurium (including multiresistant DT104 and *S. enterica* serovar 4,[5],12:i:-) from humans infected outside Norway 2001-2009. *TMS=Trimethoprim-sulfamethoxazole.

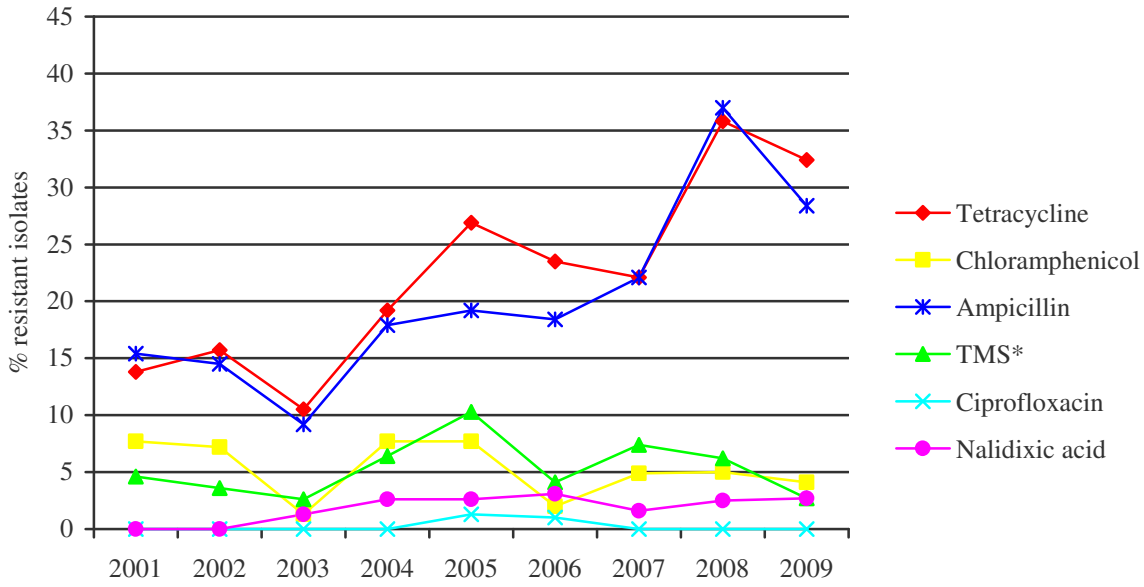


FIGURE 17. Prevalence of resistance to various antimicrobial agents in *Salmonella* Typhimurium from humans infected in Norway 2001-2009 (multiresistant DT104 excluded). *TMS=Trimethoprim-sulfamethoxazole.

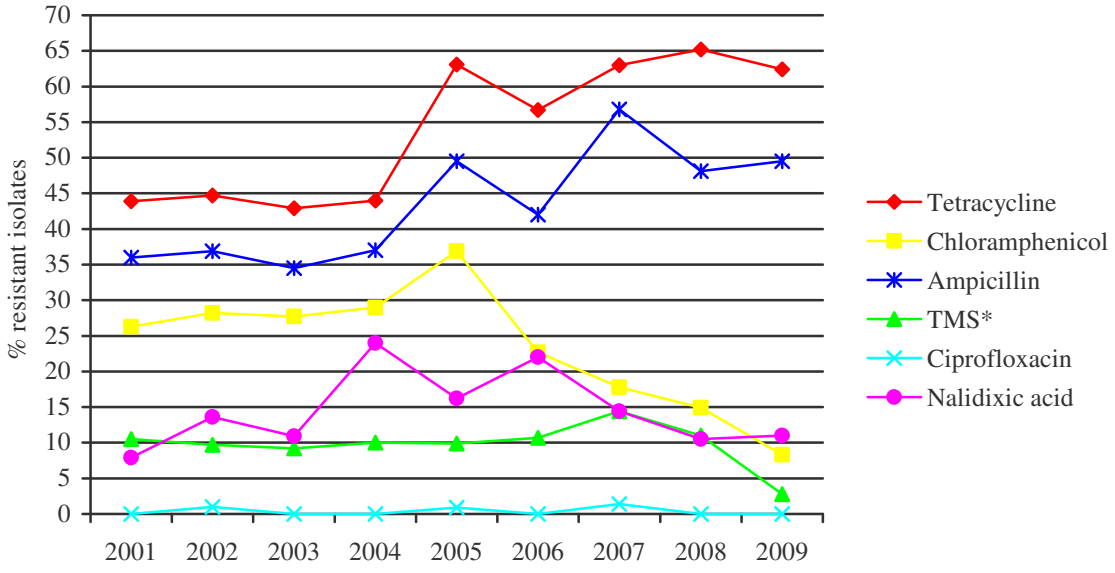


FIGURE 18. Prevalence of resistance to various antimicrobial agents in *Salmonella* Typhimurium from humans infected outside Norway 2001-2009, excluding multiresistant DT104. *TMS=Trimethoprim-sulfamethoxazole.

RESULTS AND COMMENTS

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

The proportion of *S.* Typhimurium isolates susceptible to all antimicrobial agents tested was higher for the category "infected in Norway" (57.3%) than for the "infected abroad" category (30.8%) (Figure 19). Multiresistant strains, defined as resistant to two or more antimicrobial agents, were more common in the category "infected abroad" (49.2%) than in the category "infected in Norway" (29.3%). The prevalence of resistance for the years 2001-2009 to various antimicrobial agents in human isolates of *S.* Typhimurium, acquired in Norway (Figure 15) and acquired abroad (Figure 16) shows an increasing trend regarding resistance against tetracycline and ampicillin, whereas for the other antibiotics tested there is no clear trend. Regarding the proportion of multiresistant *S. enterica* serovar 4,[5],12:i:-, there has been an increase from 72.9% in 2008 to 95.6% in 2009, whereas the absolute number of isolates has decreased from 59 isolates in 2008 to 45 isolates in 2009.

The vast majority of *S.* Enteritidis isolates has been acquired abroad (Table 18). The proportion of *S.* Enteritidis isolates resistant to the different antimicrobial agents included was, except for nalidixic acid, considerably lower than for *S.* Typhimurium. In total, 23.6% of the isolates of *S.* Enteritidis were resistant to nalidixic acid. Resistance to ciprofloxacin was found in 0.2% and none of the isolates were intermediately susceptible as found in 2008. This seems to be a significant decrease compared to 2007 when 13.4% were found to be intermediately susceptible, but more in accordance with the results from the previous years.

With regard to *Salmonella* spp. isolates other than *S.* Typhimurium and *S.* Enteritidis, most infections have been acquired abroad and antimicrobial resistance was frequently detected (Table 19). Resistance to tetracycline was most common, followed by resistance to nalidixic acid and ampicillin. Resistance to ciprofloxacin was observed in 1.4% of the isolates and the same proportion showed intermediate susceptibility. It is emphasized that the use of fluoroquinolones in Norway is very limited in both human and veterinary medicine.

The few isolates of *S.* Typhi (n=10), *S.* Paratyphi A (n=9) and *S.* Paratyphi B (n=4) in 2009 indicate that multiresistance, including resistance to nalidixic acid, is common in these serovars. With the exception of three cases of unknown origin, all infections with these serovars were acquired abroad. Thirteen isolates (52.2%, four *S.* Typhi, five *S.* Paratyphi A and four *S.* Paratyphi B) were resistant to one or more of the antimicrobial agents included in the survey.

In 2009, the marker for possible extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefpodoxime. All isolates with reduced susceptibility to cefpodoxime were further characterized in order to verify the presence of ESBL. A total of three isolates displayed reduced susceptibility to cefpodoxime; all were identified as ESBL producers.

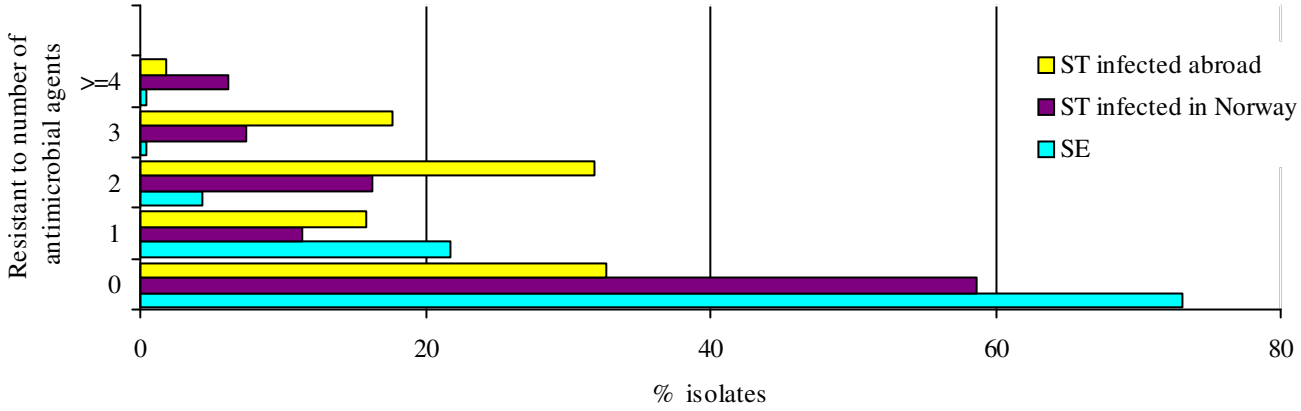


FIGURE 19. Antimicrobial resistance profiles for all *Salmonella* Enteritidis (SE) from humans (n=543) and for *Salmonella* Typhimurium (ST) from humans infected in Norway (n=80) and abroad (n=113), respectively. Proportion of isolates in 2009 resistant to none, one, two, three, or four or more antimicrobial agents are illustrated.

CAMPYLOBACTER SPP.

Campylobacter coli from swine

A total of 183 faecal samples from 92 swine herds were collected. *Campylobacter coli* strains were isolated from 67 herds and one isolate from each herd was susceptibility tested. The data are presented in Table 20 and in the text.

TABLE 20. Antimicrobial resistance in *Campylobacter coli* (n=67) from swine in 2009.

	Resistance		Distribution (%) of MIC values (mg/L)													
Substance	(%)	[95% CI]	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
Tetracycline	0.0	[0.0-6.8]		61.2	29.9	9.0										
Erythromycin	0.0	[0.0-6.8]				68.7	29.9	1.5								
Streptomycin	22.4	[13.5-34.5]						4.5	53.7	19.4			1.5	20.9		
Gentamicin	0.0	[0.0-6.8]				23.9	67.2	9.0								
Ciprofloxacin	4.5	[1.2-13.4]	34.3	56.7	4.5					1.5	3.0					
Nalidixic acid	6.0	[1.9-15.4]							43.3	49.3	1.5		6.0			

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 are given as the lowest MIC-value above the range. MIC-values equal to or lower than the lowest concentration tested are given as the lowest concentration tested.

RESULTS AND COMMENTS

The results show that the occurrence of antimicrobial resistance among *C. coli* isolates from Norwegian swine is moderate. A total of 73.1% of the included isolates were susceptible to all antimicrobial agents tested. However, streptomycin resistance was frequently identified (22.4%). The prevalence of resistance to ciprofloxacin and nalidixic acid was relatively low, 4.5% and 6.0%, respectively. Resistance to tetracycline, gentamicin and erythromycin was not detected.

Campylobacter spp. from human clinical specimens

Of the 2,850 cases of human campylobacteriosis registered in Norway in 2009 (incidence rate 59.4 per 100,000), 47% were reported as acquired abroad. Based on epidemiological data on patients, the vast majority of cases were judged as sporadic. However, molecular epidemiology data are not available regarding *Campylobacter* due to resource priority matters. Thus outbreaks with less clear epidemiological links may have been overlooked. Case-control studies in Norway have revealed that consumption of broiler meat purchased fresh and drinking of untreated water are important risk factors for domestically acquired campylobacteriosis. Susceptibility testing was performed on a total of 280 isolates of *C. jejuni* (121 from patients infected in Norway, 151 from patients infected abroad and 8 from patients where the origin of infection was unknown) and 9 *C. coli* isolates. The results for *C. jejuni* are presented in Tables 21-24, Figures 20-22, and in the text.

TABLE 21. *Campylobacter jejuni* isolates from patients infected in Norway (n=121). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	98.3	-	1.7
Erythromycin	≤ 4	> 4	100.0	-	0.0
Gentamicin	≤ 2	> 4	99.2	0.8	0.0
Nalidixic acid	≤ 16	> 16	86.0	-	14.0
Ciprofloxacin	≤ 0.5	> 1	87.6	0.0	12.4

TABLE 22. *Campylobacter jejuni* isolates from patients infected in Norway (n=121). Distribution (%) of MICs (mg/L).

	≤ 0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Tetracycline		3.3	33.9	49.6	9.1	1.7	0.8				0.8			0.8
Erythromycin				0.8	11.6	52.1	32.2	3.3						
Gentamicin			0.8	5.8	29.8	54.5	8.3	0.8						
Nalidixic acid						0.8	12.4	62.0	9.0	1.7	2.5			11.6
Ciprofloxacin	0.8	7.5	56.2	22.3	0.8						12.4			

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

TABLE 23. *Campylobacter jejuni* isolates from patients infected outside Norway (n=151). Distribution (%) of antimicrobial susceptibility categories.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Tetracycline	≤ 2	> 2	43.0	-	57.0
Erythromycin	≤ 4	> 4	98.7	-	1.3
Gentamicin	≤ 2	> 4	98.0	1.3	0.7
Nalidixic acid	≤ 16	> 16	25.8	-	74.2
Ciprofloxacin	≤ 0.5	> 1	25.2	0.6	74.2

TABLE 24. *Campylobacter jejuni* isolates from patients infected outside Norway (n=151). Distribution (%) of MICs (mg/L).

	≤ 0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Tetracycline		1.3	12.6	17.9	7.9	2.0	1.3	1.3	3.3	2.0	11.3	10.6	6.6	21.9
Erythromycin				0.7	9.3	35.0	45.7	7.9	0.7	0.7				
Gentamicin			2.0	7.3	35.7	45.7	7.3	1.3	0.7					
Nalidixic acid							4.6	16.5	4.0	0.7				74.2
Ciprofloxacin	0.7	2.0	19.2	3.3		0.7			1.3	2.0	70.8			

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

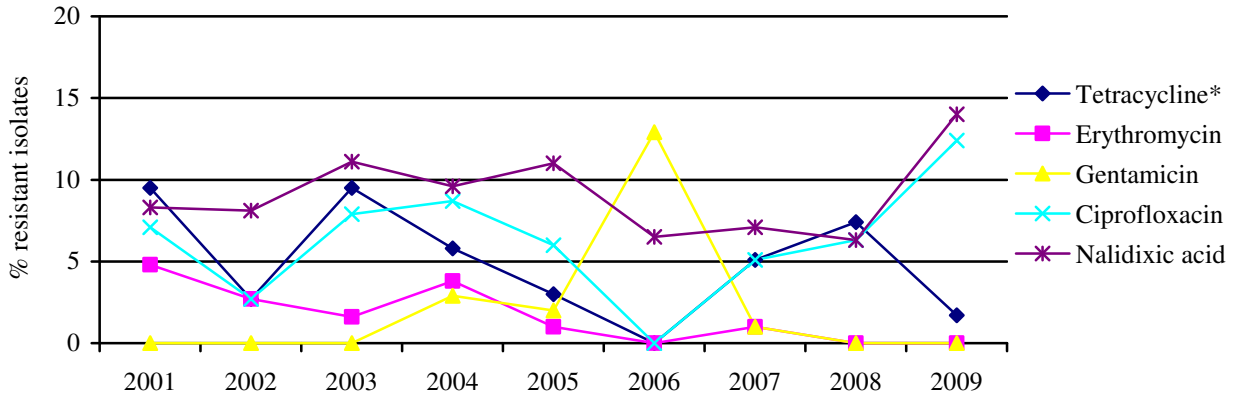


FIGURE 20. Prevalence of resistance in *Campylobacter jejuni,* isolated from humans infected in Norway 2001-2009, to various antimicrobials. * Doxycycline before 2006.

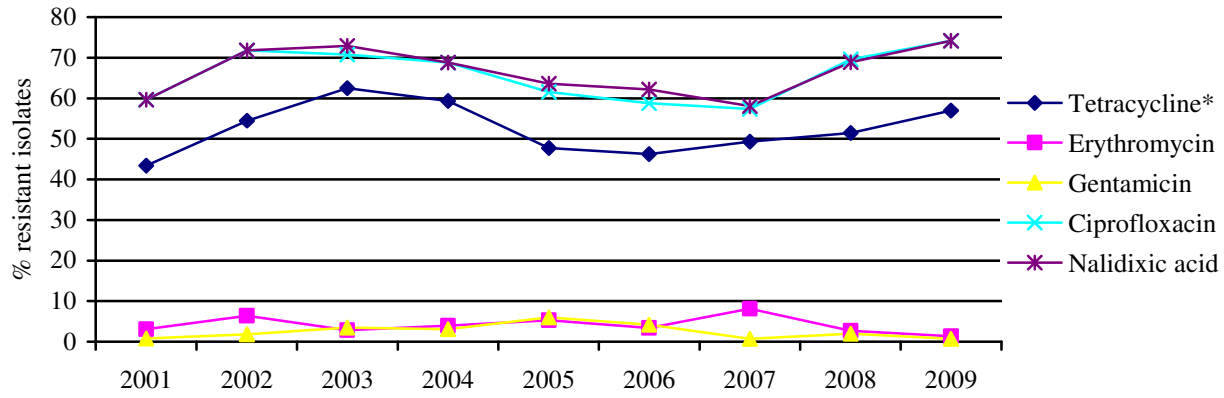


FIGURE 21. Prevalence of resistance to various antimicrobial agents in *Campylobacter jejuni* from humans infected outside Norway 2001-2009. * Doxycycline before 2006.

RESULTS AND COMMENTS

The data show that resistance was more widespread among *C. jejuni* isolates recovered from patients infected abroad than in patients infected in Norway. Only 17.2% of isolates from infections acquired abroad were susceptible to all antimicrobial agents tested compared to 85.1% of the isolates from patients infected in Norway (Figure 22). The main differences between the two groups were seen for quinolones (ciprofloxacin/nalidixic acid) with 74.2% resistance in isolates acquired abroad versus 14.0% resistance in isolates acquired in Norway, and tetracycline with 57.0% resistance in isolates acquired abroad versus 1.7% resistance for those acquired in Norway.

The prevalence of resistance to various antimicrobial agents for *C. jejuni* acquired inside and outside Norway (Figure 20 and 21) was fairly stable during the period 2001-2008 except for an unexplained increase in the resistance to gentamicin in domestic isolates in 2006. In 2009, however, there was a marked increase in quinolone resistance, and a lowering in resistance for tetracycline. These changes may be due to unknown methodological problems. Alternatively, it may be explained by a selection bias, or it may reflect a real increase in the prevalence of a *C. jejuni* clone with this specific resistance pattern.

As in earlier years, a high agreement between the prevalence of resistance for *C. jejuni* from humans infected within Norway and isolates from Norwegian broilers were observed, although, domestically aquired human isolates have prevalences of resistance towards quinolones (nalidixic acid and ciprofloxacin) and tetracycline.

Seven *C. coli* isolates were acquired abroad, and one was acquired in Norway. All seven isolates acquired abroad were resistant to at least one of the antimicrobial agents, mainly to quinolones or tetracycline. *C. coli* is typically associated with pigs and pork.

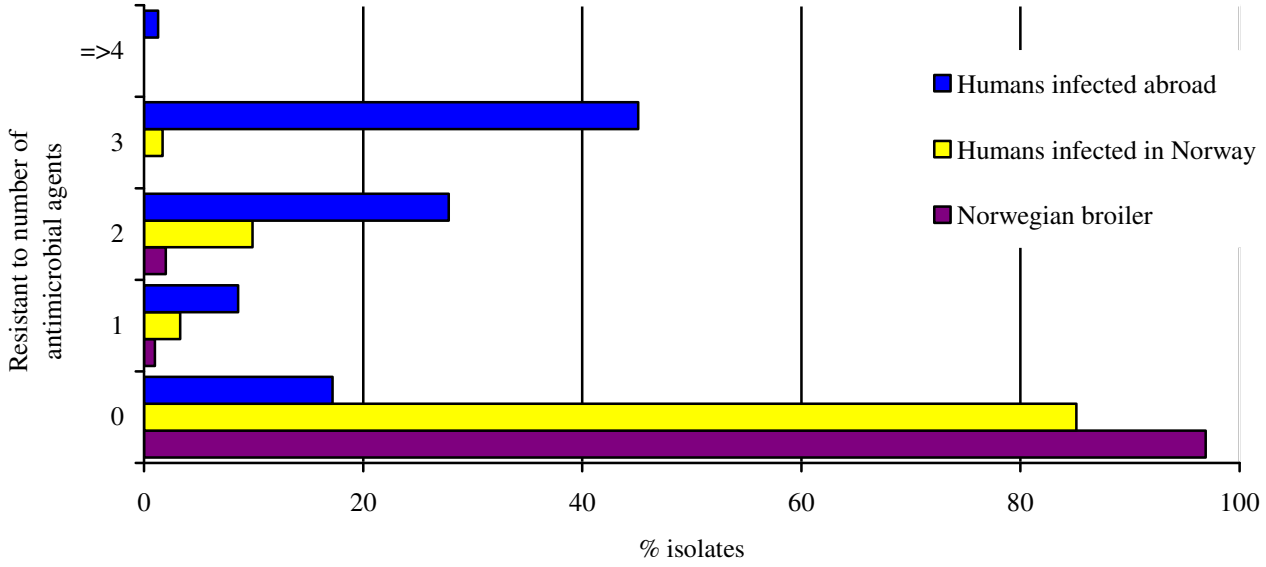


FIGURE 22. Antimicrobial resistance profiles for *Campylobacter jejuni* from humans infected in Norway (n=121), humans infected abroad (n=151) and Norwegian broilers (n=128, data from 2008). Proportion of isolates resistant to none, one, two, three, or four or more antimicrobial agents respectively are illustrated. The isolates from humans were tested for susceptibility to tetracycline, erythromycin, gentamicin, ciprofloxacin and nalidixic acid, whereas the broiler isolates in addition were tested for susceptibility to streptomycin.

Yersinia enterocolitica from human clinical specimens

Most cases of *Yersinia enterocolitica* infections in Norway are domestically acquired. A total of 53 cases of yersiniosis were reported in 2009 (against 50 cases in 2008) giving an incidence rate of 1.3 per 100,000. Of the 53 cases, 44 belonged to serogroup 3 (28 acquired in Norway, 13 abroad and 3 with unknown place of infection), eight belonging to serogroup 9 (3 acquired in Norway, 2 abroad and 3 with unknown place of infection) and one belonging to serogroup 8. All *Y. enterocolitica* isolates were susceptibility tested. The results for *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 are presented in Table 25 and Figure 23.

TABLE 25. *Yersinia enterocolitica* serogroup O:3 and serogroup O:9 isolates from human clinical cases (n=52[#]). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	0.0	100.0
Chloramphenicol	≤ 8	> 8	90.4	-	9.6
Tetracycline*			94.2	-	5.8
Nalidixic acid	≤ 16	> 16	94.2	-	5.8
Ciprofloxacin	≤ 0.5	> 1	96.2	1.9	1.9
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	90.4	1.9	7.7

* The epidemiological cut-off value defined by EUCAST is applied. There are no clinical breakpoints defined by AFA as this substance is not relevant for treatment. **Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.
[#] Place of infection; Norway (n=31), abroad (n=15), unknown (n=6).

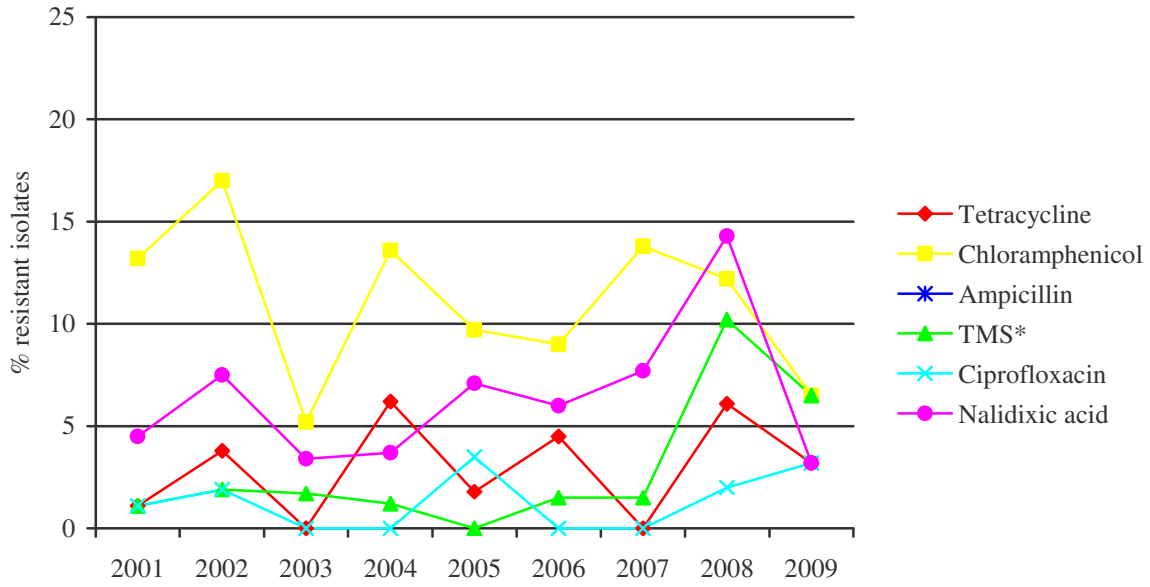


FIGURE 23. Prevalence of resistance to various antimicrobials in *Yersinia enterocolitica* from humans in Norway 2001-2009. *TMS=Trimethoprim-sulfamethoxazole.

RESULTS AND COMMENTS

The infections in 2009 were mainly domestically acquired. All serogroup O:3 and O:9 isolates expressed intrinsic resistance to ampicillin. The prevalence of resistance to other antimicrobial agents has been fairly stable during the years 2001-2007, but in 2008 there seemed to be a tendency towards higher prevalence of resistance for all antimicrobial agents except for chloramphenicol. (Figure 23). These tendencies seem to be counteracted to some extent in 2009. More likely these fluctuations may be due to a small absolute number of isolates, and thus, to chance, rather than true changes. One of the isolates was identified as ESBL producer in 2009.

Shigella spp. from human clinical specimens

It should be emphasized that almost all reported *Shigella* infections in Norway are acquired abroad. In 2009, 46 (30.3%) of the 152 reported cases were classified as domestically acquired, the majority of these was most probably secondary to imported cases. Thus, the prevalence of resistance presented in this report predominantly relates to isolates originating from other countries. The species distribution of the 130 *Shigella* isolates that were susceptibility tested was as follows: *S. sonnei* 81 (62.3%), *S. flexneri* 39 (30.0%), *S. boydii* 7 (5.4%), and *S. dysenteriae* 3 (2.3%). The results for *S. sonnei* and *S. flexneri* are presented in Table 26 and Figure 24 and in Table 27 and Figure 25, respectively.

TABLE 26. *Shigella sonnei* isolates from human clinical cases (n=81). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	0.0	88.9	11.1
Chloramphenicol	≤ 8	> 8	95.1	-	4.9
Tetracycline*			17.3	-	82.7
Nalidixic acid	≤ 16	> 16	67.9	-	32.1
Ciprofloxacin	≤ 0.5	> 1	92.6	0.0	7.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	6.2	2.5	91.3

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

TABLE 27. *Shigella flexneri* isolates from human clinical cases (n=39). Distribution (%) of antimicrobial susceptibility categories. Sampling, laboratory methods, and data handling are described in Appendix 4. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 0.5	> 8	2.6	20.5	76.9
Chloramphenicol	≤ 8	> 8	35.9	-	64.1
Tetracycline*			17.9	-	82.1
Nalidixic acid	≤ 16	> 16	82.1	-	17.9
Ciprofloxacin	≤ 0.5	> 1	92.3	2.6	5.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	35.9	5.1	59.0

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

RESULTS AND COMMENTS

The resistance patterns for *S. sonnei* and *S. flexneri* have been fairly stable during the period 2001 – 2009. The resistance has been most prevalent among *S. flexneri* and least prevalent among *S. sonnei* isolates. Resistance in *S. flexneri* has been high for all the tested antimicrobial agents excluding quinolones, but from 2006 *S. flexneri* has shown a tendency towards higher prevalence of resistance also against these antibiotics. In *S. sonnei,* the prevalence of resistance has been particularly high for tetracycline and for trimethoprim-sulfamethoxazole.

All the tested antimicrobials are commonly used for various clinical purposes within human medicine in many parts of the world. The few isolates of *S. dysenteriae* (n=3) and *S. boydii* (n=7) recovered and susceptibility tested in 2009 indicate that multiresistance is also fairly frequent in these species; two isolates of each species were resistant to two or more antimicrobial agents. None of the isolates were susceptible to all antimicrobial agents included in the survey.

In 2009 two *S. sonnei* isolates displayed reduced susceptibility to cefpodoxime (as a marker for possible ESBL-production) and both of them were verified as ESBL producers.

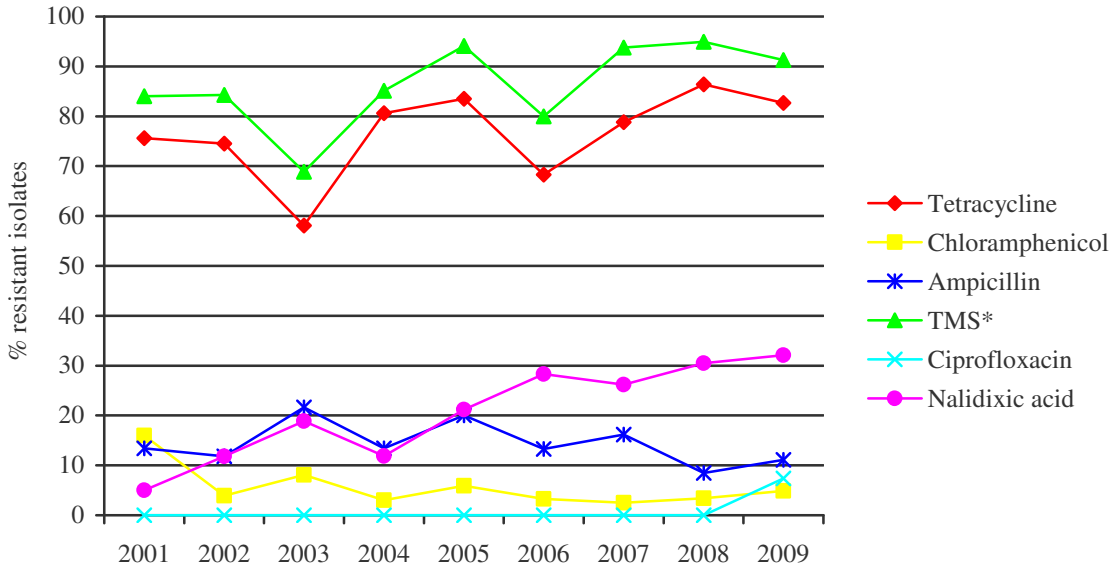


FIGURE 24. Prevalence of resistance to various antimicrobial agents in *Shigella sonnei* from humans in Norway 2001-2009. *TMS=Trimethoprim-sulfamethoxazole.

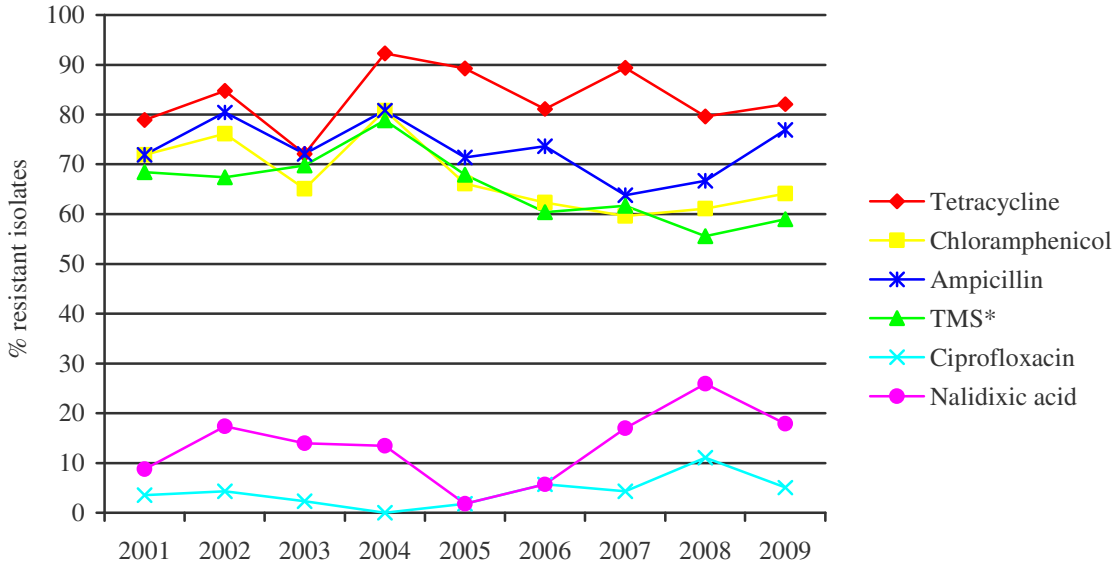


FIGURE 25. Prevalence of resistance to various antimicrobial agents in *Shigella flexneri* from humans in Norway 2001-2009. *TMS=Trimethoprim-sulfamethoxazole.

D. HUMAN CLINICAL ISOLATES

Gunnar Skov Simonsen, Karin Rønning, Ingvild Nordøy, Andreas Radtke

Distribution of bacterial species in blood cultures

Surveillance of antimicrobial resistance is usually based on prevalences of reduced susceptibility and resistance to certain combinations of antimicrobials and bacterial species in clinical samples. The NORM surveillance programme generally follows this approach. However, there is a serious limitation to the model because a transition in the distribution from susceptible bacterial species to inherently more resistant ones will represent de facto emergence of resistance which is not easily detected. In order to complement the surveillance of individual species, NORM collects data on all positive blood cultures from the laboratory information systems of the participating institutions. A patient with a given microbial isolate was excluded from registration with a new isolate of the same species within a month from the first entry. This rule was applied irrespectively of changes in the organism´s susceptibility pattern. Isolates of a different species were included in the surveillance. It proved difficult to systematically evaluate the clinical significance of species which are commonly part of the normal skin flora. In Table 28, proportions are therefore estimated for all isolates and for all isolates excluding species considered to be common skin contaminants such as coagulase negative staphylococci, *Micrococcus* spp., *Corynebacterium* spp., *Bacillus* spp. and *Propioni-bacterium* spp. This does not imply that such isolates cannot cause infections, but only that it was not possible to enforce a standardised protocol for inclusion of the clinically significant isolates. Similarly, all isolates were registered as individual findings although polymicrobial bloodstream infections are regularly detected in some patients. Limitations in the data extraction procedure prohibited in-depth analysis of these parameters.

TABLE 28. Number of blood culture isolates in 2009, proportion of all isolates, and proportion of isolates excluding possible skin contaminants (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) 2005-2009. The table is based on data from the information systems of all laboratories in Norway except one in 2009.

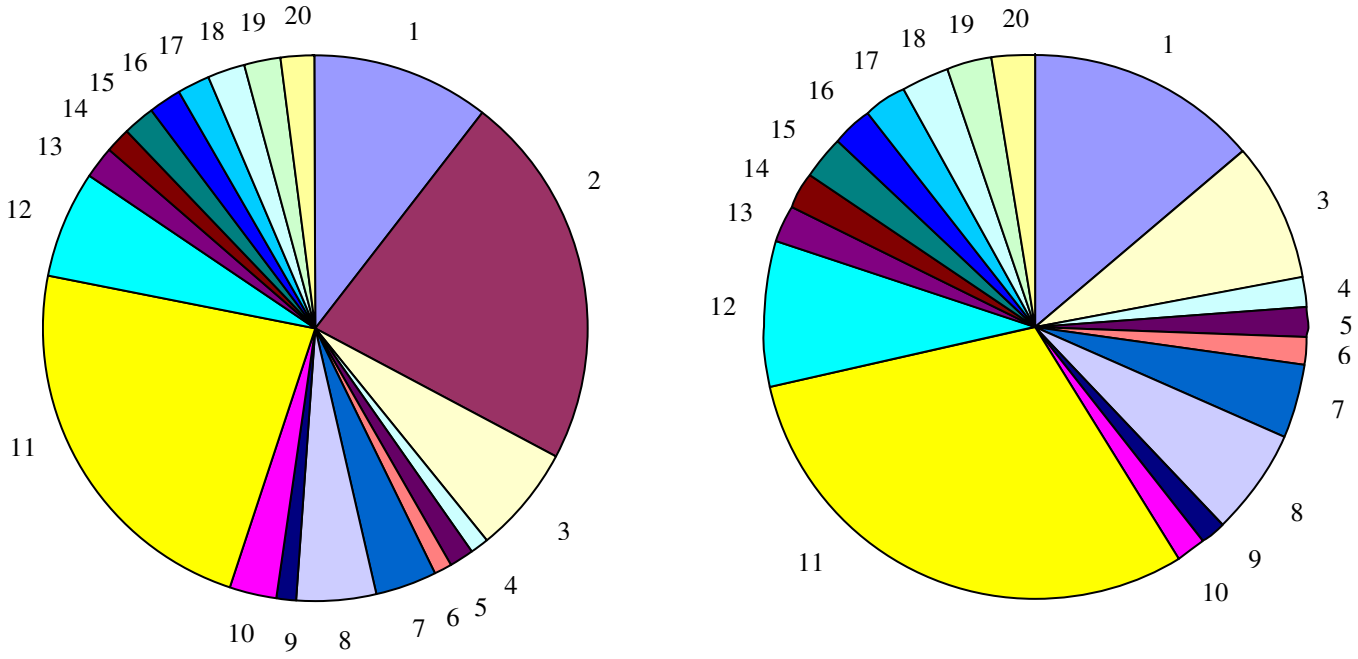
Species	No. of isolates 2009	% of all isolates					% of isolates excluding skin flora				
		2005	2006	2007	2008	2009	2005	2006	2007	2008	2009
Staphylococcus aureus	1,244	10.3	10.3	10.1	10.6	10.6	13.3	13.7	13.3	13.9	13.9
Coagulase negative staphylococci	2,619	20.3	22.7	21.6	21.3	22.3	-	-	-	-	-
Streptococcus pneumoniae	730	9.4	7.9	7.8	6.6	6.2	12.1	10.6	10.2	8.7	8.2
Streptococcus pyogenes	156	2.2	1.3	1.1	1.3	1.3	2.8	1.7	1.5	1.7	1.7
Streptococcus agalactiae	162	1.6	1.7	1.7	1.6	1.4	2.1	2.2	2.2	2.0	1.8
Beta-haemolytic streptococci group C and G	129	0.8	1.2	0.9	1.4	1.1	1.1	1.5	1.1	1.9	1.4
Viridans- and non-haemolytic streptococci	416	3.8	3.7	3.7	3.9	3.5	5.0	5.0	4.8	5.1	4.7
Enterococcus faecalis	536	4.0	4.3	4.3	4.0	4.6	5.2	5.7	5.7	5.2	6.0
Enterococcus faecium	156	1.1	1.1	1.4	1.4	1.3	1.5	1.5	1.8	1.9	1.7
Other Gram positive aerobic bacteria	313	3.1	3.4	3.4	3.4	2.7	1.3	1.8	2.1	1.5	1.5
Escherichia coli	2,701	22.4	21.6	22.3	22.8	23.0	29.0	28.9	29.2	29.9	30.2
Klebsiella spp.	768	5.4	5.4	6.0	5.8	6.5	7.0	7.2	7.9	7.6	8.6
Enterobacter spp.	221	1.6	1.7	1.8	1.9	1.9	2.0	2.3	2.3	2.5	2.5
Proteus spp.	178	1.9	1.8	1.7	1.5	1.5	2.4	2.4	2.2	2.0	2.0
Other *Enterobacteriaceae*	228	1.8	1.9	2.2	2.1	1.9	2.3	2.5	2.9	2.8	2.6
Pseudomonas spp.	223	2.1	1.7	1.6	1.8	1.9	2.8	2.3	2.1	2.4	2.5
Other Gram negative aerobic bacteria	224	2.2	2.3	2.1	2.1	1.9	2.8	3.1	2.7	2.8	2.5
Bacteroides spp.	257	1.8	1.9	2.2	2.3	2.2	2.4	2.5	2.9	3.0	2.9
Other anaerobic bacteria	272	2.2	2.4	2.5	2.5	2.3	2.3	2.8	2.9	2.8	2.8
Yeasts	219	2.0	1.9	1.7	1.8	1.9	2.6	2.5	2.3	2.3	2.5
Total	**11,752**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

As seen in Table 28 and Figure 26, aerobic Gram positive and Gram negative bacteria represented 55.0% and 38.7% of all isolates, respectively. The predominance of Gram positives among all isolates was at the same level as in previous years. The most common Gram positive species were coagulase negative staphylococci which represented 22.3% of all isolates. The difference between aerobic Gram positives and Gram negatives was reversed when species of the skin flora (coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp.) were excluded with 42.0% Gram positives and 50.9% Gram negatives.

Among the aerobic Gram positives, the prevalences of *S. pneumoniae* declined even when skin contaminants were excluded (12.1% in 2005, 10.6% in 2006, 10.2% in 2007, 8.7% in 2008, and 8.2% in 2009). The combined group of non-pneumococcal streptococci has remained stable after a peak among group C and G streptococci in 2008.

E. coli (30.2%) and other *Enterobacteriaceae* (15.7%) accounted for the vast majority of aerobic Gram negative isolates, and these proportions have increased compared to 29.0% and 13.7% in 2005, all figures excluding skin flora. *Pseudomonas* spp. (2.5%) has been fairly stable after a peak in 2005 (2.8%).

Anaerobic bacteria and yeasts were less prevalent. Anaerobes accounted for 4.5% (5.7% excluding skin flora) and yeasts accounted for 1.9% (2.5% excluding skin flora). The major pathogens among anaerobes were members of the *Bacteroides fragilis* group (2.2%/2.9%) and among yeasts *Candida albicans* (1.3%/1.7%). However, a multitude of other species was also represented.



1. *Staphylococcus aureus*
2. Coagulase negative staphylococci
3. *Streptococcus pneumoniae*
4. *Streptococcus pyogenes*
5. *Streptococcus agalactiae*
6. Betahaemolytic streptococci group C and G
7. Non-haemolytic and viridans streptococci
8. *Enterococcus faecalis*
9. *Enterococcus faecium*
10. Other Gram positive bacteria
11. *Escherichia coli*
12. *Klebsiella* spp.
13. *Enterobacter* spp.
14. *Proteus* spp.
15. Other *Enterobacteriaceae*
16. *Pseudomonas* spp.
17. Other Gram negative bacteria
18. *Bacteroides* spp.
19. Other anaerobic bacteria
20. Yeasts

FIGURE 26. Distribution of all blood culture isolates (left, n=11,752) and blood culture isolates excluding common skin contaminants (right, n=8,925) such as coagulase negative staphylococci, *Micrococcus* spp., *Bacillus* spp., *Corynebacterium* spp. and *Propionibacterium* spp. The figure is based on data from the information systems of all Norwegian laboratories except one in 2009.

Escherichia coli in blood cultures

TABLE 29. *Escherichia coli* blood culture isolates (n=1,379). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin*	≤ 0.5	> 8	0.2	61.5	38.3
Piperacillin-tazobactam	≤ 8	> 16	96.4	1.9	1.7
Cefuroxime*	≤ 0.5	> 8	0.1	94.4	5.5
Cefotaxime	≤ 1	> 2	97.2	0.5	2.3
Ceftazidime	≤ 1	> 8	97.2	1.2	1.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	96.0	0.4	3.6
Tobramycin	≤ 2	> 4	96.9	0.7	2.4
Nalidixic acid	≤ 16	> 16	85.6	-	14.4
Ciprofloxacin	≤ 0.5	> 1	91.4	0.3	8.3
Tigecycline	≤ 1	> 2	99.4	0.2	0.4
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	75.1	1.5	23.4
ESBL	Negative	Positive	97.5	-	2.5

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

RESULTS AND COMMENTS

The NORM results are interpreted according to the breakpoints of the Norwegian Working Group for Antibiotics (NWGA) at the time of analysis. The NWGA participates in the European breakpoint harmonization process. Norwegian breakpoints therefore correspond to common EUCAST breakpoints except for ampicillin and cefuroxime where the wild type is defined as intermediately susceptible by NWGA. In NORM 2009, ertapenem was replaced by meropenem which is the most commonly used carbapenem in Norway. In addition, tobramycin was included to give a more comprehensive analysis of aminoglycoside resistance. The breakpoints are presented in Table 29.

The vast majority of isolates remained fully susceptible to traditional broad-spectrum antimicrobial agents such as cefotaxime (97.2%), ceftazidime (97.2%), gentamicin (96.0%) and piperacillin-tazobactam (96.4%) (Table 29). The increasing prevalence of non-susceptibility to gentamicin noted from 2004 to 2007 was again seen from 2008 (0.2% I and 2.7% R) to 2009 (0.4% I and 3.6% R, Figure 27). Most isolates with reduced susceptibility to aminoglycosides displayed non-susceptibility to both gentamicin and tobramycin. The molecular basis for aminoglycoside resistance in Norway will be further explored.

The prevalence of non-suscpetibility to ciprofloxacin continued to increase from a total of 3.3% in 2004, 5.0% in 2005, 5.7% in 2006, 7.1% in 2007 and 8.1% in 2008, to 8.6% in 2009. The temporal association between ciprofloxacin non-susceptibility and ciprofloxacin usage is depicted in Figure 28. A similar increase in quinolone resistance in systemic *E. coli* isolates is reported from many other European countries. The prevalence of resistance to the indicator antibiotic nalidixic acid (14.4%) as well as ampicillin (38.3%) and trimethoprim-sulfamethoxazole (23.4%) all increased slightly from 2008 to 2009.

In 2009, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidime. All isolates with reduced susceptibility to ceftazidime and/or cefotaxime were further characterized by combination Etests. A total of 34 isolates (2.5%) were reported as ESBL positive which is an increase from 1.2% in 2007 and 1.5% in 2008. The 34 isolates originated from 14 different hospitals with up to five isolates from each institution. The ESBL isolates were all non-susceptible to ampicillin and cefuroxime, and most of them were non-susceptible to cefotaxime (n=31) and ceftazidime (n=24). Many isolates were intermediately (n=5) or even fully susceptible (n=23) to piperacillin/tazobactam. All isolates remained susceptible to meropenem and tigecycline, but the majority were co-resistant to ciprofloxacin (25/34), gentamicin (14/34) and/or trimethoprim-sulfamethoxazole (22/34). The ESBL isolates were molecularly characterized by PCR and DNA sequencing which revealed a predominance of CTX-M groups 1 (n=21) and 9 (n=7). A single isolate harboured a sequence belonging to the SHV family. The results are in accordance with previous surveys from Norway. It should be noted that classification of ESBLs solely on the basis of non-susceptibility to cefotaxime or ceftazidime would have overestimated the prevalence of ESBL by approximately 30% (3.3% instead of 2.5%).

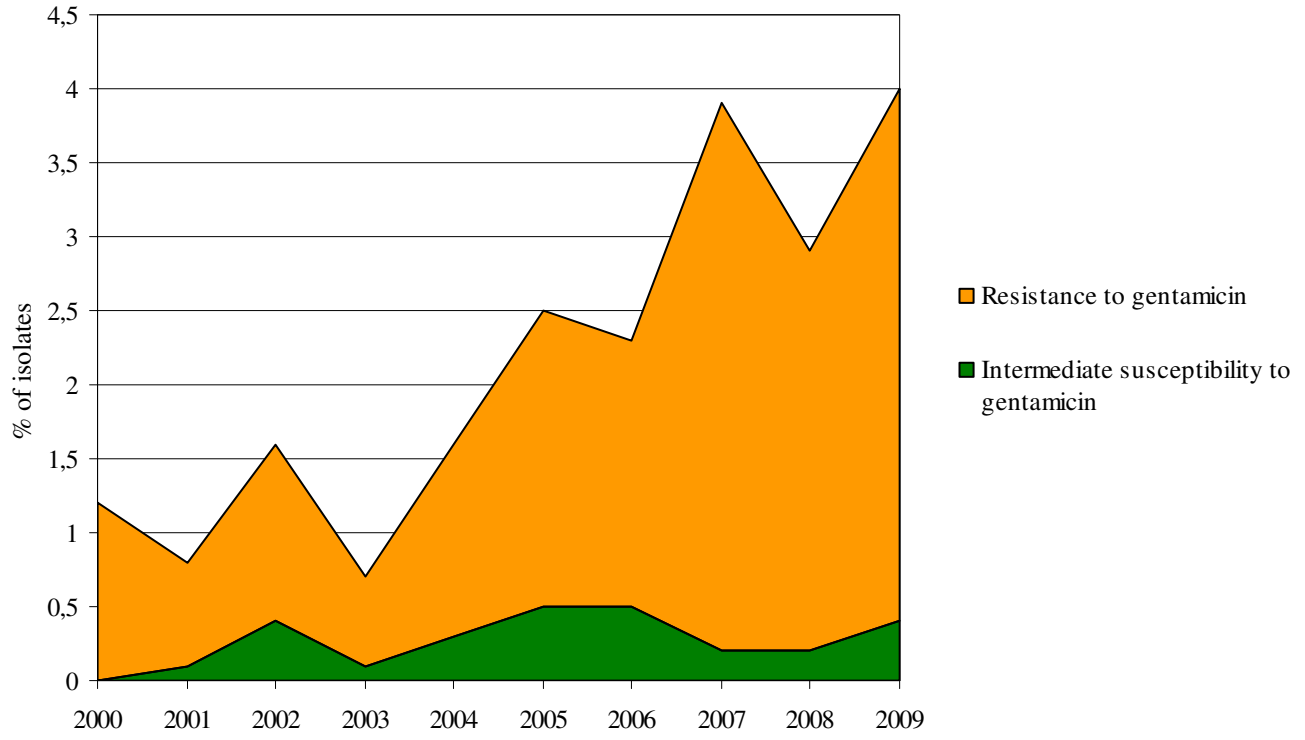


FIGURE 27. Prevalence of intermediate susceptibility and resistance to gentamicin in *Escherichia coli* blood culture isolates 2000-2009.

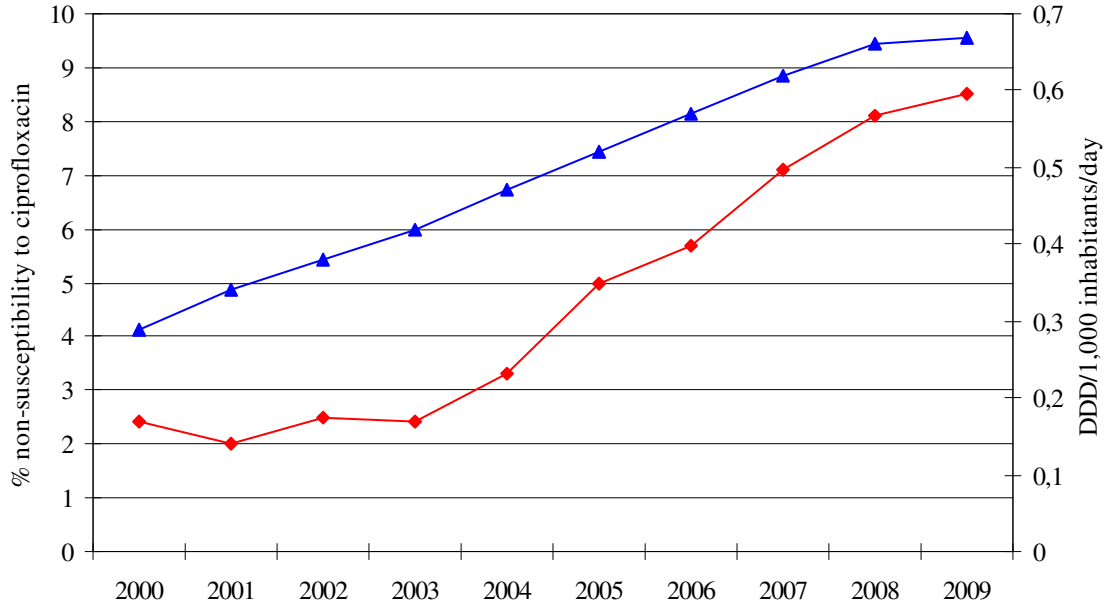


FIGURE 28. Prevalence of ciprofloxacin non-susceptibility in *Escherichia coli* blood culture isolates as defined by the 2009 breakpoints (red) versus usage of ciprofloxacin (blue) 2000-2009.

Escherichia coli in urine

TABLE 30. *Escherichia coli* urinary tract isolates (n=1,126). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin*	≤ 0.5	> 8	0.1	69.9	30.0
Mecillinam	≤ 8	> 8	97.4	-	2.6
Cefuroxime*	≤ 0.5	> 8	0.4	96.9	2.7
Cefotaxime	≤ 1	> 2	98.8	0.5	0.7
Ceftazidime	≤ 1	> 8	99.0	0.3	0.7
Gentamicin	≤ 2	> 4	96.9	1.0	2.1
Tobramycin	≤ 2	> 4	97.5	1.0	1.5
Nalidixic acid	≤ 16	> 16	90.7	-	9.3
Ciprofloxacin	≤ 0.5	> 1	95.3	0.6	4.1
Nitrofurantoin	≤ 64	> 64	98.0	-	2.0
Trimethoprim	≤ 2	> 4	78.5	0.4	21.1
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	78.3	1.8	19.9
ESBL	Negative	Positive	99.5	-	0.5

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

RESULTS AND COMMENTS

Urinary tract isolates of *E. coli* have been included in the surveillance programme every year since NORM was established in 2000. The prevalences of resistance for 2009 are shown in Table 30 and the results 2000-2009 are shown in Figure 29. As for *E. coli* blood culture isolates, tobramycin was added to the surveillance scheme in 2009 in order to further investigate aminoglycoside resistance. The breakpoint for susceptibility to mecillinam was increased from S ≤ 2 mg/L to S ≤ 8 mg/L in 2009 thus eliminating the intermediate category. The mecillinam curve in Figure 29 has been adjusted for this change through the whole time period. The breakpoints for susceptibility and resistance for nitrofurantoin were increased from S ≤ 32 mg/L / R > 32 mg/L to S ≤ 64 mg/L / R > 64 mg/L in 2009, but this change has not had any effect on the SIR distribution for nitrofurantoin.

The resistance rates among urinary tract isolates have remained remarkably stable over the last ten years. Approximately 30% of *E. coli* isolates are resistant to ampicillin. The remaining 70% belong to the wild type, which in Norway is categorized as intermediately susceptible. A little more than 20% of *E. coli* isolates are resistant to trimethoprim and trimethoprim-sulfamethoxazole. According to the 2009 breakpoints, resistance to mecillinam has increased slightly to 2.6%, but susceptibility testing is notoriously difficult to reproduce for this agent.

Ciprofloxacin is used as a second-line agent for urinary tract infections in Norway. The prevalence of non-susceptibility has been relatively stable around 3.5 – 4.5% over the last five years. The result for 2009 was 4.7% with 0.6% intermediate susceptibility and 4.1% resistance according to the adjusted interpretation of zone diameters. The corresponding rates for blood culture isolates were 0.3% intermediate susceptibility and 8.3% resistance. The same difference was seen for nalidixic acid with 9.3% resistance in urinary tract isolates and 14.4% resistance in bloodstream infections. One may speculate that systemic infections are caused by selected pathogenic lineages with increased virulence and accumulation of mutations in gyrase and topoisomerase genes, whereas urinary tract isolates are more representative of the wild type normal flora. Nevertheless, the increasing prevalence of first-step mutations in both bloodstream and urinary tract isolates is cause for great concern.

In total, six isolates (0.5%) were reported as ESBL producers. Two were found in hospital patients, while the others were detected in samples submitted from nursing homes and general practitioners. This prevalence is not significantly changed from 2008 (0.7%). The ESBL strains were all resistant to ampicillin, cefuroxime and cefotaxime, but two remained susceptible to ceftazidime and five were reported as mecillinam susceptible. The clinical significance of this *in vitro* susceptibility has not been determined. Most of the ESBL isolates were non-susceptible to quinolones (n=5), gentamicin (n=5) and trimethoprim-sulfamethoxazole (n=5), but remained susceptible to nitrofurantoin (n=5). All isolates were fully susceptible to fosfomycin (MIC 0.75 – 1.5 mg/L) which may be an alternative against multiresistant urinary tract isolates. By molecular characterization it was found that the six isolates harboured CTX-M group 1 (n=3), CTX-M group 9 (n=2) or derepressed AmpC (n=1) determinants. This is in accordance with findings in blood culture isolates and previous surveys. As for blood culture isolates, the ESBL rate would have been significantly higher (1.5%) if it had been reported on the basis of non-susceptibility to cefotaxime and/or ceftazidime without further verification.

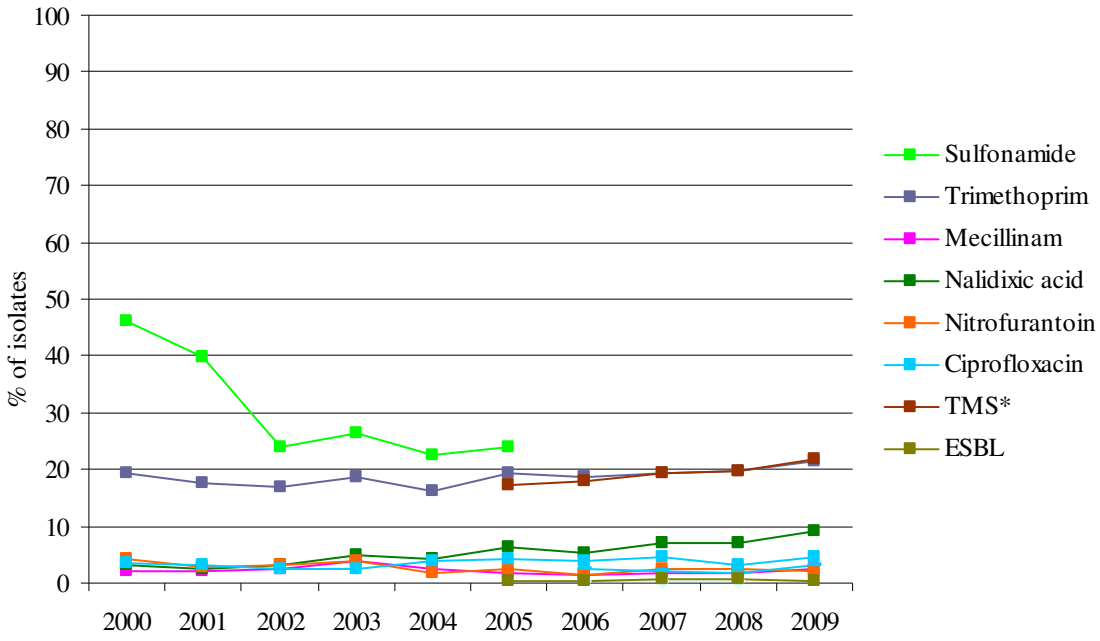


FIGURE 29. Prevalences of non-susceptibility to various antimicrobial agents in urinary tract *E. coli* isolates 2000-2009. The breakpoint for susceptibility to mecillinam was increased from S ≤ 2 mg/L to S ≤ 8 mg/L in 2009. The mecillinam data from 2000 onwards have been recalculated using the 2009 breakpoints. The breakpoints for susceptibility and resistance to nitrofurantoin were increased from S ≤ 32 mg/L and R > 32 mg/L to S ≤ 64 mg/L and R > 64 mg/L in 2009.
*TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in blood cultures

TABLE 31. *Klebsiella* spp. blood culture isolates (n=568). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	94.0	3.5	2.5
Cefuroxime*	≤ 0.5	> 8	0.4	91.9	7.7
Cefotaxime	≤ 1	> 2	94.9	1.8	3.3
Ceftazidime	≤ 1	> 8	97.0	1.4	1.6
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	98.6	0.2	1.2
Tobramycin	≤ 2	> 4	98.2	0.4	1.4
Nalidixic acid	≤ 16	> 16	88.9	-	11.1
Ciprofloxacin	≤ 0.5	> 1	95.8	1.2	3.0
Tigecycline	≤ 1	> 2	88.2	3.3	8.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	85.6	2.8	11.6
ESBL	Negative	Positive	97.4	-	2.6

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

TABLE 32. *Klebsiella pneumoniae* blood culture isolates (n=429). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	94.2	4.2	1.6
Cefuroxime*	≤ 0.5	> 8	0.2	92.6	7.2
Cefotaxime	≤ 1	> 2	94.9	1.6	3.5
Ceftazidime	≤ 1	> 8	96.9	1.2	1.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	98.2	0.2	1.6
Tobramycin	≤ 2	> 4	97.6	0.5	1.9
Nalidixic acid	≤ 16	> 16	86.2	-	13.8
Ciprofloxacin	≤ 0.5	> 1	94.7	1.6	3.7
Tigecycline	≤ 1	> 2	87.1	3.3	9.6
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	83.0	3.0	14.0
ESBL	Negative	Positive	97.0	-	3.0

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

TABLE 33. *Klebsiella oxytoca* blood culture isolates (n=115). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Piperacillin-tazobactam	≤ 8	> 16	93.9	0.0	6.1
Cefuroxime*	≤ 0.5	> 8	0.0	89.6	10.4
Cefotaxime	≤ 1	> 2	94.8	2.6	2.6
Ceftazidime	≤ 1	> 8	97.4	1.7	0.9
Meropenem	≤ 2	> 8	100.0	0.0	0.0
Gentamicin	≤ 2	> 4	100.0	0.0	0.0
Tobramycin	≤ 2	> 4	100.0	0.0	0.0
Nalidixic acid	≤ 16	> 16	98.3	-	1.7
Ciprofloxacin	≤ 0.5	> 1	99.1	0.0	0.9
Tigecycline	≤ 1	> 2	93.9	2.6	3.5
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	94.8	1.7	3.5
ESBL	Negative	Positive	99.1	-	0.9

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

RESULTS AND COMMENTS

The surveillance of *Klebsiella* spp. in blood cultures included 429 *K. pneumoniae* (75.6%), 115 *K. oxytoca* (20.2%), and 24 (4.2%) isolates not identified to the species level, giving a total of 568 *Klebsiella* spp. isolates (Tables 31-33). The species distribution was not significantly changed from 2008. As for *E. coli*, the Norwegian Working Group for Antibiotics (NWGA) has defined the *Klebsiella* spp. wild type as intermediately susceptible to cefuroxime. The breakpoints for antimicrobial agents included in the *Klebsiella* surveillance protocol were not changed in 2009. The SIR distribution for cefpirome is not given as one of the disk suppliers has not defined breakpoints for this agent.

The majority of *Klebsiella* spp. isolates remained fully susceptible to meropenem, tigecycline and aminoglycosides. The prevalence of non-susceptibility to gentamicin continued to increase from 1.0% in 2008 to 1.4% in 2009. There was excellent agreement between gentamicin and tobramycin non-susceptibility. Of note, aminoglycoside resistance was not detected in any *K. oxytoca* isolates. Further surveillance is needed to evaluate the possible emergence of aminoglycoside resistance in *K. pneumoniae* in Norway.

The overall prevalence of resistance to ciprofloxacin has been stable at 3-4% when taking into account the changes in breakpoints and interpretive rules. Non-susceptibility to trimethoprim-sulfamethoxazole is apparently increasing, but the change from 13.9% in 2008 to 14.4% in 2009 was

minor compared to previous years. There was still a significant difference in the prevalence of non-susceptibility to ciprofloxacin and trimethoprim-sulfamethoxazole between *K. pneumoniae* and *K. oxytoca*. Only 0.9% of *K. oxytoca* were non-susceptible to ciprofloxacin and only 5.2% were non-susceptible to trimethoprim-sulfamethoxazole, compared to 5.3% and 17.0% for *K. pneumoniae,* respectively. A comparison of ESBL rates and non-susceptibility to beta-lactam antibiotics is complicated by the diagnostic challenges of the chromosomal K1 beta-lactamase of *K. oxytoca*.

Most *Klebsiella* spp. isolates were susceptible to cefotaxime (94.9%), ceftazidime (97.0%) and the beta-lactam/beta-lactamase inhibitor combination piperacillin-tazobactam (94.0%, Figure 30). Nevertheless, the rate of non-susceptibility to cefotaxime increased from 1.2% in 2008 to 5.1% in 2009, and this was linked to an increasing rate of reported ESBL isolates from 1.0% in 2007 and 2.0% in 2008, to 2.6% in 2009. As for *E. coli*, the detection of extended spectrum beta-lactamases (ESBL) was based on zone diameters of cefotaxime and ceftazidime disks. Isolates with reduced zone diameters were further characterized by combination Etests, and suspected isolates were confirmed by molecular characterization of resistance determinants. A total of 15 isolates (2.6%) were reported as ESBL producers from the laboratories, of which 13 were *K. pneumoniae*, one was *K. oxytoca* and one was unspeciated. All ESBL isolates were resistant to cefotaxime, and most of them displayed non-susceptibility to ceftazidime (11/15). Cross-resistance was relatively common to ciprofloxacin (7/15), trimethoprim-sulfamethoxazole (12/15) and gentamicin (6/15), whereas most isolates were susceptible to piperacillin-tazobactam (12/15), tigecycline (13/15) and meropenem (15/15) Molecular characterization at the Reference Centre for Detection of Antimicrobial Resistance (K-Res) confirmed the presence of CTX-M group 1 (n=9), CTX-M group 9 (n=3) and SHV-2 (n=2) determinants in *K. pneumoniae*. Phenotypical ESBL production in one SHV-1 isolate may indicate the presence of an as yet undescribed ESBL genotype. The *K. oxytoca* isolate only displayed hyperproduction of the chromosomally encoded K1 beta-lactamase.

The overall prevalence of ESBL was not adjusted in spite of the molecular data due to the very limited number of isolates subjected to these analyses. As for *E. coli* blood culture and urinary tract isolates, the ESBL rate would have been significantly higher (5.5%) if it had been reported only on the basis of non-susceptibility to cefotaxime and/or ceftazidime without further verification.

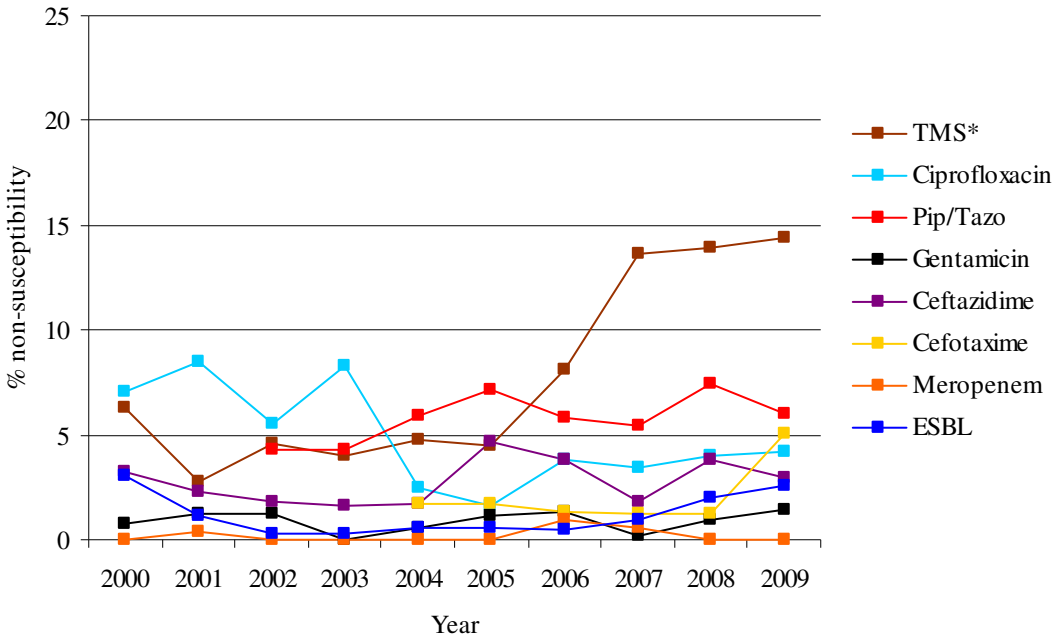


FIGURE 30. Prevalence of non-susceptibility to various antimicrobial agents in *Klebsiella* spp. blood culture isolates 2000-2009. *TMS=Trimethoprim-sulfamethoxazole.

Klebsiella spp. in urine

TABLE 34. *Klebsiella* spp. urinary tract isolates (n=1,004). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	92.0	-	8.0
Cefuroxime*	≤ 0.5	> 8	0.6	93.9	5.5
Cefotaxime	≤ 1	> 2	97.9	0.9	1.2
Ceftazidime	≤ 1	> 8	98.0	1.3	0.7
Gentamicin	≤ 2	> 4	99.1	0.3	0.6
Tobramycin	≤ 2	> 4	98.9	0.8	0.3
Nalidixic acid	≤ 16	> 16	88.8	-	11.2
Ciprofloxacin	≤ 0.5	> 1	97.1	1.1	1.8
Nitrofurantoin	≤ 64	> 64	71.0	-	29.0
Trimethoprim	≤ 2	> 4	80.3	3.5	16.2
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	83.3	3.0	13.7
ESBL	Negative	Positive	99.0	-	1.0

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

TABLE 35. *Klebsiella pneumoniae* urinary tract isolates (n=626). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	92.2	-	7.8
Cefuroxime*	≤ 0.5	> 8	0.2	95.6	4.2
Cefotaxime	≤ 1	> 2	99.0	0.5	0.5
Ceftazidime	≤ 1	> 8	98.1	1.3	0.6
Gentamicin	≤ 2	> 4	99.1	0.3	0.6
Tobramycin	≤ 2	> 4	98.9	0.6	0.5
Nalidixic acid	≤ 16	> 16	87.7	-	12.3
Ciprofloxacin	≤ 0.5	> 1	97.0	0.8	2.2
Nitrofurantoin	≤ 64	> 64	66.9	-	33.1
Trimethoprim	≤ 2	> 4	77.8	3.4	18.8
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	80.8	3.4	15.8
ESBL	Negative	Positive	99.2	-	0.8

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

TABLE 36. *Klebsiella oxytoca* urinary tract isolates (n=126). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Mecillinam	≤ 8	> 8	88.9	-	11.1
Cefuroxime*	≤ 0.5	> 8	0.0	88.9	11.1
Cefotaxime	≤ 1	> 2	94.4	3.2	2.4
Ceftazidime	≤ 1	> 8	97.6	1.6	0.8
Gentamicin	≤ 2	> 4	99.2	0.0	0.8
Tobramycin	≤ 2	> 4	99.2	0.8	0.0
Nalidixic acid	≤ 16	> 16	95.2	-	4.8
Ciprofloxacin	≤ 0.5	> 1	99.2	0.0	0.8
Nitrofurantoin	≤ 64	> 64	94.4	-	5.6
Trimethoprim	≤ 2	> 4	91.3	0.0	8.7
Trimethoprim-sulfamethoxazole**	≤ 2	> 4	92.8	2.4	4.8
ESBL	Negative	Positive	98.4	-	1.6

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

RESULTS AND COMMENTS

Klebsiella spp. isolates have previously been included in the NORM surveillance programme in 2001 and 2003. However, due to methodological changes and adjustment of breakpoints it is not possible to directly compare the results from 2009 with 2001 and 2003.

In general, the rates of resistance to urinary tract antibiotics were comparable between *E. coli* and *Klebsiella* spp. The vast majority of isolates were susceptible to gentamicin (99.1%), tobramycin (98.9%), mecillinam (92.0%), cefotaxime (97.9%) and ceftazidime (98.0%). A total of 94.5% were categorized as intermediately susceptible to cefuroxime in accordance with Norwegian definitions of wild type strains. Susceptibility to trimethoprim (80.3%) and trimethoprim-sulfamethoxazole (83.3%) was only slightly higher than in *E. coli* (78.5% and 78.3%, respectively). However, all *Klebsiella* isolates are by definition resistant to ampicillin due to the chromosomal SHV beta-lactamase, and nitrofurantoin resistance reached 29.0% compared to 2.0% in *E. coli*. Ciprofloxacin non-susceptibility was more prevalent in *E. coli* (4.7%) than in *Klebsiella* spp. (2.9%), but 11.2% resistance to nalidixic acid in *Klebsiella* isolates may indicate increasing problems with quinolone resistance in this genus. *K. oxytoca* isolates were apparently more susceptible than *K. pneumoniae* isolates to quinolones, folic acid antagonists and nitrofurantoin (Tables 34-36).

As for *Klebsiella* spp. from blood cultures, ESBL detection in urinary tract isolates was based on non-susceptibility to cefotaxime and/or ceftazidime and subsequent confirmatory ESBL Etests. Only ten isolates were reported as ESBL positive of which five were *K. pneumoniae*, two were *K. oxytoca* and three were unspeciated. The ten ESBL isolates originated from different hospitals, general practices and long term health care facilities. The 1.0% ESBL rate was lower than the 2.6% rate found in blood culture isolates of the same genus. The ten ESBL isolates were generally non-susceptible to mecillinam (n=8), cefotaxime (n=8), trimethoprim (n=8) and trimethoprim-sulfamethoxazole (n=8), but remained susceptible to gentamicin (n=6), tobramycin (n=7) and ciprofloxacin (n=6). The *K. oxytoca* isolates were susceptible to fosfomycin (MIC 2 – 8 mg/L), whereas the *K. pneumoniae* isolates had MIC values close to or above the breakpoint of 32 mg/L.

Molecular characterization of putative ESBL isolates revealed the presence of CTX-M group 9 (n=3). The other isolates displayed either hyperproduction of chromosomally encoded beta-lactamases (SHV-1 in *K. pneumoniae* and K1 in *K. oxytoca*) or the possible occurrence of an as yet undetermined ESBL genotype. Four of the seven *K. pneumoniae* strains suspected of harbouring an ESBL determinant were resistant to fosfomycin, thus limiting the value of this agent against multiresistant *K. pneumoniae* isolates in the urinary tract. The overall prevalence of ESBL was not adjusted in spite of the molecular data due to the very limited number of isolates subjected to these analyses.

The EUCAST disk diffusion test for routine antimicrobial susceptibility testing

During the last 8 years EUCAST (European Committee on Antimicrobial Susceptibility Testing) has managed to harmonize breakpoints (interpretation criteria) for susceptibility testing for most antibiotics against many bacteria and some fungi. The methods are documented on the web (http://www.eucast.org) and in printed articles in peer-reviewed journals (1-5). A short description of the process of breakpoint setting was published in the 2006 edition of this report (6).

Disk diffusion is one of the oldest approaches to antimicrobial susceptibility testing (AST) and remains one of the most widely used antimicrobial susceptibility testing methods in routine clinical laboratories. It is suitable for testing the majority of bacterial pathogens, including some of the more common fastidious bacteria, is versatile in the range of antimicrobial agents that can be tested and requires little or no special equipment. There have been several different methods in use for AST using disk diffusion. After harmonizing the criteria for breakpoint (BP) setting using an MIC method it was clear that we also needed a method for disk diffusion where the zone diameter BPs were calibrated to the harmonized EUCAST MIC breakpoints.

After a wide consultation with all national breakpoint committees and scientific colleagues throughout Europe it was clear that the majority wanted a method based on Mueller Hinton agar and an inoculum which results in confluent growth. Only some of the countries (mainly from northern part of Europe) favoured the lighter inoculum which results in semi-confluent growth. The method is described in detail on www.eucast.org, and a link to the first edition of the method is available at http://www.eucast.org/fileadmin/src/media/PDFs/ EUCAST_files/Disk_test_documents/Disk_method_description_v1.0.pdf**.**

In common with several other disk diffusion techniques, the EUCAST method is a standardized method based on the principles defined in the report of the International Collaborative Study of Antimicrobial Susceptibility Testing, 1972, and the experience of expert groups worldwide. The zone diameter breakpoints in the EUCAST method are calibrated to the harmonized European breakpoints that are published by EUCAST and are freely available from the EUCAST website (http://www.eucast.org). As with all methods, the described technique must be strictly adhered to in order to produce reliable results.

The method uses Mueller Hinton agar plates (MH) for non-fastidious organisms (e.g. *Enterobacteriaceae*, Staphylococci, Enterococci) and Mueller Hinton agar plates with 5% defibrinated horse blood and 20 mg/L NAD (MH-F) for fastidious organisms like *Streptococcus pneumoniae*, beta-haemolytic streptococci (A, B, C and G), other streptococci, *Haemophilus influenzae* etc. The method describes the amount of agar to be added to each plate (depth of medium of 4 mm $\pm$ 0.5 mm (25 mL in a 90 mm Petri dish)). The preparation of the inoculum is described for both fastidious and non-fastidious organisms. EUCAST recommends a 15 min interval between the preparation of the inoculum, the streaking of the plates and then the application of the disks. EUCAST recommends incubation in air for 16-20 hours for non-fastidious organism and incubation in air with 4-6% CO_2 for 16-20 hours for fastidious organism.

Manufacturers of disks, tablets, media and automated AST systems are working to calibrate their products to the EUCAST standards. Some are ready while others are still facing difficulties. Users of European breakpoints are adviced to consult with EUCAST before choosing AST systems alternative to:

1. MIC-determination using European breakpoints
2. European disk test method calibrated to European breakpoints
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

EUCAST has published some documents to help in implementation of the EUCAST Disk Diffusion Test in clinical microbiological laboratories. EUCAST MIC- and zone diameter breakpoint tables are freely available on the internet (http://www.eucast.org).

Note that in the EUCAST tables, the I-category is not listed. It is implied as the values between the S-breakpoint and the R-breakpoint. For a breakpoint listed as S $\leq$ 1 mg/L and R > 8 mg/L the intermediate category is 2 - 8 (technically > 1 - 8 mg/L). For a breakpoint listed as S $\leq$ 22 mm and R < 18 mm the intermediate category is 18-21 mm. A new version (v.1.1) of the breakpoint tables was released on April 27, 2010. All changes are listed separately on one of the first pages. The zone diameter breakpoints are tentative during 2010. More data correlating MIC to zone diameter will be added and breakpoint correlates refined as needed. EUCAST invites you to participate in the validation of the breakpoints!

1. Kahlmeter G, Brown DFJ, Goldstein FW et al. European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. J Antimicrob Chemother 2003; 52:145-148.
2. Kahlmeter G, Brown DFJ. (2004) Harmonisation of antimicrobial breakpoints in Europe – can it be achieved?. Clinical Microbiology Newsletter 2004; 26:187-192.
3. Kahlmeter G, Brown DFJ, Goldstein FW, et al. Editorial: European Committee on Antimicrobial Susceptibility Testing (EUCAST). CMI 2006; 12:501-503. [Technical Notes Documents]
4. Arendrup MC, Kahlmeter G, Rodriguez-Tudela JL, Donnelly JP. Antimicrob Agents Chemother 2009; 53:1628-9. Breakpoints for Susceptibility Testing Should Not Divide Wild-Type Distributions of Important Target Species
5. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) Steering Committee. EUCAST technical note on linezolid. CMI 2006; 12:1243-124.
6. Steinbakk M. The EUCAST process of vreakpoint setting in antibiotic susceptibility testing, p58-9. In NORM/NORM-VET 2006. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. Tromsø/Oslo 2007. ISSN:1502-2307.

Martin Steinbakk, Department of Bacteriology and Immunology, Norwegian Institute of Publich Health, Oslo.

Staphylococcus aureus in blood cultures

TABLE 37. *Staphylococcus aureus* blood culture isolates (n=929). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	96.2	0.0	3.8
Clindamycin	≤ 0.25	> 0.5	98.4	0.2	1.4
Fusidic acid	≤ 1	> 1	95.5	-	4.5
Ciprofloxacin	≤ 1	> 1	96.4	-	3.6
Gentamicin	≤ 1	> 1	99.1	-	0.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.6	0.1	0.3
Tetracycline	≤ 1	> 2	96.5	0.1	3.4
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	98.4	1.1	0.5
Beta-lactamase	Negative	Positive	29.0	-	71.0
Cefoxitin screen	Negative	Positive	99.0	-	1.0
MRSA (*mecA*)	Negative	Positive	99.6	-	0.4
Vancomycin screen	Negative	Positive	100.0	-	0.0

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

RESULTS AND COMMENTS

Four methicillin resistant *S. aureus* (MRSA) isolates were detected in the NORM surveillance system in 2009 (Table 37) corresponding to a prevalence of 0.4%. This is a slight decrease from 0.7% in 2008. The resistance phenotype was confirmed by *mecA* PCR in all cases.

Laboratory screening for MRSA in NORM is performed using cefoxitin disks. All MRSA isolates had cefoxitin zone diameters below the screening breakpoint. Cross resistance was detected towards ciprofloxacin (2/4) and erythromycin (2/4). All MRSA isolates were fully susceptible to gentamicin, linezolid, rifampicin, vancomycin and trimethoprim-sulfamethoxazole. Five methicillin susceptible *S. aureus* (MSSA) isolates (0.5%) displayed reduced cefoxitin zone diameters but were not confirmed as MRSA by genotypic analysis. All these isolates had cefoxitin zone diameters within two millimeters of the screening breakpoint.

The findings are in accordance with reports from the databases of the participating laboratories where seven out of 1,344 (0.5%) *S. aureus* blood culture isolates were MRSA. None of the 15 *S. aureus* isolates recovered from cerebrospinal fluids were methicillin resistant, thus bringing the total number of systemic MRSA isolates to 7/1,359 (0.5%). The Norwegian Surveillance System for Communicable Diseases (MSIS) reported a total number of 816 MRSA cases in 2008. This is a 25% increase from 652 cases in 2008. However, the cases reported to MSIS were predominantly skin and soft tissue infections (80% of infections) and colonisations (n=402). The number of MRSA infections increased to 414 in 2009 compared to 348 in 2008 (+19%), and the number of MRSA colonisations from 304 in 2008 to 402 in 2009 (+32%). Further information about MRSA cases in MSIS is presented on page 61.

A total of 40 *S. aureus* isolates (3.8%) were non-susceptible to erythromycin. This is a minor decrease from 2008 (4.6%). The macrolide resistance phenotypes were determined by the double disk diffusion (DDD) test. Eight (23%) were constitutively MLS_B resistant, 19 (54%) were inducibly MLS_B resistant and eight (23%) displayed efflux mediated M type resistance. These figures represent 0.9%, 2.0% and 0.9% of all *S. aureus* isolates from blood cultures, respectively. The distribution of macrolide resistance phenotypes was similar to the results from previous years.

The prevalence of resistance to fusidic acid remained unchanged in 2009 (4.5%) compared to 2008 (4.6%) and 2007 (4.2%). This may indicate that the epidemiology of fusidic acid resistant *S. aureus* has now stabilized in Norway. There were no significant changes for ciprofloxacin, gentamicin, rifampicin or trimethoprim-sulfamethoxazole. No isolates displayed growth on the vancomycin agar screen, and all isolates were fully susceptible to linezolid. Figure 31 shows the prevalences of non-susceptibility to various antimicrobials. A total of 71.0% of the isolates were beta-lactamase positive which is unchanged from previous years. A subgroup analysis revealed that beta-lactamase positive isolates were more often resistant than beta-lactamase negative isolates to ciprofloxacin (4.1% vs 2.2%), fusidic acid (5.3% vs 2.6%), erythromycin (4.2% vs 2.6%), clindamycin (1.8% vs 1.1%) and tetracycline (4.5% vs 1.1%).

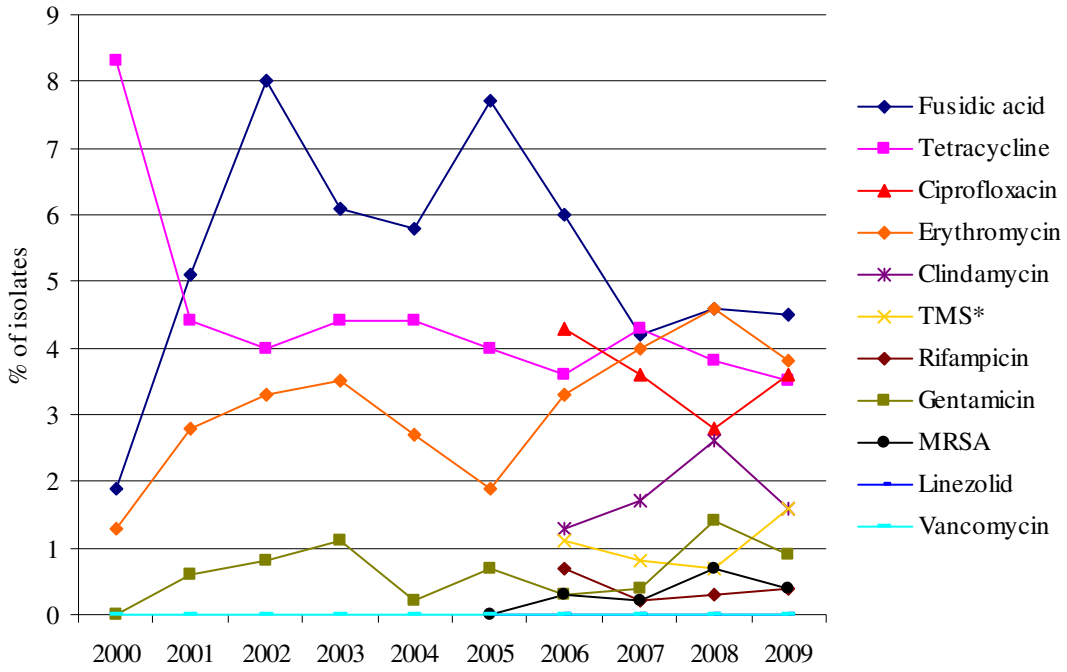


FIGURE 31. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* blood culture isolates 2000-2009. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

Staphylococcus aureus in wound specimens

TABLE 38. *Staphylococcus aureus* isolates from wound specimens (n=1,763). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Erythromycin	≤ 1	> 2	95.3	0.1	4.6
Clindamycin	≤ 0.25	> 0.5	98.1	0.4	1.5
Fusidic acid	≤ 1	> 1	91.9	-	8.1
Ciprofloxacin	≤ 1	> 1	97.0	-	3.0
Gentamicin	≤ 1	> 1	99.6	-	0.4
Linezolid	≤ 4	> 4	100.0	-	0.0
Rifampicin	≤ 0.06	> 0.5	99.6	0.2	0.2
Tetracycline	≤ 1	> 2	94.8	0.2	5.0
Trimethoprim-sulfamethoxazole*	≤ 2	> 4	98.7	0.7	0.6
Beta-lactamase	Negative	Positive	27.5	-	72.5
Cefoxitin screen	Negative	Positive	99.0	-	1.0
MRSA (*mecA*)	Negative	Positive	99.2	-	0.8
Vancomycin screen	Negative	Positive	100.0	-	0.0

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

RESULTS AND COMMENTS

S. aureus from wound specimens were screened for methicillin resistance by the cefoxitin disk method in the same way as blood culture isolates. Fourteen out of 1,763 (0.8%) isolates were confirmed as MRSA by *mecA* PCR. This is about the same prevalence as in 2008 (0.7%) and slightly higher than in blood cultures (0.4%, see above). The 14 MRSA isolates all displayed cefoxitin zone diameters below the screening breakpoints for the respective test systems. Some of the MRSA isolates were cross-resistant to ciprofloxacin (4/14), gentamicin (4/14), tetracycline (3/14) and/or fusidic acid (3/14). Seven isolates were resistant to erythromycin, and four of these were constitutively resistant to clindamycin. All MRSA isolates were susceptible to rifampicin, linezolid and vancomycin. Only four out of 1,749 MSSA isolates were false positive by the cefoxitin test (0.2%), and none of these isolates had zone diameters more than two millimeters below the sceening breakpoint.

The high prevalence of resistance to fusidic acid in *S. aureus* wound isolates continued to decline from 25.0% in 2004, 14.5% in 2006, 11.1% in 2007 and 10.3% in 2008, to 8.1% in 2009, see Table 38 and Figure 32. One may speculate that this is due to herd immunity to the fusidic acid resistant clone which has caused a high incidence of bullous impetigo in previous years. The prevalence of resistance to fusidic acid is still significantly lower in blood culture isolates (4.5%). For other antimicrobial agents such as tetracycline and erythromycin there were only minor changes from 2008 to 2009, and the prevalences of non-susceptibility were in general similar for blood culture isolates and isolates from wound specimens. A total of 83 (4.7%) isolates were non-susceptible to erythromycin, and 81 of these were further examined for determination of resistance phenotype. The majority (46/81, 57% of macrolide resistant isolates) were inducibly resistant to clindamycin, thus representing the $iMLS_B$ phenotype. Only a few isolates were either constitutively resistant to clindamycin (n=19) or low-level resistant to erythromycin (n=16), expressing efflux mediated M type resistance. The findings are in accordance with the results from blood culture isolates.

A total of 72.5% of the isolates were beta-lactamase positive, which is unchanged from 2008. Resistance to fusidic acid was significantly more common among the 1,279 beta-lactamase positive isolates (9.4%) than among the 484 beta-lactamase negative ones (4.8%). A similar trend was seen for erythromycin (5.1% vs 3.7%) and tetracycline (6.2% vs 2.7%), but the opposite was the case for ciprofloxacin with 4.1% resistance in beta-lactamase negative isolates and 2.6% resistance in beta-lactamase positive ones.

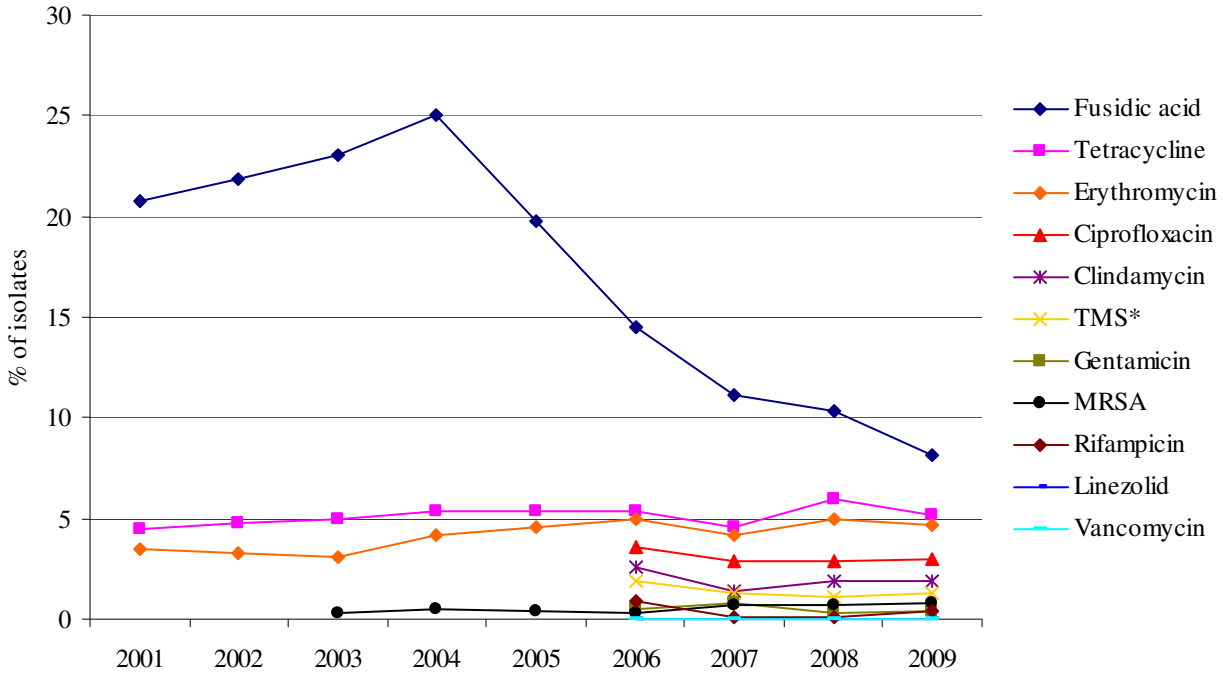


FIGURE 32. Prevalences of non-susceptibility to various antimicrobial agents among *Staphylococcus aureus* wound isolates 2000 – 2009. Doxycycline was replaced by tetracycline in 2006. *TMS=Trimethoprim-sulfamethoxazole.

MRSA infections in humans in Norway 2009

Infections with methicillin resistant *Staphylococcus aureus* (MRSA) have been notifiable in Norway since 1995 and colonisation without infection was made notifiable in 2005. A total of 816 cases of MRSA were notified in 2009. Among these, 414 cases were reported as infections and 402 as colonizations (Fig. 33). Males and females were equally affected. At the time of diagnosis 152 (19%) were inpatients, 63 (8%) were residents in nursing homes, and 572 (70%) were outpatients (Fig. 34). Fifty-five persons were reported as health care workers, of whom 42 were colonised with MRSA and 13 had MRSA-infections.
The main objective of the Norwegian MRSA guidelines is to prevent MRSA from becoming endemic in health care institutions. So far this objective has been fulfilled. In the last four years the number of hospitalised patients notified with MRSA has flattened out, and there has been a clear decline in the number of nursing home residents notified with MRSA.
The majority of the 414 cases notified with MRSA-infections were reported with a clinical picture of skin- or wound infections (80% of reported infections). Thirty-five cases were notified with other non-severe infections, while 12 were reported with systemic infections or infections in inner organs.
The measured increase in MRSA detections has to be interpreted with caution. Throughout the whole surveillance period there has never been more than 18 cases annually notified with an infection in the bloodstream, central nervous system or inner organs. Less than 10 cases annually have been reported with MRSA bloodstream infections. The low incidence of severe MRSA infections corresponds with the results of the NORM surveillance system where less than 1% of *Staphylococcus aureus* isolates are resistant to methicillin. This may indicate that the increasing number of MRSA colonisations and non-severe infections, mainly among outpatients, to a large extend is a result of more active screening and contact tracing, while the stable low number of severe infections indicates that the incidence of MRSA in the general population still is on a low level.

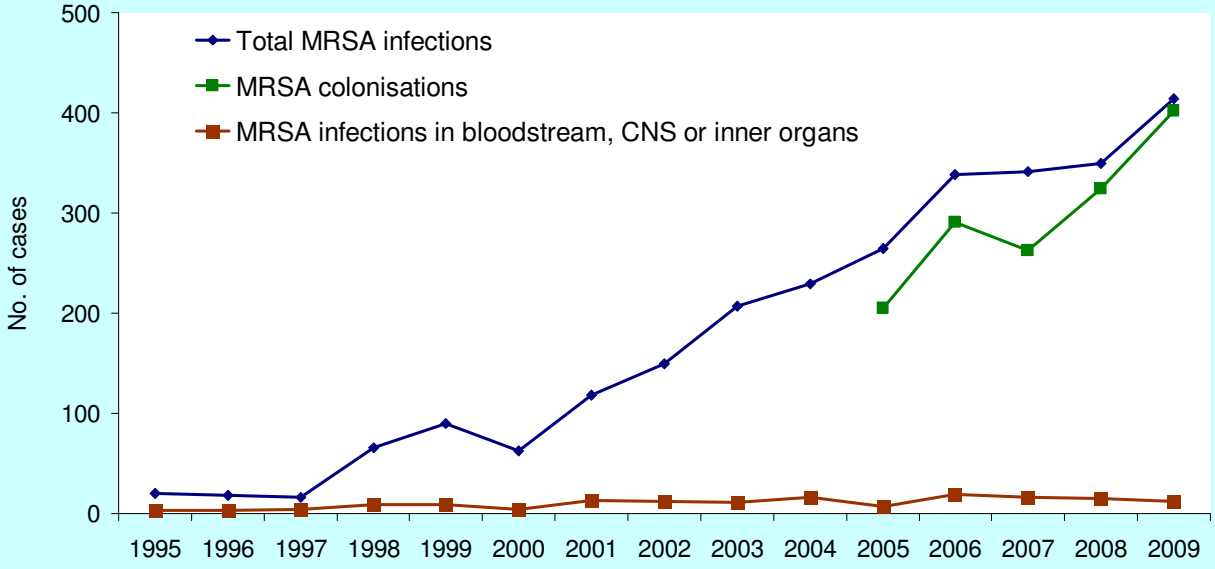


FIGURE 33. Reported cases of MRSA infection (1995 – 2009) and MRSA colonisation (2005 – 2009).

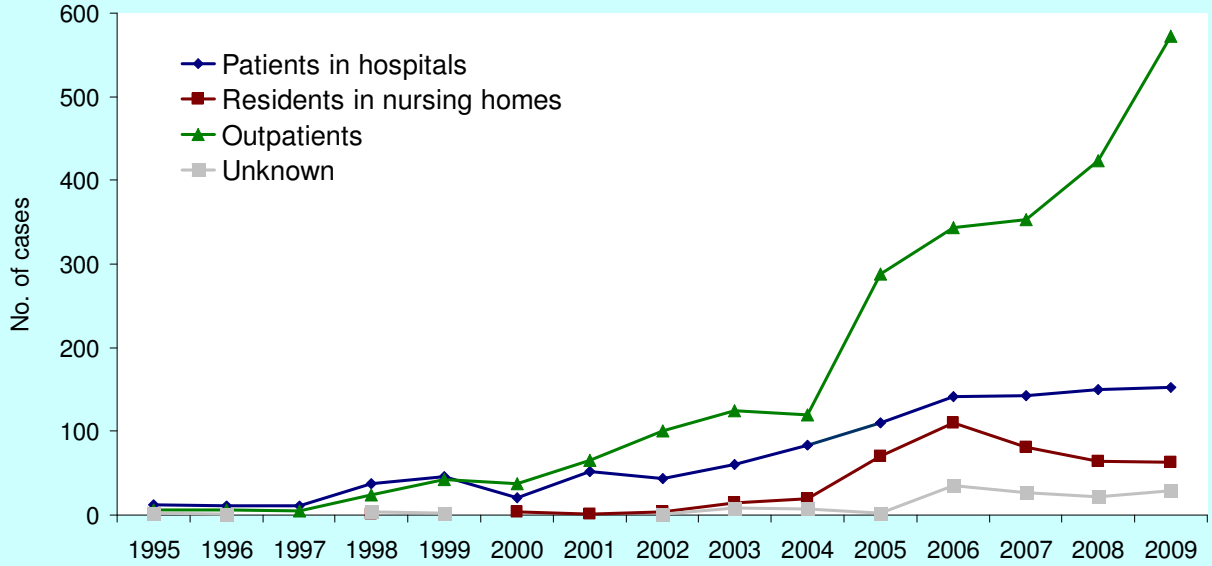


FIGURE 34. Reported cases of MRSA infections and colonisations in Norway 1995 – 2009 by type of health care contact.

Among the 414 cases reported as MRSA-infections, we found 109 different spa-types in 2009. The five most frequent were t008 (14.7%), t019 (9.7%), t002 (9.7%), t044 (6.8%) and t437 (4.8%). The ten most frequent spa-types reported as infections accounted for 53.3% of all the isolates reported as MRSA-infections. In total they accounted for 48.5% of all the strains compared to 53.1% in 2007 and 58% in 2008. Regarding PVL, 51% of the strains were found positive. If we isolate the five most common spa-types causing infections, the PVL positive rate has increased to 82.3%.

TABLE 39. Most frequent spa-types causing infection distributed on clinical diagnosis.

Clinical diagnosis	Spa-types (n)					
	Total	t008	t019	t002	t044	t437
Skin and soft tissue infection	334	55	35	25	25	17
Urinary tract infection	11	2		2		
Blood stream infection	6	1		1		
Respiratory tract infection	8			2		1
Bone and joint infection	1					
Meningitis	1					
Others	26	1		6		1
Unknown	27	2	5	4	3	1
Total	414*	61	40	40	28	20

* 28 of the strains causing infections were not received by the Reference Laboratory.

Among the 402 cases reported as colonisations, we found 115 different spa-types in 2009. The five most frequent were t002 (11.7%), t008 (6.2%), t032 (6.2%), t044 (4.2%) and t019 (3.7%). The ten most frequent spa-types reported as colonisations accounted for 45% of all the isolates. Regarding PVL, 20.9% of the strains were found positive.

TABLE 40. Most frequent spa-types associated with colonisation.

	Spa-types (n)					
	Total	t002	t008	t032	t044	t019
Carriers	402*	47	25	25	17	15

* 13 of the strains associated with colonisation were not received by the Reference Laboratory.

Petter Elstrøm, Norwegian Institute of Public Health, Oslo.
Trond Jacobsen, Lillian Marstein, Anne Kilnes, Frode Width Gran, Norwegian Reference Laboratory on MRSA, St. Olavs University Hospital, Trondheim.

Enterococcus spp. in blood cultures

TABLE 41. *Enterococcus* spp. blood culture isolates (n=550). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	81.8	0.2	18.0
Gentamicin	≤ 128	> 128	67.8	-	32.2
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 8	98.2	-	1.8

TABLE 42. *Enterococcus faecalis* blood culture isolates (n=402). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	100.0	0.0	0.0
Gentamicin	≤ 128	> 128	70.1	-	29.9
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 8	100.0	-	0.0

TABLE 43. *Enterococcus faecium* blood culture isolates (n=116). Sampling, laboratory methods, and data handling are described in Appendix 5. Distributions of zone diameters are available at www.antibiotikaresistens.no.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Ampicillin	≤ 4	> 8	17.2	0.9	81.9
Gentamicin	≤ 128	> 128	55.2	-	44.8
Linezolid	≤ 4	> 4	100.0	-	0.0
Vancomycin	≤ 4	> 8	100.0	-	0.0

RESULTS AND COMMENTS

As in previous years, enterococci were analysed both as a group and separately for *E. faecalis* and *E. faecium*. The results for each species are microbiologically more valid as resistance rates differ significantly between *E. faecalis* and *E. faecium*. However, overall rates of resistance are of interest when formulating empirical treatment strategies because they include the probability of systemic infections with each enterococcal species. The overall results for enterococci are presented in Table 41. The surveillance in NORM 2009 included 402 (73.1%) *E. faecalis* isolates, 116 (21.1%) *E. faecium* isolates and 32 (5.8%) unspeciated enterococcal isolates. The proportion of isolates not speciated to the genus level or identified as *E. faecalis* or *E. faecium* has decreased over the last four years.

The panel of antimicrobial agents examined was unchanged from 2008. Streptomycin is not included in the printed tables as one of the disk diffusion systems does not provide breakpoints for this substance. Distributions of zone diameters for both systems are available at www.antibiotikaresistens.no. The breakpoint for susceptibility to ampicillin was increased from S ≤ 2 mg/L to S ≤ 4 mg/L in 2009. The results from previous years have been recalculated according to the new breakpoint.

E. faecalis was universally susceptible to ampicillin (Table 42). The prevalence of non-susceptibility to ampicillin in *E. faecium* remained relatively stable at 82.8% compared to 78.2% in 2008, 80.3% in 2007 and 82.7% in 2006 (Table 43 and Figure 35). The prevalence of high-level gentamicin resistance (HLGR) in *E. faecalis* decreased from 34.4% in 2008 to 29.9% in 2009 (Figure 36). The same trend was seen in *E. faecium* where the prevalence of HLGR decreased from 55.1% in 2007 and 53.6% in 2008 to 44.8% in 2009. Virtually all (49/52, 94.2%) HLGR *E. faecium* isolates were concomitantly non-susceptible to ampicillin. Conversely, 49 out of 96 (51.0%) ampicillin non-susceptible *E. faecium* also displayed HLGR. These findings are similar to the results from previous years.

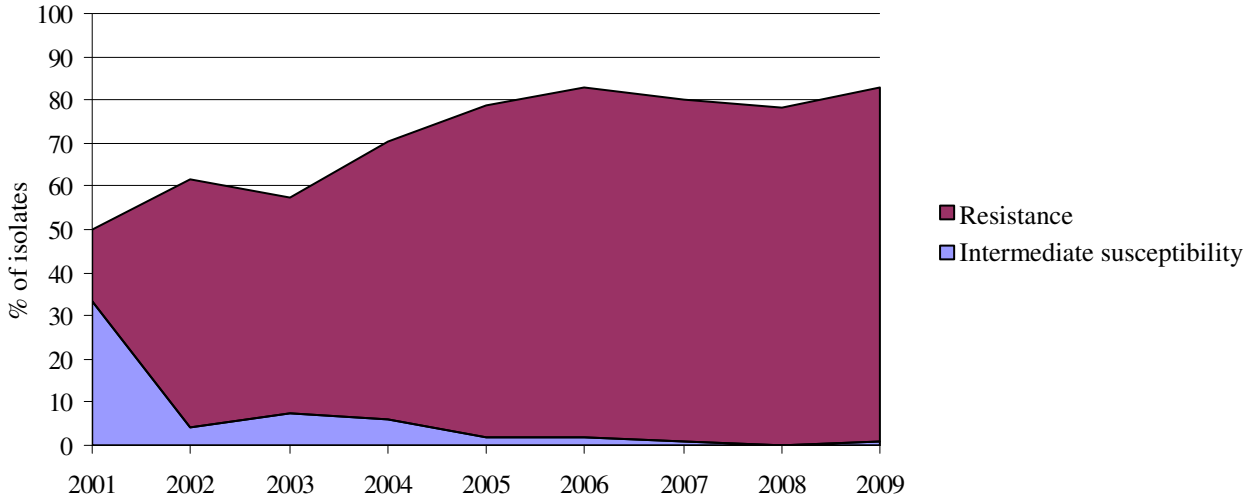


FIGURE 35. Prevalence of intermediate susceptibility and resistance to ampicillin in *E. facium* blood culture isolates 2001-2009. The results are interpreted according to the 2009 breakpoint protocol of S ≤ 4 mg/L and R > 8 mg/L.

The strong linkage between ampicillin resistance and HLGR may indicate the continuing presence of the internationally disseminated *E. faecium* clonal complex (CC) 17 which is non-susceptible to ampicillin and often harbors high-level resistance to aminoglycosides and vancomycin. The wide dissemination of high-level gentamicin resistance in enterococci is of great concern as it abolishes the bactericidal synergy between aminoglycosides and beta-lactams often used for treatment of severe enterococcal infections.

Transferable vancomycin resistance has not yet been established in clinical enterococcal isolates in Norway. Ten isolates were reported as vancomycin resistant (1.8%), but only a single one contained transferable glycopeptide resistance. The phenotypical high-level resistance to vancomycin and teicoplanin was confirmed by a positive *vanA* PCR. The remaining vancomycin resistant isolates were all registered as either *E. gallinarum* (n=5) or *E. casseliflavus* (n=4) which are inherently low-level resistant to vancomycin due to expression of the VanC ligase. All the ten isolates were fully susceptible to linezolid.

FIGURE 36. Prevalence of high-level resistance to gentamicin in blood culture isolates of *E. faecalis*, *E. faecium* and all enterococci combined during 2000-2009. The breakpoint for high-level resistance was decreased from R ≥ 1,024 mg/L to R > 128 mg/L in 2004.

Nationwide outbreak of a vancomycin-resistant *Enterococcus faecium* with *vanB* in Sweden

Vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE) in infection as well as colonization, have been mandatory notifiable according to the Swedish Communicable Diseases Act since year 2000. Mandatory contact tracing was implemented 2004. The basic epidemiological information of the notified cases has been given in the SWEDERES report for *Enterococcus faecalis* and *Enterococcus faecium*. In this highlighted area we describe the rise and decline of this widespread dissemination in more detail.

The recognition of an outbreak situation in 2007 lead to intensive contact tracing and screening activities and also to other infection control measures. Since August 2007 until the end of 2009 altogether 1,057 cases of VRE were found and reported from 17 counties. Of these, 11 counties reported 986 cases as acquired domestically, and a majority of these (95%, n=941) were healthcare-related. Among the domestic cases only 7% had clinical symptoms. 73% were identified through contact tracing, 13% by screening, and for 7% the indication for sampling was unknown. According to the first laboratory notifications of the domestic cases 88% (n=868) were isolated from faeces, 3.5% (n=35) from urine, 3.5% (n=34) from wounds, and 4 cases (0.4%) isolated from blood.

Typing and antibiotic resistance of the epidemic VRE

Verification by PCR of species and vancomycin resistance mechanism showed that 856 of the domestic cases were *E. faecium* with *vanB* gene, 125 *E. faecium* with *vanA* gene and in five cases the resistance gene was not reported. *E. faecalis* were reported for only 9 cases during the whole period, six with *vanA* gene and in three cases the resistance gene was not reported. The species and resistance genotype distribution per county for the 941 domestic cases reported as healthcare-related are presented in Table 44.

TABLE 44. Species and resistance genotype for the domestic, healthcare-related VRE cases, August 1st 2007 to 31st December 2009.

County	Number of cases	Efm*, *vanA*	Efm*, *vanB**	Efs*, *vanA*	Efs*, *vanB*
Stockholm	571	110	463	2	-
Västmanland	211	2	207	1	-
Halland	138	2	136	-	-
Uppsala	9	-	8	-	-
Gotland	4	-	3	1	-
Skåne	4	-	4	-	-
Västra Götaland	2	-	2	-	-
Värmland	1	-	1	-	-
Västerbotten	1	-	1	-	-

* Efm =*Enterococcus faecium*, Efs = *Enterococcus faecalis* . The numbers per county of species and resistance genotype do not always match exactly with the total number of cases due to double infections or missing information of resistance genotype.

Epidemiological typing of the *E. faecium* isolates with *vanB* gene was performed by PFGE. The results showed that all examined isolates from Västmanland and Halland, as well as the majority of the isolates from Stockholm County, had closely related PFGE patterns, suggesting dissemination of the same strain in these counties. Preliminary, but still incomplete, data indicate that this pattern has not been seen in VRE isolates reported before 2007 in Sweden. Moreover, this PFGE pattern could not be recognised in a large collection of recent VRE isolates from Germany (G Werner, personal communication).

The isolates of the epidemic strain were typically resistant to vancomycin (MICs 8-64 mg/L) but susceptible to teicoplanin (MICs 0.125-1 mg/L), and they were also resistant to ampicillin, imipenem, ciprofloxacin and macrolides but showed only low-level resistance to gentamicin. The epidemic curve for the domestic, healthcare-related cases of *E. faecium* with *vanB* (n=825) is presented in Figure 37.

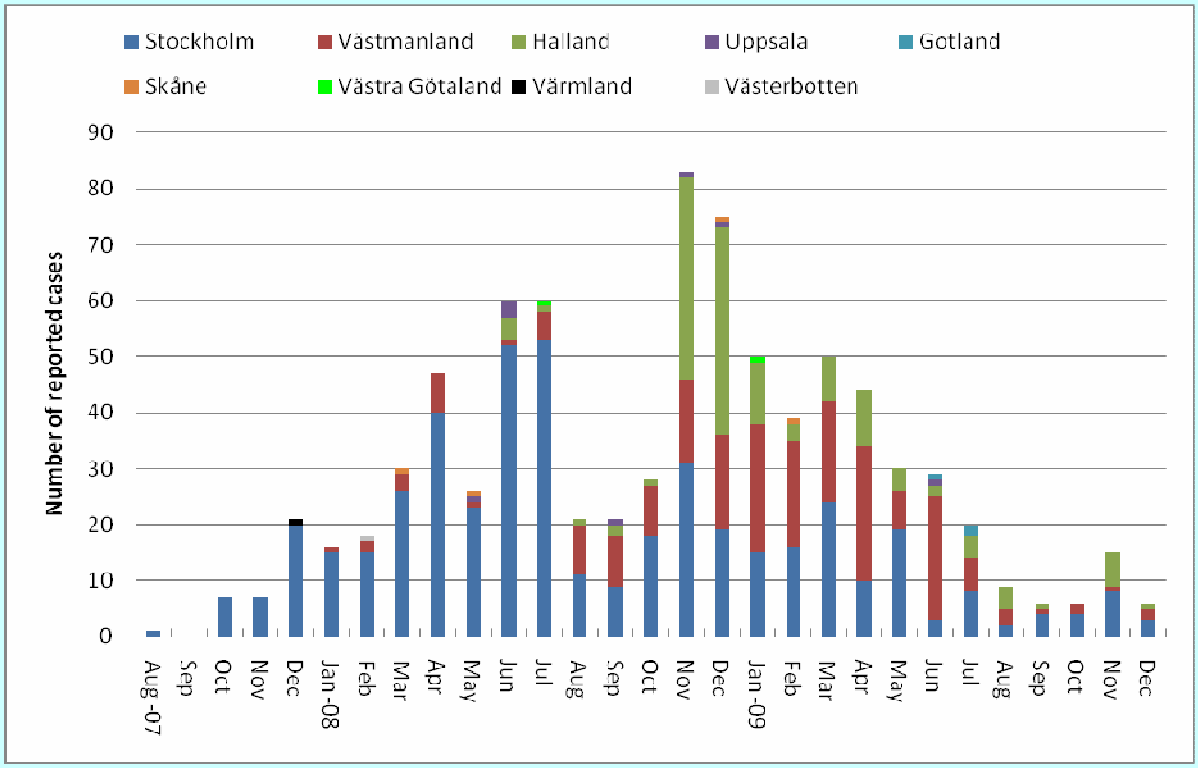


FIGURE 37. Epidemic curve for spread of healthcare-related domestic *Enterococcus faecium* with *vanB* (n=825).

Conclusions

Intensive efforts have been made in the respective regions, with support from national authorities, to control the outbreaks and disseminations of VRE. Control measures and interventions have consisted of increased awareness of hand hygiene, not only for staff but also for patients, withdrawing of food buffets from the hospital wards, extensive cleaning of the patient environment, and use of probiotics (*Lactobacillus rhamnosus* GG). At the end of 2009 there was a dramatic decrease in the number of newly detected cases, but it is too early to state that this will be a permanent situation. A central field epidemiology group was recruited for an assessment of the management of the outbreaks. Based on its report and on expertise presented at a timely workshop in December 2008, a new nation-wide action-programme will soon be launched.

Tomas Söderblom, Dep of Epidemiology, Swedish Institute for Infectious Disease Control; Olov Aspevall, Infection Control, Karolinska University Hospital Huddinge; Mats Erntell, Communicable Disease Control, Halland; Ingegerd Sjögren, Dep of Clinical Microbiology, Halmstad Hospital; Göran Hedin, Dep of Clinical Microbiology, Falun Hospital; Daniel Heimer, Dep of Clinical Microbiology and Infection Control, Västerås Hospital; Ingegerd Hökeberg, Communicable Disease Control, Stockholm; Karin Kidd-Ljunggren, Infection Control, Halmstad Hospital; Åsa Melhus, Dep of Clinical Microbiology, Uppsala Akademiska University Hospital; Barbro Olsson-Liljequist, Dep of Bacteriology, Swedish Institute for Infectious Disease Control; Jan Smedjegård, Communicable Disease Control, Västmanland; Staffan Sylvan, Communicable Disease Control, Uppsala; Karin Tegmark-Wisell, Dep of Bacteriology, Swedish Institute for Infectious Disease Control; Magnus Thore, Dep of Bacteriology, Swedish Institute for Infectious Disease Control; Johan Struwe, Strama/Dep of Epidemiology, Swedish Institute for Infectious Disease Control.

Streptococcus pneumoniae in blood cultures and cerebrospinal fluids

TABLE 45. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=784). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.06	> 2	97.1	2.9	0.0
Cefotaxime	≤ 0.5	> 2	99.9	0.1	0.0
Ceftriaxone	≤ 0.5	> 2	99.9	0.1	0.0
Erythromycin	≤ 0.25	> 0.5	95.4	0.0	4.6
Clindamycin	≤ 0.5	> 0.5	98.2	-	1.8
Tetracycline	≤ 1	> 2	97.1	0.0	2.9
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	96.2	0.9	2.9
Chloramphenicol	≤ 8	> 8	99.6	-	0.4
Oxacillin screen (mm)	≥ 20	< 20	95.7	-	4.3

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

TABLE 46. *Streptococcus pneumoniae* in blood cultures and cerebrospinal fluids (n=784). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G		10.2	77.4	8.0	1.4	1.3	0.1	0.9	0.6							
Cefotaxime		6.9	80.2	7.3	2.4	1.4	0.5	1.1	0.1							
Ceftriaxone		11.5	73.5	10.2	2.0	1.0	0.8	0.9	0.1							
Erythromycin			0.1		0.8	57.0	37.5			0.1	0.4	1.4	0.9		0.1	1.7
Clindamycin			0.1	0.4	19.1	69.5	8.9	0.1	0.1							1.7
Tetracycline			0.1		4.8	89.8	2.2	0.1			0.4	1.0	0.9	0.6		
TMS**					0.1	15.4	68.0	8.7	4.0	0.9	0.5	1.1	0.5	0.8		
Chloramph.									0.3	34.3	65.1		0.4			
Norfloxacin										2.7	44.3	51.1	1.5	0.1		0.3

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	4.3	0.4	0.3	1.9	3.2	5.7	10.5	13.0	21.3	19.8	10.5	7.4	1.3	0.3	0.1	0.1

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

RESULTS AND COMMENTS

The results are summarized in Tables 45-46 and Figures 38-39. All systemic *S. pneumoniae* isolates submitted to the reference laboratory at the Norwegian Institute of Public Health during 2009 were included in the surveillance protocol. The sample size was therefore increased from 507 isolates in 2008 to 784 in 2009. Twenty-six isolates were recovered from cerebrospinal fluids, and seven of these were found in patients who had positive blood cultures with growth of pneumococci. Both blood culture isolates and isolates from cerebrospinal fluids were included from patients with positive cultures from both materials.

The general breakpoint for resistance to penicillin G was increased from R > 1 mg/L to R > 2 mg/L in 2009. In cases of meningitis, a breakpoint for resistance of R > 0.06 mg/L should be used. The breakpoint for susceptibility to tetracycline was decreased from S ≤ 2 mg/L to S ≤ 1 mg/L, whereas the breakpoint for susceptibility to trimethoprim-sulfamethoxazole was increased from S ≤ 0.5 mg/L to S ≤ 1 mg/L. The breakpoints for resistance remained unchanged for both substances. In the following, all historical data are recategorized according to the new breakpoints. In 2009, cefuroxime was omitted from the protocol whereas ceftriaxone and chloramphenicol were added.

A total of 2.9% (23/784) *S. pneumoniae* isolates were non-susceptible to penicillin G. Four of these isolates were recovered from the cerebrospinal fluids of three patients and should therefore be categorized as resistant (MIC 0.125 – 0.5 mg/L). The remaining 19 blood culture isolates (two of them from one patient with concomitant penicillin resistant pneumococci in the cerebrospinal fluid) were intermediately susceptible to penicillin G (MIC 0.125 – 1 mg/L). The prevalence of non-susceptibility to penicillin was on the same level as in 2008 (3.0%). A single blood culture isolate was intermediately susceptible to cefotaxime (1 mg/L) and ceftriaxone (1 mg/L). This isolate had penicillin G MIC of 1 mg/L. No penicillin G susceptible isolates displayed reduced susceptibility to

cephalosporins. The oxacillin screening disk is often used to discriminate between penicillin susceptible and non-susceptible isolates. All the 23 penicillin G non-susceptible isolates were resistant to oxacillin. Conversely, 11 penicillin G susceptible isolates were oxacillin resistant. The sensitivity and specificity of the screening test was thus 100.0% and 98.6%, respectively. Many of the penicillin non-susceptible *S. pneumoniae* isolates were concomitantly non-susceptible to erythromycin (12/23), trimethoprim-sulfamethoxazole (12/23) and tetracycline (10/23).

The decrease in the prevalence of macrolide resistance seen in previous years continued in 2009 (Figure 37). A total of 4.6% of the isolates were erythromycin resistant in 2009 compared to 8.3% in 2008 and 9.4% in 2007. The results support the hypothesis that the epidemiology of systemic *S. pneumoniae* infections is changing with decreasing absolute numbers and proportions of resistant serotypes included in the 7-valent conjugated pneumococcal vaccine (PCV-7). Among the 36 erythromycin non-susceptible isolates, 35 were subjected to double disk diffusion (DDD) tests for characterization of MLS phenotypes. A majority of isolates (n=22, 62.8% of erythromycin non-susceptible isolates, 2.9% of all isolates) displayed a phenotype compatible with efflux-based M-type resistance to erythromycin only. The remaining isolates were either inducibly (n=1, 2.9% of erythromycin non-susceptible isolates, 0.1% of all isolates) or constitutively (n=12, 34.3% of erythromycin non-susceptible isolates, 1.6% of all isolates) resistant to clindamycin, thus indicating the presence of *erm*-encoded MLS resistance to both macrolides and lincosamides. The distribution of MLS phenotypes was not significantly altered from 2008. Further studies are needed to explore the relationship between vaccination, incidence of systemic pneumococcal infections, serotype distribution and burden of resistance in different age groups.

There was a minor decrease in the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole from 6.6% in 2007 and 5.4% in 2008, to 3.8% in 2009. Similarly, the prevalence of non-susceptibility to tetracycline decreased from 5.2% in 2007 and 4.4% in 2008, to 2.9% in 2009 (Figure 38). The low prevalence of high-level norfloxacin resistance (Table 46) reflects that levofloxacin and other "respiratory fluoroquinolones" are not marketed in Norway.

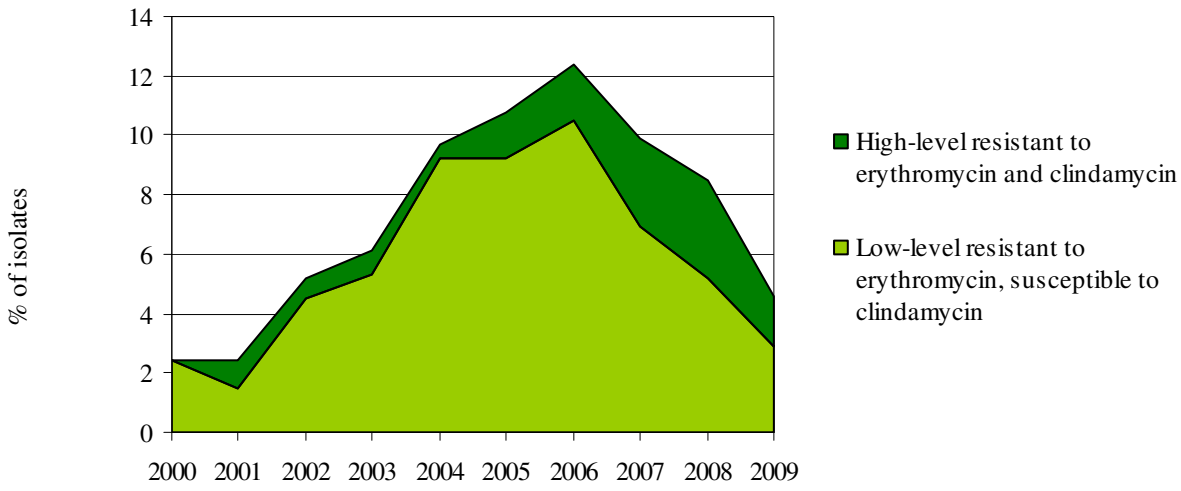


FIGURE 38. Prevalence (%) of macrolide non-susceptible *Streptococcus pneumoniae* blood culture isolates with constitutive or inducible MLS_B phenotype (high-level resistance to erythromycin and clindamycin) and M phenotype resistance (low-level resistance to erythromycin, susceptibility to clindamycin) 2000-2009. A breakpoint for susceptibility of S ≤ 0.25 mg/L was used for inclusion of isolates which were subsequently categorized on the basis of the double disk diffusion (DDD) test.

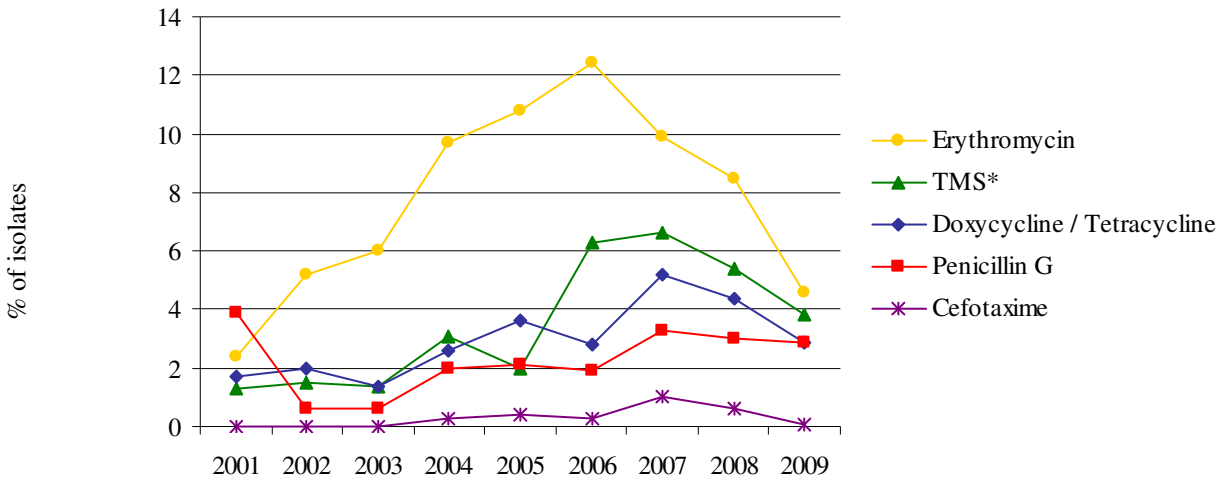


FIGURE 39. Prevalences (%) of non-susceptibility to various antimicrobial agents in *Streptococcus pneumoniae* blood culture isolates during 2000-2009. Doxycycline was substituted by tetracycline in 2005. All results are categorized according to the 2009 breakpoint protocol. *TMS=Trimethoprim-sulfamethoxazole.

Streptococcus pneumoniae in respiratory tract specimens

TABLE 47. *Streptococcus pneumoniae* respiratory tract isolates (n=551). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.06	> 2	96.2	3.6	0.2
Cefotaxime	≤ 0.5	> 2	99.6	0.4	0.0
Ceftriaxone	≤ 0.5	> 2	99.6	0.4	0.0
Erythromycin	≤ 0.25	> 0.5	92.4	0.2	7.4
Clindamycin	≤ 0.5	> 0.5	96.2	-	3.8
Tetracycline	≤ 1	> 2	92.6	0.7	6.7
Trimethoprim-sulfamethoxazole*	≤ 1	> 2	92.9	3.3	3.8
Chloramphenicol	≤ 8	> 8	99.5	-	0.5
Oxacillin screen (mm)	≥ 20	< 20	95.5	-	4.5

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

TABLE 48. *Streptococcus pneumoniae* respiratory tract isolates (n=551). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G	7.3	24.7	53.7	9.3	1.3	1.8	1.3		0.5		0.2					
Cefotaxime	0.2	9.4	54.8	26.0	3.8	4.4	0.9	0.2	0.2	0.2						
Ceftriaxone		8.7	58.4	22.9	5.1	3.6	0.7	0.2	0.2	0.2						
Erythromycin				2.5	24.7	55.4	9.8	0.2	0.5	0.4	0.7	1.1	0.9	0.4	0.1	3.3
Clindamycin			2.0	8.0	33.8	41.4	10.7	0.4	0.4							3.4
Tetracycline		0.2	0.2		4.9	62.6	23.4	0.9	0.4	0.7	0.5	0.9	2.9	2.4		
TMS**				0.4	2.0	27.0	55.4	5.4	2.7	3.3	1.5	0.9	0.4	1.1		
Chloramph.								0.4	7.4	55.4	34.7	1.6	0.4	0.2		
Norfloxacin										4.7	23.0	46.3	22.9	2.5	0.4	0.2

	< 20	20	21	22	23	24	25	26	27	28	29	30	31	32	33	≥ 34
Oxacillin disk	4.5	1.1	0.7	1.1	2.7	2.7	2.7	7.3	6.5	8.9	8.9	17.8	8.3	7.4	4.9	14.3

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

RESULTS AND COMMENTS

S. pneumoniae isolates from respiratory tract specimens have previously been surveyed in NORM in 2000, 2001, 2003, 2005 and 2007. The prevalences of non-susceptibility to various antimicrobials are shown in Tables 47-48 and Figure 40. There were no significant changes in the prevalence of resistance to penicillin G (3.4% in 2005, 3.3% in 2007 and 3.8% in 2009) or erythromycin (6.6% in 2005, 8.0% in 2007 and 7.6% in 2009). The prevalence of non-susceptibility to tetracycline was slightly increased (7.4%) compared to 2007 (5.6%), while the prevalence of non-susceptibility to trimethoprim-sulfamethoxazole (7.1%) returned to the range of 6-8% after a peak of 13.9% in 2007. Technical difficulties with susceptibility testing of this substance may at least in part explain these fluctuations.

A total of 21/551 isolates (3.8%) were non-susceptible to penicillin G. One isolate was penicillin G resistant (MIC 4 mg/L) while the remaining 20 were intermediately susceptible (MIC 0.125-1 mg/L). The penicillin G resistant isolate as well as one of the penicillin intermediately susceptible isolates were non-susceptible to cefotaxime with MICs of 2 and 1 mg/L, respectively. Eighteen of the penicillin G non-susceptible isolates were detected by the oxacillin screening test (sensitivity 85.7%), whereas seven fully penicillin G susceptible isolates were classified as oxacillin resistant (specificity 98.7%). Beta-lactam resistant isolates were commonly cross-resistant to other antimicrobial agents such as trimethoprim-sulfamethoxazole (13/21), erythromycin (10/21) and tetracycline (10/21).

The prevalence of non-susceptibility to macrolides in *S. pneumoniae* blood culture isolates increased steadily from 2000 until it peaked at 12.4% in 2006. Over the last three years the prevalence has decreased sharply to 4.6%. The epidemic spread of macrolide non-susceptible pneumococcal clones was less pronounced among respiratory tract isolates with 8.0% erythromycin resistance in 2007. The 7.6% prevalence in 2009 was the first point of observation when macrolide resistance rates in respiratory tract isolates were higher than the corresponding values in blood culture isolates. However, there was still an interesting difference in resistance phenotypes between the two specimen types. Whereas the majority of erythromycin resistant blood culture isolates displayed the M-phenotype (22/35, 62.5% of erythromycin non-susceptible isolates), a major proportion of respiratory tract isolates (23/41; 4.2% of all isolates; 56.1% of erythromycin non-susceptible isolates) displayed the MLS_B-phenotype either constitutively (n=17; 3.1% of all isolates; 40.5% of erythromycin resistant isolates) or inducibly (n=6; 1.1% of all isolates; 14.3% of erythromycin resistant isolates). This may indicate that different pneumococcal clones are causing systemic and localized infections. A total of ten isolates (1.8%) were concomitantly non-susceptible to penicillin G and erythromycin.

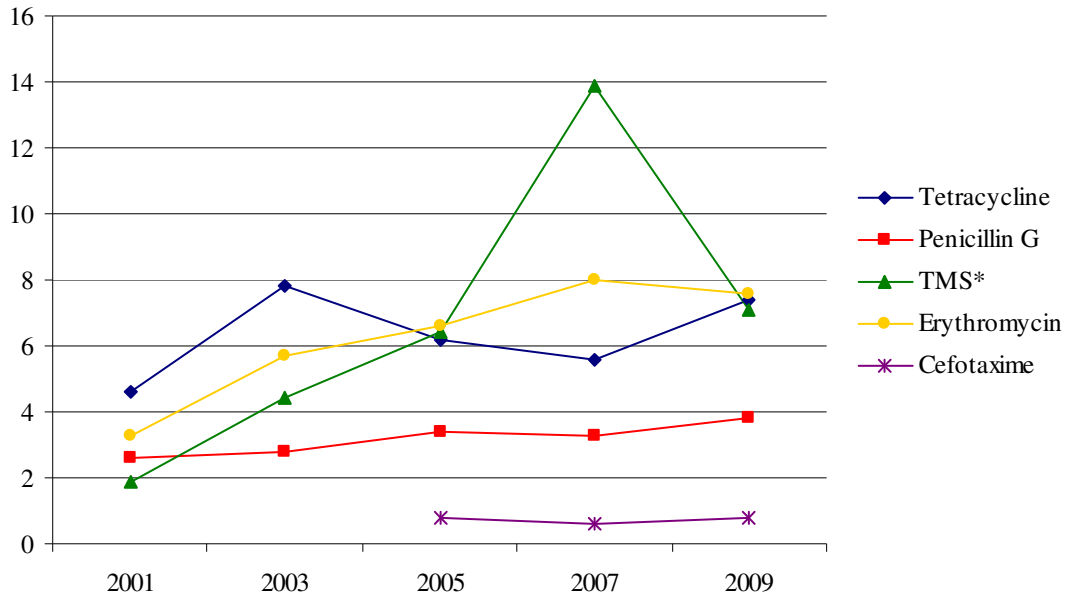


FIGURE 40. Prevalences of non-susceptibility to various antimicrobials in *S. pneumoniae* from respiratory tract samples 2001-2009. Doxycycline was replaced by tetracycline in 2005. *TMS=Trimethoprim-sulfamethoxazole.

Streptococcus agalactiae in blood cultures and cerebrospinal fluids

TABLE 49. *Streptococcus agalactiae* isolates from blood cultures and cerebrospinal fluids (n=168). Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Penicillin G	≤ 0.25	> 0.25	100.0	-	0.0
Cefotaxime	≤ 0.5	> 0.5	100.0	-	0.0
Erythromycin	≤ 0.25	> 0.5	81.6	10.7	7.7
Clindamycin	≤ 0.5	> 0.5	97.6	-	2.4
Tetracycline	≤ 1	> 2	25.0	0.0	75.0
Vancomycin	≤ 2	> 2	100.0	-	0.0

TABLE 50. *Streptococcus agalactiae* isolates from blood cultures and cerebrospinal fluids (n=168). Distribution (%) of MICs (mg/L) and zone diameters for oxacillin (mm).*

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	≥ 128
Penicillin G				8.3	83.9	7.7										
Cefotaxime				24.4	67.9	7.7										
Erythromycin					1.2	19.0	61.3	10.7		0.6	2.4	0.6	0.6			3.6
Clindamycin						63.1	32.1	2.4								2.4
Tetracycline			0.6		3.6	14.3	5.9	0.6				3.6	33.3	35.1	3.0	
Vancomycin								56.0	44.0							

*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.

RESULTS AND COMMENTS

Streptococcus agalactiae isolates (beta-haemolytic group B streptococci) were included in NORM for the first time in 2006. All systemic isolates in Norway are referred to the national reference laboratory at St. Olavs Hospital in Trondheim where confirmatory identification and susceptibility testing was performed. A total of 168 consecutive strains were included in the survey. Thirty-eight isolates originated from neonates and small children < 1 year of age. Most isolates were recovered from blood cultures, but there were also four isolates recovered from cerebrospinal fluids and single isolates from other normally sterile materials. Only one isolate was included from each patient.

As seen in Tables 49-50 there were no isolates with reduced susceptibility to penicillin G, cefotaxime or vancomycin. A total of 31 isolates (18.4%) displayed either intermediate susceptibility (n=18, 10.7%) or resistance (n=13, 7.7%) to erythromycin. The breakpoint for susceptibility to erythromycin has been adjusted from S ≤ 0.5 mg/L to S ≤ 0.25 mg/L since 2006. After recalculating the 2006 results according to the present breakpoint, a significant reduction in the prevalence of intermediate susceptibility from 70.0% in 2006 to 10.7% in 2009 was apparent. This change was mainly due to a change of the median value from 0.5 mg/L in 2006 to 0.25 mg/L in 2009. This is interpreted as a methodological aberration in the 2006 results which does not reflect changes in the epidemiology of *S. agalactiae*.

Four high-level erythromycin resistant isolates were concomitantly resistant to clindamycin, thus indicating constitutive MLS_B resistance. Seven additional erythromycin resistant isolates displayed blunting towards clindamycin, thus indicating inducible MLS_B resistance. The remaining low-level erythromycin non-susceptible isolates were fully clindamycin susceptible, which is compatible with an efflux-mediated M phenotype. The prevalence of resistance to tetracycline (75.0%) was surprisingly high, but the MIC distribution clearly demonstrated the presence of two distinct subpopulations (Table 50). A subgroup analysis of isolates from neonates and small children (< 1 year) did not reveal any differences from the overall population.

Mycobacterium tuberculosis

A total of 351 cases of infection with *M. tuberculosis* complex (not BCG) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS) in 2009. Seventeen of the cases had previously been treated with drugs against tuberculosis; ten from Africa, four from Europe and three from Asia. Nine patients had an earlier history of tuberculosis not treated with antituberculosis drugs. A total of 283 of the cases were confirmed by culture followed by susceptibility testing of the strain isolated. The results are presented in Table 51.

TABLE 51. Susceptibility to 1st line antituberculous drugs among 283 isolates of *M. tuberculosis* complex isolated from human infections in 2009.

	No. of	No. of	Resistance to antimicrobial agents (No. of isolates)					
Origin of birth	cases	isolates	Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamid	MDR TB*
Norway	42	23			1		1	
Europe outside Norway	19	17	2	1		2	1	1
Asia	106	94	3	1		6	8	
Africa	169	137	18	6	1	20	9	6
America	1	1						
No information	14	11	1			1	1	
Total	351	283	24	8	2	29	20	7
Proportion of resistant isolates (%)			8.5	2.8	0.7	10.2	7.1	2.5

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

Candida spp. in blood cultures

TABLE 52. Antimicrobial susceptibility of *Candida albicans* blood culture isolates (n=139)*. Sampling, laboratory methods, and data handling are described in Appendix 5.

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

*69 isolates were susceptibility tested for micafungin. ** Recommended breakpoints by the Norwegian Working Group on Antibiotics - NWGA.
*** Recommended breakpoints by the European Commitee on antimicrobial susceptibility testing – EUCAST. **** There are no European breakpoints for caspofungin, anidulafungin and micafungin. Strains with MICs ≤ 1 mg/l are considered susceptible.

TABLE 53. *Candida albicans* blood culture isolates (n=139)*. Distribution (%) of MICs (mg/L).**

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B						5.1	33.1	60.4	1.4								
Fluconazole				0.7	2.2	18.0	66.2	12.2	0.7								
Voriconazole	5.8	70.5	22.3		0.7	0.7											
Caspofungin	0.7	0.7	2.2	18.0	38.8	30.9	6.5	2.2									
Anidulafungin	76.2	20.9	2.2		0.7												
Micafungin	30.5	44.9	24.6														

* 69 isolates were susceptibility tested for micafungin. ** Shaded areas in each row indicate susceptibility (light) and resistance (dark).

TABLE 54. Antimicrobial susceptibility of *Candida glabrata* blood culture isolates (n=33)*. Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B**	≤ 1	> 1	97.0	-	3.0
Fluconazole***	≤ 2	> 2	9.0	-	91.0
Voriconazole***	≤ 0.125	> 0.125	33.3	-	66.7
Caspofungin****	≤ 1	> 1	100.0	-	0.0
Anidulafungin****	≤ 1	> 1	100.0	-	0.0
Micafungin****	≤ 1	> 1	100.0	-	0.0

*14 isolates were susceptibility tested for micafungin. ** Recommended breakpoints by the Norwegian Working Group on Antibiotics - NWGA.
*** There are no EUCAST breakpoints for fluconazole or voriconazole as there is insufficient evidence for their use in treating *C. glabrata* infections. The breakpoints given are those made for *C. albicans*, *C. tropicalis* and *C. parapsilosis*. **** There are no European breakpoints for caspofungin, anidulafungin and micafungin. Strains with MICs ≤ 1 mg/l are considered susceptible.

TABLE 55. *Candida glabrata* blood culture isolates (n=33)*. 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						3.0	18.2	72.8	3.0	3.0							
Fluconazole***										9.0	21.1	18.6	6.0	3.0		3.0	39.3
Voricon. ***					6.0	24.2	15.2	9.1		6.0	9.1		12.1	18.3			
Caspofungin						30.3	66.7	3.0									
Anidulafungin		6.0	91.0				3.0										
Micafungin		85.7	14.3														

* 14 isolates were susceptibility tested for micafungin. ** Shaded areas in each row indicate susceptibility (light) and resistance (dark). *** White areas indicate that breakpoints have not been set for this species.

TABLE 56. Antimicrobial susceptibility of *Candida tropicalis* blood culture isolates (n=13)*. Sampling, laboratory methods, and data handling are described in Appendix 5.

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

*9 isolates were susceptibility tested for micafungin. ** Recommended breakpoints by the Norwegian Working Group on Antibiotics - NWGA.
*** Recommended breakpoints by the European Commitee on antimicrobial susceptibility testing – EUCAST. **** There are no European breakpoints for caspofungin, anidulafungin and micafungin. Strains with MICs ≤ 1 mg/l are considered susceptible.

TABLE 57. *Candida tropicalis* blood culture isolates (n=13)*. Distribution (%) of MICs (mg/L).**

	≤0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	≥ 256
Ampho. B						7.7	15.4	30.8	46.1								
Fluconazole						15.4	30.8	38.4	15.4								
Voriconazole			15.4	15.4	61.5	7.7											
Caspofungin				7.7	7.7	61.5	23.1										
Anidulafungin		7.7	76.9	7.7				7.7									
Micafungin			88.9	11.1													

* 9 isolates were susceptibility tested for micafungin. ** Shaded areas in each row indicate susceptibility (light) and resistance (dark).

TABLE 58. Antimicrobial susceptibility of *Candida parapsilosis* blood culture isolates (n=10)*. Sampling, laboratory methods, and data handling are described in Appendix 5.

	Breakpoints (mg/L)		Proportion of isolates (%)		
	Susceptible	Resistant	Susceptible	Intermediately susceptible	Resistant
Amphotericin B**	≤ 1	> 1	80.0	-	20.0
Fluconazole***	≤ 2	> 2	90.0	-	10.0
Voriconazole***	≤ 0.125	> 0.125	90.0	-	10.0
Caspofungin****	≤ 1	> 1	90.0	-	10.0
Anidulafungin****	≤ 1	> 1	60.0	-	40.0
Micafungin****	≤ 1	> 1	85.7	-	14.3

*7 isolates were susceptibility tested for micafungin. ** Recommended breakpoints by the Norwegian Working Group on Antibiotics - NWGA.
*** Recommended breakpoints by the European Commitee on antimicrobial susceptibility testing – EUCAST. **** There are no European breakpoints for caspofungin, anidulafungin and micafungin. Strains with MICs ≤ 1 mg/l are considered susceptible.

TABLE 59. *Candida parapsilosis* 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	40.0	30.0	20.0							
Fluconazole							40.0	30.0	20.0					10.0			
Voriconazole	10.0	20.0	40.0	20.0				10.0									
Caspofungin							10.0	70.0	10.0		10.0						
Anidulafungin						10.0		10.0	40.0		20.0	10.0	10.0				
Micafungin								57.1	28.6	14.3							

* 7 isolates were susceptibility tested for micafungin. ** Shaded areas in each row indicate susceptibility (light) and resistance (dark).

RESULTS AND COMMENTS

In 2009, 205 isolates of eight different *Candida* species were isolated from blood stream infections in 197 patients, and they were received at the National Mycology Reference Laboratory. In 2008, 214 isolates of nine different species were received. All isolates were susceptibility tested for amphotericin B, fluconazole, voriconazole, caspofungin and anidulafungin by Etest according to the manufacturers` instructions (AB bioMérieux). From the summer of 2009, micafungin was included in the test panel.

Candida albicans is still the most common *Candida* species observed (n=139, 67.8%) followed by *C. glabrata* (n=33, 16.1%), *C. tropicalis* (n=13, 6.3%) and *C. parapsilosis* (n=10, 4.8%). The results are presented in Tables 52-59.

All *C. albicans* and *C. tropicalis* isolates were susceptible to all antifungal drugs tested, with the lowest MIC values noted for voriconazole and the echinocandins (caspofungin, anidulafungin and micafungin).

All *C. glabrata* isolates were found to be susceptible to all echinocandins tested given a breakpoint of S ≤ 1 mg/L. All isolates, except one, were susceptible to amphotericin B. When testing fluconazole susceptibility, only three isolates (9%) had an MIC ≤ 2 mg/L. Thirteen isolates (39.3%) had an MIC > 256 mg/L. Nineteen isolates (57.7%) had an MIC < 64 mg/L (susceptible to dose-dependent susceptible according to Clinical Laboratory Standard Institute - CLSI). When testing for voriconazole susceptibility, 10 isolates (24.1%) had MIC ≤ 0,125 mg/L, 23 isolates (69.7%) had an MIC ≥ 0.25 mg/l and six isolates (18.3%) had an MIC > 32 mg/L. The occurrence of heteroresistance to both fluconazole and voriconazole increased from 8 isolates (21.6%) in 2008 to 12 isolates (36.5%) in 2009. Although our numbers of *C. glabrata* are small, compared to 2008 there is a remarkable increase in the number of highly resistant fluconazole isolates (MIC > 256 mg/L) from 18.9% to 39.3%. For voriconazole, there is a lower percentage of isolates with low MIC values (≤ 0.125 mg/L) in 2009 (24.1%) compared to 2008 (59.5 %), but there is no increase in the percentage with MIC values above 32 mg/L (16.2 % vs 18.3%).

EUCAST has still refrained from setting breakpoints for the azols and *C. glabr*ata due to insufficient data to support the use of these drugs in such infections. Our findings of high MIC values, especially for fluconazol, support the view that azols should not be recommended in treating serious *C. glabrata* infections.

We have few *C. parapsilosis* blood stream infections in Norway. They do, however, have higher MIC levels for the echinocandins than what we observe in other *Candida* sp. with 10% (caspofungin) and 40 % (anidulafungin) having MIC > 1 mg/L.

We still lack breakpoints for *Candida* spp. and the echinocandins (caspofungin, anidulafungin and micafungin) and the azoles (fluconazol and voriconazole) in Europe. In this report the breakpoints recommended by the Norwegian Working Group on Antibiotics (NWGA) are used for amphotericin B. The EUCAST breakpoints for fluconazole and voriconazole are used for certain *Candida* species. For the echinocandins, strains with MICs ≤ 1 mg/L are presumably susceptible.

Resistance in influenza viruses

Background

Two classes of antiviral drugs are being used against influenza virus infection. M2 blockers inhibit replication of influenza type A viruses, while the more recently developed neuraminidase inhibitors (NIs) inhibit the replication of both type A and B. The Department of Virology at the Norwegian Institute of Public Health (NIPH) functions as a WHO National Influenza Centre (NIC) and is designated by the Ministry of Health as national reference laboratory for influenza. In the latter function lies also the obligation to monitor and assess the occurrence of resistance. In addition to national monitoring, a selection of influenza viruses that are shipped by European NICs to the WHO Collaborating Centre in the United Kingdom is also tested for antiviral susceptibility there.

Effective treatment initiated within the first 48 hours is imperative for severe influenza. The type of antiviral treatment must be chosen on empirical grounds and knowledge on the occurrence of resistance at population level is therefore needed. Usage of influenza antivirals in Norway has earlier been very sparse, but a substantial peak in NI (primarily oseltamivir) usage was recorded during the pandemic wave in October-November 2009.

Historically, resistance has been known to develop quite easily against the M2 blockers. Over the last decade, increasing proportions of resistant viruses have been observed, particularly of subtype A(H3N2) (1). The more recently developed NIs initially seemed to be much less affected by resistance development and resistant mutants in general have seemed less viable. However, an oseltamivir resistant seasonal A(H1N1) virus variant, carrying the neuraminidase mutation H274Y, emerged in 2007 (2,3) and within a year reached almost total predominance among seasonal viruses of this subtype. A novel influenza A(H1N1) virus that appears to have originated from influenza viruses circulating in pigs emerged in the spring of 2009 and caused an influenza pandemic. The main epidemic wave in Norway was in October-November 2009.

Surveillance findings

The pandemic influenza A(H1N1) virus has been monitored very closely for resistance, from the first occurence in Norway in May 2009 and onward. To date, as elsewhere in the world, these viruses are uniformly resistant to M2 blockers but with very few exceptions they remain fully susceptible to the neuraminidase inhibitors oseltamivir and zanamivir. In Norway none of the tested viruses were oseltamivir resistant. In Europe (from nine reporting countries) 2.5% of the tested viruses were resistant to oseltamivir while none were resistant to zanamivir. Most of the cases of oseltamivir resistance were in persons with altered immunological competence who had been treated with oseltamivir. Certainly, the pandemic strain does not appear to have developed the same capability to transmit efficiently with the H275Y mutation as the seasonal influenza A(H1N1) viruses [4]. During the pandemic, the uniformly oseltamivir resistant seasonal A(H1N1) viruses seem to have been displaced and may be on the brink of extinction.

Findings from Norwegian surveillance are summarised in Table 60. Since the influenza viruses at the end of the year are invariably closer related to viruses occurring early next year than to the viruses from the preceding spring, it is meaningful to summarise according to winter seasons rather than by calendar years. For NIs, resistant viruses were very rare in most countries; this is also reflected in the Norwegian data up to 2007. However, during the 2007-08 season, an unprecedented proportion of high-level resistance to oseltamivir (but not zanamivir) was found (2,3). This global emergence of resistance was discovered first through analysis of viruses from Norwegian influenza surveillance, and it took place with no association to recorded usage of drug. The findings for M2 blocker resistance is largely in accordance with the global patterns, with high proportion of resistant H3N2 and pandemic H1N1 viruses. Fortunately, viruses resistant to both NIs and M2 blockers have been extremely rare.

TABLE 60. Norwegian influenza viruses resistant to M2 blockers (adamantanes) and the NIs oseltamivir and zanamivir, during the influenza seasons 2005/06 through 2009.

	Adamantane resistance		Oseltamivir resistance*			Zanamivir resistance*		
	A(H1N1)	A(H3N2)	A(H1N1)	A(H3N2)	B	A(H1N1)	A(H3N2)	B
2005/06	nd	75% (n=4)	0% (n=6)	0% (n=13)	0% (n=21)	0% (n=6)	0% (n=13)	0% (n=21)
2006/07	0% (n=6)	90% (n=10)	0% (n=5)	0% (n=10)	nd	0% (n=5)	0% (n=10)	Nd
2007/08	0% (n=112)	100% (n=2)	68% (n=272)	0% (n=2)	0% (n=59)	0% (n=114)	0% (n=2)	0% (n=59)
2008/09	0% (n=5)	100% (n=65)	100% (n=33)	0% (n=13)	0% (n=1)	0% (n=5)	0% (n=12)	0% (n=1)
2009-pdmH1	100% (n=258)	100% (n=2)	0% (n=884)		0% (n=11)	0% (n=36)		0% (n=9)

*Two screening tools were used to determine oseltamivir/zanamivir resistance: sequence analysis of viral genes or a neuraminidase inhibition assay

References

1. Hungnes O, Dudman SG. Resistance in influenza viruses (Article in Norwegian) Tidsskr Nor Laegeforen. 2008 Nov 20;128(22):2601-6.
2. Lackenby A, Hungnes O, Dudman SG, Meijer A, Paget WJ, Hay AJ, et al. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill 2008;13
3. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007-08. Emerg Infect Dis. 2009 Feb;15(2):155-62
4. Meijer A, Lackenby A, Hay A, Zambon M. Influenza antiviral susceptibility monitoring activities in relation to national antiviral stockpiles in Europe during the winter 2006/2007 season. Euro Surveill. 2007 Apr 1;12(4):E3-4

Anette Kilander, Susanne Dudman and Olav Hungnes, Department of Virology, Norwegian Institute of Public Health, Oslo.

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

Data sources

Feed additives

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

Antimicrobial agents for therapeutic use

In Norway, veterinary antimicrobial agents for therapeutic use in domestic animals or farmed fish are prescription drugs only. Moreover, veterinary antimicrobial agents have to be dispensed through pharmacies, which are supplied by drug wholesalers only. An exemption from the pharmacy/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 antimicrobial agents from wholesalers and feed mills are thought to roughly equal the use of these drugs. Sales figures for veterinary antimicrobial agents are therefore used as a synonym for usage of veterinary antimicrobial agents. Drug wholesalers and feed mills report their sales figures to the Norwegian Institute of Public Health. This reporting was made mandatory from January 1st 2002. Number of items sold in 2009 for the various veterinary drug formulations, strengths and package sizes were obtained from the Norwegian Institute of Public Health and calculated to express kg active substance.

Drug classification system

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

Unit of measurement

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

Inclusion criteria – veterinary drugs

The veterinary drugs included for terrestrial animals were all the approved veterinary antimicrobial products belonging to the following ATCvet groups: QA07AA (gastrointestinal infections) (no product in ATCvet group QA07AB on the market in Norway), QG01AA+AE (uterine infections) (no products in ATCvet groups QG51AC, -AE, -AX, -BA, -BC or -BE on the market in Norway) and, QJ (antimicrobial agents for systemic use that includes intramammary dose applicators (QJ51)). Additionally, a few antimicrobial products sold on special exemption from market authorization have been included following a case by case assessment (se footnotes for the various tables and figures). Sales of antimicrobial agents as medicated feeds and as premixes, both intended for use in farmed fish, belonging to QJ are presented separately. An exemption has been made for an antimicrobial premix approved for farmed fish only (trimethoprim+sulfadiazine 1:5) but sold solely for use in terrestrial animals since 1995 (unpublished data). In the present report, the sales of this premix has for the first time been included in Table 5 that presents detailed sales figures for antimicrobial agents for terrestrial animals for the latest year; for Fig. 1 and 2 this premix has been included for the whole period. Consequently, the sales of the antimicrobial agents in terrestrial animals reported for the years 1995-2005 were underestimated, although only slightly. However, the updated usage figures for 1995-2005 correlated highly positive (r=0.998) with the data reported previously for these years confirming the formerly reported reduction in the usage of antimicrobial agents in terrestrial animals. Dermatological preparations (QD) and preparations intended for sensory organs (QS) are not included in the material. Human antimicrobial preparations are used in small animal practice. However, data on the use of such antimicrobial preparations in animals are not included in this report as such sales cannot be separated from sales intended for use in humans.

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

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

The wholesales database covers total sales of antibacterials in Norway and is based on sales of medicaments from drug wholesalers to pharmacies and hospitals in Norway. The figures presented should be regarded as maximum figures based on the assumption that all medicaments sold are actually consumed. The actual drug consumption will probably be somewhat lower. The Norwegian Institute of Public Health collects the data. Data on drug use from wholesalers has been collected since the beginning of the seventies.

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

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

Drug Classification
The data is categorized according to the ATC classification system (1). Defined Daily Doses (DDDs) are employed as units of measurement. The ATC/DDD index of 2010 is used.

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

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

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

Inclusion criteria
The antibacterials for human use included in this report belong to ATC group J01 antibacterials for systemic use. Oral vancomycin (A07AA09) and oral and rectal metronidazole (P01AB01) are also included. Of the antimycobacterials, only rifampicin is included and data are presented as total amount rifampicin used. Antibacterials used in dermatological preparations (ATC group D) and preparations intended for sensory organs (ATC group S) are not included in the material, except for mupirocin, which is included in one table.

References
1. WHO Collaborating Centre for Drug Statistics Methodology (2009). ATC index with DDDs 2010. WHO Collaborating Centre, Oslo

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

Sampling strategy

Escherichia coli isolates from cattle with clinical mastitis were obtained from the diagnostics laboratoires at the National Veterinary Institute (NVI).

The indicator isolates of *Escherichia coli* were collected from healthy animals of broiler, sheep, and horse. In addition, *E. coli* isolates were obtained from bulk milk samples from dairy cattle collected by TINE Mastittlaboratoriet i Molde.

The samples from broiler (a piece of boot swabs) were obtained from samples collected according to the Norwegian Salmonella control programme for live animals analysed at the Regional laboratory of NVI in Trondheim. A sample from each of the first five flocks to be processed at a specific weekday during the whole sampling period (January –November) was collected for NORM-VET. The samples were also used for the selective isolation of vancomycin resistant *Enterococcus* spp.

The *E. coli* isolates from sheep primarily consisted of isolates belonging to serotypes O26 and O103. These isolates were obtained from a survey of entero-haemorrhagic *E. coli* in sheep running in 2006-2007.

Faecal samples from horses for isolation of indicator *E. coli* and nasal swabs for screening of methicillin resistant *Staphylococcus aureus* (MRSA) from horses were collected by ten veterinary horse practitioners either in the field or at the arrival of a horse to a clinic. The clinics/practises were geographically spread throughout Norway and not more than one horse per owner and maximum two horses per stable were included.

Faecal samples from swine for screening for ESBL producing *E. coli* were obtained from samples collected according to the Norwegian Salmonella control programme for live animals analysed at the Regional laboratory of NVI in Bergen. Samples from approximately two animals per herd (92 herds) were included.

Isolation and identification of bacteria

Escherichia coli

E. coli was isolated and identified at NVI. Sample material was plated onto the surface of lactose-saccarose-bromthymol blue agar without broth enrichment and incubated at 35-37°C for 24 h. For screening of ESBL producing isolates, the samples were plated on MacConkey agar with 1 mg/L cefotaxime and incubated at 37°C for 48 h. Typical colonies were plated onto blood agar (Heart infusion agar (Difco) containing 5% bovine blood) and incubated at 35-37°C for 24 h. Colonies were identified as *E. coli* by typical appearance, lactose and/or saccarose fermentation, a positive indole reaction and oxidase reaction.

Enterococcus spp.

Enterococcus spp. was isolated and identified at NVI. Sample material was plated onto the surface of Slanetz & Bartley agar (Oxoid) with 32 mg/L vancomycin and incubated at 44°C for 48 h. Colonies from each positive sample were selected, and the isolates confirmed as *Enterococcus* spp. by phenotypic characterization. The isolates were further identified to the species level and tested for the presence of the *vanA* gene using PCR (Dutka-Malen et al., 1995, Simonsen et al 2000).

***Staphylococcus* spp.**

Staphylococcus spp. was isolated and identified at NVI. The screening for MRSA from horses was performed by incubation of each individual nasal swab in Trypton-Soya-Broth (TSB) with 2.5% NaCl, 20 mg/L aztreonam and 3.5 mg/L cefoxitin at 35°C for 18-20 h. Subsequently, 10 µL of the broth was inoculated onto the surface of Oxoid Brilliance MRSA agar and incubated at 35°C for 18-24h. Suspected colonies were subjected to further identification with positive reaction on catalase, coagulase, growth on P-agar with 7mg/L acriflavin and positive anaerobe mannitol fermentation. Investigation for the *mec*A/*nuc* genes was performed using PCR (Brakstad et al, 1992).

Susceptibility testing

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

Epidemiological cut-off values recommended by the European Food Safety Authority (EFSA 2008) were used with the exception of ciprofloxacin for *E. coli*. For this exception, and for additional antimicrobial agents not defined in the EFSA recommendations but included in NORM-VET, a cut-off value was defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also appendix 6).

Quality assurance systems

The following susceptible bacteria were included as quality controls on a regular basis, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213. The following resistant bacteria were tested on a regular basis: *E. faecium* CCUG 33829, CCUG 36804, *S. aureus* CCUG 35603. The results were approved according to reference values given by CLSI when available. Additional control strains were included when necessary. The participating laboratories at NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in two external quality assurance programmes: For veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit, Loughborough, UK) and for resistance monitoring (EU CRL for Antimicrobial Resistance in Denmark).

Data processing

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

Appendix 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 (NVI). One isolate of each serovar per incident was included for susceptibility testing.

Campylobacter coli
Swabs with faecal content from swine were obtained from samples collected according to the Norwegian Salmonella control programme for live animals analysed at the Regional laboratory of NVI in Bergen.

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

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

Isolation and identification of bacteria
Isolation and identification of *Salmonella* spp. from animals was carried out at the National Veterinary Institute according to ISO 6579:2002/Amd.1:2007: Annex D: Detection of *Salmonella* spp. in animal faeces and in environmental samples from the primary production stage.
For isolation of *Campylobacter* spp. from swine, the method ISO 10272-1:2006 was used. Identification of the isolates was carried out by the National Veterinary Institute.
Isolation and identification of bacteria from humans was performed according to conventional methods described in standard reference literature (e.g. Murray PR & al.: Manual of Clinical Microbiology, 8th edition ASM-Press, Washington 2003 and Ewing WH: Edwards and Ewing's Identification of *Enterobacteriaceae*, 4. edition, Elsevier, New York 1986). The identification of all isolates from animals and humans was verified at the National Reference Laboratory for Enteropathogenic Bacteria at the Norwegian Institute of Public Health.

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

Salmonella spp., *Yersinia* spp. and *Shigella* spp. isolates from humans were susceptibility tested at the Norwegian Institute of Public Health by an agar disk diffusion test using BD Sensi-Disc and Mueller-Hinton II-medium. The *Campylobacter* isolates from humans were tested for antimicrobial susceptibility at the Norwegian Institute of Public Health using Etest (AB Biodisk).
For animal isolates, epidemiological cut-off values recommended by the European Food Safety Authority (EFSA 2007) were used with the exception of streptomycin for *Campylobacter coli*. For this exception, and for additional antimicrobial agents included in NORM-VET, a cut-off value was defined on the basis of the actual MIC distributions obtained in the NORM-VET programme (see also appendix 6).
For human isolates, MIC breakpoints defined by AFA (Norwegian Reference Group on Antibiotic Susceptibility Testing) were applied. For disk diffusion results, population based breakpoints were used. Breakpoints for *Campylobacter* spp. are based on MIC distributions.

Quality assurance systems
NVI and the Reference Laboratory for Enteropathogenic Bacteria/NIPH have a quality assurance system according to the requirements of NS-EN ISO/IEC 17025.
Campylobacter jejuni subsp. *jejuni* CCUG 11284 was used as quality control strains at NVI on a weekly basis. The participating laboratories at NVI are accredited according to the requirements of NS-EN ISO/IEC 17025 and participate in two external quality assurance programmes: For veterinary pathogens (Veterinary Laboratories Agency Quality Assurance Unit, Loughborough, UK) and for resistance monitoring (EU CRL for Antimicrobial Resistance in Denmark).

The Norwegian Institute of Public Health participates in the external quality assessment programme for *Salmonella* spp. and antimicrobial susceptibility testing, in 2009 still organized by Enter-Net.

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

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

General considerations

NORM is based upon periodic sampling and testing in each participating laboratory of microbial isolates from defined clinical conditions such as respiratory tract infections, wound infections, urinary tract infections, or septicaemiae. For enteric infections see Appendix 4. 2009 was the tenth year of surveillance, and all 22 laboratories in Norway participated in the surveillance system in addition to the Norwegian Institute of Public Health. All laboratories followed the same sampling strategy and used identical criteria for the inclusion of microbial strains. Only one isolate per patient and infectious episode was included unless otherwise stated. All microbes were identified using conventional methods as described in the ASM Manual of Clinical Microbiology. The surveillance period started in the beginning of January, and consecutive isolates were included for defined time periods for each surveillance category. The surveillance categories and sampling periods in 2009 were as follows: *E. coli* in blood cultures (6 months); *Klebsiella* spp., *Staphylococcus aureus* and *Enterococcus* spp. in blood cultures (9 months); *Streptococcus pneumoniae, Streptococcus agalactiae* and *Candida* spp. in blood cultures (12 months), *S. aureus* from wound specimens (2 weeks), *Streptococcus pneumoniae* from respiratory tract specimens (3 weeks); *E. coli* from urinary tract infections (2 days); *Klebsiella* spp. from urinary tract infections (3 weeks), and *Mycobacterium tuberculosis* from all samples (12 months). *S. pneumoniae* from blood cultures were further analysed at the the Norwegian Institute of Public Health in Oslo. *S. agalactiae* from blood cultures were further analysed at St. Olav University Hospital in Trondheim. *Candida* spp. from blood cultures were further analysed at Oslo University Hospital, Rikshospitalet, Oslo.

Susceptibility testing

E. coli, *Klebsiella* spp., *Enterococcus* spp. and *S. aureus* isolates were examined by disk duffusion using either Oxoid disks on Isosensitest agar, or Beckton Dickinson disks on Mueller Hinton II agar with nutritional additives as specified by the manufacturers. Suitable antibiotics were selected for each bacterial species, and the results were interpreted according to the respective manufacturers´ recommendations using the breakpoints of the Norwegian Working Group on Antibiotics (NWGA). The NWGA breakpoints are harmonized with EUCAST breakpoints with few exceptions as explained in the text. All *S. aureus* isolates were tested for beta-lactamase production by nitrocefin disks, acidometric agar plates (3.6 mg/L penicillin G and phenol red) or the clover leaf test. All *S. aureus* and *Enterococcus* spp. isolates were screened for glycopeptide resistance using the vancomycin 6 mg/L BHI agar. *S. pneumoniae* and *S. agalactiae* isolates were susceptibility tested using Etest on MH II agar supplemented with 5% lysed sheep blood (AB Biodisk, Solna, Sweden). All resistance values were recorded either as mm inhibition zone sizes or MIC values in order to monitor trends in the occurrence of resistance.

Confirmation of resistance phenotypes

E. coli and *Klebsiella* spp. with reduced susceptibility to 3rd generation cephalosporins were examined for ESBL production using the ESBL Etest according to the instructions of the manufacturer. ESBL positive strains were subjected to PCR and DNA sequencing for determination of ESBL genotype. *S. aureus* isolates with reduced susceptibility to cefoxitin were examined by *mecA* PCR for confirmation of methicillin resistance (MRSA). *Enterococcus* spp. isolates displaying growth on the vancomycin screening agar were examined by *van* gene PCRs for confirmation of VRE. Erythromycin resistant *S. pneumoniae*, *S. agalactiae* and *S. aureus* isolates were analysed for determination of MLS phenotype using the double disk diffusion (DDD) synergy assay with erythromycin and clindamycin disks.

Quality control

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

Data processing

The specially designed eNORM computer program was used for the registration of patient data, sample data and resistance data. The results were further analysed by WHONET5.3 with the aid of the NORMlink program, both developed by John Stelling. The distribution of microbial species in blood culture was based on extraction of routine data from the laboratory information systems of the participants. All isolates of the same species recovered within 1 month after the initial finding were considered duplicates and omitted from the survey. No attempt was made to evaluate the clinical significance of each finding.

Mycobacterium tuberculosis

Susceptibility testing (DST) was performed at the Norwegian Institute of Public Health, Ullevål University Hospital and Rikshospitalet. All isolates were tested using the BACTEC 460 or BACTEC MGIT 960 systems. All three laboratories participate in the WHO external DST quality control program. The same three laboratories and Haukeland University Hospital also perform tests for mutations in *rpoB* gene to detect resistance to rifampicin.

Yeasts

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

Appendix 6:
Cut-off values NORM-VET

Epidemiological cut-off values recommended by the European Food Safety Authority (EFSA 2007 and 2008) were used with the exception of ciprofloxacin for *E. coli* and streptomycin for *Campylobacter coli*. For these exceptions, and for additional antimicrobial agents not defined in the EFSA recommendations, cut-off values were defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.

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

Squares: Cut-off values recommended by EFSA (*Campylobacter* and *Salmonella*: EFSA 2007, *E. coli* and *Enterococcus* spp.: EFSA 2008)
Filled circles: Cut-off values not defined by EFSA - defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.
Open circles: Cut-off values different than defined by EFSA - defined on the basis of the actual MIC distributions obtained in the NORM-VET programme.
*Units/L

Appendix 7: Breakpoints NORM

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

	MIC values mg/L													
Antimicrobials	S	R	*Escherichia coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus agalactiae*	*Candida* spp.
Amphotericin B	≤ 1	> 1											■
Ampicillin	≤ 0.5	> 8	■		■	■	■						
	≤ 4	> 8								■			
Anidulafungin	≤ 1	> 1											■
Caspofungin	≤ 1	> 1											■
Cefotaxime	≤ 0.5	> 0.5										■	
	≤ 0.5	> 2									■		
	≤ 1	> 2	■	■									
Ceftazidime	≤ 1	> 8	■	■									
Ceftriaxone	≤ 0.5	> 2									■		
Cefuroxime	≤ 0.5	> 1									■		
	≤ 0.5	> 8	■	■									
Chloramphenicol	≤ 8	> 8			■	■	■				■		
Ciprofloxacin	≤ 0.5	> 0.5											
	≤ 0.5	> 1	■	■	■	■	■	■					
	≤ 1	> 1							■				
Clindamycin	≤ 0.25	> 0.5							■				
	≤ 0.5	> 0.5									■	■	
Erythromycin	≤ 0.25	> 0.5									■	■	
	≤ 1	> 2							■				
	≤ 4	> 4						■					
Fluconazole	≤ 2	> 2											■
Fusidic acid	≤ 1	> 1							■				

Antimicrobials	MIC values mg/L S	R	*Escherichia coli*	*Klebsiella* spp.	*Salmonella* spp.	*Yersinia enterocolitica*	*Shigella* spp.	*Campylobacter* spp.	*Staphylococcus aureus*	*Enterococcus* spp.	*Streptococcus pneumoniae*	*Streptococcus pyogenes*	*Candida* spp.
Gentamicin	≤ 1	> 1							■				
	≤ 2	> 4	■	■				■					
	≤ 128	> 128								■			
Linezolid	≤ 4	> 4							■	■			
Mecillinam	≤ 8	> 8	■	■									
Meropenem	≤ 2	> 8	■	■									
Micafungin	≤ 1	> 1											■
Nalidixic acid	≤ 16	> 16	■	■	■	■	■	■					
Nitrofurantoin	≤ 64	> 64	■	■									
Penicillin G	≤ 0.064	> 2									■		
	≤ 0.25	> 0.25										■	
Pip./Tazo.*	≤ 8	> 16	■	■									
Rifampicin	≤ 0.06	> 0.5							■				
Tetracycline	≤ 1	> 2							■		■	■	
	≤ 2	> 2						■#					
	≤ 4	> 8			■#	■#	■#						
Tigecycline	≤ 1	> 2	■	■									
Tobramycin	≤ 2	> 4	■	■									
Trimethoprim	≤ 2	> 4	■	■									
TMS*	≤ 1	> 2									■		
	≤ 2	> 4	■	■	■	■	■		■				
Vancomycin	≤ 2	> 2							■			■	
	≤ 4	> 4								■			
Voriconazole	≤ 0.125	> 0.125											■

* TMS Trimethoprim-sulfamethoxazole. Breakpoints for the trimethoprim-sulfamethoxazole combination are given for the trimethoprim component only.
# Epidemiological cut-off value based on the wild-type distribution by EUCAST.