DANMAP 2007

DANMAP 2007 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark

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Introduction

This report, DANMAP 2007, describes the annual consumption of antimicrobial agents and the occurrence of resistance in different reservoirs. This years report starts with three focus areas which focus on important trends and observations. Other trends and comparison to previous years are included, but in this report MIC tables and some trend figures have been moved to Appendix 1. In addition to the monitoring of antimicrobial resistance and consumption of antimicrobial agents the DANMAP programme includes considerable research activities. A few selected research projects are presented as textboxes. Appendix 3 provides a more comprehensive list of DANMAP publications in the international scientific literature.

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, DANMAP, was established in 1995 on the initiative of the Danish Ministry of Health and the Danish Ministry of Food, Agriculture and Fisheries, as a coordinated national surveillance and research programme for antimicrobial consumption and antimicrobial resistance in bacteria from animals, foods and humans. The participants in the programme are Statens Serum Institut, the National Veterinary Institute DTU, the National Food Institute DTU, the Danish Veterinary and Food Administration and the Danish Medicines Agency.

The objectives of DANMAP are:

- To monitor the consumption of antimicrobial agents for food animals and humans
- To monitor the occurrence of antimicrobial resistance in bacteria isolated from food animals, food of animal origin and humans
- To study associations between antimicrobial consumption and antimicrobial resistance
- To identify routes of transmission and areas for further research studies

The monitoring of antimicrobial resistance is based on three categories of bacteria: human and animal pathogens, zoonotic bacteria and indicator bacteria. Human and animal pathogens are included because these cause infections and they primarily reflect resistance caused by use of antimicrobial agents in the respective reservoirs. Zoonotic bacteria are included because they can develop resistance in the animal reservoir, which may subsequently compromise treatment effect when causing infection in humans. Indicator bacteria are included due to their ubiquitous nature in animals, foods and humans and their ability to readily develop antimicrobial resistance in response to selective pressure in both reservoirs.

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List of abbreviations

ADD	Defined Animal Daily Dose
ADDkg	Defined Animal Daily Dose per kg animal
AGP	Antimicrobial Growth Promoter
ATC	Anatomical Therapeutic Chemical
CHR	Central Husbandry Register
CI	Confidence Interval
CNS	Central Nervous System
CPR	Danish Civil Registry
DCM	Department of Clinical Microbiology
DDD	Defined Daily Dose
DMA	Danish Medicines Agency
DVFA	Danish Veterinary and Food Administration
ESBL	Extended Spectrum Beta Lactamases
GAS	Group A Streptococcus
GI	Gastrointestinal
GP	General Practitioner
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
N	Number of samples
n	Number of isolates tested for antimicrobial susceptibility
PMWS	Postweaning multisystemic wasting syndrome
RFCA	Regional Veterinary and Food Control Authorities
SSI	Statens Serum Institut
VetStat	Danish Register of Veterinary Medicines
VRE	Vancomycin Resistant Enterococci
WHO	World Health Organization
WT	Wild type

Anatomical Therapeutic Chemical (ATC) classification. This is the international classification system for drug consumption studies. The ATC code identifies the therapeutic ingredient(s) of each drug for human use according to the organ or system on which it acts and its chemical, pharmacological and therapeutic properties. Antibacterials for systemic use are known as ATC group J01. The ATC classification is maintained by the WHO Collaborating Centre for Drug Statistics and Methodology (Oslo, Norway) (http://www.whocc.no/atcddd/indexdatabase/). The ATC classification for veterinary medicinal products, ATCvet, is based on the same main principles as the ATC classification system for medicines for human use and is also maintained by the WHO Collaborating Centre for Drug Statistics and Methodology (http://www.whocc.no/atcvet/database/).

Antibacterials. Synthetic (chemotherapeutics) or natural (antibiotics) compounds that destroy bacteria or suppresses bacterial growth or reproduction (Source: Dorland's Illustrated Medical Dictionary). Antimycobacterials are not included in the section on human consumption. Only antibacterials for systemic use are included (J01 in the ATC system).

Antimicrobial agents: The term "antimicrobial agents" covers antibacterial, antiviral, coccidiostatic and antimycotic agents. In the section on veterinary consumption, the broad term "antimicrobial agents" is usually used because coccidiostats are included. Antiviral compounds are not used in veterinary medicine, and antimycotics are only registered for topical veterinary use, and used mainly in companion animals. The term "antibacterial agents" is only used in the veterinary section for precision, to distinguish from use of coccidiostats as feed additives (poultry only).

Broiler. A type of chicken raised specifically for meat production. In Denmark, the average weight after slaughter is 1.66 kg.

Central Husbandry Register (CHR). This is a register of all Danish farms defined as geographical sites housing production animals. It contains numerous information concerning ownership, farm size, animal species, age groups, number of animals and production type. Each farm has a unique farm identity number (CHR-number).

Defined Daily Dose (DDD). This is the assumed average maintenance dose per day in adults. It should be emphasized that the Defined Daily Dose is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. DDDs provide a fixed unit of measurement independent of price and formulation, enabling the assessment of trends in drug consumption and to perform comparisons between population groups. The DDDs are defined and revised yearly by the WHO Collaborating Centre for Drug Statistics and Methodology (http://www.whocc.no/atcddd/indexdatabase/).

Defined Animal Daily Dose (ADD and ADDkg). This is an assumed average daily dose per animal, defined as the daily maintenance dose for a drug used for its main indication in a specified species. The dose is defined for a „standard animal", i.e. an animal with an estimated average weight within a specified age group. In VetStat, ADDs are calculated for each age group. Otherwise, the general principles for standardisation of dosage for animals are similar to that used by the

WHO Collaborating Centre for Drug Statistics and Methodology to calculate Defined Daily Dose (DDD) in humans (Jensen VF, Jacobsen E, Bager F. 2004. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. Prev. Vet. Med. 64:201-215).
The ADDkg is the ADD per kg animal. Consumption calculated in ADDkg allows summation of consumption across different age groups and animal species.
Defined Animal Course Dose (ACD and ACDkg). The length of the recommended treatment period may vary substantially between antimicrobial drugs. To correct for this, total course dose has been introduced as unit of measurement for antimicrobial usage. Course doses is assigned per kilogram (live weight) of the animal species (kgACD) or age group of the relevant species (xxACD) and are based on the corresponding ADDkg or ADDxx, respectively, for the relevant animal species and drug formulations.
Finishers. Pigs from 30 kilogram live weight to time of slaughter at 90-100 kilogram live weight.
Heifer. A young female cow before first calving.
Intramammaria. Antimicrobials for local application in the mammary gland (udder for the treatment of mastitis.
Intramammary syringe. A one dose applicator for use in the udder (pl: intramammaries).
Minimum Inhibitory Concentration (MIC). This is the lowest concentration of antimicrobial in a given culture medium, e.g. broth or agar, below which growth of the bacteria is not inhibited.
Layer. A hen raised to produce eggs for consumption.
Piglet. The newborn pig is called at piglet from birth till they are permanently separated from the sow at 3-4 weeks of age. The weight of the piglet at weaning is 7 kilogram.
Poultry. In the DANMAP reports the term poultry is used when antimicrobial resistance among bacteria from broilers and layers are reported together.
Rearing, broilers. Parent flocks producing chickens for broiler production.
Sows. Any breeding female that has been served and is on the farm.
Steer. Castrated male cattle.
Travel associated infections. Infections where travel was reported and therefore most likely acquired in a foreign country.
Weaners. Any pig between 7 and 30 kilogram live weight.
Wild type. The typical form of an organism, strain, gene, or characteristic as it occurs in nature.

Sammendrag

Dette er den tolvte DANMAP rapport. DANMAP 2007 beskriver det årlige forbrug af antibiotika og forekomsten af resistens i forskellige reservoirs. Den kontinuerlige overvågning af antibiotikaresistens og -forbrug gør det muligt at analysere tendenserne i antibiotikaforbrug og -resistens over tid. I dette års rapport præsenteres udviklingen over tid og andre vigtige observationer i tre fokusområder.

Fokusområde: De sidste 11 års ændringer i fordelingen af serotyper, fagtyper og resistensprofiler blandt *Salmonella* bakterier fra danske svin
Dette fokusområde præsenterer en analyse af de sidste 11 års ændringer i fordelingen af serotyper, fagtyper og resistensprofiler blandt *Salmonella* bakterier indsamlet fra danske svin. Den største ændring over tid blev observeret for *S*. Typhimurium DT12, hvor forekomsten faldt fra 47 % i 1998 til 13 % i 2007. I den samme periode steg forekomsten af *S.* Typhimurium DT120, DT170 og DT104. Fra 1997 til 2007 forblev 81 % af alle DT12 isolater fuldt følsomme overfor alle ni antibiotika i testpanelet, på trods af at antibiotikaforbruget generelt og især tetracyklin forbruget steg i den samme periode, mens kun 21-34 % af alle DT120, DT170 og DT104 var følsomme overfor alle ni antibiotika. Blandt de resistente fagtyper (DT120, DT170 og DT104) var en bestemt resistensprofil dominerende for hver fagtype. Disse resultater viser, at brug af antibiotika kan selektere for multiresistente kloner, og at dette kan være afgørende for ændringer i forekomsten af antibiotikaresistens indenfor en serotype.

Fokusområde: Prævalensen af ESBL-producerende bakterier blandt mennesker og dyr i Danmark i 2007
Fra september til oktober 2007 blev den første landsdækkende prævalens-undersøgelse vedr. ESBL-producerende bakterier gennemført. ESBL-producerende *Escherichia coli* og *Klebsiella pneumoniae* blev fundet i hhv. 4,2 % og 5 % af bloddyrkningerne og i hhv. 2,3 % og 6,6 % af urinprøverne fra hospitalerne. I april 2007 sås det første større udbrud med en gentamicin- og ciprofloxacin-resistent ESBL-producerende *K. pneumoniae* i Danmark. Siden da blev det fundet, at totalt 33 patienter var inficeret eller koloniseret med denne udbrudsstamme.
Antallet af ESBL-producerende *E. coli* isoleret fra diagnostiske prøver fra danske svin og kvæg steg til 7 tilfælde i 2006 og 23 tilfælde i 2007.
Det øgede forbrug af cephalosporiner i dyreproduktionen og til mennesker har utvivlsomt ført til den nuværende situation med stigende forekomst af ESBL-producerende bakterier.

Fokusområde: Stigende antibiotikaforbrug på danske hospitaler
Forbruget af bredspektrede og nye antibiotika er fortsat med at stige på danske hospitaler. Tilsammen udgjorde forbruget af disse antibiotika 19 % af det totale forbrug på hospitalerne i Danmark i 2001, og det steg til 34 % i 2007. Konsekvenserne af dette er undersøgt. Fluorokinolon resistensen i *E. coli* isolater fra blodinfektioner er steget kraftigt og signifikant fra 4 % i 2003 til 13 % i 2007. Andre konsekvenser af det stigende forbrug af antibiotika er fundet af ESBL-producerende bakterier og stigningen i *Enterococcus faecium* infektioner på hospitalerne. I Danmark er antibiotikaforbruget stadig lavt sammenlignet med andre europæiske lande, men stigningen er grund til bekymring.

Antibiotikaforbruget til dyr
Det veterinære antibiotikaforbrug steg med 5,2 % fra 115,2 tons i 2006 til 121,1 tons i 2007.

I svineproduktionen steg forbruget af antibiotika 6,3 % fra 91 tons i 2006 til 97 tons i 2007, svarende til en 3,9 % stigning per kg svinekød produceret. Forbruget af tetracykliner og makrolider steg med hhv. 26 % og 6,5 %, mens forbruget af aminoglykosider faldt med 46 %. Forbrugsstigningen var relateret til so-besætninger og fravænnede grise (7,5-30 kg grise). Anvendelsen af bredspektrede cephalosporiner er steget gradvist fra 24 kg i 2001 til 129 kg i 2007 og anvendes primært i so-besætninger. Ordinationsmønsteret tyder på, at anvendelsen af cephalosporiner går fra en lejlighedsvis anvendelse mod mere systematisk anvendelse i en række besætninger, som opdrætter 14-29 % af den årlige produktion af pattegrise.

I kvægbruget anvendes fortsat ca. 15 tons antibiotika årligt. Til køer er smalspektrede, beta-lactam-følsomme penicilliner mest anvendt, efterfulgt af tetracykliner.
Til kalve anvendes hovedsageligt tetracykliner og makrolider. Siden 2004 er anvendelsen af makrolid til behandling af luftvejsinfektioner steget signifikant, og i 2007 blev makrolid det hyppigst valgte antibiotikum ved behandling af kalve.
Anvendelsen af bredspektrede cephalosporiner til kvæg steg både til systemisk behandling (27 kg i 2001, 65 kg i 2007) og yverbehandling (14 kg in 2001, 27 kg i 2007). Ved lokal behandling af yveret anvendes nu i

23 % af tilfældene bredspektrede cephalosporiner. Da mælk fra køer under behandling for yverbetændelse hyppigt anvendes til fodring af kalve, udsættes kalvene potentielt for cephalosporin i mange tilfælde.

I fjerkræproduktionen har amoxicillin i en årrække været anvendt i mere end 90 % af behandlinger. I kalkunproduktionen faldt denne andel fra 92 % i 2006 til 47 % i 2007 som følge af problemer med amoxicillinresistente *E. coli*. Samtidig steg anvendelsen af fluorokinoloner fra 7 % til 16 % af behandlingerne, og en række andre ikke tidligere anvendte antibiotika blev taget i anvendelse, herunder tetracykliner og makrolider. Antibiotikaforbruget i slagtekyllingeproduktionen faldt 26 % trods en 5 % produktionsstigning og nåede det laveste niveau siden 2003. Fluorokinolon blev anvendt i 6 % af behandlingerne, svarende til et fald i forbruget på 75 %.

I akvakulturproduktionen blev der anvendt 3,7 tons antibiotika, hvilket var lidt lavere end i 2006, men 54 % højere end i 2005. Dette skyldes formentlig høje vandtemperaturer i de usædvanligt varme somre. Kombination af sulfonamid/trimethoprim udgjorde 86 % af antibiotikaforbruget i akvakultur. I havdambrug/saltvandsdambrug blev der brugt 217 mg/kg fisk produceret og i ferskvandsdambrug 67 mg/kg fisk produceret (under antagelse af uændret produktionsniveau i 2007).

Antibiotikaforbruget til mennesker

Fra 2006 til 2007 steg forbruget af antibiotika til behandling af mennesker med 7 %, til 35,6 millioner DDD eller 17,9 DDD/1.000 indbygger-dage.

I primærsektoren steg det totale forbrug af antibiotika med 6,6 % til 16,2 DDD/1.000 indbygger-dage. Forholdet mellem forbrug af de forskellige antibiotikaklasser var uændret, og 55 % af forbruget bestod af beta-laktamase sensitive penicilliner og penicilliner med udvidet spektrum.
I 2007 steg forbruget af bl.a. kombinationen af penicilliner inkl. beta-laktamase inhibitorer, fluorokinoloner og tetracykliner yderligere. Stigningen i forbruget af tetracykliner kunne forklares ved et øget forbrug af doxycyklin, der toppede i januar 2007. Dette var sammenfaldende med et rapporteret udbrud af resistent *Plasmodium falciparum* malaria i Goa, Indien, hvilket førte til en ændret malaria-profylakse rekommandation mod type IV profylakse (bl.a. doxycyklin).

Forbruget af antibiotika var fortsat stigende på de danske sygehuse. Fra 1997 til 2007 steg det gennemsnitlige antibiotikaforbrug på sygehusene med 63 % til estimeret 689 DDD/1.000 sengedage. Derimod var stigningen kun 17 % i den samme periode, når den blev opgjort i DDD/1.000 udskrevne patienter. Forskellen mellem de to målemetoder kan forklares med et vedblivende fald i antallet af sengedage, samt en modsat rettet, fortsat stigning i antallet af udskrevne patienter. Imidlertid er der også markante ændringer i forbrugsmønstret. Den tidligere påpegede tendens med stigende forbrug af kombinationer af penicilliner med beta-laktamase hæmmere, cephalosporiner, fluorokinoloner og carbapenemer, på bekostning af beta-laktamase følsomme penicilliner, penicilliner med udvidet spektrum, aminoglykosider og makrolider, fortsatte som tidligere beskrevet. I 2007 udgjorde cephalosporiner, fluorokinoloner og carbapenemer 34 % af totalforbruget sammenlignet med 15 % i 1997. Nye data viser, at ændringerne til fordel for nye bredspektrede antibiotika allerede resulterer i en øget resistensforekomst på hospitalerne (se fokusområde om hospitalsforbrug).

Resistens i zoonotiske bakterier

I 2007 var det muligt at få bedre rejse-information fra mennesker med *Salmonella* infektioner. Baseret på telefoninterviews estimeres det, at 40 % af alle humane *Salmonella* infektioner i 2007 var rejseassocieret. Mellem 2006 og 2007 sås ingen signifikante ændringer i antibiotikaresistens når man sammenligner *Salmonella* Typhimurium fra svin og dansk svinekød, på nær et signifikant fald i ampicillin resistens i *S*. Typhimurium fra dansk svinekød. I 2007 var kun chloramphenicol resistens signifikant højere i importeret svinekød sammenlignet med dansk svinekød. Tetracyklin-, ciprofloxacin- og nalidixansyre-resistens i *S*. Typhimurium isolater fra humane infektioner var signifikant højere blandt isolater fra infektioner erhvervet i udlandet end blandt isolater fra infektioner erhvervet i Danmark.

Forekomsten af resistens overfor ampicillin og ciprofloxacin i *Salmonella* Enteritidis var signifikant højere i isolater fra infektioner erhvervet i udlandet sammenlignet med isolater erhvervet i Danmark.

For at opnå bedre information om rejseaktivitet blev en del af patienterne med en *Campylobacter* infektion erhvervet i 2007, og hvor der ikke allerede var information om rejseaktivitet, telefoninterviewet. Baseret på telefoninterviews samt information om rejseaktivitet fra de praktiserende læger estimeres det, at 30 % af alle humane *Campylobacter* infektioner i 2007 var erhvervet i udlandet.

Som i tidligere år var resistens overfor ciprofloxacin, nalidixansyre og tetracyklin signifikant højere i *C. jejuni* fra importeret kyllingekød sammenlignet med dansk kyllingekød. Forekomsten af resistens overfor ciprofloxacin, nalidixansyre og tetracyklin var signifikant højere i *C. jejuni* isolater erhvervet i udlandet sammenlignet med isolater erhvervet i Danmark.

Resistens i Indikator bakterier

Til denne rapport var der kun gennemført resistensbestemmelser af *E. faecium*, *E. faecalis* og *E. coli* isoleret fra produktionsdyr på slagtetidspunktet. En signifikant stigning i forekomsten af erythromycin resistens blandt *E. faecium* fra svin blev påvist fra 2006 til 2007. Denne stigning faldt sammen med en signifikant stigning i makrolid forbruget til svin i samme periode.

Resistens i bakterier fra diagnostiske indsendelser fra mennesker

Antallet af nye tilfælde af methicillin resistente *Staphylococcus aureus* (MRSA) faldt for andet år i træk til 659 tilfælde i 650 patienter (fra 851 og 706 tilfælde i hhv. 2005 og 2006). 114 tilfælde (17 %) var erhvervet i udlandet. Af tilfælde erhvervet i Danmark blev 461 tilfælde (70 %) diagnosticeret i primærsektoren. Af disse var 125 tilfælde en del af et udbrud relateret til sundhedsvæsenet eller havde været indlagt på hospital/plejehjem indenfor de seneste 12 måneder. I 336 tilfælde (73 %) var der ikke hospitals/plejehjems associerede risikofaktorer, og dermed tale om såkaldt samfundserhvervet MRSA. I 42 % af samfundserhvervede tilfælde fandtes spredning til andre personer i husstanden.

MRSA infektioner: I alt 370 personer (56 %) havde infektion ved diagnosetidspunktet, oftest hud- og bløddelsinfektioner. Antallet af infektioner erhvervet på hospitalerne samt antallet af infektioner hos personer med hospitals/plejehjems-kontakt indenfor de seneste 12 måneder faldt signifikant i 2007. Antallet af MRSA bakteriæmier faldt ligeledes fra 19 tilfælde i 2006 til 8 tilfælde i 2007 (0,6 % af alle *S. aureus* bakteriæmi tilfælde). I modsætning hertil steg antallet af samfundserhvervede infektioner samt infektioner erhvervet i udlandet. Af de samfundserhvervede infektioner var 66 % hos personer med ikke-dansk oprindelse. Den totale reduktion i antallet af nye tilfælde og specielt faldet i antallet af infektioner relateret til hospital og sundhedsvæsen er meget positiv og sandsynligvis relateret til implementeringen af de nye MRSA guidelines. I 2007 blev der fundet 14 humane tilfælde af MRSA CC398; de fleste af disse tilfælde havde tæt kontakt til svin. Den sandsynlige tilstedeværelse af et zoonotisk reservoir er stærkt bekymrende og bør overvåges tæt.

Blandt *Streptococcus pneumoniae* og Gruppe A, B, C og G streptokokker var der i 2007 fortsat lav resistens overfor penicillin og makrolid.

Ciprofloxacin resistens blandt *E. coli* isoleret fra urin i primærsektoren steg igen signifikant til 6,4 % i 2007. Blandt *E. coli* isoleret på hospitaler steg ciprofloxacin resistensen også signifikant til 8,4 % i urin-isolater og 11,2 % i blod-isolater. Stigningen i ciprofloxacin resistens er sket sideløbende med et fortsat øget forbrug af fluorokinoloner (primært ciprofloxacin) gennem de seneste år – både i primærsektoren og på hospitalerne.

Resistens overfor ampicillin blandt *E. coli* steg signifikant såvel i primærsektoren som på hospitalerne fra 2006 til 2007. I *E. coli* urin-isolater fra både primærsektoren og hospitalerne steg ampicillin resistensen til 41 %, og i *E. coli* blod-isolater fra hospitalerne nåede resistensen 44 %. Det høje niveau af ampicillin resistens afspejler den tilsvarende jævne stigning gennem en årrække i forbruget af penicilliner med udvidet spektrum.

Resistens overfor sulfonamider i *E. coli* isoleret fra urin i primærsektoren og på hospitalerne steg signifikant til henholdsvis 38 % og 35 % i 2007.

Gentamicin resistensen steg signifikant til 3,8 % i 2007 blandt *E. coli* isoleret fra blod. Cefuroxim resistensen steg ligeledes signifikant i *E. coli* blod-isolater til 5,4 % i 2007. Stigningen i cefuroxim resistens er sket sideløbende med en kraftig stigning i forbruget af cephalosporiner på hospitalerne gennem de seneste år.

Niveauet af antibiotikaresistens var generelt stadig lavt for de fleste antibiotika i de mest almindelige bakterier isoleret fra kliniske prøver fra inficerede patienter i Danmark. På trods heraf antyder stigningerne i antibiotikaresistens, der er blevet observeret i de seneste år, at resistens-niveauet er under forandring, og dette understreger vigtigheden af en tæt overvågning af antibiotikaresistens, både i primærsektoren og på hospitalerne.

Summary

This report is the 12th DANMAP report. DANMAP 2007 describes the annual consumption of antimicrobial agents and the occurrence of resistance in different reservoirs. The continuous monitoring of antimicrobial resistance and consumption makes it possible to analyse the trends in antimicrobial consumption and resistance over time. The trend analyses and other important observations are in this years report presented in three focus areas.

Focus area: Changes over 11 years in *Salmonella* serovar and phage type distributions as well as resistance profiles in the Danish pig population
Over the last 11 years, changes in the *Salmonella* serovars, phage type distributions and resistance profiles in the Danish pig population were studied. The largest change over time was observed for *S.* Typhimurium DT12. This phage type declined from 47% in 1998 to 13% in 2007. From 1997 through 2007, 81% of all DT12 isolates remained fully susceptible to all nine tested antimicrobial agents despite that in particular tetracycline consumption has increased in the pig production. During the same period, *S.* Typhimurium DT120, DT170 and DT104 have emerged and in contrast only 21% - 34% of these isolates were fully susceptible to all nine antimicrobial agents. Among the resistant phage types (DT104, DT120 and DT170) one resistance profile in each phage type was dominating. These results support that the use of antimicrobial agents might select for multiple resistant clones and that this might be the driver of changes in antimicrobial resistance within a serovar.

Focus area: Prevalence of ESBL-producing bacteria among humans and animals in Denmark in 2007
From September through October 2007, the first nationwide prevalence study on ESBL-producing bacteria was conducted. ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* were detected in 4.2% and 5% of the blood cultures, and in 2.3% and 6.6% of urine samples from hospitals, respectively.
In April 2007, the first major outbreak of a gentamicin and ciprofloxacin-resistant ESBL-producing *K. pneumoniae* in Denmark was detected. Since then, a total of 33 patients infected or colonized with this outbreak strain were detected.
The number of ESBL-producing *E. coli* isolated from diagnostic samples from domestic bred pigs and cattle increased to 7 cases in 2006 and 23 cases in 2007. Increased use of cephalosporins in the animal production and for humans has undoubtedly led to the present situation with increasing prevalence of ESBL-producing bacteria.

Focus area: Increased antibacterial consumption in the Danish hospitals
The consumption of “broad-spectrum” and newer antibacterial agents has continued to increase at Danish hospitals. Together, these amounted to 19% of the total consumption in hospitals in Denmark in 2001, rising to 34% in 2007. Fluoroquinolone resistance in *E. coli* isolates from blood infections has been increasing steeply and significantly from 4% in 2003 to 13% in 2007. Other consequences of the increased consumption of antibacterials were the findings on ESBL-producing bacteria and the increase in *Enterococcus faecium* infections in the hospitals. In Denmark, antibacterial consumption is still low compared to other European countries, but the increase is cause of concern.

Antimicrobial consumption in animals
The veterinary antimicrobial consumption in animals increased by 5.2% from 115.2 tonnes in 2006 to 121.1 tonnes in 2007.
In pigs, the antimicrobial consumption increased by 6.3% from 91 tonnes in 2006 to 97 tonnes in 2007 or a 3.9% increase per kg pork produced. The consumption of tetracycline and macrolides increased by 26% and 6.5%, respectively, while the consumption of aminoglycosides decreased by 46%. The increase in antimicrobial consumption was observed in sows/piglets and weaners. The prescription of 3rd and 4th generation cephalosporins for pigs has gradually increased from 24 kg in 2001 to 129 kg in 2007, of which the majority was used in sow herds. The prescription habits suggest that the consumption of cephalosporin in pigs is changing from occasional prescription to more systematic prescription in herds housing 14-29% of the sows and piglets.

As in previous years, an estimated 15 tonnes of antimicrobial was used in cattle. In cows, beta-lactam sensitive penicillins followed by tetracyclines continued to be the most frequently used antimicrobials for systemic treatment. In calves, the most commonly used antimicrobials are tetracyclines and macrolides. Since 2004, the use of macrolides for treatment of respiratory disease in calves has increased significantly, and in 2007 macrolides became the drug of choice when instituting therapy in calves.
In cattle, the use of third and fourth generation cephalosporin for systemic use increased from 27 kg in 2001 to 65 kg in 2007, while the intramammary use increased from 14 kg in 2001 to 27 kg in 2007. The

prescription of intramammaries based on 3rd and 4th generation cephalosporins now comprises 23% of the total use of intramammaria in ADD. Milk from cows treated with intramammaria is often used as feed for the calves, and thus, the calves may be exposed to cephalosporins.

In 2006, amoxicillin was used for 92% of the treatments in turkeys but only for 47% in 2007, while the use of fluoroquinolones doubled from 7% of the treatments in 2006 to 16% in 2007. A number of other antimicrobial agents, including tetracyclines and macrolides which have not previously been prescribed routinely for turkeys, accounted for a significant part of the antimicrobial consumption in turkeys in 2007.
The antimicrobial consumption in broilers decreased by 26% from 2006 to 2007 despite a 5% increase in production and reached the lowest level since 2003. The use of fluoroquinolones in broilers decreased by 75% and was used in 6% of the treatments of broilers.
The use of antimicrobial in aquaculture was 3.7 tones in 2007, which was 54% higher than in 2005, probably due to unusually high summer temperatures in 2007. Sulfonamide/trimethoprim combination remained the most frequently used antimicrobial in aquaculture, comprising 86% of the consumption. The antimicrobial consumption was 217 mg/kg fish produced in salt water and 67 mg/kg fish produced in fresh water (assuming an unchanged production volume in 2007).

Antimicrobial consumption in humans
From 2006 to 2007, the overall consumption of antibacterial agents for systemic use in humans in Denmark increased by 7% to 35.6 million DDDs or 17.9 DDD/1,000 inhabitant-days.
In the primary health care sector, consumption of antibacterial agents increased by 6.6% to 16.2 DDD/1,000 inhabitant-days in 2007, without significant changes in the distribution of the antibacterial agents used. Consumption of beta-lactamase sensitive penicillins and penicillins with extended spectrum represented 55% of the total consumption. As for other agents the consumption of combinations of penicillins, including beta-lactamase inhibitors, fluoroquinolones and tetracyclines increased further in 2007. For tetracyclines one likely explanation was an increased use of doxycycline with a major peak value consumption in January 2007 which coincided with a change in recommendations for malaria prophylaxis to type IV prophylaxis (incl. doxycycline) after an outbreak of *Plasmodium falciparum* malaria in Goa, India reported on January 10.

In Danish hospitals, consumption of antibacterial agents continued to increase. From 1997 to 2007, average hospital consumption increased by 63% to an estimated 689 DDD/1,000 bed-days, whereas this increase was only 17% for the same period when presented as DDD/1,000 discharged patients. The difference between both indicators could be explained by the continuous decrease of the number of registered bed-days and, conversely, by the continuous increase of the number of registered discharges in Denmark. However, as in previous years, a change was observed in the distribution of antibacterial agents used – i.e. an increasing consumption of combinations of penicillins, including beta-lactamase inhibitors, cephalosporins, fluoroquinolones and carbapenems on behalf of β-lactamase sensitive penicillins, broad spectrum penicillins, aminoglycosides and macrolides. In 2007, cephalosporins, fluoroquinolones and carbapenems together comprised 34% of hospital antibacterial consumption as compared to 15% in 1997. Recent data suggest that this shift towards newer, broad-spectrum antimicrobial agents is already resulting in increased resistance in hospitals (see focus area on hospital consumption).

Resistance in zoonotic bacteria
In 2007, better travel information was obtained from humans with *Salmonella* infections. Based on telephone interviews, an estimated 40% of all human *Salmonella* infections were travel associated in 2007. Between 2006 and 2007, no significant changes in antimicrobial resistance were observed when comparing *Salmonella* Typhimurium from pigs and Danish pork except a significant decrease in ampicillin resistance in *S.* Typhimurium from Danish pork. In 2007, only chloramphenicol resistance was significantly higher in imported pork as compared to Danish pork. Resistance to tetracycline, ciprofloxacin and nalidixic acid in *S.* Typhimurium isolates from infections in humans was significantly higher among isolates from infections acquired abroad than among isolates from infections acquired in Denmark.
The occurrence of resistance to ampicillin and ciprofloxacin in *Salmonella* Enteritidis was significantly higher in travel associated human isolates as compared to domestically acquired isolates.
To achieve better travel information a sub sample of patients with a *Campylobacter* infection acquired in 2007 and where no information about travel was available were phone interviewed. Based on the phone interviews and information about travel provided by the general practitioners an estimated 30% of all human *Campylobacter* infections were travel associated in 2007.

Like in previous years, resistance to ciprofloxacin, nalidixic acid and tetracycline was significantly higher in *C. jejuni* from imported broiler meat compared to Danish broiler meat. The occurrence of resistance to ciprofloxacin, nalidixic acid and tetracycline was significantly higher in travel associated *C. jejuni* isolates compared to isolates acquired domestically.

Resistance in indicator bacteria

Only susceptibility results from *Enterococcus faecium, E. faecalis* and *Escherichia coli* from food producing animals collected at the time of slaughter were available in this report. From 2006 to 2007, a significant increase in erythromycin resistance was observed among *E. faecium* from pigs, this increase occurred concomitant with a significant increase in macrolide consumption in the pig production.

Resistance in bacteria from diagnostic submissions

The number of new cases with methicillin resistant *Staphylococcus aureus* (MRSA) decreased for the second year in row to 659 cases in 650 patients (from 851 and 706 cases in 2005 and 2006, respectively). 114 cases (17%) were acquired abroad. Of cases acquired in Denmark, 461 (70%) were diagnosed in primary health care. Of these, 125 cases were part of a health care related outbreak or had been admitted to hospital/nursing home within the previous 12 months. In 336 cases (73%) there were no hospital/nursing home associated risk factors, and thus the MRSA was community associated. In 42% of community associated cases, household transmission was seen. MRSA infections: Overall, 370 persons (56%) had infection at the time of diagnosis, most often skin and soft tissue infections. In 2007, both the number of hospital acquired infections and community onset but hospital associated infections fell significantly. The number of MRSA bacteremia cases fell also from 19 cases in 2006 to 8 cases in 2007 (0.6% of all *S. aureus* bacteremia cases). In contrast, the number of community associated infections and imported infections increased. Thirty-six percent of community associated infections were seen in persons of non-Danish origin.

The total reduction in the number of new cases and especially the decrease in hospital and health care related infections is very positive and probably related to the implementation of the new MRSA guidelines. In 2007, 14 human cases of MRSA CC398 were found and most of these had close contact to pigs. The probable existence of a zoonotic reservoir is of great concern and should be monitored closely.

Resistance to penicillins and macrolides in *Streptococcus pneumoniae* and Group A, B, C and G streptococci remained low in 2007.

Among *E. coli* urine isolates from primary health care, resistance to ciprofloxacin once again increased significantly, reaching 6.4% in 2007. In *E. coli* isolates from hospitals, ciprofloxacin resistance also increased significantly to 8.4% in urine isolates and 11.2% in blood isolates. These increases in ciprofloxacin resistance were consistent with parallel increases in consumption of fluoroquinolones (mainly ciprofloxacin) observed in recent years, both in primary health care and hospitals.

Resistance to ampicillin increased significantly among *E. coli* isolates from primary health care and hospitals. In urine isolates from both primary health care and hospitals ampicillin resistance reached 41%, and in *E. coli* blood isolates from hospitals it was 44%. The high level of ampicillin resistance corresponds to the steady increase over the years in the consumption of penicillins with extended spectrum.

In *E. coli* urine isolates from both primary health care and hospitals resistance to sulfonamides increased significantly in 2007 reaching 38% and 35%, respectively.

Among *E. coli* blood isolates, gentamicin resistance increased significantly to 3.8% in 2007. Also, cefuroxime resistance in *E. coli* blood isolates increased significantly to 5.4% in 2007. This increase in cefuroxime resistance is concomitant to a steep increase in the consumption of cephalosporins in hospitals in recent years.

Although antimicrobial resistance generally remains low for most antimicrobial agents and most bacteria commonly isolated from clinical samples from infected patients in Denmark, the increases observed in recent years suggest that this is changing and underline the importance of close monitoring of antimicrobial resistance, both in primary health care and in hospitals.

Focus Areas

Changes over 11 years in *Salmonella* serovar and phage type distributions as well as resistance profiles in the Danish pig population

In 1995, the Danish serological *Salmonella* surveillance programme in pigs was initiated, which identifies farms with a medium to high level *Salmonella* infection. In order to further characterize this *Salmonella* infection veterinarians are required to collect 20 pen faecal samples in each farm. A pen faecal sample is a composite sample from the pigs in the pen. A sub sample of the *Salmonella* isolates collected through this surveillance programme was serotyped, phage typed and tested for antimicrobial susceptibility to the following nine antimicrobial agents: ampicillin, chloramphenicol, gentamicin, nalidixic acid, colistin, streptomycin, sulfonamide, tetracycline and trimethoprim representing different antimicrobial classes. From mid 2005 and onwards, non-Typhimurium isolates were no longer antimicrobial susceptibility tested.

In a recent paper, changes in the *Salmonella* serovars, phage type distributions and resistance profiles in the Danish pig population were studied [Emborg H-D *et al.* 2008. J Antimicrob Chemother, published online]. A total of 13,396 *Salmonella* isolates were available for the analysis. Changes in serotype distribution among the most prevalent *Salmonella* serotypes are shown in Figure 1. *Salmonella* Typhimurium accounted for 9,109 isolates (68%) and of these 7,774 *S*. Typhimurium isolates were characterized by phage typing (529 - 1,075 isolates per year). A significant decrease was observed for *S*. Typhimurium from 75% in 1996 to 63% in 2007. The largest change over time was observed for *S*. Typhimurium DT12. In 1998, DT12 was the far most common S. Typhimurium phage type accounting for 47% of all *S*. Typhimurium phage types in Danish pigs and in 2007 the

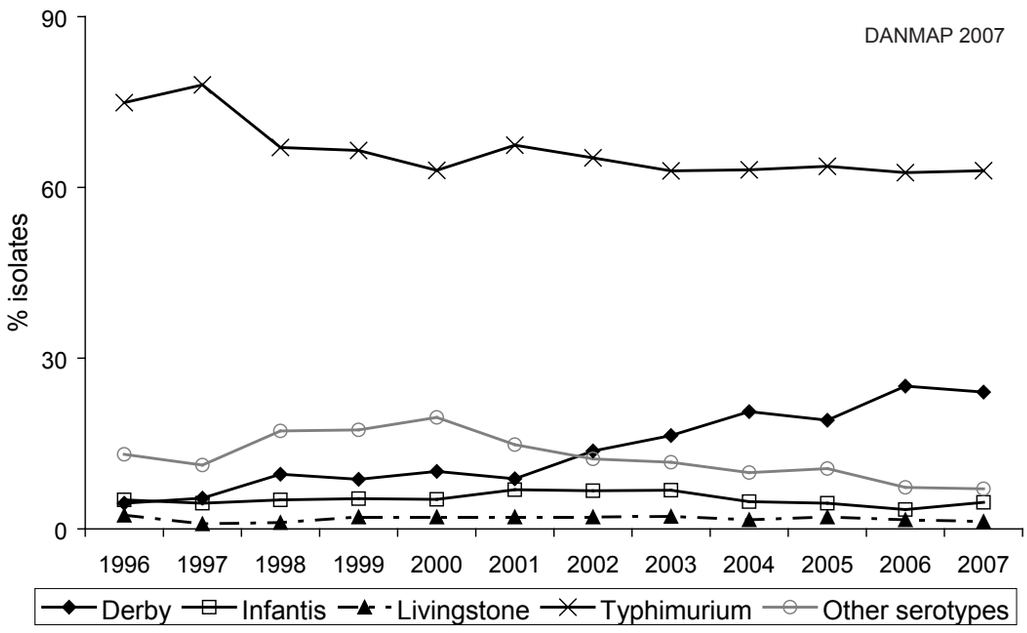

Figure 1. Changes in the distribution of the most prevalent Salmonella *serovars isolated from pig farms from 1996 to 2007. Source: Danish* Salmonella *surveillance programme in pigs 1996-2007*

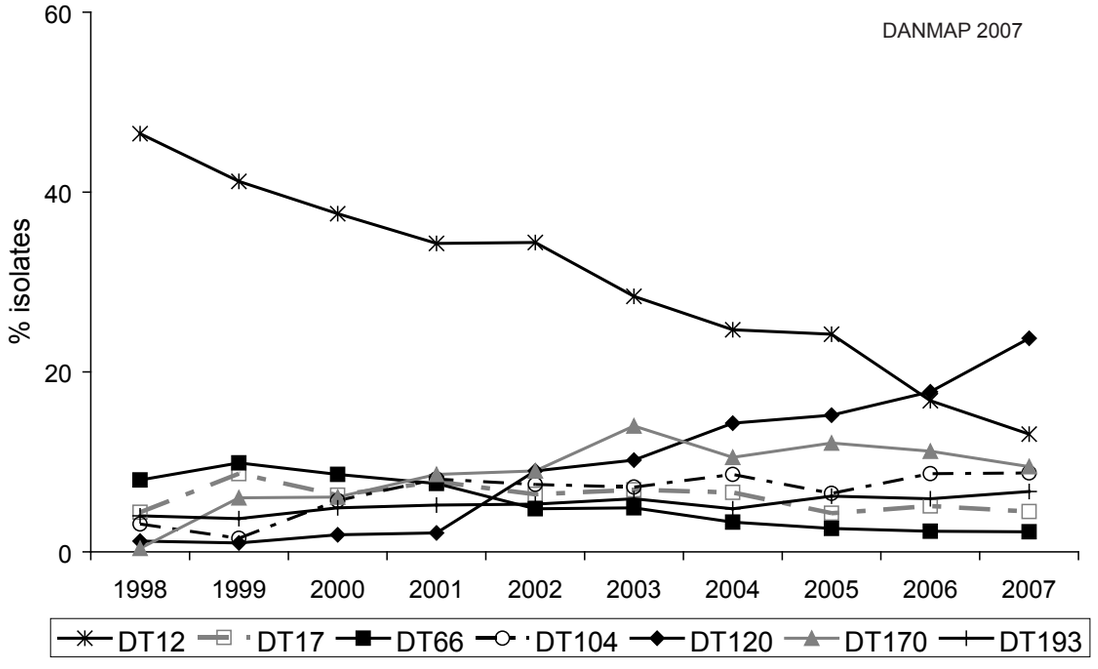

Figure 2. Changes in the distribution of the most prevalent Salmonella *Typhimurium phage types isolated from pig farms from 1998 to 2007. Source: Danish* Salmonella *surveillance programme in pigs 1998-2007*

Table 1. Occurrence of dominant resistance profiles (%) among the most common Salmonella *serovars and* Salmonella *Typhimurium phage types from Danish pigs*

DANMAP 2007

Serotypes	Phage types	Resistance profile	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	No. of isolates (%)
Derby		Fully susceptible	40	77	69	47	59	43	45	46	45			369 (47)
		TET	7	14	7	37	22	34	31	31	34			236 (30)
		No. of isolates	15	22	29	30	37	154	137	265	96			785
Infantis		Fully susceptible	90	80	91	78	75	81	93	85	96			256 (86)
		No. of isolates	10	15	11	18	24	75	58	61	27			299
Livingstone		Fully susceptible	0	67	100	71	100	91	75	81	43			76 (80)
		No. of isolates	1	3	5	7	8	23	20	21	7			95
Typhimurium	DT12	Fully susceptible	76	75	86	81	78	77	86	84	87	77	82	1188 (81)
		No. of isolates	139	92	81	94	83	266	160	207	181	88	76	1467
	DT17	Fully susceptible	64	36	88	75	92	83	94	89	79	85	100	257(85)
		No. of isolates	11	11	17	12	24	50	36	57	33	26	26	303
	DT66	Fully susceptible	69	75	84	100	93	84	70	89	60	82	93	190 (82)
		No. of isolates	16	16	25	22	14	38	27	28	20	11	14	231
	DT104	Fully susceptible	0	0	0	8	23	25	37	26	26	11	15	73 (22)
		AMP-CHL-STR-SUL-TET	0	60	67	85	62	52	47	44	50	64	72	188 (56)
		No. of isolates	1	5	3	13	13	48	38	70	46	45	53	335
	DT120	Fully susceptible	80	100	100	33	0	22	17	19	14	23	24	128 (21)
		AMP-STR-SUL-TET	0	0	0	0	25	49	52	51	59	49	49	305 (50)
		No. of isolates	5	3	1	6	4	67	54	122	114	92	140	608
	DT170	Fully susceptible	-	-		50	33	19	39	32	27	31	42	42	164 (34)
		STR-SUL-TET	-	-		50	42	62	50	61	65	60	46	53	272 (57)
		No. of isolates	0	0	6	12	21	66	77	89	93	59	57	480

occurrence had declined to 13% (Figure 2). From 1997 though 2007, 81% - 85% of all DT12, DT17 and DT66 isolates remained fully susceptible to all nine tested antimicrobial agents (Table 1) despite that the antimicrobial consumption in pigs and in particular tetracycline consumption has increased (see Figure 6 in Antimicrobial consumption). During the same period, *S*. Typhimurium DT120, DT170 and DT104 have emerged and in contrast only 21% - 34% of these isolates were fully susceptible to all nine antimicrobial agents (Table 1). Among the resistant phage types (DT104, DT120 and DT170) one resistance profile in each phage type was dominating. In DT104 the presence of the multidrug–resistant region *Salmonella* genomic island 1 (SGI1) is well described [Boyd *et al*., 2001. J Bacteriol. 183: 5725-32] which results in the resistance profile Ampicillin-Chloramphenicol-Streptomycin-Sulfonamide-Tetracycline. In DT120 the dominant resistance profile was Ampicillin-Streptomycin-Sulfonamide-Tetracycline, which occurred in 50% of all DT120 isolates (Table 1) while the resistance profile Streptomycin-Sulfonamide-Tetracycline dominanting in DT170 was present in less than 1% of the isolates. For DT170 the distribution between the two resistance profiles Ampicillin-Streptomycin-Sulfonamide-Tetracycline and Streptomycin-Sulfonamide-Tetracycline was opposite (Table 1).

Based on the experiences from especially United Kingdom where DT104 has spread rapidly it was expected that DT104 would have become more prevalent in Danish pig production [Threlfall *et al.*, 2000. Int J Food Microbiol. 62: 1-5]. However, since DT104 was first detected in the Danish pig production a trace back strategy based on trade relations was initiated to reduce the spread of DT104. These precautions were not taken against any other phage types [Wegener *et al.*, 2003. Emerg Infect Dis. 9: 774-80]. Results from this study and results from a recent study indicated that the occurrence of DT104 in the Danish pig production would have been higher if no precautions had been taken [Skov *et al*., 2008. Epidemiol Infect. 136(8): 1124-30].

Salmonella Derby was the second most common *Salmonella* serovar in pigs and the occurrence increased significantly from 5% in 1996 to 25% in 2006 (Figure 1). Tetracycline resistance alone (30%) was the most common resistance profile in *S*. Derby (Table 1). This profile was most prevalent from 2000 to 2006 where tetracycline consumption also doubled. The prevalence of *Salmonella* Infantis and *Salmonella* Livingstone remained unchanged during the study period (Figure 1) and between 80% and 86% of the isolates were susceptible to all nine antimicrobial agents tested.

This analysis indicates that antimicrobial susceptible serovars and *S*. Typhimurium phage types only slowly become resistant although antimicrobial consumption increases. The observed emergence of resistance is caused by a change in clones. A previous study indicated that an increase in tetracycline consumption in Danish pigs selected for *S*. Typhimurium phage types that were resistant to tetracycline, resulting in a change in the phage type distribution over time [Emborg *et al.*, 2007. Microb Drug Resist. 13: 289-94]. These results support that the use of antimicrobial agents might select for multiple resistant clones and that this might be the driver of changes in antimicrobial resistance within a serovar.

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Prevalence of ESBL-producing bacteria among humans and animals in Denmark in 2007

Extended-spectrum beta-lactamases (ESBL) are bacterial enzymes that protect bacteria by degrading essential beta-lactam antibiotics, penicillins and cefalosporins, including 3rd generation cephalosporins. The ESBL genes are located on plasmids which also often carry genes that cause resistance to aminoglycosides and fluoroquinolones. Treatment options may therefore be limited to carbapenem antibiotics. ESBL-producing bacteria can occur as part of the intestinal flora in hospitalized patients, in healthy persons in the community and in production animals, and are like other enterobacteria transferred via the faecal-oral transmission route or via foods. The carrier state is a risk factor for subsequent infection with the same ESBL-producing bacterium, and infection is furthered by the presence of catheters and other foreign bodies. In the community, ESBL-producing bacteria are in humans most frequently seen in connection with urinary infection in elderly patients and patients with underlying diseases. In humans, a high correlation between increased use of cephalosporins and fluoroquinolones and selection of ESBL-producing enterobacteria is observed.

Human prevalence study

In previous DANMAP reports, sporadic cases of ESBL-producing bacteria have mostly been described and sufficient data on their prevalence have been lacking. From September through October 2007, we conducted the first nationwide prevalence study on ESBL-producing *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* from blood cultures and urine samples. During the two months, 13 of 15 Departments of Clinical Microbiology (covering 95% of the Danish population) participated in the study. A total of 18,259 patients were blood cultured and 47,504 patients had an urine culture taken. Among these patients we found a total of 14,674 positive cultures with *E. coli*, *K. pneumoniae* or *P. mirabilis,* of which 352 cultures were positive with an ESBL-producing bacteria (257 *E. coli*, 93 *K. pneumoniae* and 2 *P. mirabilis*), resulting in the prevalences shown in Table 2.

Table 2. Prevalences of ESBL-producing bacteria (%) in Danish hospitals from September through October 2007, Denmark

DANMAP 2007

Origin of the specimen	*E. coli*	*K. pneumoniae*
Blood cultures	4.2%	5.0%
Urine from hospital	2.3%	6.6%
Urine from outpatients	1.5%	2.7%

When numbers were correlated to population size in the different regions covered by the 13 laboratories we found an average of 6.9 (range 3.1 – 14.5) ESBL-producing bacteria per 100,000 inhabitants.
Preliminary results of 294 isolates showed that the ESBL enzymes responsible for the ESBL phenotype were CTX-M group 1 (72%), CTX-M group 2 (15%), SHV (8%), TEM (4%) and unknown (1%).
Susceptibility testing of the 298 isolates using tablet diffusion test with Rosco NeoSensitabs showed that all isolates were susceptible to meropenem while 90% were susceptible to cefoxitin and tigecycline, 80% to mecillinam, amikacin and temocillin, 60% to fosfomycin and nitrofurantoin, and 50% to gentamicin. The inhibitor combinations (piperacillin+tazobactam, amoxicillin+clavulanate, ticarcillin+clavulanate and ampicillin+sulbactam) had poor activity, 60% of the isolates were resistant to all combinations with the most active being piperacillin+tazobactam (40% susceptible).

Outbreak of a multiresistant ESBL-producing *K. pneumoniae* in a hospital

In April 2007, the first major outbreak of a gentamicin and ciprofloxacin-resistant ESBL-producing *K. pneumoniae* in Denmark was detected at the gastroenterology ward at Frederikssund Hospital. Since then a total of 33 patients infected or colonized with this outbreak strain was detected. The majority of patients had a urinary tract infection,

while three had bacteraemia/sepsis. The majority of the patients had severe underlying conditions such as cancer, hepatic cirrhosis, renal failure, etc. Seven of the 33 patients were detected by rectal screening of more than 280 patients in the seven most affected wards at Frederikssund and Hillerød Hospitals.

ESBL-positive patients were placed in strict isolation, the importance of proper hand hygiene and the use of hand disinfectants were emphasized, the patients' records were marked and a note detailing their infection status was added to the discharge summaries. At the affected wards the cleaning frequency in toilets and bathing facilities was doubled and disinfectants were used. Infection control nurses reviewed procedures and trained the staff and a number of toilets and bathing facilities were renovated.

ESBL-producing bacteria in food and animal production

Until august 2003, ESBL-producing *E. coli* and *Salmonella* were not isolated from production animals or food products in Denmark. As described in DANMAP reports from previous years, initial cases of ESBL-resistance were all associated with imported animals and imported food products. However, in 2005 the first two ESBL-producing *E. coli* from domestic bred pigs and cattle were reported and in the following year, the first ESBL-producing *Salmonella* isolate was detected in a Danish pig herd [Aarestrup *et al*., 2006. J. Antimicrob. Chemother. 57: 1258-9]. In 2006 and 2007, the number of ESBL-producing *E. coli* isolated from diagnostic samples from domestic bred pigs and cattle increased to seven cases in 2006 and 23 cases in 2007.

Food products in Denmark are not routinely tested for the presence of ESBL-producing bacteria. However, 1,650 *E. coli* samples were collected from imported and Danish broiler and turkey retail meat sold in Denmark in 2006 as part of the DANMAP surveillance program. Of these, approximately 1/3 of the isolates originated from Denmark and app. 1/3 from Germany. Among the 1,650 individual isolates, 21 (1.3%) isolates (19 originating from German broiler meat, and two from Brazilian and French broiler meat, respectively) were resistant to 3rd generation cephalosporins. All 19 German broiler meat products originated from the same German slaughterhouse but were not clonally related (manuscript in preparation).

Commentary

The mortality for bacteraemia caused by susceptible *E. coli* and *Klebsiella* strains is app. 20%, which increases two or three fold for ESBL-producing bacteria, as detection of resistance takes time and relevant antibiotic treatment may therefore be delayed. If the empirical sepsis treatment consists of monotherapy with a cephalosporin - which is a trend in Denmark due to exaggerated fear of adverse reactions to aminoglycosides - mortality may be even higher. Increased use of cephalosporins in humans (see Figure 3) has undoubtedly led to the present situation with increasing prevalence of ESBL-producing bacteria.

The increased use of 3rd and 4th generation cephalosporins in the pig and cattle production seems to be followed by a similar increase in the occurrence of ESBL-producing *E. coli* from these animals. From 2004 to 2007, the prevalence of ESBL-producing bacteria from pigs and cattle has more than tripled each year. If the use of 3rd and 4th generation cephalosporins to animals continues to increase, there is a risk that the prevalence of ESBL-producing bacteria in animals increase to a level, where these antimicrobial agents will no longer be effective for treatment of animals. Furthermore, the probability that ESBL-producing *E. coli* and *Salmonella* spread to the human population has increased, which, in worst case, could lead to treatment failure in humans.

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Increased antibacterial consumption in the Danish hospitals

To monitor the consumption and cost of medicinal products in Denmark, a national register of drug statistics was implemented in the early 1990s by the Danish Medicines Agency (Lægemiddelstyrelsen). On a monthly basis, community pharmacies report data on each prescription redeemed by patients, and hospital pharmacies report data on drugs dispensed to hospital wards.

Although 90% of antibacterial agents are consumed in primary healthcare, there is evidence to suggest that antibacterial selection pressure is much higher in hospitals [Monnet *et al.* 2000. Infect Control Hosp Epidemiol. 21: 91]. Therefore, monitoring antibacterial consumption in hospitals is important in order to establish a relationship with the occurrence of resistance.

Antibacterial consumption in Denmark, both in the community and in hospitals, has been considered one of the lowest per capita and one of the most narrow-spectrum amongst developed countries [Cars *et al.* 2001. Lancet 357: 1851-3]. Müller-Pebody *et al.* reported an increase and a change in pattern of antibacterial use between 1997 through 2001 at Danish hospitals. Especially the “broad-spectrum” and newer antibacterial agents i.e. of combinations of penicillins, including beta-lactamase inhibitor (J01CR), of cephalosporins (J01DC), of carbapenems (J01DH) and of fluoroquinolones (J01MA) increased during this period. Antibacterial resistance in the microorganisms commonly isolated from clinical samples remained very low and showed no significant increase during the study period. For example, resistance to cefuroxime, gentamicin and ciprofloxacin in *E. coli* clinical isolates in Denmark was still <5% in 2001 [Müller-Pebody *et al.* 2004. J Antimicrobial Chemother. 54: 1122-6].

In our study, the increase in antibacterial consumption in hospitals has been investigated further for the following years up to 2007.

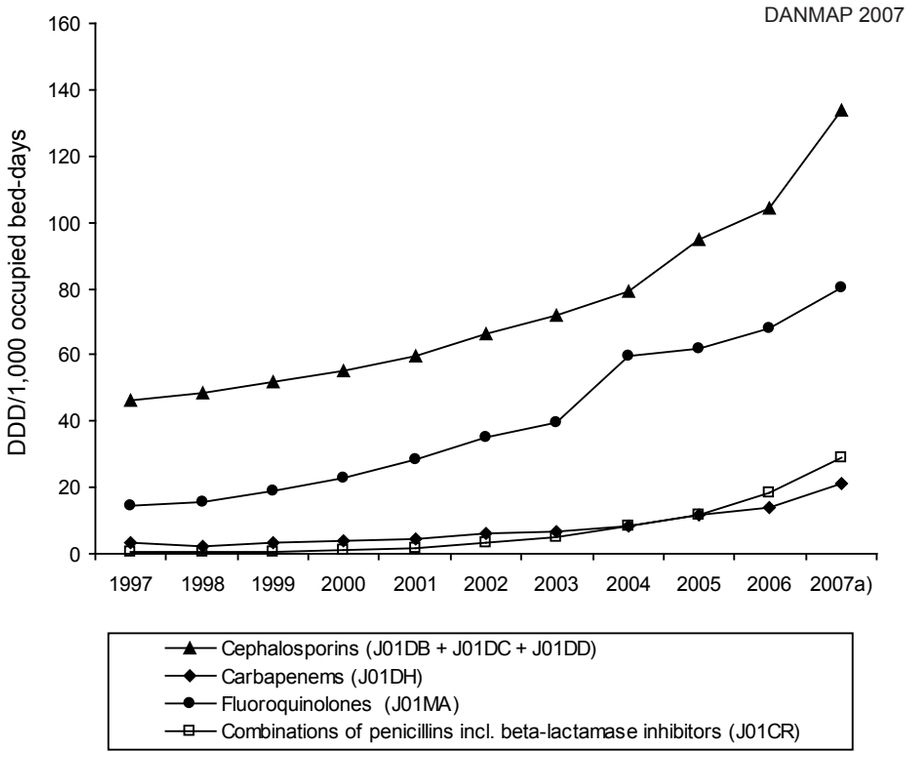

Figure 3. Hospital consumption represented by selected classes of antibacterials for systemic use, Denmark.
a) Estimated number of occupied bed-days

The consumption of “broad-spectrum” and newer antibacterial agents has continued to increase (Figure 3). Together, these amounted to 19% of the total consumption in hospitals in Denmark in 2001, rising to 34% in 2007. Antibacterial use is widely accepted as being responsible for selection and maintenance of antibacterial resistance in bacteria.

Trends in the use of fluoroquinolones (J01MA) and occurrence of fluoroquinolone resistance among *E. coli* isolates from blood infections are shown in Figure 4. Fluoroquinolone resistance in *E. coli* isolates from bacteraemic infections has been increasing steeply and significantly from 4% in 2003 to 13% in 2007. Consecutive data from eleven selected DCM on fluoroquinolone (ciprofloxacin and nalidixic acid) resistance among *E. coli* isolates from bacteraemic infections was available during the period 2003-2007. Data on either nalidixic acid (preferred) or ciprofloxacin resistance for the individual DCM were used. The increase in fluoroquinolone resistance was concomitant to the steady increase in the consumption of fluoroquinolones reported from hospitals (Figure 4) as well as from primary health care (Table 11) in recent years.

In *E. coli* urine isolates from hospitals a corresponding increase in fluoroquinolone resistance over the years has been observed (Figure 31) (See section on *E. coli* urine isolates obtained from hospital patients).

In contrast to the findings in the study by Müller-Pebody *et al.* a significant increase in gentamicin and cefuroxime resistance among *E. coli* isolates from bacteraemic infections has been observed during this study period (Figures 28-29). Other consequences of the increased consumption of antibacterials were the findings on ESBL-producing bacteria and the increase in *E. faecium* infections in the hospitals. (See Focus Area on ESBL and textbox on *E. faecium)*.

In Denmark, the observed increase in hospital antibacterial use, expressed in DDD/1,000 occupied bed-days, was

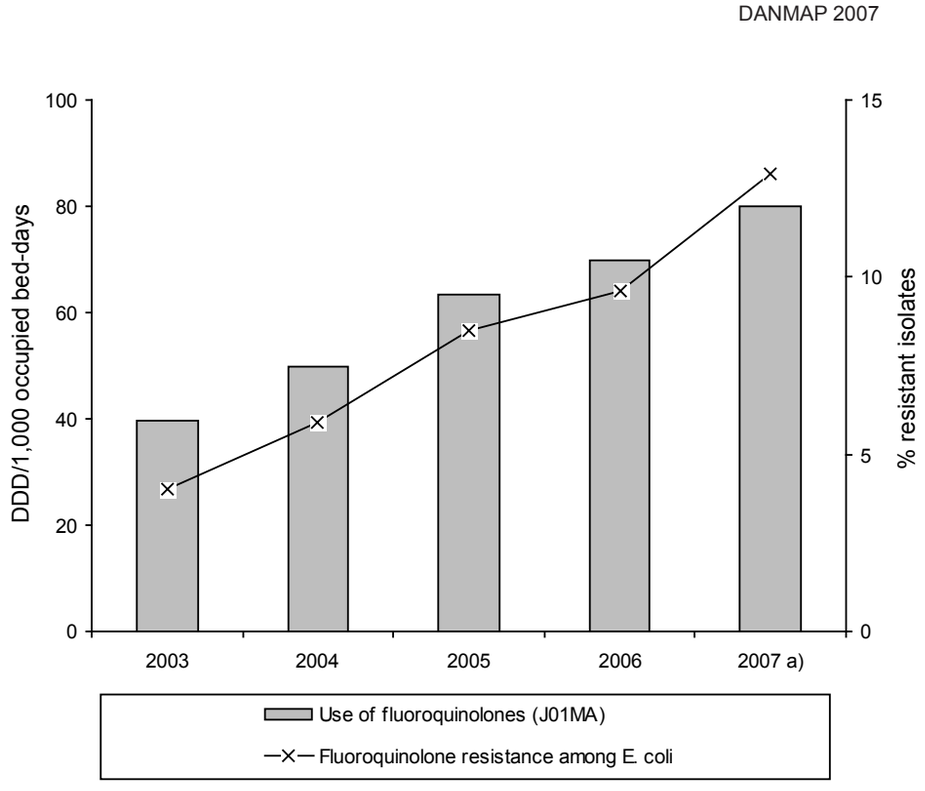

Figure 4. Trends in the use of fluoroquinolones (J01MA) and occurrence of fluoroquinolone resistance among E. coli *from blood infections*

a) Estimated number of occupied bed-days

due to both an increase in the number of antibacterial DDDs (numerator) and a decrease in the number of hospital bed-days (denominator).
The increase in the number of DDDs of antibacterials used in Danish hospitals may be explained by an increase in the daily dosage or by an increase in the number of antibacterial treatments (treatments given to an increasing number of admitted patients who more frequently required an antibiotic, e.g. for peri-operative antibiotic prophylaxis). The observed decrease in the number of hospital bed-days and increase in the number of hospital discharges shows that the average length of inpatient hospital stay has decreased. This trend could have contributed to the increase in antibacterial prescribing, at least as related to bed-days. As the number of surgical procedures has increased during the study period, increasingly greater quantities of antibacterials for surgical prophylaxis have probably been required.
However, more detailed data on the quality of antibacterial prescriptions including information on the indication for treatment, the dosage and the duration of treatment, are necessary to verify these hypotheses and interpret the changes in consumption. Unfortunately, antibacterial-consumption data are only made available to the Danish Medicines Agency as aggregated data at ward level.
Antibacterial consumption is still low in Denmark compared to other European countries, but the increase is cause of concern [http://www.esac.ua.ac.be/]. More detailed information on the specific consumption of the antibacterials might help to change the increasing use of the “broad-spectrum” and newer antibacterial agents.

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Demographic data

Demographic data - general information

Demographic information is presented in order to show the magnitude of animal and human populations in which antimicrobial agents were used during 2007.

The production of food animals (including animals for live export), meat, and the population of dairy cattle is shown in Table 3. Regarding pigs, the export of fattening pigs (15-50 kg) is shown, because pigs at this age have used a large amount of antimicrobial agents relative to their bodyweight at export.

Demographic data - New government structure in Denmark

On January 1st 2007 five new regions replaced the counties of Denmark as a result of the passing of the new local government reform (Figure 5). The reform defines a new public sector where municipalities, regions and the state each have their own identity in terms of tasks. The state establishes the general framework. The municipalities will be responsible for tasks that involve the citizens directly and therefore become the primary access point to the public sector for citizens and companies. Five new regions will be responsible for the health care service, the instigators of regional development and responsible for solving major operational tasks for the municipalities.

Table 4 provides information on the distribution of the human population in Denmark and on the Danish health care system by region.

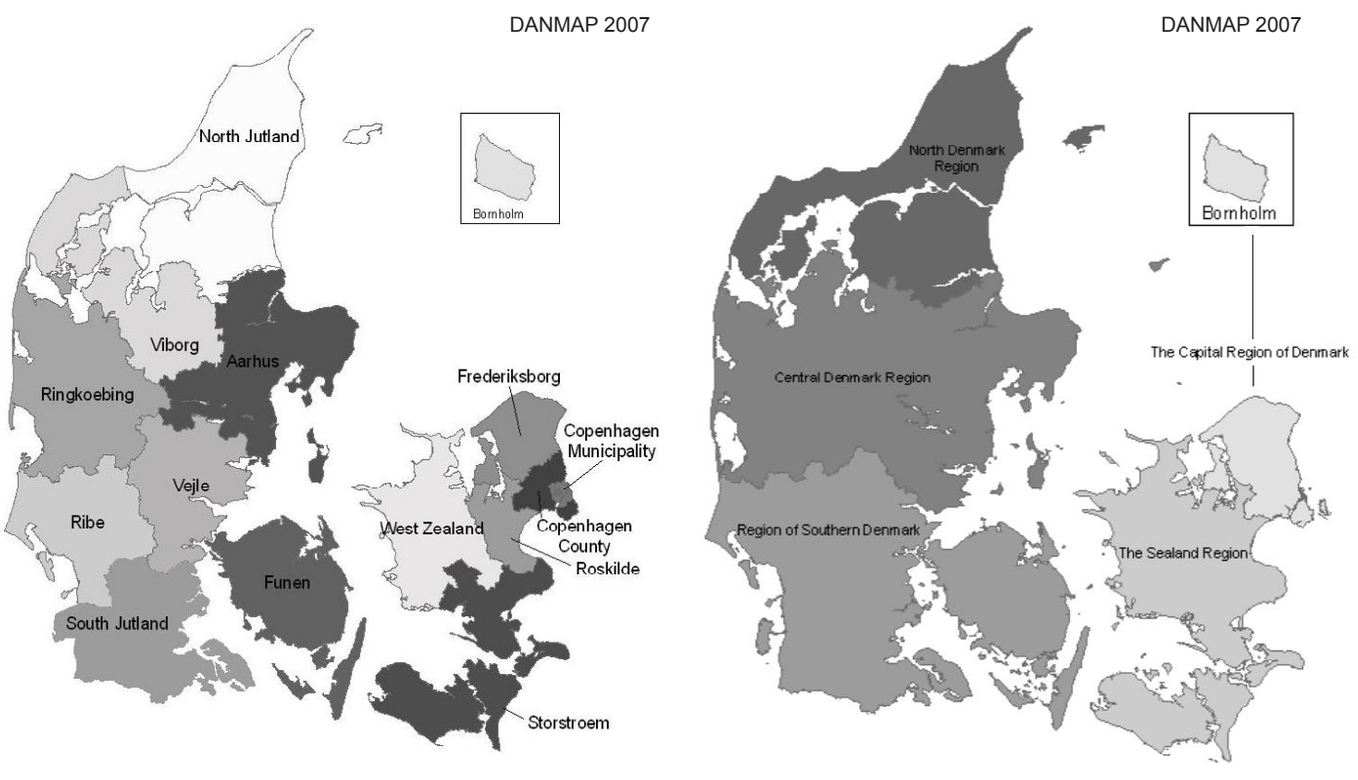

Figure 5. Former counties (left) and new regions (right) in Denmark

Table 3. Production of food animals (including export of live animals) and the production of meat and milk, Denmark

DANMAP 2007

Year	Broilers		Turkeys		Cattle (slaughtered)		Dairy cows		Pigs			Farmed fish	
												Fresh water	Salt water
	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg	1,000 heads	mill. kg milk	a) 1,000 heads	Export b) 1,000 heads	mill. kg	mill. kg	mill. kg
1990	94,560	116	571	2.5	789	219	753	4,542	16,425	-	1,260	-	-
1992	107,188	137	761	5.4	862	236	712	4,405	18,442	-	1,442	35	7
1994	116,036	152	1,091	8.6	813	210	700	4,442	20,651	-	1,604	35	7
1996	107,895	149	961	9.3	789	198	701	4,494	20,424	-	1,592	32	8
1998	126,063	168	1,124	11.6	732	179	669	4,468	22,738	-	1,770	32	7
2000	133,987	181	1,042	10.3	691	171	636	4,520	22,414	-	1,748	32	7
2001	136,603	192	1,086	13.2	653	169	623	4,418	23,199	-	1,836	31	8
2002	136,350	190	1,073	12.8	668	169	611	4,455	24,203	-	1,892	32	8
2003	129,861	181	777	11.2	625	161	596	4,540	24,434	-	1,898	34	8
2004	130,674	181	1,086	19.6	632	165	569	4,434	25,141	1,712	1,965	34	9
2005	120,498	180	1,237	17.4	549	145	559	4,449	25,758	2,720	1,988	31	8
2006	105,888	163	785	11.3	509	140	556	4,492	25,763	3,204	1,957	29	8
2007	103,236	171	1,009	14.4	512	141	545	4,515	26,311	3,522	2,046	-	-
Increase c) (%)	-3	5	29	27	1	1	-2	1	2	10	5		

Source: Statistics Denmark (www.dst.dk) and The Danish Directorate for Fisheries
a) Including export of all age groups
b) Export of 15-50 kg pigs
c) Increase from 2006 to 2007

Table 4. Distribution of the human population and health care structure by region, Denmark

DANMAP 2007

Region name	No. inhabitants (01/01/2007)	No. inh./km2 (2007)	No. inh./GP a) (2007)	No. bed-days b) (2006)	No. discharges b) (2006)	No. hospitals b) (2007)
The Capital Region of Denmark	1,636,749	639	1,493	1,777,222	407,717	10
The Sealand Region	816,118	112	1,531	697,163	167,624	4
Region of Southern Denmark	1,189,817	98	1,484	1,035,310	252,728	6
Central Denmark Region	1,227,428	94	1,439	1,047,919	262,584	12
North Denmark Region	576,972	73	1,555	519,530	112,479	4
Denmark c)	5,447,084	126	1,490	5,077,144	1,203,132	36

a) GP, general practitioner
b) Excluding private hospitals, psychiatric hospitals, specialised clinics, rehabilitation centres and hospices
c) Compared to the previous year no. inhabitants have increased by 0.4%, no. bed-days by 0.4% and no. discharges by 3.7%

Antimicrobial consumption

Antimicrobial consumption in animals

General view of antimicrobial consumption in animals

In Denmark all antimicrobial consumption is prescription only since 1998, with the exception of coccidiostats for poultry. The animal production and the total consumption of antimicrobials prescribed for production animals have increased gradually since 1996 (Table 3 and Table 5). From 2006 to 2007 an additional 5.2% increase was observed from 115.2 tonnes active antimicrobial compound in 2006 to 121.1 tonnes in 2007. The antimicrobial consumption in pigs comprised 80% of the total veterinary consumption while cattle, poultry and aquaculture comprised 12%, 0.5% and 3%, respectively.

Antimicrobial consumption in pigs

In 2007, the total antimicrobial consumption in pigs increased by 6.3% from 91 tonnes in 2006 to 97 tonnes, in 2007 (See Table 6 for details). In the same period, the production of pork increased by 4.5%, while the production of pigs (heads) increased by 2.1% (Table 3). In 2007, the consumption amounted to 3.9 ADD_{kg}/kg-pork-produced, representing a 3.9% increase per kg pork and a 6.9% increase per pig (head) produced (ADD_{kg}: see Appendix 1).

In 2007, tetracyclines, macrolides and pleuromutilins remained the most commonly used antimicrobials in pigs. Compared to 2006, tetracycline and macrolide consumption increased by 26% and 6.5%, respectively, per pig produced (Figure 6 and Table 27 in Appendix 1). In 2006 and 2007, tetracycline became the most commonly used drug in pigs, probably due to new treatment guidelines launched by the veterinary authorities in 2005, as an attempt to reduce the use of macrolides. The relative macrolide consumption in pigs decreased in 2005 and 2006, but an increase was observed again in 2007 (Figure 6). In 2007, the most commonly used aminoglycoside compound was taken off the marked, which resulted in a 46% decrease in aminoglycoside consumption in 2007 (Figure 6). The aminoglycosides are used for local intestinal treatment and was substituted mainly by tetracyclines and macrolides; this may explain up to one third of the increase in tetracycline consumption.

From 2001 to 2007, the overall antimicrobial consumption in pigs measured in ADDkg per pig produced increased by 19% (Figure 6). The major increase in antimicrobial consumption from 2002 to 2003 in sows and from 2003 to 2004 in weaners and finishers was, at least in part, related to the emergence of Postweaning Multisystemic Wasting Syndrom (Table 27 and Figures 40-42 in Appendix 1). A temporary decrease in the overall consumption per pig was observed from 2004 to 2006. The increase in 2007 was related to an increasing consumption in weaners and sows/piglets, and thus not related to increasing body weight at slaughter (Table 27 and Figures 40-42 in Appendix 1). In sows, the increase was mainly associated with use of tetracyclines and pleuromutilins. In weaners, the increase was associated with increased consumption of tetracyclines and macrolides.

Table 5. Trends in the estimated total consumption (kg active compound) of prescribed antimicrobials for production animals, Denmark

DANMAP 2007

ATC_{vet} group a)	Therapeutic group	1990	1992	1994	1996	1998	2000	2002	2004	2006	2007
QJ01AA	Tetracyclines	9,300 b)	22,000	36,500	12,900	12,100	24,000	24,500	29,500	32,650	38,200
QJ01CE	Penicillins, β–lactamase sensitive	5,000	6,700	9,400	7,200	14,300	15,100	17,400	20,900	22,600	23,850
QJ01C/QJ01D	Other penicillins, cephalosporins	1,200	2,500	4,400	5,800	6,700	7,300	9,900	12,900	11,550	11,500
QJ01EW	Sulfonamides + trimethoprim c)	3,800	7,900	9,500	4,800	7,700	7,000	10,600	11,500	13,800	13,850
QJ01EQ	Sulfonamides	8,700	5,900	5,600	2,100	1,000	1,000	900	850	750	750
QJ01F/QJ01XQ	Macrolides, lincosamides, pleuromutilins	10,900	12,900	11,400	7,600	7,100	15,600	19,200	24,200	22,050	23,800
QJ01G/QA07AA	Aminoglycosides	7,700	8,500	8,600	7,100	7,800	10,400	11,700	11,600	10,500	8,150
	Others c)	6,700	6,800	4,400	600	650	300	1,600	1,000	1,250	1,100
Total		53,400	73,200	89,900	48,000	57,300	80,700	95,900	112,500	115,150	121,100

1990-2000: Data based on reports from the pharmaceutical industry of total annual sales. (Data 1990-1994: Use of antibiotics in the pig production. Federation of Danish pig producers and slaughterhouses. N. E. Rønn (Ed.). 1996-2000: Danish Medicines Agency). Data 2001-2007: VetStat. For comparability between VetStat data and previous data, see DANMAP 2000. Only veterinary drugs are included. Veterinary drugs almost exclusively used in pets (tablets, capsules, ointment, eye/ear drops) are excluded. Dermal spray with tetracycline, used in production animals, is the only topical drug included

a) Only the major contributing ATCvet groups are mentioned

b) Kg active compound rounded to nearest 50 or 100

c) Consumption in aquaculture was not included before 2001

Antimicrobial consumption in cattle

In 2007, approximately 15 tonnes of antimicrobials was prescribed for cattle, which is the same level as in previous years. Among the antimicrobials for systemic treatment, 78% were used in cows and bulls, 18% in calves and 4% in heifers and steers (Table 7).

In cows, beta-lactamase sensitive penicillins followed by tetracyclines continued to be the most frequently used antimicrobials for systemic treatment (Table 7). In 2007, the consumption of intramammaria decreased by 3%. Cephalosporins, narrow spectrum and broad spectrum penicillins represented 39%, 22%, and 17% respectively of the intramammary use. The consumption of antimicrobials for systemic treatment increases by 10%, mainly due to an increase in beta-lactamase and tetracycline. From 2006 to 2007, the milk production increased by 0.5% and the beef production increased by 0.7% (Table 3).

In calves, the most important antimicrobials are tetracycline and macrolides (Table 7 and the section on macrolides below). From 2006 to 2007, the production of veal decreased by 5%, while the consumption of antimicrobials decreased by 17%. However, during the previous year, an increase in the consumption of antimicrobials in calves was observed concomitant to a decrease in the production of veal.

Antimicrobial consumption in poultry

The use of antimicrobials in poultry increased by 24% from 502 kg active compound in 2006 to 623 kg in 2007 (Table 6). This increase was due to a significant change in the choice of antimicrobials in 2007. The

Table 6. Antimicrobials (kg active compound) sold from pharmacies and feedmills by animal species and age group, Denmark

DANMAP 2007

Therapeutic group	Amcol	Amglc	Ceph	FQ	Quinol	Linco	Macro	Pleuro	Pen-β-sens	Pen-other	Sulfa-TMP	Tet	Others	Total
ATC_{vet} groups a)	QJ01B	QJ01G	QJ01DA	QJ01MA	QJ01MB	QJ01FF	QJ01FA	QJ01XX	QJ01CE	QJ01CA	QJ01E	QJ01AA	QJ01X	
Pigs														
- Sows and piglets	30	2,200	109	0	0	905	1,260	1,637	9,024	3,758	5,404	3,840	27	28,196
- Weaners	17	3,893	13	0	0	830	6,904	2,439	1,519	2,649	1,658	17,659	220	37,801
- Finishers	15	447	6	0	0	1,207	3,879	3,153	6,013	1,956	188	13,617	3	30,484
- Age not given	0	91	1	<0.1	0	47	137	147	203	89	83	468	3	1,270
Cattle b)														
- Cows and bulls	2	27	19	<0.1	0	3	22	4	807	41	23	97	0.2	1,044
- Calves <12 months	129	201	2	<0.1	0	6	32	1	278	132	305	323	3	1,412
- Heifers, steers	1	3	<0.1	<0.1	0	1	3	0	10	4	3	7	<0.1	31
- Age not given	4	31	3	0.4	0	11	35	34	120	56	57	144	1	497
Poultry														
- Broilers	0.8	0	0	0.7	0	0	21	0	0	24	10	0	0	56
- Rearing, broilers	0	0	0	2	0	0	2	0	0	38	5	0	0	47
- Layers, primarily rearing	0	0	0	0	0	0	0	0	0	16	5	0	0.4	21
- Turkeys	4	16	0	23	0	4	193	0	4	98	0	46	0.1	388
- Geese and ducks	0	<0.1	0	0.0	0	<0.1	0	0	0	2	1	0	0	3
- Gamebirds	0	0.9	0	0.4	0	<0.1	1	0.1	0.3	19	24	7	0.1	53
-Production category unknown	0.9	0.7	0	1.4	0	0.4	9	0.4	1.1	10	24	7	0.1	55
Other species														
- Small ruminants	<0.1	8	<0.1	<0.1	0	1	6	3	6	3	4	23	<0.1	54
- Fur animals	0.3	204	<0.1	<0.1	0	82	283	1	1	798	287	195	0.3	1,851
- Aquaculture	167	<0.1	<0.1	<0.1	327	0	0	0	<0.1	18	3,196	16	0.0	3,725
- Other production animals	<0.1	1	0.4	<0.1	0	0.5	0.4	0.1	3	4	48	1	0.1	59
- Horses	<0.1	3	27	1	0	3	1	0	16	24	124	10	4	212
- Pet animals	0.1	5	89	4	0	9	1	1	12	83	58	18	11	292
- Farm identified c)	<0.1	1	1	<0.1	0	<0.1	6	0	19	11	30	19	<0.1	86
For use in vet. practice d)														
- Pet animal practice	3	41	260	10	0	42	13	0.4	335	502	274	75	24	1,581
- Companion animal practice	0	31	0.7	2	0	0.5	0.6	<0.1	74	17	104	3	0	233
- Topical drugs	<0.1	4	0	0	0	0	0	0	0	0	0.2	58	11	73
- Cattle	91	720	51	4	0	55	373	25	5,008	1,105	2,229	1,430	2	11,093
- Intramammaries	0	32	77	0	0	4	0	0	72	127	12	0	1	325
- Miscellaneous d)	3	168	5	5	0	31	121	14	366	176	494	184	0.5	1,567
Total	469	8,131	664	53	327	3,242	13,301	7,459	23,893	11,762	14,650	38,247	312	122,508

Amcol=amphenicols; Amglc=aminoglycosides; Ceph=cephalosporins; FQ=fluoroquinolones; Quinol=other quinolones; Linco=lincosamides; Macro=macrolides; Pleuro=pleuromutilins; Pen-β-sens=beta-lactamase sensitive penicillins; Pen-other=penicillins with extended spectrum, cloxacillin and amoxicillin/clavulanic acid; Sulfa-TMP=sulfonamides+trimethoprim; Tet=tetracyclines. Sulfaclozin (a prescription coccidiostat) is included in the sulfonamide/trimethoprim group

a) Only the ATC group contributing mostly to the antimicrobial group are mentioned. Combination drugs are divided into active compounds

b) Only 20% of the prescribed antimicrobials for cattle are purchased at pharmacies. The remaining 80% are either administered or handed out by veterinary practitioners. Therefore, 80% of the antimicrobial consumption in cattle is registered as miscellaneous and intramammaries for use in practice

c) Sales to farmers (valid farm ID code recorded), valid code for animal species not recorded

d) This group contains drugs purchased mainly by veterinarians working in mixed practice, including an estimated 220 kg used by swine practitioners and an estimated 100 kg used in fur animals

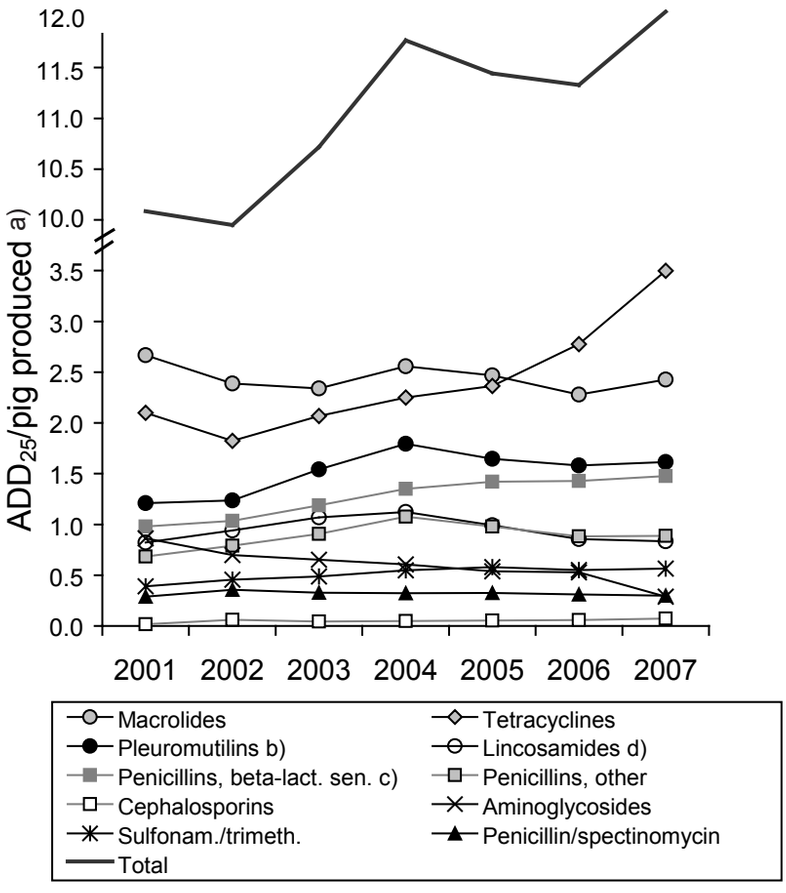

Figure 6. Trends in antimicrobial consumption (in ADDkg) in pigs, 2001-2007, Denmark

Amphenicols, colistin, fluoroquinolones, intramammaries and gynecologicals are not included in the figure. Data from veterinary practice are not included (<1% of the consumption in pigs)
a) The pigs are treated from <2 kg bodyweight (piglets) to more than 200 kg bodyweight (sows), and the majority of the treatments are for pigs between 7.5 to 50 kg. See also Figure 40-42 in Appendix 1 for relative consumption in the different age groups
b) Pleuromutilins comprise primarily tiamulin
c) Beta-lactamase sensitive penicillins
d) Lincosamide/spectinomycin combinations comprise 65% of this group

consumption of amoxicillin decreased while the use of macrolides and tetracycline increased. For the the latter, the dose is relatively high compared to the dose for amoxicillin in poultry. In turkey production the consumption decreases by 26% in 2007 measured in ADD_{kg} /kg turkey produced (Table 9). In 2006, amoxicillin was used for 92% of the treatments in turkeys but only for 47% in 2007, while the use of fluoroquinolones doubled from 7% of the treatments in 2006 to 16% in 2007. A number of other antimicrobials, including tetracycline and macrolides which have not previously been prescribed for turkeys, accounted for a significant part of the antimicrobial consumption in turkeys in 2007 (Table 9). According to the major poultry practioners,the shift away from amoxicillin was caused by increasing problems with broad spectrum penicillin resistance in *E. coli* infections in imported chicks. The antimicrobial consumption in broilers decreased by 26% from 2006 to 2007 despite a 5% increase in production and reached the lowest level since 2003. The use of fluoroquinolones in broilers decreased by 75%, and was used in 6% of the treatments of broilers in 2007. Like in turkeys an increase in other antimicrobials like sulfonamide and macrolides was observed (Table 8).

In 2007, the veterinary practitioners specialised in poultry received instructions from the veterinary control authority to use antimicrobials approved for other animal species rather than fluoroquinolones in case of resistance to amoxicillin. These instructions together with problems with antimicrobial resistance have probably caused the changes in antimicrobial choices observed in the poultry production in 2007. Large annual fluctuations in antimicrobial consumption were seen for broilers and turkeys, reflecting that disease outbreaks in individual farms have large effect on the - usually low - annual antimicrobial consumption (Tables

Table 7. Consumption of antimicrobials in cattle given as Defined Animal Daily Doses (ADDs), 2004-2007, Denmark

DANMAP 2007

		Pharmacies and feed mills a)															
Age group		Cows, bulls				Calves				Heifers and steers				Unknown			
Animal standard weight		600 kg				100 kg				300 kg				100 kg			
		2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007
ATC_{vet} group	Therapeutic group	ADD (1,000s)															
QJ01A	Tetracyclines	6	5	6	18	415	405	387	410	3	2	2	2	22	41	101	76
QJ01B	Amphenicols	<1	<1	0	<1	38	40	44	62	<1	<1	<1	<1	2	2	3	2
QJ01CE	Penicillin b)	15	24	24	100	151	123	122	129	1	1	1	2	15	73	86	77
QJ01CA/CR	Penicillins, other	2	2	2	3	178	147	102	85	2	<1	<1	<1	24	178	216	108
QJ01DA	Cephalosporins	2	3	3	10	20	14	12	17	<1	<1	<1	<1	1	4	7	7
QJ01E	Sulfonamid./trimeth.	3	2	2	2	127	126	111	121	<1	<1	<1	<1	8	14	30	23
QJ01FA	Macrolides	5	4	4	3	29	56	103	97	<1	<1	<1	2	6	103	182	69
QJ01FF	Lincosamides c)	1	1	1	1	14	9	8	11	<1	<1	<1	<1	3	23	46	18
QJ01G/QA07AA	Aminoglycosides	<1	<1	<1	0	62	52	57	45	0	<1	<1	<1	3	10	33	6
QA07AA10	Colistin (local GI)	0	0	0	0	4	4	5	6	0	0	<1	<1	1	2	4	1
QJ01MA	Fluoroquinolones	0	0	0	0	3	0	<1	0	0	0	0	<1	0	<1	<1	1
QJ01RA01	Penicillin/spectin. d)	1	1	1	3	92	96	96	86	<1	<1	<1	<1	5	7	13	13
QJ01X	Other antimicrobials	1	0	<1	1	1	0	0	1	<1	0	0	0	11	12	89	38
QJ51	Intramammaries e)	49	51	60	137	1	1	<1	<1	<1	<1	<1	<1	0	1	0	0
QG01AA	Gynecologic (local)	<1	1	<1	<1	0	0	0	0	0	0	0	0	0	0	0	0
Total		85	94	106	281	1,142	1,087	1,385	1,081	9	7	7	8	100	468	809	441

		Veterinary practice a)											
Age group		Cows, bulls				Calves				Heifers and steers			
Animal standard weight		600 kg				100 kg				300 kg			
		2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007
ATC_{vet} group	Therapeutic group	ADD (1,000s)											
QJ01A	Tetracyclines	163	173	181	205	153	187	158	155	14	16	16	22
QJ01B	Amphenicols	<1	1	1	1	14	24	23	30	<1	0	<1	0
QJ01CE	Penicillin b)	447	450	459	480	50	46	53	50	26	25	25	30
QJ01CA/CR	Penicillins, other	88	76	75	85	63	71	57	54	6	5	4	6
QJ01DA	Cephalosporins	56	41	41	50	17	12	10	11	4	2	2	3
QJ01E	Sulfonamid./trimeth.	68	59	59	62	51	38	46	41	3	2	2	3
QJ01FA	Macrolides	97	81	74	55	17	43	29	31	5	4	4	3
QJ01FF	Lincosamides c)	3	1	<1	<1	13	9	4	4	<1	<1	<1	<1
QJ01G/QA07AA	Aminoglycosides	3	1	1	1	42	64	50	44	<1	0	0	<1
QA07AA10	Colistin (local GI)	0	0	0	0	2	17	2	2	0	0	0	0
QJ01MA	Fluoroquinolones	<1	0	0	0	4	1	1	<1	<1	0	<1	<1
QJ01RA01	Penicillin/spectin d)	18	20	19	24	45	42	38	43	5	2	3	3
QJ01X	Other antimicrobials	1	0	<1	0	0	0	<1	0	0	0	0	0
QJ51	Intramammaries e)	1,074	1,085	1,082	974	0	0	0	0	14	13	11	14
QG01AA	Gynecologic (local)	119	99	97	98	0	0	0	0	4	4	3	6
Total		2,145	2,099	2,135	2,032	473	511	470	462	82	73	71	96

a) Data from veterinary practice are shown separately, because the use in cattle practice is underestimated by up to 20%
b) Beta-lactamase sensitive penicillins
c) Comprises both lincomycin and lincomycin/spectinomycin combinations
d) Combination of benzylpenicillin and spectinomycin
e) Regarding intramammaries, data from pharmacies are used to estimate use in practice (<1% overestimated)

8 and 9). In 2007, the consumption of antimicrobials in the broiler production (including parent flocks) was 0.03 ADDkg/kg-broiler-meat produced, and in turkeys, the consumption was 1.0 ADDkg/kg-turkey-meat produced. The consumption was considerably higher in game birds, with an estimated 2.5 ADDkg/kg-meat produced.

Antimicrobial consumption in fur animals, aquaculture and companion animals

In Denmark in 2007, the production of fur animals included 14.5 million mink, 28,000 chinchillas and a minor production of foxes. The production of mink increased by 7% compared to 2006. The use of antimicrobial in fur animals increased by 8% from 1800 kg in 2006 to 1950 kg in 2007 (incl. use in practice). The use of aminoglycosides decreased by 45%, probably because some of the products have been taken of the marked. Instead, the use of tetracyclines and broad-spectrum penicillins has increased. Broad-spectrum penicillins remain the most commonly used drugs in fur animals, comprising 43% of the antimicrobial consumption in 2007.

Table 8. Consumption of prescribed antimicrobials in domestic fowl given as Animal Daily Doses per kg (ADDkg), Denmark

DANMAP 2007

Production type		Broilers				Rearing for broiler production				Layers and layer rearing				Production type unknown a)			
		2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007
ATC_{vet} code	Therapeutic group	ADD_{kg} (1,000s)															
QA07AA	Aminoglycosides	0	0	0	0	0	0	0	0	0	0	0	0	300	81	133	0
QA07AA	Colistin				0				0				75				3
QJ01A	Tetracyclines	2	32	0	0	0	0	0	0	2	8	0	0	106	56	148	136
QJ01B	Amphenicol				36				0				0				33
QJ01CA	Amoxicillin	4,469	3,708	2,570	1,708	5,760	3,896	6,100	2,754	1,066	675	437	1,150	3,657	2,223	3,538	721
QJ01E/QP51	Sulfonamides b)	56	48	40	168	0	0	15	79	210	228	125	96	439	165	178	383
QJ01FA	Macrolides	29	3	0	289	0	0	0	22	0	0	11	0	90	3	4	118
QJ01FF	Lincosamides c)	20	0	0	0	0	0	0	0	8	0	0	0	4	40	0	22
QJ01MA	Fluoroquinolones	603	171	550	130	420	400	104	190	100	0	0	0	131	40	162	23
QJ01X	Pleuromutilins	75	0	0	0	0	0	0	0	0	3	0	0	3	5	0	8
Total		5,254	3,962	3,160	2,331	6,180	4,296	6,219	3,045	1,386	913	573	1,321	4,729	2,613	4,162	1,445

Includes data from all sources (pharmacies, feedmills and veterinary practice)
a) May include other species than domestic fowl
b) Includes sulfaclozin, a coccidiostat/antibacterial on prescription
c) Lincomycin in combination with spectinomycin

Table 9. Consumption of antimicrobials in other than domestic fowl given as Animal Daily Doses per kg (ADDkg), Denmark

DANMAP 2007

Production type		Turkeys				Ducks, geese				Game birds			
		2004	2005	2006	2007	2004	2005	2006	2007	2004	2005	2006	2007
ATC_{vet} code	Therapeutic group	ADD_{kg} (1,000s)											
QA07AA	Aminoglycosides	200	100	0	380	0	0	0	0	167	100	12	33
QA07AA	Colistin	0	0	0	162	0	0	0	0	0	0	15	15
QJ01A	Tetracyclines	0	60	150	1,525	14	0	0	0	148	94	76	146
QJ01B	Amphenicol	0	0	0	214	0	0	0	0	0	0	0	0
QJ01CE	Penicillin, β-lact. sens a)	0	0	0	263	0	0	0	0	0	0	0	0
QJ01CA	Amoxicillin	4,871	8,363	14,083	6,788	400	375	1,025	113	966	1,852	1,750	1,346
QJ01E/QP51	Sulfonamides b)	36	68	45	0	0	0	0	21	459	398	235	406
QJ01FA	Macrolides	7	0	0	2,547	11	12	1	0	113	177	36	16
QJ01FF	Lincosamides c)	0	100	0	242	0	0	0	2	0	14	8	6
QJ01MA	Fluoroquinolones	1,607	1,260	1,040	2,320	150	0	0	0	30	0	10	40
QJ01X	Pleuromutilins	0	0	0	0	3	0	0	0	18	13	0	5
Total		6,721	9,950	15,318	14,446	578	387	1,026	136	1,900	2,647	2,141	2,013

a) Beta-lactamase sensitive penicillins
a) Includes sulfaclozin, a coccidiostat/antibacaterial on prescription
b) Lincomycin in combination with spectinomycin

The use of antimicrobial agents in aquaculture is affected by water temperature. In 2006, the average air temperature during June-August was 2.10^{0}C above normal and in 2007 it was 0.90^{0}C above normal. The unusually warm summer period is the most likely reason why the consumption of antimicrobial in aquaculture increased by 54% from 2400 kg in 2005 to 3720 kg in 2007.
Sulfonamide/trimethoprim remained the most frequently used antimicrobial in aquaculture in 2007, comprising 86% of the consumption. Additionally, quinolones (9%) and amfenicoles (5%) are commonly used.
The antimicrobial consumption was 217 mg/kg fish produced in salt water and 67 mg/kg fish produced in fresh water (assuming an unchanged production in 2007 compared to 2006).

In pet animals, an estimated 2.2 tonnes of antimicrobial was used in 2007 for a population of app. 550,000 dogs, 650.000 cats and other pets. (Table 6). The most commonly used antimicrobials were amoxicillin with clavulanic acid (425 kg) and cephalosporin (350 kg) mainly for oral use, and narrow spectrum penicillin (estimated 380 kg) and sulfonamide/trimethoprim (est. 400 kg) mainly for parenteral use. An estimated 16 kg fluoroquinolones was used in pet animals, comprising 30% of the total veterinary consumption of fluoroquinolones.

Cephalosporins

In Denmark, the 3rd and 4th generation cephalosporins ceftiofur og cefquinome are approved for systemic treatment of cattle and pigs, and cefoperazone and cefquinome are approved for intramammary treatment in cattle. In addition, the 4th generation cephalosporin cefovecin was marketed for systemic treatment of dogs and cats in 2007. First generation cephalosporins are approved for intramammary treatment of cows (cefapirin, cefalexin) and for systemic treatment of dogs and cats (cefadroxil and cefalexin).

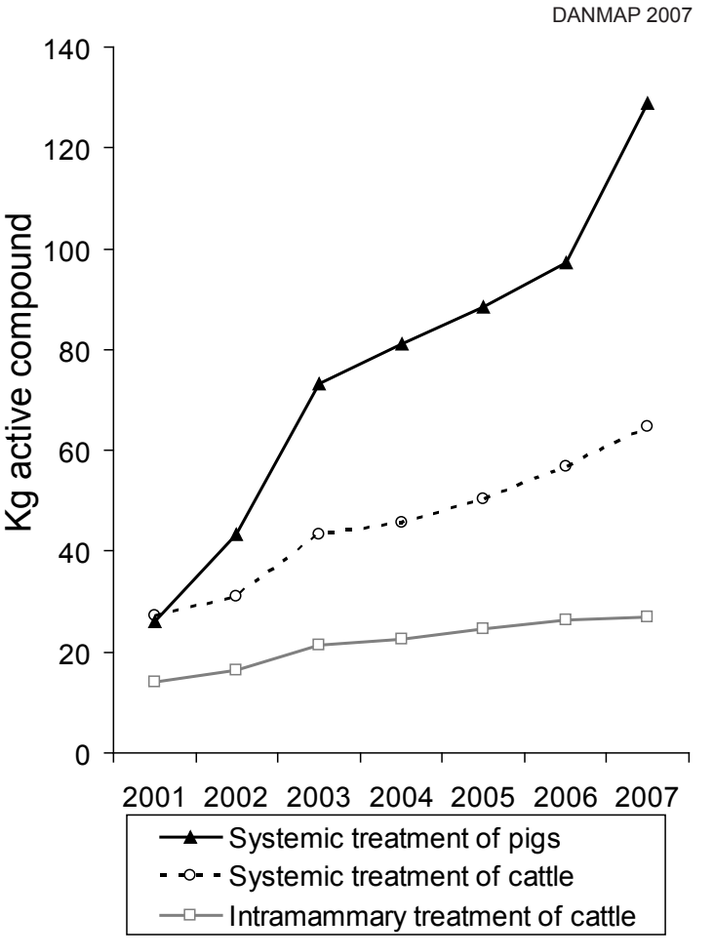

Figure 7. Use of 3rd and 4th generation cephalosporins in pigs and cattle, 2001-2007, Denmark

Broad spectrum cephalosporins (3rd and 4th generation) comprise only 1% of the cephalosporin used in pet animals, 100% of the systemic use of cephalosporin in cattle and pigs, and 32% of the intramammary use of cephalosporin. The use of broad-spectrum cephalosporins is of particular importance in selection of extended spectrum beta-lactamase (ESBL) resistance. The emergence of ESBL is critical, both due to the potential spread to humans and because it compromises the use of penicillins in animals.

The prescription of cephalosporins for pigs increased from 24 kg in 2001 to 129 kg in 2007 (Figure 7) of which 83% was used in sow herds. A previous study indicated that cephalosporins were commonly used for prophylactic treatment of umbilical infection in the piglets as one injection on the 1st or 2nd day after birth. Feedback from veterinarians and the medical industry has supported that umbilical infection was an important indication for cephalosporin prescriptions in pigs. Most pig farms have a monthly visit by a veterinarian and at these visits antimicrobials are prescribed for treatment the next 30 days. Data from VetStat show that in 2001, 42 farms with sows/piglets received nine or more cephalosporin prescriptions, while in 2007 this had increased to 282 farms (Figure 8). These 282 farms produced 14% of all sows/piglets in Denmark in 2007 and received 59% of the cephalosporin prescribed for sows/piglets. In these farms, the consumption corresponded to 0.8 ADD_{200}/sow-year or 3.5 ADD_2 (dose for 2 kg pig) per piglet produced. Farms receiving 3 to 8 cephalosporin prescriptions produced 15% of the weaners in 2007. In these farms, the consumption corresponded to 0.3 ADD_{200}/sow-year or 1.5 ADD_2 per piglet produced. This change in prescription habits suggests that the consumption of cephalosporins in pigs is changing from occasional prescription to more systematic prescription in herds producing 14-29% of the weaned pigs.

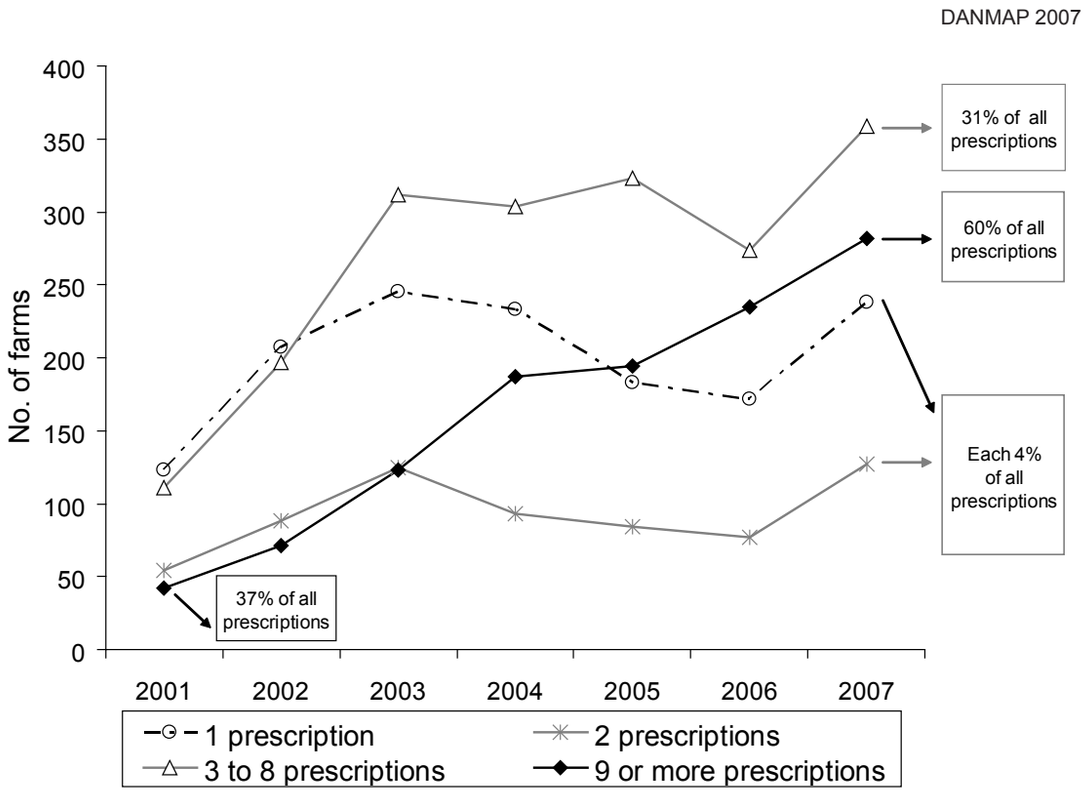

Figure 8. Number of cephalosporin prescriptions for sows and piglets per farm, 2001-2007, Denmark

In cattle, the use of cephalosporin for systemic use increased from 27 kg in 2001 to 65 kg in 2007 while the intramammary use increased from 14 kg in 2001 to 27 kg in 2007 (Figure 7). Herds with frequent parenteral use of cephalosporin (> 25 annual prescriptions, mostly for individual treatment) have increased from 127 herds in 2003 to 327 herds in 2007. In cattle, 90% of all cephalosporin prescriptions for parenteral treatment were for cows (Table 7) and the primary indication was for treatment of infection in "limbs, CNS or skin". Systemic treatment with cephalosporin is used frequently (> 25 annual prescriptions) for individual treatment in herds housing 11% of the cows, while in calves it is mainly used occasionally (60% of the antimicrobial is prescribed for farms receiving only 1 or 2 annual prescriptions). However, milk from cows treated with antimicrobials is often used as feed for the calves, thus, exposing the calves to antimicrobial including cephalosporin. The prescription of intramammaries based on 3rd and 4th generation cephalosporin now comprises 23% of the total use of intramammaria in ADD. Thus, a large proportion of the cattle population is treated or exposed to these antimicrobials.

Macrolide consumption and use of long-acting drugs

The consumption of macrolides in pigs decreased from 2004 to 2006 probably due to introduction of new treatment guidelines by the veterinary authorities in 2005. However, from 2006 to 2007 the macrolide consumption increased again by 19% from 10,110 kg active compound in 2006 to 12,180 kg in 2007, corresponding to a 6.5% increase per pig produced. In particular, in weaners a 20% increase in use of macrolide was observed (Table 27 in Appendix 1). Measured in course doses, the increase in macrolide consumption is larger than indicated in Figure 6, due to an 18% increase in long-acting macrolide from 2006-2007.

In 2005, acetylisovaleryltylosin and tulathromycin were approved for oral and parenteral use, respectively. Tulathromycin is a highly potent, long acting parenteral macrolide, and one injection constitutes a full treatment course dose (approved course dose, ACD). Therefore, when tulathromycin is commonly used, the trend in macrolide consumption is not well described using neither the ADD-system nor kg-active-compound. The

use of tulathromycin is of particular interest, due to prior experience in the human sector with the closely related macrolide azithromycin - which also exhibits extended elimination. These experiences suggests a higher correlation with development of resistance against macrolides than that of the shorter-acting erythromycin.

In weaners and finishers, tulathromycin comprised less than 1% of the macrolide consumption in 2007 and did not significantly affect the overall trend observed in use of macrolides (Table 27 in Appendix 1).
In sows, parenteral treatment is widely used and the consumption of tulathromycin has increased significantly since the marketing in 2005. While the use of macrolides in sows measured in ADD seemed to decrease during 2004 through 2006, the use of macrolides in sows actually increased slightly as measured in ACD's (Figure 9). From 2004 to 2007, the macrolide use in sows increased by 93% measured in ACD's, but only by 16% measured in ADD's. In Figure 9, the distance between the curve showing number of ADD's and the curve showing number of ACD's is an indicator of the proportion of long acting drugs.

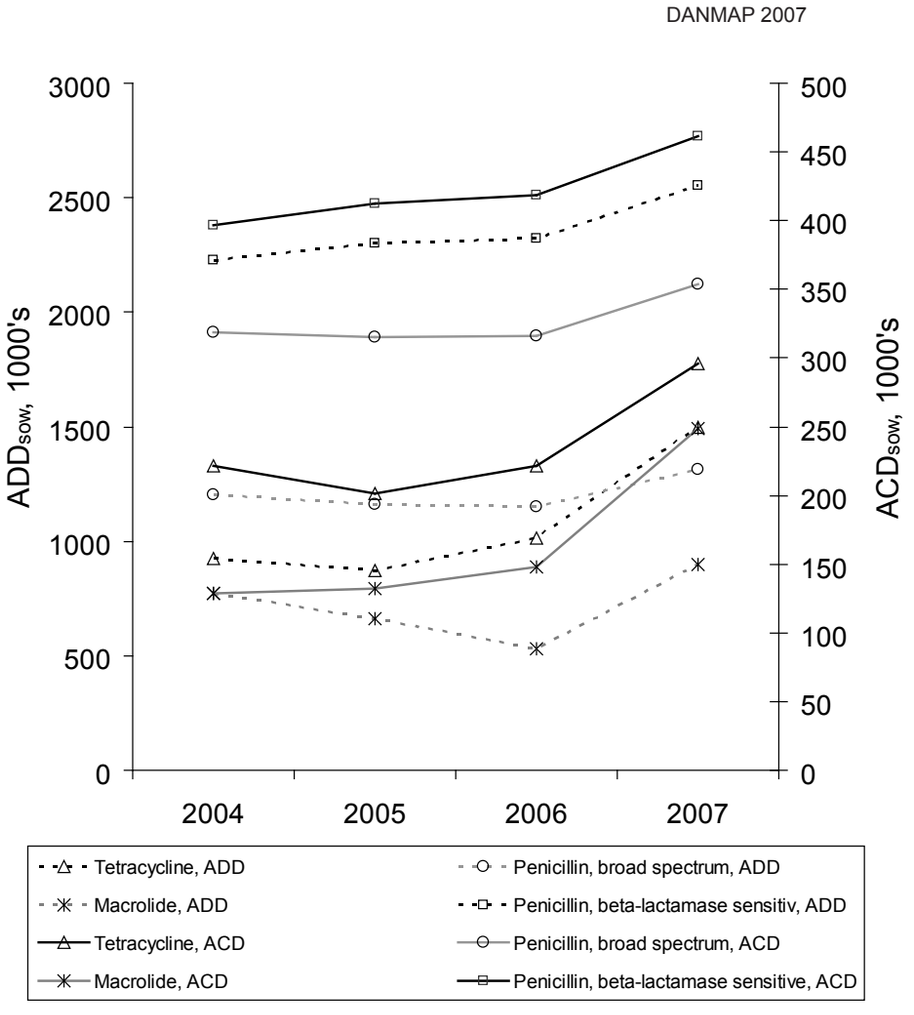

Figure 9. Trends in consumption of tetracyclines, penicillins and macrolides in sows measured in defined animal course doses (ACD) and defined animal daily doses (ADD), 2004-2007, Denmark

ACD_{sow} is the average course dose for sows (bodyweight 200 kg). It is assumed that 6 days parenteral treatment (eg. 2 injections of 3 days duration) correspond to the therapeutic duration of one treatment with tulathromycin. The duration of oral treatment is defined according to Cleveland-Nielsen A. and Jensen VF. 2006 proceedings (050-3), IPVS Congress. (6.1 day for tetracyclines, 6 days for macrolides and 5.3 days for penicillin)

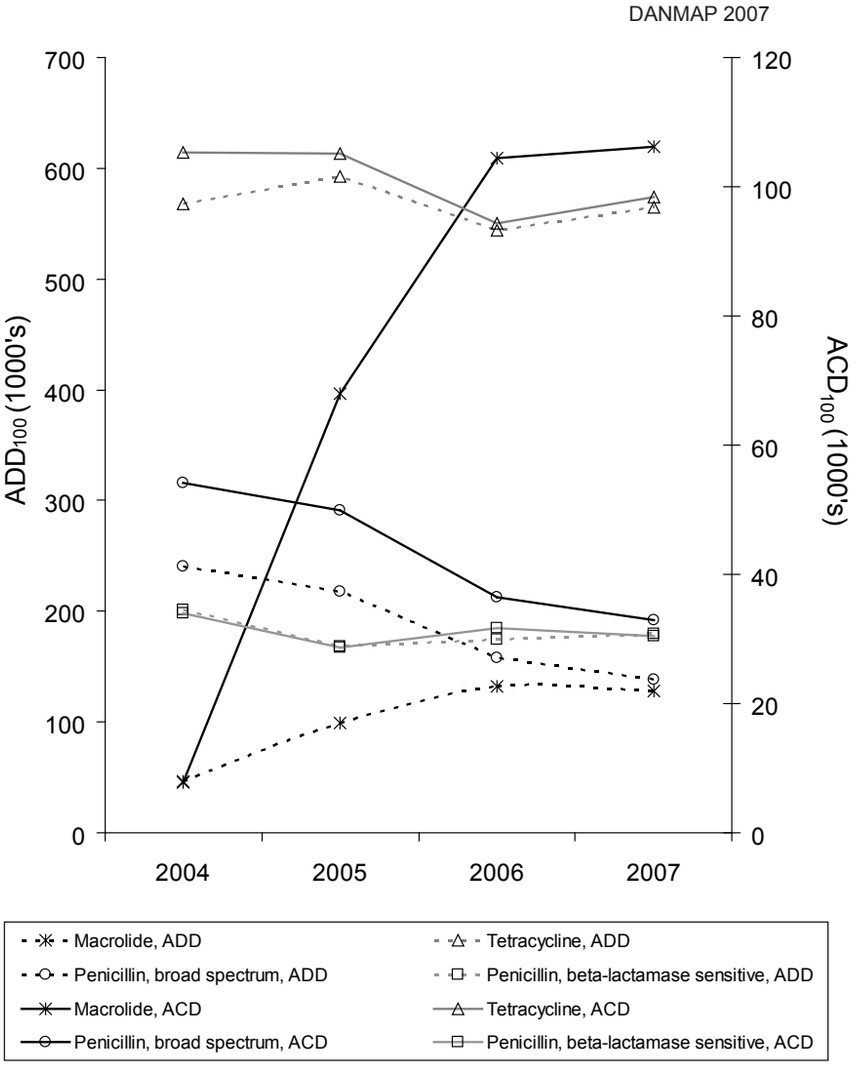

Figure 10. Trends in consumption of tetracyclines, penicillins and macrolides in calves measured in defined animal course doses (ACD) and defined animal daily doses (ADD), 2004-2007, Denmark
ACD_{100} is the average course dose for calves (bodyweight 100 kg). It is assumed that the average treatment course is 6 days. For longacting drugs with a therapeutic effect of 96 hours or more a course dose is assumed to be one injection

In cattle, macrolides are mostly used for parenteral treatment. Until 2004, macrolides constituted less than 3% of the antimicrobial use in calves and 4% of the use in cows. Since 2005, the use of macrolides for treatment of respiratory disease in calves has increased, and in 2007 the use of macrolides constituted 8% of the ADD's used in calves (Table V5). Because a major part of this increase is due to use of tulathromycin, the increase is much higher when measured in course doses (Figure 10). With the introduction of tulathromycin in 2005, the use of macrolides increased 10 times (in ACD's). From 2005 to 2007, the consumption of macrolides increased further by 56% (Figure 10). This means that macrolides have become the drug of choice when instituting therapy in calves, as macrolide therapy is instituted more frequently than tetracycline therapy. The proportion of long acting tetacyclines has decreased from 2004 to 2006 (Figure 10). It is most likely that the relatively limited use of long-acting tetracycline has been replaced by long-acting macrolide.

Antimicrobial consumption in humans

Overall

The term ”antimicrobial” covers antibacterial, antiviral, coccidiostatic and antimycotic agents. In this section, the term antibacterial is used for human consumption implying that only this type of drugs is reported in the following. This term includes synthetic and natural compounds that destroy bacteria or suppresses bacterial growth or reproduction (J01 in the ATC system).

In 2007, the overall consumption of antibacterials for systemic use (ATC group J01, 2007 definition) in humans in Denmark increased to 35.6 million DDDs or 17.9 DDD/1,000 inhabitant-days representing an increase of 7% compared to 2006. The percentage of DDDs prescribed in the primary health care sector remained stable at 90% of the total human consumption.

Figure 11 shows the distribution of the total number of DDDs of antibacterials between the primary health care sector and hospitals. For combinations of penicillins with beta-lactamase inhibitors and for fluoroquinolones, the ratio of consumption in primary health care vs. consumption in hospitals was around 2/1.

To follow overall changes in the consumption of antibacterials and to allow comparison with consumption of antibacterials in animals, total human consumption is presented in kilograms (Table 10). In 2007, 49.8 tonnes of antibacterials for systemic use were used in humans in Denmark, representing an increase by 4.5% as compared to 2006 and by 25% compared to 1997.

Primary health care sector - General view

Data on the consumption of antibacterials for systemic use in human primary health care from the Danish Medicines Agency has been updated and corrected for 2006. This update has led to only minor changes in the reported consumption.

In 2007, the overall consumption of antibacterials for systemic use in the primary health care sector was 16.2 DDD/1,000 inhabitant-days. Beta-lactamase sensitive penicillins still represented 35% of the total consumption of antibacterials followed by penicillins with extended spectrum (20%) and macrolides (15%) (Figure 12). This distribution was similar to previous years.

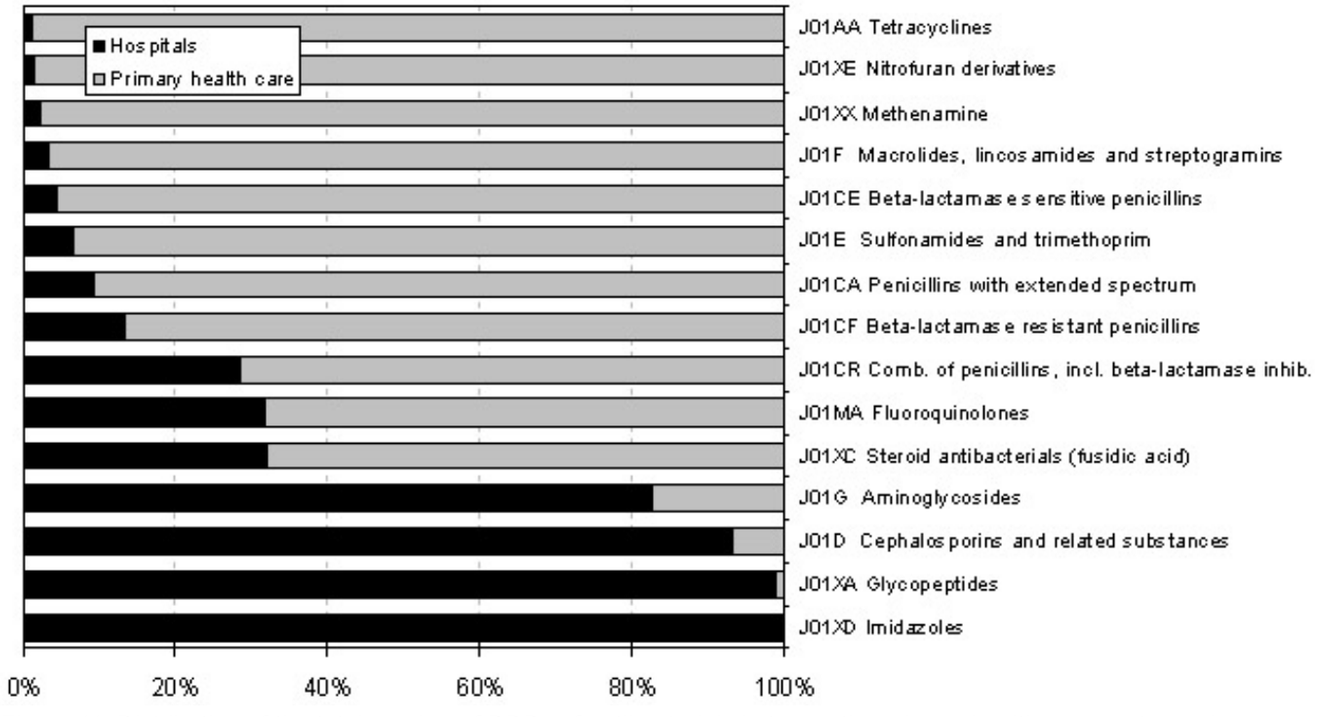

Figure 11. Distribution of the total number of DDDs of antibacterials between the primary health care sector and hospitals, Denmark

Table 10. Consumption of antibacterials for systemic use in humans (kg active compound), Denmark. These data include data from both primary health care and hospitals and have been re-calculated from original data expressed as a number of DDDs. For monitoring in human primary health care and hospitals, the recommended way of expressing consumption is DDDs per 1,000 inhabitant-days and DDDs per 1,000 occupied bed-days, respectively (see Tables 11 and 15)

DANMAP 2007

ATC group a)	Therapeutic group	Year										
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	1,519	1,486	1,383	1,486	1,475	1,501	1,542	1,636	1,748	1,835	1,855
J01B	Amphenicols	1	1	0	0	1	0	0	0	0	0	0
J01CA	Penicillins with extended spectrum	5,525	5,477	5,202	5,141	5,385	5,356	5,295	5,346	5,561	5,722	6,188
J01CE	Beta-lactamase sensitive penicillins	18,840	19,969	18,825	19,749	20,730	21,263	21,630	22,230	22,520	22,760	24,003
J01CF	Beta-lactamase resistant penicillins	1,919	2,120	2,425	2,655	3,230	3,738	4,075	4,377	4,564	4,842	5,037
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	49	56	52	93	146	249	336	480	534	724	1,012
J01D	Cephalosporins and related substances d)	626	614	650	692	739	811	830	894	1,582	1,778	2,285
J01EA	Trimethoprim and derivatives	245	256	258	262	280	293	307	334	359	382	402
J01EB	Short-acting sulfonamides	3,503	3,497	3,296	3,142	3,113	3,092	3,064	3,067	2,987	2,865	2,565
J01EE	Comb. of sulfonamides and trimethoprim, including derivatives	350	330	286	291	289	288	273	185	208	208	148
J01FA	Macrolides b)	4,227	4,536	4,147	4,040	4,089	4,150	3,876	3,743	3,775	3,524	3,434
J01FF	Lincosamides d)	25	34	29	29	37	40	45	53	52	66	78
J01G	Aminoglycosides	61	35	42	32	30	31	28	31	31	27	27
J01MA	Fluoroquinolones d)	384	405	383	344	398	451	611	722	866	979	1,162
J01MB	Other quinolones	15	17	16	0	0	0	0	0	0	0	0
J01XA	Glycopeptides	25	27	33	37	36	42	43	46	51	56	61
J01XC	Steroid antibacterials (fusidic acid)	74	73	78	70	59	59	58	52	62	65	67
J01XD	Imidazoles	129	129	142	155	168	179	191	195	206	198	202
J01XE	Nitrofuran derivatives (nitrofurantoin)	141	144	145	151	155	163	166	171	180	185	190
J01XX05	Methenamine d)	2,234	2,132	1,956	1,788	1,637	1,662	1,590	1,473	1,107	1,076	1,060
J01XX08	Linezolid	0	0	0	0	0	3	4	5	10	14	12
J01	Antibacterials for systemic use (total) c)	39,892	41,338	39,348	40,157	41,997	43,371	43,964	45,040	46,404	47,324	49,788

a) From the 2007 edition of the ATC classification system
b) When two different DDDs of an antimicrobial existed for different presentations an average DDD was used. Estimates using the lowest and the highest calculated limit are 2,683 - 4,185
c) Does not include polymyxins
d) Since 2005, the kg active compound was estimated taking into account the DDD for each route of administration, e.g. cefuroxime parenteral DDD=3 g and cefuroxime oral DDD=0.5 g. From 1997 to 2004, it was estimated with a DDD corresponding to an average for the various routes, e.g. for cefuroxime: 1.75 g

Table 11. Consumption of antibacterials for systemic use in human primary health care (DDD/1,000 inhabitant-days), Denmark

DANMAP 2007

ATC group a)	Therapeutic group	Year										
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	0.98	0.98	0.93	0.98	0.99	1.04	1.07	1.17	1.28	1.37	1.48
J01CA	Penicillins with extended spectrum	2.39	2.39	2.29	2.30	2.47	2.51	2.52	2.63	2.79	2.94	3.25
J01CE	Beta-lactamase sensitive penicillins	4.57	4.81	4.48	4.70	4.91	5.00	5.07	5.20	5.28	5.37	5.67
J01CF	Beta-lactamase resistant penicillins	0.34	0.40	0.48	0.52	0.65	0.77	0.85	0.92	0.97	1.04	1.09
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	0.02	0.03	0.02	0.02	0.03	0.04	0.05	0.06	0.08	0.12	0.19
J01D	Cephalosporins and related substances	0.02	0.03	0.02	0.02	0.03	0.03	0.02	0.02	0.03	0.03	0.03
J01EA	Trimethoprim and derivatives	0.30	0.32	0.32	0.33	0.35	0.36	0.38	0.41	0.44	0.47	0.49
J01EB	Short-acting sulfonamides	0.41	0.41	0.38	0.37	0.36	0.36	0.36	0.36	0.35	0.35	0.31
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	0.08	0.04	0.03	0.03	0.04	0.03	0.03	0.00	0.00	0.00	0.00
J01FA	Macrolides	2.03	2.28	2.17	2.02	2.10	2.15	2.13	2.23	2.41	2.31	2.42
J01FF	Lincosamides	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02
J01GB	Aminoglycosides	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluoroquinolones	0.22	0.23	0.20	0.15	0.17	0.18	0.25	0.28	0.33	0.37	0.44
J01XA	Glycopeptides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
J01XB	Polymyxins	0.03	0.02	0.03	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02
J01XC	Steroid antibacterials (fusidic acid)	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.02
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.35	0.36	0.36	0.38	0.39	0.41	0.42	0.43	0.45	0.46	0.47
J01XX05	Methenamine	0.46	0.43	0.40	0.36	0.33	0.34	0.32	0.30	0.28	0.27	0.26
J01XX08	Linezolid	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
J01	Antibacterials for systemic use (total)	12.24	12.76	12.14	12.24	12.86	13.26	13.53	14.06	14.75	15.17	16.17

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

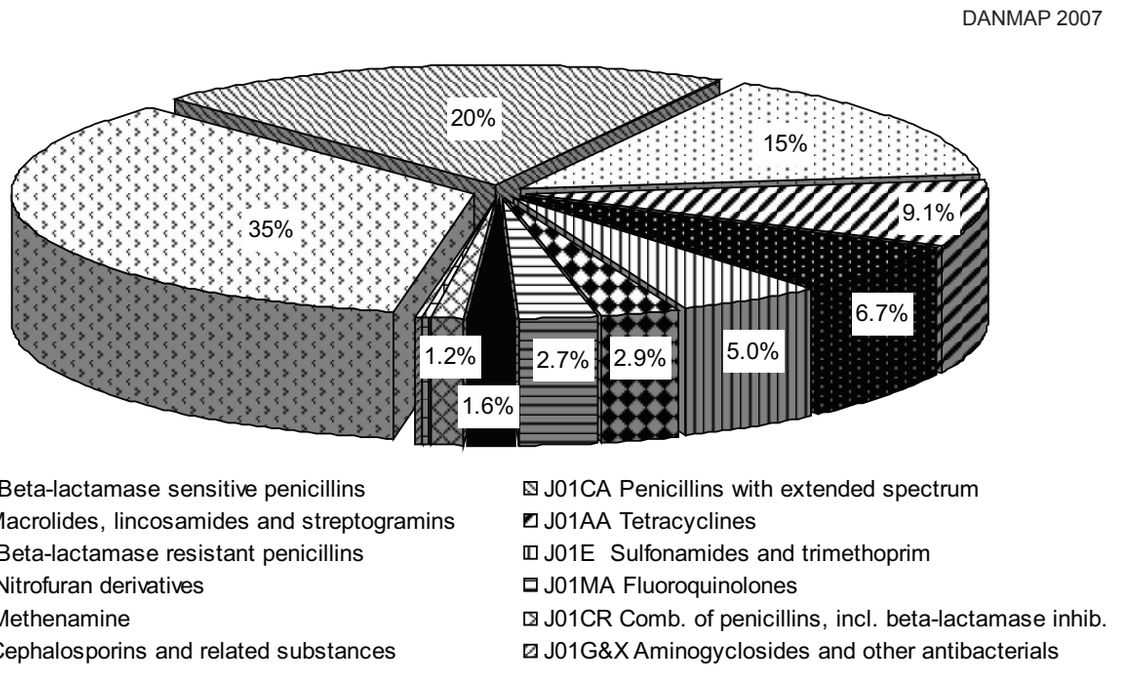

Figure 12. Distribution of the total number of DDDs of antibacterials in the primary health care sector, Denmark

Total consumption expressed in DDD/1,000 inhabitant-days increased by 6.6% as compared to 2006 (Table 11). Since 2000, there has been a steady increase in antibacterial consumption in DDD/1,000 inhabitant-days ranging from 2% to 7% yearly. Overall, antibacterial consumption increased by 32% between 2000 and 2007.

Primary health care sector - Penicillins

Approximately 60% in the increase of the total consumption between 2006 and 2007 was due to an increased consumption of penicillins with extended spectrum and beta-lactamase sensitive penicillins (Table 11). Between 2006 and 2007, the increase in consumption of penicillins with extended spectrum was due to both pivmecillinam and amoxicillin. As in 2006, the antimicrobial class that increased the most was combinations of penicillins, including beta-lactamase inhibitors with an increase by 50%.

Since 2000, an extensive increase in the consumption of certain classes of antibacterials in primary health care has been observed. During this period, the consumption of combinations of penicillins, including beta-lactamase inhibitors and beta-lactamase resistant penicillins has increased by 850%, and 110%, respectively. Between 1997 and 2007 the overall increase has been 850% and 221%, respectively.

The consumption of combinations of penicillins, including beta-lactamase inhibitors is still at a low level and the indications of the prescriptions of both classes are well understood.

Figure 13 shows the changes in consumption for selected classes of antibacterials for 1997-2007.

Primary health care sector - Macrolides

In 2007, consumption of macrolides increased by 4% compared to 2006, to the same level as in 2005. This increase was due to a renewed increase in roxithromycin as well as clarithromycin and azithromycin consumption (Figure 14). The change in the guidelines towards clarithromycin as first-choice macrolide, which occurred in September 2006 does not explain this change in pattern. In 2004 and 2005, the increase in roxithromycin consumption was likely due to an outbreak of *Mycoplasma pneumoniae*. However, none such outbreak was detected in Denmark in 2007.

Primary health care sector - Tetracyclines and Fluoroquinolones

Since 2000, an extensive increase in the consumption of certain classes of antibacterials in primary health care has been observed. During this period, the

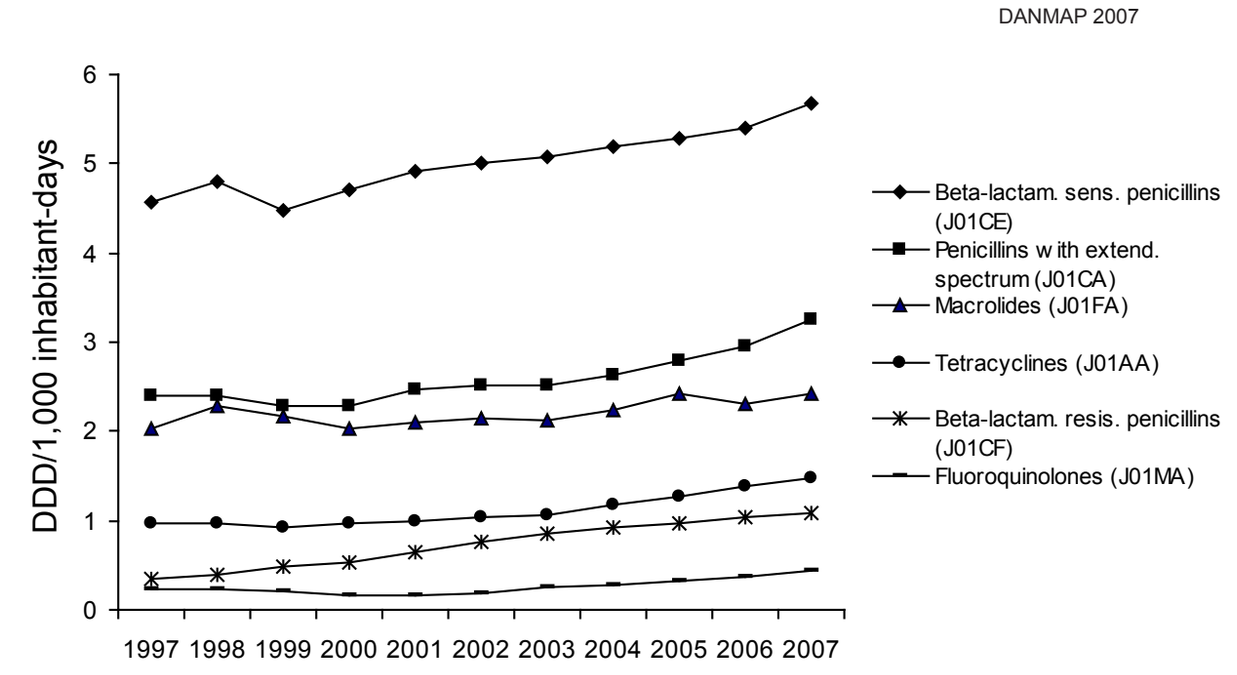

Figure 13. Consumption of selected antibacterials for systemic use in primary health care, Denmark

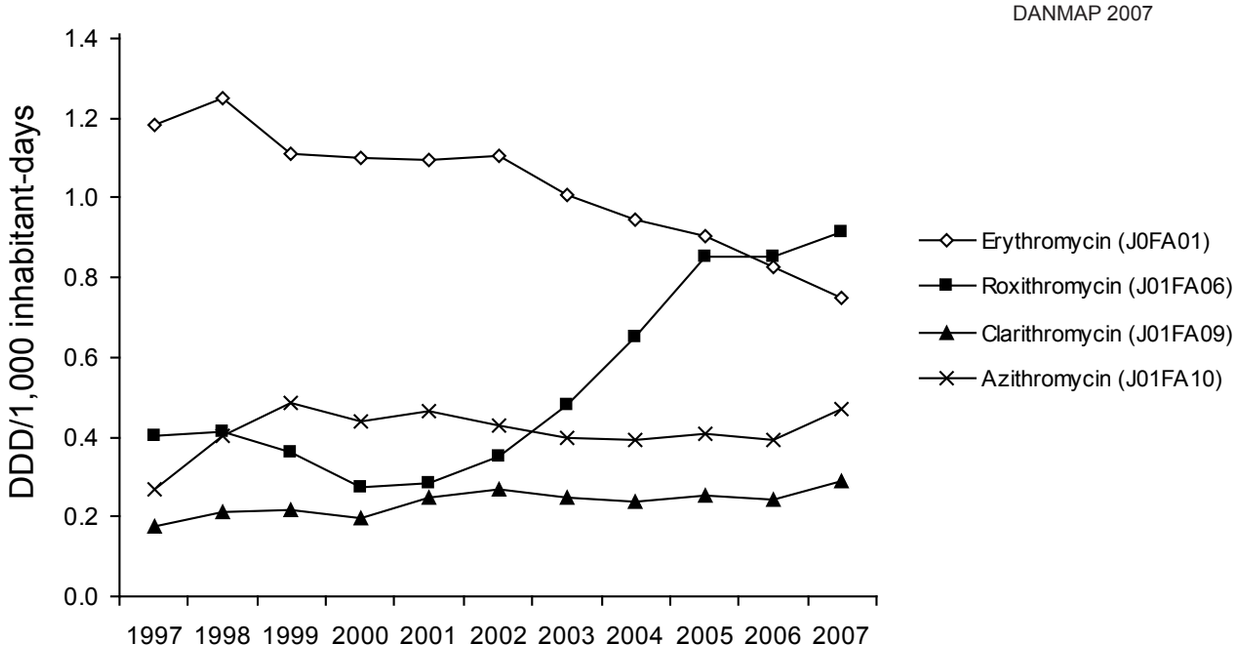

Figure 14. Consumption of macrolides in primary heath care, Denmark

consumption of fluoroquinolones and tetracyclines has increased by 193% and 51%, respectively (Table 11). Prescriptions of tetracyclines and to some extent fluoroquinolones contain limited information on the indication of the prescriptions.

The continuous significantly increasing consumption of fluoroquinolones is most likely explained by a markedly reduced price per DDD due to the opening of the market to generic ciprofloxacin as previously pointed out in the DANMAP 2006 report.

In 2007, consumption of tetracyclines increased by 8% compared to 2006. The most important part of the consumption was composed by tetracycline, which is mainly used for the treatment of acne, and doxycycline which amongst others is recommended for malaria prophylaxis for some destinations.

The majority of the tetracyclines used in 2007 was prescribed for adolescents and young adults (Figure 15). This corresponds nicely to the supposed main indications of these antibacterials. During the last six years, the consumption of doxycycline has increased with peak values in January and in June each year (Figure 16). Many Danes travel to countries with high risk of malaria in January/February and June/July. Doxycycline is recommended for malaria prophylaxis in areas of type IV risk (risk of *Plasmodium falciparum* malaria in combination with reported antimalarial drug resistance) and malaria prophylaxis might be the explanation for the peaks. In January 2007, the consumption of doxycycline had a major peak value (Figure 16). This coincided with reported cases of *P. falciparum* malaria in Goa, India (EPI-NEWS 2007, no. 1/2: http//:www.ssi.dk/sw47284.asp) and type IV pharmacological prophylaxis was recommended to travellers going to Goa. This outbreak could partly explain the increased consumption of doxycycline in 2007.

Primary health care sector - Measures at treated patients level

Between 1999 and 2007, the average total number of DDDs per treated patient increased from 15 to over 17 – a relative increase of 15% – whereas the number of packages per treated patient remained stable at around 2 (Table 12).

Overall, each patient received an average 17.3 DDDs in 2 packages. When assuming that one package is prescribed for one prescription, the number of packages could be considered as a surrogate for the number of prescriptions when the latter are not available. For all classes with the exception of aminoglycosides, polymyxins and methenamine, the number of DDDs per treated patient ranged between 3.9 and 41.1 and the number of packages per treated

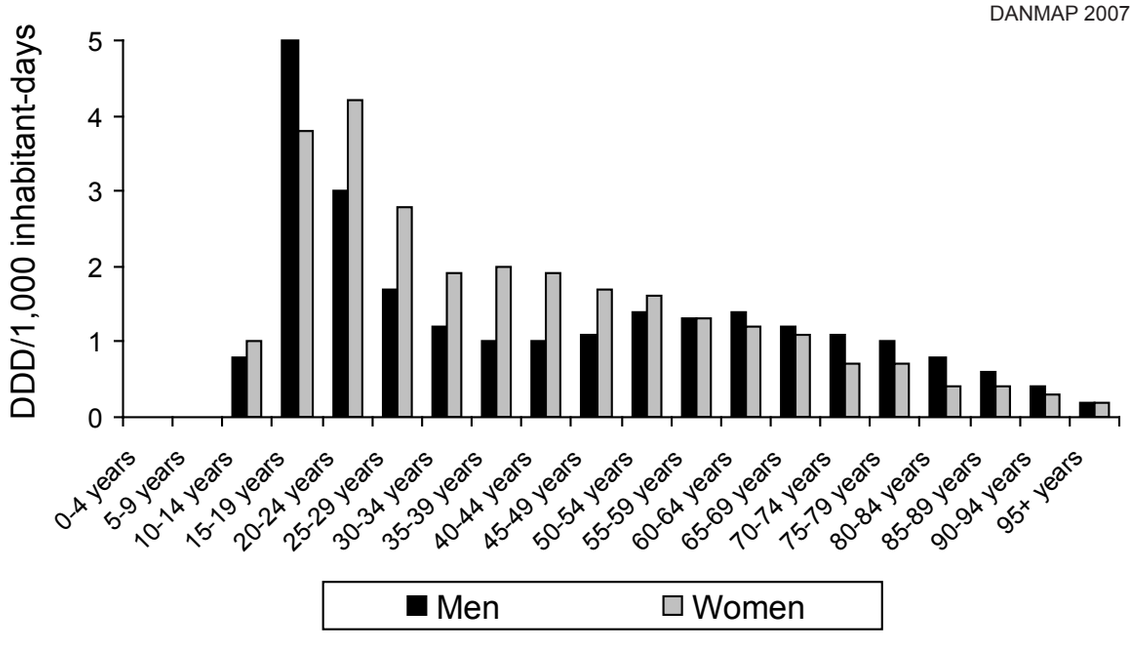

Figure 15. Consumption of tetracyclines by age and gender in primary health care, Denmark

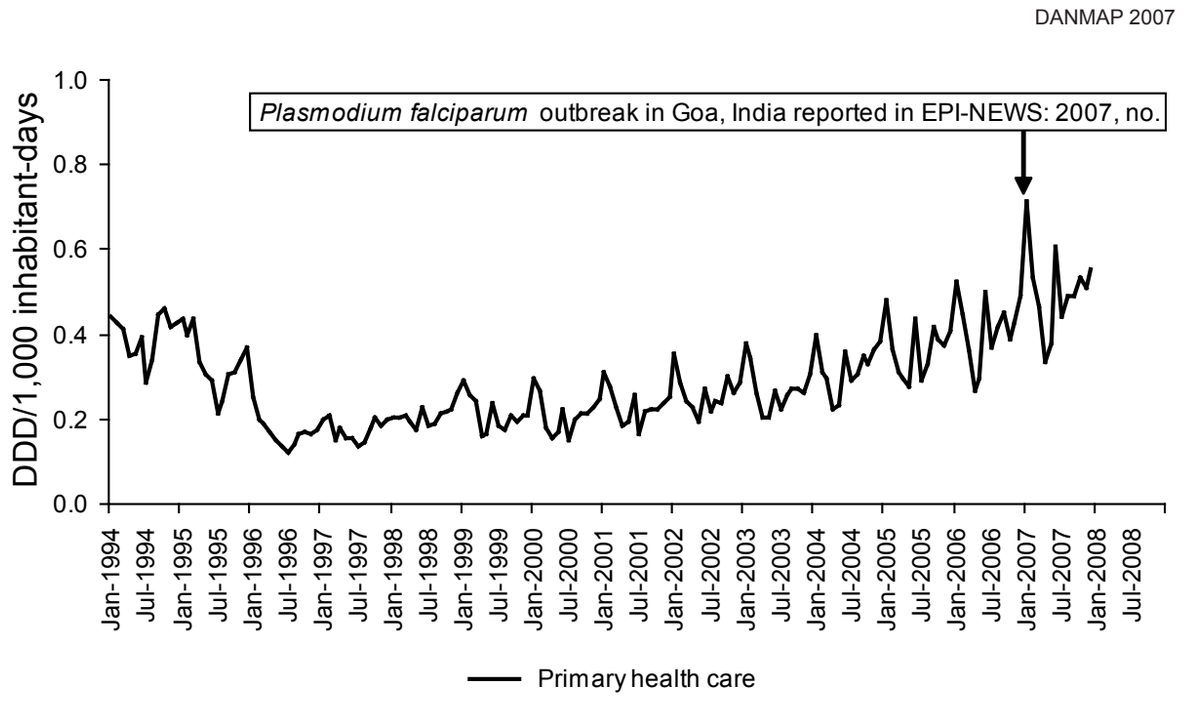

Figure 16. Monthly consumption of doxycycline in primary health care, Denmark

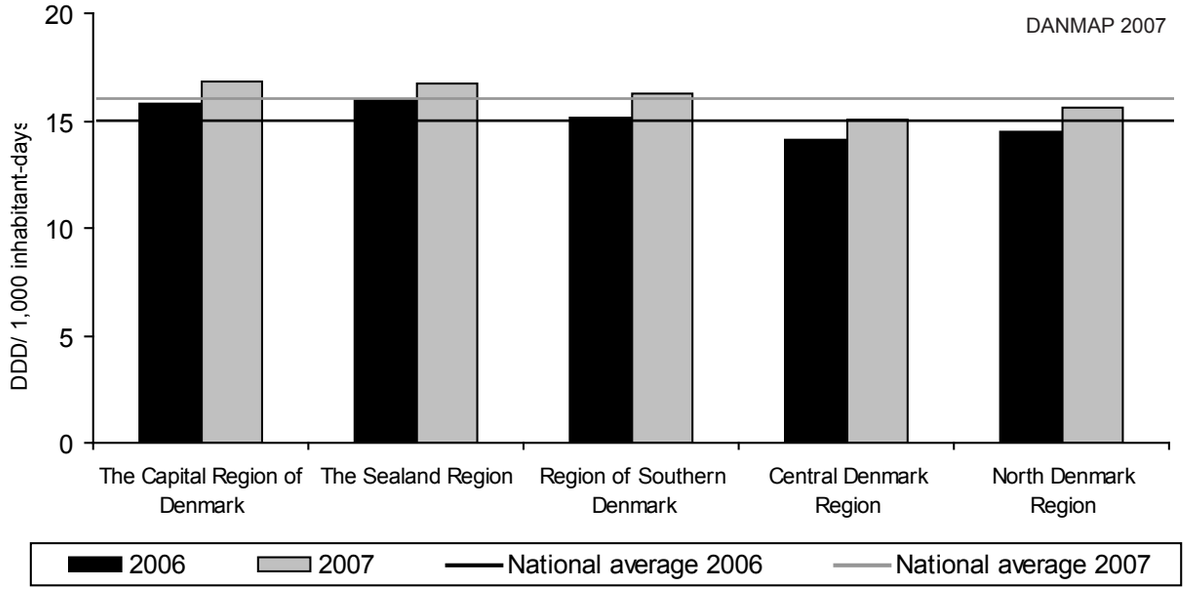

Figure 17. Trends in total use of antibacterials in primary health care in individual regions, Denmark

patient ranged between 1.4 and 3.6 (Table 12). For aminoglycosides, polymixins and methenamine, two hypotheses could explain the very high number of DDDs per treated patient for these three antimicrobial classes: the use of aminoglycosides and polymyxins by inhalation and the prophylactic use of methenamine for the treatment of chronic urinary tract infections as reported in the DANMAP 2006 report.
Combinations of penicillins, including beta-lactamase inhibitors and tetracyclines had the largest discrepancies between relative trends in the number of DDDs per treated patient and in the number of packages per treated patient (Table 12). Between 1999 and 2007, the number of DDDs per treated patient increased by 53% and 64%, respectively, whereas the number of packages per treated patient only increased by 7% and -7%, respectively. Regarding tetracyclines, a change in the prescription-choice of packaging i.e. prescriptions with a higher number of tablets per package could be explanatory for this trend. For combinations of penicillins, including beta-lactamase inhibitors, the explanation for this trend should be found in the decreasing proportion of children (<15 years) receiving this antibacterial compared to adults. Children treated with antibacterials get the same number of packages as adults do, but the number of DDDs is lower because the DDD is expressed as “The average adult dose used for the main indication as reflected by the ATC code” for both children and adults.
From 2003 through 2007 the proportion of children (<15 years) treated with combinations of penicillins with beta-lactamase inhibitors decreased from 53% to 28%. Concomitantly, the number of DDDs per treated patient has increased by 15%.

Primary health care sector - Regional use

In 2006 (county data recalculated into regional data) and 2007, consumption in the Eastern Danish regions was higher than consumption in the Southern and Western Danish regions, which showed wider variations. The Eastern regions had an overall consumption higher than the Danish average (Figure

Table 12. Number of DDDs per treated patient and of packages per treated patient in primary health care, Denmark

DANMAP 2007

ATC group a)	Therapeutic group	Indicator	Year								
			1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	DDDs / patient	28.1	29.8	30.6	33.0	34.4	36.9	38.8	41.1	43.0
		Packages / patient	1.8	1.9	1.9	1.9	1.9	1.9	2.0	1.9	2.0
J01CA	Penicillins with extended spectrum	DDDs / patient	12.5	12.8	13.0	13.2	13.4	13.6	13.9	14.2	14.4
		Packages / patient	1.5	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
J01CE	Beta-lactamase sensitive penicillins	DDDs / patient	10.0	10.2	10.3	10.5	10.7	11.1	11.3	11.5	11.7
		Packages / patient	1.4	1.4	1.4	1.5	1.5	1.5	1.5	1.4	1.4
J01CF	Beta-lactamase resistant penicillins	DDDs / patient	12.5	12.2	12.4	11.8	11.8	12.4	12.7	13.0	13.4
		Packages / patient	1.5	1.5	1.6	1.6	1.6	1.6	1.6	1.5	1.5
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	DDDs / patient	11.6	11.8	15.9	14.7	16.6	17.2	16.8	19.3	19.1
		Packages / patient	1.7	1.8	1.7	1.7	1.8	2.0	2.0	1.8	1.6
J01D	Cephalosporins and related substances	DDDs / patient	19.7	18.8	25.5	24.9	18.3	15.9	23.8	22.8	21.8
		Packages / patient	2.7	2.6	3.0	3.2	3.3	3.0	3.5	3.5	3.6
J01EA	Trimethoprim and derivatives	DDDs / patient	28.2	29.5	30.4	29.3	30.0	29.8	30.0	30.6	30.5
		Packages / patient	1.9	1.9	2.0	2.0	2.0	2.0	2.0	1.9	1.9
J01EB	Short-acting sulfonamides	DDDs / patient	4.0	4.0	4.0	4.0	4.0	4.0	3.9	3.9	3.9
		Packages / patient	1.4	1.4	1.4	1.4	1.4	1.5	1.5	1.4	1.4
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	DDDs / patient	14.2	14.3	19.5	15.6	18.3				
		Packages / patient	1.7	1.8	1.9	1.9	1.7				
J01FA	Macrolides	DDDs / patient	10.8	11.3	11.3	11.7	12.1	12.4	12.4	12.6	12.4
		Packages / patient	1.4	1.5	1.5	1.5	1.6	1.6	1.6	1.5	1.5
J01FF	Lincosamides	DDDs / patient	20.3	17.4	15.2	11.1	11.1	9.6	9.1	14.9	13.3
		Packages / patient	1.7	1.9	2.1	1.8	1.8	1.8	2.8	2.9	2.7
J01GB	Aminoglycosides	DDDs / patient	0.0	0.0	0.0	121.7	121.7	122.0	121.7	182.5	128.0
		Packages / patient	0.0	0.0	0.0	6.7	3.3	3.3	3.3	5.0	4.9
J01MA	Fluoroquinolones	DDDs / patient	8.0	7.8	8.3	8.6	10.3	9.5	9.6	10.3	10.6
		Packages / patient	1.4	1.4	1.4	1.4	1.6	1.5	1.5	1.5	1.5
J01XB	Polymyxins	DDDs / patient	273.8	274.5	182.5	243.3	243.3	183.0	182.5	182.5	219.3
		Packages / patient	72.5	70.0	52.5	66.7	66.7	52.5	50.0	37.5	21.9
J01XC	Steroid antibacterials (fusidic acid)	DDDs / patient	11.8	14.9	7.6	8.7	11.1	12.2	11.1	10.4	17.1
		Packages / patient	1.8	1.8	1.7	1.9	2.1	2.0	2.1	2.0	2.1
J01XE	Nitrofuran derivatives (nitrofurantoin)	DDDs / patient	23.1	23.9	24.8	24.5	24.8	24.6	24.5	24.0	26.3
		Packages / patient	1.7	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
J01XX05	Methenamine	DDDs / patient	202.8	212.5	227.3	225.6	220.4	224.1	222.2	234.6	237.5
		Packages / patient	5.3	5.6	6.0	5.8	4.9	4.9	5.0	4.8	4.7
J01	Antibacterials for systemic use (total)	DDDs / patient	15.0	15.3	15.6	16.0	16.4	17.0	17.5	17.9	17.3
		Packages / patient	2.0	2.0	2.0	2.0	2.1	2.1	2.1	2.0	1.9

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

17). In all the Danish regions, an overall increase in antibacterial consumption between the two years was observed.
Among the regions, the difference between the region with the lowest and the highest consumption remained about 1.12 times, i.e. the region (The Capital Region of Denmark) with the highest consumption used about 12% more antibacterials in primary health care than the region (Central Denmark Region) with the lowest consumption.

Primary health care sector - Other measures

Antimicrobial consumption in primary health care is also presented in Table 13 as a number of packages per 1,000 inhabitants, and in Table 14 as a number of treated patients per 1,000 inhabitants. In 2007, the overall consumption of antibacterials for systemic use in the primary health care sector was 664 packages/1,000 inhabitants or 320 treated patients/1,000 inhabitants. Year by year, total consumption expressed as a number of packages/1,000 inhabitants as well as a number of treated patients/1,000 inhabitants showed a persistent increase as compared to 1999 with the exception of one year each. The increases were by 15% and 9%, respectively.

Hospital sector - General information

Data from the Danish Medicines Agency on the consumption of antibacterials for systemic use in the hospital sector has been updated and corrected from 2005 through 2007.
Due to procedural rearrangements of certain chemical entities for infusion the reporting of sales (consumption) from the hospital pharmacies to the Danish Medicines Agency has been inaccurate for some classes.
Cephalosporins, carbapenems and combinations of sulfonamides and trimethoprim, including derivatives have been updated. In 2007, combinations of sulfonamides and trimethoprim, including derivatives are only reported from the hospitals of one region. This update has led to substantial changes in the reported consumption in the involved classes of antibacterials.
Data on the number of hospital bed-days from the National Board of Health has been updated and corrected for 2005 and 2006. This update has led to only minor changes in the reported consumption.

Table 13. Consumption of antibacterials for systemic use in human primary health care (No. packages/1,000 inhabitants), Denmark

DANMAP 2007

ATC group a)	Therapeutic group	Year										
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	24.3	24.0	22.2	22.8	22.4	21.7	21.6	22.5	23.8	23.9	24.5
J01CA	Penicillins with extended spectrum	111.0	111.2	102.9	103.7	110.9	111.8	111.5	115.3	119.9	119.7	131.3
J01CE	Beta-lactamase sensitive penicillins	246.4	256.0	232.5	243.7	251.0	254.4	254.5	253.7	251.1	243.3	253.0
J01CF	Beta-lactamase resistant penicillins	15.0	17.3	21.5	24.0	30.1	37.5	41.9	43.0	44.4	44.0	45.8
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	1.1	1.3	1.1	1.1	1.2	1.7	2.0	2.5	3.0	4.0	5.8
J01D	Cephalosporins and related substances	0.9	1.0	1.0	1.0	1.3	1.4	1.3	1.4	1.6	1.7	1.8
J01EA	Trimethoprim and derivatives	7.6	7.9	7.8	7.9	8.2	8.8	9.3	10.2	10.6	10.7	11.5
J01EB	Short-acting sulfonamides	51.0	51.4	48.9	47.8	47.8	47.6	47.9	48.3	47.5	45.8	41.0
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	2.6	1.6	1.3	1.4	1.4	1.3	1.0	0.0	0.0	0.0	0.0
J01FA	Macrolides	91.8	108.0	106.3	97.3	102.2	102.8	99.8	102.7	110.3	101.8	108.6
J01FF	Lincosamides	0.3	0.3	0.3	0.4	0.5	0.6	0.6	0.7	1.1	1.4	1.6
J01GB	Aminoglycosides	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1
J01MA	Fluoroquinolones	13.9	14.6	12.7	9.7	10.6	11.0	13.8	16.2	18.3	19.4	22.9
J01XA	Glycopeptides	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2
J01XB	Polymyxins	2.8	2.8	2.9	2.8	2.1	2.0	2.0	2.1	2.0	1.5	0.8
J01XC	Steroid antibacterials (fusidic acid)	1.0	0.9	1.1	0.9	0.8	0.8	0.7	0.6	0.7	0.7	0.7
J01XE	Nitrofuran derivatives (nitrofurantoin)	9.7	10.0	9.8	10.4	10.4	11.1	11.3	11.7	12.3	12.5	11.9
J01XX05	Methenamine	4.5	4.2	3.8	3.5	3.2	3.2	2.6	2.4	2.3	2.0	1.9
J01XX08	Linezolid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01	Antibacterials for systemic use (total)	584.6	612.9	576.6	578.5	604.4	618.0	622.3	633.6	649.3	632.6	663.5

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 14. Consumption of antibacterials for systemic use in human primary health care (No. treated patients/1,000 inhabitants), Denmark.

DANMAP 2007

ATC group a)	Therapeutic group	Year								
		1999	2000	2001	2002	2003	2004	2005	2006	2007
J01AA	Tetracyclines	12.1	12.0	11.8	11.5	11.4	11.6	12.0	12.3	12.5
J01CA	Penicillins with extended spectrum	66.7	65.6	69.4	69.2	68.8	70.6	73.0	75.8	82.1
J01CE	Beta-lactamase sensitive penicillins	163.9	168.9	173.3	173.4	172.6	171.2	170.2	171.3	177.1
J01CF	Beta-lactamase resistant penicillins	14.0	15.6	19.2	23.9	26.4	27.1	27.8	29.4	29.7
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	0.6	0.6	0.7	1.0	1.1	1.3	1.5	2.3	3.6
J01D	Cephalosporins and related substances	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5
J01EA	Trimethoprim and derivatives	4.1	4.1	4.2	4.5	4.6	5.0	5.4	5.6	5.9
J01EB	Short-acting sulfonamides	34.4	33.5	33.2	33.0	33.1	33.3	32.7	33.0	29.7
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	0.8	0.8	0.8	0.7	0.6	0.0	0.0	0.0	0.0
J01FA	Macrolides	73.5	65.7	67.7	66.9	64.1	65.9	70.7	67.0	71.4
J01FF	Lincosamides	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.5	0.6
J01GB	Aminoglycosides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01MA	Fluoroquinolones	9.2	7.0	7.5	7.7	8.9	10.8	12.2	13.1	15.2
J01XA	Glycopeptides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01XB	Polymyxins	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
J01XC	Steroid antibacterials (fusidic acid)	0.6	0.5	0.5	0.4	0.3	0.3	0.3	0.4	0.3
J01XE	Nitrofuran derivatives (nitrofurantoin)	5.7	5.8	5.7	6.1	6.2	6.4	6.7	7.0	6.5
J01XX05	Methenamine	0.7	0.6	0.5	0.6	0.5	0.5	0.5	0.4	0.4
J01XX08	Linezolid	-	-	-	0.0	0.0	0.0	0.0	0.0	0.0
J01 b)	Antibacterials for systemic use (total)	294.6	292.0	300.6	301.5	301.4	302.6	308.0	310.3	320.4

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system
b) Total no. of patients treated with an antibiotic is lower than the sum of all antibiotic classes. This is because the Danish Medicines Agency only counts the first treatment for each patient, each year

DANMAP 2007

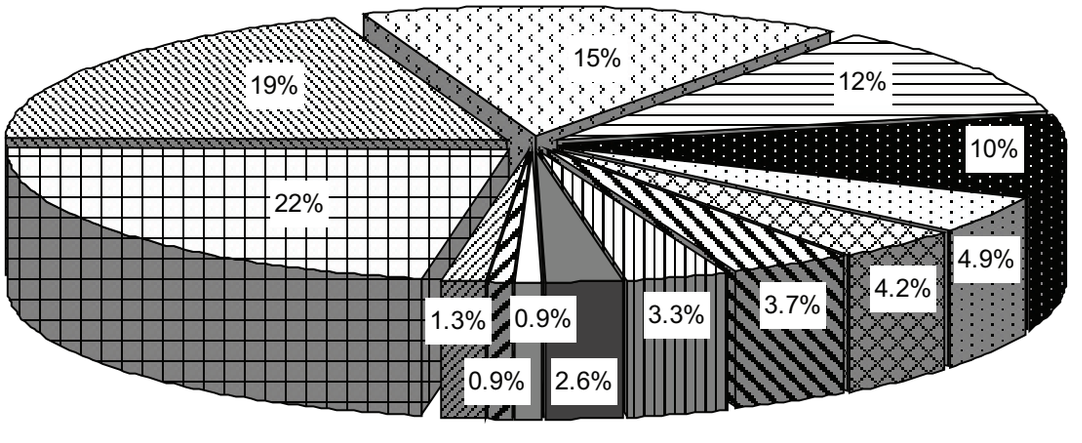

Figure 18. Distribution of the total number of DDDs of antibacterials in hospitals, Denmark

Barometer of Antibacterials

In association with the Danish Medicines Agency, Statens Serum Institut recently launched the Barometer of Antibacterials (http://www.ssi.dk/sw54720.asp).
The barometer is a tool enabling the viewer to follow the development of the human antibacterial consumption in the primary health care sector in Denmark, month by month. The total consumption (Figure 19) as well as each class of antibacterials expressed by DDD/1,000 inhabitant-days is on display.
The Barometer of Antibacterials is the first of its kind and one of a kind since it shows such detailed and well-arranged information on national antibacterial consumption over a vast period of time.

At all time, the consumption of the past 15 years is shown and the barometer is updated twice a year.

For further information: Ulrich S. Jensen (uje@ssi.dk)

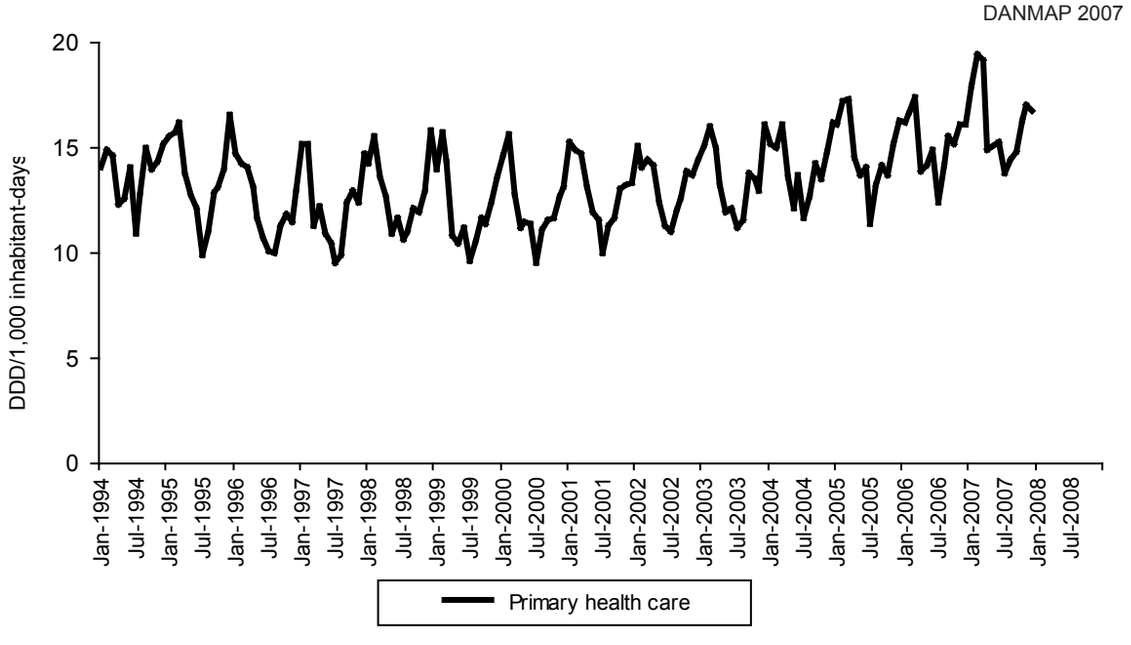

Figure 19. Monthly consumption of antibacterials (J01) in primary health care, Denmark

Hospital sector - DDD

The distribution of the different classes of antibacterials used in hospitals differed compared to 2006. Cephalosporins and related substances replaced penicillins with extended spectrum as the most used class of antibacterials in 2007 (Figure 18).

Hospital sector - DDD/1,000 occupied bed-days

Figure 20 illustrates the steady shift towards increasing consumption of newer, broad-spectrum antibacterials in Danish hospitals. In 1997, consumption of penicillins with extended spectrum represented 27% of total hospital antibacterial consumption in Denmark, but has since decreased to 21% in 2006 and to 19% in 2007. The decrease mainly concerned amoxicillin whereas consumption of pivmecillinam increased. The increase in hospital use of combinations of penicillins, including beta-lactamase inhibitors by 57% between 2006 and 2007 is parallel to the increase by 59% in primary care. The consequences of these changes in the pattern of antibacterial consumption could be a better coverage by empirical treatment of bacteria responsible for infection. However, this potential gain seems to be rapidly counterbalanced by the emergence of resistance towards newer classes of antibacterials (see Focus Area on Hospital Consumption).

Total consumption in hospitals increased by 52% between 1997 and 2006 when using DDD/1,000 occupied bed-days and by 63% between 1997 and 2007 (estimated). The increase in consumption from 1997 to 2007 was due to a 26% increase in the number of DDDs of antibacterials registered by hospital pharmacies, while there was a concurrent 16% decrease in the total number of hospital bed-days registered in Denmark in the same period (Table 15).

Hospital sector - DDD/1,000 discharged patients

When expressed as a number of DDDs per 1,000 discharged patients the total consumption in hospitals increased by 12% between 1997 and 2006 and by an estimated 17% between 1997 and 2007 (Table 16).

Between 2006 and 2007, antibacterial use in hospitals continued to increase whether it was expressed as number of DDDs, as in DDD/1,000 occupied bed-days or as in DDD/1,000 discharged patients, respectively. This increase however, should be interpreted with caution since data for 2007 were estimated.

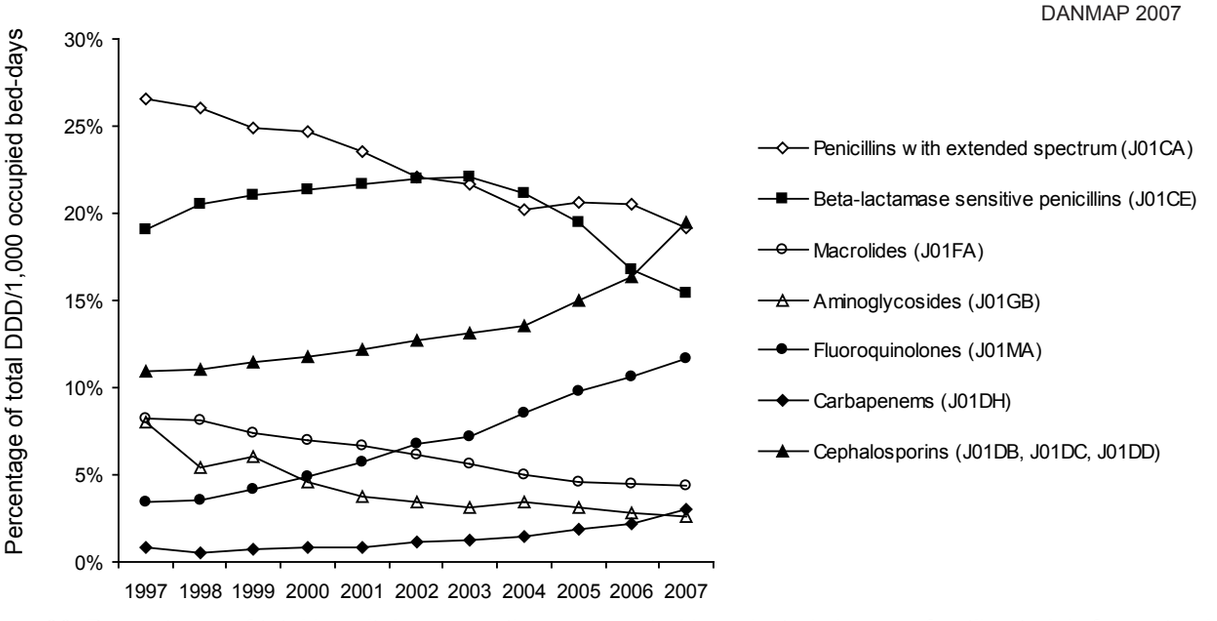

Figure 20. Percentages of total hospital consumption represented by selected classes of antibacterials for systemic use, Denmark

Table 15. Consumption of antibacterials for systemic use in hospitals (DDD/1,000 occupied bed-days), Denmark. Private hospitals, psychiatric hospitals, specialised clinics, rehabilitation centres and hospices were excluded.

DANMAP 2007

ATC group a)	Therapeutic group	Year										
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 b)
J01AA	Tetracyclines	3.4	3.3	2.8	2.9	2.8	3.2	3.1	3.5	3.4	4.0	6.2
J01CA	Penicillins with extended spectrum	112.1	113.4	112.7	115.7	116.1	115.2	119.2	117.9	130.1	130.9	131.8
J01CE	Beta-lactamase sensitive penicillins	80.2	89.2	95.3	100.3	106.5	114.3	121.2	123.1	122.6	107.4	106.0
J01CF	Beta-lactamase resistant penicillins	44.4	45.8	48.3	53.5	60.2	62.8	66.8	69.9	67.6	65.5	65.8
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	0.3	0.4	0.4	0.9	1.7	3.1	5.0	8.5	11.7	18.5	28.9
J01DB	First-generation cephalosporins	1.3	1.0	1.2	1.0	1.2	1.4	1.4	1.7	1.5	1.4	1.3
J01DC	Second-generation cephalosporins	39.9	41.9	44.0	47.4	52.1	58.5	63.9	70.6	84.6	94.4	122.5
J01DD	Third-generation cephalosporins	5.0	5.4	6.4	6.7	6.5	6.5	6.7	6.8	8.3	8.4	10.2
J01DF	Monobactams	0.6	0.1	0.1	0.2	0.1	0.0	0.0	0.1	0.0	0.0	0.4
J01DH	Carbapenems	3.6	2.4	3.2	3.9	4.2	6.0	6.9	8.6	11.6	13.9	21.0
J01EA	Trimethoprim and derivatives	4.2	4.4	3.8	3.7	4.3	4.2	4.4	4.2	4.1	4.2	4.3
J01EB	Short-acting sulfonamides	12.9	13.3	12.9	12.3	12.5	12.4	11.8	10.8	9.9	7.6	3.4
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	4.4	13.9	13.7	14.0	13.4	14.6	15.4	18.3	21.2	21.3	15.0
J01FA	Macrolides	34.5	35.3	33.5	32.8	32.6	32.3	30.9	29.4	29.1	28.5	30.2
J01FF	Lincosamides	1.3	1.8	1.5	1.6	1.7	1.9	1.9	2.3	2.4	3.1	3.5
J01GB	Aminoglycosides	33.8	23.6	27.6	21.3	18.5	17.7	17.4	20.3	19.7	18.2	17.6
J01MA	Fluoroquinolones	14.6	15.5	18.8	23.1	28.4	35.2	39.6	59.8	61.9	67.8	80.1
J01XA	Glycopeptides	2.1	2.3	2.8	3.3	3.2	3.7	4.2	4.7	5.2	5.6	6.2
J01XB	Polymyxins	0.4	0.2	0.3	0.4	0.3	0.3	0.3	0.6	1.2	1.2	0.5
J01XC	Steroid antibacterials (fusidic acid)	2.5	2.5	2.6	2.3	2.0	1.9	2.2	2.2	2.6	2.8	2.8
J01XD	Imidazole derivatives	14.2	14.4	16.2	17.9	19.6	21.1	23.7	24.7	26.4	28.0	25.8
J01XE	Nitrofuran derivatives (nitrofurantoin)	3.7	3.5	3.0	2.9	2.9	2.8	2.8	2.8	3.0	2.9	2.8
J01XX05	Methenamine	1.8	1.8	1.6	1.4	1.3	1.2	0.8	1.0	0.8	1.1	0.9
J01XX08	Linezolid	0.0	0.0	0.0	0.0	0.0	0.4	0.4	0.7	1.5	2.0	1.6
J01XX09	Daptomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
J01	Antibacterials for systemic use (total)	421.3	435.3	452.9	469.5	492.1	521.0	550.0	582.4	630.8	639.0	688.7

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system
b) Estimate calculated with the actual number of DDDs and the estimated number of occupied bed-days based on the variation observed previously between 2005 and 2006

Table 16. Consumption of antibacterials for systemic use in hospitals (DDD/1,000 discharged patients), Denmark Private hospitals, psychiatric hospitals, specialised clinics, rehabilitation centres and hospices were excluded.

DANMAP 2007

ATC group a)	Therapeutic group	Year										
		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007 b)
J01AA	Tetracyclines	19.3	18.2	15.4	15.4	14.8	16.3	14.8	15.8	14.6	16.8	25.3
J01CA	Penicillins with extended spectrum	641.8	634.4	608.7	610.5	604.9	578.0	566.2	535.2	567.1	552.2	541.3
J01CE	Beta-lactamase sensitive penicillins	459.3	498.9	514.6	529.1	555.0	573.5	575.9	558.5	534.6	453.3	435.3
J01CF	Beta-lactamase resistant penicillins	254.4	256.3	260.9	282.5	313.7	314.9	317.3	317.0	294.8	276.5	270.1
J01CR	Combinations of penicillins, incl. beta-lactamase inhibitors	1.8	2.1	2.4	4.9	8.9	15.6	23.6	38.5	51.1	77.9	118.9
J01DB	First-generation cephalosporins	7.4	5.4	6.7	5.2	6.1	7.2	6.8	7.7	6.7	6.0	5.4
J01DC	Second-generation cephalosporins	228.7	234.2	237.7	250.2	271.5	293.6	303.6	320.5	368.8	398.3	503.1
J01DD	Third-generation cephalosporins	28.6	29.9	34.8	35.6	34.0	32.5	32.0	30.9	36.4	35.4	41.8
J01DF	Monobactams	3.3	0.7	0.8	0.9	0.5	0.2	0.2	0.2	0.2	0.0	1.8
J01DH	Carbapenems	20.6	13.5	17.2	20.6	21.9	29.9	32.7	38.8	50.8	58.7	86.3
J01EA	Trimethoprim and derivatives	24.0	24.6	20.7	19.5	22.6	21.0	21.0	19.0	17.9	17.8	17.7
J01EB	Short-acting sulfonamides	73.9	74.4	69.7	64.9	64.9	62.2	55.8	49.2	43.4	31.9	13.8
J01EE	Combinations of sulfonamides and trimethoprim, incl. derivatives	25.1	77.5	74.1	73.6	70.0	73.2	73.1	83.2	92.6	89.9	61.4
J01FA	Macrolides	197.6	197.3	180.8	173.1	170.1	161.9	146.7	133.3	127.0	120.3	124.1
J01FF	Lincosamides	7.6	10.0	8.1	8.5	9.0	9.5	9.0	10.4	10.5	13.1	14.3
J01GB	Aminoglycosides	193.6	131.9	149.0	112.5	96.4	88.6	82.8	91.9	85.9	76.9	72.3
J01MA	Fluoroquinolones	83.4	86.8	101.4	121.8	148.1	176.7	188.0	226.0	270.0	286.3	329.0
J01XA	Glycopeptides	12.3	13.1	15.3	17.2	16.6	18.8	19.9	21.2	22.9	23.8	25.5
J01XB	Polymyxins	2.5	1.4	1.8	2.1	1.5	1.7	1.5	2.7	5.4	5.3	2.2
J01XC	Steroid antibacterials (fusidic acid)	14.4	14.1	14.2	12.1	10.2	9.7	10.5	10.2	11.1	12.0	11.5
J01XD	Imidazole derivatives	81.5	80.6	87.6	94.5	102.0	106.0	112.5	112.1	115.3	118.3	105.8
J01XE	Nitrofuran derivatives (nitrofurantoin)	21.3	19.5	16.3	15.5	15.0	14.2	13.1	12.8	12.9	12.4	11.4
J01XX05	Methenamine	10.2	10.3	8.6	7.5	6.7	6.1	3.9	4.6	3.6	4.6	3.7
J01XX08	Linezolid	0.0	0.0	0.0	0.0	0.0	2.2	2.1	3.3	6.4	8.6	6.6
J01XX09	Daptomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
J01	Antibacterials for systemic use (total)	2,412.6	2,435.2	2,446.2	2,477.6	2,564.6	2,613.3	2,613.0	2,642.8	2,750.0	2,696.5	2,829.1

a) From the 2007 edition of the Anatomical Therapeutic Chemical (ATC) classification system
b) Estimate calculated with the actual number of DDDs and the estimated number of discharged patients based on the variation observed previously between 2005 and 2006

Clinical breakpoints and epidemiological cut-off values

In this DANMAP report interpretation of the minimum inhibitory concentration (MIC) values for *Salmonella, Campylobacter,* Indicator enterococci*, E. coli* and *Staphylococcus hyicus* has been changed from clinical breakpoints to epidemiological cut-off values for most of the tested antimicrobial agents.
Below, the difference between the two methods is described (Figure 21) [Aarestrup *et al.* Newslett. Nation. Ref. Lab. Antimicrob. Res. 2007 2: 3-5].

Clinical breakpoints

The development of clinical breakpoints requires microbiological MIC data generated using standardized in vitro testing methods, pharmacokinetic and pharmacodynamic information and most importantly outcome data from clinical efficacy trials. These three types of data taken together usually are sufficient to establish interpretative criteria for individuals likely to respond when treated with that agent at the approved dosage (susceptible organisms), and those likely to fail therapy when treated with the approved dosage (resistant organisms). The “intermediate” category is used as a buffer zone to account for day-to-day variability in *in vitro* antimicrobial susceptibility testing, to provide flexibility for sites of infection where the agent is concentrated, or for agents where increased dosage ranges are defined.

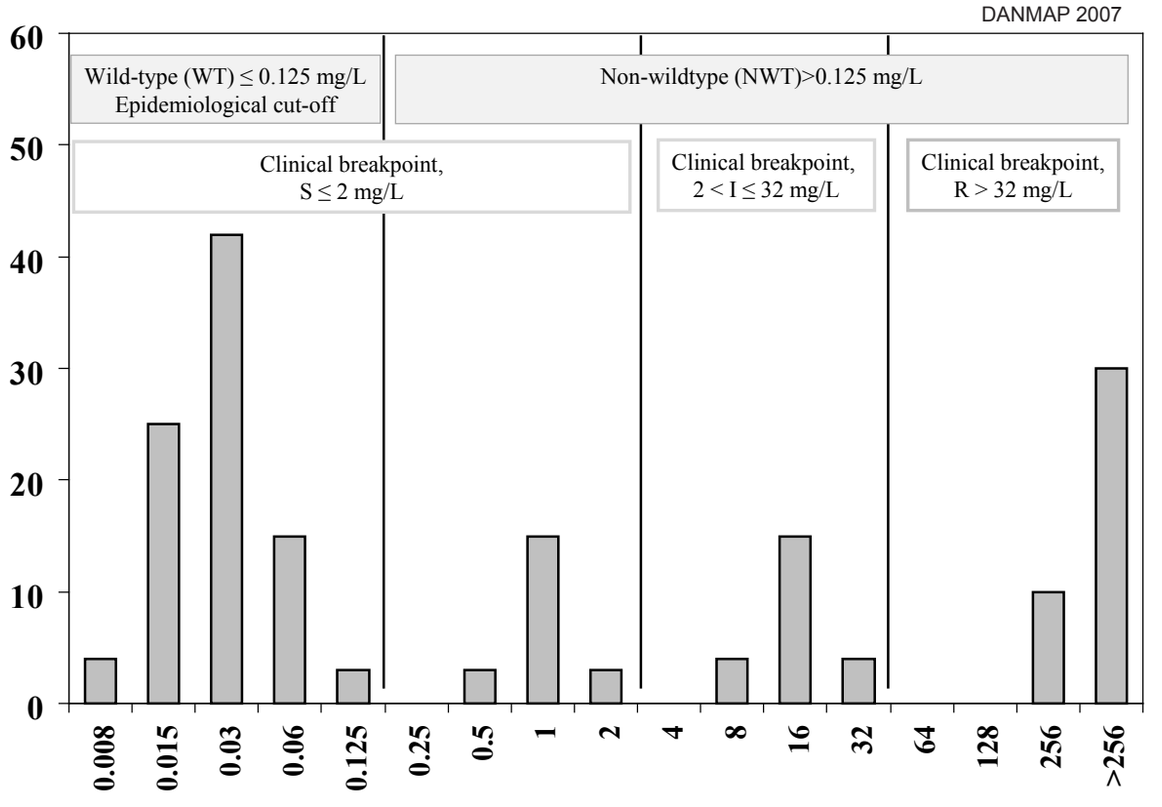

Figure 21. Example showing the difference between clinical breakpoints and epidemiological cut-off values

Epidemiological cut-off values

Epidemiological cut-off values focus on separating isolates in the normal wild type population from isolates with some type of acquired mechanisms that reduces the normal susceptibility of these isolates. Thus, the epidemiological cut-off does not take into consideration any data on dosages or clinical efficacy, but is aimed at optimizing the phenotypic detection of isolates with acquired resistance. When working with epidemiological cut-off values there is not an intermediate category; isolates are recorded as either wild type or non-wild-type. Epidemiological cut-off values are mostly used for the monitoring of antimicrobial resistance, and since wild type MIC distributions of bacteria of human and animal origin coincide completely, the same epidemiological cut-off can be used for monitoring resistance in bacteria obtained from animals, foods and humans.

Sources of clinical breakpoints and epidemiological cut-off values

Several national and international committees determine clinical breakpoints. The most widely used are those provided by the Clinical Laboratory Standards Institute (CLSI, www.clsi.org), which publishes methods for susceptibility testing and tables with clinical breakpoints, both MIC-tables and zone diameter tables as approved by the Food and Drug Administration (FDA) in the USA. In Europe, the European Committee for Antimicrobial Susceptibility Testing (EUCAST, www.eucast.org) provides epidemiological cut-off values, clinical breakpoints and the huge database of MIC distributions needed to determine epidemiological cut-off values. The data is freely available on the EUCAST website but currently only available for MIC-values.

Change from clinical breakpoints to epidemiological cut-off values in DANMAP

In this DANMAP report, data in the “Farm to Table” tables are interpreted by use of epidemiological cut-off values for most antimicrobial agents. In all MIC tables in Appendix 1, the clinical breakpoints and epidemiological cut-off values are both marked to make the transition visible.

For further information: Frank M. Aarestrup (fmaa@food.dtu.dk)

Resistance in zoonotic bacteria

Salmonella

In 2007, a total of 1,649 cases of human salmonellosis were reported to Statens Serum Institut (30 per 100,000), which was nearly the same number of *Salmonella* cases as reported in 2006.
Compared to 2006, the number of *Salmonella* Enteritidis infections remained unchanged with 566 cases, while a 17% decrease was observed for *Salmonella* Typhimurium resulting in 343 cases. The remaining group, containing 102 different serotypes, increased by 8% to 740 cases [EPI-NEWS 2008, no. 10: http://www.ssi.dk/sw55440.asp].

Interview of patients with *Salmonella* infections

Humans can acquire *Salmonella* infections outside Denmark, but travel information is not always provided by the general practitioners (GPs). In the previous DANMAP reports, human *Salmonella* infections were only categorised as associated with travel if information about travel was provided by the GPs, whereas all other *Salmonella* infections were reported as domestically acquired. Therefore in previous years an unknown proportion of the domestically acquired *Salmonella* infections were travel associated. To get better travel information, all patients from three former counties (Århus, Funen and Roskilde) with a *Salmonella* infection acquired in 2007 and where no information about travel was available were interviewed by phone from the Interview Center at Statens Serum Institut. Furthermore, all patients that acquired a *Salmonella* infection from October 2007 through December 2007 were also phone interviewed.

The *Salmonella* infection was categorised as "domestically acquired" if the patient had not been travelling one week prior to the infection, whereas it was categorised as "travel associated" if the patient had travelled one week prior to the onset of infection. *Salmonella* infections where patients had not reported travel to the GP or not been interviewed by phone were categorised as "unknown origin".

In 2007, a total of 412 *Salmonella* infections were registered in the three counties Århus, Funen and Roskilde. The GP had already reported history of travel for 40 patients and the remaining 372 patients were included for phone interview. In total, 299 patients responded, of these 141 patients or 47% had a history of travel, however between counties the percentage of travel associated infections varied. In Århus County 52% (64/120) of the infections were travel associated, in Funen County it was 28% (36/127) and in Roskilde County it was 47% (41/87). The lower percentage in Funen County might partly be explained by a *Salmonella* Heidelberg outbreak with 19 cases in May 2007.

From October 2007 through December 2007, 329 patients with a registered *Salmonella* infection were included in the phone interview. Of these, 248 patients responded and for 33% (81 patients) the infection was categorised as travel associated.

Based on the telephone interviews an estimated 40% of all human *Salmonella* infections were travel associated in 2007.

Table 17. Distribution (%) of Salmonella *Typhimurium phage types from food animals, pork of Danish and imported origin and human cases categorized as acquired domestically, reported as associated with travel abroad or unknown origin among the isolates selected for susceptibility testing, Denmark* DANMAP 2007

Phage types	Poultry	Cattle	Pigs	Pork		Humans a) b)		
	Danish	Danish	Danish	Danish	Imported	Domestically acquired	Travel abroad reported	Unknown origin
	%	%	%	%	%	%	%	%
12	0	15	13	18	0	13	3	6
15a	0	0	2	0	0	0	0	1
17	10	0	4	7	0	0	0	<1
41	20	0	<1	0	0	2	0	0
104/104b/104c	20	31	9	6	24	7	17	16
120	10	31	23	25	14	21	17	27
170	10	0	9	7	0	0	0	2
193	0	8	6	4	19	7	17	7
U302	0	0	3	1	0	7	6	6
Others including non-typeable	30	15	30	32	43	43	40	35
Number of isolates	10	13	575	71	21	56	35	244

a) Not all isolates selected for susceptibility testing were phage typed
b) The isolate was categorized as 'domestically acquired' if the patient did not travel one week prior to the infection, and it was characterized as 'travel abroad reported' if the patient travelled one week prior to the infection. Isolates from patients which had not reported travel to the GP or was not interviewed by phone was characterized as 'unknown origin'

Table 18. Comparison of resistance (%) among Salmonella *Typhimurium from food animals, pork of Danish and imported origin and human cases acquired domestically, reported as associated with travel abroad or with an unknown origin, Denmark*

DANMAP 2007

Compound	Poultry	Cattle	Pigs	Pork		Humans a)		
				Danish	Imported	Domestically acquired	Travel abroad reported	Unknown origin
	%	%	%	%	%	%	%	%
Tetracycline	20	62	47	38	52	34	57	52
Chloramphenicol	10	15	11	6	24	12	27	17
Florfenicol	10	15	7	4	14	9	21	12
Ampicillin	10	62	36	35	48	32	55	49
Cephalothin	0	0	1	0	0	0	0	2
Ceftiofur	0	0	0	0	0	0	0	1
Cefpodoxime	0	0	0	0	0	2	0	1
Sulfonamide	10	69	47	39	52	47	57	54
Apramycin	0	0	1	3	0	1	2	1
Gentamicin	0	0	1	3	0	3	2	2
Neomycin	0	0	8	10	0	1	2	2
Spectinomycin	10	38	17	13	29	20	30	19
Streptomycin	10	54	43	41	48	44	53	50
Ciprofloxacin	0	0	1	0	0	2	18	3
Nalidixic acid	0	0	1	0	0	2	7	2
Number of isolates	10	13	575	71	21	90	44	206

a) The isolate was categorized as 'domestically acquired' if the patient did not travel one week prior to the infection, and it was characterized as 'travel abroad reported' if the patient travelled one week prior to the infection. Isolates from patients which had not reported travel to the GP or was not interviewed by phone was characterized as 'unknown origin'

DANMAP 2007

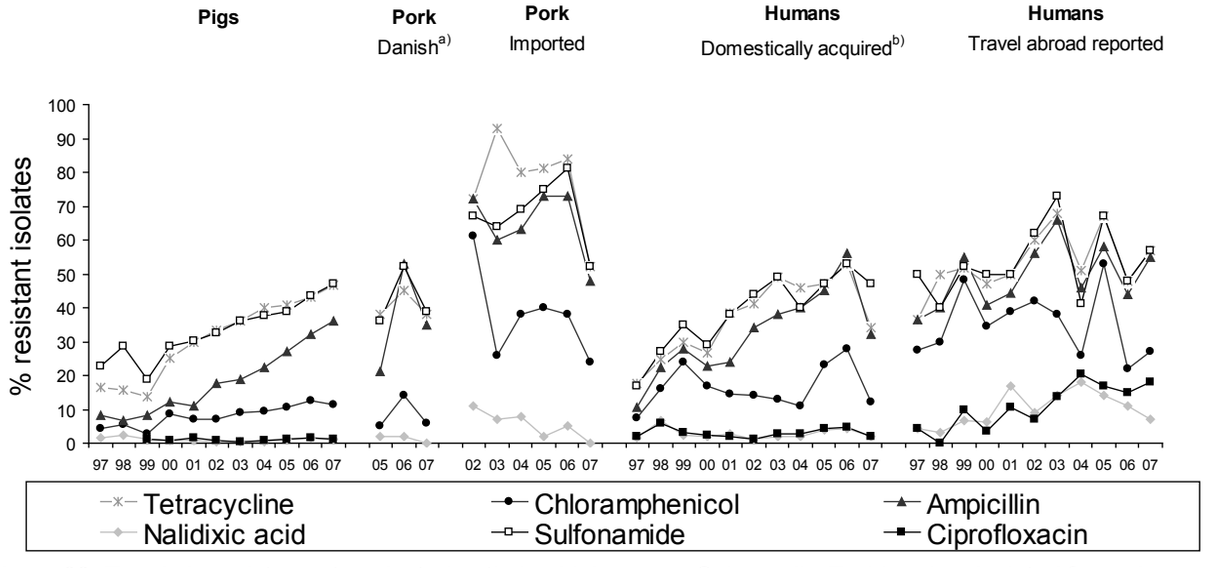

Figure 22. Trends in resistance to selected antimicrobials among Salmonella *Typhimurium isolated from pigs, pork and from human cases, Denmark*

a) Few *Salmonella* Typhimurium isolates were avaiable from Danish pork before 2005
b) Until 2007, includes cases where origin of infection is not documented and may therefore include some isolates acquired abroad but not documented as such

Comparison of resistance in *Salmonella* Typhimurium isolates from pig, pork, and human clinical infections

One of the sources for *S*. Typhimurium infections in humans is pork. *S*. Typhimurium DT120 was the most prevalent phage type in Danish pork followed by DT12 which is similar to the phage type distribution in Danish pigs and domestically acquired human infections (Table 17). No significant differences in antimicrobial resistance were observed between *S*. Typhimurium from pigs and Danish pork and between danish pork and domestically acquired human infections (Table 18).

Between 2006 and 2007, no significant changes in antimicrobial resistance were observed when comparing *S*. Typhimurium from pigs and Danish pork except a significant decrease in ampicillin resistance in *S*. Typhimurium from Danish pork. However, over the last years a continuous increase in ampicillin, streptomycin, sulfonamide and tetracycline resistance was observed among *S*. Typhimurium from pigs which is caused by a shift in phage type distribution (please see the *Salmonella* Focus Area).

Trends in resistance towards six antimicrobial agents in *S.* Typhimurium isolates from pigs, pork and human cases are shown in Figure 22. Until 2006, *Salmonella* isolates from food were obtained from meat sampled at wholesale and retail outlets. Due to a low occurrence of *Salmonella* in Danish pork very few *Salmonella* isolates were obtained and for most years it was not possible to draw a graph representing antimicrobial resistance in Danish pork (Figure 22). In 2006 and 2007, *Salmonella* isolates were obtained from Danish pork sampled at the slaughterhouse.

In imported pork, DT104 was the most prevalent phage type while DT12 was not detected (Table 17). Among *S.* Typhimurium from imported pork a significant decrease in sulfonamide and tetracycline resistance was observed from 2006 to 2007 while the remaining antimicrobials were unchanged during the same period. When comparing Danish and imported pork over time (Figure 22) the occurrence of resistance in previous years has been higher in imported pork compared to Danish pork. In 2007, only chloramphenicol resistance was significantly higher in imported pork as compared to Danish pork.

Among the *S*. Typhimurium infections categorised as associated with travel, DT120 and DT104 were the most common phage types (Table 17). The occurrence of resistance to tetracycline, ampicillin and ciprofloxacin was significantly higher in isolates from patients with

Table 19. Comparison of resistance (%) among Salmonella *Enteritidis from human cases acquired domestically, reported as associated with travel abroad or with an unknown origin, Denmark a)*

DANMAP 2007

Compound	Domestically acquired %	Travel abroad reported %	Unknown origin %
Tetracycline	0	7	2
Chloramphenicol	0	1	<1
Florfenicol	0	0	0
Ampicillin	0	15	4
Cephalothin	0	0	1
Cefpodoxime	0	0	0
Ceftiofur	0	0	0
Sulfonamide	0	3	1
Apramycin	0	0	0
Gentamicin	0	0	0
Neomycin	0	0	0
Spectinomycin	0	1	1
Streptomycin	0	2	<1
Ciprofloxacin	9	31	12
Nalidixic acid	9	31	12
Number of isolates	67	88	183

a) The isolate was categorized as 'domestically acquired' if the patient did not travel one week prior to the infection, and it was characterized as 'travel abroad reported' if the patient travelled one week prior to the infection. Isolates from patients which had not reported travel to the GP or was not interviewed by phone was characterized as 'unknown origin'

travel associated infections compared to domestically acquired infections (Table 18). The elevated occurrence of resistance in travel associated *S.* Typhimurium isolates obtained abroad compared to domestically acquired infections, probably reflects differences in the use of veterinary antimicrobials between Denmark and the countries which the patients have travelled to.

Ciprofloxacin resistance was detected in 18% of the isolates from travel-associated infections, whereas only 7% of these isolates were resistant to nalidixic acid (Table 18). This discrepancy was due to the occurrence of five isolates positive for the plasmid-borne *qnr* genes, which can have the phenotype ciprofloxacin resistance and nalidixic acid susceptible.

MIC distributions and occurrence of antimicrobial resistance among *S.* Typhimurium is presented in Tables 28-30 in Appendix 1.

Comparison of resistance in *Salmonella* Typhimurium isolates from cattle and poultry

S. Typhimurium isolates from poultry (broilers and layers) were mainly from sub-clinical infections, while the majority of isolates from cattle were from clinical cases of salmonellosis. Only one isolate per farm of each serotype was included in this report. No significant changes in antimicrobial resistance were observed from 2006 to 2007 when comparing *S.* Typhimurium from poultry and cattle (Table 18).

Comparison of resistance in *Salmonella* Enteritidis

The most common source of *Salmonella* Enteritidis infections in humans is eggs, but other sources can be various poultry meat. In 2007, *S.* Enteritidis was rare in layers and broilers in Denmark, only two poultry isolates were susceptibility tested (data not shown).

The occurrence of resistance to ampicillin and ciprofloxacin in *S.* Enteritidis was significantly higher in travel associated human isolates as compared to domestically acquired isolates (Table 19).

As for *S.* Typhimurium, the elevated occurrence of resistance in travel associated *S.* Enteritidis isolates compared to domestically acquired isolates, probably reflects differences in the use of veterinary antimicrobials between Denmark and the countries which the patients have travelled to.

MIC distributions and occurrence of antimicrobial resistance among *S.* Enteritidis is presented in Table 31 in Appendix 1.

Transferable quinolone resistance detected in *Salmonella* isolates from turkey meat

Transferable mechanisms conferring quinolone resistance have recently been described. First *qnrA*, then other *qnr* genes (B and S) and a large number of other variants have emerged all over the world [Robicsek *et al.* Lancet Infect. Dis., 2006, 6: 629-40]. Furthermore, other genes encoding quinolone resistance have been described: *aac(6')Ib-cr* encodes an aminoglycoside modifying enzyme able to modify ciprofloxacin and norfloxacin [Robicsek *et al*., Nat. Med., 2006, 12: 83-8] and *qepA* was described as a putative specific efflux pump [Yamane *et al.*, Antimicrob. Agents. Chemother., 2007, 9: 3354-60].

In a recent study, *qnr* genes were described in isolates of *Salmonella enterica* serovars Hadar, Newport and Saintpaul isolated from imported turkey meat [Cavaco *et al.*, J. Antimicrob. Chemother., 2008, published online].

In Denmark, a case-by-case surveillance control programme is implemented for control of *Salmonella.* As part of this programme, meat batches are sampled and twelve samples of each batch are cultured for isolation of *Salmonella enterica* and antimicrobial susceptibility testing is performed [Anonymous, Annual Report of Zoonosis in Denmark, 2006]. In 2007, 1,536 batches of meat were analysed, including chicken, turkey, beef and pork. In total, 209 batches of imported turkey meat were analysed and 39 (19%) of these were positive for *Salmonella*. Among *Salmonella* isolates from turkey meat, 116 of 175 were resistant to ciprofloxacin (MIC >0.06 µg/ml). Eight *Salmonella* isolates (6.9%) belonging to three turkey meat batches were resistant to ciprofloxacin (MIC range 0.5-1 µg/ml) but were found susceptible to nalidixic acid (MIC range 8-16 µg/ml). The serovars were Saintpaul (n=1), Newport (n=3), and Hadar (n=4). Additionally, three isolates of *Salmonella* Saintpaul obtained from two batches of turkey meat collected in January-February 2008 showed the same resistance phenotype. The isolates were screened for *qnrA*, *qnrB*, *qnrS* and *aac(6')Ib* by PCR amplification and amplicons were sequenced. The PCR and sequencing results showed that all four Saintpaul isolates carried *qnrS1* and the remaining isolates harboured *qnrB5*. These resistance determinants are emerging and *qnr* genes have previously been described in *Salmonella* from several countries: *qnrA* in serovar Concord in France, *qnrB2* and *qnrB5* in the UK and in *Salmonella* Berta in the US, *qnrS1* in *Salmonella* Typhimurium, Corvallis, Stanley, Saintpaul, Typhimurium, Virchow and Virginia in the UK, Turkey and the Netherlands, and *qnrS2* in serovar Anatum in the US [Cattoir *et al.*, J. Antimicrob. Chemother., 2007, 59: 751-4; Hopkins *et al.*, J. Antimicrob. Chemother., 2007, 59: 1071-1075; Gay *et al.*, Clin. Infect. Dis., 2006, 43: 297-304; Veldman *et al.*, J. Antimicrob. Chemother. 2008, 61: 452-3; Avsaroglu *et al.*, J. Antimicrob. Chemother. 2007, 60: 1146-50]. The findings indicate that turkey meat might be a possible source of *Salmonella* harbouring transferable quinolone resistance determinants.

This is to our knowledge the first report on *qnr* genes in *Salmonella* isolates from turkey meat. However, *qnrS1* in *Salmonella enterica* from poultry origin was first detected in Germany in serotype Infantis, and was later also found in poultry products from the UK, Turkey and Thailand [Kehrenberg *et al.*, J. Antimicrob. Chemother., 2006, 58: 18-22; Hopkins *et al.*, J. Antimicrob. Chemother., 2007, 59: 1071-1075; Avsaroglu *et al.*, J. Antimicrob. Chemother. 2007, 60: 1146-50.; Cavaco *et al* J. Antimicrob. Chemother. 2007, 60: 704-6]. Furthermore, *Salmonella* Virchow strains found to carry *qnrS1* have been associated to an outbreak in the UK [Hopkins *et al.*, J. Antimicrob. Chemother., 2007, 59: 1071-1075].

The emergence of *qnr* genes in isolates from meat products is concerning, although the clinical implications of transferable quinolone resistance are still unknown.

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Campylobacter

In 2007, campylobacteriosis was the most common bacterial cause of human diarrhoeal illness in Denmark; 3,868 laboratory confirmed cases were reported (71 per 100,000 inhabitants). This constitutes a 19% increase compared to the previous year [EPI-NEWS 2008, no. 10: http://www.ssi.dk/sw55440.asp].

Interview of patients with *Campylobacter* infections

Information about travel before onset of a *Campylobacter* infection was only in some cases provided by the general practitioners. To achieve better travel information a sub sample of patients with a *Campylobacter* infection acquired in 2007 and where no information about travel was available were phone interviewed. The infection was categorised as "domestically acquired" if the patient did not travel one week prior to the onset of infection, whereas it was categorised as "travel associated" if the patient had travelled one week prior to the infection. Based on the phone interviews and information about travel provided by the general practitioners an estimated 30% of all human *Campylobacter* infections were travel associated in 2007.

Comparison of resistance in *Campylobacter jejuni* isolates from broilers, broiler meat and human clinical infections

The primary source of human *Campylobacter jejuni* infections in Denmark was fresh broiler meat. No significant differences in resistance were observed between *C. jejuni* from Danish broilers and Danish broiler meat in 2007 (Table 20). Like in previous years, resistance to ciprofloxacin, nalidixic acid and tetracycline was significantly higher in *C. jejuni* from imported broiler meat compared to Danish broiler meat (Figure 23). Similar to imported broiler meat, ciprofloxacin, nalidixic acid and tetracycline resistance was also high in *C. jejuni* from imported turkey meat (Table 20).

Resistance to ciprofloxacin and nalidixic acid was significantly higher in domestically acquired human isolates compared to isolates from Danish broiler meat, whereas the resistance level was similar among isolates from imported broiler meat and domestically aquired human isolates. The level of resistance to ciprofloxacin and tetracycline was significantly higher in *C. jejuni* from turkey meat compared to human *C. jejuni* isolates acquired domestically. As stated in previous DANMAP reports, the consumption of imported broiler meat and imported turkey meat is increasing in Denmark. It is likely that imported broiler meat and imported turkey meat contribute to the high level of ciprofloxacin and nalidixic acid resistance in *C. jejuni* isolates from domestically acquired human infections.

The occurrence of resistance to ciprofloxacin, nalidixic acid and tetracycline was significantly higher in travel associated *C. jejuni* isolates compared to isolates acquired domestically. For the other antimicrobial agents tested, no significant differences in the resistance level could be detected.

Ciprofloxacin or other fluoroquinolones are often used for empiric treatment of adults with bacterial gastroenteritis because of the activity against enteric bacterial pathogens. Fluoroquinolones are also used in animal husbandry, however in Denmark the use of fluoroquinolones in animal husbandry has been restricted since 2002. Travelling to or consuming meat from these countries where such fluoroquinolone restrictions are not implemented can be associated with a higher risk of acquiring infection with ciprofloxacin-resistant *C. jejuni.*

MIC distributions and the occurrence of antimicrobial resistance among *C. jejuni* from broiler, broiler meat of Danish and imported origin, domestically acquired human cases, and human cases associated with travel are shown in Tables 32-34 in Appendix 1.

Campylobacter jejuni from cattle

From 2005 and onwards, ciprofloxacin and nalidixic acid resistance was observed quite often among *C. jejuni* from cattle (Figure 24). The consumption of fluoroquinolones in cattle is low and the fluoroquinolone resistant isolates were not resistant to other antimicrobial agents in the test panel. This indicates that co-selection was not a likely explanation for the high occurrence of fluoroquinolone resistance. In particular in 2007, cattle farms where the fluoroquinolone resistant isolates were detected were clustered in the southern part of Jutland. This indicates that other risk factors like contact between herds might be a possible explanation for the high occurrence of fluoroquinolone resistance in cattle herds. Further investigations are needed to clarify this.

Table 20. Comparison of resistance (%) among Campylobacter jejuni *from food animals, food of Danish or imported origin and human cases categorised as acquired domestically or reported as associated with travel abroad, Denmark*

DANMAP 2007

Compound	Cattle	Broilers	Broiler meat		Turkey meat	Humans	
	Danish	Danish	Danish	Imported	Imported	Domestically acquired	Travel abroad reported
	%	%	%	%	%	%	%
Tetracycline	1	10	10	39	67	14	36
Chloramphenicol	0	0	-	-	-	1	0
Erythromycin	1	1	2	1	7	0	5
Gentamicin	0	1	0	0	0	0	3
Streptomycin	4	3	4	5	14	4	10
Ciprofloxacin	17	9	11	42	60	39	70
Nalidixic acid	17	9	11	42	57	39	70
Number of isolates	84	94	114	137	42	70	61

DANMAP 2007

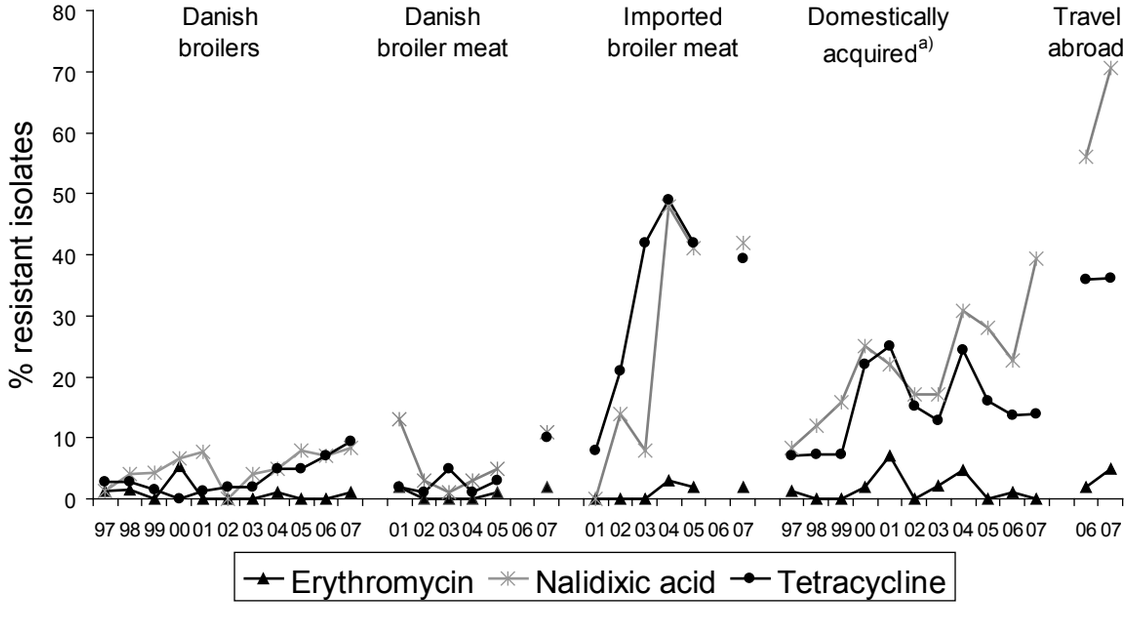

Figure 23. Trends in resistance to selected antimicrobials among Campylobacter jejuni *isolates from broilers, Danish and imported broiler meat and human cases categorised as acquired domestically or associated with travel abroad, Denmark*

a) Until 2007, includes cases where origin of infection was not documented and may therefore include isolates acquired abroad but not documented as such

Campylobacter coli from pigs

In 2007, the Danish Veterinary and Food Administration collected samples from meat sold at wholesale and retail outlets from which *C. jejuni* and *Campylobacter coli* were isolated. The species identification and susceptibility testing was outsourced to a private company. Due to the quality of the species identification of the *C. coli* isolates these could not be published in this report. Species determination was available for 145 of the human *Campylobacter* isolates. Among these, 4 *C.coli* isolates from domestically acquired infections and 10 isolates from travel associated infections were detected (data not shown). Therefore, only antimicrobial resistance among *C. coli* isolates from pigs is reported in this DANMAP report. From 2006 to 2007, no significant changes in resistance were observed among *C. coli* from pigs.

After withdrawal of the growth promoter tylosin from the Danish pig production in 1998-1999 a continuous decrease in erythromycin resistance in *C. coli* was observed from 68% in 1998 to 11% in 2007 (Figure 25). From 2006 to 2007, a significant increase in macrolide consumption was observed especially in weaners, however this increase has not yet affected the continuous decrease in erythromycin resistance among *C. coli* from pigs.

MIC distributions and the occurrence of antimicrobial resistance among *C. coli* from pigs are shown in Table 35 in Appendix 1.

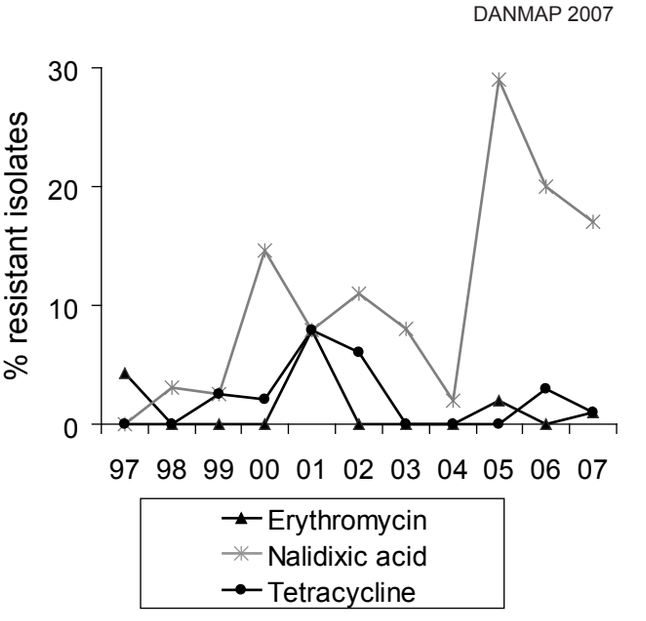

Figure 24. Trends in resistance to selected antimicrobials among Campylobacter jejuni *isolates from cattle, Denmark*

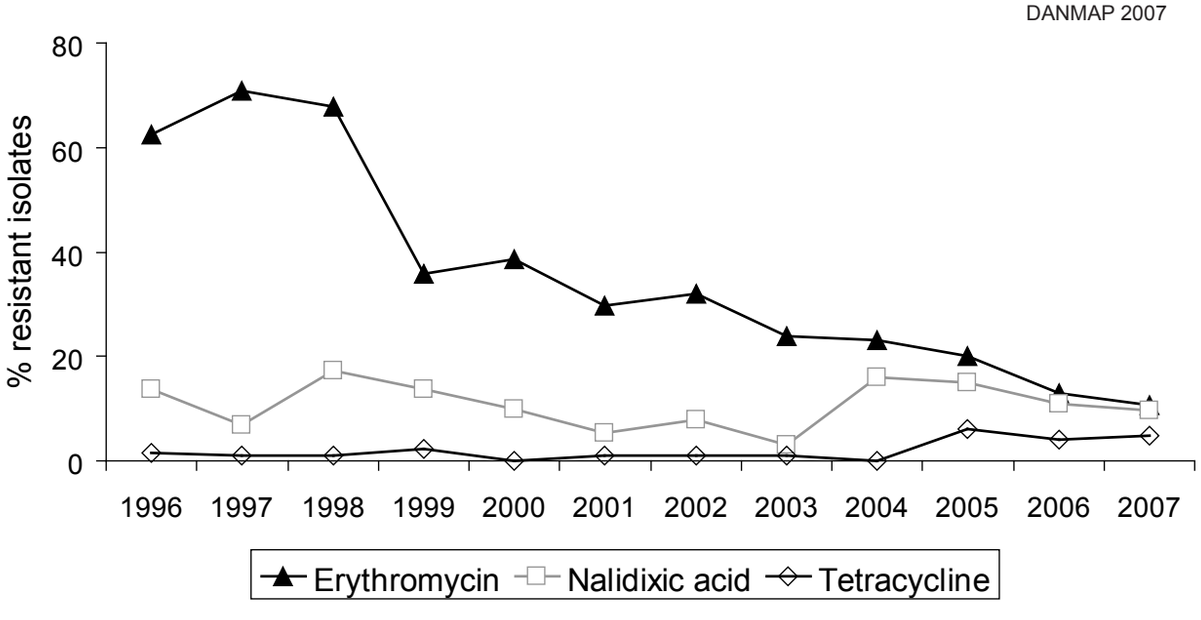

Figure 25. Trends in resistance to selected antimicrobials among Campylobacter coli *isolates from pigs, Denmark*

Resistance in indicator bacteria

Enterococci

In 2007, the Danish Veterinary and Food Administration collected samples from meat sold at wholesale and retail outlets from which *Enterococcus faecalis* and *Enterococcus faecium* were isolated. The species identification and susceptibility testing was outsourced to a private company. Due to the quality of the susceptibility testing the results cannot be published in this report. In addition, no faecal samples were collected from human volunteers resulting in lack of isolation of enterococci from this reservoir. Therefore only results for enterococci isolated from food producing animals collected at the time of slaughter are presented in this report.

The occurrence of vancomycin, avilamycin and quinupristin/dalfopristin resistance still prevails among enterococci although the glycopetide growth promoter avoparcin was banned in 1995, virginiamycin in 1998 and avilamycin was phased out by the end of 1999 (Table 21). From 2006 to 2007, erythromycin resistance increased significantly among *E. faecium* from pigs (Figure 26). This increase occurred concomitant to a significant increase in macrolide consumption in the pig production. MIC distributions of *E. faecium* and *E. faecalis* are presented in Tables 36 and 37. Trends in resistance among *E. faecium* to selected antimicrobial agents from 1995 to 2007 are presented in Figures 43-48 (Appendix 1).

Table 21. Comparison of resistance (%) among Enterococcus *faecalis and* Enterococcus faecium *from broilers and pigs, Denmark*

DANMAP 2007

Compound	Broilers		Pigs	
	E. faecalis	*E. faecium*	*E. faecalis*	*E. faecium*
	%		%	
Tetracycline	40	11	89	67
Tigecycline	0	0	0	0
Chloramphenicol	0	0	11	0
Florfenicol	0	0	0	0
Ampicillin	0	6	0	1
Erythromycin	23	30	41	47
Gentamicin	0	0	9	0
Kanamycin	0	3	22	31
Streptomycin	4	12	30	41
Vancomycin	0	2	0	2
Quinupristin/dalfopristin	-	2	-	3
Avilamycin	0	3	0	0
Flavomycin	2	-	1	-
Salinomycin	4	0	0	0
Linezolid	0	0	0	0
Daptomycin	0	0	0	0
Number of isolates	57	64	148	153

DANMAP 2007

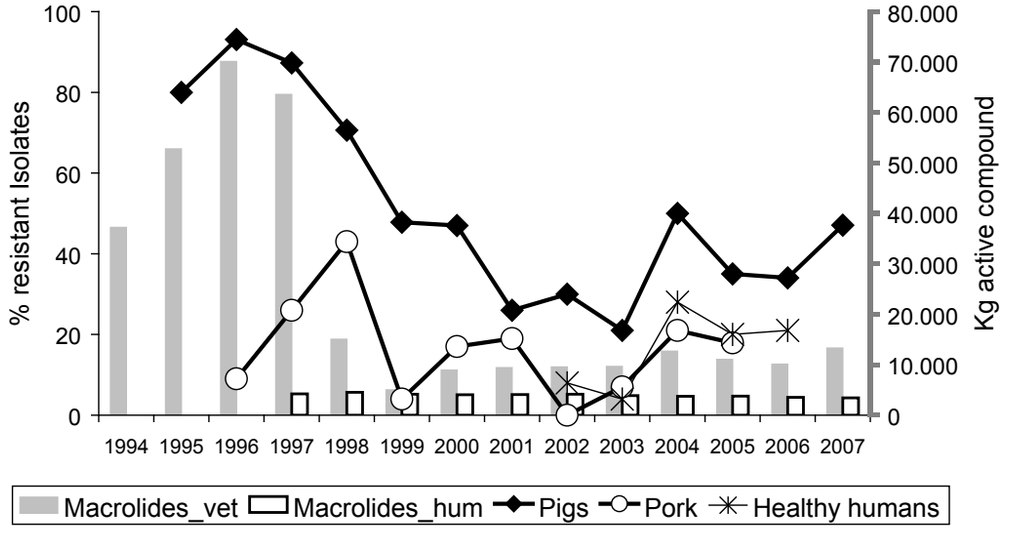

Figure 26. Trends in erythromycin resistance among Enterococcus faecium *from pigs, pork and healthy humans in the community and the total comsumption of macrolides, both as growth promoters in animals and therapeutics in animals and humans, Denmark*

Escherichia coli from healthy animals

In 2007, the Danish Veterinary and Food Administration collected samples from meat sold at wholesale and retail outlets from which *E. coli* was isolated. The susceptibility testing was outsourced to a private company and due to the quality of the susceptibility testing the results can not be published in this report. In addition, no faecal samples were collected from healthy human volunteers. Therefore only results of the susceptibility testing of *E. coli* isolates from food producing animals collected at the time of slaughter are available in this report.

Figure 27 presents the trends in resistance to selected antimicrobial agents from 1996 to 2007. Throughout the whole study period the highest nalidixic acid resistance was observed among *E. coli* from broilers. This probably reflects that since 2002 poultry has been the type of animal production with the highest fluoroquinolone consumption. The last three years the occurrence of resistance in *E. coli* from pigs has remained unchanged despite an increase in antimicrobial consumption in the pig production.

The level of resistance was lowest in *E. coli* isolates from cattle where 91% of the isolates were fully susceptible to all antimicrobials in the test panel. For broilers and pigs it was 58% and 49%, respectively (Table 22). The MIC distribution of indicator *E. coli* isolates is presented in Table 38 in Appendix 1.

Table 22. Comparison of resistance (%) among Escherichia coli *from broilers, cattle and pigs, Denmark*

DANMAP 2007

Compound	Broilers	Cattle	Pigs
	%	%	%
Tetracycline	8	7	28
Chloramphenicol	0	0	4
Florfenicol	0	0	0
Ampicillin	11	4	19
Cephalothin	4	0	1
Ceftiofur	2	0	1
Cefpodoxime	1	0	1
Sulfonamide	18	6	24
Apramycin	0	0	0
Gentamicin	0	0	0
Neomycin	0	1	2
Spectinomycin	3	0	20
Streptomycin	7	3	34
Ciprofloxacin	14	0	0
Nalidixic acid	11	0	0
Number of isolates	114	98	150

DANMAP 2007

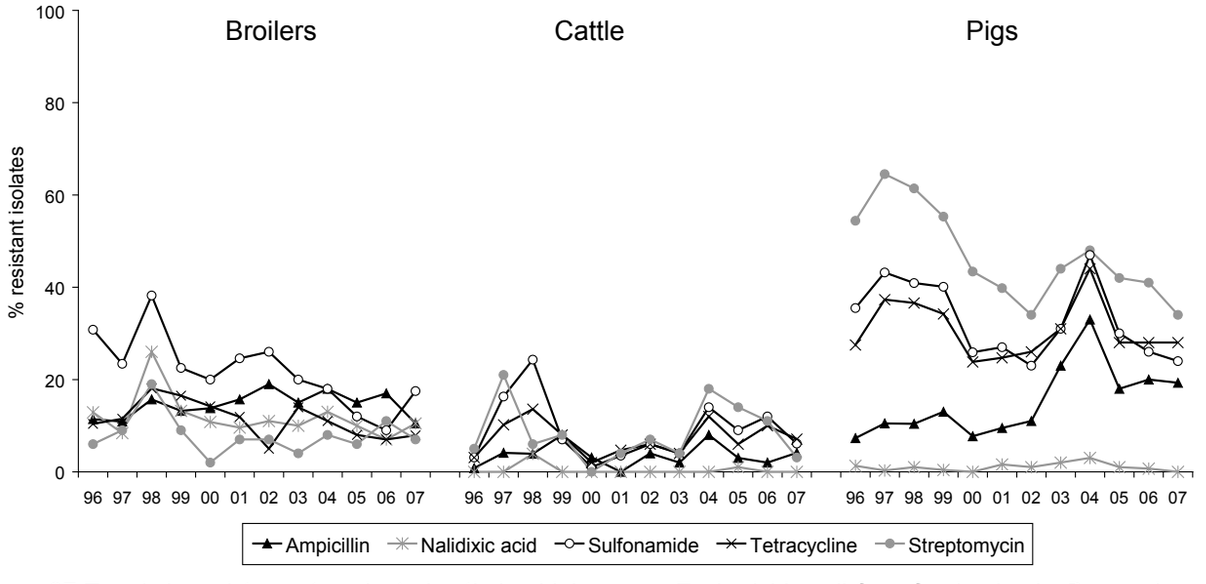

Figure 27 Trends in resistance to selected antimicrobials among Escherichia coli *from food animals, Denmark*

Resistance in human clinical bacteria

Escherichia coli

For *E. coli* this report includes data from 14 Departments of Clinical Microbiology (DCM), representing 95% of the Danish population. Results from blood and urine isolates of *E. coli* in hospitals were obtained from 14 DCM. Twelve DCM contributed data on urine isolates in primary health care (Table23).

E. coli blood isolates obtained from hospital patients

In *E. coli* blood isolates, a significant increase in resistance from 2006 to 2007 was seen for the following antibacterial agents: ampicillin, gentamicin, cefuroxime, mecillinam and the fluoroquinolones ciprofloxacin and nalidixic acid (Figures 28 and 29) (Figure 4 (Figure 51 in Appendix 1 show each individual DCM).

The high level of ampicillin resistance corresponds to the steady increase over the years in the consumption of penicillins with extended spectrum (Table 15).

The observed increase in cefuroxime resistance was concomitant to the steep increase in the consumption of cephalosporins in hospitals in recent years (see Figure 3). The increasing fluoroquinolone resistance and consumption are further discussed in the Focus Area on Hospital Consumption.

Table 23. Resistance (%) to ampicillin, sulfonamide, gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *isolates from humans, Denmark*

DANMAP 2007

Compound	Blood isolates, hospitals a)	Urine isolates, hospitals b)	Urine isolates, primary health care c)
	%	%	%
Ampicillin	44 *	41 *	41 *
Sulfonamide		35 *	38 *
Gentamicin	4 *		
Cefuroxime	5 *		
Mecillinam	5 *	5	4
Ciprofloxacin	11 *	8 *	6 *
Nalidixic acid	12 *	10 *	10

*) An asterisk indicates a significant change (increase) from 2006 to 2007

a) All 14 DCM reported data on gentamicin and cefuroxime resistance, 13 DCM reported ampicillin resistance, 12 DCM reported mecillinam and ciprofloxacin resistance, and eight DCM reported data on nalidixic acid resistance

b) All 14 DCM reported data on mecillinam resistance, 13 DCM reported ampicillin resistance, 12 DCM reported sulfonamide resistance, nine DCM reported ciprofloxacin resistance, and eight DCM reported data on nalidixic acid resistance

c) All 12 contributing DCM reported data on mecillinam and sulfonamide resistance, 11 DCM reported ampicillin resistance, seven DCM reported ciprofloxacin resistance, and six DCM reported data on nalidixic acid resistance

DANMAP 2007

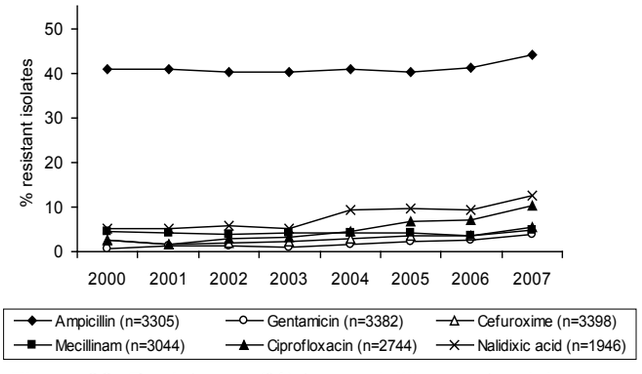

Figure 28. Resistance (%) to ampicillin, gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans, Denmark*

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

DANMAP 2007

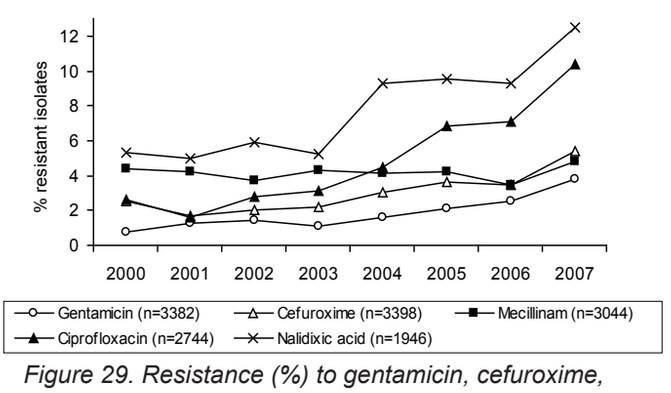

Figure 29. Resistance (%) to gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans, Denmark*

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

Regional variations
The level of ampicillin resistance increased significantly to 44% in 2007 and generally remained high between 30% and 50% (Figure 28). Rigshospitalet, the national referral hospital, reported a resistance level of 56%. Between 2006 and 2007, one DCM (Hvidovre Hospital) reported a significant increase in ampicillin resistance from 41% to 50%.

Several DCM (among others DCM Hvidovre and Skejby Hospitals) reported local significant increases in resistance to cefuroxime.

Among the eight DCM that reported data on ciprofloxacin resistance in both 2006 and 2007, resistance increased significantly to 11.2% in 2007 (Figure 28 and 29). Two DCM (Århus and Viborg Hospitals) reported significant increases in ciprofloxacin resistance in 2007, as compared to 2006.
Among the six DCM that reported data on nalidixic acid resistance in both 2006 and 2007, resistance was at an average 12.4% in 2007 (Figure 28 and 29). One DCM showed a significant increase in nalidixic acid resistance from 2006 to 2007 (DCM Århus Hospital).

E. coli urine isolates obtained from hospital patients

In *E. coli* urine isolates from hospital patients, a significant increase in resistance from 2006 to 2007 was seen for the following antibacterial agents: ampicillin, sulfonamide, and the fluoroquinolones ciprofloxacin and nalidixic acid (Table23) (Figures 30 and 31) (Figure 52 in Appendix 1 show each individual DCM).

Regional variations
Four DCM reported significant increases in ampicillin resistance from 2006 to 2007 (DCM Hvidovre, Herlev, Hillerød and Århus Hospitals).

A significant increase in sulfonamide resistance was reported locally from three DCM (Hillerød, Odense and Vejle Hospitals). However, at Rigshospitalet, the national referral hospital, a significant decrease in resistance was observed, from 50% in 2006 to 40% in 2007.

The level of mecillinam resistance has been relatively constant over the years, and overall it was 5.2% in 2007 (Figures 30 and 31). One DCM reported a significant increase in resistance (DCM Odense Hospital), and one reported a significant decrease (DCM Rigshospitalet, the national referral hospital).

Among the nine DCM that tested for ciprofloxacin resistance in 2007, all but one DCM showed a significant increase in ciprofloxacin resistance in hospitals, as compared to 2006.
Two DCM showed a significant increase in nalidixic acid resistance from 2006 to 2007 (DCM Hvidovre and Århus Hospitals), whereas one DCM (DCM Slagelse Hospital) showed a significant decrease.

E. coli obtained from urine isolates from primary health care

In *E. coli* urine isolates from primary health care in Denmark, a significant increase in resistance from 2006 to 2007 was seen for ampicillin, sulfonamide, and the fluoroquinolone ciprofloxacin (Table23) (Figures 32 and 33) (Figure 53 in Appendix 1 show each individual DCM).

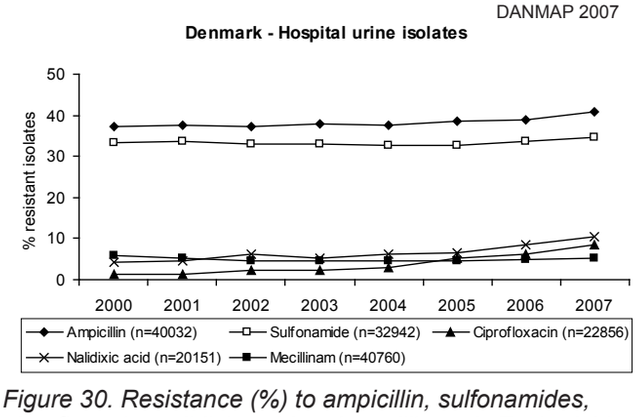

Figure 30. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

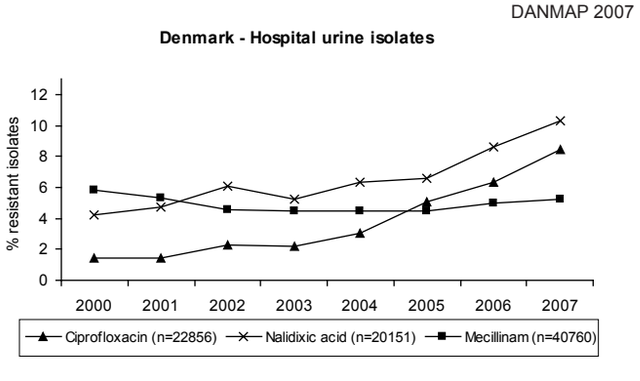

Figure 31. Resistance (%) to ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

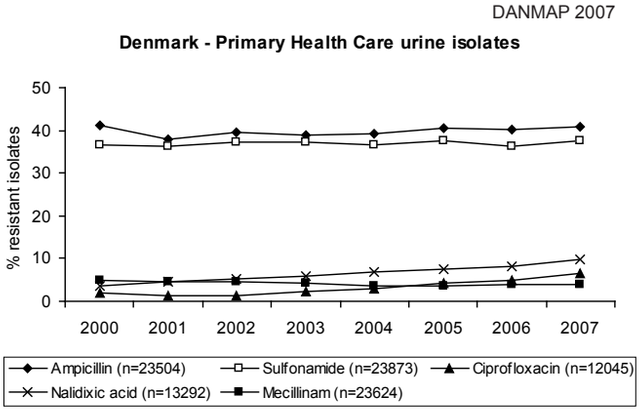

Figure 32. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans, Denmark*

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

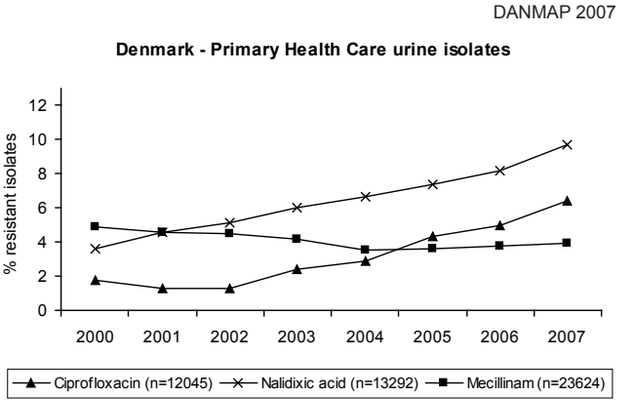

Figure 33. Resistance (%) to ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans, Denmark*

The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007

Overall, the level of ampicillin resistance in *E. coli* urine isolates from primary health care remained high and increased significantly to 41% in 2007 (Figure 32). The high level of resistance to ampicillin and sulfonamides in *E. coli* from urine makes these antibacterial agents obsolete for the empiric treatment of urinary tract infections. However, the reported resistance levels may be biased due to a significant proportion of urine samples submitted for microbiological diagnosis following failure of empirical treatment. A study performed in 1997-1999 showed that ampicillin and sulfonamide resistance in *E. coli* isolates from uncomplicated urinary tract infections in primary health care in Denmark was at only 20% and 22%, respectively, compared to 34% and 39%, respectively, in complicated urinary tract infections [Kerrn *et al*. 2002. J. Antimicrob. Chemother. 50: 513-6].

Between 2006 and 2007, consumption of fluoroquinolones in primary health care increased from 0.37 to 0.44 DDD per 1,000 inhabitant-days (Table 11). This might be the reason for the increasing resistance to ciprofloxacin in the urine *E. coli* isolates.

Regional variations

One DCM (Herlev Hospital) reported a significant increase in ampicillin resistance from 2006 to 2007.

Two DCM (Hvidovre and Hillerød Hospitals) reported increases in sulfonamide resistance, whereas one DCM (Odense Hospital) reported a decrease in resistance.

One DCM reported a significant increase in mecillinam resistance (DCM Odense Hospital).

Three of the seven DCM that tested for ciprofloxacin resistance reported a significant increase in resistance from 2006 to 2007 (Herlev, Hillerød and Odense Hospitals).

Among the five DCM that reported data on nalidixic acid resistance in both 2006 and 2007, resistance was at an average 9.5% in 2007 and unchanged from 2006 (Figures 32 and 33). One DCM showed a significant increase in nalidixic acid resistance from 2006 to 2007 (DCM Hvidovre Hospital), whereas one DCM (DCM Slagelse Hospital) showed a significant decrease.

Invasive *Streptococcus*

Data on resistance levels in *Streptococcus* isolates cover all five regions (16 former counties) in Denmark.

All invasive (from blood or cerebrospinal fluid) non-duplicate *Streptococcus pneumoniae*, Group A, B, C and G streptococci from Denmark were susceptibility tested to erythromycin and penicillin.

Streptococcus pneumoniae

In 2007, susceptibility testing was performed on 1.054 non-duplicate *S. pneumoniae* isolates.

Macrolide resistance in *S. pneumoniae* isolates from blood and cerebrospinal fluid has been around 5% since 2000. The percentage of macrolide resistant *S. pneumoniae* was 5.4% in 2005, 5.5% in 2006, and 6.2% in 2007 (Figure 34).

The percentage of *S. pneumoniae* isolates that were not susceptible (resistant plus intermediate) to penicillin was 4.2% in 2005, 3.4% in 2006, and 3.2% in 2007

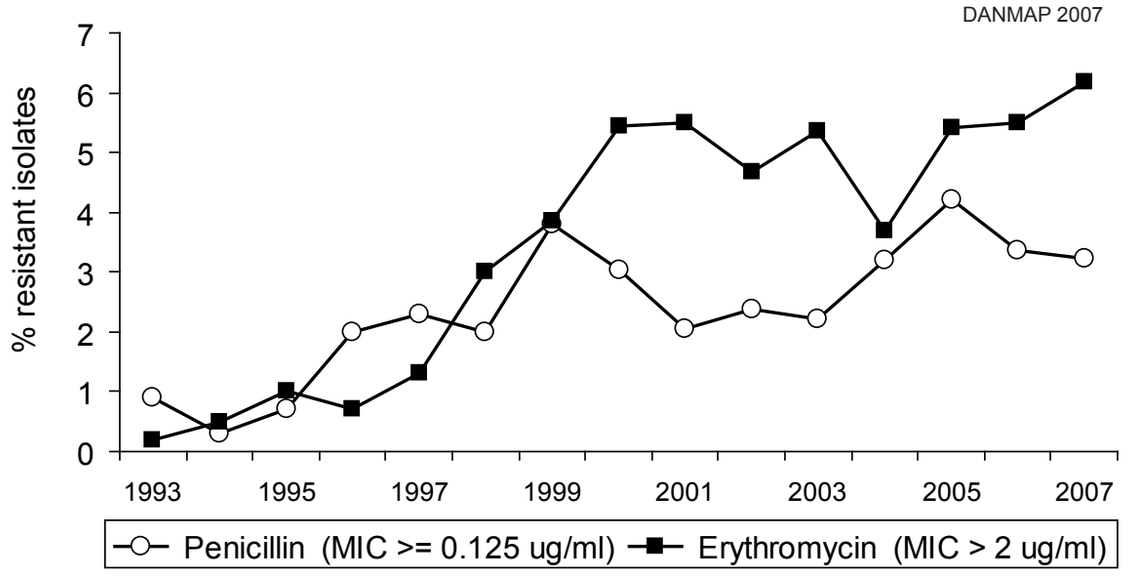

Figure 34. Resistance (%) to penicillin and macrolides in Streptococcus pneumoniae *blood and spinal fluid isolates from humans, Denmark*

(Figure 34). This level of resistance is similar to the level detected in other Scandinavian countries, but the resistance level is much lower than reported in many of the other European countries [http://www.rivm.nl/earss/database/].

Group A, B, C and G Streptococci

In 2007, 107 invasive Group A streptococci (*Streptococcus pyogenes*) isolates were susceptibility tested. Erythromycin resistance was detected in four isolates (3.7%) as compared to one of 131 isolates (0.8%) in 2006.

Furthermore, 97 invasive group B streptococci (*Streptococcus agalactiae*) isolates were tested. Erythromycin resistance was detected in 8 isolates (8.2%) compared to 4.6% in 2006.

Twenty isolates were invasive group C streptococci with 5% (1 isolate) resistant to macrolide compared to 3.7% in 2006.

Ten (8.1%) of the 123 invasive group G streptococci were resistant to macrolide compared to 2.3% in 2006.

As in previous years, no resistance to penicillin in group A, B, C or G isolates was reported in 2007.

Coagulase-negative staphylococci

In 2007, data on penicillin resistance in coagulase-negative staphylococci blood isolates from hospitals was reported from 13 DCM (3,413 isolates). The average level of penicillin resistance was at an average 81% (min. 61% - max. 91%), which corresponds to the level of resistance seen since 1996.

Macrolide resistance was reported by 13 DCM (3,499 isolates) and was at an average 39%. It varied largely among the participating DCM (min. 26% - max. 56%), but the level of resistance generally corresponds well with the level of resistance seen in several years.

In 2007, nine DCM (2,788 isolates) reported data on methicillin resistance. This was at an average 55% but a wide variation was seen among DCM (min. 26% - max. 72%). As stated in previous reports, it is however possible that the large variability in resistance is a consequence of the procedure for selection of isolates that are submitted for susceptibility testing. Caution is therefore warranted when making comparisons of resistance levels between DCM.

Emergence of ampicillin resistant *Enterococcus faecium* in Danish hospitals

Enterococci are becoming an important cause of nosocomial infections, including bacteraemia, endocarditis, and surgical wound infections. Optimal antimicrobial therapy for serious enterococcal infections requires the use of synergistic combinations of a cell-wall-active agent such as penicillin or a glycopeptide, and an aminoglycoside. Enterococci with ampicillin resistance and high-level gentamicin resistance are therefore the cause of considerable therapeutic problems; acquired vancomycin resistance has further aggravated these problems.

Microbiology data from 2002 through 2006 on *E. faecium* and *E. faecalis* blood isolates was received from Departments of Clinical Microbiology in 11 Danish counties. A 68% increase in the number of infections caused by enterococci was observed from 2002 through 2006 (Figure 35). The increase was mainly caused by *E. faecium* isolates which increased by 202% whereas the number of *E. faecalis* isolates increased by only 23% during the same period. There was also a significant increase in the number of ampicillin resistant *E. faecium* isolates (Lester *et al.* J. antimicrob. Chemother. accepted). A reason for the increasing frequency of *E. faecium* as a cause of bloodstream and other infections could be its ability to acquire many different resistance genes; the antimicrobial pressure in a hospital environment therefore allows for its selection. The consumption of broad-spectrum antimicrobial agents results in the elimination of the normal flora, leading to colonization of strains endemic in the environment of hospitals; this could be an ampicillin resistant *E. faecium*. This is followed by overgrowth of the strain and ultimately clinical infection when host defences are overwhelmed. Treatment with fluoroquinolones, cephalosporins or carbapenems has been described as a risk factor for development of an *E. faecium* infection. An increasing consumption of these antimicrobial agents has also been observed in hospitals in Denmark during the past five years in the previous DANMAP reports. This might be an explanation of the changing *E. faecalis/E. faecium* ratio.

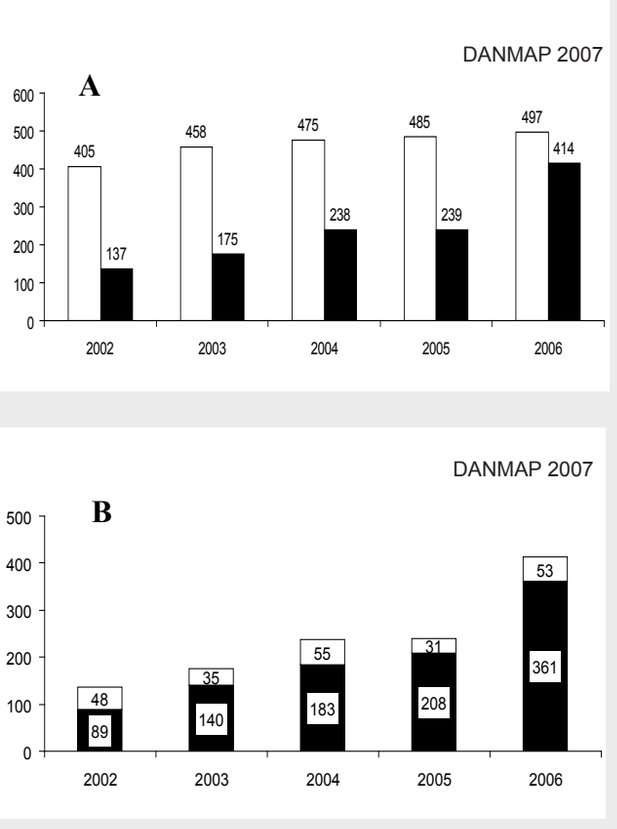

Figure 35. Data on enterococcal blood culture isolates from 11 Danish counties representing 73% of the Danish population. (A) The number of enterococcal bacteraemias from 2002 to 2006. The white bars represent E. faecalis *and the black bars represent* E. faecium. *(B) The number of ampicillin resistant and sensitive* E. faecium *blood culture isolates from 2002 to 2006. The black bars represent the ampicillin resistant isolates and the white bars represent the ampicillin sensitive isolates*

In conclusion, infections caused by ampicillin resistant *E. faecium* are an increasing problem in Denmark. This may necessitate a change of treatment of enterococcal infections from ampicillin to vancomycin, which in turn will increase the risk of spread of Vancomycin resistant enterococci in Danish hospitals.

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Staphylococcus aureus

Surveillance of bacteraemia

In 2007, a total of 1,345 *Staphylococcus aureus* bacteraemia cases were reported from 15 participating Danish counties/municipalities covering 95% of the Danish population. This corresponded to an incidence of 24.5 per 100,000 inhabitants, which is similar to 2006. Eight (0.6%) of the bacteraemia cases were caused by methicillin resistant *S. aureus* (MRSA), which is a decrease compared to 2006 (19 cases (1.4%)). Table 24 presents occurrence of antimicrobial resistance among *S. aureus* bacteraemia and MRSA in 2007. A more detailed description of the *S. aureus* bacteraemia cases is published in the annual *S. aureus* bacteraemia report [http://www.ssi.dk/sw3425.asp].

Table 24. Occurence of resistance (%) among isolates from Staphylococcus aureus *bacteraemia and methicillin resistant* Staphylococcus aureus *(MRSA) cases, Denmark*

DANMAP 2007

Compound	*S. aureus* bacteraemia isolates	MRSA All body sites a)
Methicillin	<1	100
Penicillin	77	100
Erythromycin	4	48
Clindamycin	3	36
Tetracycline	2	21
Fusidic acid	9	20
Rifampicin	<1	3
Norfloxacin	1	31
Streptomycin	<1	18
Kanamycin	<1	38
Mupirocin	<1	<1
Numbers of isolates	1345	659

a) One isolate being heteroresistant against vancomycin (hVISA)

Surveillance of Methicillin Resistant *S. aureus* (MRSA) Incidence of MRSA

In 2007, the total number of new MRSA cases decreased to 659 (12 per 100,000 inhabitants) in 650 persons (9 persons had two different MRSA strains) (Figure 36). The decrease in 2007 was primarily due to a reduction of cases in the Greater Copenhagen area (Copenhagen and Frederiksberg Municipalities and Copenhagen County) and in Vejle County (Figure 37). In both regions this has been the result of a very active policy against MRSA. In Copenhagen, this has in particular led to a reduction in the number of hospital acquired cases and cases from nursing homes. In Vejle, the reduction represents the management of a long outbreak that has been occurring at the hospitals since 2002 but seemed to be in control by the end of 2007 (Figure 36).

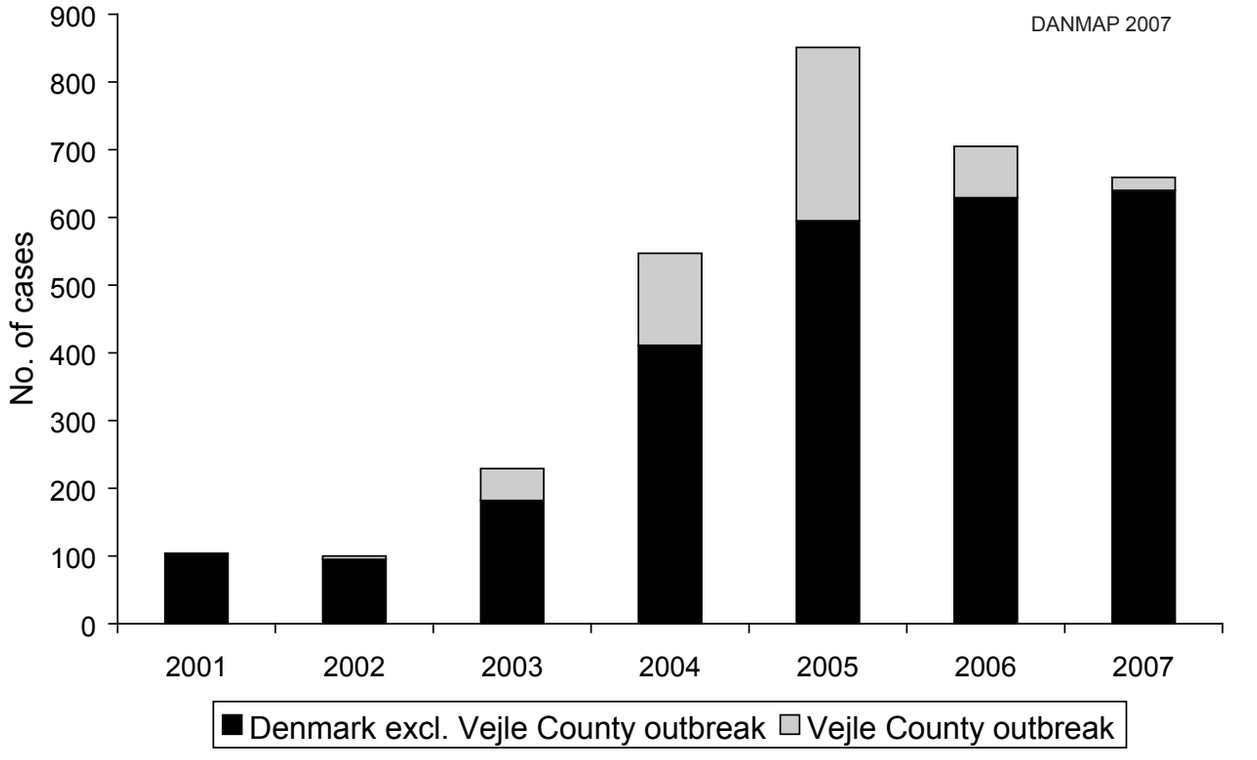
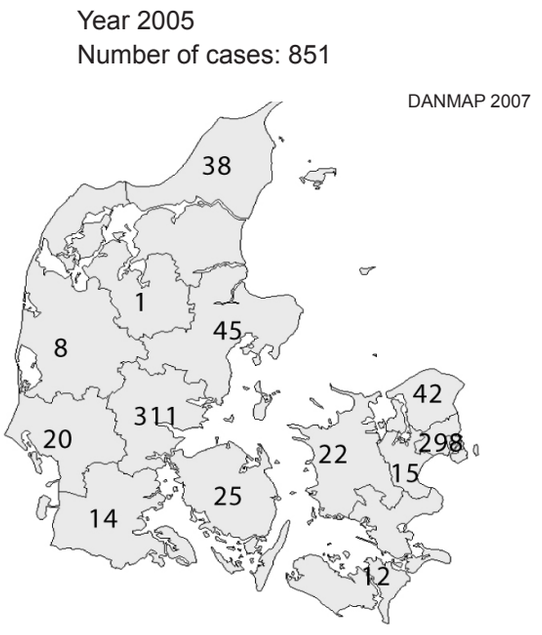
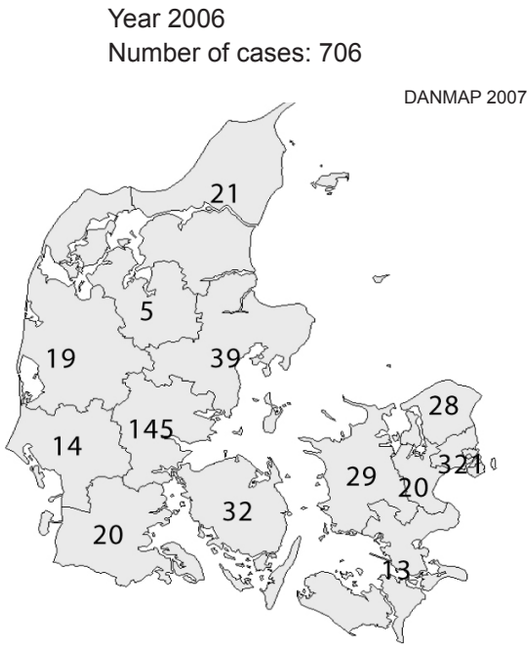


Figure 36. Number of new human MRSA cases per year in Denmark





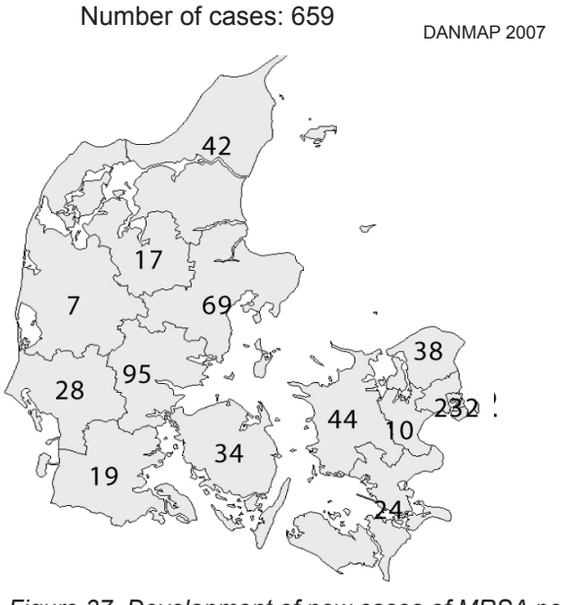


Figure 37. Development of new cases of MRSA per Department of Clinical Microbiology, 2005-2007, Denmark

Large regional variations in the incidence of MRSA cases were observed in 2007 (Figure 37). The highest incidence was reported in Vejle County (26 cases per 100,000 inhabitants), which was largely due to cases found by screening of healthy carriers. Outside Vejle County the highest incidence was found in Greater Copenhagen with 19 cases per 100,000 inhabitants. For the rest of Denmark, the incidence was between two and ten cases per 100,000 inhabitants.

Origin of the MRSA infection

The number of cases according to epidemiological classification (import (IMP), hospital associated (HA), community onset with exposure to hospitals or nursing homes within the last 12 months (HACO) or without such exposure i.e. community associated (CA)) is shown in Table 25. The majority of cases were acquired in Denmark. Most cases were diagnosed in primary health care (70%). Of cases with health care contact within the last 12 months (HACO) only 25% of the persons had exposure to a MRSA positive person. Among the CA cases, 42% had known exposure to a MRSA positive person, which most often was a member of the same household or a close contact. In six cases, all infected/colonised with the same type of MRSA(CC398), there was known direct or indirect exposure to pigs (see MRSA textbox). It is noteworthy, that 36% of the CA infectious cases had a non-Danish origin, whereas people of non-Danish origin constitute approximately 3% of the Danish population. This over-representation most likely represents transmission from relatives in high prevalence countries.

Fifty-six percent of all cases had an infection at the time of diagnosis. The number of both HA and HACO infections decreased in 2007. Furthermore, the number of MRSA bacteraemia cases decreased from 19 in 2006 to eight in 2007, which can be due to the implementation of the new national guidelines (Figure 38).

The decrease in the number of health care associated cases represents an important success in the combat of MRSA. In 2007, the number of imported and CA infectious cases both continued to increase. In both

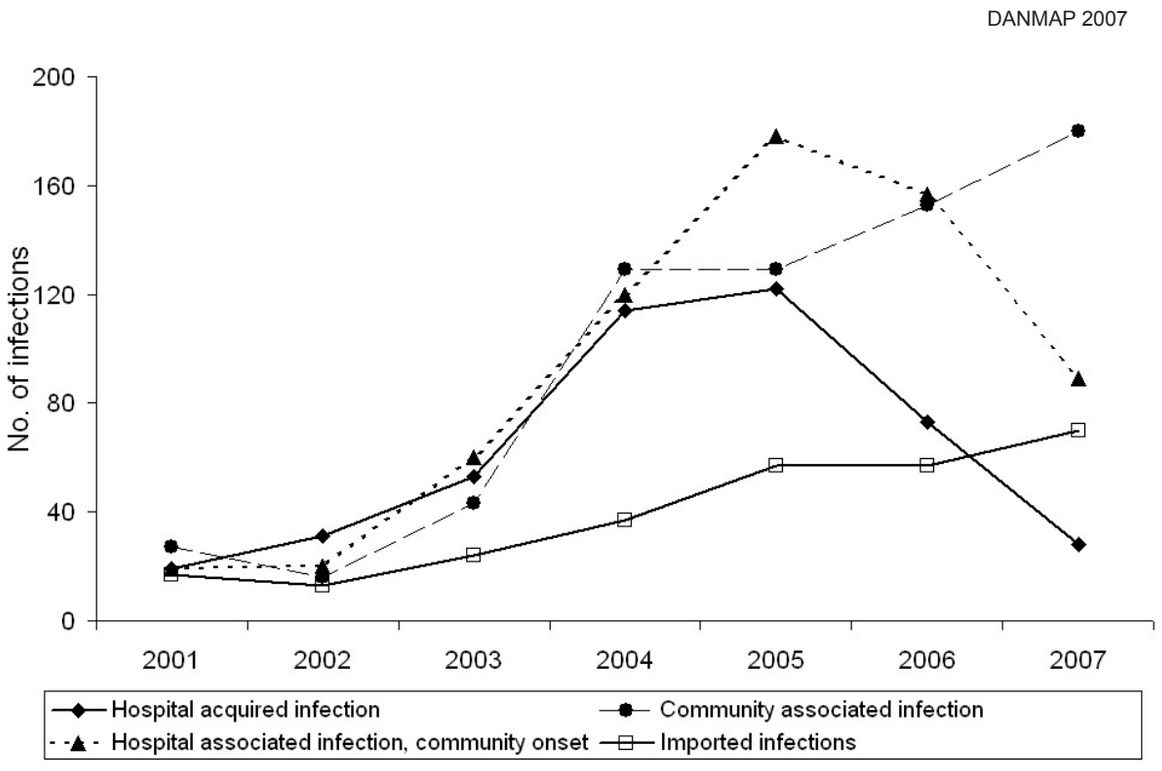


Figure 38. Number of methicillin resistant Staphylococcus aureus *infections according to epidemiological classification, Denmark*

instances this probably reflect the general increase of CA-MRSA in most parts of the world resulting in an increased risk of becoming colonised with MRSA when visiting or having visitors from countries with high endemic levels of MRSA. This needs to be investigated more thoroughly in the future. Risk factors were reported for 241 cases, with wounds as the most frequent risk factor (n=105), followed by chronic skin disease (n=42) and foreign bodies (n=35).

The data from 2007 strongly indicates that control of MRSA is possible both in hospital outbreak situations as well as in the community. However, the increase in cases acquired outside Denmark (import) and the increase in community associated cases clearly indicate that continued efforts are necessary to keep Denmark as a low endemic country.

Table 26 shows the resistance frequencies according to epidemiologic classification. Resistance only to beta-lactams was seen in 24% of the isolates, which is an increase from 17% in 2006 and 13% in 2005. Furthermore, the number of multiresistant isolates, i.e. isolates resistant to three or more classes of antimicrobial agents, decreased from 57% in 2006 to 45% in 2007.

For fusidic acid (27% to 20%), norfloxacin (44% to 31%) and rifampicin (6% to 2.5%) resistance decreased from 2006 to 2007. Similar to 2006, resistance to mupirocin was recorded in three isolates, of which two were high-level resistant. All MRSA isolates from 2007 were susceptible to glycopeptides, except one which was intermediate resistant (hVISA).

Molecular typing of the MRSA isolates

Molecular typing (spa typing) showed a high degree of heterogeneity with 110 different spa types. Most of the isolates (n=648) could be assigned into 18 clonal complexes (CC), whereas the CC association for the remaining 11 isolates could not be determined. In 2007, 83% of the isolates belonged to seven clonal complexes: CC8 (31%), CC5 (16%), CC22 (10%), CC80 (9%), CC30 (8%), CC45 (5%) and CC1 (3%). The major CC groups found in Denmark are also among the most frequently isolated in other countries. Compared to 2006, the number of CC22 and CC80 has decreased, which is reflected in the decrease in norfloxacin and fusidic acid resistance observed in 2007.

Fourteen cases of MRSA CC398 were detected in 2007. This is a recently identified *S. aureus* type that has been associated with animal husbandry, see textbox MRSA.

Notification of MRSA in Denmark

November 1st. 2006, MRSA became both laboratory and clinically reportable in Denmark. All new cases, i.e. the first time a person is found positive with a given MRSA strain (both colonisation and infection), are reportable and the isolates are collected at SSI. Secondary infections, i.e. cases presenting as asymptomatic colonisation but with subsequent development of infections, are not reported, thus the number of infective cases are most likely underestimated.

The change of MRSA into a notifiable disease is not expected to influence the number of new cases reported since a very strong voluntary system to report MRSA has been in place in Denmark for several years. At the same time, new guidelines for management of MRSA, not only in hospitals but also in nursing homes and in primary health care, were implemented [http://www.sst.dk/publ/publ2008/CFF/MRSA/MRSA_vejl_en_19mar08.pdf]. Eradication strategies of MRSA carriage, both in health care and in the community, are important parts of these new guidelines including topical treatment with mupirocin and chlorhexidine with addition of systemic antibiotics in case of treatment failure. For community associated MRSA cases it is recommended that the whole household of an MRSA positive person is treated simultaneously regardless of carrier status.

Table 25. Epidemiological classification of new MRSA cases, Denmark, 2007

DANMAP 2007

MRSA classification	Exposure	No. of cases a)	No. (%) of cases with infection
Imported infections (IMP)		114	70 (61)
Hospital acquired infections (HA)		52	28 (54)
Hospital associated infection, community onset (HACO)	Known b)	31	11 (35)
	Unknown	94	66 (70)
Health care worker		27	12 (44)
Community associated infection (CA)	Known c)	142	43 (30)
	Unknown	194	137 (71)
Unclassified		5	3 (66)
Total number of cases		659	370

a) Both colonisation and infection
b) Part of an existing outbreak
c) Most often infected by a person from the same household

Table 26. Occurrence of resistance (%) among methicillin resistant Staphylococcus aureaus *(MRSA) isolates from infections according to epidemiologic classification, Denmark*

DANMAP 2007

Compound	Imported infection	Hospital acquired infection	Hospital associated infection, community onset	Community associated infection
Erythromycin	51	58	61	33
Kanamycin	52	22	20	41
Clindamycin	29	42	48	24
Norfloxacin	38	31	44	25
Tetracycline	30	19	5	24
Fusidic acid	9	11	14	25
Streptomycin	20	17	3	20
Rifampicin	7	6	0	2
Mupirocin	1	0	1	1
Number of isolates	69	36	80	178

Detection of Methicillin-resistant *Staphylococcus aureus* in pigs and humans in Denmark

Methicillin-resistant *Staphylococcus aureus* (MRSA) in animals has been sporadically reported since the 1970s but in the last five years there has been a substantial increase in the number of reports and MRSA in animals now seem to be a significant reservoir. MRSA has been detected in several animal species including cattle, chickens, horses, pigs, dogs, rabbits, seals, birds and cats. It is, however, important to distinguish between the epidemiology of MRSA in relation to production animals, where isolates of one clonal complex (MRSA CC398) are emerging, and pet animals, which are colonised or infected with classical human variants of MRSA.

With our current knowledge the clonal complex CC398 is a MRSA clone transmitted from production animals to humans and should therefore be considered a zoonosis. The origin of the clone and its natural host range is presently unknown.
In Denmark, MRSA CC398 has been detected in 48 persons since 2003, including four veterinarians found to be carriers by convenience screening at conferences. Approximately half of the cases have had infections (mostly as skin and soft tissue infections). A case-control investigation, involving 21 cases and two groups of controls (random selected persons and MRSA patients of non-CC398) was conducted in the spring 2007. This study clearly showed that contact to farm animals was a major risk factor with an OR of 35 (2.7-469.8) compared to healthy persons and an OR of 11.4 (2.7-75.4) compared to patients infected with MRSA of other types than CC398. Follow-up investigations in pigs on farms with which some of the patients had contacts showed MRSA CC398 in pigs on 4 of 5 farms examined [Skov et al., Emerg. Inf. Dis. published online].
The first isolate in pigs in Denmark was found in 2006. Since then, it has been detected in 5 of 6 investigated farms including those in the case-control study. It should be noted that only farms with known human cases have been examined, why this is not a reflection of the prevalence of farms positive for MRSA CC398. An investigation on a large pig farm in 2007 (yearly production of 10,000 pigs) showed that seven of nine persons with close contact to pigs were MRSA carriers whereas only one relative was found positive although some of the relatives had occasional contact to the pigs. Only one person had experienced an infection. Samples from the pigs showed that 80% of both sows and slaughter pigs were positive for MRSA.
Recently, MRSA have also been identified in two pig farms as the cause of infections associated with lack of treatment efficacy. This emphazises the need to carry out a nationwide survey of the MRSA situation in the pig production.
Screening for MRSA among veterinarians in both Denmark, the Netherlands and England have shown much higher carriage rates as compared to the general population, not only of CC398 but also of “normal human MRSA” i.e. CC22, CC8 and CC5. In Denmark, convenience screening at three veterinary conferences showed a carriage rate of 2.7% (11 of 405 persons investigated). Similarly, in the Netherlands an average of 4.6% of veterinarians and veterinary students were carriers of MRSA. In both countries MRSA carriage is below 0.1% in the general healthy population and the finding of increased prevalence of MRSA in veterinarians suggests that this should be investigated further.

Comments and recommendation

MRSA is still primarily a human pathogen but should based on our current knowledge also be considered a zoonosis. MRSA positive pet animals have not been found in Denmark. However, companion animals can be infected by their human owners and subsequently act as a reservoir for the bacterium from where it can transfer to and cause infections in humans. In case of treatment failure of MRSA carriage the companion animals should therefore be tested.

In production animals the situation is different and still somewhat unclear. The MRSA belong to one clonal lineage that seems to have pigs and possibly other animals as natural hosts from where it can spread to humans. The prevalence in pigs and in humans with close contact to pigs and the importance for human health as well as the possibilities for infection control are currently unclear. One case of serious infection in humans has been encountered. There is an urgent need for investigations that will elucidate: 1) What is the size of the reservoir in pigs and other production animals; 2) how often are humans in close contact to pigs MRSA positive; 3) What is the transmission rate for persons without close contact to pigs; 4) How often does this MRSA type cause infections in humans; and 5) which factors select for MRSA in production animals and how does MRSA spread between farms.
Diagnostic laboratories should be aware that MRSA might be isolated from animals. Whenever any suspicion arises the isolates should be sent to a reference laboratory for verification. Surveys using selective enrichment procedures should be conducted.

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Appendix 1
Antimicrobial consumption

Antimicrobial consumption in animals

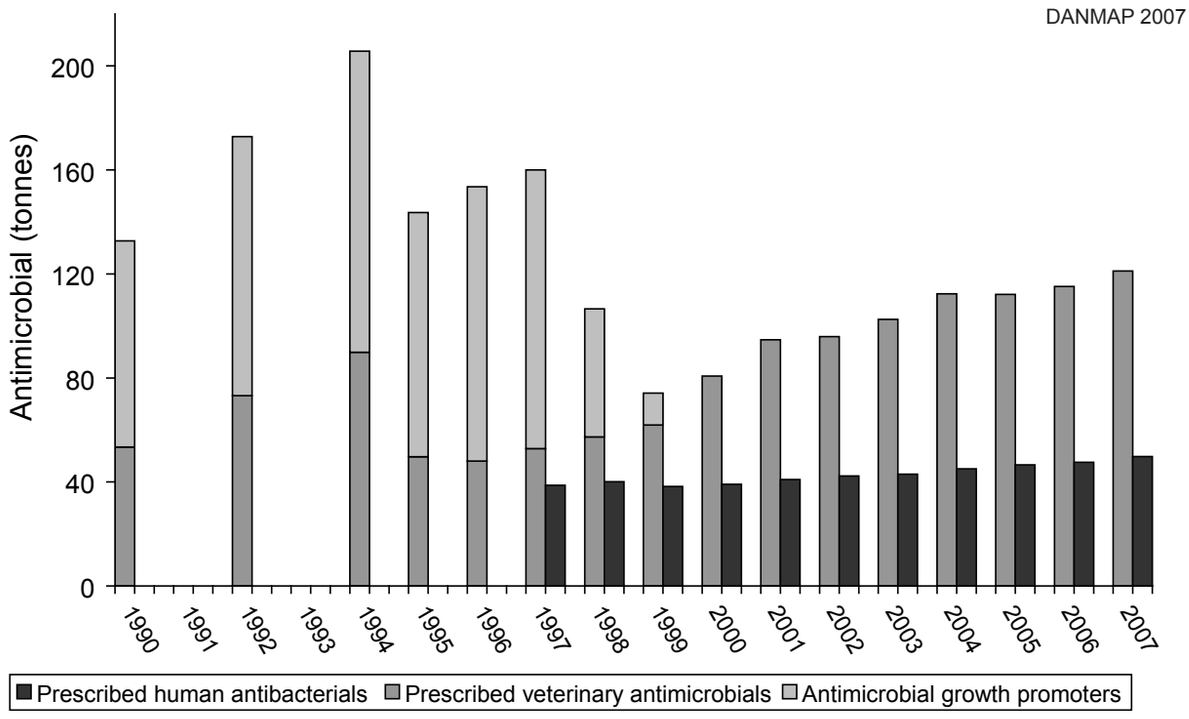


Figure 39. Consumption of prescribed antimicrobials and growth promoters in animal production and prescribed antibacterials in humans, Denmark

Sources: Human therapeutics: The Danish medicines Agency. Veterinary consumption: 1990-2000, data based on reports from the pharmaceutical industry of total annual sales. (Data 1990-1994: Use of antibiotics in the pig production. Federation of Danish pig producers and slaughterhouses. N. E. Rønn (Ed.). 1996-2000: Danish Medicines Agency and Danish Plant Directorate). 2001-2007: Data from VetStat.

Table 27. Consumption of antimicrobials in pigs given as Animal Daily Doses (ADDs) from 2003 to 2007, Denmark

DANMAP 2007

		Pharmacies and feed mills a)																	
Age group		Sows/piglets					Weaners					Finishers					Age not given		
Animal standard weight		200 kg					15 kg					50 kg					50 kg		
		2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2003	2004	2005	2006	2007	2005	2006	2007
ATC_{vet} group	Therapeutic group	ADD (1,000s)																	
QJ01A	Tetracyclines	915	927	877	1,013	1,497	32,367	38,207	43,419	52,339	72,029	11,138	12,212	13,096	14,843	17,754	824	1,154	654
QJ01B	Amphenicols	6	7	7	7	8	84	105	71	36	79	22	32	26	25	15	3	1	<1
QJ01CE	Penicillins, β-lact. sen. b)	2,015	2,230	2,315	2,321	2,553	2,903	3,969	4,089	3,865	4,299	5,121	6,323	7,262	7,426	7,682	549	512	250
QJ01CA/CR	Penicillins, other	1,118	1,201	1,169	1,150	1,315	12,720	16,348	14,414	11,933	12,071	2,420	3,500	3,282	2,805	2,699	318	392	104
QJ01DA	Cephalosporins	99	113	132	148	202	254	263	267	290	352	56	60	62	49	52	10	12	5
QJ01E/QP51	Sulfonam./trimeth.	1,084	1,217	1,301	1,353	1,489	4,146	5,454	6,124	4,483	4,134	174	232	238	151	166	181	180	84
QJ01FA	Macrolides	746	772	661	531	899	41,173	52,225	49,734	47,546	56,940	12,255	12,261	12,423	10,634	10,879	881	885	373
QJ01FF	Lincosamides c)	580	588	574	541	620	19,821	22,411	19,192	16,492	16,859	4,412	4,622	4,382	3,607	3,252	330	319	188
QJ01G/A07AA	Aminoglycosides	237	220	171	154	105	22,231	21,469	19,782	19,410	10,671	194	124	237	213	109	75	148	49
QA07AA10	Colistin (local GI)	23	24	23	24	28	2,910	3,017	2,656	2,793	3,009	18	14	13	18	13	21	22	13
QJ01MA	Fluoroquinolones	23	3	4	7	6	17	8	5	11	0	6	4	2	0	0	<1	2	0
QJ01RA01	Penicillin/spectinomycin	703	669	661	643	662	2,211	3,075	3,589	3,478	3,438	423	380	369	292	226	84	75	26
QJ01X	Pleuromutilins	946	987	811	856	1,299	19,759	24,811	23,494	22,539	22,498	8,478	10,177	10,157	9,479	8,902	735	699	397
QJ51	Intramammaries	4	2	1	<1	<1	<1	<1	0	<1	0.03	<1	1	<1	<1	<1	<1	<1	<1
QG01AA	Gynecologic (local)	0	<1	<1	<1	<1	0	0	0	0	0	0	0	0	0	0	0	<1	0
Total		8,500	8,958	8,707	8,748	10,682	160,597	191,362	186,837	185,215	206,379	44,718	49,943	51,802	49,542	51,750	4,009	4,401	2,142

a) Consumption in veterinary practice comprises less than 1% of the total consumption in pigs. These data are not included, except the use of fluoroquinolone
b) Beta-lactamase sensitive penicillins
c) Lincosamide/spectinomycin combinations

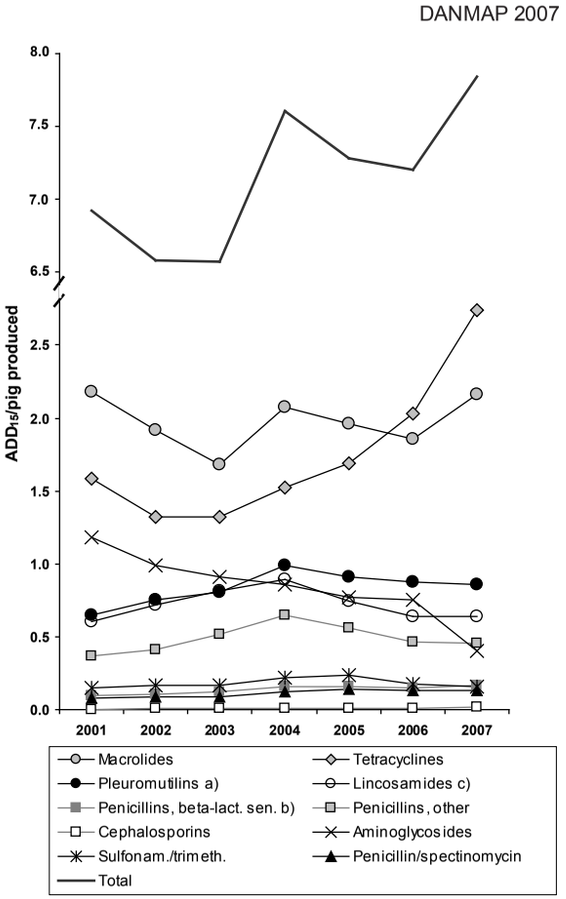


Figure 40. Trends in antimicrobial consumption in weaners, 2001-2007, Denmark
ADD_{15} are assumed average doses for treatment of weaners (7.5 to 30 kg)

Amphenicols, colistin, fluoroquinolones, intramammaries and gynecologicals are not included in the figure. Data from veterinary practice are not included (amounts to <1% of the consumption in pigs)
a) Pleuromutilins comprise primarily tiamulin
b) Beta-lactamase sensitive penicillins
c) Lincosamide/spectinomycin combinations comprise 65% of this group

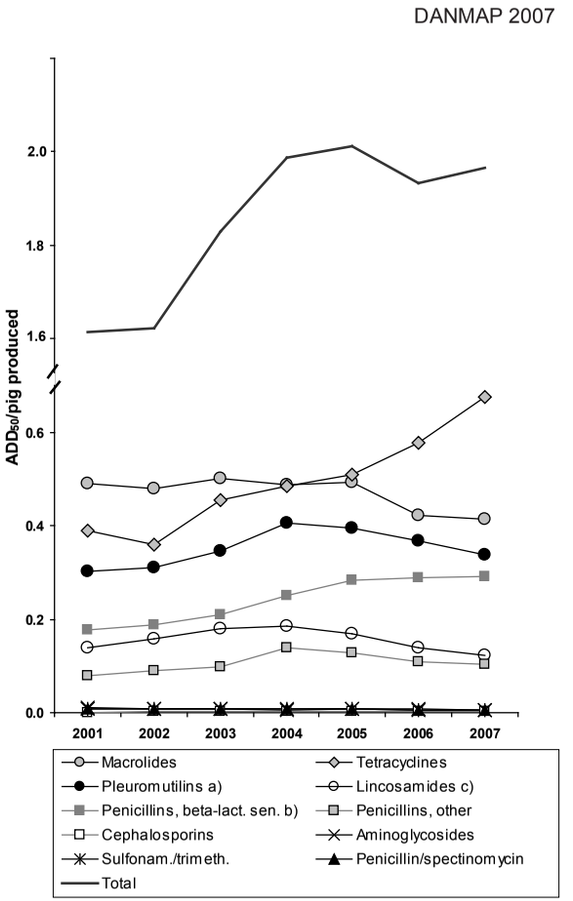


Figure 41. Trends in antimicrobial consumption in finishers, 2001-2007, Denmark
ADD_{50} are doses for treatment of 50 kg pigs which is an assumed average dose for treatment of finishers (30 to 100 kg)

Please see footnotes, Figure V10

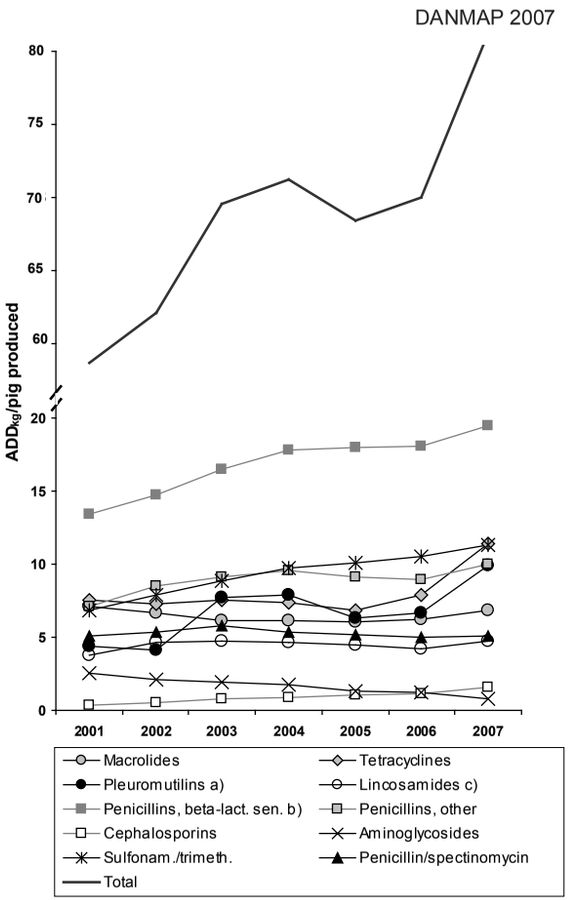


Figure 42. Trends in antimicrobial consumption in sows and piglets, 2001-2007, Denmark
ADD_{kg} are doses for treatment of one kg pig. The drugs prescribed for sows are used in either sows (bodyweigt >200 kg) or in piglets (below 2 kg to 7.5 kg)

Please see footnotes, Figure V10

Table 28. Distribution of MICs and occurrence of resistance in Salmonella *Typhimurium from poultry (n=10), cattle (n=13) and pigs (n=575), Denmark*

DANMAP 2007

Compound	Animal species	% Resistant	95% Confidence interval	Distribution (%) of MICs																
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	Poultry	20.0	[2.5-55.6]							80.0				10.0	10.0					
	Cattle	61.5	[31.6-86.1]							38.5				7.7	53.8					
	Pigs	46.6	[42.5-50.8]							51.7	1.7		0.7	5.7	40.2					
Chloramphenicol	Poultry	10.0	[0.3-44.5]								70.0	20.0				10.0				
	Cattle	15.4	[1.9-45.4]								61.5	23.1				15.4				
	Pigs	11.5	[9.0-14.4]							0.9	69.4	17.7	0.5	0.5	1.0	9.9				
Florfenicol	Poultry	10.0	[0.3-44.5]							50.0	40.0			10.0						
	Cattle	15.4	[1.9-45.4]							7.7	61.5	15.4			7.7	7.7				
	Pigs	7.1	[5.2-9.5]							1.9	80.3	9.6	1.0	5.0	0.7	1.4				
Ampicillin	Poultry	10.0	[0.3-44.5]						80.0	10.0					10.0					
	Cattle	61.5	[31.6-86.1]						38.5						61.5					
	Pigs	36.2	[32.2-40.3]						51.3	11.0	1.6				36.2					
Cephalothin	Poultry	0	[0-30.8]								100									
	Cattle	0	[0-24.7]								69.2	30.8								
	Pigs	1.2	[0.5-2.5]								77.6	16.9	4.3	1.0	0.2					
Ceftiofur	Poultry	0	[0-30.8]					100												
	Cattle	0	[0-24.7]					53.8	46.2											
	Pigs	0	[0-0.6]					55.1	42.1	2.8										
Cefpodoxime	Poultry	0	[0-30.8]			30.0	70.0													
	Cattle	0	[0-24.7]				76.9	23.1												
	Pigs	0	[0-0.6]			1.0	78.8	16.9	3.3											
Sulfonamide	Poultry	10.0	[0.3-44.5]												80.0	10.0				10.0
	Cattle	69.2	[38.6-90.9]												30.8					69.2
	Pigs	47.0	[42.8-51.1]												52.5	0.5				47.0
Apramycin	Poultry	0	[0-30.8]								100									
	Cattle	0	[0-24.7]								100									
	Pigs	1.2	[0.5-2.5]								96.9	1.7	0.2		1.2					
Gentamicin	Poultry	0	[0-30.8]						100											
	Cattle	0	[0-24.7]						100											
	Pigs	1.2	[0.5-2.5]						98.1	0.7		0.3	0.7	0.2						
Neomycin	Poultry	0	[0-30.8]							100										
	Cattle	0	[0-24.7]							100										
	Pigs	8.3	[6.2-10.9]							90.4	1.2	0.2		0.2	8.0					
Spectinomycin	Poultry	10.0	[0.3-44.5]											70.0	20.0			10.0		
	Cattle	38.5	[13.9-68.4]										7.7	53.8		7.7		30.8		
	Pigs	16.7	[13.7-20.0]										2.3	76.3	4.7	1.4	2.1	13.2		
Streptomycin	Poultry	10.0	[0.3-44.5]									40.0	50.0		10.0					
	Cattle	61.5	[31.6-86.1]								15.4	23.1		7.7	15.4	38.5				
	Pigs	44.3	[40.2-48.5]								8.5	41.6	5.6	1.2	5.4	37.7				
Ciprofloxacin	Poultry	0	[0-30.8]	100																
	Cattle	0	[0-24.7]	84.6	15.4															
	Pigs	1.0	[0.4-2.3]	92.9	6.1			0.9	0.2											
Nalidixic acid	Poultry	0	[0-30.8]								100									
	Cattle	0	[0-24.7]								84.6	15.4								
	Pigs	1.0	[0.4-2.3]								89.2	9.7				1.0				

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 29. Distribution of MICs and occurrence of resistance in Salmonella *Typhimurium from pork (Danish n=71; imported n=21), Denmark*

DANMAP 2007

Compound	Origin	% Resistant	95% Confidence interval	Distribution (%) of MICs																
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	Danish	38.0	[26.8-50.3]							62.0				4.2	33.8					
	Imported	52.4	[29.8-74.3]							47.6				19.0	33.3					
Chloramphenicol	Danish	5.6	[1.6-13.8]								71.8	22.5				5.6				
	Imported	23.8	[8.2-47.2]								57.1	19.0		4.8		19.0				
Florfenicol	Danish	4.2	[0.9-11.9]							4.2	83.1	7.0	1.4	4.2						
	Imported	14.3	[3.0-36.3]							9.5	66.7	9.5		9.5	4.8					
Ampicillin	Danish	35.2	[24.2-47.5]						45.1	19.7				1.4	33.8					
	Imported	47.6	[25.7-70.2]						33.3	19.0					47.6					
Cephalothin	Danish	0	[0-5.1]								77.5	19.7	2.8							
	Imported	0	[0-16.1]								76.2	14.3	9.5							
Ceftiofur	Danish	0	[0-5.1]					60.6	39.4											
	Imported	0	[0-16.1]					57.1	42.9											
Cefpodoxime	Danish	0	[0-5.1]			1.4	71.8	23.9	2.8											
	Imported	0	[0-16.1]				76.2	19.0	4.8											
Sulfonamide	Danish	39.4	[28.0-51.7]												60.6					39.4
	Imported	52.4	[29.8-74.3]												47.6					52.4
Apramycin	Danish	1.4	[0.04-7.6]								97.2		1.4		1.4					
	Imported	0	[0-16.1]								100									
Gentamicin	Danish	2.8	[0.3-9.8]						97.2					2.8						
	Imported	0	[0-16.1]						100											
Neomycin	Danish	9.9	[4.1-19.3]							85.9	4.2				9.9					
	Imported	0	[0-16.1]							100										
Spectinomycin	Danish	12.7	[6.0-22.7]										1.4	84.5	1.4	1.4	1.4	9.9		
	Imported	28.6	[11.3-52.2]											71.4			4.8	23.8		
Streptomycin	Danish	40.8	[29.3-53.2]								12.7	39.4	7.0		5.6	35.2				
	Imported	47.6	[25.7-70.2]								9.5	28.6	14.3		14.3	33.3				
Ciprofloxacin	Danish	0	[0-5.1]	94.4	5.6															
	Imported	0	[0-16.1]	95.2	4.8															
Nalidixic acid	Danish	0	[0-5.1]								88.7	11.3								
	Imported	0	[0-16.1]								90.5	9.5								

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 30. Distribution of MICs and occurrence of resistance among Salmonella *Typhimurium from human cases acquired domestically (n=90), reported as associated with travel abroad (n=44) or with an unknown origin (n=206), Denmark* DANMAP 2007

Compound	Origin a)	% Resistant	[95% Confidence interval]	Distribution (%) of MICs															
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	Domestically acquired	34.4	[24.7-45.2]							64.4	1.1			7.8	26.7					
	Travel abroad reported	56.8	[41.0-71.7]							43.2				18.2	38.6					
	Unknown origin	51.9	[44.9-58.9]							47.1	0.5	0.5	0.5	11.7	39.8					
Chloramphenicol	Domestically acquired	12.2	[6.3-20.8]							1.1	54.4	30.0	2.2		1.1	11.1				
	Travel abroad reported	27.3	[15.0-42.8]							2.3	36.4	31.8	2.3	6.8	6.8	13.6				
	Unknown origin	16.5	[11.7-22.3]							1.9	47.1	32.0	2.4	0.5	4.4	11.7				
Florfenicol	Domestically acquired	8.9	[3.9-16.8]							11.1	70.0	7.8	2.2	8.9						
	Travel abroad reported	20.5	[9.8-35.3]							4.6	63.6	4.6	6.8	18.2		2.3				
	Unknown origin	12.1	[8.0-17.4]							12.6	67.0	6.3	1.9	11.7		0.5				
Ampicillin	Domestically acquired	32.2	[22.75-42.9]						56.7	11.1					32.2					
	Travel abroad reported	54.6	[38.9-69.6]						36.4	9.1					54.6					
	Unknown origin	48.5	[41.5-55.6]						44.7	6.8			1.0		47.6					
Cephalothin	Domestically acquired	0	[0-4.0]								83.3	12.2	4.4							
	Travel abroad reported	0	[0-8.0]								77.3	18.2	4.6							
	Unknown origin	1.9	[0.5-4.9]								74.3	20.4	3.4	0.5	1.5					
Ceftiofur	Domestically acquired	0	[0-4.0]					77.8	18.9	3.3										
	Travel abroad reported	0	[0-8.0]					81.8	18.2											
	Unknown origin	1.0	[0.12-3.5]					76.7	19.9	2.4		0.5	0.5							
Cefpodoxime	Domestically acquired	2.2	[0.3-7.8]			1.1	85.6	8.9	2.2	1.1	1.1									
	Travel abroad reported	0	[0-8.0]			2.3	84.1	11.4	2.3											
	Unknown origin	1.0	[0.12-3.5]			2.4	85.4	9.7	1.5		0.5	0.5								
Sulfonamide	Domestically acquired	46.7	[36.1-57.5]												52.2	1.1				46.7
	Travel abroad reported	56.8	[41.0-71.7]												43.2					56.8
	Unknown origin	54.4	[47.3-61.3]												45.6					54.4
Apramycin	Domestically acquired	1.1	[0.03-6.0]								97.8	1.1			1.1					
	Travel abroad reported	2.3	[0.06-12.0]								97.7				2.3					
	Unknown origin	1.0	[0.12-3.5]								97.1	1.5	0.5		1.0					
Gentamicin	Domestically acquired	3.3	[0.7-9.4]						96.7			2.2	1.1							
	Travel abroad reported	2.3	[0.06-12.0]						97.7			2.3								
	Unknown origin	2.4	[0.8-5.6]						97.6		0.5	0.5	0.97	0.5						
Neomycin	Domestically acquired	1.1	[0.03-6.0]							97.8	1.1				1.1					
	Travel abroad reported	2.3	[0.06-12.0]							97.7					2.3					
	Unknown origin	1.9	[0.5-4.9]							97.1	1.0			0.5	1.5					
Spectinomycin	Domestically acquired	20.0	[12.3-29.8]										2.2	75.6	2.2			20.0		
	Travel abroad reported	29.6	[16.8-45.2]										2.3	61.4	6.8	2.3	2.3	25.0		
	Unknown origin	18.9	[13.8-25.0]										1.9	76.7	2.4	0.5		18.5		
Streptomycin	Domestically acquired	44.4	[34.0-55.3]								11.1	38.9	5.6	2.2	14.4	27.8				
	Travel abroad reported	52.3	[36.7-67.5]								6.8	38.6	2.3	11.4	11.4	29.6				
	Unknown origin	49.5	[42.5-56.6]								7.8	37.4	5.3	1.5	14.1	34.0				
Ciprofloxacin	Domestically acquired	2.2	[0.3-7.8]	92.2	5.6			1.1	1.1											
	Travel abroad reported	18.2	[8.2-32.7]	79.6	2.3			6.8	9.1	2.3										
	Unknown origin	3.4	[1.4-6.9]	91.8	4.9	1.0		1.9	0.5											
Nalidixic acid	Domestically acquired	2.2	[0.3-7.8]								88.9	8.9				2.2				
	Travel abroad reported	6.8	[1.4-18.7]								77.3	9.1	6.8			6.8				
	Unknown origin	1.9	[0.5-4.9]								91.3	6.3	0.5			1.9				

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

a) The isolate was categorized as 'domestically acquired' if the patient did not travel one week prior to the infection, and it was characterized as 'travel abroad reported' if the patient travelled one week prior to the infection. Isolates from patients which had not reported travel to the GP or was not interviewed by phone was characterized as 'unknown origin'

Table 31. Distribution of MICs and occurrence of resistance among Salmonella *Enteritidis from human cases acquired domestically (n= 67), reported as associated with travel abroad (n=88) or with an unknown origin (n=183), Denmark*

DANMAP 2007

Compound	Origin a)	% Resistant	[95% Confidence interval]	Distribution (%) of MICs															
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	Domestically acquired	0	[0-5.4]							100										
	Travel abroad reported	6.8	[2.5-14.3]							93.2					6.8					
	Unknown origin	1.6	[0.3-4.7]							96.2	2.2				1.6					
Chloramphenicol	Domestically acquired	0	[0-5.4]							1.5	80.6	17.9								
	Travel abroad reported	1.1	[0.03-6.17]								72.7	26.1			1.1					
	Unknown origin	0.6	[0.01-3.01]								73.2	25.1	1.1		0.6					
Florfenicol	Domestically acquired	0	[0-5.4]							1.5	98.5									
	Travel abroad reported	0	[0-4.1]								97.7	1.1	1.1							
	Unknown origin	0	[0-2.0]							1.1	94.5	4.4								
Ampicillin	Domestically acquired	0	[0-5.4]						73.1	26.9										
	Travel abroad reported	14.8	[8.1-24.0]						54.6	30.7		1.1			13.6					
	Unknown origin	4.4	[1.9-8.4]						61.2	33.3	1.1			0.6	3.8					
Cephalothin	Domestically acquired	0	[0-5.4]								100									
	Travel abroad reported	0	[0-4.1]								88.6	11.4								
	Unknown origin	1.1	[0.1-3.9]								93.4	5.5		0.6	0.6					
Ceftiofur	Domestically acquired	0	[0-5.4]					79.1	20.9											
	Travel abroad reported	0	[0-4.1]					69.3	30.7											
	Unknown origin	0	[0-2.0]					70.5	28.4	1.1										
Cefpodoxime	Domestically acquired	0	[0-5.4]			1.5	95.5	3.0												
	Travel abroad reported	0	[0-4.1]			2.3	92.1	5.7												
	Unknown origin	0	[0-2.0]			0.6	91.8	6.6	1.1											
Sulfonamide	Domestically acquired	0	[0-5.4]												100					
	Travel abroad reported	3.4	[0.7-9.6]												96.6					3.4
	Unknown origin	1.1	[0.1-3.9]												98.9					1.1
Apramycin	Domestically acquired	0	[0-5.4]								100									
	Travel abroad reported	0	[0-4.1]								98.9	1.1								
	Unknown origin	0	[0-2.0]								98.9	1.1								
Gentamicin	Domestically acquired	0	[0-5.4]						100											
	Travel abroad reported	0	[0-4.1]						98.9	1.1										
	Unknown origin	0	[0-2.0]						98.9	1.1										
Neomycin	Domestically acquired	0	[0-5.4]							100										
	Travel abroad reported	0	[0-4.1]							98.9	1.1									
	Unknown origin	0	[0-2.0]							100										
Spectinomycin	Domestically acquired	0	[0-5.4]										73.1	26.9						
	Travel abroad reported	1.1	[0.03-6.2]										78.4	20.5				1.1		
	Unknown origin	1.1	[0.1-3.9]										76.0	21.9	1.1	0.6	0.6			
Streptomycin	Domestically acquired	0	[0-5.4]								98.5	1.5								
	Travel abroad reported	2.3	[0.3-8.0]								94.3	2.3	1.1			2.3				
	Unknown origin	0.6	[0.01-3.01]								93.4	5.5	0.6			0.6				
Ciprofloxacin	Domestically acquired	9.0	[6.3-24.0]	91.0			9.0													
	Travel abroad reported	30.7	[21.3-41.4]	67.1	2.3	5.7	19.3	5.7												
	Unknown origin	12.0	[7.7-17.6]	85.8	2.2	1.6	9.3	1.1												
Nalidixic acid	Domestically acquired	9.0	[6.3-24.0]								91.0					9.0				
	Travel abroad reported	30.7	[21.3-41.4]								67.1	2.3				30.7				
	Unknown origin	12.0	[7.7-17.6]								85.3	2.7			0.6	11.5				

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

a) The isolate was categorized as 'domestically acquired' if the patient did not travel one week prior to the infection, and it was characterized as 'travel abroad reported' if the patient travelled one week prior to the infection. Isolates from patients which had not reported travel to the GP or was not interviewed by phone was characterized as 'unknown origin'

Table 32. Distribution of MICs and occurrence of resistance in Campylobacter jejuni *from broilers (n=94) and cattle (n=84), Denmark*

DANMAP 2007

Compound	Animal species	% Resistant	95% Confidence interval	Distribution (%) of MICs												
				0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Tetracycline	Broilers	9.6	[4.5-17.4]			55.3	30.9	4.3					9.6		
	Cattle	1.2	[0.03-6.5]			88.1	8.3	1.2	1.2				1.2		
Chloramphenicol	Broilers	0	[0-3.8]						16.0	79.8	3.2	1.1			
	Cattle	0	[0-4.3]						94.0	4.8		1.2			
Erythromycin	Broilers	1.1	[0.03-5.8]				3.2	22.3	59.6	13.8	1.1				
	Cattle	1.2	[0.03-6.5]				54.8	29.8	14.3					1.2	
Gentamicin	Broilers	0	[0-3.8]		10.6	62.8	26.6								
	Cattle	0	[0-4.3]		22.6	57.1	15.5	4.8							
Streptomycin	Broilers	2.1	[0.3-7.5]						97.9				2.1		
	Cattle	3.6	[0.7-10.1]						96.4	1.2		1.2	1.2		
Ciprofloxacin	Broilers	8.5	[3.7-16.1]	11.7	55.3	22.3	2.1				8.5				
	Cattle	16.7	[9.4-26.4]	35.7	44.0	3.6					16.7				
Nalidixic acid	Broilers	8.5	[3.7-16.1]						13.8	68.1	8.5	1.1	1.1	1.1	6.4
	Cattle	16.7	[9.4-26.4]						26.2	48.8	7.1	1.2		2.4	14.3

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 33. Distribution of MICs and occurrence of resistance in Campylobacter jejuni *from broiler meat (Danish n=114; imported n=137) and turkey meat (imported n=42), Denmark*

DANMAP 2007

Compound	Food type	Origin	% Resistant	95% Confidence interval	Distribution (%) of MICs											
					0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Tetracycline	Broiler meat	Danish	9.6	[4.9-16.6]			88.6	0.9		0.9				9.6		
		Imported	39.4	[31.2-48.1]			54.0	2.2	2.2	2.2		3.6	3.6	32.1		
	Turkey meat	Imported	66.7	[50.5-80.4]			31.0		2.4				2.4	64.3		
Erythromycin	Broiler meat	Danish	1.8	[0.2-6.2]				93.0	4.4	0.9				0.9	0.9	
		Imported	1.5	[0.2-5.3]				85.8	12.7						1.5	
	Turkey meat	Imported	7.3	[1.5-19.9]				82.9	7.3	2.4					7.3	
Gentamicin	Broiler meat	Danish	0	[0-3.2]		8.8	48.7	40.7	1.8							
		Imported	0	[0-2.7]		7.3	54.7	36.5	1.5							
	Turkey meat	Imported	0	[0-8.6]		4.9	53.7	39.0	2.4							
Streptomycin	Broiler meat	Danish	3.5	[1-8.7]						96.5				3.5		
		Imported	5.1	[2.1-10.2]						94.9	0.7		0.7	3.6		
	Turkey meat	Imported	14.3	[5.4-28.5]						85.7		2.4	2.4	9.5		
Ciprofloxacin	Broiler meat	Danish	11.4	[6.2-18.7]	78.9	7.0	2.6			0.9	2.6	7.9				
		Imported	41.6	[33.3-50.3]	43.1	10.2	3.6	1.5			10.2	31.4				
	Turkey meat	Imported	59.5	[43.3-74.4]	26.2	9.5	4.8				19.0	40.5				
Nalidixic acid	Broiler meat	Danish	11.4	[6.2-18.7]						14.0	71.1	3.5		0.9	3.5	7.0
		Imported	41.6	[33.3-50.3]						15.3	35.0	5.8	2.2	1.5	9.5	30.7
	Turkey meat	Imported	57.1	[41-72.3]						11.9	26.2	2.4	2.4	7.1	19.0	31.0

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 34. Distribution of MICs and occurrence of resistance among Campylobacter jejuni *from human cases categorized as acquired domestically (n=70) or reported as associated with travel abroad (n=61), Denmark*

DANMAP 2007

Compound	Origin	% Resistant [95% Confidence interval]		Distribution (%) of MICs												
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Tetracycline	Domestically acquired	14.3	[7.1-24.7]				62.9	11.4	5.7	5.7				14.3		
	Travel abroad reported	36.1	[24.2-49.4]				49.2	11.5	3.3					36.1		
Chloramphenicol	Domestically acquired	1.4	[0.04-7.7]							65.7	24.3	5.7	2.9		1.4	
	Travel abroad reported	0	[0-5.9]							63.9	29.5	4.9	1.6			
Erythromycin	Domestically acquired	0	[0-5.1]					50.0	34.3	15.7						
	Travel abroad reported	4.9	[1.0-13.7]					50.8	37.7	4.9	1.6	1.6			3.3	
Gentamicin	Domestically acquired	0	[0-5.1]			28.6	41.4	30.0								
	Travel abroad reported	3.2	[0.4-11.3]			23.0	47.5	24.6	1.6		1.6		1.6			
Streptomycin	Domestically acquired	4.3	[0.9-12.0]							95.7		1.4		2.9		
	Travel abroad reported	9.9	[3.7-20.2]							90.2			3.3	6.6		
Ciprofloxacin	Domestically acquired	38.6	[27.2-51.0]	1.4	32.9	24.3	2.9				7.1	31.4				
	Travel abroad reported	70.5	[57.4-81.5]	1.6	18.1	8.2			1.6	1.6	11.5	57.3				
Nalidixic acid	Domestically acquired	38.8	[27.2-51.0]							24.3	32.9	4.3			4.3	34.3
	Travel abroad reported	70.5	[57.4-81.5]							11.5	18.0				4.9	65.6

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 35. Distribution of MICs and occurrence of resistance in Campylobacter coli *from pigs (n=104), Denmark*

DANMAP 2007

Compound	% Resistant	95% Confidence interval	Distribution (%) of MICs											
			0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	>64
Tetracycline	4.8	[1.6-10.9]			51.0	30.8	12.5	1.0			1.0	3.8		
Chloramphenicol	0	[0-3.5]						26.9	52.9	16.3	3.8			
Erythromycin	10.6	[5.4-18.1]				25.0	23.1	31.7	8.7	1.0			10.6	
Gentamicin	0	[0-3.5]		2.9	26.0	68.3	2.9							
Streptomycin	55.8	[45.7-65.5]						44.2		1.9	4.8	49.0		
Ciprofloxacin	9.6	[4.7-17.0]	32.7	33.7	22.1	1.9			4.8	4.8				
Nalidixic acid	9.6	[4.7-17.0]						2.9	27.9	42.3	15.4	1.9	2.9	6.7

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

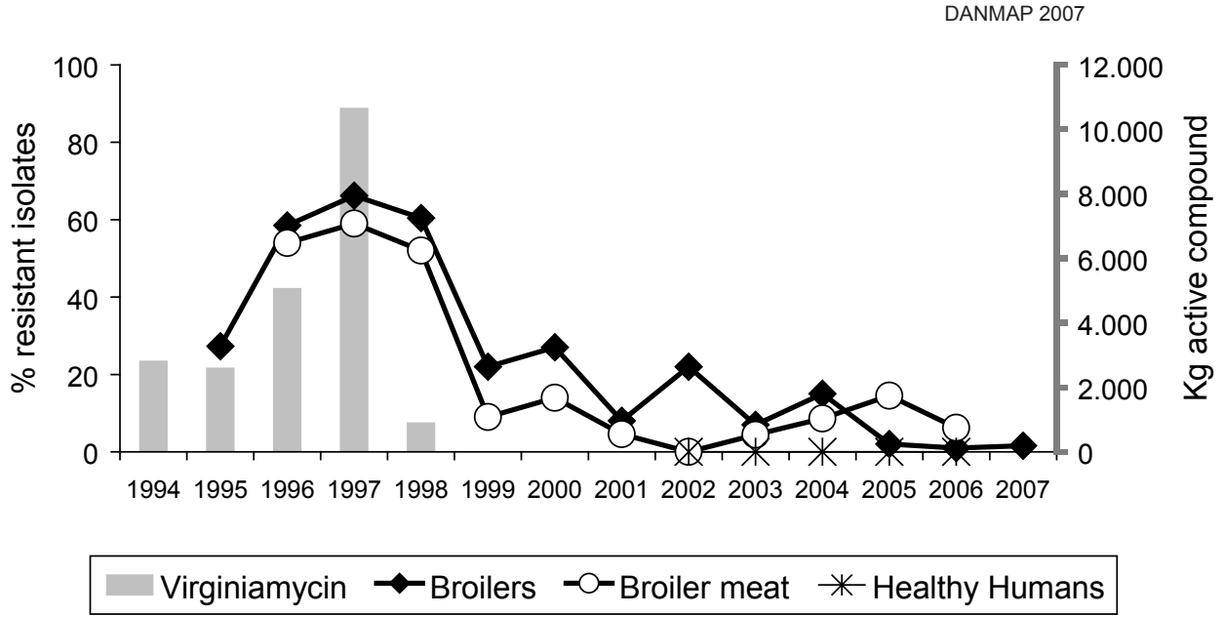


Figure 43. Trends in streptogramin resistance among Enterococcus faecium *from broilers, broiler meat and healthy humans in the community and the consumption of the growth promoter virginiamycin in animals, Denmark*

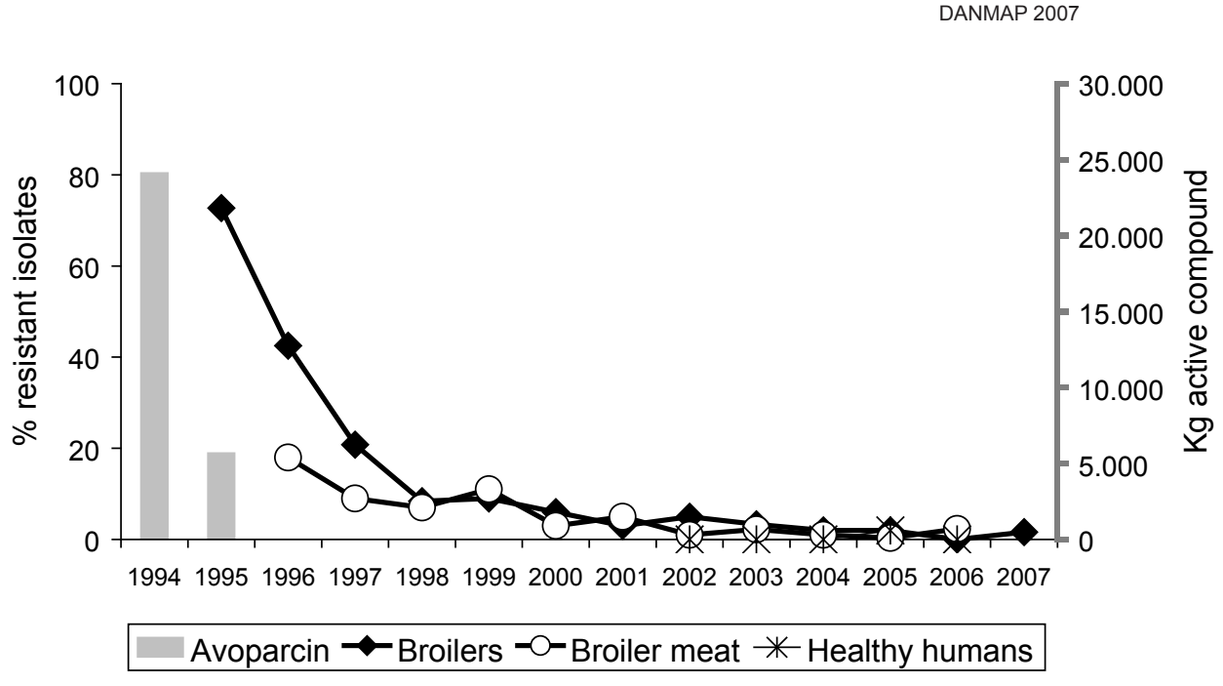


Figure 44. Trends in glycopeptide resistance among Enterococcus faecium *from broilers, broiler meat and healthy humans in the community and consumption of the growth promoter avoparcin in animals, Denmark*

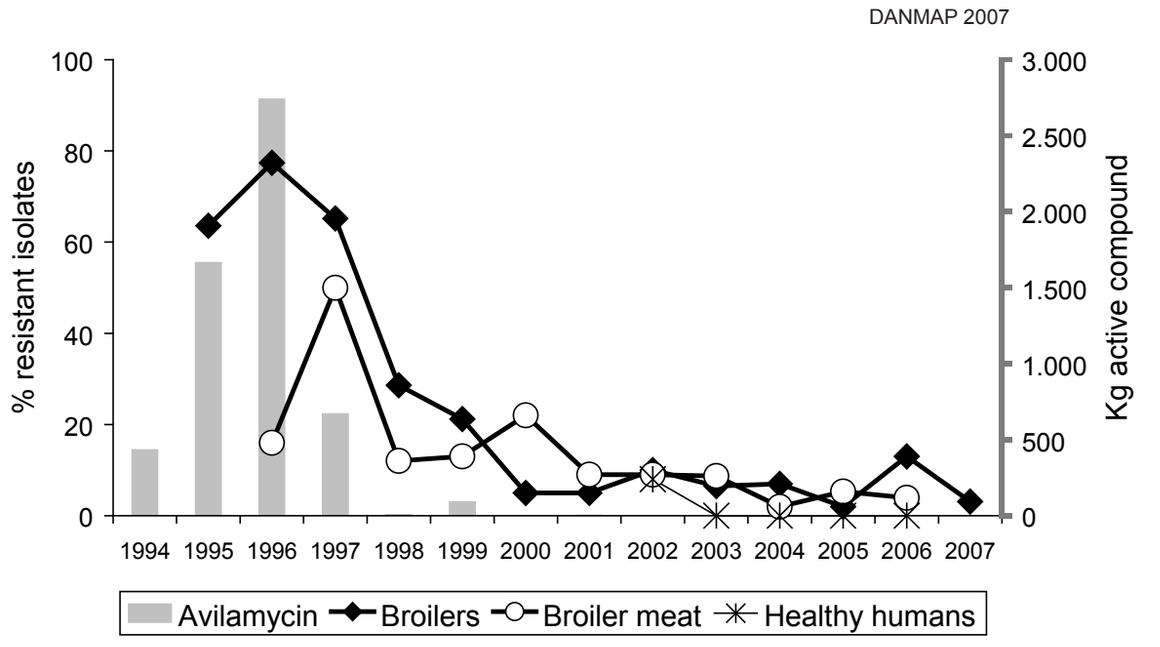


Figure 45. Trends in avilamycin resistance among Enterococcus faecium *from broilers, broiler meat and healthy humans in the community and consumption of the growth promoter avilamycin in animals, Denmark*

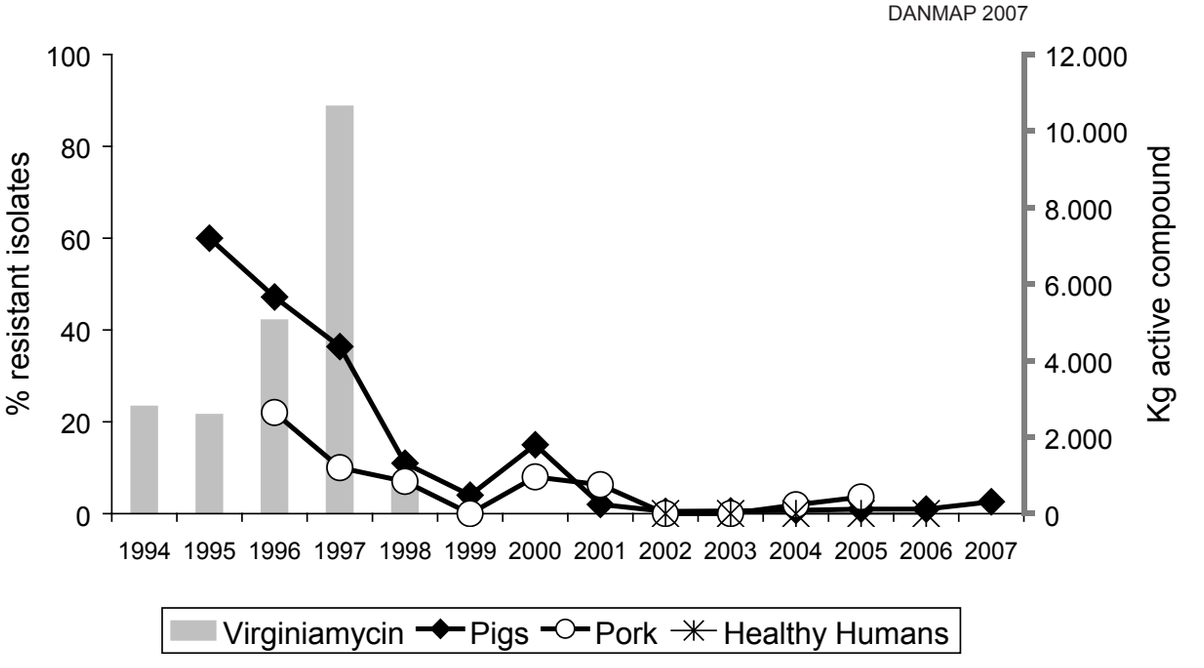


Figure 46. Trends in streptogramin resistance among Enterococcus faecium *from pigs, pork and healthy humans in the community and the consumption of the growth promoter virginiamycin in animals, Denmark*

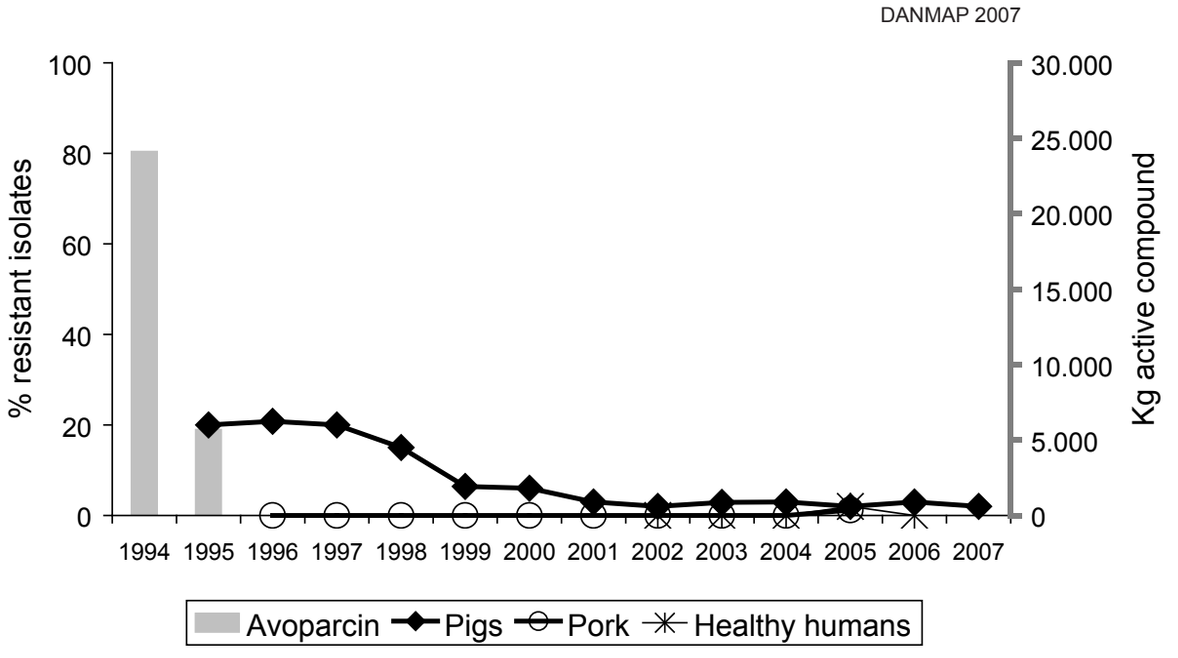


Figure 47. Trends in glycopeptide resistance among Enterococcus faecium *from pigs, pork and healthy humans in the community and consumption of the growth promoter avoparcin in animals, Denmark*

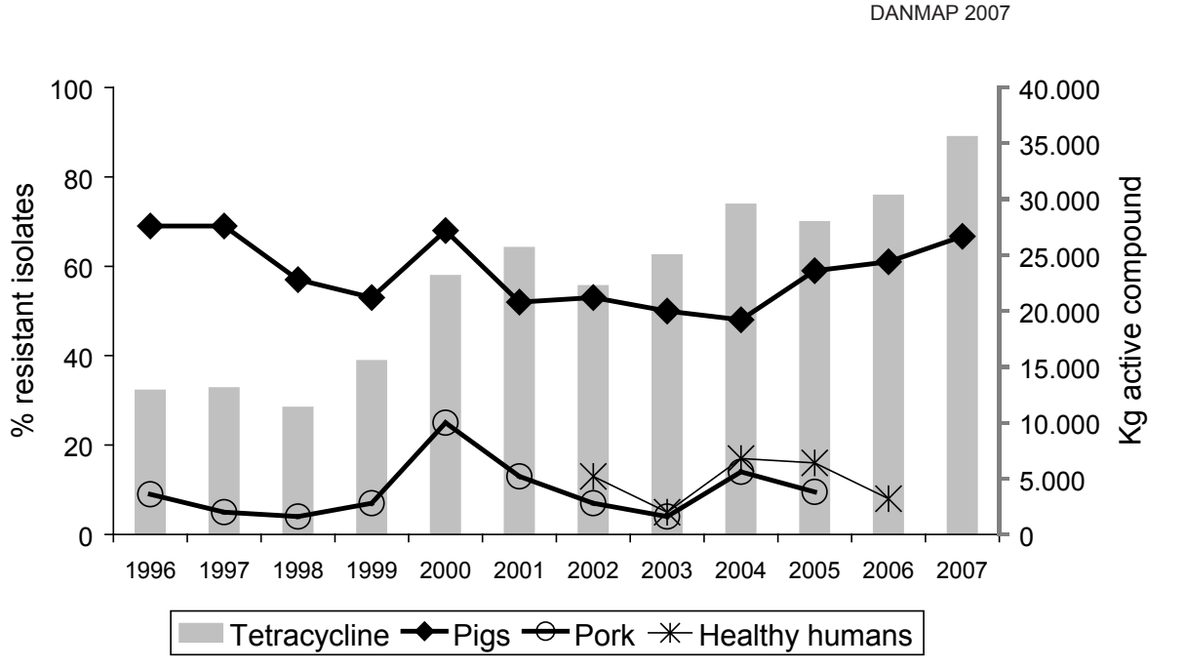


Figure 48. Trends in tetracycline resistance among Enterococcus faecium *from pigs, pork and healthy humans and the consumption of tetracycline in pig production, Denmark*

Table 36. Distribution of MICs and occurrence of resistance in Enterococcus faecalis *from broilers (n=57) and pigs (n=148), Denmark*

DANMAP 2007

Compound	Animal species	% Resistant	95% Confidence interval	Distribution (%) of MICs																		
				0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048
Tetracycline	Broilers	40.4	[27.6-54.2]							59.6			1.8	7.0	10.5	21.1						
	Pigs	89.2	[83.0-93.7]							10.1	0.7			2.0	12.8	74.3						
Tigecycline	Broilers	0	[0-6.3]	5.3	12.3	45.6	35.1	1.8														
	Pigs	0	[0-2.5]		2.7	14.9	66.2	16.2														
Chloramphenicol	Broilers	0	[0-6.3]								1.8	17.5	78.9	1.8								
	Pigs	10.8	[6.3-17.0]								1.4	40.5	47.3			6.1	4.7					
Florfenicol	Broilers	0	[0-6.3]									100										
	Pigs	0	[0-2.5]									99.3	0.7									
Ampicillin	Broilers	0	[0-6.3]								100											
	Pigs	0	[0-2.5]								100											
Erythromycin	Broilers	22.8	[12.7-35.8]						22.8	19.3	19.3	15.8	1.8		5.3	15.8						
	Pigs	40.5	[32.6-48.9]						14.9	39.9	4.7		0.7			39.9						
Gentamicin	Broilers	0	[0-6.3]														100					
	Pigs	8.8	[4.8-14.6]														89.2	0.7	1.4	6.8	0.7	1.4
Kanamycin	Broilers	0	[0-6.3]														96.5	1.8		1.8		
	Pigs	22.3	[15.9-29.9]														77.0	0.7			0.7	21.6
Streptomycin	Broilers	3.5	[0.4-12.1]														91.2	5.3				3.5
	Pigs	30.4	[23.1-38.5]														66.9	2.0	0.7	0.7	2.7	27.0
Vancomycin	Broilers	0	[0-6.3]								98.2	1.8										
	Pigs	0	[0-2.5]								98.6	1.4										
Avilamycin	Broilers	0	[0-6.3]								96.5	3.5										
	Pigs	0	[0-2.5]								100											
Flavomycin	Broilers	1.8	[0.04-9.4]									98.2				1.8						
	Pigs	0.7	[0.02-3.7]									99.3			0.7							
Salinomycin	Broilers	3.5	[0.4-12.1]								70.2	26.3	3.5									
	Pigs	0	[0-2.5]								100											
Linezolid	Broilers	0	[0-6.3]							26.3	73.7											
	Pigs	0	[0-2.5]							29.7	70.3											
Daptomycin	Broilers	0	[0-6.3]				12.3	1.8		61.4	21.1	3.5										
	Pigs	0	[0-2.5]				1.4	2.0	8.8	70.3	12.2	5.4										

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 37. Distribution of MICs and occurrence of resistance in Enterococcus faecium *from broilers (n=64) and pigs (n=153), Denmark*

DANMAP 2007

Compound	Animal species	% Resistant	95% Confidence interval	Distribution (%) of MICs																		
				0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	2048	>2048
Tetracycline	Broilers	10.9	[4.5-21.2]							89.1				1.6	1.6	7.8						
	Pigs	66.7	[58.6-74.1]							32.7	0.7			0.7	5.9	60.1						
Tigecycline	Broilers	0	[0-5.6]		50.0	35.9	14.1															
	Pigs	0	[0-2.4]	0.7	5.9	55.6	32.0	5.9														
Chloramphenicol	Broilers	0	[0-5.6]								10.9	51.6	35.9		1.6							
	Pigs	0	[0-2.4]								7.8	65.4	25.5	1.3								
Florfenicol	Broilers	0	[0-5.6]									100										
	Pigs	0	[0-2.4]									100										
Ampicillin	Broilers	6.2	[1.7-15.2]								78.1	15.6	6.3									
	Pigs	0.7	[0.02-3.6]								54.2	45.1	0.7									
Erythromycin	Broilers	29.7	[18.9-42.4]						32.8	4.7	23.4	9.4	6.3	6.3	4.7	12.5						
	Pigs	47.1	[38.9-55.3]						8.5	2.0	7.8	34.6	11.8	0.7		34.6						
Gentamicin	Broilers	0	[0-5.6]														100					
	Pigs	0	[0-2.4]														100					
Kanamycin	Broilers	3.1	[0.4-10.8]														21.9	57.8	17.2		1.6	1.6
	Pigs	30.7	[23.5-38.7]														19.6	40.5	7.2	2.0	0.7	30.1
Streptomycin	Broilers	12.5	[5.6-23.2]														87.5					12.5
	Pigs	41.2	[33.3-49.4]														58.8	0.7	1.3	2.6	13.1	23.5
Vancomycin	Broilers	1.6	[0.04-8.4]								98.4					1.6						
	Pigs	2.0	[0.4-5.6]								96.1	2.0	2.0									
Quinupristin/dalfopristin	Broilers	1.6	[0.04-8.4]						28.1	21.9	37.5	10.9	1.6									
	Pigs	2.6	[0.7-6.6]						8.5	4.6	64.1	20.3	2.0	0.7								
Avilamycin	Broilers	3.1	[0.4-10.8]								53.1	37.5	3.1	3.1	3.1							
	Pigs	0	[0-2.4]								90.8	9.2										
Salinomycin	Broilers	75.0	[62.6-85.0]								1.6	23.4	75.0									
	Pigs	0	[0-2.4]								99.3	0.7										
Linezolid	Broilers	0	[0-5.6]							20.3	76.6	3.1										
	Pigs	0	[0-2.4]							19.6	80.4											
Daptomycin	Broilers	0	[0-5.6]							15.6	45.3	39.1										
	Pigs	0	[0-2.4]					5.9	9.2	27.5	41.8	15.7										

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

Table 38. Distribution of MICs and occurrence of resistance in Escherichia coli *from broilers (n=114), cattle (n=98) and pigs (n=150), Denmark*

DANMAP 2007

Compound	Animal species	% Resistant	95% Confidence interval	Distribution (%) of MICs																
				0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	Broilers	7.9	[3.7-14.5]							92.1					7.9					
	Cattle	7.1	[2.9-14.2]							91.8	1.0		1.0		6.1					
	Pigs	28.0	[21.0-35.9]							71.3	0.7			2.0	26.0					
Chloramphenicol	Broilers	0	[0-3.2]							11.4	56.1	32.5								
	Cattle	0	[0-3.7]							3.1	44.9	52.0								
	Pigs	4.0	[1.5-8.5]							3.3	58.0	34.0	0.7	2.7		1.3				
Florfenicol	Broilers	0	[0-3.2]							13.2	65.8	21.1								
	Cattle	0	[0-3.7]							1.0	40.8	57.1	1.0							
	Pigs	0	[0-2.4]							2.7	56.7	38.0	2.7							
Ampicillin	Broilers	10.5	[5.6-17.7]						21.1	50.9	17.5				10.5					
	Cattle	4.1	[1.1-10.1]						2.0	45.9	45.9	2.0			4.1					
	Pigs	19.3	[13.3-26.6]						4.7	39.3	35.3	1.3			19.3					
Cephalothin	Broilers	3.5	[1.0-8.7]								33.3	38.6	21.9	2.6	3.5					
	Cattle	0	[0-4.6]								11.5	67.9	19.2	1.3						
	Pigs	0.7	[0.02-3.7]								30.9	53.0	13.4	2.0	0.7					
Ceftiofur	Broilers	1.8	[0.2-6.2]					96.5	1.8	1.8										
	Cattle	0	[0-3.7]					100												
	Pigs	0.7	[0.02-3.7]					98.7	0.7	0.7										
Cefpodoxime	Broilers	0.9	[0.02-4.8]			16.7	55.3	24.6	2.6	0.9										
	Cattle	0	[0-4.6]			2.6	47.4	46.2	3.8											
	Pigs	1.3	[0.2-4.8]			5.4	55.7	32.9	4.7	0.7		0.7								
Sulfonamide	Broilers	17.5	[11.1-25.8]												81.6		0.9	0.9		16.7
	Cattle	6.1	[2.3-12.9]												93.9					6.1
	Pigs	24.0	[17.4-31.6]												76.0					24.0
Apramycin	Broilers	0	[0-3.2]								81.6	18.4								
	Cattle	0	[0-3.7]								94.9	5.1								
	Pigs	0	[0-2.4]								95.3	4.7								
Gentamicin	Broilers	0	[0-3.2]						98.2	1.8										
	Cattle	0	[0-3.7]						98.0	2.0										
	Pigs	0	[0-2.4]						98.7	1.3										
Neomycin	Broilers	0	[0-3.2]							98.2	1.8									
	Cattle	1.0	[0.03-5.6]							95.9	1.0	2.0			1.0					
	Pigs	2.0	[0.4-5.7]							97.3	0.7			0.7	1.3					
Spectinomycin	Broilers	2.6	[0.5-7.5]										32.5	59.6	5.3	0.9	0.9	0.9		
	Cattle	0	[0-3.7]										96.9	2.0	1.0					
	Pigs	20.0	[13.9-27.3]										68.0	8.0	4.0	10.0	8.0	2.0		
Streptomycin	Broilers	7.0	[3.1-13.4]									81.6	11.4	0.9	3.5	2.6				
	Cattle	3.1	[0.6-8.7]									94.9	2.0		1.0	2.0				
	Pigs	34.0	[26.5-42.2]									61.3	4.7	12.0	11.3	10.7				
Ciprofloxacin	Broilers	14.0	[8.2-21.8]	86.0	0.9	6.1	5.3	0.9	0.9											
	Cattle	0	[0-3.7]	100																
	Pigs	0	[0-2.4]	100																
Nalidixic acid	Broilers	10.5	[5.6-17.7]								88.6		0.9	0.9	2.6	7.0				
	Cattle	0	[0-3.7]								100									
	Pigs	0	[0-2.4]								99.3	0.7								

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

DANMAP 2007

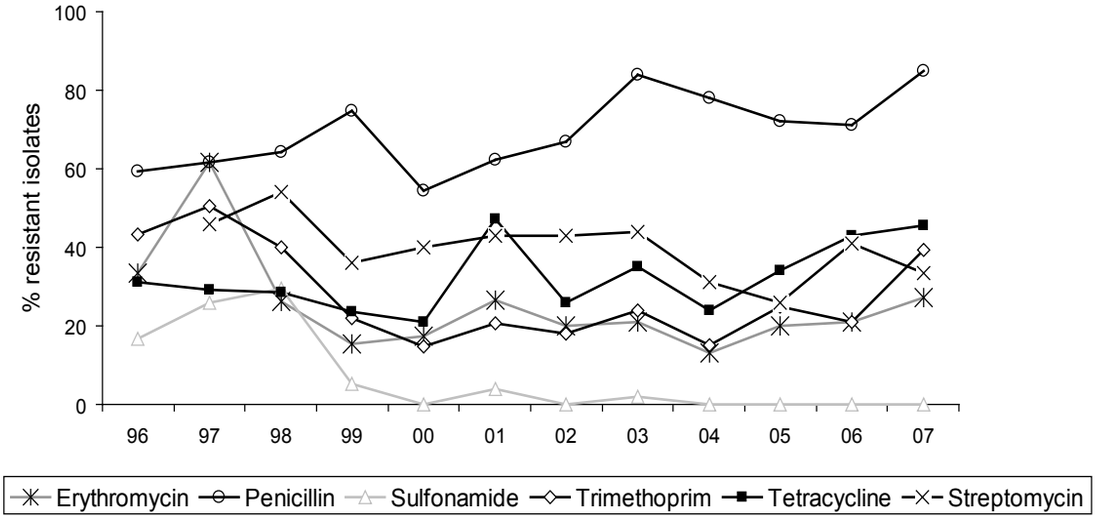


Figure 49. Trends in resistance to some selected antimicrobials among Staphylococcus hyicus *from diagnostic submissions from pigs, Denmark*

Table 39. Distribution of MICs and occurrence of resistance among Staphylococcus hyicus *from pigs (n=33), Denmark*

DANMAP 2007

Compound	% Resistant	95% Confidence interval	Distribution (%) of MICs														
			0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	>512
Tetracycline	45.5	[28.1-63.7]				54.5					3.0	21.2	21.2				
Chlorampenicol	0	[0-10.6]						3.0	78.8	18.2							
Florfenicol	0	[0-10.6]						87.9	12.1								
Penicillin	84.8	[68.1-94.9]	15.2		3.0	6.1	3.0	3.0	12.1	21.2	18.2	18.2					
Ceftiofur	0	[0-10.6]				78.8	21.2										
Sulfonamide	0	[0-10.6]								33.3	36.4	27.3	3.0				
Trimethoprim	39.4	[22.9-57.9]					18.2	36.4	6.1				39.4				
Erythromycin	27.3	[13.3-45.5]			57.6	15.2						27.3					
Spectinomycin	24.2	[11.1-42.3]										33.3	42.4			24.2	
Streptomycin	33.3	[18.0-51.8]						27.3	36.4		3.0	9.1		3.0	21.2		
Ciprofloxacin	0	[0-10.6]		75.8	24.2												
Tiamulin	51.5	[33.5-69.2]			3.0	27.3	18.2				6.1	6.1	39.4				

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

DANMAP 2007

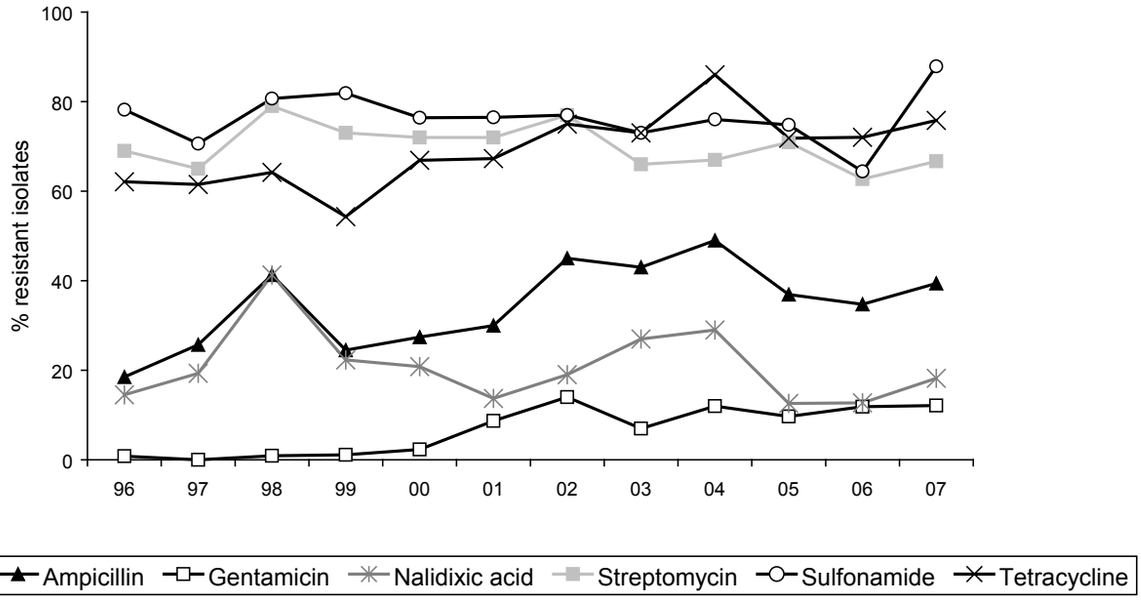


Figure 50. Trends in resistance to selected antimicrobials among Escherichia coli *O149 from diagnostic submissions from pigs, Denmark*

Table 40. Distribution of MICs and occurrence of resistance in Escherichia coli O149 *from diagnostic submissions from pigs (n=33), Denmark*

DANMAP 2007

Compound	% Resistant	95% Confidence interval	Distribution (%) of MICs																
			0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Tetracycline	75.8	[57.7-88.9]							24.2				3.0	72.7					
Chloramphenicol	24.2	[11.1-42.3]							3.0	69.7	3.0		6.1	3.0	15.2				
Florfenicol	0	[0-10.6]							6.1	84.8	3.0	6.1							
Ampicillin	39.4	[22.9-57.9]						15.2	42.4	3.0				39.4					
Cephalothin	0	[0-10.6]								36.4	54.5	9.1							
Ceftiofur	0	[0-10.6]					100												
Cefpodoxime	0	[0-10.6]				84.8	15.2												
Sulfonamide	87.9	[71.8-96.6]												12.1				3.0	84.8
Apramycin	12.1	[3.4-28.2]								87.9				12.1					
Gentamicin	12.1	[3.4-28.2]						87.9		6.1	3.0	3.0							
Neomycin	33.3	[18-51.8]							57.6	6.1	3.0		18.2	15.2					
Spectinomycin	63.6	[45.1-79.6]										27.3	6.1	3.0	21.2	12.1	30.3		
Streptomycin	66.7	[48.2-82]									27.3	6.1	15.2	18.2	33.3				
Ciprofloxacin	21.2	[9-38.9]	78.8	3.0	3.0	15.2													
Nalidixic acid	18.2	[7-35.5]								81.8					18.2				

Vertical dotted lines indicate breakpoints for resistance and vertical solid lines indicate EUCAST cut-off values. When only a solid line is shown, breakpoint and cut-off values are identical

The white fields denote range of dilutions tested for each antimicrobial. Values above the range denote MIC values greater than the highest concentration in the range. MICs equal to or lower than the lowest concentration tested are given as the lowest concentration

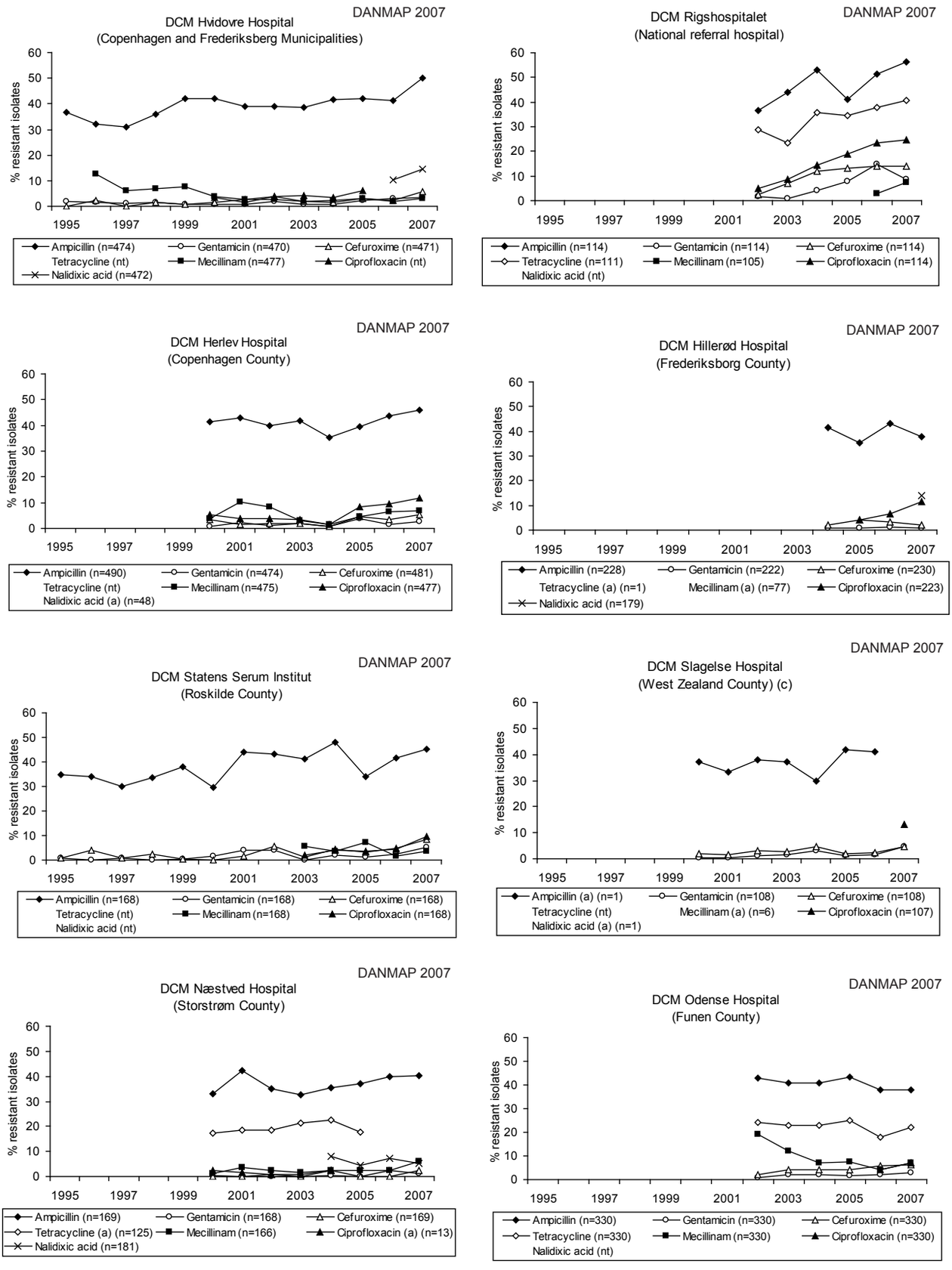
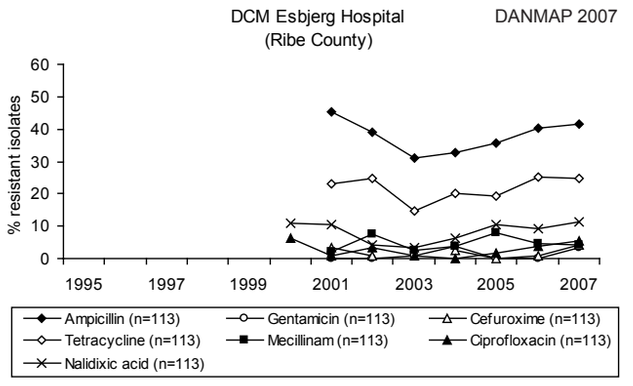
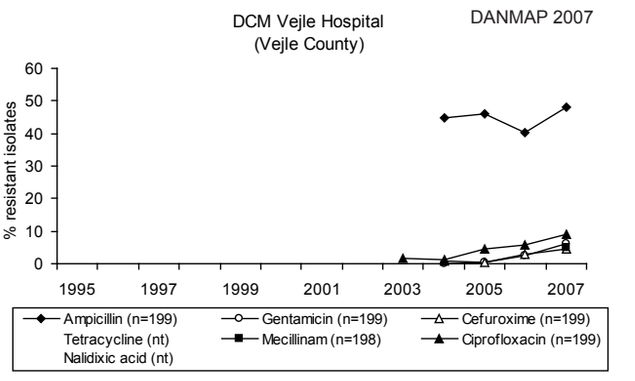
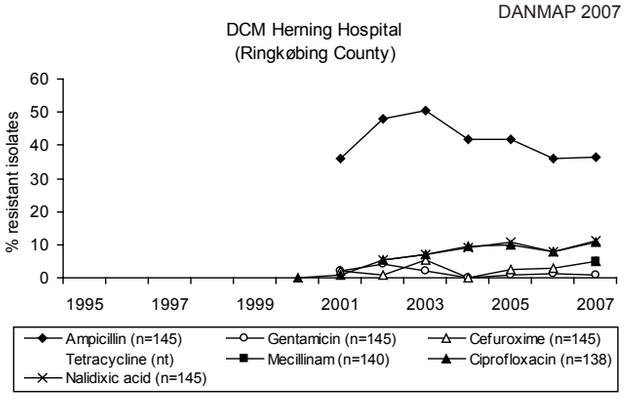


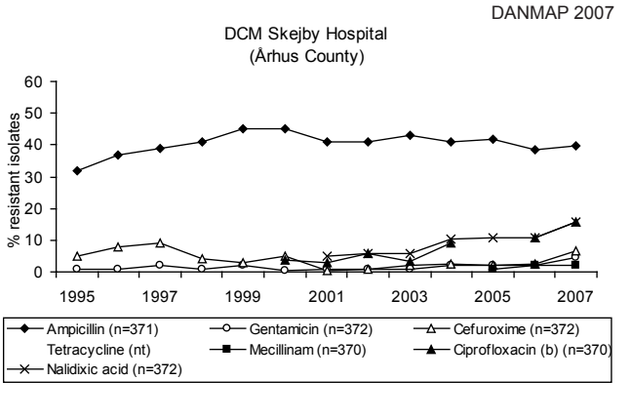
Figure 51. Resistance (%) to ampicillin, gentamicin, cefuroxime, mecillinam, tetracycline, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans presented by Department of Clinical Microbiology (DCM), Denmark. Rigshospitalet is the national referral hospital. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

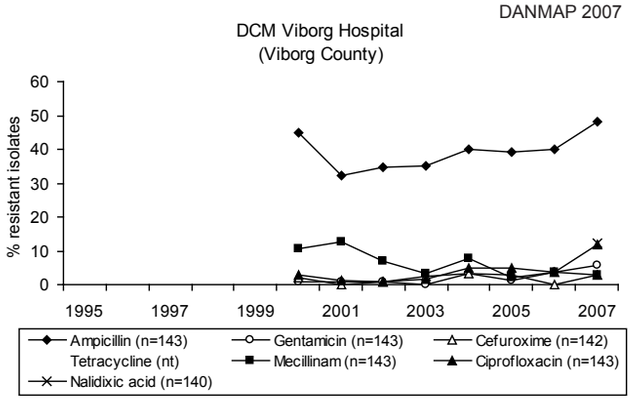
(a) Data is not shown where tests were carried out on selected isolates only
(b) Ciprofloxacin non-susceptible isolates (intermediary and resistant)
(c) Data from DCM Slagelse Hospital (West Zealand County) are from the last eight months of 2007











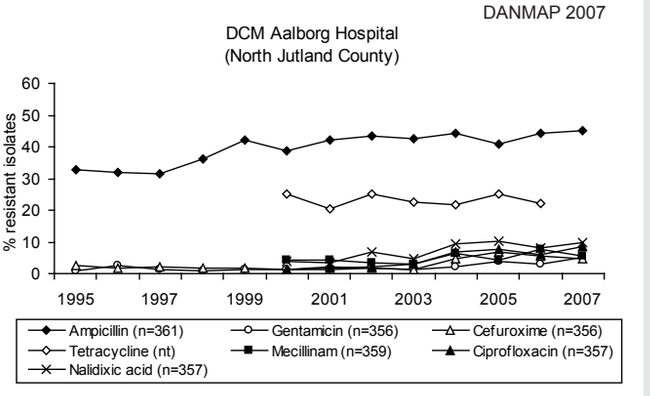


Figure 51. (Continued). Resistance (%) to ampicillin, gentamicin, cefuroxime, mecillinam, tetracycline, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans presented by Department of Clinical Microbiology (DCM), Denmark. Rigshospitalet is the national referral hospital. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

(a) Data is not shown where tests were carried out on selected isolates only
(b) Ciprofloxacin non-susceptible isolates (intermediary and resistant)
(c) Data from DCM Slagelse Hospital (West Zealand County) are from the last eight months of 2007

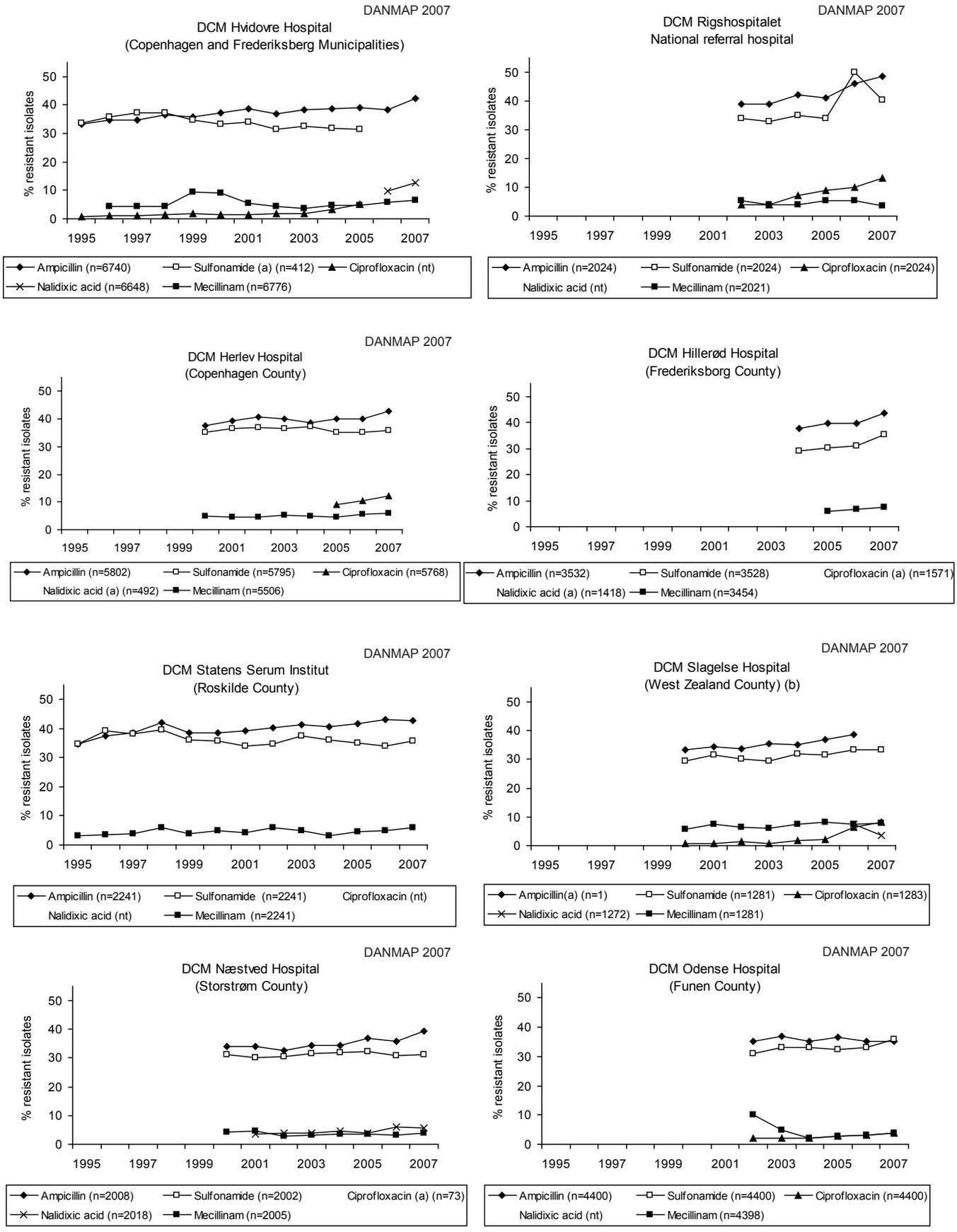
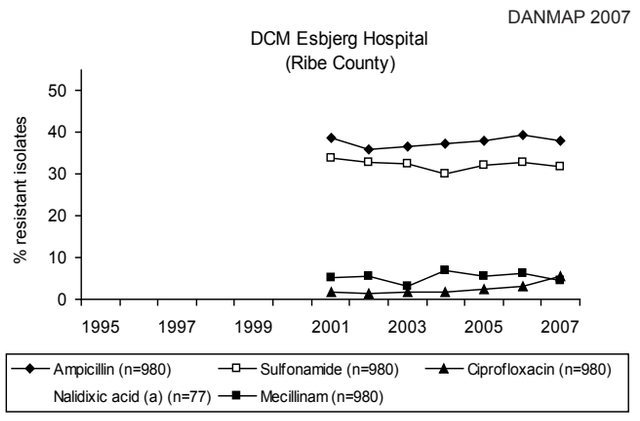
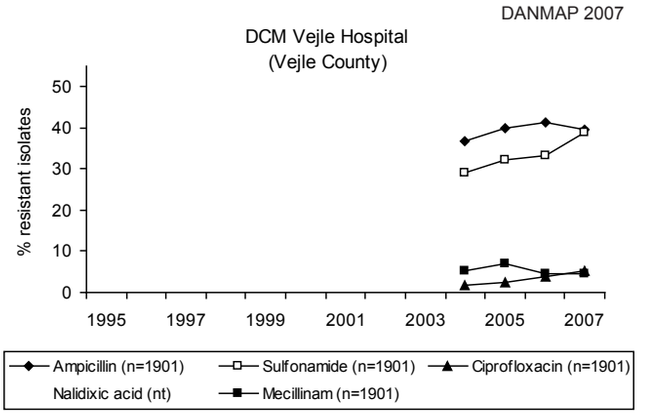
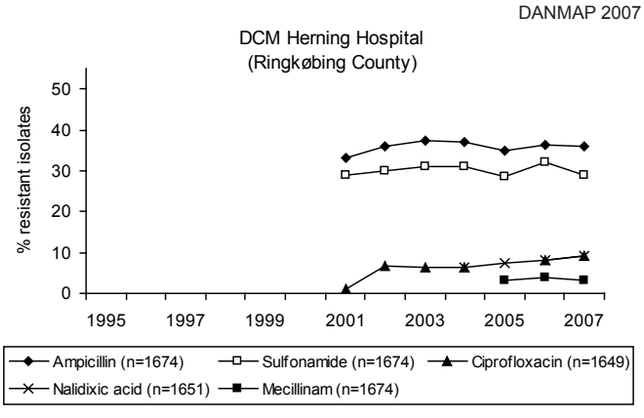


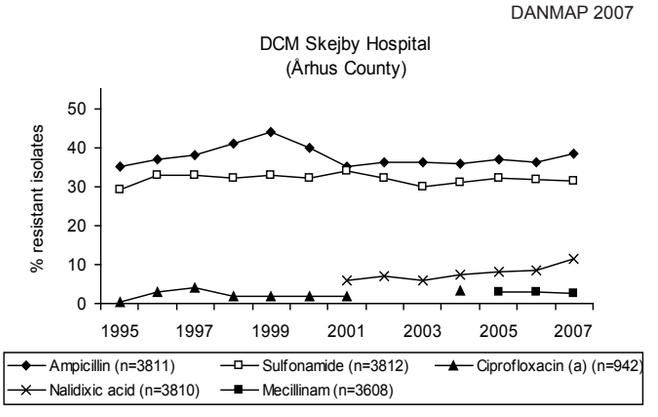
Figure 52. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals presented by DCM, Denmark. Rigshospitalet is the national referral hospital. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

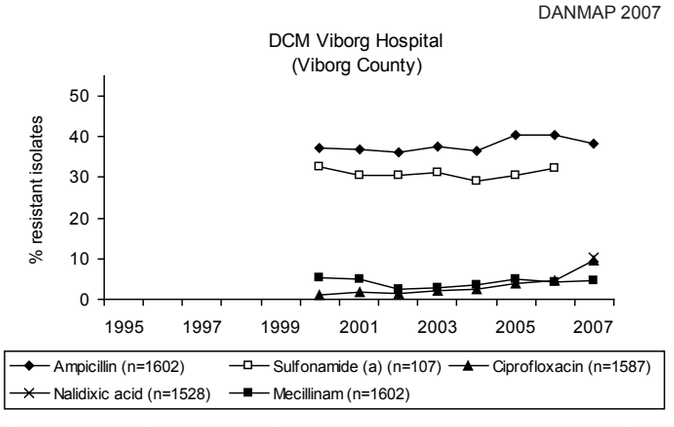
(a) Data is not shown where tests were carried out on selected isolates only
(b) Data from DCM Slagelse Hospital (West Zealand County) are from the last eight months of 2007











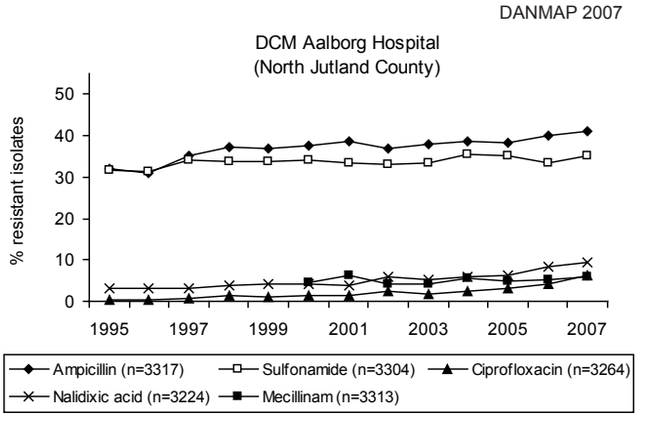


Figure_52. (Continued). Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals presented by DCM, Denmark. Rigshospitalet is the national referral hospital. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

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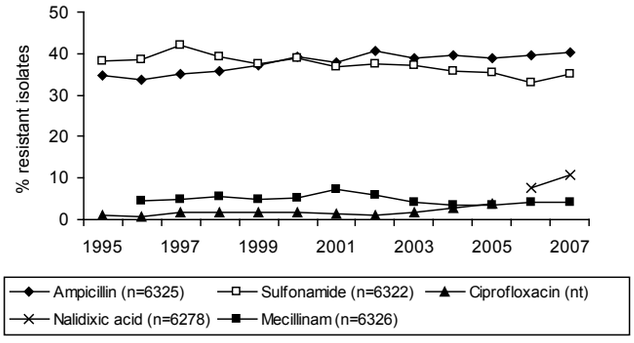
(b) Data from DCM Slagelse Hospital (West Zealand County) are from the last eight months of 2007

DANMAP 2007

DCM Hvidovre - Primary Health Care
(Copenhagen and Frederiksberg Municipalities)



DANMAP 2007

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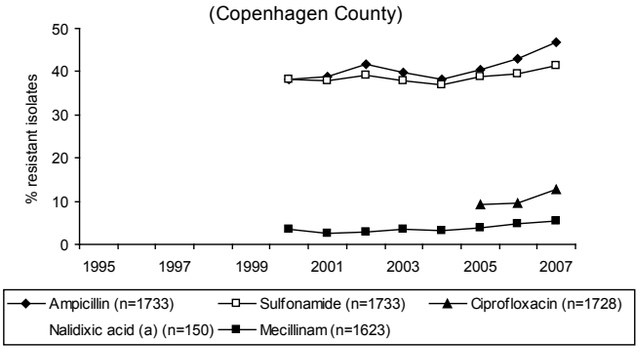
(Copenhagen County)



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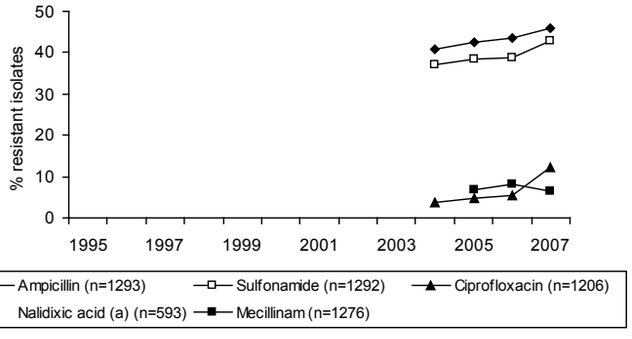
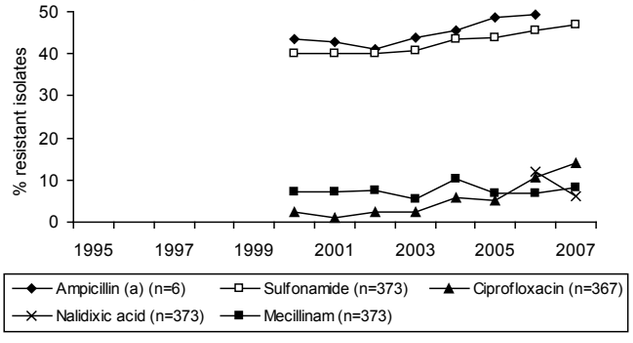


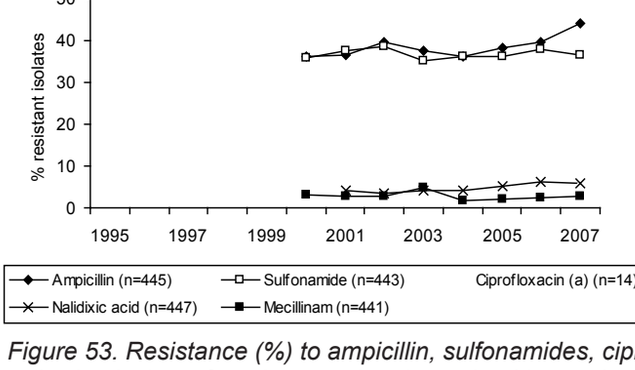
DANMAP 2007

DCM Slagelse - Primary Health Care
(West Zealand County) (b)



DANMAP 2007

DCM Næstved - Primary Health Care
(Storstrøm County)



DANMAP 2007

DCM Odense - Primary Health Care
(Funen County)

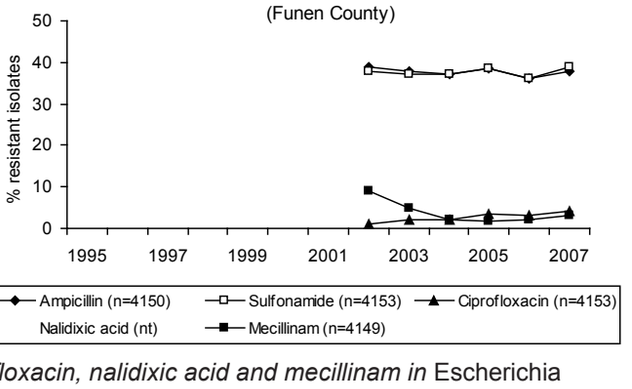


Figure 53. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in primary health care by DCM, Denmark. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

(a) Data is not shown where tests were carried out on selected isolates only
(b) Data from DCM Slagelse (West Zealand County) are from the last eight months of 2007
(nt) = not tested

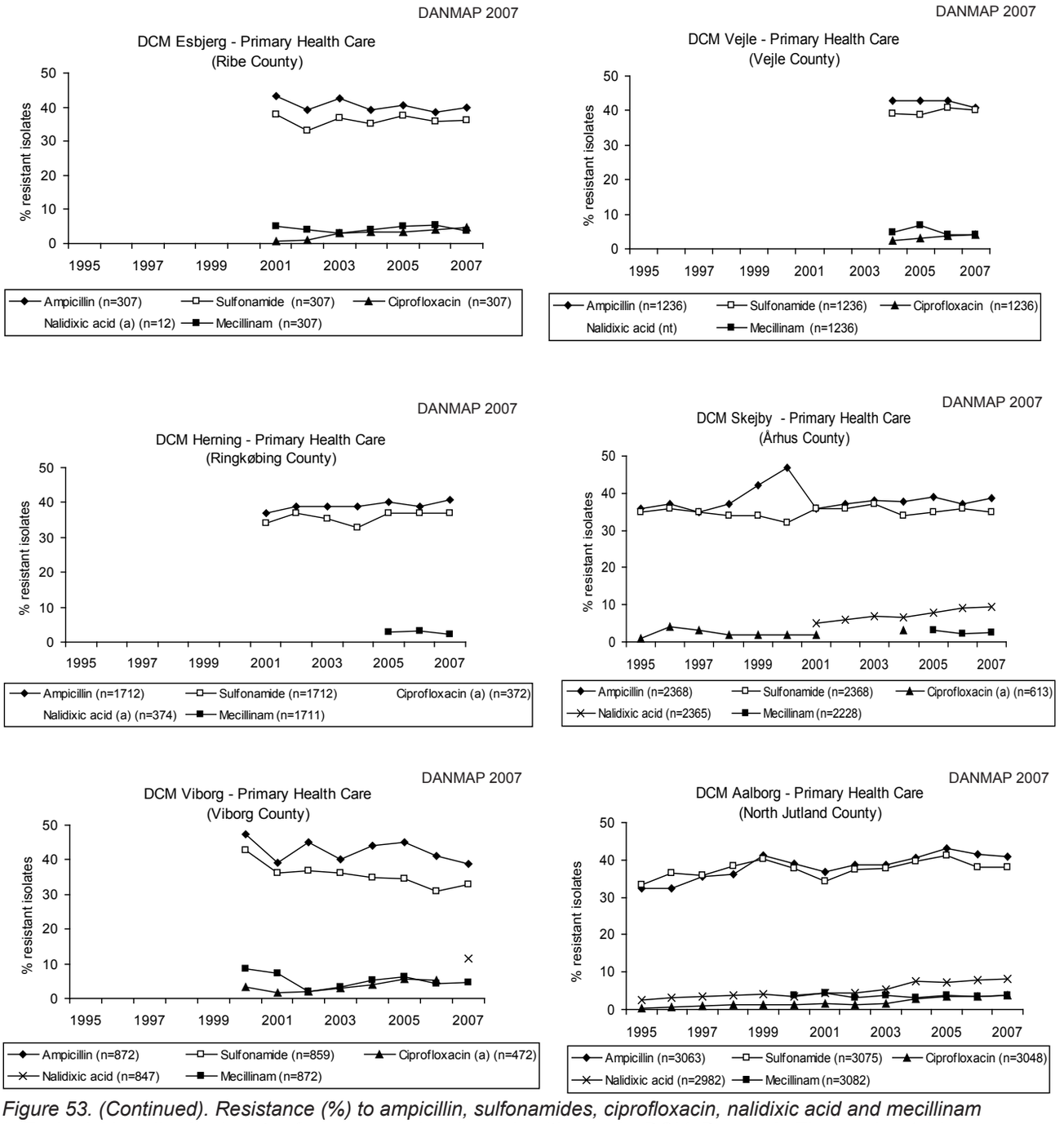


Figure 53. (Continued). Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in primary health care by DCM, Denmark. The number (n) in parentheses represents the number of isolates tested for susceptibility in 2007; (nt) = not tested.*

(a) Data is not shown where tests were carried out on selected isolates only
(b) Data from DCM Slagelse (West Zealand County) are from the last eight months of 2007
(nt) = not tested

Appendix 2
Materials and Methods

Materials and Methods

Demographics

Hospitals in Denmark

The reported number of hospitals in each Region of Denmark corresponds to the number of administratively distinct public hospitals, which do not specialize in psychiatric care (somatic hospitals) and report data to the Danish Medicines Agency and the National Board of Health. It is smaller than the geographical number of hospitals in Denmark since reorganisation of the hospital sector has resulted in regrouping hospitals that are distant geographically under the same administration and therefore the same name.

Additionally, certain categories of hospitals were excluded. This year, data from private hospitals and clinics, psychiatric hospitals, specialised non-acute care clinics, rehabilitation centres and hospices were excluded from DANMAP (representing approximately 2% of the hospital consumption and of the number of bed-days).

Data on consumption of antimicrobial agents

Consumption of antimicrobial agents in animals

Consumption data presented in this report were obtained from the national monitoring program, VetStat since 2001. Prior to 2001, data were based on overall sales figures from the pharmaceutical industry (see Table 5).
In Denmark, all therapeutic drugs are prescription-only and VetStat collects data on all medicines prescribed by veterinarians for use in animals and the consumption of coccidiostatics and antimicrobial growth promoters.

Until 2006, antimicrobials could only be purchased at the pharmacy or in medicated feed from the feed mills. The pharmacy either sells the medicines to veterinarians for use in practice or for re-sale to farmers, or sells directly to the animal owner on presentation of a prescription. By law, the profit that veterinarians can make on the sale of medicines is very limited.

From April 2 2007, the monopoly of the pharmacy was suspended, and private companies can now on certain conditions (corresponding to the pharmacies) sell veterinary drugs to farmers on prescription. In addition, price setting was liberalised, which allowed for discounts corresponding to lower administration cost related to sale of large quantities to the veterinarians. In 2007, the animal owners and veterinarians purchased the prescription drugs at pharmacies (88%), drug selling companies (9%) and feed mills (3% of the consumption). The veterinarians used or distributed 12.3% of the antimicrobials purchased at the pharmacies.

Data on all sales of veterinary prescription medicine from the pharmacies, private companies, feed mills and veterinarians are sent electronically to VetStat. Veterinarians are required by law to report to VetStat the use of all prescription medicines in production animals only. The amount of drugs reported by the veterinary practitioners is validated against pharmacy data on the total sales of therapeutic drugs for use in practice.
The VetStat database contains detailed information about source and consumption for each prescription item: date of sale, source ID (pharmacy, feed mill, veterinarian), drug identity and amount, animal species, age-group, disease category and code for farm-identity (CHR – Danish Central Husbandry Register).

Knowledge of the target animal species enables the presentation of consumption data in Defined Animal Daily Doses (ADD). The ADD system is a national veterinary equivalent to the international Defined Daily Doses (DDD) system applied in the human field (www.whocc.no). An ADDxx is defined as the average daily maintenance dose for a “standard animal” (defined by the assumed average bodyweight of the relevant age group = xx kg) within the particular animal species. Correspondingly, ADDkg is the dose necessary to treat one kg animal. The ADDkg is used to measure the consumption across age groups.

The length of the recommended treatment period may vary substantially between antimicrobial drugs, and the duration of the effect of one dose may vary considerably. To correct for this, total course dose has been introduced as unit of measurement for antimicrobial usage. Course doses is assigned per kilogram (live weight) of the animal species (ADCkg) or age group (ADCxx), based on the corresponding ADDkg or ADDxx, respectively, for the relevant animal species and drug formulations.

Antimicrobials used in humans / animals are presented in Table 41.

Consumption of antimicrobial agents in humans

Consumption data presented in this report were obtained from the Danish Medicines Agency (DMA) (http://www.laegemiddelstyrelsen.dk). The DMA has the legal responsibility for monitoring the consumption of all human medicinal products. This is carried out by monthly reporting of consumption from all pharmacies in Denmark, including hospital pharmacies, to the DMA. Data from the primary health care sector have been collected since 1994, whereas data on consumption in hospitals are available from 1997.

In Denmark, all antimicrobials for human use are prescription-only medicines and are sold by pharmacies in defined packages. Each package is uniquely identified by a code which can be related to package size, content as number of unit doses (e.g. number of tablets), content as number of Defined Daily Doses (DDD), code of the antimicrobial in the Anatomical Therapeutic Chemical (ATC) classification system, and producer. In addition, the following information is collected for each transaction: social security number (CPR number) of the patient, code identifying the prescribing physician, date and place (pharmacy, hospital pharmacy, institution) of the transaction, and information regarding reimbursement of cost, if applicable. Information on the indication for the prescription is not yet available. The data are transferred monthly to the DMA in an electronic format.

The present report includes data on the consumption of antibacterials for systemic use, or group J01 of the 2007 update of the ATC classification, in primary health care and in hospitals. As recommended by the World Health Organization (WHO), consumption of antimicrobials in primary health care is expressed as a number of DDDs per 1,000 inhabitants and per day (DDD/1,000 inhabitant-days). Consumption in primary health care is also reported as a number of packages per 1,000 inhabitants. Consumption of antimicrobials in hospitals is expressed as a number of DDDs per 1,000 occupied beds and per day (DDD/1,000 occupied bed-days). Since antimicrobial consumption expressed as DDD/1,000 occupied bed-days does not necessarily reflect changes in hospital activity and production, consumption in hospitals is also presented as DDD/1,000 discharged patients. Data on the number

Table 41. Antibacterials used in humans and/or in animals in Denmark a)
Antibacterials, which are only used in animals are mentioned in italics (animal growth promoters used before 1999 are mentioned in parentheses)
*Antibacterials, which are used both in humans and animals are **underlined**.*

DANMAP 2007

ATC/ATCvet codes	Therapeutic group	Names of antibacterials in group
J01AA/*QJ01AA/QJ51AA*	Tetracyclines	Doxycycline, *chlortetracycline*, lymecycline, oxytetracycline, tetracycline, tigecycline
J01BA/*QJ01BA*	Amphenicols	*Florfenicol*
J01CA/*QJ01CA*	Penicillins with extended spectrum	Ampicillin, pivampicillin, amoxicillin, pivmecillinam, mecillinam
J01CE/*QJ01CE*	Beta-lactamase sensitive penicillins	Benzylpenicillin, phenoxymethylpenicillin, *procaine penicillin*, *penethamate hydroiodide*
J01CF/*QJ51CF*	Beta-lactamase resistant penicillins	Dicloxacillin, *cloxacillin*, flucloxacillin, *nafcillin*
J01CR/*QJ01CR*	Comb. of penicillins, incl. beta-lactamase inhibitors	Amoxicillin/clavulanate, piperacillin/tazobactam
J01DB/*QJ01DB/QJ51DA*	First-generation cephalosporins	Cefalexin, *cefadroxil*, *cefapirin, cephalothin*
J01DC	Second-generation cephalosporins	Cefuroxime
J01DD/*QJ01DD/QJ51DA*	Third-generation cephalosporins	Cefotaxime, ceftazidime, ceftriaxone, *cefoperazone, ceftiofur, cefpodoxime*
J01DE/*QJ51DA*	Fourth-generation cephalosporins	Cefepime, *cefquinome, cefovecin*
J01DF	Monobactams	Aztreonam
J01DH	Carbapenems	Meropenem, ertapenem
J01EA	Trimethoprim and derivatives	Trimethoprim
J01EB/*QJ01EQ/QJ51R*	Short-acting sulfonamides	Sulfamethizole, *sulfadimidine, sulfathiazole*
J01EE/*QJ01EW*	Comb.of sulfonamides and trimethoprim, incl. derivatives	Sulfamethoxazole/trimethoprim, *sulfadiazine/trimethoprim*, *sulfadoxine/trimethoprim*
J01FA/*QJ01FA*	Macrolides	Erythromycin, *spiramycin*, roxithromycin, clarithromycin, azithromycin, *tylosin*, *tilmicosin, acetylisovaleryltylosin, tulathromycin*
J01FF/*QJ01FF*	Lincosamides	Clindamycin, *lincomycin*
J01FG/*QJ01XX*	Streptogramins	*(Virginiamycin) b*)
J01G/A07AA/*QJ01G/QA07AA c*)	Aminoglycosides	*Streptomycin*, *dihydrostreptomycin*, tobramycin, gentamicin, *neomycin*, netilmicin, *apramycin*
J01MA/*QJ01MA*	Fluoroquinolones	Ofloxacin, ciprofloxacin, moxifloxacin, *enrofloxacin*, *danofloxacin*, *marbofloxacin, difloxacin*
QJ01MB	Other quinolones	*Oxolinic acid*
QJ01MQ	Quinoxalines	*(Carbadox, olaquindox)*
J01XA	Glycopeptides	Vancomycin, teicoplanin, *(avoparcin)*
J01XB/A07AA/*QA07AA c*)	Polypeptides (incl. polymyxins)	Colistin, *(bacitracin)*
J01XC	Steroid antibacterials	Fusidic acid
J01XD/P01AB/*QJ01XD c*)	Imidazole derivatives	Metronidazole
J01XE/*QJ01XE*	Nitrofurane derivatives	Nitrofurantoin
J01XX/*QJ01XX/QJ01FF*	Other antibacterials	*Spectinomycin*, methenamine, linezolid, daptomycin
QJ01XX9	Pleuromutilins	*Tiamulin, valnemulin*
QP51AH	Pyranes and hydropyranes (ionophores)	*(Monensin, salinomycin)*
Not in ATCvet	Oligosaccharides	*(Avilamycin)*
Not in ATCvet	Flavofosfolipols	*(Flavomycin)*

a) Antibiotics for intrammamary use in animals are included. Antibiotics only used topically in humans or in animals are not included
b) Pristinamycin and quinupristin/dalfopristin (for humans) are not used in Denmark
c) Although intestinal antiinfectives (A07AA) and nitroimidazole derivatives for protozoal diseases (P01AB) are used to treat human patients in Denmark, their consumption is not reported by DANMAP

of occupied bed-days (or patient-days) and number of discharges in each hospital were obtained from the National Board of Health (http://www.sundhedsdata.dk).

Collection of bacterial isolates

Isolates from animals

Bacterial isolates included in the monitoring programme are collected from animals at slaughter (*E. coli*, enterococci and *Campylobacter*), as well as from diagnostic submissions (*Staphylococcus hyicus* from pigs, *E. coli* from diarrhoea pigs). Finally, *Salmonella* isolates from sub-clinical infections as well as from cases of clinical salmonellosis are included.

The samples from animals at slaughter are collected by meat inspection staff or company personnel and sent for examination to the National Food Institute, DTU or, if poultry, to the National Veterinary Institute, DTU. The number of samples taken at the slaughter plants is proportional to the number of animals slaughtered at each plant per year. Each sample represents one herd or flock. Samples are collected once a month (once weekly for broilers) in the period January-November. The broiler, cattle and pig slaughter plants included in the surveillance programme account for 95%, 90% and 95%, respectively, of the total number of animals slaughtered in Denmark per year. Accordingly, the bacterial isolates may be regarded as representing a stratified random sample of the respective populations, and the observed prevalence of resistant isolates provides an estimate of the true occurrence in the populations.

The National Food Institute, DTU is the national reference laboratory for *Salmonella* in animals, feeding stuffs and food and receives all such isolates for typing. Among all *Salmonella* isolates serotyped at the National Food Institute, DTU and for poultry, at the National Veterinary Institute, DTU, one isolate per serotype per farm is selected for the DANMAP report.

Bacterial isolates from diagnostic submissions are selected by a pseudo-random process that also includes isolates from submissions to the National Food Institute, DTU and from the Laboratory of Swine Diseases, Danish Meat Association, Kjellerup. Accordingly, the programme achieves nationwide coverage for these pathogens.

Isolates from food

All food samples were collected at wholesale and retail outlets by the Regional Veterinary and Food Control Authorities (RFCA) in all regions of Denmark during the course of routine inspection carried out by the authorities, or on specific request from the Danish Veterinary and Food Administration (DVFA) for the DANMAP surveillance programme. The collected material consisted of both Danish and imported foods. The food samples were collected according to the guidelines for microbiological examination of foods from the DVFA [Vejledning nr. 9613 af 20. Dec. 2002 om offentlig mikrobiologisk kontrol af fødevarer].

Isolates from humans

***Salmonella* spp. *Campylobacter* spp.** Antimicrobial susceptibility was performed on a sample of human faecal isolates submitted to SSI. Exact figures of the proportion tested and the sampling strategy for the different species can be found in the corresponding chapters of this report.

Campylobacter jejuni were selected among isolates from patients in three geographical regions: Northern Jutland, Funen and Roskilde/Køge. Isolates were selected randomly among travel-associated and domestically acquired infections, respectively, to obtain almost equal numbers of isolates in these two groups.

***Staphylococcus aureus* bacteremia.** One isolate from each case of *S. aureus* bacteremia (defined as a blood isolate from a patient using a 30 days window from previous positive cultures) from 15 of the 16 Danish counties were referred to SSI on a voluntary basis.

Methicillin resistant *Staphylococcus aureus* (MRSA). MRSA is a notifiable disease (since November 1 2006). One isolate from all new cases, defined as the first time a given MRSA strain is isolated in a person both from clinical samples (infections) and samples from healthy carriers is referred to SSI for characterization and storage.

Invasive *Streptococcus pneumoniae,* group A, B, C and G streptococci. All blood and spinal fluid isolates nationwide are sent to SSI for determination or confirmation of susceptibility testing and typing.

***Escherichia coli,* coagulase-negative staphylococci and *Streptococcus pyogenes*.** Data was provided on all isolates recorded from either blood samples (*E. coli,* coagulase-negative staphylococci), urine samples (*E. coli*) or all clinical samples (*S. pyogenes*) submitted for susceptibility testing to the participating DCM at Statens Serum Institut or the following hospitals: Rigshospitalet, Hvidovre, Herlev, Hillerød, Slagelse,

Næstved, Odense, Esbjerg, Vejle, Herning, Århus, Viborg, and Aalborg. From the DCM at Slagelse Hospital, only data from the last eight months of 2007 are included.

Isolation and identification of bacteria

Isolates from animals

***Salmonella* spp**. Examination of samples was done by non-selective pre-enrichment of 22-25 g material in a 1:10 dilution with buffered peptone water (BPW) and incubated 16-20 hours at 37°C. A plate with Modified Semi-solid Rappaport-Vassiliadis (MSRV) medium was inoculated with 0.1 ml of BPW deposited on the agar as 3 drops and in addition for cattle samples 1.0 ml BPW was inoculated in 9 ml selenite cystein broth. After enrichment overnight at 41.5°C material from MSRV swarming zones and 0.01 ml broth were inoculated onto Brilliant Green Agar (for samples from cattle and pigs) or onto Rambach Agar (for samples from poultry). Overnight incubation at 37°C was followed by serotyping of suspect colonies by slide agglutination.

***Campylobacter* spp.** The samples were examined by direct inoculation of selective agar (samples from pigs and poultry) or by selective enrichment (samples from cattle). The selective agar (mCCD) was incubated in micro-aerophilic atmosphere for 1-5 days at 42°C. Selective enrichment was done by inoculation of Preston broth at a ratio of 1:10, followed by incubation in microaerophilic atmosphere for 24 h at 42°C. Ten µl of the enrichment culture was inoculated onto mCCD agar and incubated 1-5 days at 42°C. *Campylobacter*-like colonies were identified by phase-contrast microscopy, by catalase activity and the ability to hydrolyse hippurate and indoxyl acetate. For isolates from cattle and pigs, oxidase activity was also tested.

***Escherichia coli* from healthy animals (indicator *E. coli*).** The material was inoculated directly onto Drigalski agar and incubated at 37°C overnight. For poultry, yellow colonies that were catalase positive and oxidase negative were identified according to the following standard criteria: indole, citrate, methyl red and Voges-Proskauer reaction. For cattle and pigs, yellow colonies were inoculated onto CHROM Orientation agar, and red colonies were identified as *E. coli* after incubation at 37°C overnight.

Enterococci from pigs. One drop of faecal material suspended in 2 ml sodium chloride (0.9%) was spread on Slanetz-Bartley agar and incubated for 2 days at 42°C. Up to three colonies showing a morphology typical of *E. faecalis* and *E. faecium* were sub-cultivated onto blood agar. White colonies were identified by the following criteria: motility, arginine dihydrolase and the ability to ferment mannitol, sorbitol, arabinose, raffinose and melibiose.

Enterococci from broilers. Cloacal swabs were incubated overnight at 42°C in Enterococcus Selective Broth, prepared with a composition identical to that of Enterococcosel broth. Cultures were streaked on Slanetz-Bartley agar and incubated for 48h at 37°C. Colonies that morphologically resembled *E. faecium* and *E. faecalis* were identified to species level using standard biochemical and physiological tests as described above.

Pathogens. The diagnostic submissions were examined according to the standard procedures employed by the participating laboratories.

Isolates from food

***Salmonella* spp.** were isolated according to the guidelines for microbiological examination of foods from the Danish Veterinary and Food Administration [NMKL No. 71, 5th ed., 1999]. Sero- and phage-typing was performed at the National Food Institute, DTU.

***Campylobacter* spp**. were isolated according to the guidelines for microbiological examination of foods from the Danish Veterinary and Food Administration. [NMKL No. 119, 3rd ed., 2007]. Subsequently, due to outsourcing, the isolates were sent to Eurofins A/S for further identification.

Indicator *E. coli* were isolated by the RFCA and subsequently, due to outsourcing, sent to Eurofins A/S for verification of species identification. *E. coli* were isolated by adding 5 g of the sample to 45 ml of MacConkey- or laurylsulfphate-broth, which was incubated overnight at 44°C, and subsequently streaked onto violet red bile agar and incubated for 24h at 44°C. Presumptive *E. coli* were identified as *E. coli* using API 20E test (BioMérieux, France).

Enterococci were isolated by the RFCA and subsequently, due to outsourcing, sent to Eurofins A/S for verification of species identification. Enterococci were isolated by adding 5 g of the sample to 45 ml of azide dextrose broth, which was incubated overnight at 44°C, and subsequently streaked onto Slanetz-Bartley agar. After incubation at 44°C for 48h the plates were examined for growth, and colonies typical of *E. faecium* and *E. faecalis* were sub-cultured on blood agar. Species identification was performed by PCR according to Dutka-Malen S *et al*. J. Clin.Microbiol., 1995; 33:24-27.

Isolates from humans

***Salmonella* spp.** isolates were serotyped according to the Kauffman-White Scheme.

***Campylobacter* spp**. Species identification was performed using a species specific PCR assay [Klena JD *et al.*, J. Clin. Microbiol. 2004; 42: 5549-5557].

***Staphylococcus aureus*.** *S. aureus* blood isolates and methicillin-resistant *S. aureus* (MRSA) in Denmark were typed using sequencing of the *S. aureus* specific spa gene as the primary typing method [Harmsen D *et al*. J. Clin. Microbiol 2003; 41: 5442-5448]. spa negative isolates were confirmed as *S. aureus* by tube coagulase test. Selected isolates were additionally typed by multi locus sequence typing (MLST) [Enright MC *et al.* J. Clin. Microbiol 2000; 38: 1008-1015] and annotated using eBURST v.3 software (www.mlst.net). Based on the spa and MLST typing, each isolate was assigned to a clonal complex (CC). For MRSA isolates, presence of the mecA methicillin resistance gene was confirmed by PCR [Larsen AR *et al*. Clin. Microbiol. Infect. 2008; 14(6): 611-4].

Susceptibility testing

Antimicrobial susceptibility testing of *Salmonella* spp., *Campylobacter* spp., indicator *E. coli*, *Enterococcus* spp. and *Staphylococcus hyicus* was performed with a commercially available MIC technique using dehydrated antimicrobials in microtitre wells (Sensititre, Trek Diagnostic Systems Ltd., UK). The wells were inoculated and incubated according to the CLSI guidelines. The MIC was defined as the lowest concentration of antimicrobial with no visible growth. In DANMAP 2007, the data was interpreted using epidemiological cut-off values instead of clinical breakpoints. The cut-off values are presented in Table 42. The following strains were used for quality control: *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecalis* ATCC 29212 and *Campylobacter jejuni* ATCC 33560.

Isolates of animal origin were susceptibility tested at the National Food Institute, DTU and for poultry, at the National Veterinary Institute, DTU. The *Salmonella* spp., *Campylobacter* spp., indicator *E. coli* and *Enterococcus* spp. of human origin were susceptibility tested at the SSI. Isolates from food were susceptibility tested at Eurofins A/S, but due to the quality of the data, the results on *E. coli* and *Enterococcus* spp. can not be published in the DANMAP report. All *Salmonella* spp. from foods were susceptibility tested at the National Food Institute, DTU.

One isolate per bacterial species per herd, or per food sample, or per patient was tested for antimicrobial susceptibility.

Additional information on human isolates

***Staphylococcus aureus*.** Susceptibility testing was performed using the tablet diffusion method (Neo-Sensitabs®, A/S Rosco, Denmark) on Danish Blood Agar (SSI Diagnostika, Denmark) towards: penicillin, cefoxitin, streptomycin, kanamycin, erythromycin, clindamycin (only when isolate was resistant to erythromycin), tetracycline, fusidic acid, norfloxacin and linezolid. A cefoxitin 60 µg tablet was used for screening for methicillin susceptibility. Isolates with an inhibition zone <29 mm were further tested for the presence of the mecA gene by PCR. In addition, MRSA isolates were screened for susceptibility towards glycopeptides using Etest® (AB Biodisk, Sweden) on Brain-Heart infusion agar (Becton Dickinson, Germany) with inoculum of McFarlane 2.0. In case of MIC >8 mg/L for vancomycin and teicoplanin or an MIC >12 mg/L for teicoplanin, population analysis profile against vancomycin were performed [Wootton M *et al.* J. Antimicrob. Chemother., 2001, 47:399-404].

***Streptococcus pneumoniae*.** Screening for penicillin-resistant *S. pneumoniae* was performed using a 1 µg oxacillin disk (Oxoid, Greve, Denmark) on 10% horse blood agar (SSI Diagnostika, Hillerød, Denmark), and for erythromycin-resistant *S. pneumoniae* using a 78 µg erythromycin tablet (Neo-Sensitabs®, A/S Rosco, Taastrup, Denmark) on 10% horse blood agar (SSI Diagnostika). The breakpoints used were those defined by the CLSI. Penicillin and erythromycin MIC's were determined using the Etest (AB Biodisk, Solna, Sweden) on Danish Blood Agar (Resistensplade, SSI Diagnostika) incubated at 36^0C, 5% CO2. The breakpoints used were those defined by Etest.

Invasive group A, B, C and G streptococci. Screening for penicillin-resistant streptococci was performed using a 1 µg oxacillin disk (Oxoid, Greve, Denmark) on 10% horse blood agar (SSI Diagnostika, Hillerød, Denmark), and for erythromycin-resistant streptococci using a 78 µg erythromycin tablet (Neo-Sensitabs®, A/S Rosco, Taastrup, Denmark) on 10% horse blood agar (SSI Diagnostika). Erythromycin resistant streptococci were tested with a 15 µg

Table 42. Interpretation and range of dilutions used for MIC-determination by Sensititre for bacteria from animals, foods and humans. EUCAST epidemiological cut-off values are used for interpretation (marked in grey). Exceptions are described in the footnotes

DANMAP 2007

Antimicrobial agent	*Salmonella*		*E. coli*		*Staphylococcus hyicus*		*E. faecium*		*E. faecalis*		*C. jejuni*		*C. coli*	
	Epid cut off µg/ml	Test range	Epid cut off µg/ml	Test range	Epid cut off µg/ml f)	Test range	Epid cut off µg/ml	Test range	Epid cut off µg/ml	Test range	Epid cut off µg/ml	Test range	Epid cut off µg/ml	Test range
Ampicillin	>4	1-32	>8	1-32			>4	2-64	>4	2-64				
Apramycin	>16	4-32	>16	4-32										
Avilamycin							>16	2-16	>8	2-16				
Cefpodoxime	>1	0.125-4	>1	0.125-4										
Ceftiofur	>2	0.5-8	>1	0.5-8	>2	0.125-16								
Cephalothin	>16	4-32	>32	4-32										
Chloramphenicol	>16	2-64	>16	2-64	>16	2-64	>32	2-64	>32	2-64	>16	2-32	>16	2-32
Ciprofloxacin	>0.06	0.03-4	>0.03	0.03-4	>1	0.125-8					>1	0.06-4 e)	>1	0.06-4
Daptomycin							>4	0.125-16	>4	0.125-16				
Erythromycin					>1	0.125-16	>4	0.5-32	>4	0.5-32	>4	0.5-32	>16	0.5-32
Flavomycin									>8	4-32				
Florfenicol	>16	2-64	>16	2-64	>8	1-64	>8	4-32	>8	4-32				
Gentamicin	>2	1-32	>2	1-32			>512 b)	128-2,048	>512 b)	128-2,048	>1	0.125-16	>2	0.125-16
Kanamycin							>1,024	128-2,048	>1,024	128-2,048				
Linezolid							>4	1-8	>4	1-8				
Nalidixic acid	>16	4-64	>16	4-64							>16	2-64	>32	2-64
Neomycin	>4	2-32	>8	2-32										
Penicillin					>0.125	0.06-16								
Salinomycin							>4	2-16	>4	2-16				
Spectinomycin	>64	16-256	>64	16-256	>128	8-256								
Streptomycin	>16	4-64	>16	4-64	>16	2-128	>128	128-2,048	>512	128-2,048	>2	2-16	>4	2-16
Sulfonamide	>256 d)	64-1,024	>256 d)	64-1,024	>128	8-512								
Quinupristin/dalfopristin a)							>4 c)	0.5-16						
Tetracycline	>8	2-32	>8	2-32	>1	0.5-32	>2	1-32	>2	1-32	>2	0.25-16	>2	0.25-16
Tiamulin					>2	0.25-32								
Tigecycline							>0.25	0.015-2	>0.25	0.015-2				
Trimethoprim					>4	1-32								
Vancomycin							>4	2-32	>4	2-32				

a) Trade name Synercid
b) CLSI clinical breakpoint is applied. The EUCAST epid. cut-off value (>32) is not within the test range
c) EUCAST epid. cut-off value (>1) is not applied according to investigations presented in the DANMAP 2006 report p. 49-50
d) CLSI clinical breakpoint is applied
e) Test range for human isolates was 0.03-4
f) EUCAST epid. cut off values for *S. aureus* is applied except for chloramphenicol, erythromycin and ceftiofur

erythromycin disk (Oxoid) and a 15 µg clindamycin disk (Oxoid, Greve, Denmark) on Danish Blood Agar (Resistensplade, SSI Diagnostika). Erythromycin MIC's were determined using the Etest (AB Biodisk, Solna, Sweden) on Danish Blood Agar (Resistensplade, SSI Diagnostika) incubated at 36^{0}C, 5% CO2. The breakpoints used were those defined by the CLSI, resistant isolates were defined as both fully and intermediate resistant isolates.

***Escherichia coli,* coagulase-negative staphylococci, and *Streptococcus pyogenes*.** In 2007, the DCM at Statens Serum Institut, the hospitals in Næstved, Odense and Viborg, and Rigshospitalet, which is the national referral hospital, used the tablet diffusion method (Neo-Sensitabs®, A/S Rosco) on Danish Blood Agar (Resistensplade, SSI Diagnostika) and the breakpoints defined for this medium by A/S Rosco. However, the DCM at Odense Hospital used Neo-Sensitabs® on Müeller-Hinton II agar (SSI Diagnostica) when testing urine isolates and Columbia agar with 4.5% NaCl (SSI Diagnostika) for oxacillin-susceptibility of staphylococci. The DCM at Vejle Hospital used the Neo-Sensitabs® on Müeller-Hinton II agar (SSI Diagnostica) and the breakpoints defined for this medium by A/S Rosco.The DCM at Esbjerg Hospital used the tablet diffusion method (Neo-Sensitabs®, A/S Rosco) on Müeller-Hinton II agar (SSI Diagnostika) when testing *E. coli.* The DCM at Aalborg Hospital also used the Neo-Sensitabs® on Mueller-Hinton II agar (SSI Diagnostika) in combination with the tablet diffusion method (A/S Rosco) and the breakpoints defined by the Swedish Reference Group for Antibiotics. The only material exception from SRGA was that the wildtype population of *E. coli* was deemed susceptible for ampicillin (and not intermediately susceptible).

In 2007, the DCM at Hvidovre, Herlev, Herning, and Århus Hospitals used the disk diffusion method (Oxoid, Basingstoke, UK) on Iso-Sensitest (ISA) medium (Oxoid). The DCM at Slagelse Hospital used the same disks on Iso-Sensitest (ISA) medium with or without 5% horse blood (Oxoid) according to test material and bacterial species. The DCM at Hillerød Hospital used the disk diffusion method on Iso-Sensitest (ISA) medium with blood from January to August, and then shifted to ISA medium without blood. All laboratories performing the disk diffusion method used the breakpoints defined by the Swedish Reference Group for Antibiotics (Available from: URL: http://www.srga.org/).

All submitting laboratories participate in national and international quality assurance collaborations such as the United Kingdom National External Quality Assessment Schemes (NEQAS).

Quinupristin/dalfopristin breakpoint

The epidemiological cut-off value suggested by EUCAST for quinupristin/dalfopristin when testing *E. faecium* is >1 µg/ml. In DANMAP, *E. faecium* isolates with MICs >4 µg/ml are reported resistant to quinupristin/dalfopristin. An evaluation study on this subject was presented in the DANMAP 2006 report, pp. 49-50.

Performance test

As part of the DANMAP programme, a performance test for susceptibility testing has been carried out once a year to ascertain the comparability of susceptibility tests of the laboratories involved in the presentation of data. By time, the susceptibility testing method used by the participating laboratories has become fully harmonized. Thus, all laboratories perform MIC-testing with use of the Sensititre system and follow the CLSI guidelines for inoculation and incubation. In 2007, it was decided to change the frequency of the performance testing to every second year with data presented in even years. The results of the previous performance test are presented in the DANMAP 2006 report, page 86: A total of 1264 antibiotic-bacterium susceptibility tests were performed on 5 *E. coli* strains, 5 *Salmonella* spp., 5 *Enterococcus* spp. and 9 *Campylobacter* spp., and the overall result was 0.48% failures. The quality of susceptibility data from future laboratories, that enter the DANMAP programme, will of course be validated when needed.

Data handling

Data on animal isolates

The results from the primary examination of samples from slaughterhouses and primary production for the bacteria of interest – positive as well as negative findings – and of the susceptibility testing were stored in an Oracle Database 8i Enterprise Edition®. The susceptibility data were stored as continuous values (MIC) as well as categorised as susceptible or resistant, respectively, as defined by the relevant epidemiological cut-off values. Each isolate was identified by the bacterial species, including subtype as applicable and by the date of sampling and the species of animal. Information on the farm of origin was also recorded. All handling and evaluation of results was carried out using SAS®Software, SAS Enterprise Guide 3.0.

Data on food isolates

Results from the analysis of food samples were reported via the database administrated by the Danish Veterinary and Food Administration. For each bacterial isolate information is available on the food type, bacterial species, date of sampling, date of examination of the sample, the Regional Veterinary and Food Control Authorities that collected and processed the sample, and an identification number, which makes it possible to obtain further information about the isolate from the Authority. Furthermore, information about the country of origin was recorded whenever possible.

Data on human isolates

***Salmonella* spp. and *Campylobacter* spp.** Data on *Salmonella* spp. and *Campylobacter* spp. infections are stored in the Danish Registry of Enteric Pathogens (Microsoft®Access) maintained by SSI. This register includes only one isolate per patient within a window of six months and includes data on susceptibility testing of gastrointestinal pathogens.

Methicillin resistant *Staphylococcus aureus* (MRSA). Characteristics of the isolates and the clinical/epidemiological information were obtained from the Danish MRSA register at SSI (mandatory reportable). This database contains both clinical information and strain characteristics on all new cases of MRSA i.e. diagnosed for the first time with a given MRSA strain regardless whether the person had an infection or was a healthy carrier. Based on the reported information, MRSA cases were classified as colonisation/active screening (i.e. surveillance samples to detect nasal, throat, gut or skin colonisation) vs. infection and classified epidemiologically as imported (i.e. acquired outside Denmark), acquired in a Danish hospital, defined as diagnosed >48 hours after hospitalization with no sign of infection at admittance (HA-MRSA) or diagnosed outside hospitals (community onset). MRSA cases with community onset were further classified according to risk factors during the previous 12 months as either health care associated with community onset (HACO) or community acquired (CA). Health care associated risk factors included prior hospitalizations or stay in long-term care facilities within 12 months prior to MRSA isolation, and being a health care worker. Community risk factors included known MRSA positive household members or other close contacts. Non-Danish origin defined as the person or one of the parents being born outside Denmark was investigated through the Danish Civil Registry.

***Streptococcus pneumoniae,* group A, B, C and G streptococci.** Data on susceptibility testing of isolates are stored as MIC's in a Microsoft® Access database at SSI. Analysis including selection of isolates from blood and spinal fluid samples and removal of duplicate isolates was performed with Microsoft® Excel.

***Escherichia coli* and coagulase-negative staphylococci.** Fourteen DCM provided aggregated data on resistance levels in *E. coli* blood and urine isolates and coagulase-negative staphylococci blood isolates. Data were extracted from the following laboratory information systems:
- ADBakt (Autonik AB, Skoldinge, Sweden) for the DCM at Hvidovre, Herlev, Slagelse, and Aalborg Hospitals;
- MADS (DCM, Skejby Hospital, Århus, Denmark) for the DCM at Rigshospitalet and Næstved, Odense, Esbjerg, Vejle, Herning, Århus (Skejby) and Viborg Hospitals;
- SafirLIS Microbiology (Profdoc Lab AB, Borlänge, Sweden) for the DCM at Hillerød Hospital.

For the former Roskilde County, resistance data on *E. coli* from blood samples was obtained from the DCM at SSI, and resistance data on *E. coli* from hospital urine samples from the chemical laboratory at Roskilde Hospital.
Laboratories were asked to provide data on the number of isolates tested and the percentage found to be resistant to selected antimicrobials. Although all laboratories were asked to remove duplicate isolates from the same patient within a window of 30 days, half of them were unable to comply with this rule. The other half removed duplicates so only one isolate was reported from each patient. Generally, resistance data were excluded if susceptibility to a certain antimicrobial was tested on only a selected number of isolates.

Calculation of confidence limits and differences between proportions

Estimation of exact 95% (two-sided) confidence intervals for proportions were based on binomial probability distributions as described in Armitage & Berry (2001), Statistical Methods in Medical Research, 4th ed. 2001, Oxford: Blackwell Scientific Publications. Significance tests of differences between proportions of resistant isolates were calculated using SAS®Software, SAS Enterprise Guide 3.0 or StatCalc in EpiInfo™ v. 6. Yates continuity correction or Fishers exact test (2-tailed) was applied when appropriate. P-values were reported to the first significant figure except P-values smaller than 0.0001, these were reported as P<0.0001.

Appendix 3
DANMAP publications

DANMAP publications

2007

Aarestrup FM, Hendriksen RS, Lockett J, Gay K, Teates K, McDermott PF, White DG, Hasman H, Sørensen G, Bangtrakulnonth A, Pornreongwong S, Pulsrikarn C, Angulo FJ, Gerner-Smith P. 2007. International spread of Multi-drug resistant *Salmonella* Schwarzengrund in food products. Emerg. Infect. Dis. 13: 726-731.

Aarestrup FM, Knöchel S, Hasman H. 2007. Antimicrobial susceptibility of *Listeria monocytogenes* from food products. Foodborne Pathog. Dis. 4: 216-221.

Agersø Y, Bruun MS, Dalsgaard I, Larsen JL. 2007. The tetracycline resistance gene *tet*(E) is frequently occurring and present on large horizontally transferable plasmids in *Aeromonas* spp. from fish farms. Aquaculture 266: 47-52.

Agersø Y, Petersen A. 2007. The tetracycline resistance determinant *Tet 39* and the sulphonamide resistance gene *sulII* are common among resistant *Acinetobacter* spp. isolated from integrated fish farms in Thailand. J. Antimicrob. Chemother. 59: 23-27.

Al-Zenki S, Al-Nasser A, Al-Safar A, Alomirah H, Al-Haddad A, Hendriksen RS, Aarestrup FM. 2007. Prevalence and antibiotic resistance of *Salmonella* isolated from a poultry farm and processing plant environment in the state of Kuwait. Foodborne Pathog. Dis. 4: 367-373.

Bagcigil FA, Moodley A, Baptiste KE, Jensen VF, Guardabassi L. 2007. Occurrence, species distribution, antimicrobial resistance and clonality of methicillin- and erythromycin-resistant staphylococci in the nasal cavity of domestic animals. Vet. Microbiol. 121: 307-315.

Bagger-Skjøt L, Nielsen EM, Sandvang D, Ethelberg S, Monnet DL, Hammerum AM. 2007. Less frequent *Salmonella* serovars as a reservoir of antimicrobial resistance. J. Antimicrob. Chemother. 59: 814-815.

Bagger-Skjøt L, Sandvang D, Frimodt-Møller N, Lester CH, Olsen KEP, Porsbo LJ, Monnet DL, Hammerum AM. 2007. Association between antimicrobial resistance and virulence genes in *Escherichia coli* obtained from blood and faeces. Scand. J. Infect. Dis. 39: 724-727.

Bartels MD, Boye K, Larsen AR, Skov R, Westh H. 2007. Rapid increase of genetically diverse methicillin-resistant *Staphylococcus aureus,* Copenhagen, Danmark. Emerg. Infect. Dis. 13: 1533-1540.

Benfield T, Espersen F, Frimodt-Møller N, Jensen AG, Larsen AR, Pallesen LV, Skov R, Westh H, Skinhøj P. 2007. Increasing incidence but decreasing in-hospital mortality of adult *Staphylococcus aureus* bacteraemia between 1981 and 2000. Clin. Microbiol. Infect. 13: 257-263.

Bhatta DR, Bangtrakulnonth A, Tishyadhigama P, Saroj SD, Bandekar JR, Hendriksen RS, Kapadnis BP. 2007. Serotyping, PCR, phage-typing and antibiotic sensitivity testing of *Salmonella* serovars isolated from urban drinking water supply systems of Nepal. Lett. Appl. Microbiol. 44: 588-594.

Cavaco LM, Hansen DS, Friis-Møller A, Aarestrup FM, Hasman H, Frimodt-Møller N. 2007. First detection of plasmid-mediated quinolone resistance (*qnrA* and *qnrS)* in *Escherichia coli* strains isolated from humans in Scandinavia. J. Antimicrob. Chemother. 59: 804-805.

Cavaco LM, Hendriksen RS, Aarestrup FM. 2007. Plasmid-mediated quinolone resistance determinant *qnrS1* detected in *Salmonella enterica* serovar Corvallis strains isolated in Denmark and Thailand. J. Antimicrob. Chemother. 60: 704-706.

Coenen S, Ferech M, Haaijer-Ruskamp FM, Butler CC, Vander Stichele RH, Verheij TJM, Monnet DL, Little P, Goossens H, the ESAC Project Group. 2007. European Surveillance of Antimicrobial Consumption: quality indicators for outpatient antibiotic use in Europe. Qual. Saf. Health Care 16: 440-445.

Collignon P, Aarestrup FM. 2007. Extended-spectrum beta-lactamases, food, and cephalosporin use in food animals. Clin. Infect. Dis. 44: 1391-1392.

Emborg HD, Vigre H, Jensen VF, Vieira ARP, Baggesen DL, Aarestrup FM. 2007. Tetracycline consumption and occurrence of tetracycline resistance in *Salmonella Typhimurium* from Danish pigs. Microb. Drug Resist. 13: 289-294.

Ethelberg S, Sorensen G, Kristensen B, Christensen K, Krusell L, Hempel-Jorgensen A, Perge A, Nielsen EM. 2007. Outbreak with multi-resistant *Salmonella* Typhimurium DT104 linked to carpaccio, Denmark, 2005. Epidemiol. Infect. 135: 900-907.

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Hald T, Lo Fo Wong DMA, Aarestrup FM. 2007. The attribution of human infections with antimicrobial resistant *Salmonella* bacteria in Denmark to sources of animal origin. Foodborne Pathog. Dis. 4: 313-326.

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Hammerum AM, Heuer OE, Emborg HD, Bagger-Skjøt L, Jensen VF, Rogues AM, Skov RL, Agersø Y, Brandt CT, Seyfarth AM, Muller A, Hovgaard K, Ajufo J, Bager F, Aarestrup FM, Frimodt-Møller N, Wegener HC, Monnet DL. 2007. Danish integrated antimicrobial resistance monetoring and research programme. Emerg. Infect. Dis. 13: 1632-1639.

Hansen LH, Jensen LB, Sorensen HI, Sorensen SJ. 2007. Substrate specificity of the *OqxAB* multidrug resistance pump in *Escherichia coli* and selected enteric bacteria. J. Antimicrob. Chemother. 60: 145-147.

Harbarth S, Monnet DL. Cultural and socioeconomic determinants of antibiotic use. In: Gould IM & van der Meer JWM (eds.). Antibiotic Policies: Fighting Resistance. Berlin, Tyskland: Springer, 2007, pp. 29-40.

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