DANMAP 2008

DANMAP 2008 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark

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This report is issued by DANMAP - The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme. It presents the results of monitoring of antimicrobial use and antimicrobial resistance in food animals, foods and humans in 2008. The report is produced in collaboration between the National Food Institute, Technical University of Denmark, the National Veterinary Institute, Technical University of Denmark, the Danish Veterinary and Food Administration, the Danish Medicines Agency and Statens Serum Institut. The DANMAP programme is funded jointly by the Ministry of Science, Technology and Innovation and the Ministry of Health and Prevention.

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A similar report from Norway is available at www.vetinst.no
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Introduction

This report, DANMAP 2008, describes the annual consumption of antimicrobial agents and the occurrence of resistance in different reservoirs. This years report starts with two focus areas focusing on important trends and observations. Other trends and comparison to previous years are included, in this report MIC tables and some trend figures are presented in 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, food 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 agent 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 reflect resistance more closely associated with 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 and terminology

List of abbreviations

ACD	Defined Animal Course Dose
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
DBD	Defined Daily Doses per 1,000 occupied bed-days
DCM	Department of Clinical Microbiology
DID	Defined Daily Doses per 1,000 inhabitants per day
DDD	Defined Daily Dose
DMA	Danish Medicines Agency
DVFA	Danish Veterinary and Food Administration
EARSS	The European Antimicrobial Resistance Surveillance System
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
OIE	World organisation for animal health
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

List of words

Anatomical Therapeutic Chemical (ATC) classification. 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/).

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

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 substancess are not used in veterinary medicine, and antimycotics are only registered for topical veterinary use, and used mainly in companion animals. Antimycobacterial agents are not included. 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/). DDD/1,000 inhabitant-days is called DID.

Defined Animal Daily Dose (ADD and ADDkg). This is a national veterinary equevalent to the DDD. 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 *et al*., 2004. 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 duratiion of the treatment related to one application may vary substantially between antimicrobial drugs. To correct for this, total course dose has been introduced as unit of measurement for antimicrobial usage. As a standard, the length of the course is here defined as 6 days, if nothing else is stated. Course doses is assigned per kilogram (live weight) of the animal species (ADCkg) or age group of the relevant species (ADCxx) 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 app.100 kilogram live weight.

Heifer. A young female cow before first calving.

Intramammaria. Antimicrobial agents for local application in the mammary gland (udder for the treatment of mastitis.

Intramammary syringe. A one dose applicator for use in the udder.

Layer. A hen raised to produce eggs for consumption.

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.

Pet animals. Dogs, cats, birds, mice, guinea pigs and more exotic species kept at home for pleasure, rather than one kept for work or food; does not include horses.

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 weigh of the piglet at weaning is 7 kilogram.

Poultry. In the DANMAP reports 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 pig, that has been served and is on the farm.

Steer. Castrated male cattle.

Weaners. Any pig 7–30 kilogram live weight.

Wild type. The typical form of an organism, strain, gene, or characteristic as it occurs in nature.

Sammendrag

Dette er den trettende DANMAP rapport. DANMAP 2008 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 to fokusområder præsenteres analyser udviklingen over tid og andre vigtige observationer, som gives særlig opmærksomhed i dette års rapport.

Fokusområde: Øget forekomst af resistente *Klebsiella pneumoniae* på danske hospitaler

Tidligere har DANMAP rapporterne ikke indeholdt data om *Klebsiella pneumonia*. Indtil 2006 var resistensforkomsten i *K. pneumoniae* lav og på same niveau som i de andre nordiske lande. Forekomsten af resistens overfor 3. generation cefalosporiner steg fra 4,4 % i 2006 til 10,8 % i 2008, hvilket svarer til niveauet i nogle af de sydeuropæiske lande. Stigningen i forekomsten af resistente *K. pneumoniae* isolater fra blod er sket parallelt med en stigning i forbruget af flere bredspektrede antibiotika (fluorkinoloner (ciprofloxacin) og 2. og 3. generation cefalosporiner). Samtidig med fremkomsten af multi-resistente *K. pneumoniae*, lige så vel som andre ESBL-producerende bakterier, er der sket en stigning i forbruget af carbapenemer, som er steget fra 8,6 DDD/1.000 sengedage i 2004 til 27,2 DDD/1.000 sengedage i 2008.

Fokusområde: Forbrugsmønstre for tetracykliner, makrolider og pleuromutiliner i besætninger med fravænnede grise og sammenhænge med stigende forbrug af tetracykliner (2001-2008)

Fra 2001 til 2008 steg forbruget af tetracykliner i svineproduktionen med 19 %, målt i ADD_{kg} per svin produceret (24% målt i ADD_{kg} per svin, justeret for eksportstigning). Stigningen var primært forbundet med en stigning i brugen af tetracyklin-præparater til foder- eller vandmedicinering. Forbruget af tetracykliner per produceret svin til fravænningsgrise (7.5-30 kg) steg med 118 % og til slagtesvin (>30 kg) med 40% i perioden 2003-2008. Fravænnings besætninger, som modtog 10 eller flere ordinationer i 2008, udgjorde 11% af besætningerne og var ansvarlige for 21 % af den nationale produktion af fravænnede grise . Analyserne præsenteret i denne rapport indikerer, at dette lille udsnit af besætningerne var ansvarlige for mere end 76 % af stigningen i det nationale forbrug af tetracykliner, 2003-2008. Forbruget af tetracykliner i disse besætninger var 150 % højere end i andre besætninger og det samlede antibiotikaforbrug var anslået 15 % højere end i andre besætninger. Forbrugsmønsteret peger på rutinemæssig brug af tetracykliner i nogle besætninger. Yderligere forskning er nødvendige for at undersøge udbredelsen af rutinemæssig brug af tetracykliner og andre antibiotika både i fravænnede grise og slagtesvin.

Antibiotika forbrug

DANMAP præsenterer antibiotikaforbrug til mennesker og dyr på årsbasis. Lægemiddelstyrelsen har overvåget forbruget af receptordineret medicin på patient niveau siden begyndelsen af 1990erne, og har bidraget med data for antibiotikaforbruget til mennesker i denne rapport. Siden 2001 er al anvendelse af receptordineret medicin til dyr registeret på dyreart, aldersgruppe og besætningsniveau i VetStat databasen på Veterinærinstituttet, Danmarks Tekniske Universitet.

Antibiotikaforbrug til dyr

Fjerkræ: I 2008 steg anvendelsen af antibiotika til kyllinger til 0,07 $ADDkg/_{kg}$ kød produceret, hvilket svarer til en stigning på 137 % sammenlignet med 2007. Antibiotikaforbrug i kyllingeproduktionen var dog fortsat meget lavt i forhold til andre produktionsdyr, og stigningen skete primært i brugen af amoxicillin. I kalkunproduktionen faldt forbruget med 23 % til 0,77 ADD_{kg}/kg kalkunkød produceret i 2008. Før 2007 udgjorde amoxacillin omkring 90 % af antibiotikaforbruget i kylllinge- og kalkunproduktionen, mens fluorkinoloner var det næst hyppigst anvendte antibiotikum. Fra 2007 og frem faldt forbruget af fluorkinoloner markant, parallelt med en stigning i andre antibiotika som sulfonamider, tetracykliner og makrolider, der tidligere kun er brugt i meget begrænset omfang til fjerkræ. Fluorkinolonforbruget i kyllingeproduktionen faldt med 97 % in 2008, sammenlignet med niveauet i 2006. I kalkunproduktionen steg fluorkinolonforbruget til 16 % af det samlede antibiotikaforbrug i 2007, men faldt til 2 % af forbruget i 2008.

Kvæg: Fra 2004 til 2008, steg anvendelsen af makrolider til kalve 13-fold, målt i kurdoser, mens brugen af tetracykliner, aminopenicilliner og sulfonamider til kalve faldt med hhv. 8 %, 47 % and 16 %. Dermed afløste makrolider tetracykliner som det mest anvendte til kalve fra 2006, og blev anvendt i 30 % af behandlingerne i 2008. Ændringen i valg af præparater afspejledes i faldende resistens overfor tetracyklin, ampicillin and sulfonamid i indikator *E. coli* fra kvæg ved slagtning. Forbruget af cefalosporiner

til kvæg var uændret 82 kg i 2008, efter et stigende forbrug fra 27 kg i 2001 til 82 kg i 2007. Der skete en ændring i forbrugsmøsteret, med 4,5 % (3 kg) stigning i det systemiske forbrug og et 11 % (3 kg) fald i det intramammære i 2008 sammenlignet med 2007. Dette betyder at færre køer blev behandlet med cefalosporin i 2008, selv om det overordnede forbrug i kg aktivt stof var konstant. Cefalosporiner blev anvendt til 26 % af alle yverbehandlinger i 2007, men dette faldt til 21% af alle yverbehandlinger i 2008.

Svin: I svineproduktionen faldt det samlede forbrug af antibiotika med 0,7 % til 97,2 ton aktivt stof i 2008. Dette betød ikke at svinene blev behandlet mindre, men afspejler en ændring i produktionen. Således steg eksporten af fravænnede svin (ca. 30 kg legemsvægt) med 40 % og antallet af svin produceret til slagtning faldt med 3 %. Justeres der for den stigende eksport steg forbruget med 1,9% målt i doser per svin produceret (ADD_{25}). Forbruget af cefalosporiner faldt til 128 kg 0,8 % i 2008, efter en årrække med stigende forbrug fra 24 kg i 2001 til 129 kg i 2007. Forbruget af cefalosporiner til søer og smågrise var uændret, hvilket tyder på at en stor del af smågrisene forsat behandles med cefalosporin.

I 2007 blev et neomycin præparat, det hyppigst anvendte aminoglykosid, taget af markedet. Dette resulterede i et 99,7 % fald i forbruget af neomycin, og et 84 % fald i forbruget af aminoglykosider målt i ADD_{25}. Samtidig steg forbruget af et andet aminoglykosid, apramycin, der steg med 24 % fra 2006 til 2008, hvilket afspejledes i stigende gentamicin/apramycin resistens i *S*. typhimurium fra svin i 2008, mens resistens overfor neomycin faldt i *S*. typhimurium fra svin og svinekød.

Antibiotikaforbruget til mennesker

Fra 2007 til 2008 faldt forbruget af antibiotika til behandling af mennesker til 35,5 millioner DDD eller 17,7 DDD/1.000 indbygger-dage (DID), svarende til fald på henholdsvis 0,3 % og 1,1 %.

Primærsektoren: I primærsektoren faldt det totale forbrug af antibiotika med 1,6 % til 15,9 DID i 2008. Dette var første gang siden 1999, at det totale antibiotikaforbrug faldt. Faldet i totalforbruget skyldtes et fald blandt tre stofgrupper (beta-laktamase sensitive penicilliner (faldt med 0,37 DID), makrolider og sulfonamider), hvorimod forbruget i de fleste andre stofgrupper steg; f.eks. tetracykliner, kombinationer af penicilliner, inkl. beta-laktamase inhibitorer og fluorkinoloner.

Beta-laktamase sensitive penicilliner repræsenterede fortsat den største gruppe antibiotika i totalforbruget (33 %) efterfulgt af penicilliner med udvidet spektrum (20 %) og makrolider (15 %).

Antibiotikaforbruget i primærsektoren - udtrykt i DID - er steget med 31 % mellem 1999 og 2008.

I 2008 modtog 308 ud af 1000 danskere mindst én recept på antibiotika, året før var tallet 320 ud af 1000.

Sygehusene: Totalforbruget af antibiotika på de danske sygehuse var fortsat stigende. Fra 2007 til 2008 steg forbruget med 7 %, fra 699,4 til 749,2 DDD/1000 sengedage (DBD). Angivet i DDD/1000 udskrevne patienter steg forbruget med 6 % (fra 2887 til 3055 DDD/1000 udskrevne patienter).

Forbruget af alle betydende antibiotika stofgrupper steg med undtagelse af beta-laktamase sensitive penicilliner og aminoglykosider. Forbruget af flere bredspektrede antibiotika steg markant: cefalosporiner (9,9 %), carbapenemer (27,7 %) og fluorkinoloner (17,4 %). Cefalosporiner udgjorde 20 % af det totale hospitalsforbrug. Penicilliner med udvidet spektrum (19 %) beta-laktamase sensitive penicilliner (13 %) og fluorkinoloner (13 %) var også væsentlige bidragsydere.

Det rapporterede antibiotikaforbrug fra da danske sygehuse var større end forventet, hvad enten det blev udtrykt som DBD eller DDD/1000 udskrevne patienter. Den store sygehusstrejke i foråret 2008 var en vigtig årsag hertil, da den medførte færre udskrevne patienter og sengedage, men formentlig kun et mindre fald i antibiotikaforbrug (DDD).

Resistens i indikator og zoonotiske bakterier

Dyr

Den mest almindeligt forekommende ***Salmonella* Typhimurium** fagtype i dansk svinekød og svin var DT120, efterfulgt af DT12. Blandt *S*. Typhimurium isolater fra danske svin, steg forekomsten af gentamicin- og ampicillinresistens signifikant fra 2007 til 2008. Ampicillinresistensen er steget gradvist siden 2001. Stigningen i apramycin forbruget til svin (2006-2008) har formentlig drevet stigningen i gentamicinresistens. Et signifikant fald i neomycin- og spectinomycin-resistens observeredes i *S.* Typhimurium fra danske svin, formentlig relateret til et 99.7 % fald i neomycin forbruget fra 2006–2008 og et 30 % fald i spectinomycin forbruget til svin fra 2004–2008.

Blandt ***Campylobacter jejuni*** isolater fra danske kyllinger var 12 % resistente overfor ciprofloxacin og nalidixinsyre, hvilket var højere end for alle andre antibiotika i antibiotikapanelet. Bland disse antibiotika var fluorkinoloner var den mest almindeligt anvendte antibiotika gruppe til fjerkræ indtil 2006. Fra 2007 til 2008 sås ingen signifikante ændringer i resistensforekomsten blandt *C. jejuni* fra danske kyllinger eller blandt ***Campylobacter coli*** fra svin.

For indikator ***E. coli*** isolater fra fjerkræ og kvæg sås ingen signifikante ændringer i resistensforekomsten fra 2007 til 2008. Fra 2004 til 2008 var der en signifikant faldende trend i forekomsten af tetracyklin-, ampicillin- og sulfonamid-resistens i *E. coli* fra kvæg, hvilket falder sammen med et fald i forbruget af tetracykliner, aminopenicilliner og sulfonamider til kalve.
For indikator *E. coli* fra svin var tetracyklinresistens den mest almindelige resistens type (30 %), hvilket modsvarer det vedvarende høje forbrug af tetracykliner i svineproduktionen. Forekomsten af streptomycin- og spectinomycin resistens i indikator *E. coli* fra svin faldt signifikant i 2008, mens forbruget af spectinomycin til svin fald mere end 30 % fra 2004–2008.

For både ***Enterococcus faecium*** og ***Enterococcus faecalis*** sås den højeste resistensforekomst i isolater fra svin. Hyppigst var resistens overfor tetracyklin (hhv. 61% og 84%), erythromycin (hhv. 32% og 40%) og streptomycin (hhv. 43% og 28%). Tetracykliner og makrolider har været de mest almindeligt anvendte antibiotika til svin i det sidste årti, mens streptomycin har været almindeligt anvendt i flere årtier. Fra 2007 til 2008 skete et signifikant fald forekomsten af makrolidresistens i *E. faecium* isolater fra svin, formentlig som følge af et 6 % fald i makrolidforbrug per svin i 2008.
For *E. faecium* fra kyllinger var kun forekomsten af salinomycin resistens (65 %) signifikant højere sammenlignet med isolater fra svin. Ionophorer (salinomycin and monensin) var de mest almindeligt anvendte coccidiostatica i fjerkræproduktionen i Danmark i dette årti. For *E. faecalis* isolater fra svin sås en signifikant højere forekomst af resistens overfor tetracyklin, kloramfenicol, erythromycin og streptomycin sammenlignet med isolater fra kyllinger. Som i foregående år sås ingen resistens overfor vancomycin.

Kød
Resistensforekomsten i isolater af ***S.* Typhimurium** var signifikant højere i importeret svinekød sammenlignet med dansk svinekød, mht. resistens overfor ampicillin, kloramfenicol, florfenicol, spectinomycin, streptomycin, sulfonamid, tetracyklin og trimethoprim. Den højeste resistensforekomst sås i importeret kalkunkød, for hvilket alle *S.* Typhimurium isolater var resistente overfor tetracyklin og sulfonamid. Fluorkinolonresistens sås i 1/3 af *S*. Typhimurium isolater fra importeret kalkunkød, hvilket var signifikant højere end i alle andre undersøgte kødtyper. Endvidere var forekomsten af resistens overfor 3. generation cefalosporiner høj (6.9 %) i *S*. Typhimurium isolater fra importeret kalkunkød, sammenlignet med isolater fra andre kødtyper. Cephaloporin-resistens observeredes for første gang i *S*. Typhimurium isolater fra overvågning af dansk svinekød. I dansk kyllingekød blev *S*. typhimurium kun fundet i et tilfælde, hvorfor resistensforekomsten ikke kunne vurderes.
***S.* Enteritidis** blev ikke fundet i dansk kyllingekød. Blandt *S.* Enteritidis isolater fra importeret kyllingekød var 37 % mere resistent overfor nalidixic syre og ciprofloxacin, mens 7 % var ceftiofur og cefotaxime resistente.
I isolater af *C. jejuni* fra importeret kyllingerkød sås en signifikant højere forekomst af resistens overfor ciprofloxacin, nalidixinsyre og tetracyklin sammenlignet med *C. jejuni* isolater fra dansk kyllingekød.

For indikator ***E. faecium*** så en signifikant højere forekomst af resistens overfor tetracyklin, penicillin, ampicillin, erythromycin og streptomycin i importeret kyllingekød sammenlignet med dansk kyllingekød, mens forekomsten af resistens overfor salinomycin var lavere i importeret kyllingekød sammenlignet med det danske.
For indikator ***E. faecalis*** from imported kyllingekød sås en signifikant højere forekomst af resistens overfor tetracyklin, kloramfenikol, erythromycin, kanamycin og streptomycin sammenlignet med dansk kyllingekød. For svinekød var kun resistens overfor tetracyklin signifikant hyppigere forekommende i det udenlandske end i det danske svinekød.
I isolater af indikator ***E. coli*** fra importeret kyllingekød sås signfikant højere forekomst af resistens overfor tetracyklin, kloramfenikol, ampicillin, cefoxitime, ceftiofur, sulfonamider, trimethoprim, neomycin, spectinomycin, streptomycin, ciprofloxacin og nalidixinsyre, sammenlignet med isolater fra dansk kyllingekød.

Mennesker
***S.* Typhimurium** situationen var meget usædvanlig i 2008, hvor der forekom flere store udbrud, som udgjorde 76 % af alle humane *S.* Typhimurium isolater. Resistensprofilerne i humane *S.* Typhimurium isolater erhvervet i Danmark lignede mere resistensprofilerne fra dansk svinekød end resistensprofilerne fra isolater fra importeret svinekød.
Resistensforekomsten overfor ampicillin, kloramfenikol, cefotaxim, tetracyklin, sulfonamider, spectinomycin, streptomycin og ciprofloxacin var signifikant højere i *S.* Typhimurium isolater fra patienter med rejserelaterede infektioner sammenlignet med isolater fra infektioner erhvervet i Danmark (uanset om de blev sammenlignet med alle isolater erhvervet i Danmark med eller uden de store udbrud).
Resistensforekomsten for ciprofloxacin og nalidixan syre var signifikant højere i rejserelaterede ***S. Enteriti-***

dis isolater sammenlignet med *S.* Enteritidis isolater erhvervet i Danmark.
Resistensforekomsten for ciprofloxacin, nalidixan syre, streptomycin og tetracyklin var signifikant højere blandt rejserelaterede ***C. jejuni*** isolater sammenlignet med *C. jejuni* isolater fra infektioner erhvervet i Danmark.
Signifikant højere resistensforekomst blev fundet i ***E. faecium*** isolater fra importeret kyllingekød for tetracyklin, ampicillin, erythromycin, streptomycin, avilamycin, og lavere for salinomycin, ved sammenlignet med i *E. faecium* isolater fra rekrutter.
Ligeledes var der en signifikant højere resistensforekomst i ***E. faecalis*** isolater fra importeret kyllingekød for tetracyklin, erythromycin, kanamycin og streptomycin ved sammenligning med *E. faecalis* isolater fra rekrutter.
Tredje generation cefalosporin resistente ***E. coli*** blev isoleret fra fæces prøver fra rekrutter. Dette er første gang, 3. generation cefalosporin resistens er blevet rapporteret i *E. coli* fra fæcesprøver fra mennesker i den almindelige befolkning i DANMAP rapporterne.
Forekomsten af resistente *E. coli, E. faecium* og *E. faecalis* isolater var ikke signifikant anderledes end forekomsten i *E. coli, E. faecium* og *E. faecalis* isolater fra dansk eller importeret kød.

Resistens i bakterier fra diagnostiske indsendselser fra dyr

E. coli F5 (K99) isoleret fra diagnostiske prøver fra kvæg blev screenet for resistens, og der sås et signfikant fald i resistens overfor tetracyklin, sulfonamider og streptomycin fra 2004/2005 til 2008.
I 2008 blev resistens overfor ceftiofur observeret i to isolater (4.4 %) of *E. coli* F5 (K99), og resistens overfor cefotaxim blev observeret i 6.7 % af isolaterne.
I 2008 var 60 % af *E. coli* O149 isolater fra diagnostiske indsendelser fra svin resistente overfor tetracyklin. Af disse var 94 % mulitresistente. I 2008 var forekomsten af neomycin resistens i *E. coli* O149 fra svin faldet til 18 % fra 33 % i 2007. I 2008 blev fundet ceftiofur- og cefotaximresistente *E. coli* O149 (2.9 %) isolater isoleret fra to diagnostiske indsendelser fra svin, hvilket ikke tidligere er blevet observeret. Forbruget at 3. og 4. generation cefalosporiner til svin er steget markant fra 2001 til 2007, og forblev på dette niveau i 2008.

Resistens i bakterier fra diagnostiske indsendelser fra mennesker

Rapporteringen af antibiotikaresistens i bakterier fra diagnostiske indsendelser fra mennesker er baseret på frivillig indsendelse af data fra DANRES gruppen, som dækker de klinisk mikrobiologiske afdelinger i Danmark. De eneste udtagelser er for methicillin resistente *Staphylococcus aureus* og invasive *Streptococcus pneumoniae,* som er anmeldepligtige. Data fra disse bakterier kommer fra reference laboratorierne på SSI.

Blandt ***E. coli*** isolater fra blod var antibiotikaresistensforekomsten for alle testede antibiotika den samme som i 2007 for ampicillin, gentamicin, mecillinam, nalidixan syre og ciprofloxacin.
I denne DANMAP rapport, blev der for første gang medtaget data om resistens overfor 3. generation cefalosporiner (ceftazidim, ceftriaxon, cefpodoxim eller cefotaxim) og carbapenemer. Fire procent af *E. coli* isolaterne var 3. generation cefalosporin resistente og mindre en 1 % var carbapenemresistente.

Blandt ***E. coli*** isolater fra urin, både fra primærsektoren og fra hospitalerne, steg resistensforekomsten signifikant for ciprofloxacin, nalidixan syre og mecillinam i forhold til 2007.

Clostridium difficile 027 er et stigende problem på danske hospitaler. CD027 er resistent overfor nyere fluorkinoloner. Det er blevet foreslået, at det kan være grunden til dens udbredelse.

I denne DANMAP rapport, blev der for første gang rapporteret data over resistensforekomst i ***Pseudomonas aeruginosa*** isolater fra blod. Resistensforekomsten var lav overfor alle de testede antibiotika.

I 2008 var penicillin og erythromycin resistensforekomsten stadig lav blandt ***Streptococcus pneumoniae,*** og gruppe **A, B, C** og **G streptokokker.**

Ampicillinresistensforekomsten var høj (87 %) blandt ***Enterococcus faecium*** isolater fra blod. Hvorimod mindre end 1 % af *E. faecium* og ***Enterococcus faecalis*** isolaterne var vancomycin resistente. Høj niveau gentamicin resistens (HLGR) blev kun testet på en afdeling for klinisk mikrobiologi. Der var 36 % af *E. faecalis* isolaterne HLGR og 58 % af *E. faecium* isolaterne var HLGR. Antallet af *E. faecium* isolater er steget fra 137 i 2002 til 369 i 2008 (rapporteret fra 11 af de kliniske mikrobiologiske afdelinger). Behandling med fluorkinoloner, cefalosporiner eller carbapenemer er blevet beskrevet som risikofaktorer for udvikling af *E. faecium* infektioner. I de senere år der netop blevet observeret en stigning i forbruget af disse antibiotika.
Der blev indrapporteret 1.344 tilfælde af ***Staphylococcus aureus*** bakteriæmier i 2008, hvilket er på niveau med de foregående år. Antallet af methicillin resistente *Staphylococcus aureus* (MRSA)

bakteriæmier 17 i 2008 (1,3 %), svarende til antallet i årene forinden. Sammenlignet med landene i det øvrige Europa er det stadig en meget lille frekvens. Resistens mod øvrige testede antibiotika har ikke ændret sig signifikant i de seneste år.
Antallet af nye tilfælde af MRSA steg til 854 i 2008 (fra 706 og 659 tilfælde i hhv. 2006 og 2007). Stigningen kan blandt andet tilskrives tre udbrud på neonatalafdelinger og en større screeningseance af deltagere ved en svineproducentkongres.
134 tilfælde (16 %) var erhvervet i udlandet, 141 (17 %) på hospitaler, 115 (14 %) tilfælde blev fundet hos personer med hospitals-/plejehjemkontakt mens 417 tilfælde var samfundserhvervede. Resistensforekomsten var i 2008 på samme niveau som i 2007, bortset fra erythromycinresistensen, som faldt fra 48 % i 2007 til 39 % i 2008. Dette fald kan til dels forklares med et fald i antal af *spa* type t024, hvoraf en stor andel er resistente mod erythromycin. Der var stor forskel på resistensforekomsten imellem de forskellige *spa* typer. Typer som t189, der ofte erhverves på hospitaler, udviste de højeste resistensprocenter, mens samfundserhvervede typer som t015 og t019 var følsomme over for alle testede antibiotika med undtagelse af beta-laktamer. Der blev også registreret ændringer i resistensforekomsten for enkelte *spa* typer. For t008, som var den hyppigste *spa* type begge år, steg resistensen mod norfloxacin fra 29 % i 2007 til 57 % i 2008. Efter to års nedgang i antallet af nye MRSA tilfælde er dette års stigning bekymrende, og udviklingen bør følges nøje.

Summary

This report is the 13th DANMAP report. DANMAP 2008 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. In two focus areas, trend analyses and other observations, given particular interest this year, are presented.

Focus area: Increased frequency of resistant *Klebsiella pneumoniae* in Danish hospitals

Previously, data on *Klebsiella pneumonia* have not been included in the DANMAP reports. Until 2006, the frequency of resistance was low and at the same level as the other Nordic countries. For 3rd generation cephalosporins, resistance has increased from 4.4% in 2006 to 10.8% in 2008, which corresponds to the level reported for some southern European countries. The increased frequency of resistance in *K. pneumoniae* blood isolates parallels the increased consumption of several broad spectrum antimicrobial agents (fluoroquinolones (ciprofloxacin) and 2nd and 3rd generation cephalosporins). In addition, the emergence of multi-resistant *K. pneumoniae*, as well as other ESBL-producing bacteria, has added to the already increasing consumption of carbapenems, which increased from 8.6 DDD/1,000 occupied bed-days in 2004 to 27.2 DDD/1,000 occupied bed-days in 2008.

Focus area: Patterns of tetracycline, macrolide and pleuromutilin consumption in weaning pig herds, associated with the increasing consumption of tetracyclines (2001-2008)

From 2001 through 2008, the antimicrobial consumption in the pig production increased by 19%, measured in ADD_{kg} per pig produced (24% when adjusted for increasing export). The increase was primarily associated with an increasing consumption of tetracyclines for oral use. From 2003 through 2008, the consumption of tetracyclines per pig produced increased by 118% in weaning pigs and 40% in finishers. The results presented in this report indicated that the majority of the increase was associated with weaning pig herds receiving 10 or more prescriptions of tetracyclines per year. These results indicate that a subset of herds housing approximately 21% of the weaning pigs, accounted for a major part of the increasing consumption of tetracyclines during 2003–2008. The overall antimicrobial consumption in these herds was an estimated 15% higher than in other herds, while the use of tetracyclines was an estimated 150% higher than in other herds in 2008. The results indicate that tetracyclines are used systematically in some herds, but more research is needed to support this observation.

Antimicrobial consumption

DANMAP presents the use of antimicrobial agents in humans and animals. In humans, the use of prescription medicines has been monitored by the Danish Medicines Agency, at the level of the individual patient since the early 1990s. The Danish Medicine Agency has contributed with data for this report.
In animals, data on all medicines prescribed by veterinarians for use in animals have been registered at farm level by the VetStat programme at the Veterinary Institute (Technical University of Denmark) since 2001.

Antimicrobial consumption in animals

In the broiler production, the antimicrobial consumption was 0.07 ADD_{kg}/kg broiler-meat produced in 2008, representing an increase of 137%, mostly in amoxicillin, compared to 2007. However, the consumption continues to be very low compared to other species.
In the turkey production, the consumption decreased by 23% to 0.77 ADD_{kg}/kg turkeymeat produced in 2008. Before 2007, amoxicillin comprised approximately 90% of the antimicrobial used in poultry, and fluoroquinolones were the second most used antimicrobial group. However, a significant change in the choice of antimicrobial agents occurred in 2007 and forward. An increase in other antimicrobial agents like sulfonamides, tetracyclines and macrolides was observed for both turkeys and domestic fowl (broiler and layers). The consumption of fluoroquinolones in the broiler production was reduced by 97% in 2008, compared with the level in 2006. In the turkey production, fluoroquinolones comprised 16% of the consumption in 2007 but decreased to 2% of the consumption in 2008.

In calves, macrolides were the major drugs of choice, constituting 30% of the total consumption in calves in 2007 and 2008. From 2004 through 2008, the use of macrolides measured in course-doses increased 13-fold, while the use of tetracyclines, aminopenicillins and sulfonamides prescribed for calves decreased by 8%, 47% and 16%, respectively. This change in choice of drugs was reflected in a decreasing resistance to

tetracycline, ampicillin and sulfonamides in indicator *E. coli* from cattle at slaughter from 2004–2008. In cattle, the overall consumption of cephalosporins (3rd and 4th generation) was 82 kg in 2008 as in 2007, after a steady increase from 27 kg in 2001. In 2008, the systemic use increased by 4.6% (3 kg) compared to 2007. The intramammary use of 3rd and 4th generation cephalosporin decreased by 11% (3 kg) in 2008 compared to 2007. The consumption of intramammaria based on 3rd and 4th generation cephalosporin in 2008 comprised 21% of the total consumption of intramammaria (in ADD), representing a decrease compared to 26% in 2007.

In 2008, the overall antimicrobial consumption in pigs was at the same level as in 2007. The number of pigs produced increased by 3%, but because the export of pigs at app. 30 kg (15-50 kg) increased by 40%, the number of pig produced to slaughter weight in Denmark was reduced by 3%. Adjusting for increased export, the consumption per pig produced increased by 1.9 % in 2008. The use of cephalosporins for pigs decreased by 0.8% in 2008, after a 5-fold increase from 2001 to 2007. The consumption of cephalosporins in sows and piglets was unchanged, and a large part of the piglets may still be treated with cephalosporins.
In 2007, the most commonly used aminoglycoside drug was taken off the market, resulting in a 99.7 % decrease in consumption of neomycin and consequently, an 85% decrease in consumption of aminoglycosides from 2006–2008. Concurrently, the major aminoglycoside for oral use in weaners changed from neomycin in 2006, to apramycin in 2008; the use of apramycin increased by 24% in 2008 compared with 2006. In 2008, this was reflected in the occurrence of neomycin and gentamicin/apramycin resistance in Salmonella from pigs and pork.

Antimicrobial consumption in humans

From 2007 to 2008, the overall consumption of antibacterial agents for systemic use in humans in Denmark decreased by 0.3% to 35.5 million DDDs or when expressed in DDDs per 1,000 inhabitants per day (DID) by 1.1% to 17.7 DID.

Primary health care sector: In 2008, the overall consumption of antibacterial agents for systemic use (J01) in the primary health care sector expressed in DID decreased from 16.2 to 15.9 (1.6%) compared with 2007. This was the first time since 1999 that the overall consumption decreased. However, the decrease in total consumption was due to a reduction in only three antibacterial groups (beta-lactamase sensitive penicillins (reduction of 0.37 DID), macrolides and short-acting sulfonamides). In most other groups consumption increased: e.g. tetracyclines, combinations of penicillins, including beta-lactamase inhibitors, and fluoroquinolones.
Beta-lactamase sensitive penicillins still represented the largest group of antibacterial agents consumed (33% of the total consumption) followed by penicillins with extended spectrum (20%) and macrolides (15%). Overall, antibacterial consumption expressed in DID increased by 31% during 1999–2008.
In 2008, 308 out of 1,000 Danes received at least one prescription of antibacterial agents in primary health care. In comparison, 320 out of 1,000 Danes received at least one prescription in 2007.
Hospital sector: The overall consumption (J01) expressed in DDDs per 1,000 occupied bed-days (DBD) increased by 7% (from 699.4 to 749.2 during 2007–2008). When expressed as the number of DDDs per 1,000 discharged patients it increased from 2,887 to 3,055 during 2007–2008 (6%).
The consumption of all the major antibacterial groups increased with the exception of beta-lactamase sensitive penicillins and aminoglycosides. Several broad-spectrum antibacterial agents increased considerably: cephalosporins (9.9%), carbapenems (27.7%) and fluoroquinolones (17.4%), respectively. Cephalosporins accounted for 20% of the total consumption in the hospital sector. Penicillins with extended spectrum (19%), beta-lactamase sensitive penicillins (13%) and fluoroquinolones (13%) were other major contributing antibacterial groups.
The reported antibacterial consumption from the hospital sector was higher than expected whether expressed as DBD or DDDs per 1,000 discharged patients. An important factor was a general hospital strike during the spring of 2008 that led to fewer discharges and occupied bed-days, but presumably only to a minor decrease in the consumption of antibacterial agents (DDD).

Resistance in indicator and zoonotic bacteria

Animals

The most prevalent ***Salmonella* Typhimurium** phage type in Danish pork and Danish pigs was DT120, followed by DT12. Among *S.* Typhimurium isolates from Danish pigs, the occurrence of gentamicin and ampicillin resistance has increased significantly from 2007 to 2008. Resistance to ampicillin has been increasing continuously since 2001. A 24% increase in apramycin consumption in pigs from 2006–2008 has likely been driving the increase in gentamicin resistance. A significant decrease in neomycin and spectinomycin resistance was observed in *S.* Typhimurium from Danish pigs, likely associated with a

99.7% decrease in neomycin consumption from 2006 through 2008 and a 30% decrease in spectinomycin consumption from 2004–2008.

Among ***Campylobacter jejuni*** isolates from Danish broilers, the highest level of resistance in the panel was found for ciprofloxacin and nalidixic acid (both 12%). Among the antimicrobial groups in the panel, fluoroquinolones were the most commonly used until 2006. From 2007 to 2008, no significant changes in resistance were observed among *C. coli* from pigs or *C. jejuni* from Danish broilers.

For indicator ***E. coli*** isolates obtained from broiler and cattle, no statistically significant changes in the level of resistance were observed from 2007 through 2008. A significant decreasing trend in resistance to tetracycline, ampicillin and sulfonamides in *E. coli* from cattle at slaughter was observed from 2004 to 2008, concomitant with a decreasing consumption of tetracyclines, aminopenicillins and sulfonamides by 8%, 47% and 16% respectively.
For pigs, the highest frequency of resistance in indicator *E. coli* was found for tetracycline (30%) which parallels a high consumption of tetracyclines in the pig production. In 2008, the resistance to tetracycline in indicator *E. coli* did not increase significantly. In 2008, the level of resistance to streptomycin and spectinomycin in indicator *E. coli* from pigs decreased significantly, while the consumption of spectinomycin in pigs has decreased more than 30% since 2004.

For both ***Enterococcus faecium*** and ***Enterococcus faecalis*** isolates, the highest prevalence for antimicrobial resistance were observed among isolates of pig origin; most prevalent was resistance towards tetracycline (61% and 84% respectively), erythromycin (32% and 40% respectively) and streptomycin (43% and 28%, respectively). Tetracyclines and macrolides have been the major antimicrobial agents in pigs the last decade, while streptomycin has been an important drug in the pig production for decades. From 2007 through 2008, a statistically significant reduction in prevalence of macrolide resistance was observed in *E. faecium* isolates of pig origin most likely as a result of a reduction in usage of macrolides by 6% in the same time period.

For *E. faecium* from broilers, only salinomycin resistance (65%) had statistical significantly higher prevalence compared to pig isolates. Ionophores (salinomycin and monensin) are the major coccidiostats used in the broiler production. For *E. faecalis* isolates from pigs, a statistical significantly higher prevalence was found for resistance to tetracycline, chloramphenicol, erythromycin and streptomycin as compared to isolates from broilers. As in previous years, no resistance towards vancomycin was detected.

Meat

The occurrence of resistance in ***Salmonella* Typhimurium** to ampicillin, chloramphenicol, florfenicol, spectinomycin, streptomycin, sulfonamide, tetracyclines, trimethoprim was higher in imported pork as compared to Danish produced pork. In 2008 resistance to cephalosporins in *S*. Typhimurium was observed for the first time in Danish pork. The meat type with the highest occurrence of resistance was imported turkey meat, from which all *S.* Typhimurium isolates were resistant to tetracycline and sulfonamides. Fluoroquinolone resistance was statistically significant higher in *S.* Typhimurium obtained from imported turkey meat when compared to *S*. Typhimurium obtained from the other meat types tested, with more than 1/3 of the isolates resistant. Also resistance to 3rd generation cephalosporines was high (6.9%) compared *S*. Typhimurium obtained from other types of meat.
***Salmonella* Enteritidis** was only obtained from imported broiler meat. Among the tested isolates 37% were resistant to nalidixic acid/ciprofloxacin and 7% were ceftiofur and cefotaxime resistant.

Imported broiler meat contained ***C. jejuni*** with statistically significantly higher levels of resistance to ciprofloxacin, nalidixic acid and tetracyclines when compared to *C. jejuni* from Danish broiler meat.

For indicator ***E. faecium,*** statistically significant higher prevalence for resistance to tetracycline, penicillin, ampicillin, erythromycin and streptomycin and lower prevalence for resistance to salinomycin was found among isolates from imported broiler meat when compared to Danish broiler meat.
For indicator ***E. faecalis*** from imported meat statistically significant higher prevalences for resistance to tetracycline, chloramphenicol, erythromycin, kanamycin and streptomycin was found in imported broiler meat when compared to Danish broiler meat while only statistically significant higher prevalences of tetracycline resistance was observed in imported pork meat.
For indicator ***E. coli*** the occurrence of resistance to tetracycline, chloramphenicol, ampicillin, cefoxitime, ceftiofur, sulfonamides, trimethoprim, neomycin, spectinomycin, streptomycin, ciprofloxacin, and nalidixic acid was higher in imported broiler meat when compared to Danish produced broiler meat.

Humans

The ***S.* Typhimurium** situation was rather unusual in 2008 as several large outbreaks occurred, accounting for 76% of all human *S.* Typhimurium isolates.
The resistance pattern found in domestically acquired human isolates of *S*. Typhimurium was more like the pattern in Danish pork than the pattern of imported pork.
The occurrence of resistance to ampicillin, chloramphenicol, cefotaxime, tetracycline, sulfonamides, spectinomycin, streptomycin and ciprofloxacin was significantly higher in S. Typhimurium isolates from patients with travel associated infections compared to domestically acquired infections (whether compared to all domestically acquired isolates or without major outbreaks).
The occurrence of resistance to ciprofloxacin and nalidixic acid was significantly higher in travel associated human ***S.* Enteritidis** isolates as compared to domestically acquired isolates.
The occurrence of resistance to ciprofloxacin, nalidixic acid, streptomycin and tetracycline was statistically significantly higher in travel associated ***C. jejuni*** isolates compared to isolates acquired domestically.
When comparing ***E. faecium*** isolates from imported broilermeat with isolates from army recruits statistically significantly higher occurrence of resistant were observed for tetracycline, ampicillin, erythromycin, streptomycin, avilamycin, while lower prevalence was found for salinomycin in *E. faecium* isolates from imported broiler meat.
When ***E. faecalis*** isolates from meat were compared with *E. faecalis* isolates from army recruits statistically significantly higher prevalence was only found in imported broiler meat for tetracycline, erythromycin, kanamycin and streptomycin.
The occurrence of resistance among the ***E. coli*** isolates from the army recruits was not significantly different from the occurrence in *E. coli* isolates obtained from Danish meat or imported meat. Third generation cephalosporin resistant *E. coli* was detected in samples from army recruits. This is the first time, 3rd generation cephalosporin resistance has been reported in E. coli obtained from faecal samples from humans in the community in the DANMAP reports.

Resistance in bacteria from diagnostic submissions from animals

For *E. coli* F5 (K99) from diagnostic submissions from cattle, a significant decrease in resistance to tetracycline, sulphonamide and streptomycin was observed from 2004/2005 through 2008.
Resistance to ceftiofur was also observed for 2 isolates of *E. coli* F5 (K99) in 2008 (4.2%), and resistance to cefotaxime was observed in 6.7% of the isolates.
In 2008, 60% of the *E. coli* O149 isolates were resistant to tetracycline, and of these, 94% were mulitresistant.
In 2008, the occurrence of neomycin resistance in *E. coli* O149 from pigs decreased to 18% from 33% in 2007. From diagnostic submissions from pigs, 2 isolates of *E. coli* O149 (2.9%) were resistant to ceftiofur (and to cefotaxime) in 2008, which has not been observed in previous years. The use of third and fourth generation cephalosporins in pigs has been increasing significantly from 2001 to 2007 (by 374%), and stayed at the 2007 level in 2008.

Resistance in bacteria from diagnostic submissions in humans

Data on antibiotic resistance in bacteria from diagnostic submission is gathered by voluntary reporting from the DANRES group which covers the departments of clinical microbiology (DMC's) in Denmark. The only exceptions are methicillin resistant *Staphylococcus aureus* and invasive *Streptococcus pneumoniae* that are notifiable. Data on these bacteria are obtained from the reference laboratories at SSI.

Among ***E. coli*** blood isolates, the frequency of resistance in 2008 was not statistically different from 2007, for all the tested antimicrobial agents (Ampicillin, gentamicin, mecillinam, nalidixan acid, ciprofloxacin). However, in this DANMAP report resistance to 3rd generation cephalosporins (reported as ceftazidime, ceftriaxone, cefpodoxime or cefotaxime) and carbapenems was reported for the first time. Four percent of the isolates were resistant to 3rd generation cephalosporins and less than 1% of the isolates were resistant to carbapenems.

In ***E. coli*** urine isolates obtained from primary health care and hospitals, resistance to ciprofloxacin, nalidixic acid and mecillinam increased significantly in 2008.

***Clostridium difficile* 027** is emerging in Danish hospitals. The CD027 strain is resistant to the newer fluoroquinolones. It has been suggested that this may be the main reason for its wide dissemination.

In this DANMAP report resistance in ***Pseudomonas aeruginosa*** isolates obtained from blood infections was reported for the first time. The levels of resistance were low for all the tested antimicrobial agents.

Resistance to penicillins and erythromycin in ***Streptococcus pneumoniae***, **Group A, B, C** and **G streptococci** remained low in 2008.

Resistance to ampicillin was high (87%) in ***E. faecium*** isolates from blood cultures, whereas less than 1% of the ***E. faecium*** and ***E. faecalis*** blood isolates were vancomycin resistant. Only one of the DCMs tested all enterococci from blood infection for high level gentamicin resistance. Here 36% of tested *E. faecalis* isolates were HLGR as were 58% of the tested *E. faecium* isolates. The numbers of *E. faecium* isolates had increased from 137 in 2002 to 369 in 2008 (reported from 11 of the DCMs). 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 years.

A total of 1,344 cases of ***Staphylococcus aureus*** bacteraemia were reported in 2008. This is at the same level as the previous years. The number of methicillin-resistant *S. aureus* (MRSA) bacteraemia cases increased from 8 in 2007 to 17 in 2008 (1.3%) which is similar to the years before. The frequency is very low compared to other countries in Europe. Resistance towards other tested antimicrobial agents has not changed significantly in recent years.

The number of new **MRSA** cases increased to 854 in 2008 (from 706 in 2007 and 659 in 2006). The increase was partly due to outbreaks in three neonatal wards and an extended screening at a congress for pig producers. Of all human MRSA cases, 130 (15%) were imported from abroad, 140 (16%) were acquired at hospitals, 114 (13%) infections were hospital associated, community onset while the remaining cases were community acquired. The prevalence of resistance in 2008 was at the same level as in 2007 with the exception of erythromycin resistance which decreased from 48% in 2007 to 31% in 2008. The decrease may partly be explained by a decrease in numbers of spa type t024 where a large proportion is resistant to erythromycin. A large difference in resistance prevalences was recorded between *spa* types. Types like t189 which often are acquired in hospitals demonstrated the highest resistance prevalences while community acquired types as t015 and t019 were sensitive to most antimicrobial agents, except for beta-lactams. Variations in resistance prevalences were also recorded for certain *spa* types. Resistance towards norfloxacin increased for *spa* type t008, the most prevalent in both years, from 29% in 2007 to 57% in 2008. The increase of MRSA cases in 2008 is a matter of concern after two years of decreasing numbers. The future development will be followed closely.

Increased occurrence of resistant *Klebsiella pneumoniae* in Danish hospitals

Klebsiella pneumoniae is a part of the flora in the human intestine, but is often causing extra-intestinal infections such as urinary tract-, respiratory tract-, wound- and bloodstream infections. Many of these infections are hospital acquired and can be life threatening, especially if the strains are resistant to antimicrobial agents. *K. pneumoniae* is intrinsically resistant to aminopenicillins (e.g. ampicillin). Therefore, infections caused by *K. pneumoniae* are treated with broad spectrum antimicrobial agents such as ciprofloxacin, gentamicin and cephalosporins. Previously, data on *K. pneumoniae* have not been included in the DANMAP reports but have been reported to EARSS — the European Antimicrobial Resistance Surveillance System. Until 2007, the occurrrence of resistance was low and at the same level as the other Nordic countries reporting resistance among *K. pneumoniae* isolates from bloodstream infections to EARSS. However, the level of resistance to ciprofloxacin, gentamicin and 3rd generation cephalosporins increased significantly from 2006–2008 (Figure 1). In the same period, the rate of resistance to 3rd generation cephalosporins has increased from 4.4% to 10.8% and was at the same level as reported for some South European countries [EARSS 2007, http://www.rivm.nl/earss/result/Monitoring_reports]. In 2006, 1.0% of the isolates were multi-resistant (3rd gen. cephalosporins, gentamicin, ciprofloxacin) and this occurrence increased to 5.3% in 2008. The level of resistance differed among the Departments of Clinical Microbiology, where rates of up to 24% of the *K. pneumoniae* isolates were reported multi-resistant from a few laboratories. Third generation cephalosporin resistance in *K. pneumoniae* is usually encoded by acquired beta-lactamases with hydrololytic activity against extended spectrum cephalosporins of the types $ESBL_A$ or $ESBL_M$ [Giske *et al*. 2009 J. Antimicrob. Agents 63:1-4].

The increased frequency of resistance in *K. pneumoniae* blood isolates parallels the increased consumption of broad spectrum antimicrobial agents (Figure 2). Especially the 2nd generation cephalosporins have increased, from 70.6 DDD/1,000 occupied bed-days in 2004 to 133.8 DDD/1,000 occupied bed-days in 2008. The emergence of multi-resistant *K. pneumoniae* as well as other ESBL-producing bacteria has led to an increased use of carbapenems, which has increased from 8.6 DDD/1,000 occupied bed-days in 2004 to 27.2 DDD/1,000 occupied bed-days in 2008. In one hospital, the consumption of carbapenems was 172 DDD/1,000 occupied bed-days in 2008. This means that more than every 6th patient was treated daily with a carbapenem at this hospital in 2008. Another possible explanation for the increased number of multi-resistant *K. pneumoniae* is outbreaks. During the spring and summer of 2007, an outbreak of gentamicin- and ciprofloxacin-resistant ESBL-producing *K. pneumoniae* (EpiKpn) was reported from North Zealand hospitals [Hansen and Frimodt-Møller, EPI-NEWS No. 11 2008]. The same clone of *K. pneumoniae* was reported from other hospitals on Zealand in 2008 [Ole Heltberg, personal communication]. In Denmark, it is not mandatory to report findings of ESBL-producing or multi-resistant bacteria, and there is no continuous national outbreak surveillance on ESBL-producing bacteria. Therefore, it is not possible to interpret how and when these bacteria have spread from one hospital to the other.

Perspectives:

The increased consumption of broad spectrum antimicrobial agents, especially 2nd and 3rd generation cephalosporins, is associated with the development of cephalosporin resistant *K. pneumoniae* in Denmark. Occurrence of these resistant bacteria has led to consumption of even more broad-spectrum antimicrobial agents e.g. carbapenems. Therefore, surveillance of the consumption of broad spectrum antimicrobial agents is essential, including both local and national monitoring. Furthermore, guidelines for treatment of infections in hospitals should be revised to curb the increasing consumption of especially 2nd generation cephalosporins. A national outbreak surveillance of resistant bacteria, using typing and epidemiology data, is needed to improve the understanding of the spread of ESBL-producing *K. pneumoniae* and other resistant bacteria. In the case of an outbreak of resistant bacteria, infection control guidelines have to be followed to minimize the spread of resistant bacteria from patient to patient and between hospitals.

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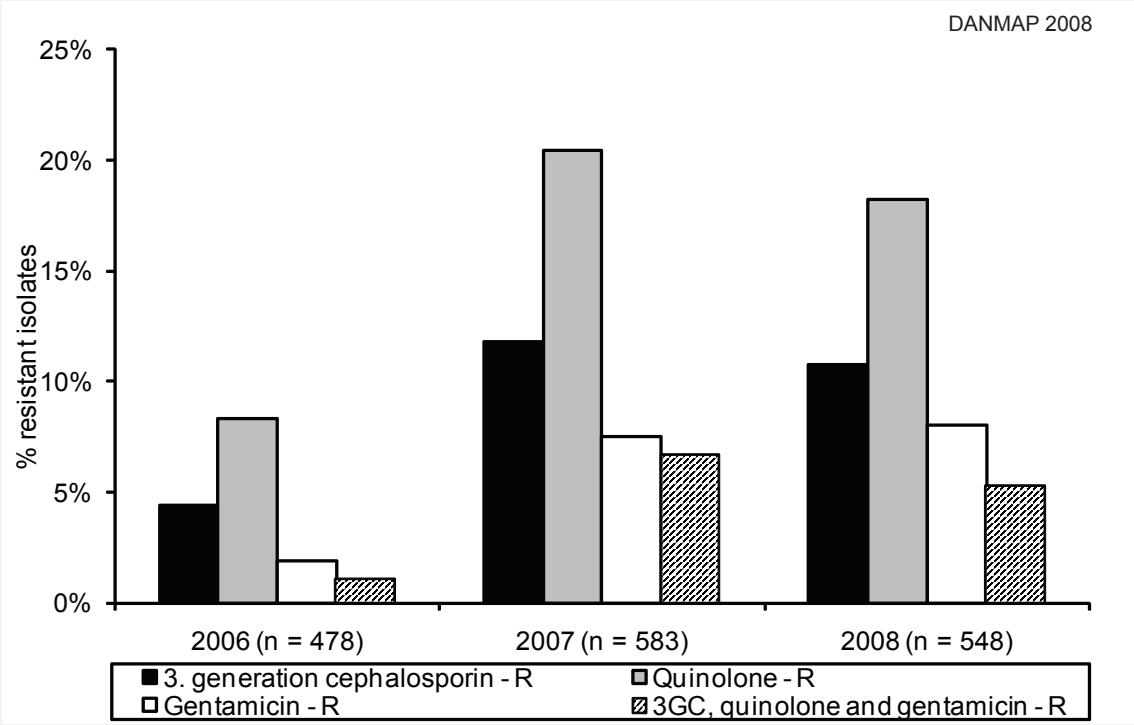

Figure 1. 3. generation cephalosporin, quinolone and gentamicin resistant Klebsiella pneumoniae *from blood 2006–2008. Data from 8 out of 14 DCMs covering 57.6% of the Danish population*

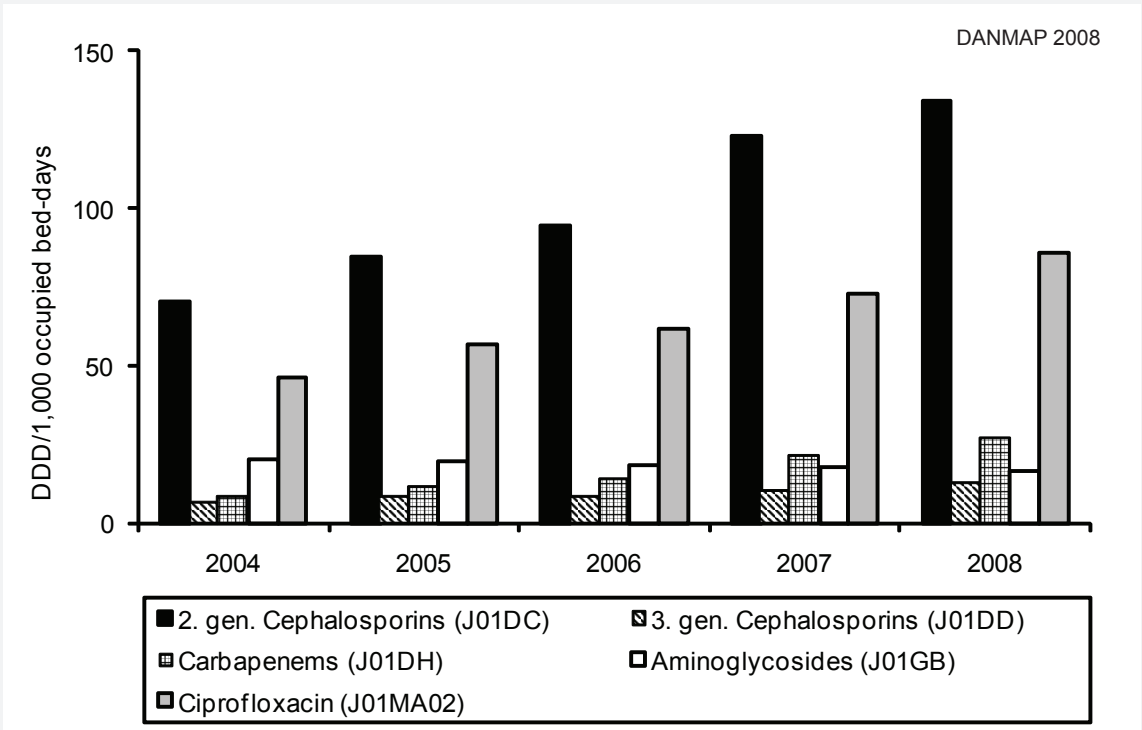

Figure 2. Consumption of major cephalosporins, carbapenems, aminoglycosides and ciprofloxacin by year in hospitals, Denmark

Patterns in consumption of tetracyclines, macrolides and pleuromutilins in weaning pig herds, associated with the increasing consumption of tetracyclines, 2003–2008

In Denmark, antimicrobial use is legal only for treatment of disease and not for growth promotion or prophylactic treatment. Patterns indicating systematic use may imply non-prudent use, such as prophylactic use, or treatment without consideration to guidelines regarding choice of antimicrobial substance.
During 2001 through 2008, the overall antimicrobial consumption in the pig production increased by 19% (24%, when adjusted for increasing export, see chapter on antimicrobial use), measured in ADD_{kg} per pig produced. This increase was primarily associated with an increasing consumption of tetracyclines for oral use. From 2003 through 2008, the consumption of tetracyclines increased by 118 % per weaning pig and 60% per finisher pig. In 2008, the consumption of tetracyclines in weaning pigs comprised 50% of the overall consumption of tetracyclines in pigs, while the consumption in finishers amounted to 37%.
The major antimicrobial class used in pigs before 2006 was macrolides. From 2006 and 2007, macrolides became second to tetracyclines, while pleuromutilins (mainly tiamulin) continued to be third. From 2007 to 2008, the consumption of pleuromutilins for weaning pigs and sows increased by 35%, while the consumption in finishers increased by 60% and became the second most used antimicrobial class after tetracyclines. This increase was temporally associated to a price reduction in some tiamulin drugs for oral use, making tiamulin pricewise competitive to macrolides and tetracyclines[1]. From 2007 to 2008, the consumption of macrolides in pigs decreased by 5.6% (3.4% adjusted) per pig produced.
In the following, the prescription patterns of tetracyclines for oral use in weaning pigs are compared to prescription patterns for macrolides and pleuromutilins for oral use. In addition, prescription patterns associated with the national increase in consumption of tetracyclines are identified.

Material and methods

Herds were identified by the CHR ID (identity number in the Central husbandry Register), identifying the geographic concentration of the herd. Data on use of antimicrobial agents on herd level were extracted from VetStat (www.vet.dtu.dk). Data on herd ownership were extracted from the CHR register. Data on herd size (pigs produced August 1st. 2007-July 31 st. 2008) were provided by the Danish Plant Directorate, where the number of animals are registered annually as part of the manure and husbandry account (GHI). For each antimicrobial agent and age group investigated, four prescription patterns were defined as 1) 1–3 prescriptions, 2) 4–6 prescriptions 3) 7–9 prescriptions and 4) 10 or more prescriptions per year per herd. The analyses of prescription patterns were performed for weaning pig (7.5 – 30 kg) and finisher pigs (30 kg to slaughter) separately.
The prescription pattern may give indication whether antimicrobial agents are prescribed for acute disease (few prescriprions per year) or whether antimicrobial agents are given more systematically (prescriptions of the same amounts and drugs consecutively over an extended period), possibly for continuous disease problems in the herd.

Results and discussion

A common trend for all three antimicrobial classes was a decrease in the number of weaning herds with prescription pattern 1. This may be partly explained by closure of many of the small herds the past years; e.g.11% of the herds receiving 1–3 prescriptions of tetracyclines for weaners in 2005, were no longer active in 2008 (Figure 3).
The number of weaning herds treated with tetracyclines increased from 2270 to 2509 herds (11%) during 2003–2008 (Figure 3). In the same period, the number of herds with prescription pattern 3 and 4 increased by 49% and 218%, respectively. The amount of tetracyclines used in herds with prescription pattern 4, increased dramatically (402%) during the same period, while the consumption in herds with the other prescription patterns increased more moderately: pattern 1, 20%; pattern 2, 45%; and pattern 3, 100% (Figure 4). The increases were particular high during 2005–2007.

Legally, the prescribed antimicrobial agents should be used with herd (CHR ID) for which it is prescribed. However, a potential bias to this study may occur if an owner of two or more weaning herds (CHR IDs) receives all antimicrobials

[1] Development in antibiotic consumption, expenses and prices for prescription veterinary medicine for production animals from April 1, 2005 to April 2008, Report of December 15, 2008 to the Ministry of Health; The Danish Medicines Agency, the Danish Veterinary and Food Administration and the Technical University of Denmark, 2008''
[In Danish. "Notat af 15. december 2008 til Ministeriet for Sundhed og Forebyggelse om udviklingen i forbrug, udgifter og priser for receptpligtig veterinær medicin til produktionsdyr fra 1. april 2005 til 1. april 2008 udarbejdet af Lægemiddelstyrelsen og Fødevarestyrelsen med bidrag fra DTU"]

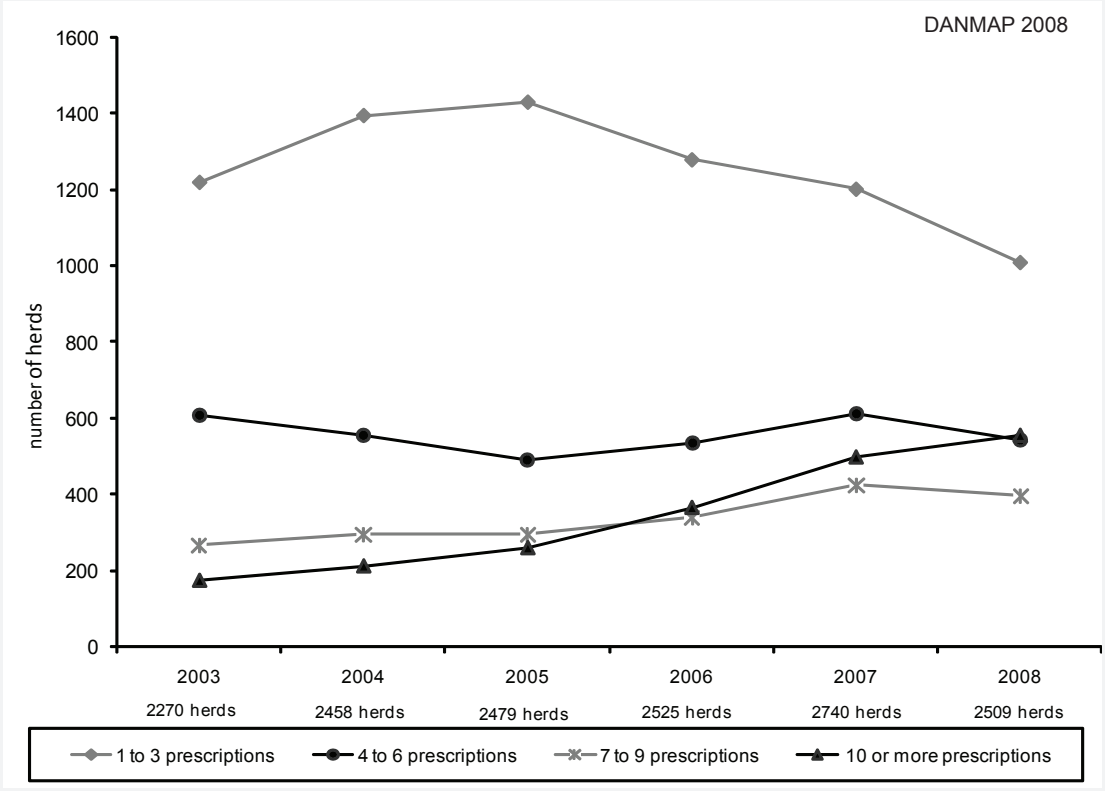

Figure 3. Number of herds using tetracycline drugs for oral use in weaning pigs, grouped by number of prescriptions per herd per year, Denmark 2003-2008
The total number of herds (N) receiving tetracyclines for oral use is shown below the x-axis.

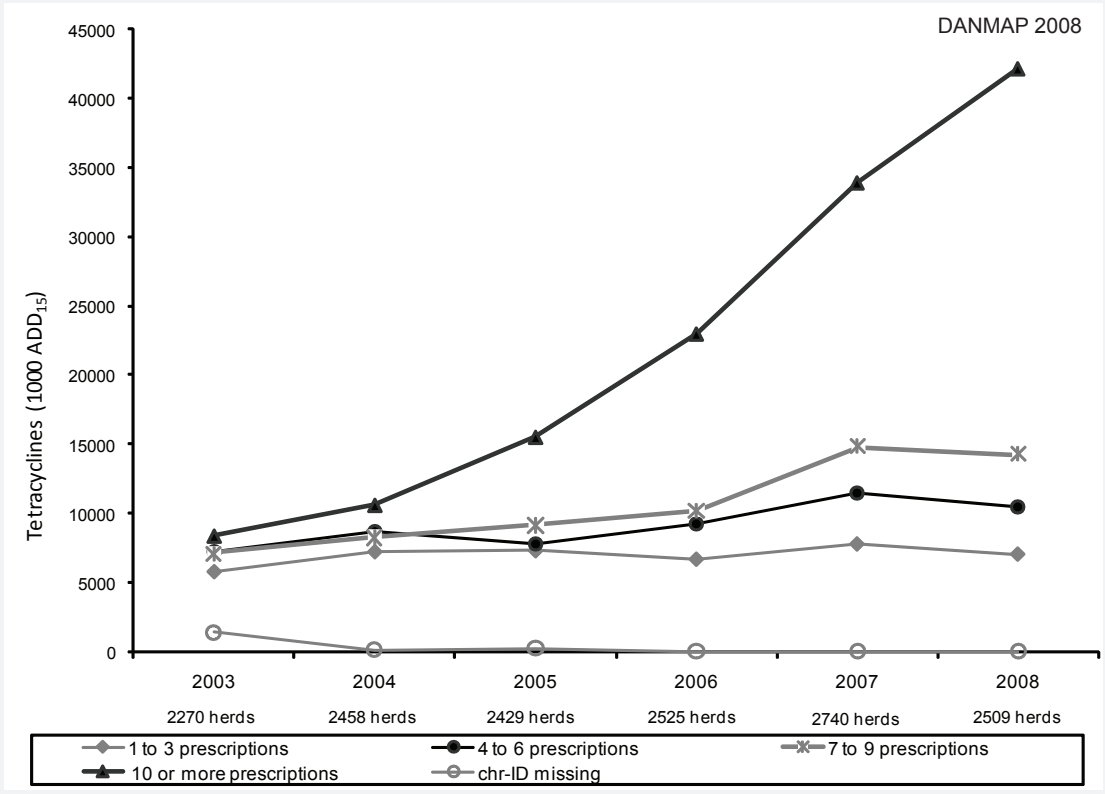

Figure 4. Amounts of tetracylines for oral use in weaning pig herds, grouped by number of prescriptions per herd per year, Denmark 2003-2008

agents for part of his CHR IDs, and distribute it to the rest of the CHR IDs. Furthermore, the owner may buy more herds during the study period, but still receive the antimicrobial agents on the same CHR IDs respresenting a limited part of his stock. Ownership was analyzed for weaning pig herds with prescription pattern 4 in 2008.The full dataset of 557 herds was reduced to 504 herds by omitting herds for which the owner had more than one herd and more than 10% of his weaning pigs were housed on CHR IDs for which tetracyclines were not prescribed in 2008. From 2003 through 2008, the national consumption of tetracyclines in weaning pigs (7-30 kg) increased by 45.9 million ADD_{15}, mainly for oral use (44.1 million ADD_{15}). In the subpopulation comprising 504 herds, with prescription pattern 4 in 2008, the consumption of tetracyclines for oral treatment increased by 33.6 million ADD_{15} (Figure 5). Thus, at least 76% of the national increase in consumption of oral tetracyclines for weaning pigs from 2003–2008 may be attributed to the herds in prescription group 4 in 2008. The increase in oral consumption of tetracyclines in these 504 herds amounted to 55 % of the national increase from 2003–2007 and 51% of the national increase, 2003–2006. Thus, a large part of the national increase from 2003–2008 was due to persistant problems in a limited number of herds, rather than acute problems in an increasing number of herds.

Figure 6 shows that the majority of the 504 farms (78%) used only one or two different medicinal specialties containing tetracyclines for oral use, but these were prescribed 10-24 times per year. Figure 7 shows that 73% of the farms received one to four different combinations of amount and ATCvet code, distributed on 10–24 prescriptions received in 2008. In most cases, the farms received the same amount of one antimicrobial item on most of the prescriptions, and occasionally received half or double of the most frequent amount. These findings support that for most of the 504 farms, the prescriptions may be annotated as systematic.

Within the 504 herds, the number of weaning pigs was given for 450 of the herds (mean herd size 2,100 weaned pigs). In these herds, the consumption of tetracyclines for oral use was an estimated 5.5 ADD_{15} per weaning pig produced, a 150% higher than the 2.2 ADD_{15} per weaning pig produced in other herds at the national level (excluding the 450 herds from the National mean). The total antimicrobial consumption in the 450 herds was 8.6 ADD_{15} per pig produced, or an estimated 15% higher than the 7.5 ADD_{15} per weaning pig produced in other herds at the National level (uncertainty regarding animal numbers on farm). The 450 herds produced 21% of the weaned pigs produced in Denmark and consumed 23.5% of the National consumption of antimicrobial agents in weaning pigs, and 40% of the tetracyclines used in weaning pigs. In relation to these comparisons, it should be noted that not all herds with systematic use are excluded from the national mean in other herds; furthermore, other herds may have systematic use of other antimicrobial agents.

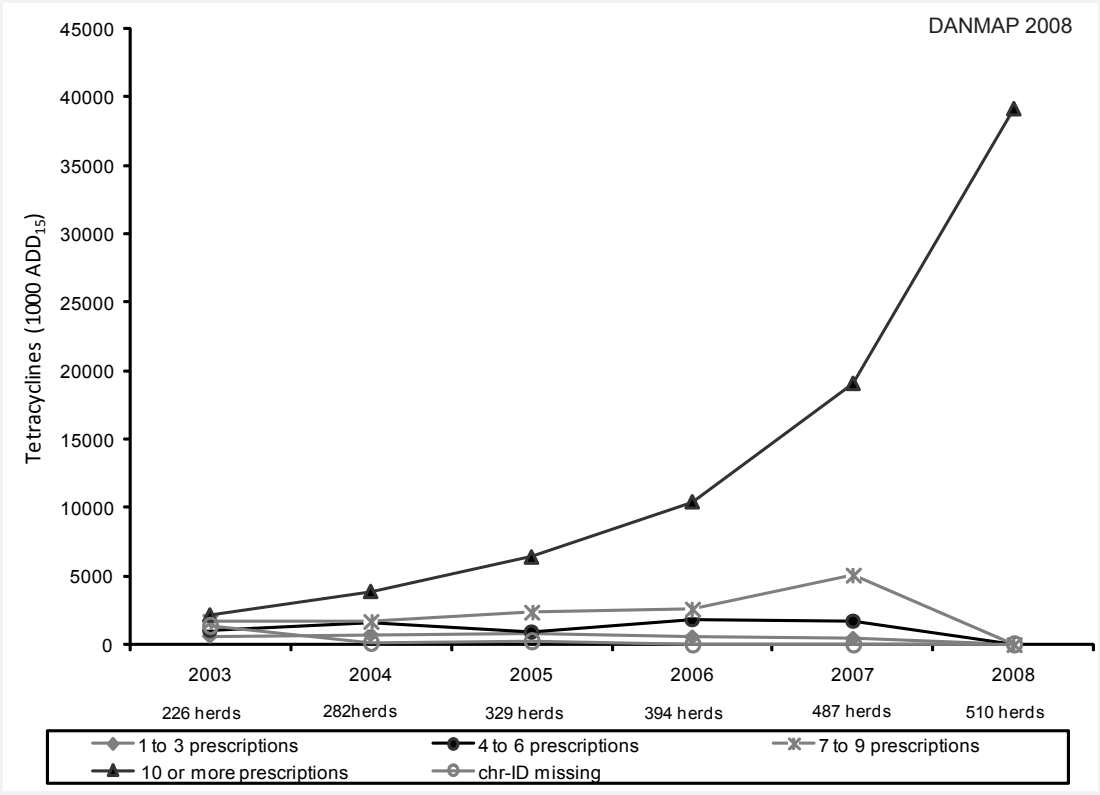

Figure 5. Amounts of tetracylines for oral use in a subpopulation[a] of weaning pig herds, grouped by number of prescriptions per herd per year, 2003-2008

a) 504 herds receiving 10 or more prescriptions in 2008, and owner reporting on all his CHR numbers. 9 of the herds did not house pigs in 2003.

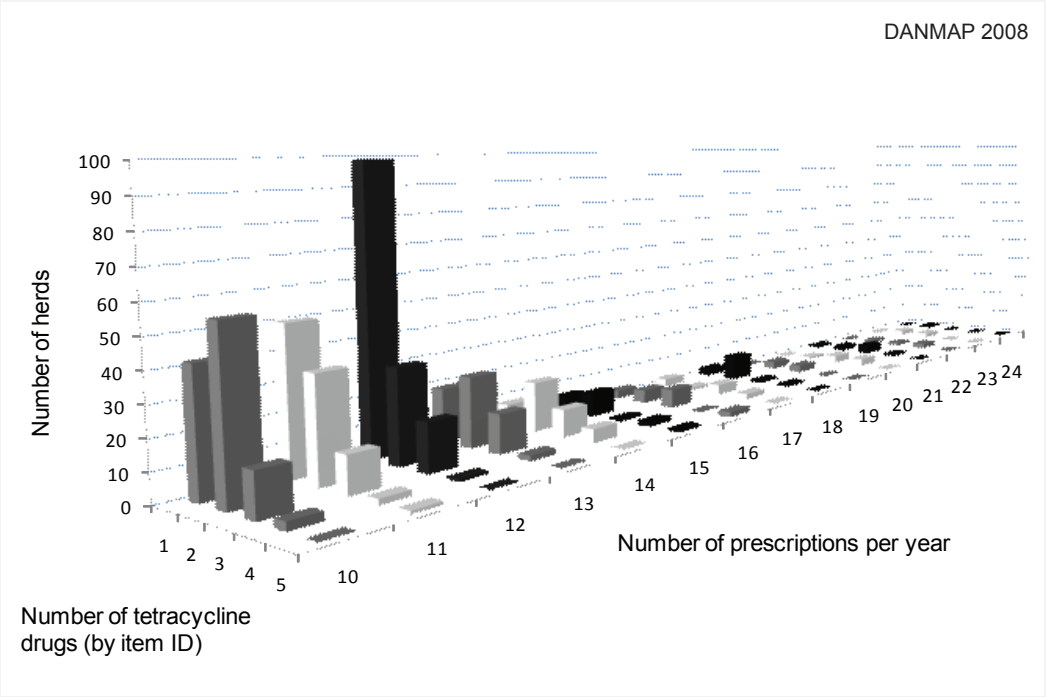

Figure 6. Number of different tetracycline drugs for oral use prescribed and number of prescriptions for a subpopulation[a] of 504 weaning pig herds, 2008
a) receiving 10 or more prescriptions in 2008
Drug items (package types) within ATCvet class QJ01AA for oral use are included

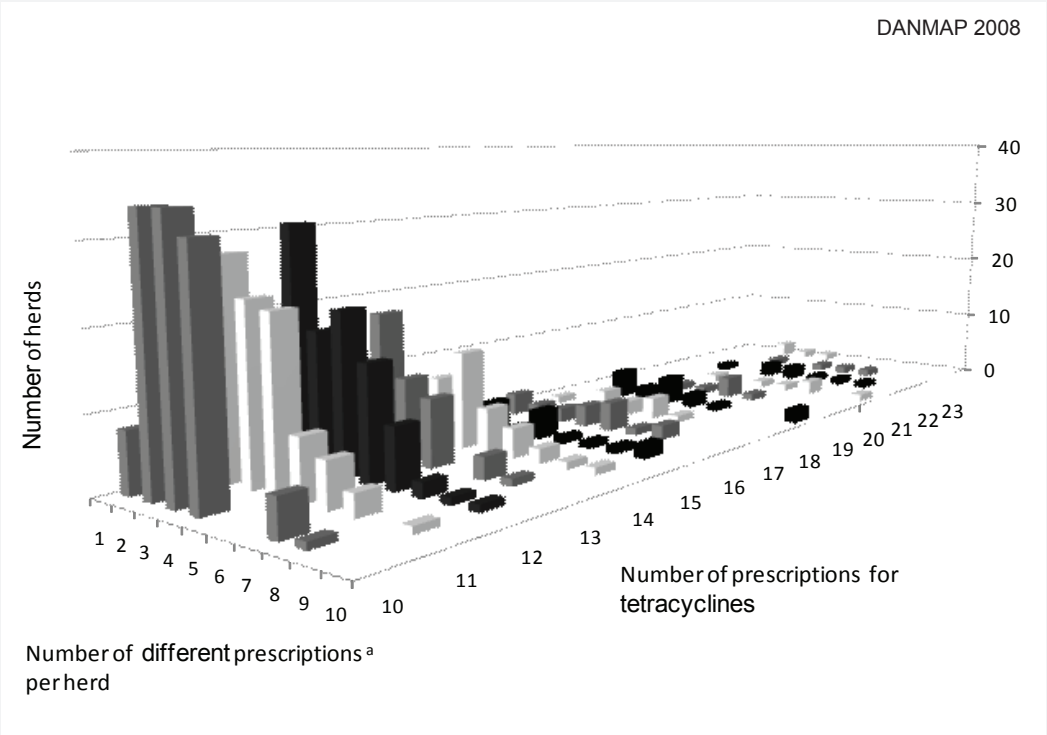

Figure 7. Variation in prescriptionsa of tetracycline agents for oral use in a subpopulation[b] of 504 weaning pig herds in 2008
a) Prescriptions are defined as "differing" if the prescribed amount or ATCvet code differs on the prescriptions for the specific herd. The substances (ATCvet level 5) included are chlortetracycline, doxycycline and oxytetracycline for oral use
b) receiving 10 or more prescriptions in 2008

Of the 504 herds receiving frequent prescription of oral tetracyclines in 2008, 8 % also received prescription of macrolides for oral treatment 10 or more times in 2008, and the number of herds with prescription pattern 4 for macrolides had not been decreasing in the previous years. However, among the 504 herds, the number of herds, receiving 1-3 prescriptions of macrolides per year for oral treatment has been decreasing since 2005. These findings indicate that the increase in use of tetracyclines among these herds was not due to substitution of macrolides by tetracycline, but it may be associated with a lesser varied prescription pattern.
The prescription patterns for macrolides (2003–2008) for all Danish weaning herds are shown in Figure 51 and 52 (Appendix 1). As for tetracyclines, the number of herds receiving 1–3 prescription was decreasing. For prescription patterns 2 and 3, the number of herds and consumption was almost unchanged over time. For prescription pattern 4, the number of herds increased by 151% and the consumption increased by 147% during 2003 through 2008, with a temporary decrease in 2006.
From 2004 through 2007, the overall consumption of pleuromutilins in weaners decreased by 9.3%, while the number of weaning herds receiving pleuromutilins decreased by 38%. These changes were related to a decrease in number of herds with prescription pattern 1 and 2. From 2006 through 2008, a 41% increase in number of herds with prescription pattern 4 occurred, associated with a 99% increase in consumption of pleuromutilins in this prescription group (Figure 53 and 54 in Appendix 1).
For weaning herds with prescription pattern 4 for pleuromutilins in 2008, the increased prescription of pleuromutilins was not associated with changes in prescription patterns for tetracyclines or the consumption of tetracyclines. However, in these herds, the consumption of macrolides decreased significantly by 30% in 2008 compared to 2007, although the number of herds with prescription pattern 4 for macrolides was similar in 2007 and 2008 (9 and 11 herds, respectively).

Conclusions

For both tetracyclines, macrolides and pleuromutilins, there was a trend towards more prescriptions per herd per year. For tetracyclines, this trend was seen throughout the study period with a particularly high increase in number of herds and consumption associated with 10 or more annual prescriptions. For macrolides and tiamulin, the trend was limited to shorter periods. These findings for weaners were much in contrast with the finding in a similar study made for finishers. In particular, for finishers, the national increase in consumption of tetracyclines from 2003 through 2008 was not associated with any particular prescription pattern, except for 2008 when associated with prescription pattern 4. The contrast between findings in weaned pigs and finishers indicates that the increased consumption of antimicrobial agents in herds with prescription pattern 4 among weaning pigs was not due to an increase in herd size on the national level.
From 2003 through 2008, the national consumption of tetracyclines in weaning pigs increased by 45.9 mill ADD_{15} (142%), corresponding to a 118% increase per pig produced. The results from this study indicate that the majority of the increase was associated with weaning pig herds receiving 10 or more prescriptions of tetracyclines (prescription pattern 4) per year. Thus 76% of the national increase in oral consumption of tetracyclines for weaning pigs 2003–2008 may be attributed to the 504 herds in prescription group 4 in 2008 These results indicate that a minor proportion of herds account for a major part of the increase in consumption of tetracyclines from 2003 through 2008. The overall antimicrobial consumption in herds with frequent prescription of tetracycline was an estimated 15% above other herds at the national level, while the use of tetracyclines was an estimated 150% higher than in other herds. The results indicate that a major part of the increase in use of tetracyclines in weaning pigs was could be due to with systematic use, which might indicate non-prudent use.
Further research is needed to elucidate if similar patterns of systematic use occur for other antimicrobial agents in other herds and for other age groups, and to elucidate the significance regarding occurrence of resistance. For macrolides, a 151% increase in herds with prescription pattern 4 was observed from 2003 to 2008. However, this increase rate was much lower than for tetracyclines, where the increase was 402%, 2003–2008.
The consumption of pleuromutilins increased from the 4th quarter of 2007, concomitantly with a reduction of price. The results from this study may indicate that pleuromutilins in some herds have replaced use of macrolides, probably as a consequence the reduction in price for pleuromutilins. The increasing use of tetracyclines in herds with prescription pattern 4 appeared to be associated with a decrease in occasional use of macrolides, suggesting a trend towards a less varied consumption pattern.

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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 2008.

The production of food animals (including animals for live export), meat, and the population of dairy cattle is shown in Table 1. 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. Therefore comparison with production of pork would overestimate the relative antimicrobial consumption, while comparison with number of pigs produced would underestimate the consumption.

Demographic data — New government structure in Denmark

On January 1st 2007, five new regions replaced the counties of Denmark as a result a new local government reform (Figure 8). 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 2 provides information on the distribution of the human population in Denmark and on the Danish health care system by region.

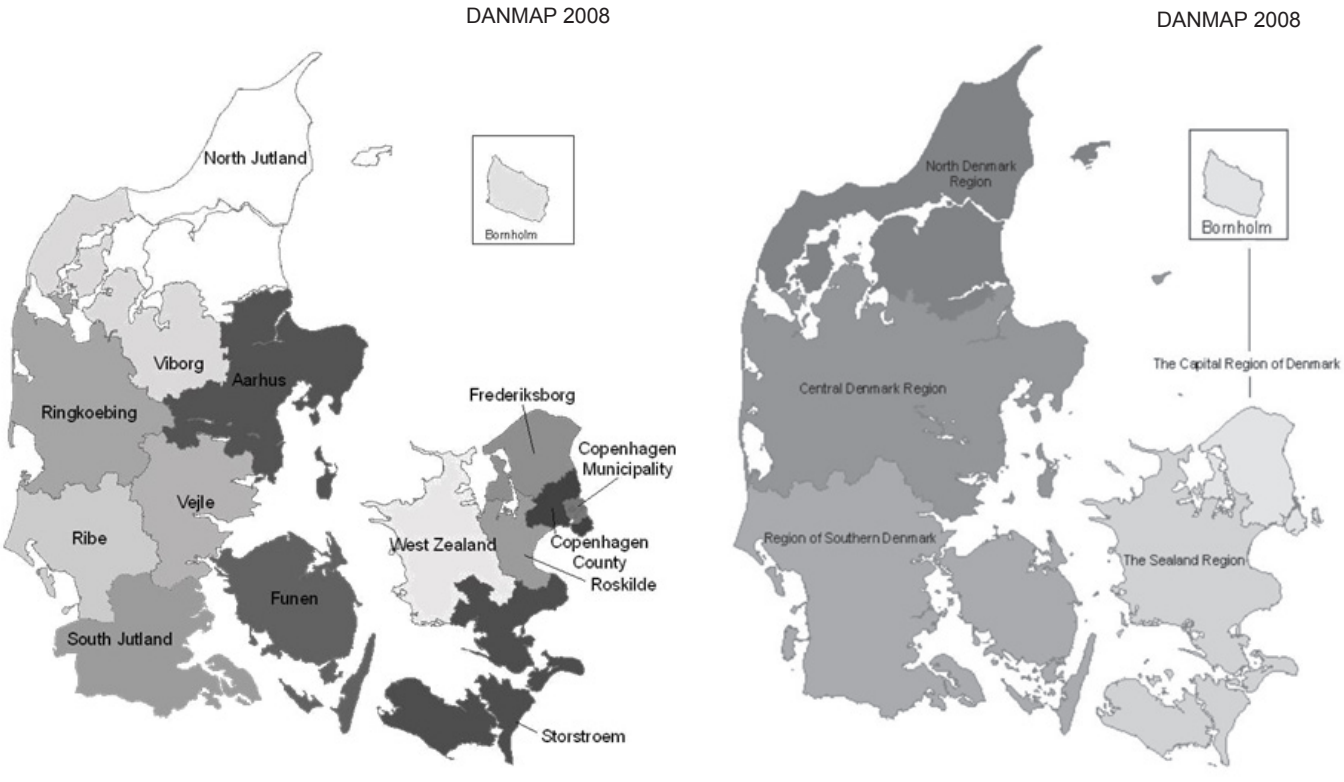

Figure 8. Former counties (left) and new regions (right) of Denmark

Table 1. Production of food animals (including export of live animals) and the production of meat and milk, Denmark

DANMAP 2008

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	122.179	180	1.237	17.4	549	145	559	4.449	25.758	2.720	1.988	31	8
2006	106.182	163	785	11.3	509	140	556	4.492	25.763	3.204	1.957	29	8
2007	107.952	178	1.009	14.4	512	141	545	4.515	26.311	3.522	2.046	31	10
2008	107.595	186	1.068	12,3	511	138	560	4.575	27.078	4.943	1.985	-	-
Increase c) (%)	0	4	6	-14	0	-2	3	1	3	40	-3	-	-

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. These are included in total number of heads, but antimicrobial use after export until slaughter is not registered
c) increase from 2007 to 2008

Table 2. Distribution of the human population and health care structure by region, Denmark

DANMAP 2008

Region name	No. inhabitants	No. inh./km2	No. inh./GP a)	No. bed-days b)	No. discharges b)
The Capital Region of Denmark	1.645.825	643	1.504	1.704.114	401.144
The Sealand Region	819.427	113	1.567	688.884	171.714
Region of Southern Denmark	1.194.659	98	1.488	989.519	248.977
Central Denmark Region	1.237.041	94	1.454	995.516	259.996
North Denmark Region	578.839	73	1.582	500.216	114.426
Denmark c)	5.475.791	127	1.506	4.878.249	1.196.257

a) GP, general practitioner
b) Excluding private hospitals, psychiatric hospitals, specialised clinics, rehabilitation centres and hospices.
c) Compared to the previous year no. discharges have decreased by 1.3%, no. bed-days by 2.5%, and no. inhabitants have increased by 0.5%.

Textbox 1

The impact of a major hospital strike on the number of occupied bed-days and discharges in 2008

Denmark has a universal public healthcare system. The public somatic hospitals of Denmark account for 97–98% of the total hospital consumption and approximately 90% of the total number of bed-days, respectively.

In 2008, twenty-two thousand nurses went on strike in Denmark 16 April–13 June together with healthcare assistants and other medical staff. The strike caused thousands of patients to have their non-acute hospital appointments cancelled. Another 13,000 nurses supported the strike but continued to work to keep emergency healthcare services running.

Since DANMAP started reporting surveillance data, the number of bed-days has continuously decreased while the number of discharges has continuously increased (Table 3). However, in 2008 the number of discharges decreased and the number of bed-days decreased more then the decrease the year before. When the number of bed-days and discharges per weekdays are calculated and separated into three calendar periods (January–March, April–June and July–December) for the years 2006–2008, it becomes apparent that both bed-days and discharges were much lower from April–June 2008 — and in 2008 in total — than the same calendar-period in the years prior to the strike (Table 4).

As hospital consumption is expressed as number of DDDs per 1,000 occupied bed-days or DDDs per 1,000 discharges, it becomes sensitive to changes in these indicators. In general, patients admitted for non-acute purposes would be expected to receive fewer antibacterial agents than acutely admitted patients; however, they would still occupy beds and each would count as one discharge. Therefore, the reported consumption in Danish hospitals in 2008 is presumably higher than if the hospital strike had not occurred. One should keep this in mind when comparing hospital consumption for 2008 to the previous and coming years.

Table 3. Bed-days and discharges in public somatic hospitals, Denmark DANMAP 2008

	Year									
	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Number of bed-days	5.857	5.767	5.709	5.648	5.389	5.240	5.097	5.077	5.005	4.878
Number of discharges	1.104	1.112	1.113	1.126	1.134	1.155	1.171	1.203	1.213	1.196
Bed-days: change compared to previous year	-1.4%	-1.5%	-1.0%	-1.1%	-4.6%	-2.8%	-2.7%	-0.4%	-1.4%	-2.5%
Discharges: change compared to previous year	2.0%	0.8%	0.0%	1.1%	0.7%	1.8%	1.4%	2.7%	0.8%	-1.3%

Table 4. Bed-days and discharges in public somatic hospitals, Denmark DANMAP 2008

		Year		
		2006	2007	2008
January–March	No. of bed-days/weekday a)	20.197	20.054	20.765
	No. of discharges/weekday	4.687	4.760	5.031
April–June b)	No. of bed-days/weekday	22.297	22.119	19.469
	No. of discharges/weekday	5.086	5.262	4.562
July–December	No. of bed-days/weekday	19.619	18.983	18.866
	No. of discharges/weekday	4.698	4.648	4.714
Total	No. of bed-days/weekday	62.113	61.157	59.100
	No. of discharges/weekday	14.471	14.670	14.308

a) Weekdays have better staffing and non-acute activities are carried out; includes Monday–Friday

b) In 2008 nurses and other medical staff went on strike 16 April–13 June. Non-acute hospital appointments were cancelled during this period.

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Antimicrobial consumption

Antimicrobial consumption in animals

In 2008, the total veterinary consumption of antimicrobial substance amounted to 121.6 tonnes, representing a 0.7% decrease relative to 2007. In 2008, the antimicrobial consumption in pigs comprised 80% of the total veterinary consumption, while the consumption in cattle, poultry and aquaculture comprised 12%, 0.5% and 2.8%, respectively. The consumption in other production species and companion animals (pet animals and horses), comprised an estimated 2.5% and 1.9%, respectively.

For production animals, the consumption has increased gradually by 110% from 1998 through 2008 (Table 5). During the same period, the meat production has increased by 32%, from 20.8 billion kg to 27.4 billion kg. In DANMAP, the consumption is measured both in kg active substance and as a National Animal Defined Daily Dose, the latter either as the dose for one kg animal bodyweight (ADD_{kg}) or as the dose for a defined animal body weight x (ADD_x), depending on species and age group. For analysis of trend, the consumption is compared to the animal production measured in kg-meat-produced (pork, poultry, fish) and number of animals slaughtered or exported (pigs). For analysis of distribution among different drugs, it is necessary to take into account the consumption of long acting drugs. For this purpose the defined animal course dose is used (in lack of information on the true average treatment length, a course of 6 days is assumed, see also List of Abbreviations).

Antimicrobial consumption in pigs

In 2008, the total antimicrobial consumption in pigs was 97,2 tonnes active substance, representing a 0.7% decrease from 2007 (See Table 6 for details),while the consumption increased by 2.5% measured in doses, ADD_{kg} (Table 7).

Number of heads produced (slaughtered or exported) increased by 2.9%, while the production decreased by 3% measured in kg meat produced, ie. slaughtered in Denmark (Table 1). This divergence is mainly due to an increasing number of weaning pigs exported in 2008. Consequently, the consumption increased by 5.7%, from 3.88 ADD_{kg} to 4.10 ADD_{kg} per kg-pork-produced, while the consumption measured in ADDkg per pig produced decreased by 0.4% from 2007 to 2008 (Figure 9). However, this was not a true decrease in treatment rate, but rather a consequence of an increase in number of pigs exported at 15-50 kg (typically pigs at 30 kg).

In 2008, an 8.0% increase was seen in antimicrobial consumption per finisher produced, while the consumption for weaning pigs decreased by 1.0% and the consumption in sow herds decreased by 0.3 (Figure 10). Adjusting for the increase in number of 15-50 kg pigs exported, the overall consumption increased by 1.9% in ADD_{kg} per pig produced from 2007 to 2008, after a 22% increase occurring from 2001 through 2007. The adjustment is based on the assumption that the consumption in pigs exported has been the same as in other Danish pigs on average (in the sow herds and weaning pig stage).

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

DANMAP 2008

ATC_{vet} group b)	Therapeutic group	1990	1992	1994	1996	1998	2000	2001	2002	2003	2004	2005	2006	2007	2008
QJ01AA	Tetracyclines	9,300 a)	22,000	36,500	12,900	12,100	24,000	28,500	24,500	27,300	29,500	30,050	32,650	38,200	37,150
QJ01CE	Penicillins, β–lactamase sensitive	5,000	6,700	9,400	7,200	14,300	15,100	16,400	17,400	19,000	20,900	22,250	22,600	23,850	23,950
QJ01C/QJ01D	Other penicillins, cephalosporins	1,200	2,500	4,400	5,800	6,700	7,300	8,800	9,900	11,100	12,900	12,300	11,550	11,500	11,052
QJ01EW	Sulfonamides + trimethoprim c)	3,800	7,900	9,500	4,800	7,700	7,000	9,200	10,600	10,600	11,500	12,200	13,800	13,800	13,300
QJ01EQ	Sulfonamides	8,700	5,900	5,600	2,100	1,000	1,000	950	900	850	850	750	750	700	600
QJ01F/QJ01XQ	Macrolides, lincosamides, pleuromutilins	10,900	12,900	11,400	7,600	7,100	15,600	18,400	19,200	20,700	24,200	22,350	22,050	23,950	26,600
QJ01G/QA07AA	Aminoglycosides	7,700	8,500	8,600	7,100	7,800	10,400	11,600	11,700	11,700	11,600	10,800	10,500	8,100	6,000
	Others c)	6,700	6,800	4,400	600	650	300	900	1,600	1,500	1,000	1,950	1,250	1,150	1,650
Total		53,400	73,200	89,900	48,000	57,300	80,700	94,700	95,900	102,500	112,500	112,650	115,150	121,250	120,200

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 2001-2008: VetStat. For comparability between VetStat data and previous data, see DANMAP 2001. Only veterinary drugs are included. Veterinary drugs almost exclusively used in pet animals (tablets, capsules, ointment, eye/ear drops) are excluded. Dermal spray with tetracycline, used in production animals, is the only topical drug included.

a) Kg active compound rounded to nearest 50 or 100

b) Only the major contributing ATCvet groups are mentioned

c) Consumption in aquaculture was not included before 2001

In 2008, tetracyclines, macrolides and pleuromutilins continued to be the most commonly used antimicrobial agents in pigs (Figure 9). Since 2006, tetracyclines have been the most common group of drug used in pigs, probably due to new treatment guidelines launched by the veterinary authorities in 2005, in an attempt to reduce the consumption of macrolides. The macrolide consumption measured in ADD_{kg}/ pig produced has decreased by 10% (not adjusted for export) from 2005 through 2008, but measured in course doses (ACD_{kg}), the consumption of macrolides increased by 1 % during this period. This deviation was related to the increased consumption of a long-acting macrolide (tulathromycin) since 2005, when it was approved. Thus, from 2005 through 2008, the macrolide consumption in sows increased by 5%, measured in ADD/sow but measured in ACD/sow an increase of 70% occurred.

The overall consumption of tetracyclines per pig produced increased by 48% from 2005 through 2007, but decreased by 0.5% in 2008 (Figure 9). However, corrected for the export of 15-50 kg pigs, the overall consumption increased by 52% from 2005 to 2007, and further by 4-6% in 2008. The consumption in tetracyclines per finisher produced, increased by 0.4%, compared to 2007 (Figure 12). In weaning pigs (7.5 –30 kg), the consumption of tetracyclines per pig produced increased by 6%, compared to 2007 (Figure 11).

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

DANMAP 2008

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	1,981	110	0.01	0	813	955	2,635	9,149	3,783	5,607	3,658	38	28,760
- Weaners	40	2,395	11	0	0	836	6,517	3,534	1,453	2,574	1,826	17,873	334	37,393
- Finishers	13	275	6	0	0	1,064	3,891	5,009	5,693	1,382	180	12,574	7	30,093
- Age not given	0.6	28	0.6	0	0	22	83	101	104	80	59	284	6	767
Cattle b)														
- Cows and bulls	3	43	30	0.1	0	1	26	0	1,384	61	50	165	0.3	1,764
- Calves<12 months	194	205	2	<0.1	0	5	30	3	266	108	254	327	4	1,398
- Heifers, Steers	2	1	0.1	0	0	0.2	1	0	19	2	1	8	0	35
- Age not given	2	3	1	0	0	<0.1	1	-1	26	8	9	13	<0.1	61
Poultry														
- Broilers	1.6	0	0	0.2	0	0	10	0	0	63	5	8	0	87
- Rearing, broilers	0.2	0	0	0	0	0	24	0	0	99	6	7	0	136
- Layers, primatily rearing	1	0	0	0	0	0	0	0	0	36	7	1	0	45
- Turkeys	11	0	0	2	0	0	70	0	0	14	0	101	0	198
- Geese and ducks	0	0	0	0	0	0	0	0	0	3	<0.1	2	0	5
- Gamebirds	0.2	2	0	0	0	1	3	0	0	18	33	6	0	63
-Production category unknown	<0.1	0.1	0	<0.1	0	<0.1	2	2	0	5	16	11	<0.1	36
Other species														
- Small ruminants	0.1	3	<0.1	0	0	1	0.04	3	3	2	2	17	0	30
- Fur animals	0.6	239	0.1	1	0	119	355	0	0.4	922	283	315	0.3	2,236
- Aquaculture	190	0	0	<0.1	646	0	0	0	0.2	1	2,599	1	0	3,438
- Other production animals	1	33	2.8	0.3	0	0.5	4	0.4	133	14	65	48	0.3	301
- Horses	0	1	0.5	<0.1	0	<0.1	1	0	10	2	71	1	0.3	86
- Pet animals	0.2	5	95	5	0	14	7	1	21	119	128	25	15	435
- Farm identified c)	0	-0.5	0.003	0	0	<0.1	0	-0.6	-0.1	2	0	-1	0	0
For use in vet. practice d)														
- Pet animal practice	3	44	263	11	0	44	8	0.3	309	528	273	80	27	1589
- horse or pet animal practice	0	9	0.4	0	0	0.7	0	0	52	5	87	5	0	159
- Pigs	1	20	0	0	0	7	9	21	64	28	9	69	0	227
- Cattle	96	614	115	3	0	51	279	23	5,252	1,268	2,112	1,488	3	11306
- Small ruminants	0	1	0	0	0	0	0	0	5	3	4	2	0	17
- Fur animals	0	50	0	0	0	24	59	0	0	154	98	97	0	483
Species unknown (practice)														
- Topical drugs	0	4	0	0	0	0	0	0	0	0	0.2	16	9	29
- Intramammaries	0	1	1	0	0	0.2	0	0	1	3	0.36	0	<0.1	6
- Micellaneous d)	0	43	-1	1	0	5	-20	8	51	80	269	4	1	441
Total	592	6,001	636	24	646	3,008	12,316	11,340	23,995	11,368	14,052	37,202	446	121,626

Amcol=amphenicols; Amglc=aminoglycosides and spectinomycin; 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 substances, and included in different groups.

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.

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

d) This group contains drugs puchased mainly by veterinarians working in mixed practice. The negative values are due to to stock variation in veterinary practice

Table 7. Consumption of antimicrobials in pigs given as Animal Daily Doses (ADDs), Denmark

DANMAP 2008

		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	2008	2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008	2005	2006	2007	2008
ATC_{vet} group	Therapeutic group	ADD (1,000s)																					
QJ01A	Tetracyclines	915	927	877	1,013	1,497	1,482	32,367	38,207	43,419	52,339	72,029	78,255	11,138	12,212	13096	14,843	17,754	17,328	824	1,154	654	382
QJ01B	Amphenicols	6	7	7	7	8	8	84	105	71	36	79	249	22	32	26	25	15	16	3	1	0.5	1
QJ01CE	Penicillin's, β–lact. sen. b)	2,015	2,230	2,315	2,321	2,553	2,613	2,903	3,969	4,089	3,865	4,299	3,989	5,121	6,323	7,262	7,426	7,682	7,312	549	512	250	145
QJ01CA/CR	Penicillin's, other	1,118	1,201	1,169	1,150	1,315	1,324	12,720	16,348	14,414	11,933	12,071	11,894	2,420	3,500	3,282	2,805	2,699	1,925	318	392	104	113
QJ01DA	Cephalosporin's	99	113	132	148	202	195	254	263	267	290	352	269	56	60	62	49	52	51	10	12	5	3
QJ01E/QP51	Sulfonam./trimeth.	1,084	1,217	1,301	1,353	1,489	1,548	4,146	5,454	6,124	4,483	4,134	4,504	174	232	238	151	166	147	181	180	84	55
QJ01FA	Macrolides	746	772	661	531	899	727	41,173	52,225	49,734	47,546	56,940	53,762	12,255	12,261	12,423	10,634	10,879	10,789	881	885	373	233
QJ01FF	Lincosamides c)	580	588	574	541	620	562	19,821	22,411	19,192	16,492	16,859	17,125	4,412	4,622	4,382	3,607	3,252	2,669	330	319	188	92
QJ01G/A07AA	Aminoglycosides	237	220	171	154	105	40	22,231	21,469	19,782	19,410	10,671	2,944	194	124	237	213	109	5	75	148	49	8
QA07AA10	Colistin (local GI)	23	24	23	24	28	22	2,910	3,017	2,656	2,793	3,009	2,559	18	14	13	18	13	15	21	22	13	9
QJ01MA	Fluoroquinolones	23	3	4	7	6	<1	17	8	5	11	0	0	6	4	2	0	0	0	<1	2	0	0
QJ01RA01	Penicillin/streptomycin	703	669	661	643	662	631	2,211	3,075	3,589	3,478	3,438	3,445	423	380	369	292	226	158	84	75	26	8
QJ01X	Pleuromutilin's	946	987	811	856	1,299	1,805	19,759	24,811	23,494	22,539	22,498	31,330	8,478	10,177	10,157	9,479	8,902	13,872	735	699	397	290
QJ51	Intramammaries	4	2	1	<1	<1	0.3	<1	<1	0	<1	<1	0	<1	1	<1	<1	<1	0	<1	<1	<1	0
QG01AA	Gynecologic (local)	0.1	<1	<1	<1	<1	<1	0	0	0	0	0	0	0	0	0	0	0	0	0	<1	0	0
Total		8,500	8,958	8,707	8,748	10,682	10,959	160,597	191,362	186,837	185,215	206,379	210,325	44,718	49,943	51,549	49,542	51,750	54,288	4,009	4,401	2,143	1,339

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

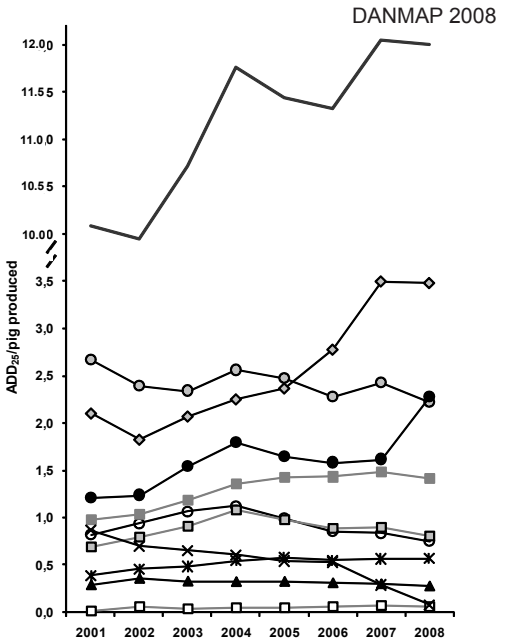


Figure 9. Trends in antimicrobial consumption (in ADD25 a)) in pigs, Denmark

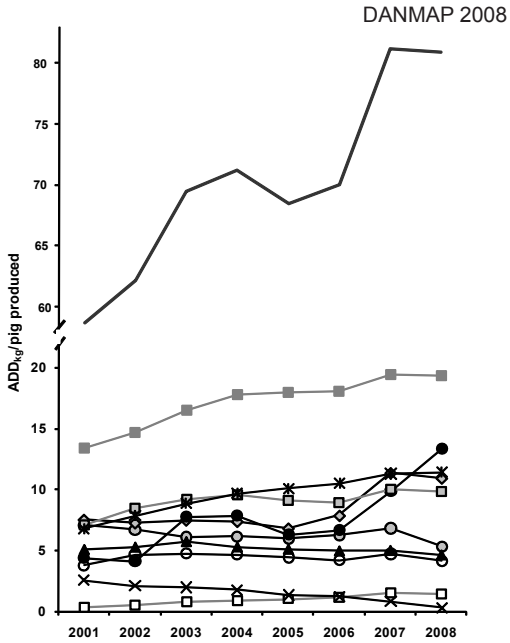


Figure 10. Trends in antimicrobial consumption (in ADDkg) in sows and piglets;

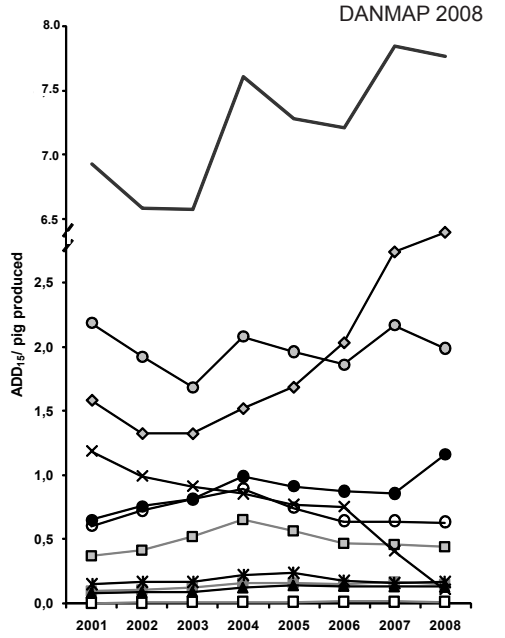


Figure 11. Trends in antimicrobial consumption (in ADD15 a) in weaners; Denmark

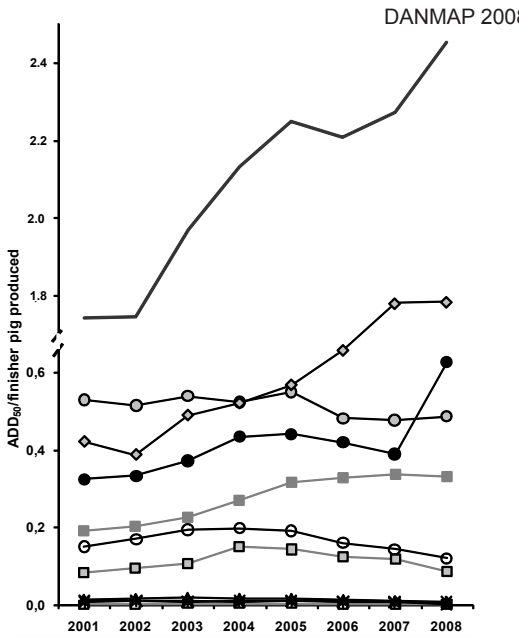
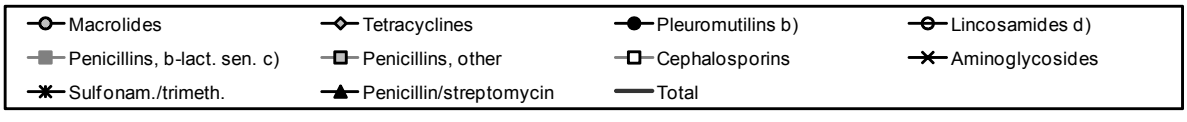


Figure 12. Trends in antimicrobial consumption (in ADD50a) in finshers; Denmark



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). In Figure V11, number of pigs produced is exclusive pigs exported at 15-50 kg kg. In all other figures pigs exported at 15-50 kg are included.

a) ADD_{25}: doses for treatment of 25 kg pigs , to compare treatment across age groups.doses for treatment of 15 kg pigs.
ADD_{15}: An assumed average dose for treatment of weaners (7.5—30 kg).
ADD_{50}:doses for treatment of 50 kg pigs. An assumed average dose for treatment of finishers (30 —110 kg). Number of pigs produced excluding pigs exported at 15-50 kg.
ADD_{kg}, doses for treatment of one kg pigs: unit used to measure antimicrobial use in sow herds; the drugs are used either in sows (bodyweight>200 kg) or in piglets (<2kg- 7.5 kg).

b) Pleuromutilins comprise primarily tiamulin

c) β-lactamase sensitive penicillins

d) Lincosamide/spectinomycin combinations comprise 65% of this group

From 2007 through 2008, the consumption of pleuromutilins increased by 41% (50%, adjusted for incresing import), while the consumption of macrolides decreased by 8.5% (3.4%, adjusted) per pig produced (Figure 9 and Table 7). In autumn 2007, the price for some tiamulin products was reduced importantly by the pharmaceutical companies. A steep increase in consumption of tiamulin was observed in the first quarter of 2008 and forward. With this increase, the average price for one course dose of pleuromutilins for oral therapy decreased by 41% to approximately 35% below the price for one course dose of both macrolides and tetracyclines[1].
In 2007, the most commonly used aminoglycoside product (neomycin) was taken of the marked, resulting in a 99.7 % decrease in consumption of neomycin and an 84% decrease in consumption of aminoglycosides from 2006 through 2008 (Figure 9). Neomycin has mainly been used in weaning pigs (7.5–30 kg). The major aminoglycoside for oral use in weaners changed from neomycin in 2006, to apramycin in 2008; thus, neomycin comprised 87% of 0.41 ADD_{15} aminoglycoside per weaning pig produced in 2006 and apramycin comprised 99% of 0.1 ADD_{15} aminoglycoside per weaning pig produced in 2008 (not including streptomycin and spectinomycin used in combination with other drugs, as these are included in other groups, QJ01RA01 and QJ01FF). The use of apramycin increased by 24% in 2008 compared to 2008.

The consumption of broad spectrum cephalosporins is of particular importance in selection of extended spectrum beta-lactamase (ESBL) resistance. The prescription of cephalosporins for pigs decreased from 129 kg in 2007 to 128 kg in 2008, following a continuous increase from 24 kg in 2001. The majority (87% in 2008) was used in sow herds (Table 6). As discussed in DANMAP 2007, it is commonly used for prophylactic treatment of umbilical infection in the piglets as one injection within the 1st or 2nd day after birth.

Antimicrobial consumption in cattle

In 2008, approximately 14.5 tonnes of antimicrobial substance was prescribed for cattle, which is the same level (14–15 tonnes) as in previous years i.e. 2004–2007. During 2004 through 2008, the beef production has decreased by 16% and the milk production has increased by 3% (Table 1). Among the antimicrobial agents for systemic treatment, 82% were used in cows and bulls, 14% in calves and 3% in heifers and steers, measured in daily doses (ADD_{kg}, see Table V5).
For systemic treatment in cows, the major indication (65% measured in ADD) was mastitis, reflecting that the population is mainly dairy cattle (Table 8). From 2007 through 2008, the milk production increased by 1%, while the consumption of intramammaria was unchanged (Table 1, Table 8).

Figures 13 and 14 show the proportion of different antimicrobial agents used in calves and cows, measured in ACD_{kg}. In cows, the proportion of beta-lactamase sensitive penicillin has been increasing by 14% since 2004, while the consumption of macrolides has decreased by 48%. In 2008, beta-lactamase sensitive penicillins, tetracyclines and other penicillins, accounted for 53%, 20% and 9 % of the consumption, respectively.
In calves, macrolides were the major drug group of choice, constituting 30% of the consumption in calves in 2007 and 2008 (Figure 14). Measured in ADDs, the consumption of macrolides constituted 8% (Table 8). The reason for this deviation is that tulathromycin (a long-acting macrolides closely related to azithromycin) is the most commonly used macrolide in calves. After the approval of the drug in 2005, the consumption of macrolides increased by 56% from 2005 through 2007. Until 2005, tetracyclines followed by different penicillins were the major antimicrobial agents (Figure 14). The proportion of long acting tetracycline drugs but also other preparations of tetracyclines decreased from 2005 through 2006, and has been maintained at this level, from 2006 to 2008. In calves, respiratory disease is the major indication, accounting for 67% of the course doses.

In cattle, cephalosporins were mainly used in cows, i.e. intramammaria and 91% of the cephalosporin used for systemic treatment (Table 8). Regarding systemic use, the consumption of cephalosporin (3rd and 4th generation) increased by additional 3 kg to 68 kg 2008, as a part of a continuous increase from 27 kg in 2001. The intramammary use of 3rd and 4th generation

[1)] Development in antibiotic consumption, expenses and prices for prescription veterinary medicine for production animals from 1. April 2005 to 1. April 2008, Report of December 15. 2008 to the Ministry of Health; The Danish Medicines Agency, the Danish Veterinary and Food Administration and the Technical University of Denmark, 2008''
[In Danish. "Notat af 15. december 2008 til Ministeriet for Sundhed og Forebyggelse om udviklingen i forbrug, udgifter og priser for receptpligtig veterinær medicin til produktionsdyr fra 1. april 2005 til 1. april 2008 udarbejdet af Lægemiddelstyrelsen og Fødevarestyrelsen med bidrag fra DTU"]

[2)] [Indfangning, udsætning og jagt på fasan agerhøne og gråand i Danmark, Rapport fra arbejdsgruppe nedsat af Vildtforvaltningsrådet, 2006.]

Table 8. Consumption of antimicrobials in cattle given as Defined Animal Daily Doses (ADDs), Denmark DANMAP 2008

		Pharmacies and veterinary practice a)																			
Age group		Cows, bulls					Calves					Heefers and steer					unknown				
Animal standard weight		600 kg					100 kg					300 kg					100 kg				
		2004	2005	2006	2007	2008	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008	2004	2005	2006	2007	2008
ATC_{vet} group	Therapeutic group	**ADD (1000's)**																			
QJ01A	Tetracyclines	169	178	187	222	260	568	592	544	565	542	17	18	19	25	26	22	41	101	76	14
QJ01B	Amphenicols	1	1	0.8	0.8	1	52	64	67	92	102	<0.1	<0.1	<0.1	<0.1	0.5	2	2	3	2	0.8
QJ01CE	Penicillin, b)	462	474	483	581	702	201	169	175	179	169	28	26	26	32	36	15	73	86	77	21
QJ01CA/CR	Penicillins, other	90	78	77	88	110	241	218	158	138	127	8	6	4	7	7	24	178	216	108	4
QJ01DA	Cephalosporins	58	43	44	60	68	37	27	22	29	25	4	2	2	3	3	1	4	7	7	2
QJ01E	Sulfonamid./trimeth.	70	61	61	64	77	178	164	157	162	143	3	2	3	3	3	8	14	30	23	3
QJ01FA	Macrolides	101	84	78	57	51	47	99	132	128	116	6	5	4	5	3	6	103	182	69	2
QJ01FF	Lincosamides c)	4	2	2	2	1	27	17	12	15	14	0.4	0.6	0.3	1	2	3	23	46	18	<0.1
QJ01G/QA07AA	Aminoglycosides	3	1	1	1	1	104	116	108	89	81	<0.1	<0.1	<0.1	<0.1	<0.1	3	10	33	6	0.8
QA07AA10	Colistin (local GI)	<0.1	<0.1	<0.1	<0.1	<0.1	6	21	7	8	11	<0.1	0	<0.1	<0.1	<0.1	0.6	2	4	1	<0.1
QJ01MA	Fluoroquinolones	<0.1	<0.1	<0.1	<0.1	<0.1	6	2	1	0.5	0.2	<0.1	<1	<0.1	<0.1	0	0	<0.1	<0.1	1	<0.1
QJ01RA01	Penicillin/strepto d)	19	21	21	26	33	137	138	134	128	113	5	2	3	3	4	5	7	13	13	0.8
QJ01X	Pleuromutilins	2	0	1	1	0	1	0	<0.1	0.9	4	<0.1	0	0	0	0	11	12	89	38	0
QJ51	Intramammaries e)	1,123	1,136	1,142	1,111	1,108	1	0.7	0	<0.1	0	14	13	11	14	6	0	1	0	0	0
QG01AA	Gynecologic (local)	119	100	97	98	100	0	0	0	0	0	4	4	3	6	13	0	0	0	0	0
Total		2,223	2,180	2,195	2,312	2,513	1,606	1,628	1,518	1,534	1,448	89	80	75	99	104	100	468	809	441	50

The ADD's for intramammaries were defined as treatment of one teat. However, several teats on each cow are treated on average

a) The consumption in calves is underestimated by up to 5% and consumption in cows is underestimated by up to 17% in individual years, cause the use in cattle practice is underestimated by up to 20%. This does NOT concern intramammaries, because data from pharmacies was used to estimate use in practice (app. 2 % overestimation of intrammaries in cows, before 2008).

b) β-lactamase sensitive penicillins

c) Comprises both lincomycin and lincomycin/spectinomycin combinations

d) Combination of benzylpenicillin and streptomycin

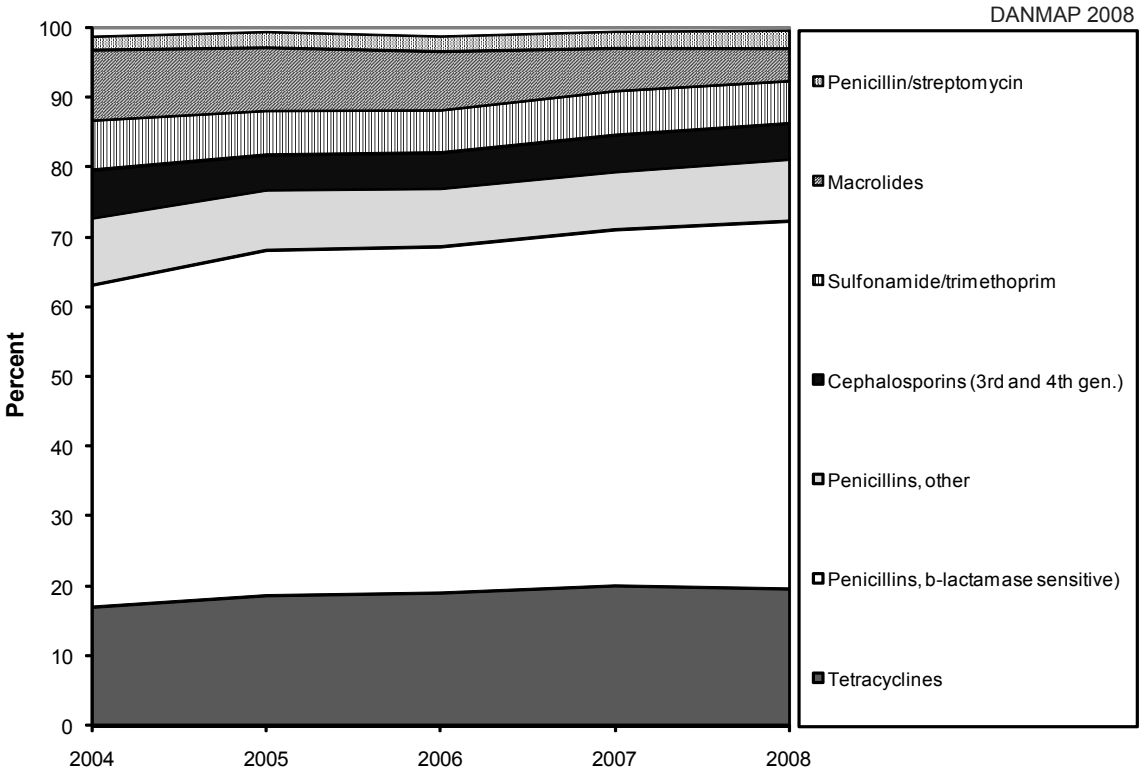


Figure 13. Relative consumption of systemic antimicrobial drugs in cows and bulls, given as Defined Course Doses[a]; Denmark

The antimicrobials not shown (summing up to 100%), each accounts for less than 1 percent of the consumption.
a) The course doses were defined as 6 days of treatment both for parenteral and oral drugs, for this specific comparative purpose. Eg. an ACD (defined animal course dose) for a long acting drug, used with three days inteval, was defined as two daily doses (=2 ADD)

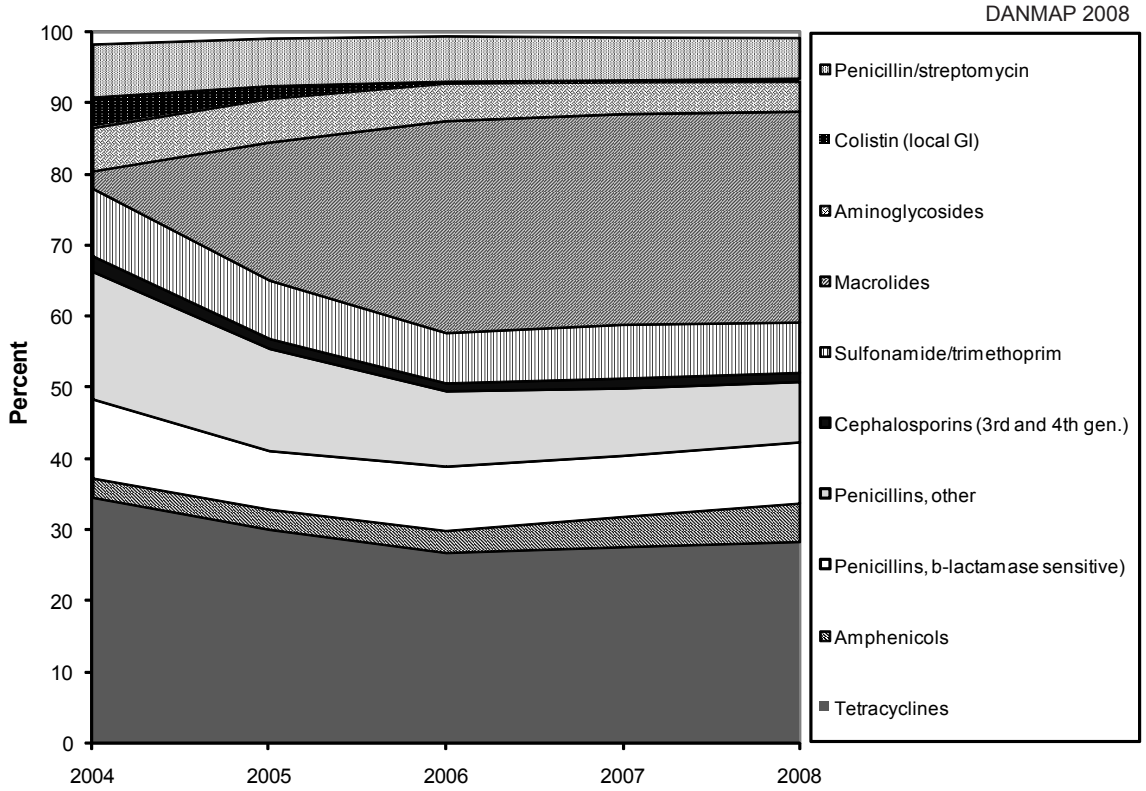


Figure 14. Relative consumption of systemic antimicrobial drugs in calves, given as Defined Course Doses[a]; Denmark

The antimicrobials not shown (summing up to 100%), each accounts for less than 1 percent of the consumption.
a) The course doses were defined as 6 days of treatment both for parenteral and oral drugs, for this specific comparative purpose. Eg. an ACD (defined animal course dose) for a long acting drug, used with three days inteval, was defined as two daily doses (=2 ADD)

cephalosporin decreased by 11% (3 kg) from 27 kg in 2007 to 24 kg 2008, after a continuous increase from 14 kg in 2001. Because the dose for intramammary treatment is much lower than for systemic treatment, this change most likely represents a decrease in number of animals treated. The consumption of intramammaria based on 3rd and 4th generation cephalosporin now comprises 21% of the total consumption of intramammaria (in ADD), representing a decrease from 26% in 2007. Thus, a large but now decreasing proportion of the cattle population was treated with or exposed to these antimicrobial agents despite the relatively low amounts consumed, measured in kg active substance.

Antimicrobial consumption in poultry

The consumption of antimicrobial agents in poultry decreased by 8.3% from 623 kg active substance in 2007 to 571 kg in 2008 (Table 9). Since 2002, the overall antimicrobial consumption in poultry has fluctuated between 400–623 kg active substances. These fluctuations are usually caused by disease outbreaks in few farms, because the antimicrobial consumption in poultry, particularly in domestic fowl, is generally very low in Denmark compared to other species.

Before 2007–2008, amoxicillin comprised approximately 90% of the antimicrobial used in poultry, and fluoroquinolones were the second most used antimicrobial group (Table 9). However, a significant change in the choice of antimicrobial agents occurred in 2007. An increase in other antimicrobial agents like sulfonamides, tetracyclines and macrolides was observed for both turkeys and domestic fowl, the two major species (Table 10).

In 2007, the veterinary practitioners specialised in poultry medicine received instructions from The Veterinary and Food Administration, that in case of resistance to amoxicillin, antimicrobial agents approved for veterinary use in other species should be used in accordance with the cascade rules, taking into consideration national restrictions in use of fluoroquinolones.These guidelines together with problems with resistance to amoxicillin have probably caused the changes in antimicrobial choices observed in the poultry production in 2007. Accordingly, the consumption of fluoroquinolones in the broiler production was reduced by 51% in 2007, and 97% in 2008, both compared with the level in 2006.

In the broiler production, the antimicrobial consumption was 0.07 ADD_{kg}/kg broiler-meat produced in 2008 (including consumption in parent flocks) (Table 9). This represented an increase of 137% compared to 0.03 ADD_{kg}/kg broiler-meat produced in 2007, which was the lowest level since 2003. The increased consumption in 2008 was almost entirely related to an increasing consumption of amoxicillin, comprising 87% of the antimicrobial consumption in the broiler production in 2008. According to the major poultry practitioners, the increase was due to problems with infectious bronchitis (viral) and related secondary infections in the broilers; the increase in consumption for parent flocks and rearing was related to different disease problems in the locomotor systems, such as arthritis. However, 0.07 ADD_{kg} per kg broiler-meat produced was still very low compared to the consumption in other species.

In 2008, the consumption in turkeys decreased by 23% to 0.77 ADD_{kg} per kg turkey meat compared to 2007 (Table 10). This represented a continuous decrease after a maximum was reached in 2006, when 1.3 ADD_{kg}/kg-turkey-meat produced was used. Despite the aforementioned guidelines, fluoroquinolones comprised 16% of the consumption in turkeys in 2007. However, the use of fluoroquinolones decreased by 92% in 2008 compared to 2007, comprising 2% of the antimicrobial consumption in turkeys in 2008.

In game birds, the consumption was relatively stable since 2004, with minor annual fluctuations. The production of game birds is relatively unchanged over the past decade. Assuming an average slaughter weight of 0.5 kg for an approximately 1 million pheasants, 0.5 million wild ducks and 0.1 million other game birds produced, the consumption was an estimated 2.6 ADD_{kg} per kg meat produced in 2008.

Antimicrobial consumption in fur animals, aquaculture and pet animals

In 2008, the production of fur animals included 14 million mink, 30,000 chinchillas and a minor production of foxes. The consumption of antimicrobial agents in fur animals increased by 39% - from 1950 kg in 2007 to 2720 kg in 2008 (Table 6). Aminopenicillins remain the most commonly used drug group in fur animals, comprising 40% of the antimicrobial consumption in 2008. Macrolides, tetracyclines and sulfonamide-trimethoprim combinations comprised another 44% of the consumption in 2008 in kg active compound.

In 2008, the consumption in aquaculture decreased by 8% to 3438 kg active substance. Unusually warm summers are the most likely reason why the use of antimicrobial agents in aquaculture was significantly higher in 2007 and 2008 as compared to previous years (eg. 2400 kg in 2005). The use of sulfonamide/trimethoprim combinations decreased by 19% in 2008, as compared to 2007, but remained the most frequently

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

DANMAP 2008

Production type		Broilers						Rearing for broiler production						Layers and layer rearing						Production type unknown a)					
		2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008
ATC_{vet} code	Therapeutic group	ADD_{kg} (1,000s)																							
QA07AA	Aminoglycosides	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	200	300	81	133	0	0
QA07AA	Colistin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	75	0	0	0	0	0	3	3
QJ01A	Tetracyclines	60	2	32	0	0	500	0	0	0	0	0	467	540	2	8	0	0	12	91	106	63	148	136	360
QJ01B	Amphenicol	0	0	0	0	36	80	0	0	0	0	0	10	0	0	0	0	0	70	0	0	0	0	33	5
QJ01CA	Amoxicillin	2,988	4,469	3,708	2,570	1,708	4,646	1,358	5,760	3,896	6,100	2,754	6,963	350	1,066	675	437	1,150	2,588	2,342	3,657	2,223	3,538	721	338
QJ01E/QP	Sulfonamides a)	8	56	48	40	168	83	0	0	0	15	79	100	328	210	228	125	96	115	348	439	165	178	383	218
QJ01FA	Macrolides	0	29	3	0	289	133	0	0	0	0	22	322	0	0	0	11	0	0	186	90	3	4	118	26
QJ01FF	Lincosamides b)	0	20	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	4	40	0	22	4
QJ01MA	Fluoroquinolones	270	603	171	550	130	20	80	420	400	104	190	0	0	100	0	0	0	0	411	131	40	162	23	3
QJ01X	Pleuromutilins	0	75	0	0	0	0	0	0	0	0	0	0	3	0	3	0	0	0	5	3	5	0	8	0
Total		3,325	5,254	3,962	3,160	2,331	5,461	1,438	6,180	4,296	6,219	3,045	7,861	1,220	1,386	913	573	1,321	2,785	3,582	4,729	2,613	4,162	1,445	956
Production (mill. Kg meat)		181	181	180	163	178	186																		

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

DANMAP 2008

Production type		Turkeys						Ducks, geese						Game birds					
		2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008	2003	2004	2005	2006	2007	2008
ATC_{vet} code	Therapeutic group	ADD_{kg} (1,000s)																	
QA07AA	Aminoglycosides	0	200	100	0	380	0	0	0	0	0	0	0	100	167	100	12	33	0
QA07AA	Colistin	0	0	0	0	162	0	0	0	0	0	0	0	0	0	0	15	15	0
QJ01A	Tetracyclines	0	0	60	150	2,033	6,733	154	14	0	0	0	36	128	148	94	76	146	112
QJ01B	Amphenicol	0	0	0	0	214	561	0	0	0	0	0	0	0	0	0	0	0	13
QJ01CE	Penicillin, β-lact. sens c)	0	0	0	0	263		0	0	0	0	0	0	0	0	0	0	0	0
QJ01CA	Amoxicillin	10,867	4,871	8,363	14,083	6,788	1,038	250	400	375	1,025	113	250	904	966	1,852	1,750	1,346	1,288
QJ01E/QP	Sulfonamides a)	58	36	68	45	0	4	0	0	0	0	21	1	316	459	398	235	406	542
QJ01FA	Macrolides	0	7	0	0	2,547	933	0	11	12	1	0	0	273	113	177	36	16	37
QJ01FF	Lincosamides b)	0	0	100	0	242	0	0	0	0	0	2	0	0	0	14	8	6	60
QJ01MA	Fluoroquinolones	340	1,607	1,260	1,040	2,320	190	0	150	0	0	0	0	1	30	0	10	40	0
QJ01X	Pleuromutilins	0	0	0	0	0	0	0	3	0	0	0	0	10	18	13	0	5	0
Total		11,264	6,721	9,950	15,318	14,446	9,459	404	578	387	1,026	136	287	1,732	1,900	2,647	2,141	2,013	2,051
Production (mill. kg meat)		11	20	17	11	14	12	4	4	4	5	2	3						

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

used antimicrobial agents in aquaculture, comprising 76% of the consumption in 2008. The consumption of quinolones (oxolinic acid) increased by 97% to 646 kg comprising 19% of the consumption in 2008. Additionally, amphenicoles (5%) are commonly used. The antimicrobial consumption for fish in salt water decreased from 176 mg/kg fish produced in 2007 to 163 mg/kg fish in 2008. Regarding fish produced in fresh water, the consumption decreased from 63 mg/kg fish produced in 2007 to 46 mg/kg fish produced in 2008 (assuming an unchanged production in 2008 compared to 2007, Table 1).

In pet animals, an estimated 2 tonnes of antimicrobial substance was used in 2008 (Table 6). The major antimicrobial agent used in pet animals was amoxicillin in combination with clavulanic acid, which increased by 12% to 477 kg in 2008. Other frequently used antimicrobial agents were cephalosporins (357 kg), mainly for oral use; and sulfonamide/trimethoprim (est. 400 kg), and narrow spectrum penicillin (estimated 330 kg), both mainly for parenteral use. Cephalosporins used in pet animals are predominantly first generation (cefadroxil and cefalexin), while 4th generation cephalosporin comprised 0.8 % of the cephalosporins used in pet animals in 2008. An estimated 1% of the veterinary consumption of 3rd and 4th generation cephalosporin was used in pet animals. An estimated 17 kg fluoroquinolones was used in pet animals, comprising 68% of the total veterinary use of fluoroquinolones in Denmark 2008.

Textbox 2

Guidelines for antimicrobial treatment of food-producing animals

From 2002 to 2004, an increase of 18% occurred in the antimicrobial consumption per pigs produced and strategies to investigate and possible reduce this were required. As a part of Denmark's ongoing risk management strategy for optimization of antimicrobial consumption and reduction of antimicrobial resistance, the Danish Veterinary and Food Administration (DVFA) commenced elaboration of dynamic treatment guidelines for food-producing animals, starting with swine in 2005, followed by a new reviewed concept for treatment guidelines for the main food-producing animals in 2008 (www.foedevarestyrelsen.dk/Kontrol/Laegemidler_til_dyr/Valg_af_laegemidler_til_dyr/forside.htm).The guidelines are a result of animal species specific working groups established by the DVFA and with participants from the Danish Veterinary Association, the Danish Animal Health Industry, the Danish Meat Association, the Faculty of Life Sciences, Copenhagen University, Statens Serum Institut, the National Food Institute, the National Veterinary Institute and the DVFA. Additionally, supervision of all veterinary practitioners working with food-producing animals was implemented in 2008.

The guidelines list all registered veterinary antimicrobial agents in Denmark for the specific animal species and their most common diseases and related pathogen(s). The antimicrobials are categorized from five different criteria (Table 11) and following their performance in all five criteria, the drugs are prioritized in recommended and non-recommended antimicrobial agents. The guidelines are dynamic lists, which can be changed on request from collaborators in the working groups, if new information or new drugs emerge. The guidelines are directed towards veterinary practitioners, as all veterinary medicinal products are prescription only and this places the veterinary practitioners as key persons in prudent antimicrobial usage. The veterinary practitioners may use the guidelines as a working tool in their counselling of preventive veterinary strategies in herds of food-producing animals, thereby optimizing antimicrobial usage with due consideration to animal health and welfare. Moreover, the guidelines are used as a reference tool in the regular supervisions of the veterinarians. The supervisions focus on the practitioner's usage and treatment patterns for food-producing animals; the aim being to, by self recognition, motivate the practitioners towards prudent usage. The veterinarian's treatment patterns and usage are compared to their colleagues on the country level. The data on consumption are from the National monitoring program, VetStat.

Other parts of the risk management strategy and supervision are: 1) an order from 2002 restricting the use of fluoroquinolones i.e. they can only be used if a current laboratory test shows, that no other approved antimicrobial agent is effective for the specific disease in the specific herd, 2) the rule of cascade for veterinary medicine is for poultry overruled by the order restricting the use of fluoroquinolones i.e. diseases in poultry can be treated with antimicrobials not registered for this specie instead of being treated with fluoroquinolones, as there is lack of registered antimicrobials for poultry, 3) if the supervision reveals a very simple treatment pattern or a treatment pattern not in alignment with the guidelines or reveals signs of ongoing systematic treatments with antimicrobials, and the reason for this is not documented by laboratory testing (bacteriology, serology or autopsy), then the supervision can order proper laboratory testing documenting the need for antimicrobial treatment of the animals, 4) if this ordering is not fulfilled, the veterinarian may be prosecuted.

The animal species-specific treatment guidelines focus on the following five criteria for categorizing antimicrobial agents for the different common animal species specific diseases, Table 11: efficacy of treatment, development of resistance in veterinary pathogens on the national level, significance of the antimicrobial agent in human treatments, WHO´s and OIE´s criteria for importance of antimicrobial agents in human and animal treatment, respectively. Thereby the guidelines focus on efficacy of treatment of animals, low development of resistance and minimal public health concerns. An antimicrobial agent is prioritised based on the performance in all five criteria. Preferably, an antimicrobial agent should have a performance of three on all five criteria, but often this will not be the case.

Table 11. Categorization of antimicrobial agents in the guidelines DANMAP 2008

Category	Score 1	Score 2	Score 3
Efficacy	Documented in Summary of Product Characteristics (SPC)	As 1 plus good and recognised efficacy in clinical practice	As 2 plus specifically approved for the indication and/or documented in peer-reviewed papers.
Susceptibility	<= 30%	31-60	> 60
Human importance	First choice for humans and/or direct transmission and/or treatment failure. Ought not to be used in animals.	Important and indirect or direct transmission is likely.	No or limited use in humans or not important and indirect transmission is unlikely.
WHO	Critically important for humans	Highly important	Important
OIE	Important for animals	Highly important	Critically important

From 2005 through 2006, the antimicrobial consumption of kg active compound in swine decreased by 1.2%, (DANMAP 2006), but increased 6.3% in 2007, taking into account an increase in the swine production by 2.1% from 2005 to 2007. In the guidelines, and at the supervisions, it is specifically stated, that tiamulins and tetracyclines should be used for treatment of GI infections in swine instead of macrolides, as macrolides are critically important in human treatment. Also, the critical importance of 3rd and 4th generation cephalosporins and fluoroquinolones, is the reason why it is stated that their use in animals should be restricted and preferably only be used when other antimicrobial agents are not effective. The macrolide consumption in swine decreased by 7% in 2006 compared to 2005, but increased 6.5% in 2007. Simultaneously, the tetracycline consumption increased, and alone in 2007 the tetracycline consumption increased by 26%. Concerning the macrolide consumption, the veterinarians initially adjusted their prescription pattern in compliance with the guidelines, but without the trends in consumption indicated the effect is not lasting without continuation of the focus imposed by the supervision team. It is likely that this is the case for the trend in overall consumption, where a decrease was observed in 2006 following supervision in 2005, and the following increase in 2007. The tetracycline consumption has increased constantly and since 2005 tetracyclines have been the most used antimicrobial agents for swine in Denmark (DANMAP 2007). In 2008 consumption of tiamulin has increased 35%, in compliance with the guidelines. Analysis of the relationships between price and consumption from 2005 to 2008[1] (Anone, 2008) revealed that macrolide prices were markedly reduced after the treatment guidelines were introduced in 2005. This might have started a price competition on gastrointestinal antimicrobial agents for swine, as tetracyclines followed with price reductions in 2006 and the price for tiamulins were reduced by more than 50% in 2007 and 2008, making them cost-effective compared to macrolides and tetracyclines. These are examples showing how cost and price competition may counteract or support the compliance with guidelines.
The treatment guidelines and the supervision also focused on consumption of 3rd and 4th generation cephalosporins for intramammary treatment in cows and from 2007 to 2008 these have decreased 11 %. In the broiler production, focus has been on fluoroquinolones and these decreased 75% in 2007 in compliance with the instructions from the supervision team. Due to amoxicillin resistant *E.coli* in the turkey production, the treatments with fluoroquinolones increased by 9% for this type of poultry - an example of prudent usage under due consideration of the welfare of the animals, which is the precise aim of the guidelines. In the future focus will be directed towards use of cephalosporins in swine, as these has increased markedly for the past years, and the effect of the guidelines and the supervision of the veterinary practitioners will continuously be analysed.

For further information: Annette Cleveland Nielsen (acln@fvst.dk)

[1] Development in antibiotic consumption, expenses and prices for prescription veterinary medicine for production animals from 1. April 2005 to 1. April 2008, Report of December 15. 2008 to the Ministry of Health; The Danish Medicines Agency, the Danish Veterinary and Food Administration and the Technical University of Denmark, 2008''
[In Danish. "Notat af 15. december 2008 til Ministeriet for Sundhed og Forebyggelse om udviklingen i forbrug, udgifter og priser for receptpligtig veterinær medicin til produktionsdyr fra 1. april 2005 til 1. april 2008 udarbejdet af Lægemiddelstyrelsen og Fødevarestyrelsen med bidrag fra DTU"]

Antimicrobial consumption in humans

Antimicrobial consumption in humans

Overall

Throughout this section, the consumption in 2008 will be compared with the previous year (2007) and one decade back (1999). When measuring antibacterial consumption, the unit of measurement is the Defined Daily Dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasised that DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. The sector-specific quality indicators used to measure and described antibacterial consumption will be introduced at the beginning of the passage of each sector.

In 2008, the overall (primary health care and hospital sectors) consumption of antibacterial agents for systemic use (ATC group J01, 2008 definition) in humans amounted to 35.5 million DDDs or 17.7 DDDs per 1,000 inhabitants per day (DID), representing a decrease of 0.1 million DDDs (0.3%) or 0.2 DID (1.1%) compared with 2007. However, an increase in consumption of 9.3 million DDDs (35.6%) or 4.2 DID (31.2%) has been observed compared with 1999. The percentage of DDDs prescribed in the primary health care sector remained stable at 90% of the total human consumption.

Figure 15 shows the distribution of the total number of DDDs of antibacterial agents between the primary health care sector and hospitals. For penicillins with extended spectrum (J01CA) and fluoroquinolones (J01MA), the ratio of consumption in primary health care vs. consumption in hospitals was around 9/1 and 2/1, respectively.

To allow comparison with consumption of antibacterial agents in animals, the total human consumption is presented in kilograms (Table 12). In 2008, 48.6 tonnes of antibacterial agents for systemic use were used in humans in Denmark, representing a decrease of 1.2 tonnes (2.4%) compared with 2007 but an increase of 9.2 tonnes (23.5%) compared with 1999.

Primary health care sector — Definitions

In the primary health care sector, consumption should preferably be presented as numbers of DDDs per 1,000 inhabitants per day (DID). Data presented in DDD per 1,000 inhabitants per day provide a rough estimate of the population proportion within a defined area treated daily with certain drugs. For example, the figure 10

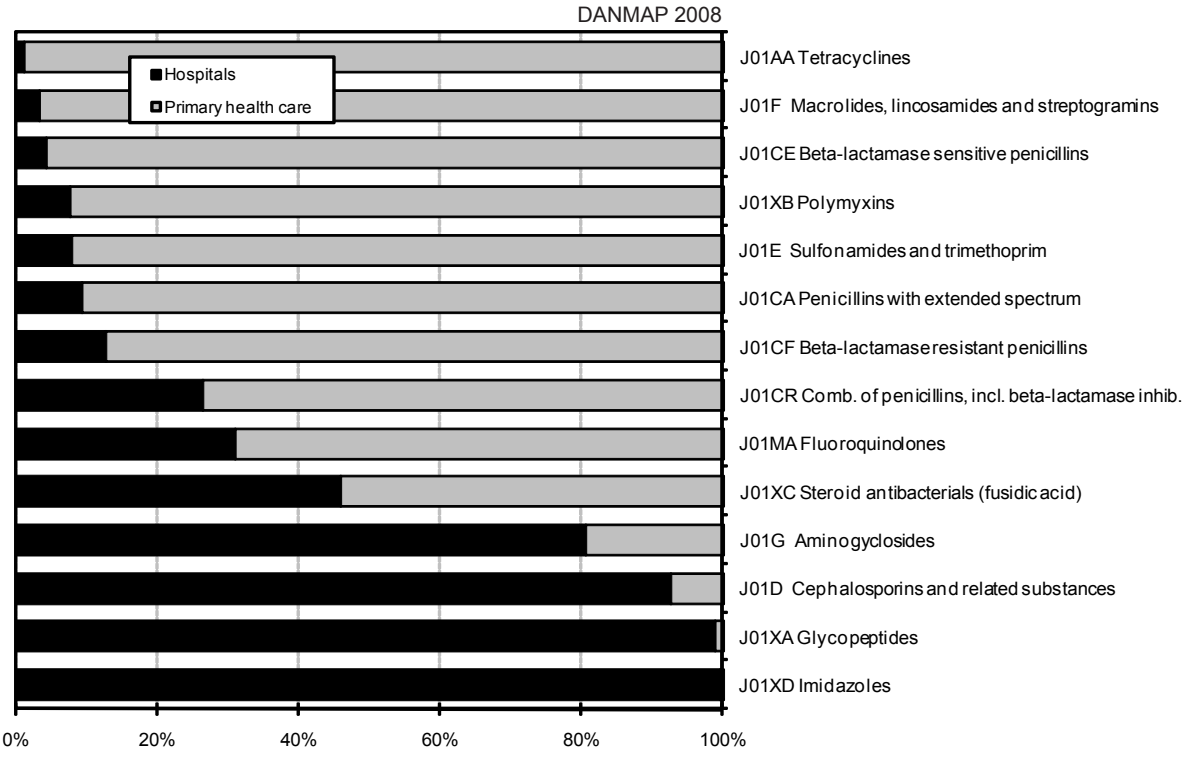


Figure 15. Distribution of DDDs between somatic hospitals and the primary health care sector, Denmark (selected antibacterial classes)

Table 12. Consumption of antibacterials for systemic use in humans (kg active substance), 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 ABH2 and ABH6)

DANMAP 2008

ATC group a)	Therapeutic group	Year									
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	1,383	1,486	1,475	1,501	1,542	1,636	1,748	1,835	1,855	1,884
J01B	Amphenicols	0	0	1	0	0	0	0	0	0	0
J01CA	Penicillins with extended spectrum	5,202	5,141	5,385	5,356	5,295	5,346	5,561	5,722	6,188	6,061
J01CE	Beta-lactamase sensitive penicillins	18,825	19,749	20,730	21,263	21,630	22,230	22,520	22,760	24,003	22,466
J01CF	Beta-lactamase resistant penicillins	2,425	2,655	3,230	3,738	4,075	4,377	4,565	4,842	5,037	5,183
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	52	93	146	249	336	480	534	724	1,012	1,348
J01D	Cephalosporins and related substances d)	650	692	739	811	830	894	1,582	1,778	2,285	2,530
J01EA	Trimethoprim and derivatives	258	262	280	293	307	334	359	382	402	402
J01EB	Short-acting sulfonamides	3,296	3,142	3,113	3,092	3,064	3,067	2,987	2,865	2,565	2,273
J01EE	Comb. of sulfonamides and trimethoprim, including derivatives	286	291	289	288	273	185	208	208	148	183
J01FA	Macrolides b)	4,147	4,040	4,089	4,150	3,876	3,743	3,775	3,542	3,434	3,164
J01FF	Lincosamides d)	29	29	37	40	45	53	52	66,01	78	94
J01G	Aminoglycosides	42	32	30	31	28	31	31	27	27	25
J01MA	Fluoroquinolones d)	383	344	398	451	611	722	866	979	1,162	1,351
J01MB	Other quinolones	16	0	0	0	0	0	0	0	0	0
J01XA	Glycopeptides	33	37	36	42	43	46	51	56	61	64
J01XC	Steroid antibacterials (fusidic acid)	78	70	59	59	58	52	62	65	67	64
J01XD	Imidazoles	142	155	168	179	191	195	206	198	202	191
J01XE	Nitrofuran derivatives (nitrofurantoin)	145	151	155	163	166	171	180	185	190	192
J01XX05	Methenamine d)	1,956	1,788	1,637	1,662	1,590	1,473	1,107	1,076	1,060	1,087
J01XX08	Linezolid	0	0	0	3	4	5	10	14	12	14
J01	Antibacterials for systemic use (total) c)	39,348	40,157	41,997	43,371	43,964	45,040	46,404	47,324	49,788	48,579

a) From the 2008 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 2,495 - 3,833
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 1999 to 2004, it was estimated with a DDD corresponding to an average for the various routes, e.g. for cefuroxime: 1.75 g

DDDs per 1,000 inhabitants per day indicates that on average, 1% of the population gets a certain treatment daily. Antibacterial consumption in primary health care may also be presented as a number of packages per 1,000 inhabitants, and as a number of treated patients per 1,000 inhabitants. These measures reflect antibacterial consumption less accurately than DID, but may be used for comparison with countries that do not have the option of reporting consumption in DID. Also, when combining these measures, consumption measures at treated patient level are achievable, i.e. DDDs/patient or DDDs/package.

Primary health care sector — Penicillins

In 2008, the consumption of beta-lactamase sensitive penicillins (J01CE) decreased by 0.37 DID (6.5%) compared with 2007. This decrease from 2007–2008 was larger than the overall decrease (0.26 DID) in antibacterial agents for systemic use (J01) (Table 13). In all other groups of penicillins, consumption increased.

Within the group of penicillins with extended spectrum (J01CA), the increase in consumption was due to an increasing consumption of pivmecillinam — the only substance increasing in 2008 and for the first time, the most used substance within this group. Since 2007, pivmecillinam has become the first-line antibiotic for the treatment of urinary tract infections. (See Textbox 4). Compared with 2007, the antibacterial group that proportionally increased the most was combinations of penicillins, including beta-lactamase inhibitors (J01CR), increasing by 42%. The consumption level of combinations of penicillins, including beta-lactamase inhibitors used is still low, but the indications for the prescriptions of this group are poorly understood (See Textbox 3).

Over the last decade (1999–2008), the consumption of penicillins with extended spectrum increased by 0.97 DID (42%), beta-lactamase sensitive penicillins increased by 0.82 DID (18%), beta-lactamase resistant penicillins has increased by 0.64 DID (133%) and combinations of penicillins, including beta-lactamase

Table 13. Consumption of antibacterials for systemic use in human primary health care (DDD/1.000 inhabitant-days). Denmark

DANMAP 2008

ATC group a)	Therapeutic group	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	0.93	0.98	0.99	1.04	1.07	1.17	1.28	1.38	1.48	1.54
J01CA	Penicillins with extended spectrum	2.29	2.29	2.47	2.51	2.52	2.63	2.79	2.95	3.25	3.26
J01CE	Beta-lactamase sensitive penicillins	4.48	4.69	4.91	5.00	5.07	5.20	5.28	5.40	5.67	5.30
J01CF	Beta-lactamase resistant penicillins	0.48	0.52	0.65	0.77	0.85	0.92	0.97	1.05	1.09	1.12
J01CR	Combinations of penicillins. including beta-lactamase inhibitors	0.02	0.02	0.03	0.04	0.05	0.06	0.08	0.12	0.19	0.27
J01D	Cephalosporins and related substances	0.02	0.02	0.03	0.03	0.02	0.02	0.03	0.03	0.03	0.03
J01EA	Trimethoprim and derivatives	0.32	0.33	0.35	0.36	0.38	0.41	0.44	0.47	0.49	0.49
J01EB	Short-acting sulfonamides	0.38	0.37	0.36	0.36	0.36	0.36	0.35	0.35	0.31	0.28
J01EE	Combinations of sulfonamides and trimethoprim. including derivatives	0.03	0.03	0.04	0.03	0.03	0.00	0.00	0.00	0.00	0.00
J01FA	Macrolides	2.17	2.02	2.10	2.15	2.13	2.23	2.41	2.31	2.42	2.28
J01FF	Lincosamides	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02	0.03
J01GB	Aminoglycosides	0.00	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluoroquinolones	0.20	0.15	0.17	0.18	0.25	0.28	0.33	0.37	0.44	0.51
J01XA	Glycopeptides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
J01XB	Polymyxins	0.03	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
J01XC	Steroid antibacterials (fusidic acid)	0.02	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02
J01XE	Nitrofuran derivatives (nitrofurantoin)	0.36	0.38	0.39	0.41	0.42	0.43	0.45	0.46	0.47	0.47
J01XX05	Methenamine	0.40	0.36	0.33	0.34	0.32	0.30	0.28	0.27	0.26	0.27
J01XX08	Linezolid	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)	12.15	12.21	12.85	13.26	13.53	14.06	14.75	15.23	16.17	15.91

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

inhibitors increased by 0.25 DID (1250%), respectively (Table 13).

Figure 17 displays the changes in consumption penicillins and other selected groups of antibacterial agents during 1999–2008.

Primary health care sector — Macrolides

A decrease of 0.14 DID (5.8%) occurred in the consumption of macrolides from 2007 to 2008 (Table 13). Over the last decade, a fluctuating pattern of the consumption of macrolides has been observed; however, since 2003 roxithromycin consumption, and to some extend clarithromycin and azithromycin consumption, has increased while erythromycin consumption has decreased (Figure 18). These changes correspond to changes in treatment guidelines for primary health care from erythromycin towards first roxithromycin (2004 version), and to a lesser extend to the subsequent change to clarithromycin (2007 version) as first-choice macrolide (See Textbox 4). Throughout the last decade, azithromycin has been recommended for urethritis/cervicitis and epididymitis. In 2004 and 2005, part of the increase in roxithromycin consumption was likely due to an outbreak of *Mycoplasma pneumoniae* [DANMAP 2005]. In 2008, less than 20% of the macrolides prescribed had a code of indication other than ‘infection’ or ‘indication missing’ (See Textbox 3).

Primary health care sector — Tetracyclines

In 2008, consumption of tetracyclines increased by 0.06 DID (4.1%) compared with 2007.

Since 1999, an extensive increase in the consumption of certain substances of antibacterial agents in primary health care has been observed. The consumption of tetracyclines has increased by 66% during 1999–2008 (Table 13).

As previously pointed out in the DANMAP 2007 report, a major part of the consumption of tetracyclines was composed by tetracycline and doxycycline. Also, the majority of the tetracyclines used were prescribed for teenagers and young adults. During the last decade, the consumption of tetracycline has increased with peak values in the spring and autumn each year (Figure 19). This binary pattern might reflect doctors handing out six-month prescriptions for acne to adolescents when spring arrives, with follow-up in autumn. Conversely, the consumption of doxycycline has increased with peak values in January and in June each year. Many Danes travel to countries with high risk of malaria in January/February and June/July. Doxycycline is one of the substances recommended for malaria prophylaxis in areas of type IV risk (risk of *Plasmodium falciparum* malaria in combination with reported anti-malarial drug resistance) and malaria prophylaxis might be the explanation for the peaks. However, only 9% of the doxycycline prescribed

was documented by a code of indication as being prescribed for malaria, whereas 43% of the tetracycline prescribed was documented as being prescribed for acne. Otherwise, we have no information about the indication for prescription of this group (Textbox 3).

Primary health care sector — Fluoroquinolones

In 2008, consumption of fluoroquinolones increased by 0.07 DID (16%) compared with 2007. During 1999–2008, the consumption of fluoroquinolones has increased by 155% (Table 13). The continuously 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. However, prescriptions of fluoroquinolones contained very limited information on the indication. Only 30% of the prescriptions had an indication other than 'infection' or no indication at all (See Textbox 3).

Primary health care sector — Measures at treated patient level

The overall number (J01) of DDDs per treated patient increased from 17.3 in 2007 to 18.9in 2008. For all displayed substances, the number of DDDs per treated patient ranged from 10–20 in 2008 with the exception of tetracyclines (44.4) (Table 14). 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 is not available.

Tetracyclines and combinations of penicillins, including beta-lactamase inhibitors showed the largest increase in DDDs per treated patient and DDDs per prescribed package during 1999–2008 (Table 14). 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; e.g. for long-time (6-month) treatments of acne with tetracycline, the number of DDDs per prescribed package would increase. However, we lack detailed knowledge of the reasons for prescribing (See Textbox 3).

For combinations of penicillins, including beta-lactamase inhibitors, an explanation for this trend should be found in the decreasing proportion of children (<15 years) receiving this antibacterial compared with adults as pointed out in the DANMAP 2007 report. Packages of combinations of penicillins, including beta-lactamase inhibitors marketed in Denmark contain either 15 DDD (for adults) or 5 DDD (for children).

Primary health care sector — Other measures

Antibacterial consumption in primary health care is also presented in Table 15 as a number of packages per 1,000 inhabitants, and in Table 16 as a number of treated patients per 1,000 inhabitants. In 2008, the overall consumption of antibacterial agents (J01) for systemic use in the primary health care sector was 641 packages/1,000 inhabitants or 308 treated patients/1,000 inhabitants. Both measures were lower than in 2007, and both measures displayed similar (increasing and decreasing) trends as the consumption expressed as DID for each individual group of antibacterial agents in 2008 compared with 2007.

Table 14. Number of DDDs per treated patient and per package among selected groups in primary health care, Denmark

DANMAP 2008

ATC group a)	Therapeutic group	Indicator	Year									
			1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	DDDs / patient	28.1	29.8	30.6	33.0	34.4	36.9	39.0	40.9	43.0	44.4
		DDDs / package	15.3	15.7	16.1	17.5	18.1	19.0	19.6	21.0	22.0	22.7
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	14.7
		DDDs / package	8.1	8.1	8.1	8.2	8.2	8.4	8.5	8.9	9.0	9.2
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	11.8
		DDDs / package	7.0	7.1	7.1	7.2	7.3	7.5	7.7	8.0	8.2	8.2
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	13.7
		DDDs / package	8.1	7.9	7.9	7.5	7.4	7.8	8.0	8.6	8.7	9.0
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	19.9
		DDDs / package	6.6	6.7	9.1	8.6	9.1	9.1	9.3	10.7	11.7	12.4
J01FA	Macrolides	DDDs / patient	10.8	11.3	11.3	11.7	12.1	12.4	12.4	12.6	12.4	12.5
		DDDs / package	7.5	7.6	7.5	7.6	7.8	7.9	8.0	8.3	8.1	8.1
J01MA	Fluoroquinolones	DDDs / patient	8.0	7.8	8.3	8.6	10.3	9.5	9.6	10.3	10.6	11.0
		DDDs / package	5.7	5.7	5.9	6.0	6.6	6.4	6.5	6.9	7.0	7.5
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	18.9
		DDDs / package	7.7	7.7	7.8	7.8	7.9	8.1	8.3	8.7	8.9	9.1

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Primary health care sector — Main points

DANMAP 2008

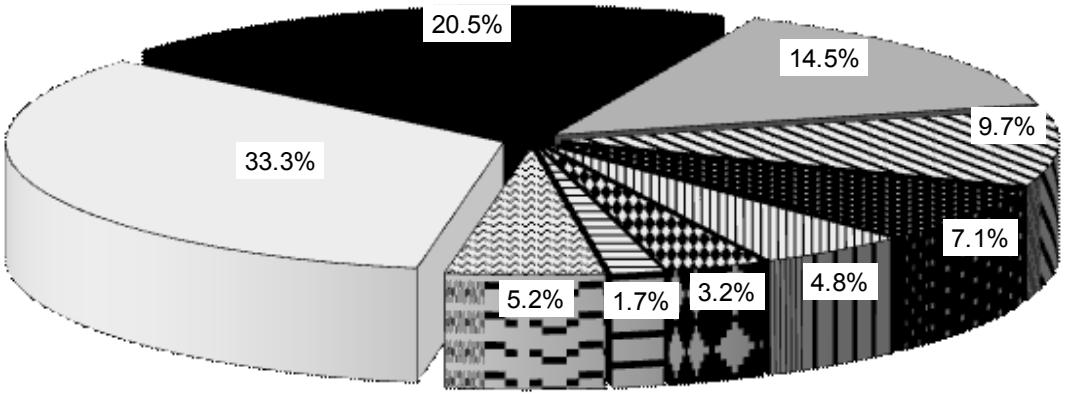


Figure 16. Distribution of the total number of DDDs of antibacterials in the primary health care sector, Denmark

Table 15. Consumption of antibacterials for systemic use in human primary health care (No. packages/1,000 inhabitants), Denmark

DANMAP 2008

ATC group a)	Therapeutic group	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	22.2	22.8	22.4	21.7	21.6	22.5	23.8	23.9	24.5	25.0
J01CA	Penicillins with extended spectrum	102.9	103.7	110.9	111.8	111.5	115.3	119.9	119.7	131.3	130.0
J01CE	Beta-lactamase sensitive penicillins	232.5	243.7	251.0	254.4	254.5	253.7	251.1	243.3	253.0	235.9
J01CF	Beta-lactamase resistant penicillins	21.5	24.0	30.1	37.5	41.9	43.0	44.4	44.0	45.8	45.4
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	1.1	1.1	1.2	1.7	2.0	2.5	3.0	4.0	5.8	8.0
J01D	Cephalosporins and related substances	1.0	1.0	1.3	1.4	1.3	1.39	1.6	1.7	1.8	2.1
J01EA	Trimethoprim and derivatives	7.8	7.9	8.2	8.8	9.3	10.2	10.6	10.7	11.5	12.4
J01EB	Short-acting sulfonamides	48.9	47.8	47.8	47.6	47.9	48.3	47.5	45.8	41.0	36.0
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	1.3	1.4	1.4	1.3	1.0	0.0	0.0	0.0	0.0	0.0
J01FA	Macrolides	106.3	97.3	102.2	102.8	99.8	102.7	110.3	101.8	108.6	103.3
J01FF	Lincosamides	0.3	0.4	0.5	0.6	0.6	0.7	1.1	1.4	1.6	2.0
J01GB	Aminoglycosides	0.1	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1
J01MA	Fluoroquinolones	12.7	9.7	10.6	11.0	13.8	16.2	18.3	19.4	22.9	25.1
J01XA	Glycopeptides	0.2	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2
J01XB	Polymyxins	2.9	2.8	2.1	2.0	2.0	2.1	2.0	1.5	0.8	0.8
J01XC	Steroid antibacterials (fusidic acid)	1.1	0.9	0.8	0.8	0.7	0.6	0.7	0.7	0.7	0.8
J01XE	Nitrofuran derivatives (nitrofurantoin)	9.8	10.4	10.4	11.1	11.3	11.7	12.3	12.5	11.9	12.2
J01XX05	Methenamine	3.8	3.5	3.2	3.2	2.6	2.4	2.3	2.0	1.9	2.0
J01XX08	Linezolid	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)	576.6	578.5	604.4	618.0	622.3	633.6	649.3	632.6	663.5	641.2

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

In 2008, the overall consumption of antibacterial agents for systemic use (J01) in the primary health care sector expressed in DID decreased by 1.6%, from 16.17 in 2007 to 15.91 DID (Table 13). This was the first time since 1999 that the overall consumption decreased. However, the decrease in total consumption was due to a reduction in only three antibacterial groups (beta-lactamase sensitive penicillins, macrolides and short-acting sulfonamides), especially observed in beta-lactamase sensitive penicillins (0.37 DID). In most other groups, the consumption increased: e.g. tetracyclines, combinations of penicillins, including beta-lactamase inhibitors, and fluoroquinolones. Beta-lactamase sensitive penicillins still represented the largest group of antibacterial agents consumed (33% of the total consumption) followed by penicillins with extended spectrum (20%) and macrolides (15%) (Figure 16).

Overall, antibacterial consumption expressed in DID increased by 31% during 1999–2008 (Table 13).
In 2008, 308 out of 1,000 Danes received at least one prescription of antibacterial agents in primary health care. In comparison, 320 out of 1,000 Danes received at least one prescription in 2007.
Thus, the overall decrease in the consumption expressed in DID is a product of fewer people having antibacterial agents prescribed despite an actual increase in the number of DDD prescribed for each individual patient (See Table 14 and Table 16).
When looking at trends in indicator measures of antibacterial consumption in primary health care during the last 10 years it becomes obvious that DDD is the indicator which has increased the most (Figure 20).
Data on the indications for antibacterial prescriptions in the Danish primary health care sector are in-complete; therefore, making assumptions of the nature of changes in trends is difficult (See Textbox 3).

Table 16. Consumption of antibacterials for systemic use in human primary health care (No. treated patients/1,000 inhabitants), Denmark.

DANMAP 2008

ATC group a)	Therapeutic group	Year									
		1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	12.1	12.0	11.8	11.5	11.4	11.6	12.0	12.3	12.5	12.7
J01CA	Penicillins w ith extended spectrum	66.7	65.6	69.4	69.2	68.8	70.6	73.0	75.8	82.1	81.3
J01CE	Beta-lactamase sensitive penicillins	164.0	168.9	173.3	173.4	172.6	171.2	170.2	171.3	177.1	164.4
J01CF	Beta-lactamase resistant penicillins	14.0	15.6	19.2	23.9	26.4	27.1	27.8	29.4	29.7	29.9
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.6	0.6	0.7	1.0	1.1	1.3	1.5	2.3	3.6	5.0
J01D	Cephalosporins and related substances	0.4	0.4	0.4	0.4	0.4	0.5	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	5.9
J01EB	Short-acting sulfonamides	34.4	33.5	33.2	33.0	33.1	33.3	32.7	33.0	29.7	26.3
J01EE	Combinations of sulfonamides and trimethoprim, including derivatives	0.8	0.8	0.8	0.7	0.6	0.0	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	66.9
J01FF	Lincosamides	0.2	0.2	0.2	0.3	0.3	0.4	0.4	0.5	0.6	0.8
J01GB	Aminoglycosides	0.0	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	17.1
J01XA	Glycopeptides	0.0	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	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	0.3
J01XE	Nitrofuran derivatives (nitrofurantoin)	5.7	5.8	5.7	6.1	6.2	6.4	6.7	7.0	6.5	6.8
J01XX05	Methenamine	0.7	0.6	0.5	0.6	0.5	0.5	0.5	0.4	0.4	0.4
J01XX08	Linezolid	-	-	-	0.0	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	308.2

a) From the 2008 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.

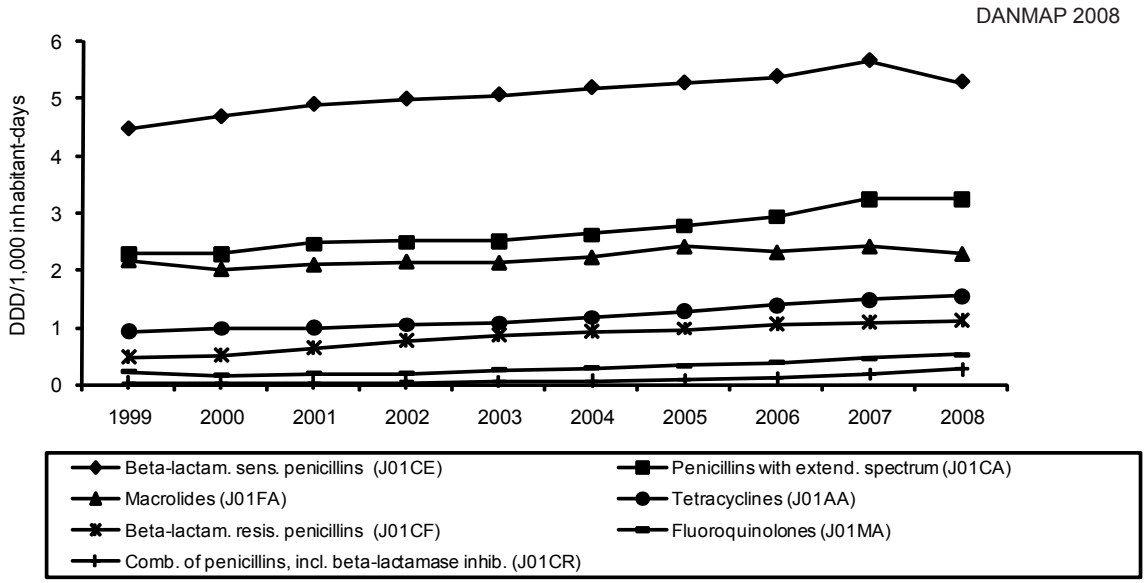


Figure 17. Consumption of selected antibacterials for systemic use in primary health care, Denmark

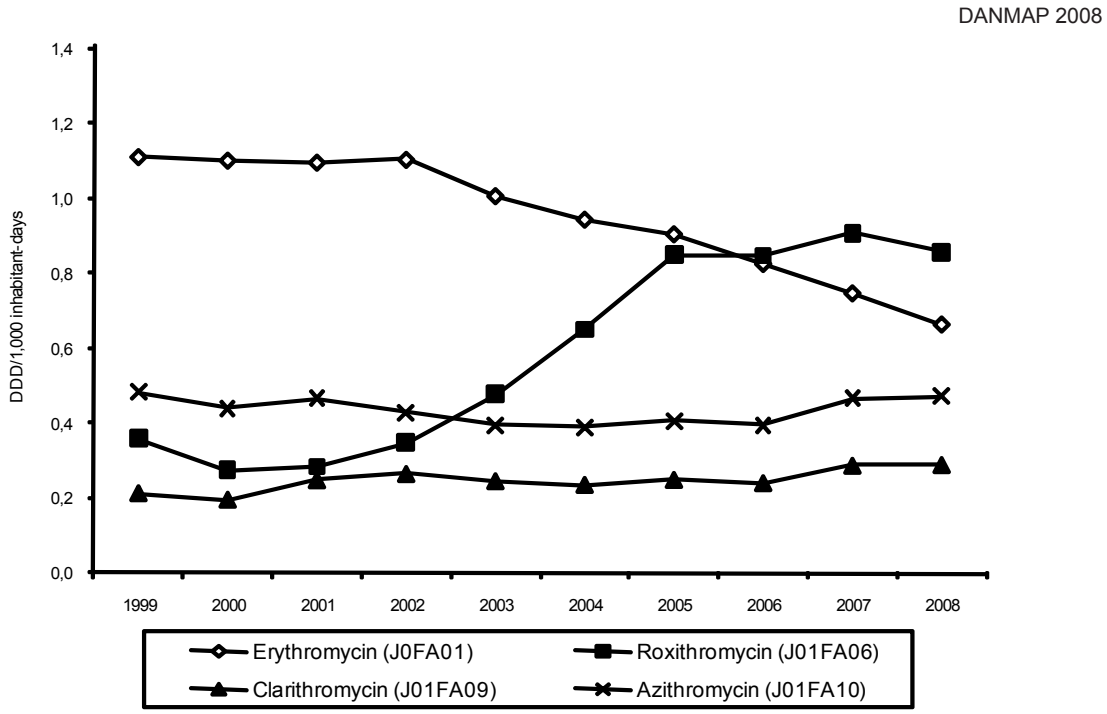


Figure 18. Consumption of macrolides in primary heath care, Denmark

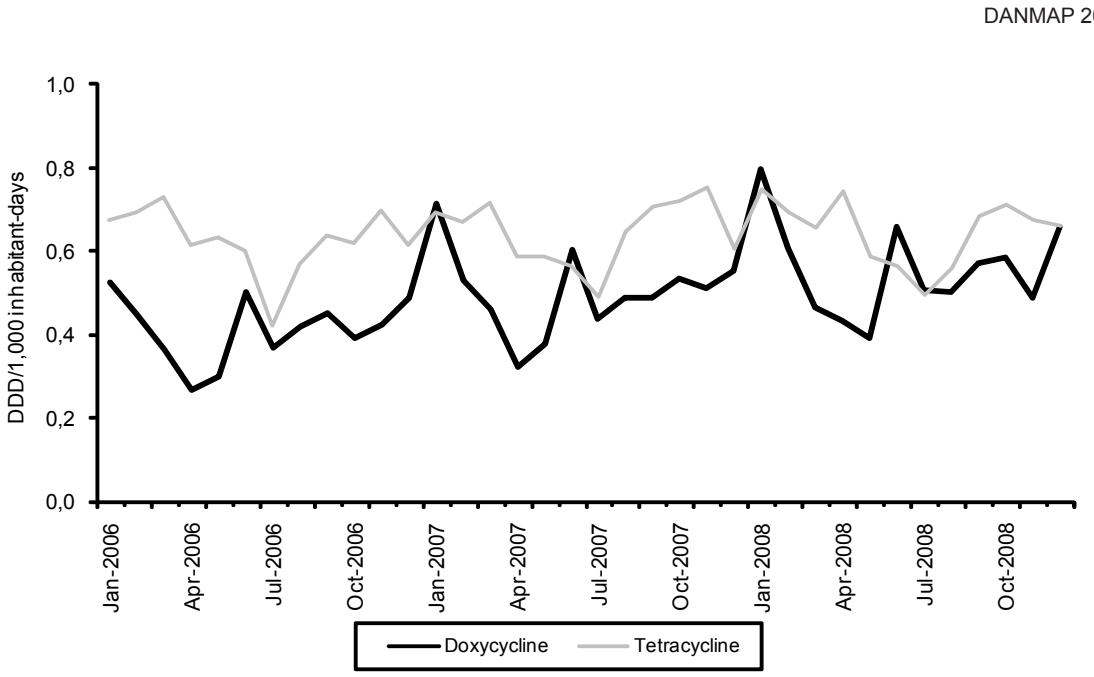


Figure 19. Monthly consumption of doxycycline and tetracycline in primary health care, Denmark

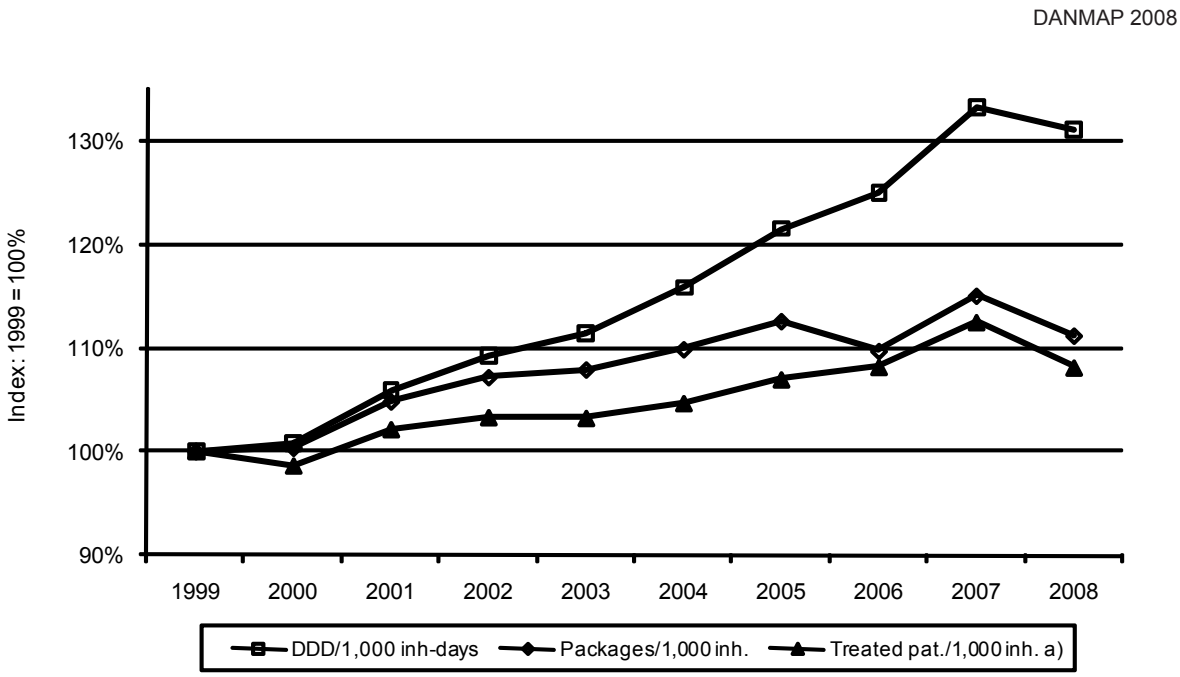


Figure 20. Trends in indicators of antibacterial consumption in primary health care, Denmark

a) Cumulated number of patients treated with anbacterials (ATC-4 level). The Danish Medicines Agency counts the first treatment within each ATC-group for each patient, each year.

Hospital sector — Definitions

Due to procedural rearrangements of certain chemical substances for infusion, the reporting of sales (consumption) by the hospital pharmacies to the Danish Medicines Agency has been inaccurate for some groups. Cephalosporins, carbapenems and combinations of sulfonamides and trimethoprim, incl. derivatives have been corrected for 2008, as it was done for 2005–2007 [DANMAP 2007]. In 2008, national data were not accessible for the consumption of combinations of sulfonamides and trimethoprim, incl. derivatives. Instead, data from eighteen hospitals within three regions are reported.

Data on the number of occupied bed-days and discharges from the National Board of Health have been updated and corrected from 2006–2007. This update has led to only minor changes in the reported consumption. This report contains up-to-date (not estimated) data on the number of occupied bed-days and discharges for 2008.

Regarding the hospital sector, consumption should preferably be presented as numbers of DDDs per 1,000 occupied bed-days (DBD). However, the number of DDDs per 1,000 discharged patients and DDD are also used.

Hospital sector — DDD

The distribution of the different classes of antibacterial agents used in hospitals was similar to 2007. Cephalosporins were the most used substances (20%) in 2008 (Figure 21).

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

The overall consumption (J01) in hospitals increased by 49.8 (7%) DDD/1,000 occupied bed-days (DBD) from 2007–2008 (699.4–749.2) (Table 17). Also, newer 'broad-spectrum' antibacterial agents (i.e. combinations of penicillins, including beta-lactamase inhibitor (J01CR), cephalosporins (J01DB, DC, DD), carbapenems (J01DH) and fluoroquinolones (J01MA) increased by 44.2 (17%) DBD (267.0–311.2). The increase of hospital consumption of combination of penicillins, including beta-lactamase inhibitors (J01CR) by 36% from 2007–2008 is parallel to the increase by 42% in primary care.

During 1999–2008, the overall consumption (J01) in hospitals increased by 296.3 (65%) DBD (452.9–749.2) (Table 17). This increase was due to a 38% increase in the number of DDDs of antibacterial agents registered by hospital pharmacies, and a concurrent 17% decrease in the total number of hospital bed-days registered in Denmark.

DANMAP 2008

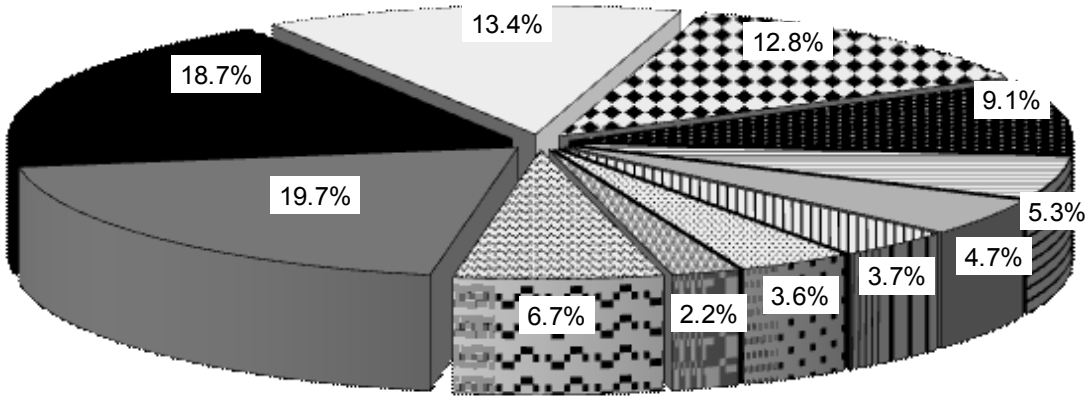


Figure 21. Distribution of the total number of DDDs of antibacterials in somatic hospitals, Denmark

From 1999–2008, a steady shift towards increasing consumption of newer, 'broad-spectrum' antibacterial agents (i.e. combinations of penicillins, including beta-lactamase inhibitor (J01CR), cephalosporins (J01DB, DC, DD), carbapenems (J01DH) and fluoroquinolones (J01MA)) has occurred. The consumption (represented by the filled symbols in Figure 22) has increased by 237.2 (321%) DBD (74.0–311.2) since 1999.
In 1999, consumption of penicillins with extended spectrum represented 25% of total hospital antibacterial consumption in Denmark, but has since decreased to 19% in 2007 and 2008. The decrease mainly concerned ampicillin/pivampicillin whereas consumption of mecillinam/pivmecillinam has increased. 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 antibacterial agents (See Focus area 1).
Due to the general hospital strike (See Textbox 1) fewer occupied bed-days have been registered in 2008 than would have been expected without the strike. Therefore, the number of DDDs per 1,000 occupied bed-days in 2008 is higher than if 2008 the general hospital strike had not occurred.

Hospital sector — DDD/1,000 discharged patients

When expressed as the number of DDDs per 1,000 discharged patients the overall consumption (J01) in hospitals increased by 168.0 (6%) from 2007–2008 and by 608.8 (25%) during 1999–2008 (Table 17).
Due to the general hospital strike (See Textbox DEM, page ZZ) fewer discharges have been registered in 2008 than would have been expected without the strike. Therefore, the number of DDDs per 1,000 discharged patients in 2008 is higher than if the general hospital strike had not taken place.

Antibacterial consumption in hospitals has continuously increased during 1999–2008 whether expressed as the number of DDDs, as DBD or as DDD/1,000 discharged patients, respectively.

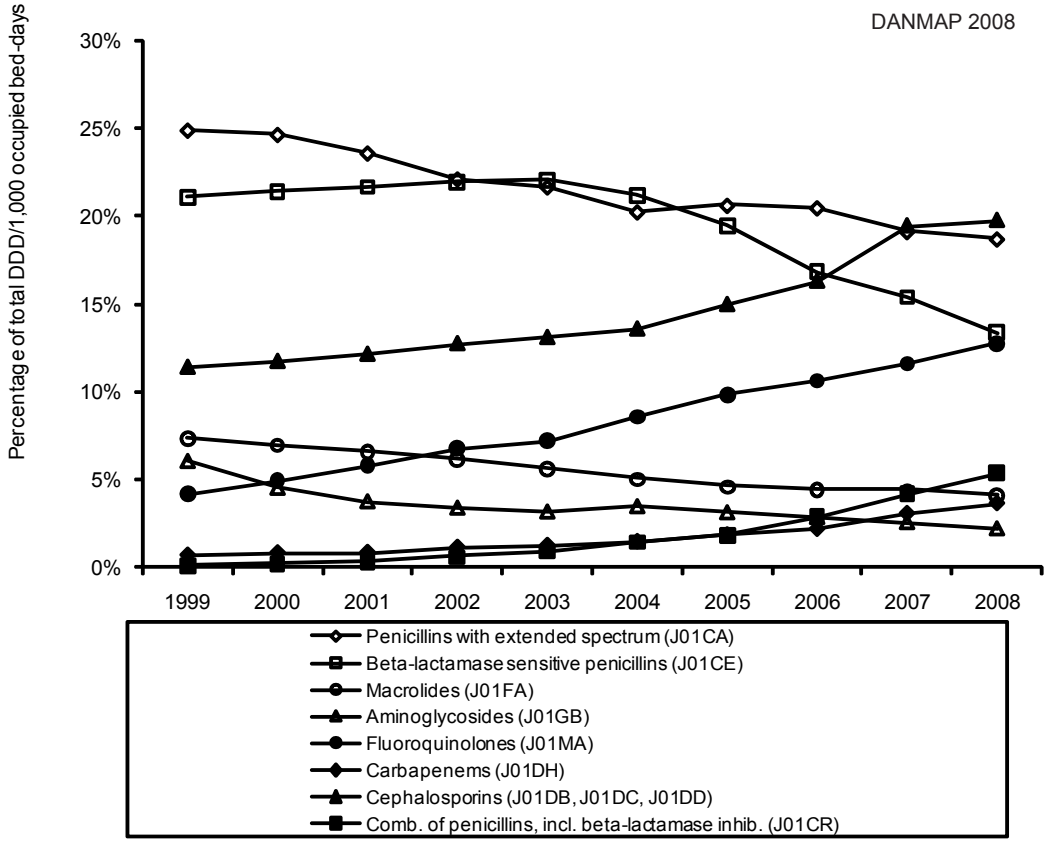


Figure 22. Percentages of total hospital consumption represented by selected groups of antibacterials for systemic use, Denmark

Hospital sector — Main points

The overall consumption (J01) expressed in DDDs per 1,000 occupied bed-days (DBD) increased by 7% from 699.4 in 2007 to 749.2 in 2008. When expressed as the number of DDDs per 1,000 discharged patients it increased from 2,887 in 2007 to 3,055 in 2008 (6%).
The consumption of all the major antibacterial groups increased with the exception of beta-lactamase sensitive penicillins and aminoglycosides.
Cephalosporins accounted for 20% of the consumption in the hospital sector, while penicillins with extended spectrum (19%), beta-lactamase sensitive penicillins (13%) and fluoroquinolones (13%) were other major contributing antibacterial groups.
The reported antibacterial consumption from the hospital sector was higher than expected whether express as DBD or DDDs per 1,000 discharged patients. An important factor was a general hospital strike during the spring of 2008 that led to fewer discharges and occupied bed-days, but presumably only to a minor decrease in the consumption of antibacterial agents (DDD).

Table 17. 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 2008

ATC group [a]	Therapeutic group	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	2.8	2.9	2.8	3.2	3.1	3.5	3.4	4.0	6.3	7.8
J01CA	Penicillins with extended spectrum	112.7	115.7	116.1	115.2	119.2	117.9	130.1	130.9	134.2	140.2
J01CE	Beta-lactamase sensitive penicillins	95.3	100.3	106.5	114.3	121.2	123.1	122.6	107.4	107.9	100.3
J01CF	Beta-lactamase resistant penicillins	48.3	53.5	60.2	62.8	66.8	69.9	67.6	65.5	67.0	68.4
J01CR	Combinations of penicillins. incl. beta-lactamase inhibitors	0.4	0.9	1.7	3.1	5.0	8.5	11.7	18.5	29.5	40.2
J01DB	First-generation cephalosporins	1.2	1.0	1.2	1.4	1.4	1.7	1.5	1.4	1.3	1.8
J01DC	Second-generation cephalosporins	44.0	47.4	52.1	58.5	63.9	70.6	84.6	94.4	123.1	133.8
J01DD	Third-generation cephalosporins	6.4	6.7	6.5	6.5	6.7	6.8	8.3	8.4	10.3	12.5
J01DF	Monobactams	0.1	0.2	0.1	0.0	0.0	0.1	0.0	0.0	0.4	0.7
J01DH	Carbapenems	3.2	3.9	4.2	6.0	6.9	8.6	11.6	13.9	21.3	27.2
J01EA	Trimethoprim and derivatives	3.8	3.7	4.3	4.2	4.4	4.2	4.1	4.2	4.4	4.4
J01EB	Short-acting sulfonamides	12.9	12.3	12.5	12.4	11.8	10.8	9.9	7.6	3.4	3.5
J01EE	Combinations of sulfonamides and trimethoprim. incl. derivatives	13.7	14.0	13.4	14.6	15.4	18.3	21.2	21.3	15.2	19.6
J01FA	Macrolides	33.5	32.8	32.6	32.3	30.9	29.4	29.1	28.5	30.8	30.7
J01FF	Lincosamides	1.5	1.6	1.7	1.9	1.9	2.3	2.4	3.1	3.5	4.2
J01GB	Aminoglycosides	27.6	21.3	18.5	17.7	17.4	20.3	19.7	18.2	17.9	16.4
J01MA	Fluoroquinolones	18.8	23.1	28.4	35.2	39.6	49.8	61.9	67.8	81.6	95.8
J01XA	Glycopeptides	2.8	3.3	3.2	3.7	4.2	4.7	5.2	5.6	6.3	6.8
J01XB	Polymyxins	0.3	0.4	0.3	0.3	0.3	0.6	1.2	1.2	0.5	0.5
J01XC	Steroid antibacterials (fusidic acid)	2.6	2.3	2.0	1.9	2.2	2.2	2.6	2.8	2.8	2.6
J01XD	Imidazole derivatives	16.2	17.9	19.6	21.1	23.7	24.7	26.4	28.0	26.2	25.6
J01XE	Nitrofuran derivatives (nitrofurantoin)	3.0	2.9	2.9	2.8	2.8	2.8	3.0	2.9	2.8	2.9
J01XX05	Methenamine	1.6	1.4	1.3	1.2	0.8	1.0	0.8	1.1	0.9	1.0
J01XX08	Linezolid	0.0	0.0	0.0	0.4	0.4	0.7	1.5	2.0	1.6	2.1
J01XX09	Daptomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2
J01	Antibacterials for systemic use (total)	452.9	469.5	492.1	521.0	550.0	582.4	630.8	639.0	699.4	749.2

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 18. 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 2008

ATC group a)	Therapeutic group	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	15.4	15.4	14.8	16.3	14.8	15.8	14.6	16.8	25.9	31.9
J01CA	Penicillins with extended spectrum	608.7	610.5	604.9	578.0	566.2	535.2	567.1	552.2	553.9	571.9
J01CE	Beta-lactamase sensitive penicillins	514.6	529.1	555.0	573.5	575.9	558.5	534.6	453.3	445.5	409.0
J01CF	Beta-lactamase resistant penicillins	260.9	282.5	313.7	314.9	317.3	317.0	294.8	276.5	276.4	278.9
J01CR	Combinations of penicillins. incl. beta-lactamase inhibitors	2.4	4.9	8.9	15.6	23.6	38.5	51.1	77.9	121.7	163.8
J01DB	First-generation cephalosporins	6.7	5.2	6.1	7.2	6.8	7.7	6.7	6.0	5.5	7.2
J01DC	Second-generation cephalosporins	237.7	250.2	271.5	293.6	303.6	320.5	368.8	398.3	508.09	545.6
J01DD	Third-generation cephalosporins	34.8	35.6	34.0	32.5	32.0	30.9	36.4	35.4	42.4	51.0
J01DF	Monobactams	0.8	0.9	0.5	0.2	0.2	0.2	0.2	0.0	1.8	2.7
J01DH	Carbapenems	17.2	20.6	21.9	29.9	32.7	38.8	50.8	58.7	87.8	110.8
J01EA	Trimethoprim and derivatives	20.7	19.5	22.6	21.0	21.0	19.0	17.9	17.8	18.1	18.0
J01EB	Short-acting sulfonamides	69.7	64.9	64.9	62.2	55.8	49.2	43.4	31.9	14.1	14.3
J01EE	Combinations of sulfonamides and trimethoprim. incl. derivatives	74.1	73.6	70.0	73.2	73.1	83.2	92.6	89.9	62.8	79.8
J01FA	Macrolides	180.8	173.1	170.1	161.9	146.7	133.3	127.0	120.3	127.0	125.4
J01FF	Lincosamides	8.1	8.5	9.0	9.5	9.0	10.4	10.5	13.1	14.6	16.9
J01GB	Aminoglycosides	149.0	112.5	96.4	88.6	82.8	91.9	85.9	76.9	73.9	67.1
J01MA	Fluoroquinolones	101.4	121.8	148.1	176.7	188.0	226.0	270.0	286.3	336.6	390.5
J01XA	Glycopeptides	15.3	17.2	16.6	18.8	19.9	21.2	22.9	23.8	26.1	27.7
J01XB	Polymyxins	1.8	2.1	1.5	1.7	1.5	2.7	5.4	5.3	2.2	2.1
J01XC	Steroid antibacterials (fusidic acid)	14.2	12.1	10.2	9.7	10.5	10.2	11.1	12.0	11.7	10.5
J01XD	Imidazole derivatives	87.6	94.5	102.0	106.0	112.5	112.1	115.3	118.3	108.3	104.6
J01XE	Nitrofuran derivatives (nitrofurantoin)	16.3	15.5	15.0	14.2	13.1	12.8	12.9	12.4	11.7	11.9
J01XX05	Methenamine	8.6	7.5	6.7	6.1	3.9	4.6	3.6	4.6	3.8	4.3
J01XX08	Linezolid	0.0	0.0	0.0	2.2	2.1	3.3	6.4	8.6	6.8	8.4
J01XX09	Daptomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.6
J01	Antibacterials for systemic use (total)	2,446.2	2,477.6	2,564.6	2,613.3	2,613.0	2,642.8	2,750.0	2,696.5	2,887.0	3,055.0

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Textbox 3

Incomplete codes of indication from prescription sales in primary health care

In the early 1990s, a national register of drug statistics was implemented by the Danish Medicines Agency to monitor the consumption and cost of medicinal products in Denmark. The Danish national register is unique since it is the only register in the world on medicinal products containing detailed and well arranged information on national antibacterial consumption of the entire population over a vast period of time.

More than > 95% of the Danish general practitioners (GPs) have implemented electronic patient records enabling them to communicate with both pharmacies and public health care institutions.

Every fortnight, the Danish Medicines Agency sends out a tariff on all medicines to the Danish general practitioners (GPs). Apart from the price on all registered medicines, the tariff includes codes of indication specific for each substance. When prescribing a substance, the PGs supposedly select one specific code of indication that is labelled on the substance at the pharmacy when distributed to the patient. The code is a piece of information for the patient on what the substance has been prescribed for. However, prescriptions without a code of indication may also be redeemed.

Unfortunately, the codes of indication were developed years before the national register of drug statistics was implemented. One of the codes: 'against infection' holds no information on the specific indication of the antibacterial substance.

We undertook a small investigation on which codes were used for selected antibacterial substances in 2008.

Two codes dominated all the examined substances — 'indication missing' and 'infection'.

Figure 23 displays four selected substances with an increasing consumption. The codes 'indica-tion missing' and 'infection' were used on 55–81% of the prescriptions. Specific codes were: cipro-floxacin (urinary tract infection (16.6%) and gastroenteritis (11.6)), amoxicillin and enzyme inhibitor (respiratory tract infection (23.5%)), tetracycline (acne (43.5%)) and doxycycline (malaria prophylaxis (8.8%), infections in the reproduction organs (3.1%) and acne (2.9%)).

All four macrolides registered in Denmark showed similar patterns of prescription. In less than 20% of the prescriptions the indication was accounted for — that is, more than 80% of the prescriptions held either 'indication missing' or 'infection'. All macrolides were used for respiratory tract infections (6–14%); azithromycin was specifically used for infections in the reproduction organs (2.6%), clarithromycin for eradication of *Helicobacter pylori* (1.9%) and erythromycin for acne (10.6%) (Figure 24).

This investigation shows that only a fraction of the prescriptions of antibacterials have codes of indication. Therefore, making assumptions on what specific antibacterial agents are prescribed for is highly unreliable and should be interpreted with caution.

There is a great need for a mandatory registration procedure that could ensure patient safety and promote surveillance of antibacterial agents. One obvious, and internationally acknowledged, approach is to link each prescription to the ICPC-2 (International Classification of Primary Care) code [Wonca. International Classification of Primary Care. ICPC-2-R. Second edition. New York: Oxford University Press, 2005].

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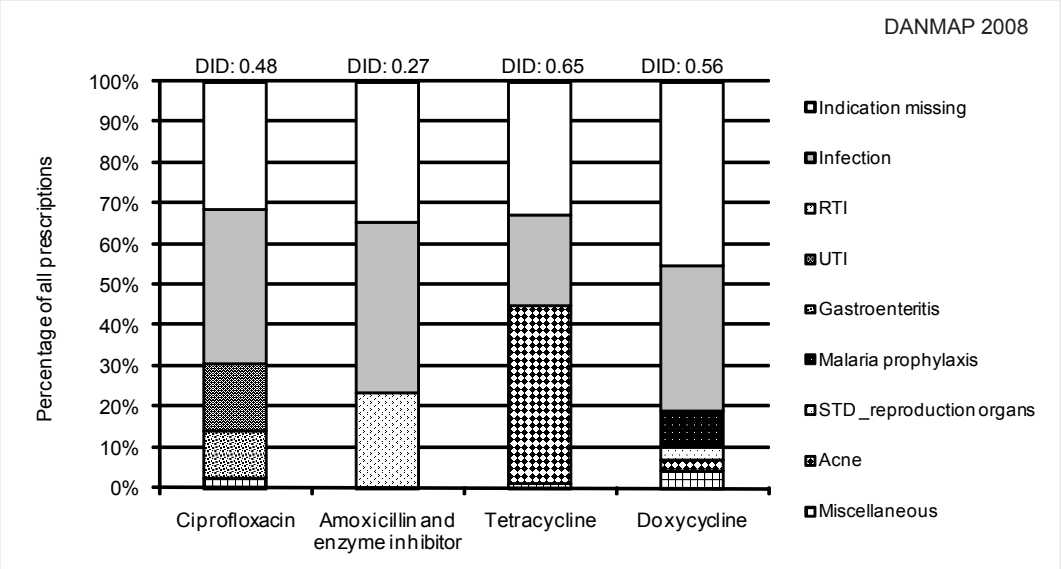

Figure 23. Indications of prescriptions of selected antibacterials for systemic use in primary health care, Denmark

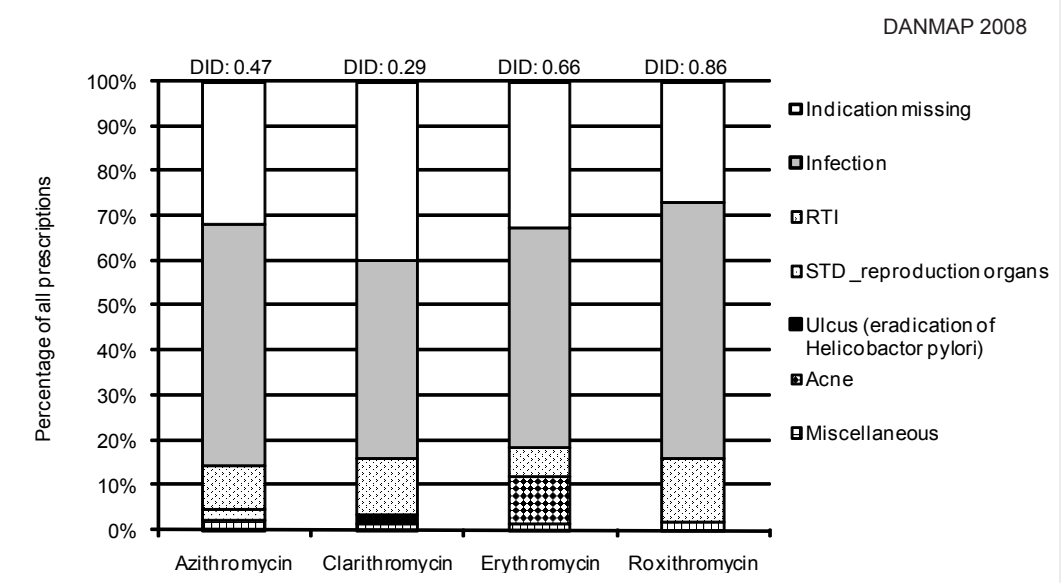

Figure 24. Indications of prescriptions of macrolides for systemic use in primary health care, Denmark

Textbox 4

Changes in antibacterial guidelines during the last 10 years in the Danish primary health care sector

In Denmark, medical doctors and dentists have the right to prescribe medicines for humans.
Overall, doctors have the legal right to choose freely any drug they find indication for. Only a few drugs are individually limited to specialists within different fields or for hospital use only.
Although regional guidelines and guidelines from individual medical societies exist, national guidelines for the prescription of antibacterials in primary health care have been published annually for more then ten years and maintained by the Danish Medical Association through 'Medicinfortegnelsen' — since 2006 published as 'medicin.dk; www.medicin.dk' by A/S Infomatum; a collaboration between the Danish Medical Association and Danish Drug Information; the latter owned by The Danish Association of the Pharmaceutical Industry.
These guidelines have been authored by specialists within their field, and have been reviewed by appointed members from relevant medical societies. All authors have been appointed by the medical societies.
In regards to several of the infectious diseases treated in PHC, the choice of antibacterial agent and dosing regimen of the agent of choice has not changed in the guidelines since 1999. However, for some infectious diseases guidelines have been altered, resulting in either an alternative antibacterial agent recommended or a different dosing regimen of the agent of choice. Thereby, changes in guidelines have resulted in an increased number of DDDs prescribed (Table 19).
Thus, the increase in primary health care consumption and changes between antibacterial groups and substances that have been observed throughout the last decade is partly due to changes in guidelines, but without data on the indications of antibacterial prescriptions, the explanation for the increasing consumption will remain undisclosed (See Textbox 3).

Table 19. Changes in guidelines during the last decade in primary health care, Denmark

DANMAP 2008

Guideline in case of	Year								
	1999–2004			2004–2006			2007–2008		
	1. choice substance	Regime	DDD/day	1. choice substance	Regime	DDD/day	1. choice substance	Regime	DDD/day
Tonsilitis	Penicillin V	666 mg x 2	0,66	Penicillin V	666 mg x 2	0,66	Penicillin V	666 mg x 3	1
Sinusitis (if necessary)	Penicillin V	1333 mg x 2	1,33	Penicillin V	1333 mg x 2	1,33	Penicillin V	666 mg x 3	1
Penicillin allergy	Erythromycin (ethylsuccinate)	500 mg x 3	0,75	Roxithromycin	300 mg x 1	1	Clarithromycin	500 mg x 2	2
Penicillin allergy (children)	Erythromycin (ethylsuccinate)	40 mg/kg/day	0.02/kg	Erythromycin (ethylsuccinate)	40 mg/kg/day	0.02/kg	Clarithromycin	7.5 mg/kg/day	0.015/kg
COPD (Acute exacerbation) a)	No treatment recommended	-	0	No treatment recommended	-	0	Penicillin V or Amoxicillin-clavulanic acid	666 mg x 3 or 500/125 mg x 3	1 or 1.5
Helicobacter pylori infection	Amoxicillin + Metronidazol	750 mg x 3 + 250 mg x 3	2.25 + 0.38	Amoxicillin + Metronidazol	750 mg x 3 + 250 mg x 3	2.25 + 0.38	Amoxicillin + Metronidazol	1000 mg x 3 + 500 mg x 2	3 + 0.5
Impetigo (bulleous)	No specific recommendation	-	0	No specific recommendation	-	0	Dicloxacillin	1000 mg x 3	1,5
Mastitis	No specific recommendation	-	0	No specific recommendation	-	0	Dicloxacillin	1000 mg x 3	1,5
Gonorrhea	Pivampicillin + Probenecid	1400 mg once + 1000 mg once	1.33 + 1	Pivampicillin + Probenecid	1400 mg once + 1000 mg once	1.33 + 1	Ceftriaxone	250 mg (i.m.) once	0,125
UTI (uncomplicated) b)	Sulfamethizol	1000 mg x 2	0,5	Sulfamethizol	1000 mg x 2	0,5	Pivmecillinam	400 mg x 3	2
UTI (complicated)	Pivmecillinam	200 mg x 3	1	Pivmecillinam	200 mg x 3	1	Pivmecillinam	400 mg x 3	2
Pyelonephritis (mild)	Trimethoprim	200 mg x 2	1	Trimethoprim	200 mg x 2	1	Pivmecillinam	400 mg x 3	2

a) COPD = chronic pulmonary obstructive disease
b) UTI = urinary tract infection

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Textbox 5

An ageing population cannot explain the increased consumption of 'broad-spectrum' antibacterials in primary health care

It is often suggested that as the population ages, the consumption of antibacterials increases overall. Figure 25 shows the actual consumption of 'broad-spectrum' antibacterials (defined as ATC groups J01AA (Tetracyclines), J01CA (Penicillins with extended spectrum), J01CR (Combinations of penicillins, incl. beta-lactamase inhibitors), J01FA (Macrolides) and J01MA (Fluoroquinolones)) in 1999 and 2007.

The consumption in 2007 was estimated by measuring the actual consumption in 1999 for each age and gender group (individuals of same gender born the same year). The measured consumption per individual was then multiplied by the number of individuals in the same age and gender group in 2007. The actual consumption increased by 43%, which is a much larger increase than the estimated increase of a mere 3%. Thus the majority of the increase cannot be explained by an ageing population.

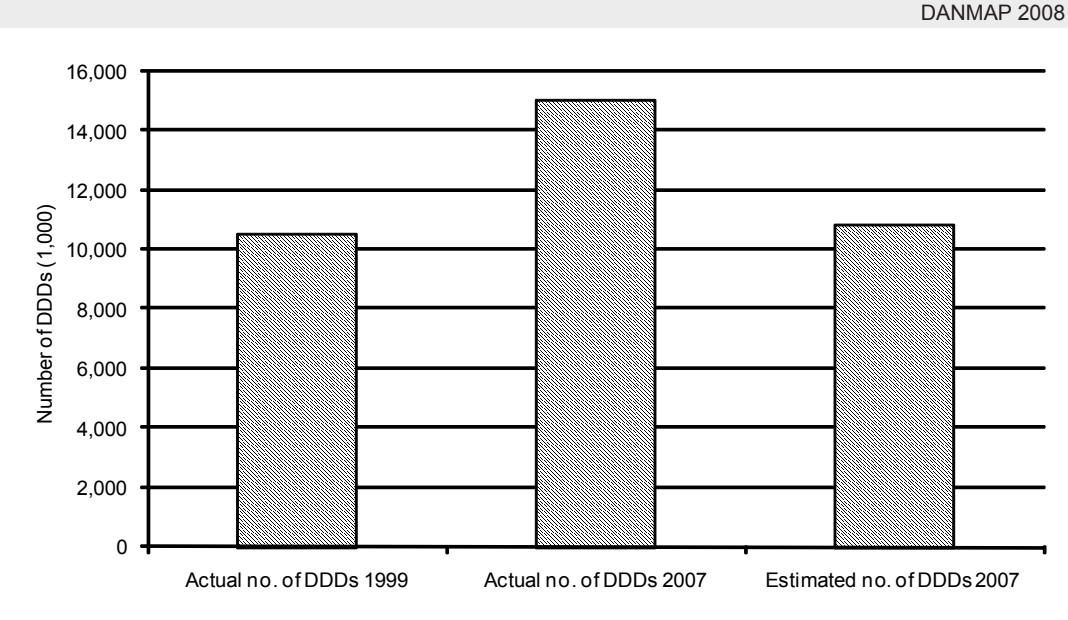

Figure 25. Consumption of 'broad-spectrum' antibacterials — actual and expected calculated from the projection of the prescription pattern of 1-year age groups and gender 1999–2007 — in primary health care, Denmark

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Textbox 6

Is it possible to explain the increased consumption of fluoroquinolones?

It is not possible to gain adequate information concerning the indications for the use of fluoroquinolones (See Textbox 3). However, if more people bring fluoroquinolones with them when travelling abroad, this could account for part of the increase. Thus, one would expect to find the highest increase in the younger adult population, as they tend to travel more than other age groups. However, the largest increase in the consumption of fluoroquinolones is seen in the older adult population (Figure 26).
In general, the consumption of fluoroquinolones is low in children and increases with age. It is not plausible that the increased consumption of fluoroquinolones from 1999–2007 is explained by an increased quantity being brought on travels, but this aspect cannot be fully elucidated on the basis of the data available.

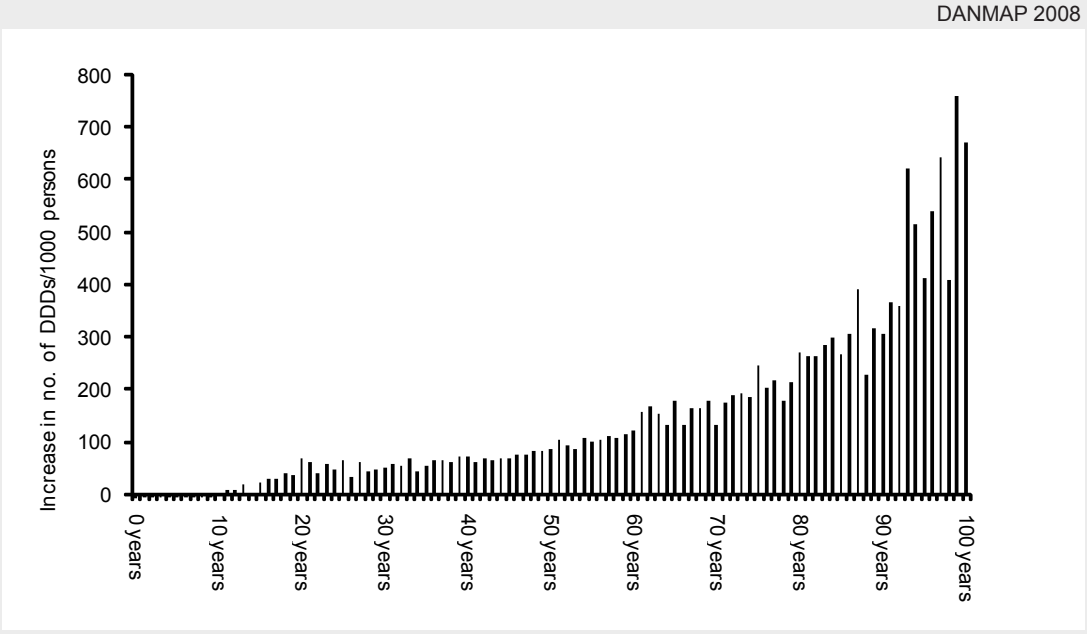

Figure 26. Increase in the number of DDDs/1,000 persons by age 1999–2007 in primary health care, Denmark

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Resistance in zoonotic bacteria

Salmonella

In 2008, a total of 3,654 human cases of salmonellosis (67 per 100,000 inhabitants) was registered. *Salmonella* Typhimurium accounted for 2,002 cases and *Salmonella* Enteritidis for 638 cases [EPI-NEWS 2009, no. 11: http://www.ssi.dk/sw64290.asp]. The remaining 1,014 cases were caused by 119 other serotypes. In 2008, SSI collected travelling information by phone interviews from all *Salmonella* patients residing in the former counties of North Jutland, Funen and Roskilde. The patients were asked about the date of disease onset and whether they had travelled abroad within a seven-day period prior to disease onset. Patients who had travelled were asked about their destinations. The case was categorised as "domestically acquired" if the patient had not been travelling one week prior to the onset of infection whereas the case was categorised as "travel abroad reported" if the patient had travelled within one week prior to the onset of infection. Cases where patients had not reported travel to the general practitioners or not been interviewed by phone were categorised as "unknown origin". Information was obtained from a total of 83% of the Salmonella cases in the three former counties.
Sixty-two percent (391) of the *S.* Enteritidis isolates and 83% (1,664) of the *S.* Typhimurium isolates were analysed for antimicrobial resistance (Table 42 and 44 in Appendix 1).

Large outbreaks

The occurrence of *S*. Typhimurium was rather unusual in 2008, with several large outbreaks, accounting for 76% of all human *S.* Typhimurium isolates. The outbreaks or "clusters" were defined by the molecular typing method MLVA (multiple locus variable number tandem repeats analysis). Outbreak-related phage types were U292, DT135, DT3, DT120, U288, and U312 (Table 20). Most of these phage types (except DT120) were rare phage types in previous years. Isolates belonging to these clusters were generally fully sensitive to all tested antimicrobial agents. The decrease in resistance level seen in 2008 for *S.* Typhimurium is in explained by the occurrence of these outbreaks. Among the isolates not belonging to the large outbreaks, 58% were fully sensitive to the tested antimicrobial agents. The majority of the *S*. Typhimurium isolates, which were not analysed for antimicrobial resistance, belonged to the cluster of phage type U292 isolates that included a total of 1200 cases in 2008.
Data with and without the major outbreaks are presented in Table 44 in Apendix 1. In Figure 27 and Table 21 are the major outbreaks (U292, DT3, DT135) excluded.

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

As in previous years *S.*Typhimurium was the most common serotype in Danish pigs and pork. The most prevalent *S.* Typhimurium phage type in Danish pigs and pork was DT120, followed by DT12. In contrast to previous years, the phage type distribution in human domestically acquired cases deviated from the isolates from pork, due to the high number of cases associated with the large outbreaks in 2008 (Table 20). Regarding *S.* Typhimurium from imported pork, DT104 was the most prevalent phage type, followed by DT193 and DT120, while DT12 were not detected. The phage types DT104 and DT193 were also frequently isolated from travel associated human cases. The phage type distribution in Danish pigs was almost identical in 2007 and 2008; for Danish pork, the phage type distribution was also similar in 2007 and 2008.
For the first time, ceftiofur resistance was detected in *S.* Typhimurium from Danish pork. Ceftiofur resistance was also detected in *S*. Typhimurium from pigs in 2008. The consumption of cephalosporins in pigs has been increasing from 2001 to 2007, but did not increase further in 2008. Although the consumption of 3rd and 4th generation cephalosporins is only 0.1% of the antimicrobial consumption in pig, an estimated 15-30% of all piglets in the Danish production are treated (see DANMAP 2007). Therefore, the consumption and increasing levels of ESBL in diagnostic submission, and now also ceftiofur resistance in healthy animals and food are of major concern. In *S*. Typhimurium isolates from Danish pigs, the occurrence of gentamicin and ampicillin resistance has increased significantly from 2007 to 2008 (Figure 27). Resistance to ampicillin has increased continuously since 2001. Furthermore, a significant decrease in neomycin and spectinomycin resistance was observed in *S*. Typhimurium from Danish pigs in 2008 compared to 2007. Neomycin consumption has deceased 99.7% from 2006 through 2008, while apramycin consumption in pigs has increased by 24% during the same period. All but one of the gentamicin resistant isolates were also resistant to apramycin. It is likely that increasing consumption of apramycin has

Table 20. 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 2008

Phage types	Poultry	Cattle	Pigs	Pork		Broiler meat	Turkey meat	Humans a) b)		
	Danish %	Danish %	Danish %	Danish %	Imported %	Imported %	Imported %	Domestically acquired %	Travel abroad reported %	Unknown origin %
3 c)	-	-	<1	-	-	-	-	4	0	2
12	0	17	13	14	0	-	-	2	1	10
15a	0	0	1	2	0	-	-	<1	0	0
17	0	0	7	11	0	-	-	<1	0	<1
41	0	0	<1	0	0	-	-	<1	1	0
104/104b/104c	0	17	9	9	30	2	41	1	9	6
120 c)	33	17	24	19	11	-	7	7	11	13
135 c)	-	-	1	2	0	-	-	7	2	2
170	0	6	8	3	0	-	-	<1	2	2
193	0	11	8	2	21	19	31	2	9	10
U288 c)	-	-	3	1	0	-	-	4	0	2
U292 d)	-	11	1	-	-	2	-	60	18	5
U302	0	11	2	7	0	-	-	2	4	6
U312 c)	-	-	<1	1	2	-	-	<1	0	2
Others including non-typeable	67	11	21	27	36	77	21	11	42	41
Number of isolates	3	18	497	99	56	48	29	1392	98	109

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'
c) In 2008, human outbreak-related S. Typhimurium phage types were DT135, DT3, DT120, U288 and U312, see info box on S. Typhimurium outbreaks in 2008
d) In 2008, a human outbreak caused by S. Typhimurium phage type U292 including 1200 cases occurred, see info box on S. Typhimurium outbreaks in 2008

DANMAP 2008

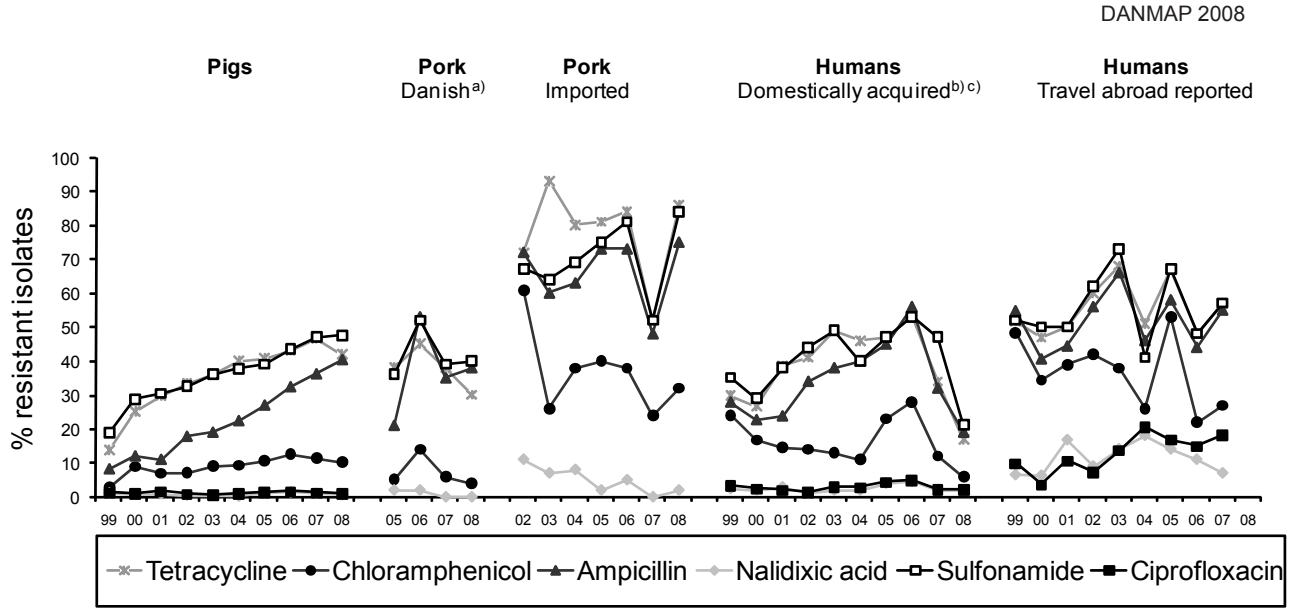

Figure 27. Trends in resistance to selected antimicrobials among Salmonella *Typhimurium isolated from pigs, pork and from human cases, Denmark*

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
c) In 2008, several larger outbreaks caused by e.g. S. Typhimurium phage type U292, DT3 and DT135 occurred. These isolates were excluded here. See also introduction on Salmonella, regarding the outbreaks in 2008.

been driving the increase in gentamicin resistance, as this association has been shown previously for *E. coli* [Jensen *et al*., 2006 J Antimicrob Chemother. 58:101-7.].

From 2007 to 2008, the only significant trend observed among *S.* Typhimurium isolates from Danish pork was a decrease in neomycin resistance (Figure 27; neomycin not shown). The occurrence of resistance to chloramphenicol, tetracycline, florfenicol and sulfonamide were all significantly higher in isolates from Danish pigs compared to isolates from Danish pork (Table 21).

Comparison of *S.* Typhimurium isolates from imported pork to isolates from Danish pork shows a significantly higher occurrence of resistance to ampicillin, chloramphenicol, florfenicol, spectinomycin, streptomycin, sulfonamide, tetracycline and trimethroprim in the isolates from imported pork (Table 21).

The occurrence of resistance in domestically acquired human *S.* Typhimurium isolates was more similar to the resistant pattern in isolates from Danish pork than isolates from imported pork (Table 21). In domestically acquired human isolates of *S.* Typhimurium the highest levels of resistance (17-21%) were found for sulfonamide, ampicillin, streptomycin and tetracycline.

In *S.* Typhimurium isolates from Danish pork, the highest level of resistance (30-41%) was found for the same antimicrobial agents. However, the level of resistance to these antimicrobial agents in the human isolates was significantly lower than in Danish pork. The resistance to all other antimicrobial agents was low (0-8%) both in Danish pork and in domestically acquired human isolates, as opposed to isolates from imported pork. Trends in the occurrence of resistance for selected antimicrobial agents in *S.* Typhimurium isolates obtained from pigs, pork and human cases are shown in Figure S1. A significant increasing trend in occurrence of resistance to tetracycline, ampicillin and sulfonamide was observed during 2001–2006 both from domestically acquired human cases of *S.* Typhimurium and from pigs, and the occurrence of resistance was similar in isolates from the two species. However, in 2007 and 2008, a decreasing trend was seen in the isolates from human. This unusual pattern, causing a significantly lower level of resistance in the isolates from human cases, was related to an increase in several outbreaks with sensitive strains additional to the three major outbreaks (also sensitive strains) in 2008.

The occurrence of resistance to ampicillin, chloramphenicol, cefotaxime, tetracycline,

Table 21. Comparison of resistance (%) among Salmonella *Typhimurium from food animals, pork of Danish and imported origin and human cases acquired domestically a), reported as associated with travel abroad or with an unknown origin, Denmark*

DANMAP 2008

Compound	Cattle	Pigs	Pork		Broiler meat	Turkey meat	Humans a)		
	%	%	Danish %	Imported %	Imported %	Imported %	Domestically acquired b) %	Travel abroad reported %	Unknown origin %
Tetracycline	39	41	30	86	8	100	17	49	30
Chloramphenicol	17	10	4	32	0	48	6	18	13
Florfenicol	11	6	2	27	0	48	3	10	9
Ampicillin	44	41	38	75	10	93	19	42	33
Ceftiofur	0	0	1	0	4	7	0	4	<1
Cefotaxime	0	0	1	0	4	7	<1	4	3
Sulfonamide	56	47	40	84	12	100	21	47	33
Trimethoprim	0	7	7	21	10	31	4	13	8
Apramycin	0	2	3	0	0	0	<1	0	0
Gentamicin	0	3	4	2	0	7	1	7	5
Neomycin	0	5	3	7	0	0	1	4	3
Spectinomycin	17	15	12	45	8	62	8	19	15
Streptomycin	50	45	41	77	2	76	18	46	27
Ciprofloxacin	0	1	0	2	4	34	2	12	4
Nalidixic acid	0	1	0	2	4	34	2	8	3
Colistin	0	0	0	0	0	0	<1	0	0
Number of isolates	18	497	99	56	48	29	391	103	120

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'

b) In 2008, several larger outbreaks caused by e.g. S. Typhimurium phage type U292, DT3 and DT135 occurred. These isolates were excluded here. See also introduction on Salmonella, regarding the outbreaks in 2008.

sulfonamides, spectinomycin, streptomycin and ciprofloxacin was significantly higher in *S.* Typhimurium isolates from patients with travel associated infections compared to isolates from domestically acquired infections (whether compared to all domestically acquired isolates or without major outbreaks) (Table 44 and Table 45 in Appendix and Figure 27). The elevated occurrence of resistance in travel associated *S.* Typhimurium isolates obtained abroad compared to domestically acquired infections, probably reflects the differences in the consumption of veterinary antimicrobial agents between Denmark and the countries to which the patients have travelled.
The occurrence of resistance to ciprofloxacin was in some cases higher than the occurrence of resistance to nalidixic acid among the human isolates. The discrepancy was in part due to the occurrence of the plasmid-borne *qnrS* genes, which can have the phenotype ciprofloxacin resistance and nalidixic susceptible.
Two $ESBL_A$ and one $ESBL_M$ isolate was obtained from patients with a domestically acquired infections. A single $ESBL_A$ producing *S.* Typhimurium isolates was detected from a patient with a travel associated infection.

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

Only a few *S*. Typhimurium were detected from Danish broilers and from Danish broiler meat (Table 20). In imported broiler meat, the most prevalent serotype was found to be *S.* Indiana. The MIC distributions in *S*. Typhimurium isolates from imported broiler meat and turkey meat are shown in Table 41 in Appendix 1. A significantly higher level of resistance to tetracycline, chloramphenicol, florfenicol, ampicillin, sulfonamide, neomycin, spectinomycin,streptomycin, ciprofloxacin and nalidixic acid was observed in isolates from turkey meat compared to broiler meat. Also, for all tested antimicrobial agents, a similar or significantly higher level of resistance was found in imported turkey meat compared to Danish and imported pork.
In general, the resistance level for the antimicrobial agents in the panel was lower in isolates from imported broiler meat than in Danish pork; an exception to this was resistance to fluoroquinolones and cephalosporins, for which the prevalence was lower in Danish pork. Resistance to cephalosporins was found in 4.2% of the imported broiler meat and 6.9% of the turkey meat, as compared to 1% in Danish pork (not significantly different).From imported turkey meat, 34% of the isolates were resistant to ciprofloxacin which was significantly higher than in all other meats tested.

In Danish cattle, *S*. Typhimurium (50%) was the most prevalent serotype followed by *S*. Dublin (36%). The most prevalent *S*. Typhimurium phage types were DT120 and DT12 (Table 20). The observed occurrence of resistance in *S*. Typhimurium from cattle in 2008 was not significantly different from the occurrence in 2007 (Table 39 in Appendix 1).
In imported beef, the most prevalent serotype was *S.* Blockley (47%). Only one *S.* Typhimurium was isolated from imported beef, with phage type DT 120.

Comparison of resistance in *Salmonella* Enteritidis from broiler meat and human clinical infections

In humans, eggs are the most common source of *S.* Enteritidis infection [Mølbak and Neiman, 2002. Am. J. Epidemiol. 156:654-61; Greig and Ravel, 2009. Int. J. Food Microbiol. 130:77-87; Annual Report on Zoonosis in Denmark, 2007 (http://www.food.dtu.dk/Default.aspx?ID=9202)] but other sources may be various poultry meats. No *S*. Enteritidis was isolated from poultry or from Danish broiler meat in 2008, however 30 *S*. Enteritidis isolates were isolated from imported broiler meat. Nalidixic acid and ciprofloxacin resistance were most commonly observed (37%) followed by ampicillin resistance (17%) while ceftiofur and cefotaxime resistance occurred in 7% of the isolates (Table 22; Table 40 in Appendix 1).
In isolates from the domestically acquired human cases, resistance to nalidixic acid, ciprofloxacin and ampicillin were also found, however the occurrence was significantly lower compared to imported broiler meat (Table 45). The MIC distributions for the human cases are shown in Table 43.
The occurrence of resistance to ciprofloxacin and nalidixic acid was significantly higher in travel associated human *S.* Enteritidis isolates compared to domestically acquired isolates (Table 45).
As for *S*. Typhimurium, the higher occurrence of resistance in travel associated *S*. Enteritidis isolates compared to domestically acquired isolates, probably reflects differences in the use of veterinary antimicrobial agents, such as fluoroquinolones in broilers and layers, between Denmark and the countries to which the patients have travelled.

Table 22. Comparison of resistance (%) among Salmonella *Enteritidis from imported poultry meat and human cases categorized as acquired domestically, reported as associated with travel abroad or unknown origin, Denmark a)*

DANMAP 2008

Compound	Poultry meat	Humans		
	Imported %	Domestically acquired %	Travel abroad reported %	Unknown origin %
Tetracycline	0	0	4	3
Chloramphenicol	0	0	2	0
Florfenicol	0	0	0	0
Ampicillin	17	2	7	6
Ceftiofur	7	0	0	0
Cefotaxime	7	<1	0	0
Sulfonamide	0	0	1	0
Trimethoprim	0	0	0	0
Apramycin	0	0	0	0
Gentamicin	0	0	0	0
Neomycin	0	0	0	0
Spectinomycin	0	0	<1	0
Streptomycin	0	0	1	0
Ciprofloxacin	37	16	29	14
Nalidixic acid	37	16	29	14
Colistin	0	5	9	1
Number of isolates	30	127	194	70

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'

Campylobacter

In 2008, 3,868 human laboratory confirmed cases of campylobacteriosis were reported (63 per 100,000 inhabitants). This constitutes an 11% decrease compared with 2007 [EPI-NEWS 2009, no. 11: http://www.ssi.dk/sw64290.asp]. For the surveillance of antimicrobial resistance, the former counties of North Jutland, Funen and Roskilde were selected, representing 22% of all cases.

In 2008, SSI collected travelling information by phone interviews from all *Campylobacter* patients residing in the former counties of North Jutland, Funen and Roskilde. The patients were asked about the date of disease onset and whether they had travelled abroad within a seven-day period prior to disease onset. Patients who had travelled were asked about their destinations. The case was categorised as "domestically acquired" if the patient had not been travelling one week prior to the onset of infection. Information was obtained from 82% of *Campylobacter* cases in the three former counties. Among the responding patients, 33% of *Campylobacter* cases were considered acquired abroad [EPI-NEWS 2009, no. 11: http://www.ssi.dk/sw64290.asp].

In 2008, 236 *Campylobacter jejuni* isolates were submitted to SSI for susceptibility testing from the three regions (North Jutland, Funen, and part of Zealand), every month during the year. Among the 236 analysed isolates, 48 were from known travel-associated cases and 188 were domestically-acquired.

The Danish Veterinary and Food Administration collected samples from meat sold at wholesale and retail outlets from which *C. jejuni* and *C. coli* were isolated, and in 2008, these were species identified and susceptibility tested at the National Food Institute, Technical University og Denmark.

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

The primary source of human *C. jejuni* diarré infections in Denmark was fresh broiler meat [Wingstrand *et al.* 2006 Emerg Infect Dis 12:280–285]. No significant differences in resistance were observed between *C. jejuni* from Danish broilers and Danish broiler meat in 2008 (Table 23). In Danish broilers, the highest level of resistance in the panel was found for ciprofloxacin and nalidixic acid, as in previous years. Among the antimicrobials groups represented in the panel, fluoroquinolones were the most commonly used in broilers until 2006. Like in previous years, resistance to ciprofloxacin, nalidixic acid and tetracycline was statistic significantly higher in *C. jejuni* from imported broiler meat compared to Danish broiler meat (Figure 28). In the Danish broiler production, the fluoroquinolone consumption was low, around 0.003 ADD_{kg}/per kg broiler meat produced during 2003 through 2006, and decreased further to 0.0001 ADD_{kg}/per kg broiler meat produced in 2008. In 2008, the level of resistance to ciprofloxacin, nalidixic acid and tetracycline from *C. jejuni* isolates from domestically acquired infections was in between the level of resistance for isolates obtained from Danish broiler meat and imported broiler meat as in previous years. As stated in previous DANMAP reports, the consumption of imported broiler meat is increasing in Denmark. It is likely that imported broiler 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, streptomycin and tetracycline was statistic significantly higher in travel associated *C. jejuni* isolates compared to isolates acquired domestically. For the other antimicrobial agents tested, no statistically significant differences in the resistance level could be detected.

Table 23. Comparison of resistance (%) among Campylobacter jejuni *from food animals, food of Danish or imported origin and human cases categorized as acquired domestically or reported as associated with travel abroad, Denmark*

DANMAP 2008

Compound	Cattle	Broilers	Broiler meat		Humans	
	Danish	Danish	Danish	Imported	Domestically acquired	Travel abroad reported
	%	%	%	%	%	%
Tetracycline	3	10	12	49	17	51
Chloramphenicol	0	0	0	0	0	0
Erythromycin	0	0	0	7	2	7
Gentamicin	0	0	0	0	2	2
Streptomycin	1	5	4	3	2	15
Ciprofloxacin	20	12	19	53	28	73
Nalidixic acid	20	12	19	53	29	73
Number of isolates	90	82	26	152	185	41

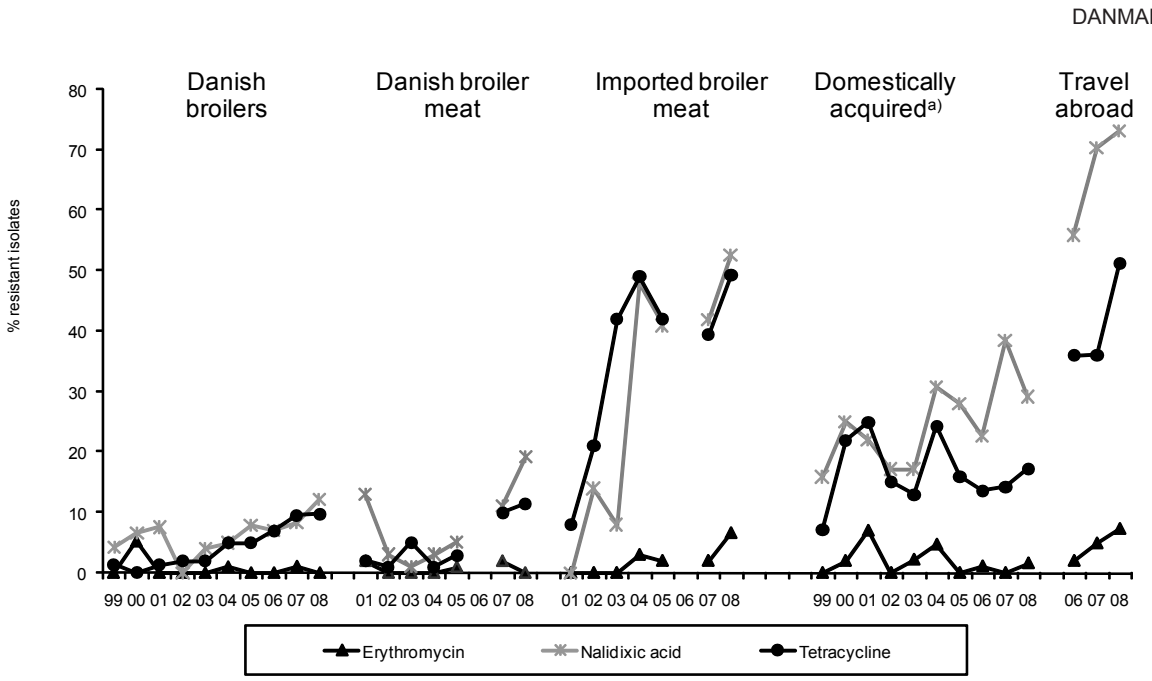

Figure 28, Trend C. jejuni. Trends in resistance to selected animicorbials among Campylobacter jejuni *isolates from broilers, broiler meat and human cases, Denmark*

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

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 countries where 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 46-48 in Appendix 1.

Campylobacter jejuni from cattle

Resistance to ciprofloxacin and nalidixic acid among *C. jejuni* from cattle was unchanged in 2008 and at the same level (around 20%) since 2005, when a statistic significant increase was observed (Figure 29). The consumption of fluoroquinolones in cattle has been low since 2003, and in 2008, only an estimated 3 kg active substance was used in the entire beef and milk production. In 2007, none of the fluoroquinolone resistant isolates were resistant to other antimicrobial agents in the test panel. In 2008, only two of the 18 fluoroquinolone resistant isolates were also resistant to tetracycline, indicating that co-selection by tetracycline was not a likely explanation for the high occurrence of fluoroquinolone resistance. All the ciprofloxacin and nalidixic acid resistant *C. jejuni* isolates found in 2006–2008 originated from farms in Jutland and south Funen, with a high prevalence in Southern Jutland. As discussed in DANMAP 2007, clonal spread particularly between farms in the Southern part of Jutland, or other risk factors in this area, might be an explanation. Tetracycline was before and through 2005 the most commonly used antimicrobial agent in calves (veal and beef production), and remained the second most used antimicrobial agent in 2008.

MIC distributions among *C. jejuni* from cattle in 2008 are shown in Table 47 in Appendix 1.

Campylobacter coli from pigs

Among the human *Campylobacter* isolates selected for susceptibility testing, only a few *Campylobacter coli* isolates from domestically acquired infections and travel associated infections were detected (data not shown). The number of *C. coli* isolates from Danish broilers, Danish broiler meat, imported broiler meat and cattle were below 10. Therefore, only antimicrobial resistance among *C. coli* isolates from pigs is reported in this DANMAP report.

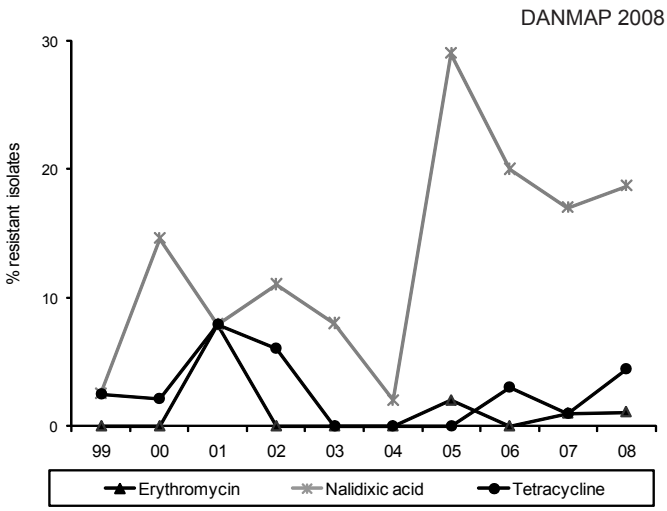

Figure 29. Trends in resistance to selected antimicrobials among Campylobacter jejuni *isolates from cattle, Denmark.*

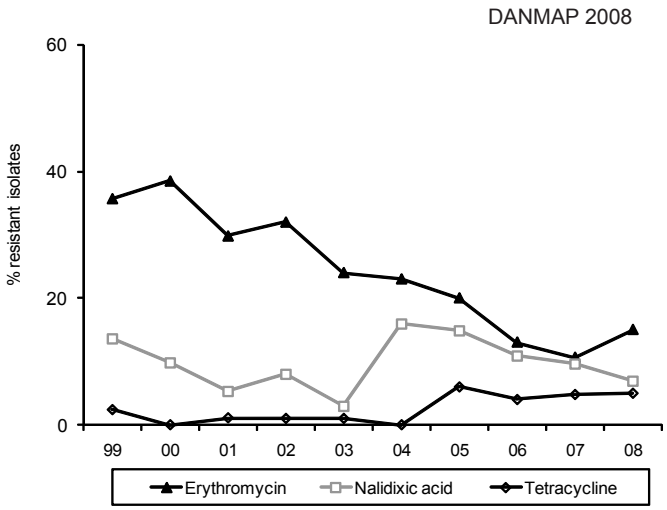

Figure 30. Trends in resistance to selected antimicrobials among Campylobacter coli *isolates from pigs, Denmark*

MIC distributions and the occurrence of antimicrobial resistance among *C. coli* from pigs are shown in Table 45 in Appendix 1.

From 2007 to 2008, no significant changes in resistance were observed among *C. coli* from pigs. Fluoroquinolone resistance was detected in 7% of the tested isolates from pigs. Resistance to fluoroquinolones has been decreasing since 2004. In 2008, the resistance had decreased by 56% compared to 2004. The consumption of fluoroquinolones in pigs has been very low since 2003.

Before 1998, tylosin was used as the most important growth promotor in the pig production, with a consumption of 62 tonnes in 1997. 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 24% in 2003 (Figure 30), but in the past years, the prevalence of resistance has not changed significantly. After the growth promoter withdrawal, an increase in macrolide consumption for therapeutic use was observed, but the overall macrolide consumption per pig produced has been decreasing slightly since 2001.

Resistance in indicator bacteria

Enterococci

Enterococcus faecium and *Enterococcus faecalis* were isolated from faecal samples from pigs and collected swabs from broilers. All samples were collected at slaughter.

The Danish Veterinary and Food Administration collected samples meat sold at whole sale and retail outlets and *Enterococcus faecium* and *Enterococcus faecalis* were isolated from broiler meat, beef and pork. Samples from both national produced meat and imported meat were included.

Between May 20th and June 17th 2008, 120 recruits from one military barrack in Denmark were invited to participate in the "Study of the intestinal microbiota from the Danish population". Faecal carriage of *E. faecium* and *E. faecalis* were studied among the 84 recruits that agreed to participate.

Among enterococci isolated from production animals in Denmark, the highest occurrence of antimicrobial resistance was found in isolates from pigs. This correlates with usage where most antimicrobial agents are used for pigs compared with other terrestrial production animals.

Until 1995, half of all the antimicrobial agents used for production animals in Denmark were used for growth promotion. Among the antimicrobial agents used were avoparcin (a glycopeptide) giving cross-resistance to vancomycin, tylosin (a macrolide) giving cross-resistance to erythromycin, virginiamycin (a streptogramin) giving cross-resistance to quinopristin/dalfopristin and avilamycin (an oligosaccharide). In 1995, the usage of avoparcin as a growth promoter was forbidden in Denmark, which was followed by European Union (EU) in December 1997. In 1998, tylosin and virginiamycin were prohibited as growth promoters in Denmark, and in July 1999, in the EU. Avilamycin and all antimicrobial agents used for growth promotion were prohibited in EU by the end of 2005. Since 1995, occurrence of resistance to these compounds and the antimicrobial group they belong to have been monitored as part of the DANMAP surveillance (Figure 44-50).

Comparison of resistance in *E. faecium* from farm, food and army recruits

Among *E. faecium* isolates from production animals the highest occurrence for antimicrobial resistance was found for tetracycline (61%), followed by streptomycin (43%) and erythromycin (32%) in isolates of pig origin (Table 24). For these three antimicrobial agents, the occurrence of resistance was statistically significant higher as compared to isolates from broilers. For isolates from broilers only resistance to salinomycin (65%) was statistically significant occurrence more frequent compared to pig isolates. Tetracycline and macrolides were the two most used antimicrobial agents for production animals, especially for pigs. From

Table 24. Occurrence of resistance (%) among Enterococcus faecium *from food animals, food of Danish and imported origin and healthy humans, Denmark*

DANMAP 2008

Compound	Broilers	Pigs	Broiler meat		Beef		Pork meat		Healthy humans
	Danish	Danish	Danish	Imported	Danish	Imported	Danish	Imported	
	%	%	%	%	%	%	%	%	%
Tetracycline	8	61	9	44	13	0	13	12	3
Tigecycline	16	0	0	0	0	0	0	0	0
Chloramphenicol	0	0	0	0	0	0	0	0	0
Penicillin	-	10	1	14	0	0	7	0	-
Ampicillin	2	9	1	14	0	0	7	0	0
Erythromycin	16	32	19	53	9	7	27	31	25
Gentamicin	0	0	0	0	0	0	0	0	0
Kanamycin	0	23	0	9	4	0	0	6	3
Streptomycin	10	43	4	21	0	0	7	6	0
Vancomycin	2	0	0	1	0	0	0	0	0
Quinupristin/dalfopristin	2	1	4	7	0	0	0	0	0
Avilamycin	2	0	0	2	0	0	0	0	0
Salinomycin	65	1	51	19	4	0	0	0	0
Linezolid	0	0	0	0	0	0	0	0	0
Number of isolates	51	145	81	115	23	15	15	16	32

Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 25. Occurrence of resistance (%) among Enterococcus faecalis *from food animals, food of Danish and imported origin and healthy humans, Denmark*

DANMAP 2008

Compound	Broilers	Pigs	Broiler meat		Beef		Pork meat		Healthy humans
	Danish %	Danish %	Danish %	Imported %	Danish %	Imported %	Danish %	Imported %	%
Tetracycline	6	84	26	67	19	21	18	32	13
Tigecycline	6	0	0	0	0	0	0	0	0
Chloramphenicol	0	13	0	8	2	3	1	5	4
Penicillin	-	0	0	0	0	0	0	0	-
Ampicillin	0	0	0	0	0	0	0	0	0
Erythromycin	10	40	12	51	5	11	8	8	9
Gentamicin	0	6	0	4	0	3	1	2	4
Kanamycin	0	18	0	22	3	8	4	4	4
Streptomycin	2	28	4	25	3	11	7	6	0
Vancomycin	0	0	0	0	0	0	0	0	0
Avilamycin	0	1	0	0	0	0	0	0	0
Flavomycin	10	-	-	-	-	-	-	-	0
Salinomycin	2	0	2	0	0	0	0	0	0
Linezolid	0	0	0	0	0	0	0	0	0
Number of isolates	49	149	50	144	59	38	72	125	23

Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

2007 though 2008, a statistically significant reduction in occurrence of macrolide was observed in *E. faecium* isolates of pig origin (Figure 48, Appendix 1) most likely as a result of a reduction in usage of macrolides by 6% in the same time period. From 2006 to 2007, a statistically significant increase had been observed in occurrence of macrolide resistance in *E. faecium* of pig origin as a consequence of 9% increased usage of macrolides. Streptomycin resistance in *E. faecium* isolated from pigs has steadily increased from 19% in 2003 to 43% in 2008. Furthermore, resistance towards vancomycin, quinopristin/dalfopristin and avilamycin still prevails (around 2%) more than a decade after banning the usage of avoparcin, virginiamycin and avilamycin for growth promotion.

When comparing occurrence of resistance among isolates from production animals with isolates from Danish produced meat, similar frequency of resistance were found except for occurrence of tetracycline resistance in Danish pork; a statistically significant lower occurrence of resistance was observed in isolates from Danish pork compared to isolates from pigs.

Statistically significant higher occurrence for tetracycline, penicillin, ampicillin, erythromycin and streptomycin and lower for salinomycin was found among *E. faecium* isolates from imported broiler meat as compared to isolates from Danish broiler meat.

In *E. faecium* isolates from army recruits, a statistically significant lower occurrence of resistance to tetracycline, ampicillin, erythromycin, streptomycin, and higher occurrence of resistance to salinomycin, was observed when compared to *E. faecium* isolates from imported broiler meat.

Comparison of resistance in *E .faecalis* from farm, food and army recruits

As for *E. faecium*, the highest occurrence of antimicrobial resistance was observed among isolates of pig origin; most prevalent was resistance towards tetracycline (84%) followed by erythromycin (40%) and streptomycin (28%). Statistically significant differences in occurrence were found for tetracycline, chloramphenicol, erythromycin and streptomycin when isolates from pigs and broilers were compared. No resistance towards vancomycin was detected as previously observed (Table 25).

When isolates from Danish meat were compared to production animals statistically significant lower occurrence was found for tetracycline, chloramphenicol, erythromycin and streptomycin among isolates from pork compared to pigs. Only statistically significant higher occurrence of tetracycline resistance was found in Danish broiler meat compared to broilers.

Statistically significant higher occurrence for tetracycline, chloramphenicol, erythromycin, kanamycin and streptomycin was detected in isolates obtained from imported broiler meat when compared to isolates from Danish broiler meat. Statistically significant higher occurrence of tetracycline was observed in isolates obtained from imported pork compared to isolates from Danish pork.

When isolates from meat were compared to isolates from army recruits statistically significant higher occurrence was only found in imported broiler meat for tetracycline, erythromycin, kanamycin and streptomycin.

Textbox 7

Vancomycin resistance Enterococci (VRE) associated to Sex Pheromone plasmids from food and human isolates

Enterococci have become the 3rd to 4th most prevalent nosocomial pathogen worldwide. *vanA* resistance is common in *E. faecium* isolates from meat and animals, whereas is rarely found in *E. faecalis*. However, DANMAP 2006 reported the first cases of vancomycin resistant *vanA E. faecalis* isolated from imported retail meat. In addition, Agersø *et al.* described three clonally related *vanA E. faecalis* isolated from faecal samples from human volunteers during the same period together with a hospitalized patient two years before [Agersø *et al.* 2008 J. Antimicrob. Chemother. 62:844-845]. These findings strongly suggested imported turkey meat as a source for vancomycin resistant *E. faecalis* in humans in Denmark. Thus, we have characterized the transposons mediating resistance to vancomycin, and the plasmids involved in the transmission from these isolates together with one vancomycin resistant *E. faecium* and one vancomycin resistant *E. faecalis* also isolated from meat in Denmark in 2007. All isolates were positive for the *vanA* gene.

In total eight *E. faecalis* and one *E. faecium* were selected (Table 26). Transferability of Tn*1546* was assessed by filter mating to two recipient strains, *E. faecium* GE-1 and *E. faecalis* JH2-2 both rifampicin and fusidic acid resistant. Characterization of Tn1546 by Long PCR was carried out as well as plasmid content by S1 nuclease and replicon typing.

Table 26. Antimicrobial resistance profile of the isolates and their corresponding transconjugants

DANMAP 2008

Name	Spp	Origin	CHL	ERY	KAN	STR	SYN	TET	VAN
4809*	*E. faecalis*	Food (2006)	8	>32	≤128	128	16	>32	>32
4809xJH2-2			8	>32	≤128	≤64	8	≤1	>32
9677*	*E. faecalis*	Food (2006)	8	>32	≤128	128	16	>32	>32
9677xJH2-2			8	>32	≤128	128	8	>32	>32
2924	*E. faecalis*	Food (2006)	8	>32	<=128	128	16	>32	>32
769374.02*	*E. faecalis*	Food (2006)	64	>32	>2048	>2048	16	>32	>32
769374.02xJH2-2			8	>32	≤128	≤64	8	≤1	>32
3230*	*E. faecalis*	Human (2006)	8	>32	≤128	≤64	16	>32	>32
3230xJH2-2			8	>32	≤128	≤64	8	≤1	>32
3268*	*E. faecalis*	Human (2006)	8	>32	≤128	≤64	16	>32	>32
3268xJH2-2			4	>32	≤128	≤64	8	≤1	>32
RHO182970*	*E. faecalis*	Human (2006)	8	>32	≤128	≤64	8	>32	>32
RHO182970xJH2-2			4	>32	≤128	≤64	8	≤1	>32
777343.07	*E. faecalis*	Food (2007)	8	>32	≤128	128	16	>32	>32
777343.07xJH2-2			8	>32	≤128	≤64	8	≤1	>32
785864.21	*E. faecium*	Food (2007)	8	>32	>2048	2048	4	>32	>32
785864.21xJH2-2			≤2	>32	≤128	≤64	8	≤1	>32
785864.21x64/3			4	>32	>2048	1024	4	>32	>32

*Isolates from Agersø *et al*. study

All eight *E. faecalis* harboured a wild type transposon. The *E. faecium* isolate did not yield an amplicon by long-PCR due to the lack of inverted repeats upstream and downstream the transposon. Eight out of nine potential donors were able to transfer the *vanA* genes to the recipient strains. However, seven of the *E. faecalis* strains could only transfer the *vanA* genes to the recipient *E. faecalis* JH2-2 whereas *E. faecium* 785864.21 was able to mobilise the *vanA* resistance genes to both recipients. All donors concurrently transferred resistance to macrolides. Furthermore, co-transfer of kanamycin and tetracycline resistance was also observed from *E. faecium.*

All *E. faecalis* had in common the presence of a replicon, similar to the one from the sex pheromone responding plasmid pAD1. S1 digestion of three representative *E. faecalis* donors revealed the presence of a common plasmid of 70Kb hybridising to the *repA* of pAD1 as well as the *vanX* gene. *E. faecium* harboured a high molecular weight plasmid of 240Kb and a smaller plasmid of 54Kb which hybridised to the *vanX* gene.

pAD1 is a pheromone response plasmids with a very successful mechanism of mating via sex pheromones. Only few cases of glycopeptide resistance sex pheromone plasmids have been described [Lim *et al*. 2006. Appl Environ Microbiol 72:6544-6553], and the presence of glycopeptide resistance in pheromone responding plasmids may increase transfer of resistance between the different ecological niches.

The presence of VRE in food has been associated with the use of the growth promoter avoparcin. Even though avoparcin was banned in Denmark in 1995 and the rest of Europe in 1999, VRE are still present at a low level in food and animals. In addition, macrolides are extensively used for animal production and also for the treatment of infections in humans, therefore might be indirectly co-selecting for VRE. As the treatment of multidrug-resistant enterococcal infections continues to be a challenge for clinicians, the emergence of VRE from food products may represent a risk for the consumer if the resistance genes are transferred from animals to humans.

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Escherichia coli

In 2008, the Danish Veterinary and Food Administration collected samples from meat sold at wholesale and retail outlets from which *E. coli* was isolated and susceptibility tested at the National Food Institute.
Faecal samples were previously collected from healthy human volunteers, but in 2008, the samples were obtained from Danish recruits. Results of the susceptibility testing of *E. coli* isolates from healthy food producing animals are collected at the time of slaughter.

Escherichia coli from food animals

Figure 31 presents the trends in resistance to selected antimicrobial agents in isolates from animals from 1996–2008. The MIC distributions for 2008 are shown in Table 57 in Appendix 1. Throughout the whole study period (1995–2008), the highest nalidixic acid resistance among indicator *E. coli* from production animals, was in *E. coli* from broilers. This finding probably reflects that since 2002, when the use of fluoroquinolones in production animals was importantly impeded, poultry has been the type of animal production with the highest fluoroquinolone consumption. However, in 2008, the use of fluoroquinolones in the broiler production was only 0.0001 ADD_{kg} per kg broiler produced, the lowest level since 2001, and only 2% of the level in 2004, when the consumption of fluroquinolones in broilers was highest.

Between 2001–2008, the occurrence level of nalidixic acid resistant *E. coli* from broilers was observed in 2004.
The last four years the occurrence of ampicillin and sulfonamide resistance in *E. coli* from pigs has not changed significantly, and the consumption of these antimicrobial agents did not change importantly in this period. The level of resistance to tetracycline was unchanged since 2004, despite an increase in tetracycline consumption in the pig production. In 2008, the occurrence of resistance to streptomycin and spectinomycin in *E. coli* from pigs decreased significantly (Figure 31), while the use of spectinomycin has been gradually decreasing by more than 30% since 2004. One ciprofloxacin resistant *E. coli* isolate was identified in 2008 (Table 27).

In cattle, no statistically significant changes in the level of resistance in *E. coli* were observed from 2007 through 2008. (Figure 31). Until 2005, the most important antimicrobial used in calves was tetracycline, but in the following years macrolides has become the drugs of choice in calves (Table 8, see also DANMAP 2007). The proportional use of tetracycline, and aminopenicillins and sulfonamide in calves has been decreasing by 18%, 53% and 25% respectively since 2004 (Figure 8), in particular related to decreasing use long-acting drugs (see also DANMAP 2007).

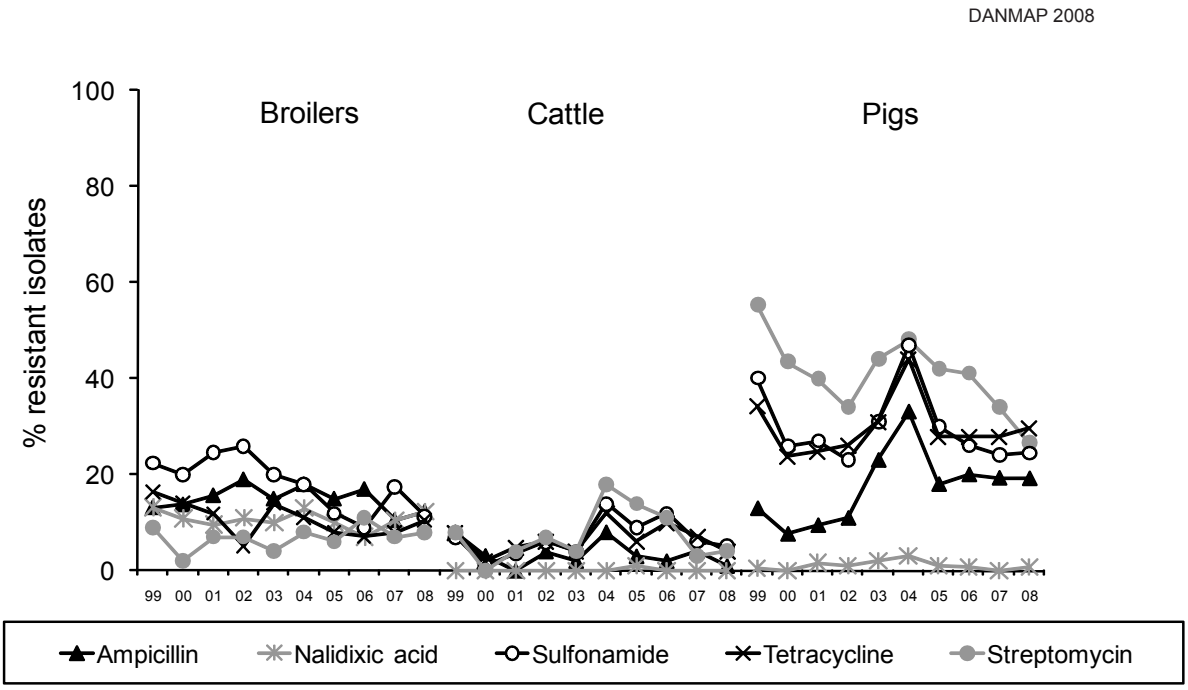

Figure 31. Trends in resistance to selected antimicrobial agents among Escherichia coli *from food animals, Denmark*

Measured in course doses, the use of tetracyclines, aminopenicillins and sulfonamides prescribed for calves decreased by 8%, 47% and 16%, respectively from 2004 through 2008. The use of tetracycline, sulfonamide, streptomycin and aminopenicillin in cows (mainly dairy cows) increased during the same period. A significant decreasing trend in resistance to tetracycline, ampicillin and sulfonamides in *E.coli* from cattle at slaughter was observed from 2004 to 2008.

Among species, the level of resistance was lowest in *E. coli* isolates from cattle, with 93% of the isolates being fully susceptible to all tested antimicrobial agents. Among the tested broiler and pig isolates, 62% and 57% respectively, were fully susceptible. The MIC distribution of indicator *E. coli* isolates is presented in Table 57 in Appendix 1.

Escherichia coli from food

Tables 55 and 56 present the MIC distributions and occurrence of antimicrobial resistance in *E. coli* isolates collected from broiler meat, pork and beef sold at retail outlets in 2008. The isolates originated from Danish broiler meat (n=113), imported broiler meat (n=304), Danish beef (n=63), imported beef (n=40), Danish pork (n=66) and imported pork (n=96). The occurrence of resistance was significantly higher for 12 of the tested antimicrobial agents in *E. coli* from imported broiler meat compared to Danish broiler meat (tetracycline, chloramphenicol, ampicillin, cefoxitime, ceftiofur, sulfonamide, trimethoprim, neomycin, spectinomycin, streptomycin, ciprofloxacin and nalidixic acid). For imported beef compared to Danish produced beef no statistically significant differences in the occurrence of resistance was observed. For imported pork compared to Danish produced pork no statistically significant differences in the occurrence of resistance was observed. (See also “Comparison of *Escherichia coli* from animals, food and army recruits volunteers”).

E. coli from Danish army recruit volunteers

In 2008, stool samples from 84 Danish healthy recruit volunteers were collected and 75 *E. coli* isolates were subsequently isolated. Table 58 (Appendix 1) presents the MIC distributions and occurrence of antimicrobial resistance of the 75 isolates. The last time resistance data on *E. coli* from healthy humans was reported in

Table 27. Occurrence of resistance (%) among Escherichia coli *from food animals, food of Danish and imported origin and army recruits, Denmark*

DANMAP 2008

Compound	Broilers	Cattle	Pigs	Broiler meat		Beef		Pork meat		Army recruits
	Danish	Danish	Danish	Danish	Imported	Danish	Imported	Danish	Imported	
	%	%	%	%	%	%	%	%	%	%
Tetracycline	11	4	30	4	42	6	12	33	44	29
Chloramphenicol	0	1	1	0	14	0	2	6	7	5
Florfenicol	0	1	0	0	1	0	2	0	1	0
Ampicillin	12	1	19	11	48	6	10	29	30	28
Cephalothin	-	-	-	-	-	-	-	-	-	3
Ceftiofur	0	0	0	1	8	0	0	0	1	1
Cefpodoxime	-	-	-	-	-	-	-	-	-	3
Cefotaxime	0	0	0	1	8	0	0	0	1	-
Sulfonamide	11	5	25	12	45	6	15	30	28	35
Trimethoprim	4	2	18	3	32	2	5	24	25	-
Apramycin	0	0	0	0	0	0	0	0	0	0
Gentamicin	1	0	1	0	3	0	0	0	2	7
Neomycin	1	0	3	0	10	0	2	2	6	9
Spectinomycin	3	1	14	6	23	0	5	20	15	11
Streptomycin	8	4	26	8	33	8	15	32	40	28
Ciprofloxacin	12	0	1	4	33	0	5	2	6	13
Nalidixic acid	12	0	1	3	32	0	5	2	4	13
Colistin	0	0	0	0	4	0	0	0	1	-
Number of isolates	114	97	151	113	304	63	40	66	96	75

DANMAP was in 2006, when samples were collected randomly among healthy volunteers in the community. No significant differences in resistance were observed between the 2006 sample and 2008 sample, but the level of resistance was higher in the isolates sampled in 2008, compared to 2006.

Comparison of resistance in *E. coli* from animals, food and army recruit volunteers

Data on the occurrence of resistance in food animals, foods and army recruit volunteers is presented in Table 27. For most of the tested antimicrobial agents, the levels of resistance in Danish meat reflected the level of resistance in the corresponding animal species with some exceptions. When comparing *E. coli* isolates from Danish broiler meat to *E. coli* from broilers, the occurrence of resistance to ciprofloxacin and nalidixic acid was significantly higher in broiler meat. Beef compared with cattle showed no significantly differences in the level of resistance. For *E. coli* from pigs compared to *E. coli* from Danish pork, no statistically significant differences were observed. The differences in the occurrence of resistance between broiler meat and broilers might be caused by cross-contamination during the slaughter process.

In general, resistance levels in *E. coli* from army recruit volunteers were similar to resistance levels in *E. coli* from broilers meat and pork. However, gentamicin resistance occurred in army recruit volunteers, but not in Danish meat or animals.

Textbox 8

Faecal carriage of ESBL-producing and *AmpC* producing *Escherichia coli* and *Citrobacter freundii* in Danish army recruits

As part of the DANMAP surveillance, the prevalence of resistant *E. coli* from faecal samples from non-hospitalised humans in Denmark has been studied. From 2002 though 2006, no third generation cephalosporin resistance in *E. coli* has been detected, but this might be because we have not used a selective method (DANMAP 2002-2006). In the present study, a selective method was used to detect third generation cephalosporin resistance in Enterobacteriaceae in the community.

Between May 20th and June 17th 2008, 120 army recruits from one military barrack in Denmark were invited to participate in the "Study of the intestinal microbiota from the Danish population". Faecal carriage of third generation cephalosporin resistant Enterobacteriaceae were studied among the 84 recruits that agreed to participate (participation rate: 70%).

Each participant mailed a fecal sample to SSI and filled in a questionnaire. The questionnaire covered information on gender, age, medications, gastrointestinal symptoms and diseases, travel, food consumption and contact with animals. The Scientific Ethics Committee for the Copenhagen and Frederiksberg municipalities approved the protocol prior to the investigation ((KF) 01-006/02). The methods used for selection are described in Appendix 2.

Three ESBL positive *E. coli* isolates belonged to the CTX-M-14. Two *E. coli* isolates and one Citrobacter freundii were *ampC* phenotype and were positive for the CIT-geno-group (Table 28).

None of the recruits with ESBL or *ampC* producing bacteria had been hospitalized within 1 month before the sample was taken or had travelled abroad within 3 months prior sampling. All were eating meat (pork, poultry meat, beef) on a regularly basis. Many of them had been in contact with companion animals or hunting animals, but not with production animals within the last week. It is therefore possible that the ESBL or *ampC* producing bacteria were of animal origin, from either meat or from contact with companion animals. Two of the three carriers of ESBL-producing *E. coli* belonging to the CTX-M-14 had within one week before sampling of the faeces been in contact with dogs. ESBL-producing *E. coli* from dogs have to our knowledge only been detected in one Danish study, where a single dog had two samples with ESBL-producing *E. coli* encoded by CTX-M-14 [Damborg *et al.* 2009 Epidemiol.Infect. published online]. In 2007, fourth generation Cephalosporins were marketed for treatment of companion animals in Denmark and therefore dogs might be a reservoir for ESBL producing *E. coli.* ESBL producing *E. coli* have been previously been detected in Danish pigs and in meat sold in Denmark [Jensen *et al*. 2006, J.Antimicrob. Chemother. 57:793-4, Cavaco *et al.* 2008, Antimicrob.Agents Chemother. 2008;52:3612-6]. Our study shows that ESBL and *ampC* producing bacteria can be detected in humans in the community.

Table 28. Description of the 6 recruits with ESBL and ampC *producing bacteria* DANMAP 2008

	Species	Phenotype	Plasmidic bla genes detected	Resistence to non-Beta-lactams	Background data				
ID					Gender	Age	Intake of antimicrobial agents[a]	Meat eaten[b]	Contact with animals
3786Z08	*E. coli*	AmpC	CIT	CHL, SPE, STR, SMX	M	22	Penicillin	Yes	Dog
3823Z08	*E. coli*	AmpC	CIT	CIP, NAL, SPE, STR, SMX, TMP	M	21	Dicloxacillin	Yes	Dog
3826Z08	*C. freundii*	AmpC	CIT	None	M	20	No	Yes	Dog, cat, wild birds,hunting animals
3792X08	*E. coli*	ESBL	CTX-M-14	None	M	21	No	Yes	Dog
3807X08	*E. coli*	ESBL	CTX-M-14	None	M	19	No	Yes	None
3827X08	*E. coli*	ESBL	CTX-M-14	None	M	19	No	Yes	Dog, cat, reptiles, parrot

[a]within 6 monhts before the fecal sample was taken
[b]pork, poultry meat, beef on a regularly basis.

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Textbox 9

Prevalence of tetracycline resistant *Escherichia coli* along the processing line in a Danish pig slaughterhouse

Previous studies showed that *E. coli* from slaughter animals and slaughterhouses serve as a pool of antimicrobial resistance and resistance genes [Aslam *et al*., 2006, J. Food. Prot., 69: 1508-13; van den Bogaard *et al*., 2000, J Antimicrob Chemother.,45: 663-71]. Environmental stress and hygiene conditions in the slaughter line, such as hyperthermia and disinfection, will influence the survival of antimicrobial resistant bacteria. However, the actual impact of the slaughter process on the antimicrobial resistance has not yet been investigated [McMahon *et al.*,2007, Appl Environ Microbiol., 73: 211-7.].

Therefore, a Danish pig slaughterhouse was investigated to determine the impact of processes along a slaughter line on the prevalence of tetracycline (TET)-resistant *E. coli* isolated from carcasses. A total of 105 pigs were sampled at specific sites along the processing line: after stunning, after scalding, after splitting, after cooling and after cutting. The results showed that both total *E. coli* and TET-resistant *E. coli* counts were reduced significantly along the process line until no *E. coli* could be detected from the post-cut carcasses (Figure 32).

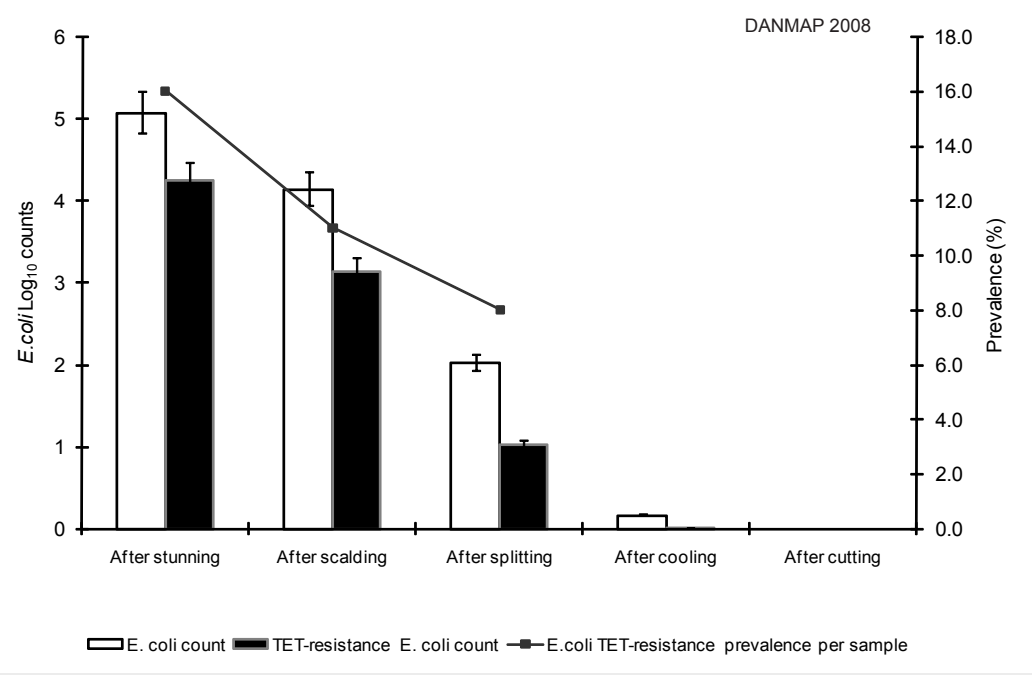

Figure 32. Mean and standard error of the total E. coli *counts, tetracycline (TET)-resistant* E. coli *counts and median of within-sample TET-resistant* E. coli *prevalence at each sampling site along the slaughter line*

To obtain more quantitative data for risk analysis purpose, prevalence of TET-resistant *E. coli* isolates was defined by the proportion of the TET-resistant *E. coli* of total *E. coli* within one sample and evaluated along the process line. It also showed a significant decrease from a median of 16% for post-stunned carcasses to 11% for post-scalded carcasses and to 8% for post-split carcasses (Figure 32).
In addition, from 15 repeatedly sampled pigs, 422 *E. coli* isolates (144 from faeces, 141 from post-stunned carcasses, 134 from post-split carcasses and 3 from post-chilled carcasses) were susceptibility tested for 17 antimicrobial agents (the same as indicator *E. coli* in DANMAP). The results showed that 36% of all the isolates were resistant to at least one of the tested antimicrobial agents. There was no significant difference in resistance percentage of the isolates from different sampling sites.
For the individual antimicrobial agents, except for tetracycline, no significant differences were found for the resistance percentage between post-split carcasses and post-stunned carcasses. However, TET-resistance was found to be declined from post-stunned carcasses to post-split ones (22% versus 11%, $P < 0.05$). Such decrease was in accordance with the decrease of the within-sample TET-resistant *E. coli* prevalence along the slaughter line. Interestingly, the percentage of multi-drug resistance (defined as resistance to more than three antimicrobial agents) in the isolates showed a significant increase from post-stunned carcasses (13%) to post-split carcasses (27%).
Further study is needed to determine why there was different impact of the slaughter process on different antimicrobial resistance. The reduction of tetracycline resistance in *E. coli* along the processing line suggests that tetracycline-sensitive *E. coli* persisted better compared to resistant ones. The quantitative data on antimicrobial resistance gathered in this study can be used for future assessments of the risk represented by antimicrobial-resistant *E. coli* in the food chain.

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Resistance in human clinical bacteria

Escherichia coli

Escherichia coli are part of the normal intestinal flora of both humans and animals, but can also cause infections. In humans, *E. coli* can cause a variety of intestinal and extra-intestinal infections, such as diarrhoea, urinary tract infections, meningitis and blood infections. 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 (Table 29).

E. coli blood isolates obtained from hospital patients

Approximately 3,500 *E. coli* isolates from blood were tested for antimicrobial susceptibility in 2008. Not all laboratories tested for the same antimicrobial agents (Table 29, Figure 33.). The level of resistance was the same as reported in 2007 for all the tested antimicrobial agents. The level of resistance to fluoroquinolones (12% for ciprofloxacin) was the same as reported to EARSS from France, the UK, and Sweden among others in 2007 [EARSS 2007, http://www.rivm.nl/earss/result/Monitoring_reports/]. One hospital reported 27% resistance to both ciprofloxacin and nalidixic acid and another hospital reported 18% resistance towards both ciprofloxacin and nalidixic acid. None of the other DCMs at the other hospitals reported a higher resistance level to fluoroquinolones than the average level.

In this DANMAP report, resistance to 3rd generation cephalosporins (reported as ceftazidime, ceftriaxone, cefpodoxime or cefotaxime) and carbapenem were reported for the first time. Four percent of the isolates were resistant to 3rd generation cephalosporins. This level was similar to the levels reported to EARSS for the other Nordic countries in 2007 [EARSS 2007]. Furthermore, carbapenem resistance was reported to the DANMAP report for the first time; less than 1% of the *E. coli* isolates from blood were carbapenem resistant.

E. coli urine isolates obtained from hospitalized patients

Approximately 38,000 *E. coli* isolates obtained from hospitalized patients with a urine tract infection were tested for susceptibility to the antimicrobial agents shown in (Table 29). A significant increase in resistance from 2007 to 2008 was detected for mecillinam and the fluoroquinolones ciprofloxacin and nalidixic acid, whereas the level of resistance for the other tested antimicrobial agents was not significantly different from the level in 2007. (Table 29, Figure 34).

Table 29. Resistance (%) to ampicillin, sulfonamide, gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *isolates from humans, Denmark 2008*

DANMAP 2008

Compound	Blood isolates, hospitals a)	Urine isolates, hospitals b)	Urine isolates, primary health care c)
	%	%	%
Ampicillin	43	41	41
Sulfonamide		34	38
Gentamicin	4		
Cefuroxime d)	6	4	2
Mecillinam	6	6 *	5 *
Ciprofloxacin	12	11 *	10 *
Nalidixic acid	13	13 *	12 *
3rd generation cephalosporin e)	4		
Carbapenem e)	<1		
Max. number of isolates tested	3.494	38.353	27.931

*) An asterisk indicates a significant change (increase) from 2007 to 2008

a) All 14 DCM reported data on ampicillin and gentamicin resistance, 13 DCM reported cefuroxime and ciprofloxacin resistance, 11 DCM reported nalidixic acid and 3rd generation cephalosporin resistance, 10 DCM reported mecillinam resistance, and nine DCM reported data on carbapenem resistance

b) All 14 DCM reported data on ampicillin and mecillinam resistance, 12 DCM reported sulfonamide and ciprofloxacin resistance, nine DCM reported nalidixic acid resistance, and eight DCM reported data on cefuroxime resistance. Since resistance to 3rd generation cephalosporin was only reported from one DCM, data is not shown

c) All 12 contributing DCM reported data on ampicillin and sulfonamide resistance, 11 DCM reported mecillinam resistance, nine DCM reported ciprofloxacin resistance, seven DCM reported nalidixic acid resistance, and five DCM reported data on cefuroxime resistance Since resistance to 3rd generation cephalosporin was only reported from one DCM, data is not shown

d) Resistance to cefuroxime in urine isolates from hospitals and primary health care was only reported in 2008

e) Resistance to 3rd generation cephalosporin (ceftazidim, ceftriaxone, cefpodoxime and cefotaxime) and carbapenem (meropenem) was only reported in 2008

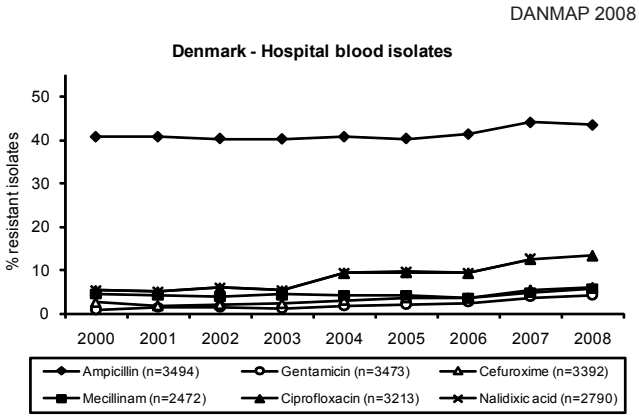

Figure 33a. Resistance (%) to ampicillin, gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

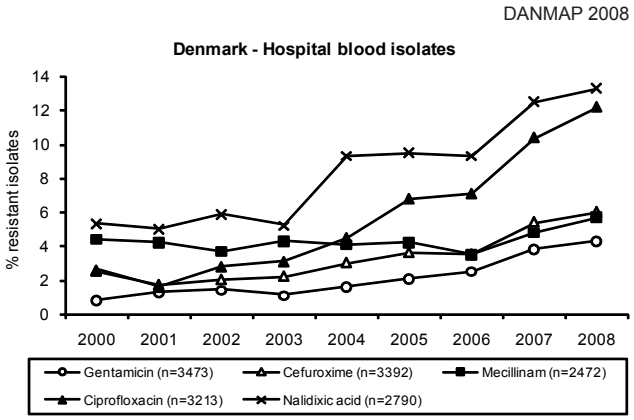

Figure 33b. Resistance (%) to gentamicin, cefuroxime, mecillinam, ciprofloxacin and nalidixic acid in Escherichia coli *blood isolates from humans, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

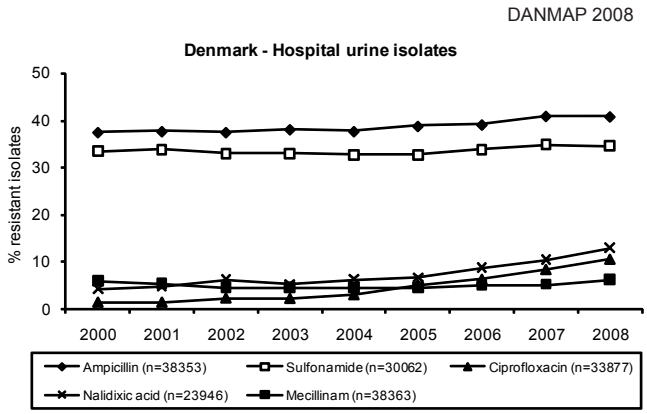

Figure 34a. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

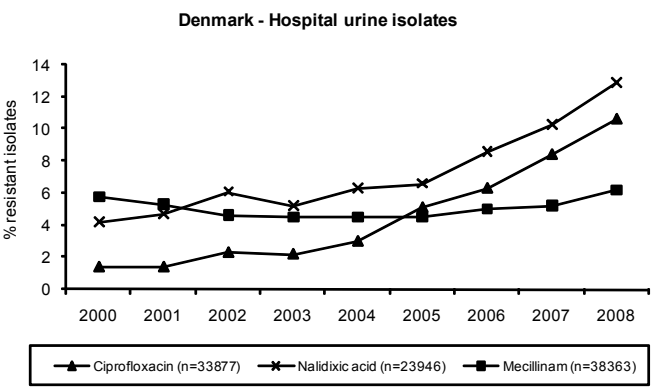

Figure 34b. Resistance (%) to ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans in hospitals, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

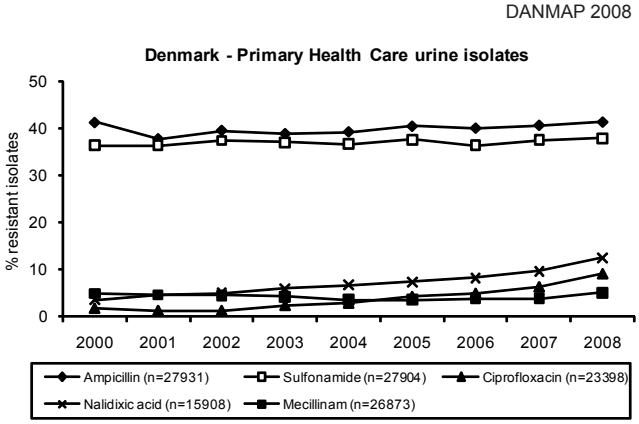

Figure 35a. Resistance (%) to ampicillin, sulfonamides, ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

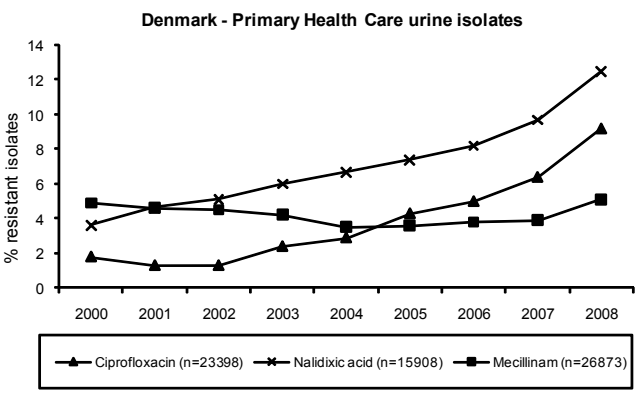

Figure 35b. Resistance (%) to ciprofloxacin, nalidixic acid and mecillinam in Escherichia coli *urine isolates from humans, Denmark*
The number (n) in parentheses represents the number of isolates tested for susceptibility in 2008

E. coli obtained from urine isolates from primary health care

Approximately 28,000 *E. coli* isolates obtained from out patients with a urine tract infection diagnosed in primary health care were tested for susceptibility to the antimicrobial agents shown in (Table 29). A significant increase in resistance from 2007 to 2008 was detected for mecillinam and the fluoroquinolones ciprofloxacin and nalidixic acid, whereas the level of resistance for the other tested antimicrobial agents was not significantly different from the level in 2007. (Table 29, Figure 35). Overall, the level of ampicillin resistance in *E. coli* urine isolates from primary health care remained high (41%) in 2008. The high level of resistance to ampicillin and sulfonamides (38%) in *E. coli* from urine makes these antimicrobial 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.

To test this hypothesis a study was seat up (see Textbox 10).

Textbox 10

Increased antimicrobial resistance in *Escherichia coli* from community-acquired urinary tract infections in Denmark

Worldwide, an increase in the frequency of antimicrobial resistance in *Escherichia coli*, the most common pathogen in urinary tract infections (UTIs), is encountered. Uncomplicated urinary tract infection (UTI) has traditionally been simple to treat with antimicrobial agents, but now the choice of empirical treatment is debated due to occurrence of resistance. The resistance levels reported in DANMAP may however be biased due to a significant proportion of urine samples submitted for microbiological diagnosis following failure of empirical treatment. A Danish study performed from 1997-1999 showed a lower resistance level in primary health care than the one reported in the DANMAP report [Kerrn *et al*. 2002. J. Antimicrob. Chemother. 50: 513-6]. Our aim was to provide updated information on the prevalence of resistance among *Escherichia coli* UTIs in general practice in Denmark.

From December 2005 to April 2006, a general practice in Roskilde County performed consecutive urine culturing on UTI patients. The UTI cases were defined as uncomplicated or complicated. All *E. coli* isolates were tested for antimicrobial susceptibility using microbroth dilution.

Of 131 *E. coli* UTIs, 26% were from uncomplicated UTI and 74% were from complicated UTI. Both among uncomplicated and complicated UTI isolates, high rates of resistance to ampicillin (27-52%), sulfamethizole (24-46%) and trimethoprim (15-41%) were found. Lower rates of resistance to mecillinam (3-5%), ciprofloxacin (3-5%) and nitrofurantoin (0-1%) were observed (Table). Resistance to ampicillin, sulfamethizole and trimethoprim among *E. coli* from uncomplicated UTI was significantly lower compared to *E. coli* from complicated UTI.

Our results were compared to data concerning resistance in *E. coli* from UTI infections from a study conducted in general practice in the same geographical area in Denmark nine years before [Kerrn *et al*. 2002. J. Antimicrob. Chemother. 50: 513-6]. When comparing all community-acquired UTIs in our study with the older study of Kerrn *et al*., a significant increase in resistance to ampicillin (from 29% to 45%) and trimethoprim (from 18% to 34%) was observed. Sulfamethizole resistance was unchanged at a high level, and the frequency of resistance to mecillinam and nitrofurantoin remained the same at a low level. It was surprising, that in our study there were considerably more patients with complicated (74%) than uncomplicated (26%) UTI, also as compared to Kerrn *et al.*, where 60% of the UTI episodes were complicated and 40% were uncomplicated. We have no explanation for this finding. When comparing isolates from complicated UTIs in our study with the complicated UTIs in Kerrn *et al.,* resistance to ampicillin and trimethoprim has also increased significantly, even though Denmark has a low level of outpatient antimicrobial consumption. Generally, our results correspond to resistance levels found in other European and especially the Nordic countries.

The choice of first-line treatment for uncomplicated UTI in Denmark (pivmecillinam or sulfamethizole) is debated. Short-acting sulfamethizole has been widely used for many years in Denmark as empiric treatment of uncomplicated UTIs, but now, consumption of pivmecillinam is increasing (from 0.33 DDD/1,000 inhabitant-days in 1997 to 1.14 DDD/1,000 inhabitant-days in 2006), whereas consumption of sulfamethizole is decreasing (from 0.41 DDD/1,000 inhabitant-days in 1997 to 0.35 DDD/1,000 inhabitant-days in 2006). Co-resistance could be the explanation for the persistence in resistance to sulfamethizole despite a decrease in consumption of this agent, whilst an increase in consumption of e.g. trimethoprim has been observed.

Pivmecillinam, a beta-lactam and a pro-drug of mecillinam, has been widely used for the treatment of acute lower UTI, mainly in the Nordic countries, including Denmark. The level of pivmecillinam resistance has remained low (<2%) despite having been used as a first-line agent in the Nordic countries for many years. In our study, a low level of mecillinam resistance (3-5%) was shown despite the fact that consumption of pivmecillinam is increasing.

The high level of resistance to sulfamethizole (24%) and trimethoprim (15%) among uncomplicated UTI isolates suggest that these agents are less effective and should only be used following confirmation of efficacy by pre-therapy urine culture and susceptibility testing. The low rates of resistance towards

mecillinam and nitrofurantoin suggest that these agents are appropriate for use as empirical therapy without pre-therapy urine culturing. The increasing consumption of pivmecillinam in primary health care clearly shows a shift towards use of this agent is already the case. When complicated UTI is suspected, pre-therapy urine culture and susceptibility testing should always be undertaken.

Since 1995, data on antimicrobial resistance in isolates from UTIs in primary health care have been published in the DANMAP reports. The rates of resistance found among all the *E. coli* UTI isolates in our study correspond well with the data reported in DANMAP 2006. In recent years, DANMAP has shown a significant and consistent increase in fluoroquinolone resistance among *E. coli* from UTIs in primary health care. Our data correspond with a current occurrence of resistance towards fluoroquinolones of around 5% in *E. coli* UTI isolates (Table 30). Since 2002, an increase in fluoroquinolone consumption (almost entirely ciprofloxacin) has been observed. The use of ciprofloxacin in primary health care is restricted to special cases of complicated UTI as well as acute gastroenteritis according to the national guidelines. The increase in both ciprofloxacin consumption and resistance continued in 2007 and 2008, which calls for a continuing close monitoring of resistance development in UTI isolates from primary health care.

Increasing resistance to first-line antimicrobial agents progressively complicates the management of UTIs, and continued surveillance of antimicrobial resistance and consumption in the community is required.

Line Skjøt-Rasmussen, Anette M. Hammerum, Ulrich Stab Jensen, Preben Larsen and Niels Frimodt-Møller

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Table 30. Antimicrobial resistance in *Escherichia coli* from community-acquired UTI

DANMAP 2008

	Total (N = 131)			Uncomplicated UTI (N = 34)			Complicated UTI (N = 97)		
Compund	*n*	%	95% CI	*n*	%	95% CI	*n*	%	95% CI
Ampicillin	59	45.0	(36.3; 54.0)	9	26.5 *a*	(12.9; 44.4)	50	51.5	(41.2; 61.8)
Mecillinam	6	4.6	(1.7; 9.7)	1	2.9	(0.1; 15.3)	5	5.2	(1.7; 11.6)
Ciprofloxacin	6	4.6	(1.7; 9.7)	1	2.9	(0.1; 15.3)	5	5.2	(1.7; 11.6)
Sulfamethizole	53	40.5	(32.0; 49.4)	8	23.5 *a*	(10.8; 41.2)	45	46.4	(36.2; 56.8)
Trimethoprim	45	34.4	(26.3; 43.2)	5	14.7 *a*	(5.0; 31.1)	40	41.2	(31.3; 51.7)
Nitrofurantoin	1	0.8	(0.02; 4.2)	0	0	(0; 10.3)	1	1.0	(0.03; 5.6)

a Significantly different from the value in complicated UTI, all isolates ($P < 0.05$)

Streptococcus

Streptococci are part of the normal commensal flora of the mouth, skin, intestine, and upper respiratory tract of humans, but streptococci can also cause infections, including otitis media, tonsillitis, bacterial pneumonia, bacteraemia/ sepsis, endocarditis and meningitis.
In this report, data on resistance levels in invasive (from blood or cerebrospinal fluid) *Streptococcus* isolates were obtained from the Nesisseria and Streptococcus Reference laboratory on isolates from all the DCMs in Denmark. In Denmark, penicillins and macrolides are often used for treatment of infections caused by streptococci and all invasive non-duplicate *Streptococcus pneumoniae*, group A, B, C and G streptococci from Denmark were susceptibility tested to erythromycin and penicillin.
In addition, isolates from non-invasive *Streptococcus pneumoniae* and Group A streptococci (GAS) (*Streptococcus pyogenes*) infections were reported in this DANMAP report. Twelve DCMs contributed with data on non-invasive *S. pneumoniae* isolates from primary health care and nine on GAS.

Streptococcus pneumoniae

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, otitis media, bacteraemia and meningitis. In 2008, susceptibility testing was performed on 941 non-duplicate *Streptococcus pneumoniae* isolates from invasive infections. Macrolide resistance in *S. pneumoniae* isolates from blood and cerebrospinal fluid has been around 6% since 2000. The percentage of macrolide resistant *S. pneumoniae* was 5.5% in 2006, 6.2% in 2007, and 6.6% in 2008; the increase was not statistically significant (Figure 36).

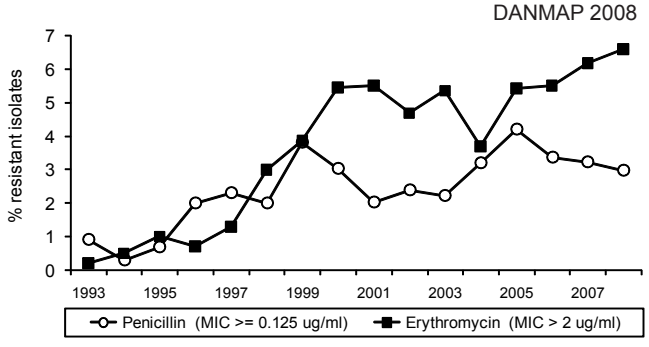


Figure 36. Resistance (%) to penicillin and macrolides in Streptococcus pneumoniae *blood and spinal fluid isolates from humans, Denmark*

The percentage of *S. pneumoniae* invasive isolates that were non-susceptible (resistant and intermediate resistant) to penicillin was 3.4% in 2006, 3.2% in 2007, and 3.0% in 2008 (Figure_HR_strep pneumo). 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 reporting to EARSS [EARSS 2007, http://www.rivm.nl/earss/result/Monitoring_reports/]. Using the new break points (launched January 2008 by CLSI) for antimicrobial susceptibility testing of isolates from patients with invasive disease treated with intravenous penicillin, except for patients with meningitis, two of the 941 (0.2%) tested isolates in 2008 were non-susceptible intermediate resistant (2 µg/ml<MIC<8 µg/m) and none were resistant (MIC≥8 µg/m).

In 2008, 3,447 *S. pneumoniae* isolates from non-invasive infections were tested for resistance to penicillin and 3,297 were tested for resistance to erythromycin. Among the tested isolates, 2.4% were reported as non-susceptible to penicillin and 3.4% were erythromycin resistant.

Group A Streptococci

In 2008, 136 invasive GAS (*Streptococcus pyogenes*) isolates were susceptibility tested. As in previous years, no resistance to penicillin in GAS isolates from invasive infections was reported in 2008. Erythromycin resistance was detected in two isolates (1.5%) as compared to four of 107 isolates (3.7%) in 2007.

In 2008, 7,009 GAS from non-invasive infections were tested for resistance to erythromycin. Among the tested isolates 2.6% were erythromycin resistant.

Group B, C and G Streptococci

In 2008, 123 invasive group B streptococci (*Streptococcus agalactiae*) isolates from invasive infections were tested. Erythromycin resistance was detected in 14 isolates (11.4%) compared to 8.2% in 2007.

Twenty-five isolates of invasive group C streptococci were tested in 2008. One isolate (4%) was resistant to erythromycin compared to 5% in 2007.

Thirteen (10%) of the 125 invasive group G streptococci were resistant to erythromycin compared to 8% in 2007.

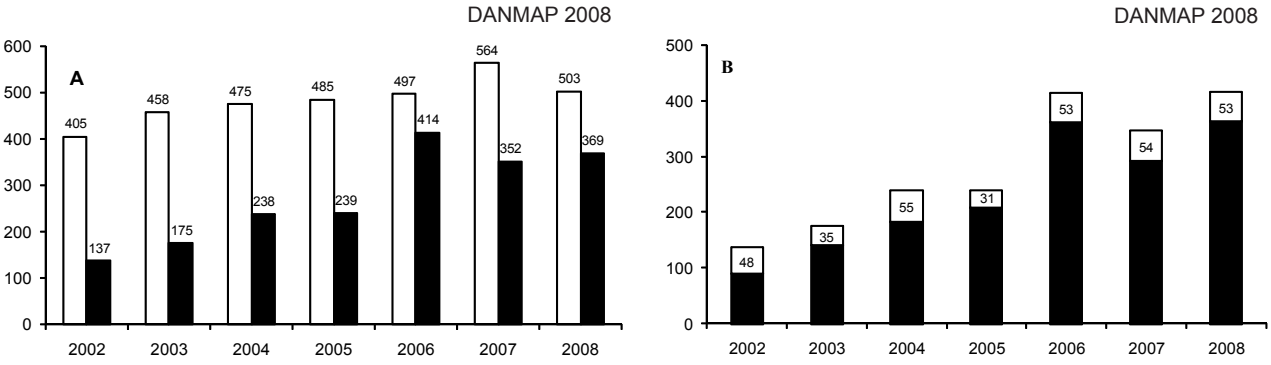
As in previous years, no resistance to penicillin in group B, C or G isolates from invasive infections was reported in 2008.

Enterococci

Important clinical infections caused by *Enterococcus* species include urinary tract infections, bacteremia and bacterial endocarditis. *E. faecalis* and *E. faecium* can cause life-threatening infections in humans, especially in the hospital environment. The naturally high levels of antibiotic resistance found in *E. faecalis* and *E. faecium* make them difficult to treat. Antimicrobial therapy for serious enterococcal infections requires the use of synergistic combinations of a cell-wall-active agent such as penicillin (ampicillin) or a glycopeptide (vancomycin), and an aminoglycoside (gentamicin).
For *E. faecalis* and *E. faecium* this report includes data from 14 Departments of Clinical Microbiology (DCMs), representing 95% of the Danish population.
Data on resistance in enterococci from blood infections has not been an integrated part of the DANMAP report before, but was in part described in DANMAP 2007 (as a Textbox).

Enterococcus faecium and *Enterococcus faecalis* blood isolates obtained from hospital patients

In 2008, a maximum of 416 *E. faecium* isolates and 599 *E. faecalis* isolates from blood were tested for antimicrobial susceptibility. Not all laboratories tested for susceptibility to the same antimicrobial agents.
From 2002 through 2008, microbiology data on *E. faecium* and *E. faecalis* blood isolates were received every year from 11 DCMs. During these years the numbers of *E. faecium* isolates obtained from blood infections has increased (Figure 37a). During the years, 2002-2008, most of the *E. faecium* isolates were resistant to ampicillin (Figure 37b). From the 14 DCM reporting on *E. faecium* in 2008, 87% of the tested *E. faecium* isolates were ampicillin resistant. A reason for the increasing frequency of *E. faecium* as a cause of bloodstream and other infections might be its ability to acquire many different resistance genes; the antimicrobial pressure in a hospital environment therefore allows for its selection. 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 years (Figure 1). This might be an explanation of the changing *E. faecalis/E. faecium* ratio.
Only one of the DCMs (Aalborg Hospital) tested all enterococcal blood isolates for high level gentamicin resistance (HLGR). Among the tested *E. faecalis* isolates in DCM Aalborg, 36% were HLGR, whereas 58% of the tested *E. faecium* isolates were HLGR. The resistance level of HLGR for *E. faecalis* was similar to the levels detected in many countries reporting to EARSS (including the UK, Spain, Norway).
Since 2005, SSI has asked the all DCMs to send presumable vancomycin resistant enterococcal isolates from both invasive and non-invasive infections for national surveillance on VRE. In 2008, 18 *vanA E. faecium*, 8 *vanB E. faecium* and five vanB *E. faecalis* isolates were obtained. Less than 1% of the E. faecium (n=2) and *E. faecalis* (n=2) blood isolates were resistant to vancomycin. As described above, most of the *E. faecium* isolates were resistant to ampicillin. This may necessitate a change of treatment of enterococcal infections from ampicillin to vancomycin, which in turn would increase the risk of spread of vancomycin resistant enterococci in Danish hospitals. This might already have happened since the consumption of glycopeptides has increased from 2.8 DDD/1,000 occupied bed-days in 1999 to 6.8 DDD/1,000 occupied bed-days in 2008 in hospitals.



Figures 37a and 37b. Data on enterococccal blood culture isolates from 11 Danish Departments of Clinical Microbiology. (A) The number of enterococcal bacteraemias from 2002 though 2008. 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. The black bars represent the ampicillin resistant isolates and the white bars represent the ampicillin sensitive isolates*

Staphylococcus aureus

Staphylococcus aureus is a part of the normal flora in approximately 50% of the population. Some persons only carry *S. aureus* intermittently whereas others carry *S. aureus* for longer times. However, *S. aureus* also cause infections ranging from superficial skin infections i.e. impetigo and boils, to invasive infections such as post operative wound infections, infections related to intravenous cathethers and prostesic devisis, arthritis, bacteremia and endocariditis. Betalactam antibiotics are the drugs of choice for treatment of *S. aureus* infections except in case of MRSA.
MRSA has been both laboratory and clinical reportable since November 2006.

Surveillance of bacteraemia

A total of 1,344 *S. aureus* bacteraemia cases were reported in 2008. Reports were received from all DCMs. The number of cases corresponded to 24.5 per 100,000 inhabitants, which was the same as in 2007 (24.5 per 100,000 inhabitants). Seventeen (1.3%) of the cases were caused by methicillin resistant *S. aureus* (MRSA), which was a doubling compared to 2007 (8 cases, 0.6%) but similar to the numbers in the previous years. The rate was very low compared to the other countries participating in the European Antimicrobial Resistance Surveillance System (EARSS) which reported an average of 22% MRSA from blood cultures in 2007.
Resistance among *S. aureus* bacteraemia isolates from 2004 though 2008 is presented in Table 31. No statistically significant changes have been observed during this period.

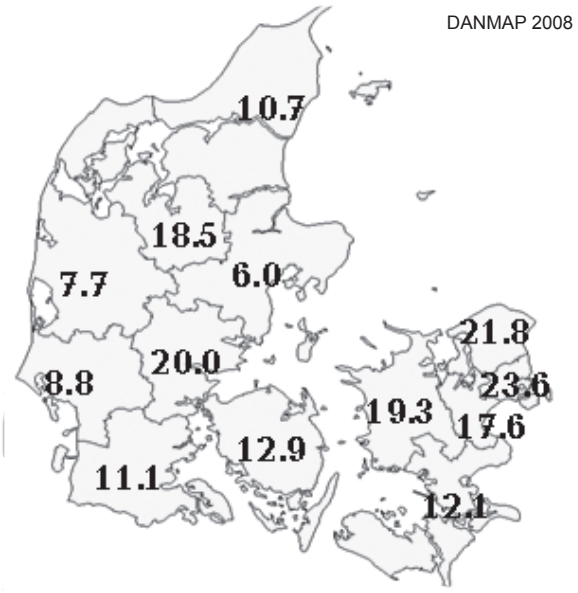


Figure 38. Incidence of new MRSA cases per 100,000 inhabitants per clinical microbiology department.

Surveillance of Methicillin Resistant *S. aureus*

The total number of new Methicillin resistant *S. aureus* (MRSA) cases increased from 659 in 2007 to 854 cases in 2008 (15.5 per 100,000 inhabitants). Three persons were found with two different MRSA strains. At the time of diagnosis, 447 (52%) had infection compared to 370 (56%) in 2007. The increase observed in 2008 was thus due to both an increase in the number of persons presenting with infections and persons with colonisation only at the time of diagnosis (i.e. screening).

Table 31. Occurrence of resistance (%) among isolates from Staphylococcus aureus *bacteraemia cases in Denmark 2004 - 2008.*

DANMAP 2008

	2004	2005	2006	2007	2008
Methicillin	1.3	1.6	1.4	0.6	1.3
Penicillin	74	78	80	78	77
Erythromycin	5	5	5	4	5
Clindamycin	4	4	4	3	4
Tetracyclin	3	3	3	2	3
Fusidic acid	8	10	10	9	9
Rifampicin	1	<1	<1	<1	<1
Norfloxacin	4	3	2	1	2
Streptomycin	<1	<1	<1	<1	<1
Kanamycin	<1	2	1	<1	1
Mupirocin	nt*	0	0	<1	<1
Number of isolates	1,487	1,428	1,329	1,345	1,344

* nt= not tested

Table 32. Number of new MRSA cases per department of clinical department, Denmark

DANMAP 2008

	2005	2006	2007	2008
Aalborg	38	21	42	63
Viborg	1	5	17	26
Herning	8	19	7	22
Århus	45	39	69	46
Vejle	311	145	95	66
Esbjerg	20	14	28	17
Sønderborg	14	20	19	26
Odense	25	32	34	62
Hillerød	42	28	38	72
Greater Copenhagen*	298	321	232	313
Statens Serum Institut**	15	20	10	49
Slagelse	22	29	44	55
Næstved	12	13	24	37
Denmark total	851	706	659	854

*Righospitalet, Hvidovre and Herlev
**Isolates from Roskilde County

The number of new MRSA cases per year for each DCM in the last four years (Greater Copenhagen is served by 3 departments of clinical microbiology, and is shown as one) is shown in Table 32. The incidence per 100,000 inhabitants in 2008 is presented in Figure SA1. The incidence varied from 23.6 per 100,000 inhabitants in the greater Copenhagen area to 6.0 per 100,000 inhabitants in Aarhus (Figure 38).

Since 2007, the old counties no longer exist and are replaced by the larger regions. However, to provide a greater resolution for the distribution of MRSA cases in Denmark, the numbers and incidences are presented for each DCM which largely corresponds to one for each of the former counties except for the Greater Copenhagen Area, which is served by 3 DCMs but the numbers is presented as one.

The total number of cases and the number of cases presenting with infection according to epidemiological classification are shown in Table 33. Most of the cases (84%) were acquired in Denmark. Infections classified as hospital acquired (HA) was 47 cases in 2008 compared to 28 cases in 2007 and constituted 10% of the total number of infections.

Molecular typing of the MRSA strains

The number of isolates belonging to the 10 dominating *spa* types isolated in 2008 is shown in Table 34. They constituted 66% of the total number of MRSA isolates. *spa* type t127 increased from 17 in 2007 to 73 in 2008. The increase in t127 was mainly due to an outbreak in a neonatal unit, and the majority of isolates were from screening samples. The increase in *spa* type t189, was caused by an outbreak in another neonatal unit. The number of CC398 *spa* type t034 increased from 13 in 2007 to 61 in 2008. This was in part due to a screening project of farmers at a conference for pig production. However, the number of infections caused by CC398 strains was 16 in 2008 compared to six in 2007. CC398 is associated with livestock animals especially pigs and people in direct contact with live pigs. In 2008, 95% of CC398 isolates were resistant to tetracycline. This was similar to what have been reported from other countries with intensive pig production. The extensive consumption of tetracycline in the Danish pig production may serve as a selective factor for this strain type.

Table 33. Epidemiological classification of new MRSA cases, 2008, with data from 2007 for comparison

DANMAP 2008

		2007		2008	
Epidemiologic classification	Exposure	No. of cases	No. (%) of cases with infections	No. of cases	No. (%) of cases with infections
Acquired outside Denmark (IMP)		114	70 (61)	137	73 (53)
Detected in Hospitals (HA)		52	28 (54)	141	47 (33)
Hospital associated, community onset (HACO)	with health care risk	125		115	
	with known exposure	31	11 (35)	17	9 (53)
	without known exposure	94	66 (70)	98	77 (79)
Health care worker		27	12 (44)	25	5 (20)
Community acquired (CA)	without health care risk	336		417	
	with known exposure	142	43 (30)	171	33 (19)
	without known exposure	194	137 (71)	246	198 (80)
Unclassified		5	3 (66)	19	7 (37)

In contrast, t024 decreased from 74 cases in 2007 to 45 in 2008. This *spa* type was causing an outbreak in nursing homes in the Greater Copenhagen area in 2007, but seems now to be more under control. *Spa* types t003 and t037, which were among the 10 most prevalent *spa* types in 2007 (n=24 and 14, respectively), decreased in numbers to 10 and 7, respectively, in 2008.

Eight *spa* types constituted 61% of the 447 clinical infections with MRSA. Most prevalent *spa* types causing clinical infections were t008 (n=56), t044 (53), t002 (42), t019 (38), t024 (28), t032 (20), t127 (17) and t034 (16). Of the 307 strains isolated from asymptomatic carriers, t127 was the most prevalent spa type (n=52), followed by t034 (40), t002 (32), t189 (23) and t008 (21).
Differences in *spa* types thus seem to exist between MRSA from infections and carriers, most notably in t189 (2/23, numbers from infection and carriers, respectively) and t019 (38/7). However, as mentioned above, the t189 isolates mostly originated from screening samples due to an outbreak in a neonatal unit.

Resistance among MRSA isolates

The resistance patterns varied considerably between *spa* types (Table 35). *spa* type t189, a *spa* type which is often hospital acquired, demonstrated the highest frequency of resistance towards all tested antimicrobial agents except for tetracycline and fusidic acid. In contrast, the majority of t015 and t019, two primarily community acquired *spa* types, were susceptible to all tested antimicrobial agents except for beta-lactams. Overall the prevalence of resistance in 2008 was similar to 2007 except for erythromycin, which decreased from 48% in 2007 to 39% in 2008. This might partly be because of a decrease in the numbers of t024 isolates, where the vast majority was resistant to erythromycin.

Table 34. Numbers of the 10 most prevalent spa *types demonstrated in MRSA cases, Denmark 2008*

DANMAP 2008

spa type	CC group*	number	No. causing infections (%)
t008	CC8	87	56 (64)
t002	CC5	85	42 (49)
t044	CC80	74	53 (72)
t127	CC1	73	17 (23)
t034	CC398	61	16 (26)
t019	CC30	47	38 (81)
t024	CC8	45	28 (62)
t032	CC22	40	20 (50)
t189	CC1	28	2 (7)
t015	CC45	20	6 (30)

* CC= Clonal complex

Within some *spa* types, differences between 2007 and 2008 were found. For *spa* type t008, the most frequent *spa* type in both years (n=83 and n=87, respectively), resistance to norfloxacin increased from 29% to 57%. For spa type t044, the third most prevalent in 2008 (n=74), resistance to erythromycin and clindamycin increased from 2% to 19% and from 2% to 17%, respectively. In contrast, t127 (n=73) demonstrated lower prevalence of resistance for five of the tested antimicrobial agents (erythromycin, clindamycin, tetracycline, streptomycin and kanamycin), but an increase in resistance to fusidic acid from 24% to 78%. Such changes may indicate emergence of new clone(s) of *spa* type t127.

Resistance frequencies of MRSA isolates from infections in 2008 according to epidemiological classification is given in Table 36. Resistance to erythromycin decreased among hospital acquired (HA) infections compared to 2007. Tetracycline resistance among infections classified as hospital associated, community onset (HACO) increased from 5% to 15%.

Table 35. Prevalence of resistance for the 10 most prevalent spa *types demonstrated in MRSA cases, Denmark 2008, compared with all MRSA cases*

DANMAP 2008

Spa type	t008	t002	t044	t127	t034	t019	t024	t032	t189	t015	All
Clonal complex	CC8	CC5	CC80	CC1	CC398	CC30	CC8	CC22	CC1	CC45	
Erythromycin	72	30	19	18	48	2	91	40	100	0	39
Clindamycin	14	29	17	15	61	2	84	40	100	0	31
Tetracycline	11	10	59	14	95	0	0	3	4	5	24
Fusidic acid	13	45	83	78	0	0	2	0	7	0	24
Rifampicin	0	0	0	0	0	0	2	3	7	0	1
Norfloxacin	57	43	3	0	16	0	19	100	100	0	32
Streptomycin	0	0	67	4	38	0	0	0	100	0	16
Kanamycin	64	13	92	12	3	0	7	0	100	0	31
Mupirocin	1	3	1	3	0	0	0	3	11	0	2
Number of isolates	87	85	75	73	61	47	45	40	28	20	854

Table 36. Occurrence of resistance (%) among methicillin resistant Staphylococcus aureus *(MRSA) isolates from infections in 2008 according to epidemiologic classification*

DANMAP 2008

Compound	Imported infections (IMP)	Hospital acquired infection (HA)	Hospital associated infection, community onset (HACO)	Community associated infection (CA)
Erythromycin	40	35	57	29
Kanamycin	40	22	24	39
Clindamycin	25	29	50	18
Norfloxacin	22	33	35	24
Tetracycline	29	18	15	27
Fusidic acid	15	22	16	25
Streptomycin	10	10	6	17
Rifampicin	1	0	1	0
Mupirocin	0	0	1	1
Number of isolates	73	51	90	230

Pseudomonas aeruginosa

Resistance in *Pseudomonas aeruginosa* isolates obtained from blood infections has not been reported in the DANMAP report before.

P. aeruginosa is an opportunistic pathogen of immunocompromised individuals. *P. aeruginosa* typically infects the pulmonary tract, urinary tract, burns, wounds, and also causes other blood infections. It is the most frequent colonizer of medical devices (e.g., catheters). *P. aeruginosa* infection is a serious problem in patients hospitalized with cancer, cystic fibrosis, and burns. The case fatality rate in these patients is high.

P. aeruginosa blood isolates obtained from hospital patients

For *P. aeruginosa* this report includes data from 14 Departments of Clinical Microbiology, representing 95% of the Danish population. Approximately 400 *P. aeruginosa* isolates from blood were tested for antimicrobial susceptibility in 2007 and 2008 (Table 37). The levels of resistance were low for all the tested antimicrobial agents and compared to the other countries reporting to the EARSS report among the lowest.

Table 37. Resistance (%) to ciprofloxacin, gentamicin, 3rd generation cephalosporin, carbapenem and piperacillin-tazobactam in Pseudomonas aeruginosa *isolates obtained from human blood, Denmark*

DANMAP 2008

Compound	2007 %	2008 %
Ciprofloxacin	5.7	4.5
Gentamicin	1.2	<1
Ceftazidime	2.4	3.4
Meropenem	2.3	<1
Piperacillin/ Tazobactam	3.4	2.3
Max. number of isolates tested	417	426

Textbox 11

Emergence of *Clostridium difficile* 027 in Danish hospitals

Since 2003, outbreaks of severe *Clostridium difficile*-associated diarrhoea (CDAD) with increased mortality rate have been caused by the emergence of a hypervirulent C. difficile strain in North America and Europe. These outbreaks have mainly been ascribed to the emergence of *C. difficile* with PCR ribotype 027 (CD027). In 2008 CD027 was discovered in 16 European countries. The true incidence of CD027 in Europe is difficult to estimate because national surveillance programmes are not fully implemented throughout the continent [Kuijper et al. 2008. Euro Surveill. 13:pii=18942]. *C. difficile* infections constitute 15-25% of all cases of antibiotic-associated diarrhoea [Bartlett and Gerding. 2008. CID. 46: S12-S18]. The manifestations of *C. difficile* acquisition range from asymptomatic carriage over mild diarrhoea to pseudomembranous colitis. The classical presentation of CDAD is non bloody, profuse diarrhoea accompanied by abdominal cramps and low-grade fever in patients who have been treated with antibacterial agents such as clindamycin, cephalosporins, broad spectrum penicillins and fluoroquinolones. CD027 is characterised by an enhanced pathogenicity possibly due to the production of Toxin A and Toxin B being 20 times higher than in common *C. difficile* strains [Warny *et al.* 2005. Lancet. 366: 1079-1084]. The unusual severty of diarrhoea caused by CD027 enables more person-to-person transmission and a possibly enhanced ability to spread via fomites. Several factors may be of importance to understand the emergence of *C. difficile* and in particular of CD027. The CD027 strain is resistant to the newer fluoroquinolones, including moxifloxacin. It has been suggested that this may be the main reason for its wide dissemination [Warny et al. 2005. Lancet. 366: 1079-1084; Loo *et al.* 2005. N Engl J Med. 353: 2442-2449]. In Denmark, the aggregated number of discharges of enterocolitis caused by *C. difficile* increased from 86 (eight per 100,000 discharges) in 1997 to 282 (23 per 100,000 discharges) in 2007. In the same period, the consumption of fluoroquinolones and cephalosporins consumption in hospitals, increased from 14.6 to 80.1 DDD/1,000 occupied bed-days and from 46, 2 to 134.7 DDD/1,000 occupied bed-days per annum, respectively. The hypothesis about resistance to fluoroquinolones and emergence of CD027 was supported by the almost parallel increase in CDI discharge diagnoses and the consumption of fluoroquinolones (Figure 39). Furthermore, increased use of broad-spectrum antimicrobial agents including cephalosporins may also be related to the emer-gence of *C. difficile*, since the same almost parallel increase is observed in CDI discharge diagnosis and consumption of cephalosporins (Figure 39). However, these possible relations should be interpreted with caution. Other circumstances may also be of considerable importance, such as the increasing challenges in the area of hospital hygiene as mentioned above. Furthermore, demographic changes such as an age distribution with an increasing proportion of elderly people and changes in the patterns of hospitalisation towards increased “turn-over” of patients may also contribute. The emergence of *C. difficile* and CD027 in particular is likely to be a result of environmental as well as person-to-person transmission in healthcare facilities rather than solely a result of increased antibiotic pressure.

The first outbreak of CD027 in Denmark occurred from October 2006 to August 2007 and was re-trospectively detected. It included 13 patients, most of them elderly, admitted to three hospitals in the same region. Most of the patients had overlapping periods of admission. All patients had been treated with broad-spectrum antibiotics, in particular cephalosporins and fluoroquinolones, prior to positive culture of CD027. Thirty days after confirmation of diagnosis, three of the 13 patients had died. Taken together, the data support the hypothesis that the increasing use of certain broadspectrum antibiotics may be related to a possible increase of *C. difficile* infection, and show that the specific contribution by CD027 in its emergence needs to be determined [Søes *et al*. 2009. Euro-surv,14:15 Art 4].

Another CD027outbreak was reported in 2009. The outbreak included 73 cases from the area north of Copenhagen, but there might have been related cases elsewhere in Zealand. Most infections were healthcare-associated and in patients who previously had received antibiotic treatment. The strain

was resistant to moxifloxacin, erythromycin, and clindamycin, and carried genes for toxin A, toxin B, and for the binary toxin. The antimicrobial pattern differed from that of the strain involved in the first outbreak in Denmark in 2006-2007, which was susceptible to erythromycin and clindamycin. Because of this outbreak, hygienic measures in the involved hospitals were reinforced. Nationwide, microbiological laboratories were alerted to the outbreak and encouraged to send isolates for toxin profiling and PCR ribotyping [Bacci *et al*. 2009. Eurosurv. 14:16 art.2]

On March 17th 2009, the Danish National Board of Health decided to intensify the surveillance of CD027. Hence, the clinical microbiology departments are now required continually to submit: 1) moxifloxacin-resistant *C. difficile* isolates, 2) *C. difficile* isolates from cases with severe clinical manifestations and 3) *C.difficile* isolates from cases suspected to be part of an outbreak to Statens Serum Institut for further investigation. National data are reported at www.Mave-tarm.dk.

Once CDAD is diagnosed in a patient, it is important to prevent further spread of *C. difficile*. This can be accomplished by patient isolation either in single rooms or by cohort isolation. Other measures which should be considered include: 1) environmental cleaning using sporicidal agents, e.g. hypochlorite solution, 2) elimination of selection pressure by discontinuing antimicrobial treatment if possible, and 3) hand hygiene: since bacterial spores are not killed by alcohols it is recommended to use soap based washing of the hands [Vonberg *et al*. 2008. Clin Microbiol Infect. 14 Suppl 5:2-20. Review].

The emerging of CD027 in Danish hospitals is of concern and need to be followed carefully in the future to avoid further spread.

Katharina E. P. Olsen and Lillian Søes

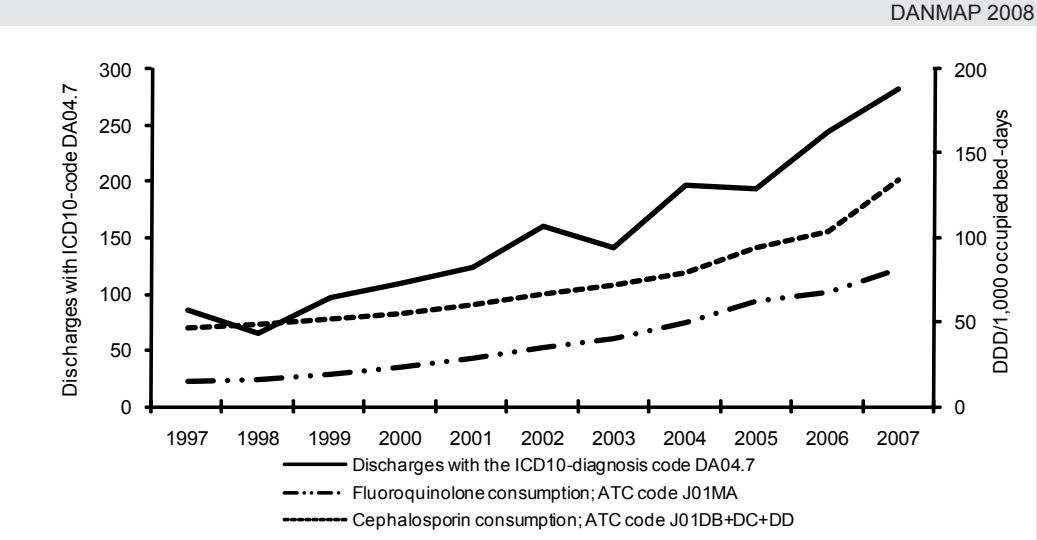


Figure 39. Annual number of hospital discharges with enterocolitis caused by Clostridium difficile *(ICD10 diagnosis code DA04.7) and annual consumption of fluoroquinolons and cephalosporins for systemic use in public somatic hospitals, Denmark, 1997–2007*

Textbox 12

Tuberculosis – results from nationwide drug susceptibility testing in 2007

The majority of the estimated annual 9 million new tuberculosis (TB) cases worldwide are caused by *Mycobacterium tuberculosis*. The World Health Organization (WHO) estimates that almost ½ million of these are caused by multi-drug resistant (MDR) *M. tuberculosis* (i.e. at least rifampin and isoniazid resistant). Rates of MDR-TB among new cases are found greater than 6% in settings in Azerbaijan, Moldova, Ukraine, Russia, Uzbekistan, Estonia, Latvia, Lithuania, Armenia, China and Georgia.

From 391 notified TB cases in Denmark in 2007, drug resistance results were available for all 291 patients with culture-verified TB caused by *M. tuberculosis*: 119 Danes and 172 immigrants. In addition, one case of *M. bovis* was found. *M. bovis* is naturally resistant to pyrazinamid and this case was found susceptible to rifampicin, isoniazid and ethambutol. In Denmark, TB treatment includes rifampin, isoniazid, ethambutol and pyrazinamide in the initial phase, and rifampin and isoniazid in the continuation phase.

Drug susceptibility testing of *M. tuberculosis* for the main first line drugs aims at detecting 1% resistant organisms in the bacterial population, as this level has been shown to be of clinical significance. A total of 24 patients (8%), three (3%) Danes and 21 (12%) immigrants had infections resistant to at least one of the first line drugs rifampicin, isoniazid and/or ethambutol. All three Danes had isoniazid mono-resistant,

DANMAP 2008

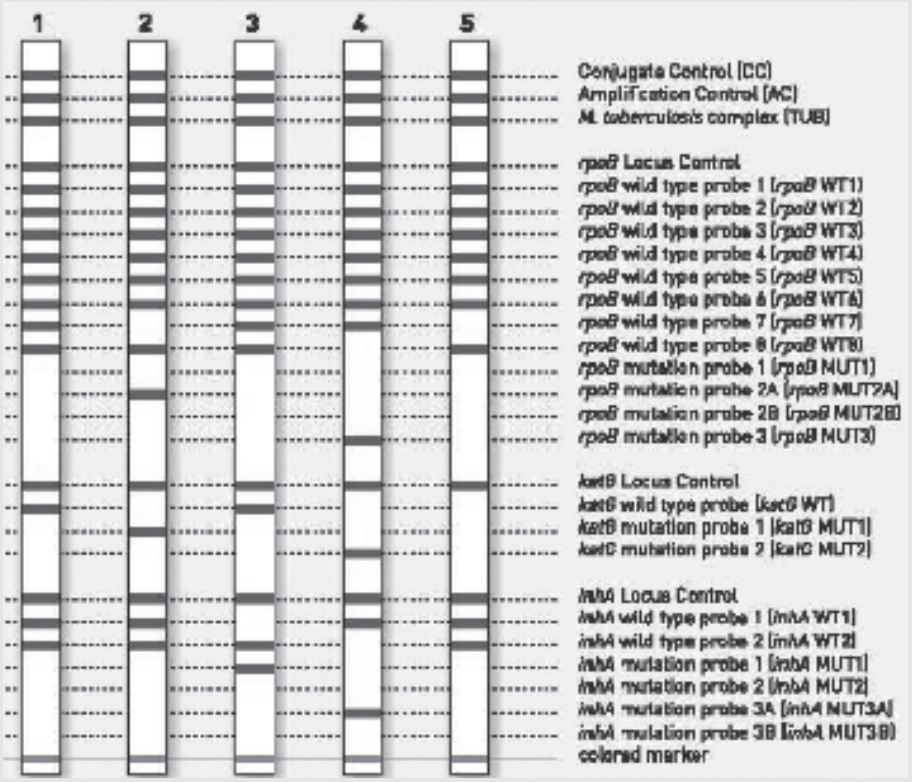


Figure 40. The Line Probe Assay for rifampicin (R) and isoniazid (H) resistance in Mycobacterium tuberculosis. Hybridisation to wildtype DNA predicts sensitivity. Lack of hybridisation to wild-type DNA or hybridisation to mutation probes predicts resistance. Lane 1:R^SH^S, lane 2: R^RH^R, lane 3: R^SH^R , lane 4: R^RH^R, lane 5: R^RH^R.

TB while the group of 21 immigrants consisted of 17 cases with isoniazid mono-resistant TB, two cases with poly-resistance to isoniazid and ethambutol, and two cases with MDR TB. Both MDR TB cases were newly diagnosed young adult immigrants. One of the cases, an immigrant from Eastern Europe, had gastrointestinal TB. The other patient, an immigrant from Southeast Asia, had disseminated TB with negative sputum smears.
Among 44 patients (16 Danes and 28 immigrants) with TB relapse, drug susceptibility testing was carried out on 29 cases with culture verified disease. Isoniazid mono-resistance was detected in two (7%) relapse cases, one Dane and one immigrant.

The observed level of <1% MDR in Denmark comparable to the 0-4% found in non-Baltic EU countries. In the Baltic States, MDR is detected among 10-21% of all patients. In the eastern part of the European WHO region (12 non-EU eastern European and central Asian countries), the MDR prevalence ranged between 14-57% (varying representativeness of data). Treatment success rates for MDR TB and extensively drug-resistant TB are much lower than treatment success for pan sensitive TB. Methods for drug susceptibility testing of second line drugs have recently been standardized at the international level and surveillance of drug resistance against second line drugs is expected in the future.

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Resistance in bacteria from diagnostic submissions

Bacteria from food animals

The DANMAP programme monitors antimicrobial resistance in *Escherichia coli* O149 and *Staphylococcus hyicus* from diagnostic submissions from pigs, and *E. coli* F5 (K99) from diagnostic submissions from cattle. *E. coli* were isolated from faecal samples, typically from pigs or calves with diarrhoea, while *S. hyicus* were isolated from pigs with dermatitis. Most isolates from diagnostic submissions originate from animals in antimicrobial therapy, or with a history of recent antimicrobial therapy. For this reason a higher frequency of resistance is expected in bacteria from diagnostic submissions compared to bacteria originating from healthy animals sampled at slaughter.

Escherichia coli

Figure 41 presents trends in resistance to selected antimicrobial agents in *E. coli* O149 isolates from pigs from 1999 to 2008. The MIC distributions are presented in Table 60 (Appendix 1). The isolates are mainly from post weaning pigs (>7.5 to 30 kg). In 2008, the occurrence of neomycin resistance in *E. coli* O149 from pigs decreased to 18% from 33% in 2007 (data are not shown). At the same time, the use of neomycin decreased by 99.7 % from 2006 to 2008, causing a major decrease in the use of aminoglycosides for weaning pigs.

In 2008, 60% of the *E. coli* O149 isolates were resistant to tetracycline, corresponding to the 1999-2000 level. From 2001 through 2004, an increasing trend was observed concomitant with an increased consumption of tetracyclines in pigs (Figure 41). Since 2004, the consumption of tetracyclines has increased continuously, while the observed resistance did not change significantly during 2004 through 2007, but decreased significantly by 22% from 2007 to 2008.
A large proportion (94%) of the tetracycline resistant isolates were resistant to three or more of the tested antimicrobial agents; 24% of the isolates were AMP-SUL-STREP-TET, and additional 27% were SUL-TET-STREP resistant. The level of resistance to ampicillin seemed to reach a maximum in 2004 with 49% of the isolates being resistant. A maximum for consumption of aminopenicillins in pigs was observed in 2004, with a decrease in consumption from 2004 through 2008.
Table 60 (Appendix 1) presents the distribution of MICs and occurrence of resistance in *E.coli* O149 and *E. coli* F5 (K99) from pigs and cattle, respectively.
The use of fluoroquinolones in production animals was reduced since 2002 due to legal restrictions. Subsequently, resistance to nalidixic acid in *E. coli* O149 from pigs has decreased from 29% in 2004 to 10.7% in 2008.

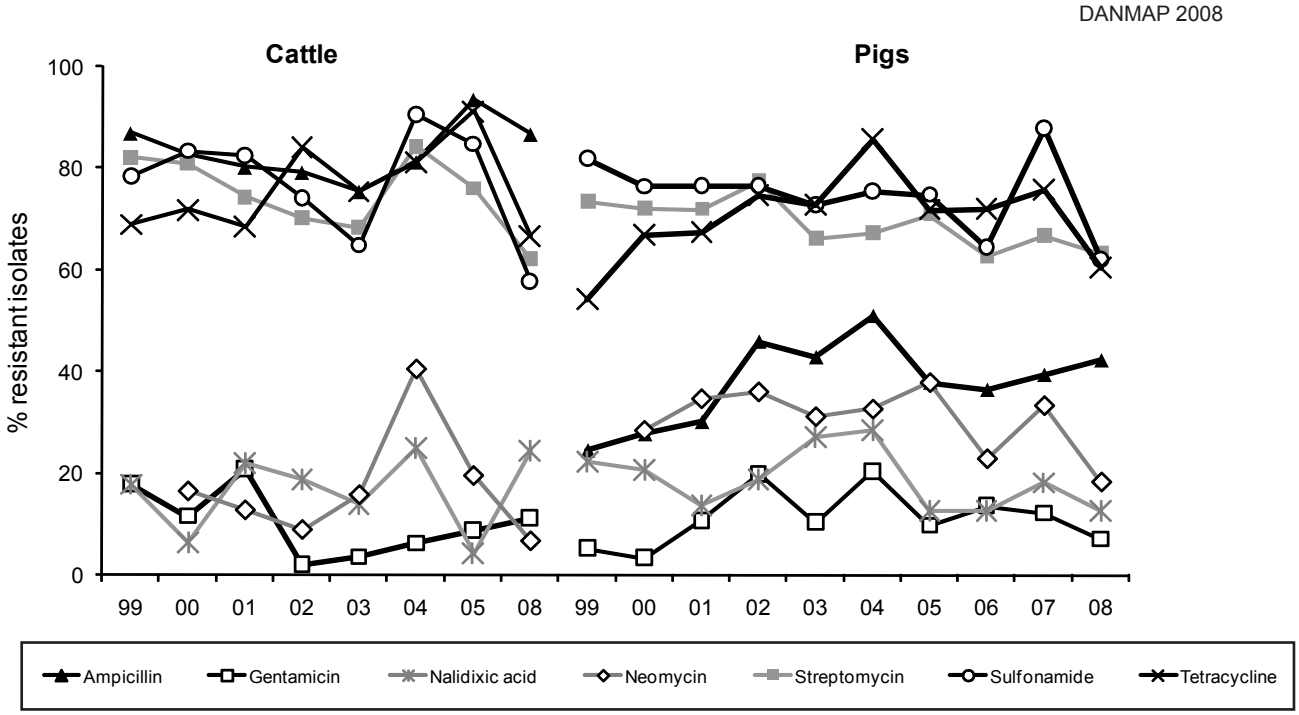

Figure 41. Trends in resistance to selected antimicrobials among Escherichia coli *from diagnostic submissions from animals, Denmark*

In cattle, *E.coli* F5 (K99) are almost entirely isolated from diagnostic submissions from calves. Figure 41 shows the significant decrease in resistance to sulphonamides and tetracyclines from 2005 through 2008. Also, a decreasing trend was observed for ampicillin and streptomycin resistance. In 2005, the most important antimicrobial group used in calves was tetracyclines, and during 2006–2008, it has been the second most used drug. The use of tetracycline, sulfonamides, streptomycin and aminopenicillins in calves has been decreasing since 2005. Resistance to three or more antimicrobials was observed for 76% of the isolates, most frequently combinations of the aforementioned drugs (33% AMP-SUL-STREP-TET and 20% resistant to three of these drugs) often in combination with other types of resistance, and 6% being AMP-CIP-NAL-TET resistant.

While resistance to ceftiofur was not observed for *E. coli* O149 in previous years, 2 isolates of O149 (2.9%) were resistant to ceftiofur (and to cefotaxime) in 2008. The use of third and fourth generation cephalosporins in pigs has been increasing significantly since 2001 (by 374%).

Resistance to ceftiofur was also observed for 2 isolates of *E. coli* F5 (K99) in 2008 (4.4%), and resistance to cefotaxime was observed in 6.7% of the isolates.

Staphylococci

Staphylococcus hyicus was isolated from 31 clinical submissions from skin infections in pigs. The MIC distributions and the occurrence of resistance among *S. hyicus* from pigs are presented in Table 59 (Appendix 1), while the trends for selected antimicrobials are presented in Figure 42. Significant changes in resistance were not observed in 2008 compared to 2007 for any of the antimicrobial agents tested.

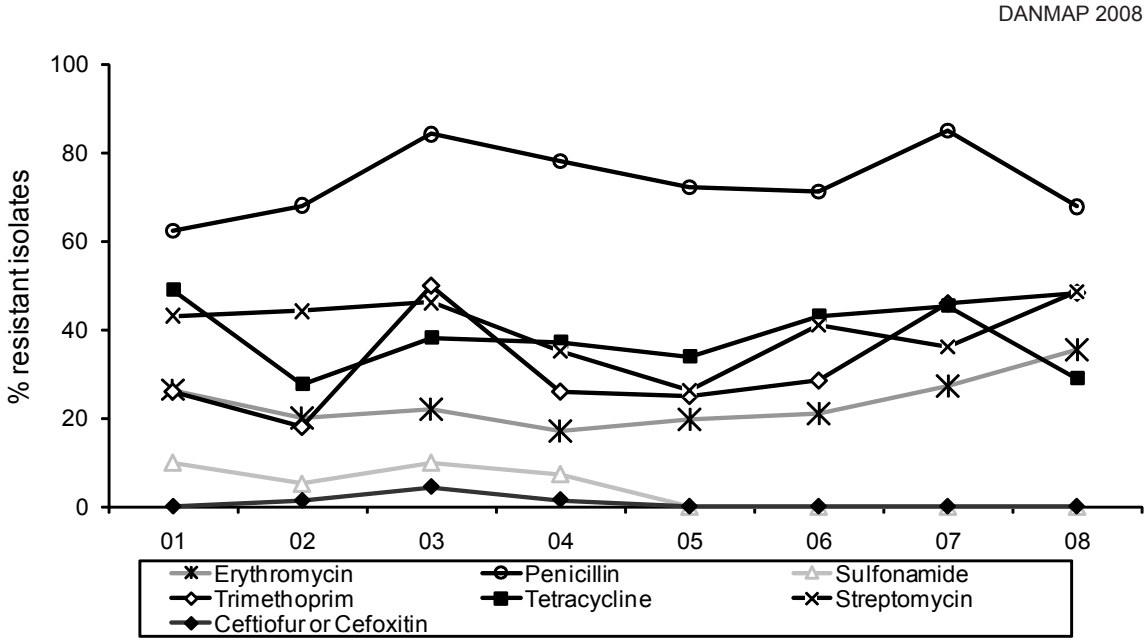

Figure 42. Trends in resistance to some selected antimicrobials among Staphylococcus hyicus *from diagnostic submissions from pigs, Denmark*

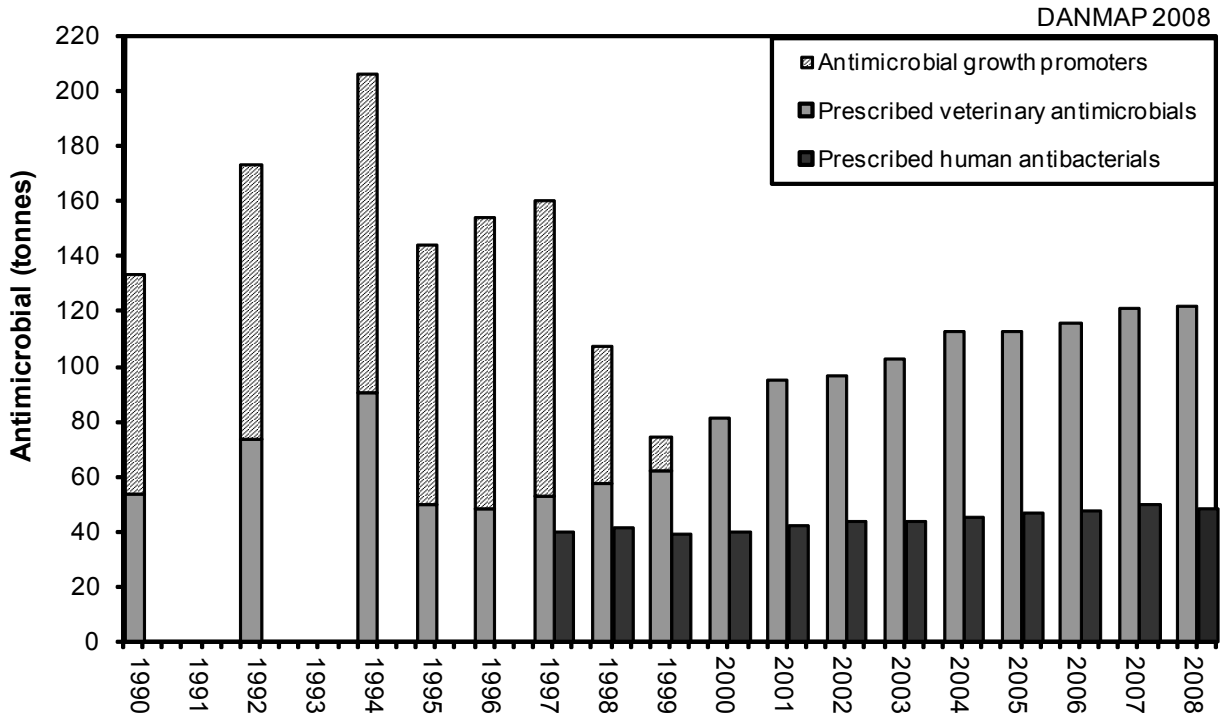

Figure 43. Consumption of prescribed antimicrobials and growth promoters in animal production and prescribed antibacterials in humans, Denmark

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—2008: Data from VetStat.

Table 38. Number of DDDs per treated patient and of packages per treated patient in primary health care, Denmark DANMAP 2008

ATC group a	Therapeutic group	Indicator	Year									
			1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
J01AA	Tetracyclines	DDDs / patient	28.1	29.8	30.6	33	34.4	36.9	38.8	41.1	43	44.4
		Packages / patient	1.8	1.9	1.9	1.9	1.9	1.9	2	1.9	2	2
J01CA	Penicillins with extended spectrum	DDDs / patient	12.5	12.8	13	13.2	13.4	13.6	13.9	14.2	14.4	14.7
		Packages / patient	1.5	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
J01CE	Beta-lactamase sensitive penicillins	DDDs / patient	10	10.2	10.3	10.5	10.7	11.1	11.3	11.5	11.7	11.8
		Packages / patient	1.4	1.4	1.4	1.5	1.5	1.5	1.5	1.4	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	13.4	13.7
		Packages / patient	1.5	1.5	1.6	1.6	1.6	1.6	1.6	1.5	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	19.9
		Packages / patient	1.7	1.8	1.7	1.7	1.8	2	2	1.8	1.6	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	23.7
		Packages / patient	2.7	2.6	3	3.2	3.3	3	3.5	3.5	3.6	4.1
J01EA	Trimethoprim and derivatives	DDDs / patient	28.2	29.5	30.4	29.3	30	29.8	30	30.6	30.5	30.2
		Packages / patient	1.9	1.9	2	2	2	2	2	1.9	1.9	2.1
J01EB	Short-acting sulfonamides	DDDs / patient	4	4	4	4	4	4	3.9	3.9	3.9	3.8
		Packages / patient	1.4	1.4	1.4	1.4	1.4	1.5	1.5	1.4	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	12.5
		Packages / patient	1.4	1.5	1.5	1.5	1.6	1.6	1.6	1.5	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	12.8
		Packages / patient	1.7	1.9	2.1	1.8	1.8	1.8	2.8	2.9	2.7	2.5
J01GB	Aminoglycosides	DDDs / patient	0	0	0	121.7	121.7	122	121.7	182.5	128	152.7
		Packages / patient	0	0	0	6.7	3.3	3.3	3.3	5	4.9	4.9
J01MA	Fluoroquinolones	DDDs / patient	8	7.8	8.3	8.6	10.3	9.5	9.6	10.3	10.6	11
		Packages / patient	1.4	1.4	1.4	1.4	1.6	1.5	1.5	1.5	1.5	1.5
J01XB	Polymyxins	DDDs / patient	273.8	274.5	182.5	243.3	243.3	183	182.5	182.5	219.3	202.8
		Packages / patient	72.5	70	52.5	66.7	66.7	52.5	50	37.5	21.9	20.3
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	18.5
		Packages / patient	1.8	1.8	1.7	1.9	2.1	2	2.1	2	2.1	2.5
J01XE	Nitrofuran derivatives (nitrofurantoin)	DDDs / patient	23.1	23.9	24.8	24.5	24.8	24.6	24.5	24	26.3	25.4
		Packages / patient	1.7	1.8	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	239.9
		Packages / patient	5.3	5.6	6	5.8	4.9	4.9	5	4.8	4.7	4.8
J01	Antibacterials for systemic use (total)	DDDs / patient	15	15.3	15.6	16	16.4	17	17.5	17.9	17.3	18.9
		Packages / patient	2	2	2	2	2.1	2.1	2.1	2	1.9	2.1

a) From the 2008 edition of the Anatomical Therapeutic Chemical (ATC) classification system

Table 39. Distribution of MICs and occurrence of resistance in Salmonella *Typhimurium from cattle (n=18) and pigs (n=497), Denmark*

DANMAP 2008

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	Cattle	38.9	[17.3-64.3]								50.0	11.1			16.7	22.2						
	Pigs	41.2	[36.9-45.7]								54.9	3.6	0.2	0.2	6.0	35.0						
Chloramphenicol	Cattle	16.7	[3.6-41.4]									66.7	16.7				16.7					
	Pigs	10.5	[7.9-13.5]								1.8	50.1	35.0	2.6		1.0	9.5					
Florfenicol	Cattle	11.1	[1.4-34.7]									77.8	5.6	5.6	11.1							
	Pigs	6.4	[4.4-9.0]								3.2	79.3	8.7	2.4	5.4	0.4	0.6					
Ampicillin	Cattle	44.4	[21.5-69.2]							50.0	5.6					44.4						
	Pigs	40.6	[36.3-45.1]							46.9	10.3	2.2				40.6						
Ceftiofur	Cattle	0	[0-18.5]						55.6	38.9	5.6											
	Pigs	0.2	[0.01-1.1]						63.2	33.0	3.6			0.2								
Cefotaxime	Cattle	0	[0-18.5]				100															
	Pigs	0.2	[0.01-1.1]				93.0	6.2	0.6				0.2									
Sulfonamide	Cattle	55.6	[30.8-78.5]													44.4					55.6	
	Pigs	47.5	[43.0-52.0]													52.3	0.2			0.4	47.1	
Trimethoprim	Cattle	0	[0-18.5]							100												
	Pigs	7.2	[5.1-9.9]							92.2	0.6					7.2						
Apramycin	Cattle	0	[0-18.5]									94.4	5.6									
	Pigs	2.4	[1.3-4.2]									95.8	1.8			2.4						
Gentamicin	Cattle	0	[0-18.5]						72.2	22.2	5.6											
	Pigs	2.6	[1.4-4.4]						78.3	18.9	0.2		0.6	0.8	1.2							
Neomycin	Cattle	0	[0-18.5]								94.4	5.6										
	Pigs	5.2	[3.4-7.6]								93.4	1.4		0.2		5.0						
Spectinomycin	Cattle	22.2	[6.4-47.6]												72.2	5.6			22.2			
	Pigs	14.7	[11.7-18.1]											1.8	75.3	8.2	1.6	1.2	11.9			
Streptomycin	Cattle	50.0	[26.0-74.0]										50.0			5.6	16.7	27.8				
	Pigs	45.5	[41.0-50.0]										50.9	3.6	1.4	5.4	13.3	25.4				
Ciprofloxacin	Cattle	0	[0-18.5]	11.1	83.3	5.6																
	Pigs	0.8	[0.2-2.0]	15.3	77.1	6.8	0.4	0.4														
Nalidixic acid	Cattle	0	[0-18.5]									88.9	11.1									
	Pigs	0.6	[0.1-1.8]									84.9	13.7	0.8			0.6					
Colistin	Cattle	0	[0-18.5]							100												
	Pigs	0	[0-0.7]							99.8	0.2											

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 40. Distribution of MICs and occurrence of resistance in Salmonella *Enteritidis from poultry meat (imported n=30), Denmark*

DANMAP 2008

Compound	% 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	>1024
Tetracycline	0	[0-11.6]								90.0	10.0									
Chloramphenicol	0	[0-11.6]									86.7	13.3								
Florfenicol	0	[0-11.6]								3.3	90.0	6.7								
Ampicillin	16.7	[5.6-34.7]							60.0	16.7	6.7				16.7					
Ceftiofur	6.7	[0.8-22.1]						46.7	46.7				6.7							
Cefotaxime	6.7	[0.8-22.1]				86.7	6.7					6.7								
Sulfonamide	0	[0-11.6]													100					
Trimethoprim	0	[0-11.6]							100											
Apramycin	0	[0-11.6]									100									
Gentamicin	0	[0-11.6]						76.7	23.3											
Neomycin	0	[0-11.6]								100										
Spectinomycin	0	[0-11.6]											70.0	30.0						
Streptomycin	0	[0-11.6]										100								
Ciprofloxacin	36.7	[19.9-56.1]	3.3	60.0		3.3	33.3													
Nalidixic acid	36.7	[19.9-56.1]									60.0	3.3				36.7				
Colistin	0	[0-11.6]							96.7	3.3										

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 41. Distribution of MICs and occurrence of resistance in Salmonella *Typhimurium from poultry meat (imported n=48), turkey meat (imported n=29) and pork (Danish n=99; imported n=56), Denmark* DANMAP 2008

Compound	Food type	Origin	% 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	Poultry meat	Imported	8.3	[2.3-20.0]								91.7					8.3						
	Turkey meat	Imported	100	[88.1-100.0]												41.4	58.6						
	Pork	Danish	30.3	[21.5-40.4]								69.7				2.0	28.3						
		Imported	85.7	[73.8-93.6]								10.7	3.6			25.0	60.7						
Chloramphenicol	Poultry meat	Imported	0	[0-7.4]								4.2	95.8										
	Turkey meat	Imported	48.3	[29.4-67.5]									31.0	17.2	3.4			48.3					
	Pork	Danish	4.0	[1.1-10.0]								1.0	53.5	41.4				4.0					
		Imported	32.1	[20.3-46.0]									48.2	19.6			1.8	30.4					
Florfenicol	Poultry meat	Imported	0	[0-7.4]								8.3	91.7										
	Turkey meat	Imported	48.3	[29.4-67.5]								6.9	37.9	3.4	3.4	44.8	3.4						
	Pork	Danish	2.0	[0.2-7.1]								3.0	90.9	4.0		1.0		1.0					
		Imported	26.8	[15.8-40.3]									67.9	1.8	3.6	25.0		1.8					
Ampicillin	Poultry meat	Imported	10.4	[3.5-22.7]							87.5	2.1					10.4						
	Turkey meat	Imported	93.1	[77.2-99.2]							3.4	3.4					93.1						
	Pork	Danish	38.4	[28.8-48.7]							53.5	8.1					38.4						
		Imported	75.0	[61.6-85.6]							21.4	3.6					75.0						
Ceftiofur	Poultry meat	Imported	4.2	[0.5-14.3]						66.7	29.2				4.2								
	Turkey meat	Imported	6.9	[0.8-22.8]						62.1	24.1	6.9			6.9								
	Pork	Danish	1.0	[0.03-5.5]						68.7	27.3	3.0			1.0								
		Imported	0	[0-6.4]						71.4	28.6												
Cefotaxime	Poultry meat	Imported	4.2	[0.5-14.3]				93.8	2.1					4.2									
	Turkey meat	Imported	6.9	[0.8-22.8]				86.2	6.9					6.9									
	Pork	Danish	1.0	[0.03-5.5]				96.0	2.0	1.0				1.0									
		Imported	0	[0-6.4]				92.9	7.1														
Sulfonamide	Poultry meat	Imported	12.5	[4.7-25.2]													87.5					12.5	
	Turkey meat	Imported	100	[88.1-100.0]																		100	
	Pork	Danish	40.4	[30.7-50.7]													59.6					40.4	
		Imported	83.9	[71.7-92.4]													16.1					83.9	
Trimethoprim	Poultry meat	Imported	10.4	[3.5-22.7]							89.6						10.4						
	Turkey meat	Imported	31.0	[15.3-50.8]							69.0						31.0						
	Pork	Danish	7.1	[2.9-14.0]							91.9	1.0	1.0				6.1						
		Imported	21.4	[11.6-34.4]							78.6						21.4						
Apramycin	Poultry meat	Imported	0	[0-7.4]									97.9	2.1									
	Turkey meat	Imported	0	[0-11.9]									96.6	3.4									
	Pork	Danish	3.0	[0.6-8.6]									96.0	1.0			3.0						
		Imported	0	[0-6.4]									98.2	1.8									
Gentamicin	Poultry meat	Imported	0	[0-7.4]						100													
	Turkey meat	Imported	6.9	[0.8-22.8]						89.7	3.4				3.4	3.4							
	Pork	Danish	4.0	[1.1-10.0]						69.7	26.3			1.0	2.0	1.0							
		Imported	1.8	[0.05-9.6]						73.2	25.0					1.8							
Neomycin	Poultry meat	Imported	0	[0-7.4]								100											
	Turkey meat	Imported	0	[0-11.9]								100											
	Pork	Danish	2.0	[0.2-7.1]								96.0	2.0				2.0						
		Imported	7.1	[2.0-17.3]								92.9					7.1						
Spectinomycin	Poultry meat	Imported	8.3	[2.3-20.0]												79.2	12.5			8.3			
	Turkey meat	Imported	62.1	[42.3-79.3]												34.5	3.4		6.9	55.2			
	Pork	Danish	12.1	[6.4-20.2]											1.0	77.8	9.1	1.0	1.0	10.1			
		Imported	44.6	[31.3-58.5]											1.8	51.8	1.8	5.4	3.6	35.7			
Streptomycin	Poultry meat	Imported	2.1	[0.05-11.1]										89.6	8.3			2.1					
	Turkey meat	Imported	75.9	[56.5-89.7]										17.2	6.9	13.8	27.6	13.8	20.7				
	Pork	Danish	41.4	[31.6-51.8]										57.6	1.0		7.1	7.1	27.3				
		Imported	76.8	[63.6-87.0]										17.9	5.4	5.4	23.2	21.4	26.8				
Ciprofloxacin	Poultry meat	Imported	4.2	[0.5-14.3]	22.9	70.8	2.1		2.1	2.1													
	Turkey meat	Imported	34.5	[17.9-54.3]		65.5			24.1	3.4				6.9									
	Pork	Danish	0	[0-3.7]	10.1	84.8	5.1																
		Imported	1.8	[0.05-9.6]	7.1	91.1			1.8														
Nalidixic acid	Poultry meat	Imported	4.2	[0.5-14.3]									93.8	2.1				4.2					
	Turkey meat	Imported	34.5	[17.9-54.3]									58.6	6.9				34.5					
	Pork	Danish	0	[0-3.7]									91.9	8.1									
		Imported	1.8	[0.05-9.6]									82.1	16.1				1.8					
Colistin	Poultry meat	Imported	0	[0-7.4]							97.9	2.1											
	Turkey meat	Imported	0	[0-11.9]							100												
	Pork	Danish	0	[0-3.7]							100												
		Imported	0	[0-6.4]							100												

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 42. Distribution (%) of Salmonella *Enteritidis phage types from imported broiler meat 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 2008

Phage type	Broiler meat	Humans a) b)		
	Imported %	Domestically acquired %	Travel abroad reported %	Unknown origin %
1	27	13	10	11
2	0	0	<1	0
4	53	7	10	9
4b	3	<1	<1	1
6	3	2	6	3
6a	0	4	5	4
8	0	38	8	17
13a	0	5	1	4
14b	0	14	12	13
21/21b	0	12	21	14
Others including non-typeable	13	6	26	23
Number of isolates	30	125	192	70

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 43. Distribution of MICs and occurrence of resistance among Salmonella Enteritidis *from human cases, acquired domestically (n= 127), reported as associated with travel abroad (n=194) or with an unknown origin (n=70), Denmark*

DANMAP 2008

Compound	Origin a)	% 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	>1024
Tetracycline	Domestically acquired	0	[0-2.9]								99.2		0.8								
	Travel abroad reported	4.1	[1.8-8.0]								90.2	5.2	0.5	0.5		3.6					
	Unknown origin	2.9	[0.4-9.9]								95.7	1.4			1.4	1.4					
Chloramphenico	Domestically acquired	0	[0-2.9]								2.4	74.0	23.6								
	Travel abroad reported	1.5	[0.3-4.5]								0.5	73.2	24.2	0.5		1.0	0.5				
	Unknown origin	0	[0-5.1]								2.9	61.4	35.7								
Florfenicol	Domestically acquired	0	[0-2.9]								3.9	92.9	3.1								
	Travel abroad reported	0	[0-1.9]								1.5	93.8	4.1	0.5							
	Unknown origin	0	[0-5.1]								2.9	94.3	2.9								
Ampicillin	Domestically acquired	1.6	[0.2-5.6]							66.1	31.5	0.8				1.6					
	Travel abroad reported	6.7	[3.6-11.2]							70.1	20.6	2.6				6.7					
	Unknown origin	5.7	[1.6-14.0]							62.9	30.0	1.4				5.7					
Ceftiofur	Domestically acquired	0	[0-2.9]						67.7	31.5	0.8										
	Travel abroad reported	0	[0-1.9]						78.9	19.6	1.5										
	Unknown origin	0	[0-5.1]						75.7	24.3											
Cefotaxime	Domestically acquired	0.8	[0.02-4.3]				96.9	2.4		0.8											
	Travel abroad reported	0	[0-1.9]				97.4	2.6													
	Unknown origin	0	[0-5.1]				97.1	2.9													
Sulfonamide	Domestically acquired	0	[0-2.9]													99.2	0.8				
	Travel abroad reported	1.0	[0.1-3.7]													99.0					1.0
	Unknown origin	0	[0-5.1]													98.6	1.4				
Trimethoprim	Domestically acquired	0	[0-2.9]							100											
	Travel abroad reported	0	[0-1.9]							99.0	1.0										
	Unknown origin	0	[0-5.1]							100											
Apramycin	Domestically acquired	0	[0-2.9]									100									
	Travel abroad reported	0	[0-1.9]									97.4	2.6								
	Unknown origin	0	[0-5.1]									100									
Gentamicin	Domestically acquired	0	[0-2.9]						99.2	0.8											
	Travel abroad reported	0	[0-1.9]						98.5	1.5											
	Unknown origin	0	[0-5.1]						100												
Neomycin	Domestically acquired	0	[0-2.9]								98.4	1.6									
	Travel abroad reported	0	[0-1.9]								99.5	0.5									
	Unknown origin	0	[0-5.1]								100										
Spectinomycin	Domestically acquired	0	[0-2.9]											55.9	40.9	3.1					
	Travel abroad reported	0.5	[0.01-2.8]											66.0	33.0	0.5			0.5		
	Unknown origin	0	[0-5.1]											58.6	38.6	2.9					
Streptomycin	Domestically acquired	0	[0-2.9]										99.2	0.8							
	Travel abroad reported	1.0	[0.1-3.7]										98.5	0.5				1.0			
	Unknown origin	0	[0-5.1]										100								
Ciprofloxacin	Domestically acquired	15.7	[9.9-23.3]	33.9	49.6	0.8	7.9	7.9													
	Travel abroad reported	29.4	[23.1-36.3]	25.8	43.3	1.5	7.7	14.9	6.7												
	Unknown origin	14.3	[7.1-24.7]	37.1	47.1	1.4	1.4	11.4	1.4												
Nalidixic acid	Domestically acquired	15.7	[9.9-23.3]									83.5	0.8			0.8	15.0				
	Travel abroad reported	28.9	[22.6-35.8]									68.6	2.1	0.5	0.5		28.4				
	Unknown origin	14.3	[7.1-24.7]									78.6	7.1				14.3				
Colistin	Domestically acquired	4.7	[1.8-10.0]							73.2	22.0	4.7									
	Travel abroad reported	8.8	[5.2-13.7]							59.8	31.4	8.8									
	Unknown origin	1.4	[0.04-7.7]							78.6	20.0	1.4									

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.
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 44. Distribution of MICs and occurrence of resistance among Salmonella Typhimurium *from human cases, acquired domestically with (n=1,441) a) and without (n=391) b) larger outbreaks included, reported as associated with travel abroad (n=103) or with an unknown origin (n=120), Denmark* DANMAP 2008

Compound	Origin a) b) c)	% 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	>1024
Tetracycline	Domestically acquired a)	5.6	[4.5-6.9]								91.7	1.5	1.2	0.1	0.8	4.6					
	Domestically acquired b)	17.1	[13.5-21.2]								81.1	1.5	0.3	0.3	2.6	14.3					
	Travel abroad reported	48.5	[38.6-58.6]								48.5	1.9	1.0		5.8	42.7					
	Unknown origin	30.0	[22.0-39.0]								65.8	3.3	0.8		5.8	24.2					
Chloramphenicol	Domestically acquired a)	1.9	[1.3-2.8]								2.3	59.8	35.6	0.4	0.3	0.6	1.0				
	Domestically acquired b)	5.9	[3.8-8.7]								7.9	45.8	39.1	1.3	1.0	1.8	3.1				
	Travel abroad reported	18.4	[11.5-27.3]								2.9	45.6	33.0		1.0	3.9	13.6				
	Unknown origin	13.3	[7.8-20.7]								2.5	47.5	36.7		0.8		12.5				
Florfenicol	Domestically acquired a)	0.8	[0.4-1.4]								6.3	90.9	1.4	0.6	0.6	0.1					
	Domestically acquired b)	2.6	[1.2-4.7]								12.3	80.3	2.6	2.3	2.0	0.5					
	Travel abroad reported	9.7	[4.8-17.1]								3.9	78.6	4.9	2.9	4.9	1.0	3.9				
	Unknown origin	9.2	[4.7-15.8]								6.7	78.3	5.8		9.2						
Ampicillin	Domestically acquired a)	6.5	[5.2-7.9]							86.7	6.2	0.6	0.3	0.1		6.1					
	Domestically acquired b)	19.4	[15.6-23.7]							75.2	4.3	1.0	0.5			18.9					
	Travel abroad reported	41.7	[32.1-51.9]							53.4	3.9	1.0				41.7					
	Unknown origin	32.5	[24.2-41.7]							63.3	4.2					32.5					
Ceftiofur	Domestically acquired a)	0.1	[0.02-0.5]						88.9	10.5	0.4	0.1		0.1							
	Domestically acquired b)	0	[0-0.9]						85.2	13.3	1.5										
	Travel abroad reported	3.9	[1.1-9.6]						75.7	20.4				3.9							
	Unknown origin	0.8	[0.02-4.6]						85.8	10.8	2.5			0.8							
Cefotaxime	Domestically acquired a)	0.2	[0.04-0.6]				98.2	1.5	0.1	0.1		0.1	0.1								
	Domestically acquired b)	0.3	[0.01-1.4]				96.4	3.1	0.3	0.3											
	Travel abroad reported	3.9	[1.1-9.6]				91.3	3.9	1.0				3.9								
	Unknown origin	2.5	[0.5-7.1]				95.8		1.7	1.7			0.8								
Sulfonamide	Domestically acquired a)	6.7	[5.5-8.2]													92.4	0.8	0.1		0.1	6.7
	Domestically acquired b)	20.7	[16.8-25.1]													78.8	0.3	0.3			20.7
	Travel abroad reported	46.6	[36.7-56.7]													53.4					46.6
	Unknown origin	32.5	[24.2-41.7]													66.7	0.8				32.5
Trimethoprim	Domestically acquired a)	2.0	[1.4-3.0]							97.3	0.7	0.1				1.9					
	Domestically acquired b)	4.3	[2.6-6.9]							94.9	0.8	0.3				4.1					
	Travel abroad reported	12.6	[6.9-20.6]							87.4						12.6					
	Unknown origin	8.3	[4.1-14.8]							90.8	0.8					8.3					
Apramycin	Domestically acquired a)	0.1	[0-0.6]									97.7	2.2			0.1					
	Domestically acquired b)	0.3	[0.01-1.4]									97.2	2.6			0.3					
	Travel abroad reported	0	[0-3.5]									98.1	1.9								
	Unknown origin	0	[0-3.0]									97.5	2.5								
Gentamicin	Domestically acquired a)	0.6	[0.2-1.1]						97.2	2.2		0.1	0.1		0.3						
	Domestically acquired b)	1.3	[0.4-3.0]						97.4	1.3		0.3	0.3		0.8						
	Travel abroad reported	6.8	[2.8-13.5]						91.3	1.9			1.0	1.0	4.9						
	Unknown origin	5.0	[1.9-10.6]						94.2	0.8				0.8	4.2						
Neomycin	Domestically acquired a)	0.5	[0.2-1.0]								99.4	0.1	0.1			0.4					
	Domestically acquired b)	1.0	[0.3-2.6]								98.5	0.5				1.0					
	Travel abroad reported	3.9	[1.1-9.6]								96.1				1.0	2.9					
	Unknown origin	3.3	[0.9-8.3]								96.7					3.3					
Spectinomycin	Domestically acquired a)	2.9	[2.1-4.0]											0.8	92.5	3.7	0.5	0.3	2.1		
	Domestically acquired b)	8.2	[5.7-11.4]											2.0	84.4	5.4	0.8	0.5	6.9		
	Travel abroad reported	19.4	[12.3-28.4]											3.9	73.8	2.9	1.0	1.0	17.5		
	Unknown origin	15.0	[9.1-22.7]											2.5	76.7	5.8	1.7		13.3		
Streptomycin	Domestically acquired a)	6.0	[4.9-7.4]										85.8	8.2	0.9	1.3	0.6	3.3			
	Domestically acquired b)	18.2	[14.5-22.3]										77.5	4.3	1.8	4.1	1.5	10.7			
	Travel abroad reported	45.6	[35.8-55.7]										53.4	1.0	5.8	5.8	8.7	25.2			
	Unknown origin	26.7	[19.0-35.5]										66.7	6.7	1.7	8.3	5.8	10.8			
Ciprofloxacin	Domestically acquired a)	1.0	[0.6-1.7]	29.9	67.5	1.7	0.2	0.6	0.1		0.1										
	Domestically acquired b)	2.0	[0.9-4.0]	40.9	54.0	3.1		1.8	0.3												
	Travel abroad reported	11.7	[6.2-19.5]	35.0	52.4	1.0	1.9	4.9	3.9				1.0								
	Unknown origin	4.2	[1.4-9.5]	32.5	61.7	1.7	1.7	1.7					0.8								
Nalidixic acid	Domestically acquired a)	0.8	[0.4-1.4]									96.9	2.3				0.8				
	Domestically acquired b)	2.0	[0.9-4.0]									92.8	5.1				2.0				
	Travel abroad reported	7.8	[3.4-14.7]									82.5	6.8	2.9			7.8				
	Unknown origin	3.3	[0.9-8.3]									91.7	4.2	0.8			3.3				
Colistin	Domestically acquired a)	0.1	[0.02-0.5]							99.1	0.8	0.1									
	Domestically acquired b)	0.3	[0.01-1.4]							98.2	1.5	0.3									
	Travel abroad reported	0	[0-3.5]							96.1		3.9									
	Unknown origin	0	[0-3.0]							99.2		0.8									

a) In 2008, a human outbreak caused by S. Typhimurium phage type U292 including 1,200 cases occurred; not all of these isolates were susceptibility tested but isolates were generally fully sensitive to the antimicrobial agents tested. See also info box on S. Typhimurium outbreaks in 2008

b) In 2008, several larger outbreaks caused by e.g. S. Typhimurium phage type U292, DT3 and DT135 occurred. These isolates were excluded from this category. See also info box on S. Typhimurium outbreaks in 2008

c) 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 45. Distribution of MICs and occurrence of resistance in Campylobacter coli *from pigs (n=98), Denmark*

DANMAP 2008

Compound	% Resistant	95% Confidence interval	Distribution (%) of MICs												
			0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128
Tetracycline	5.1	[1.7-11.5]			56.1	23.5	13.3	2.0	1.0		1.0	3.1			
Chloramphenicol	0	[0-3.7]						21.4	55.1	21.4	2.0				
Erythromycin	15.3	[8.8-24.0]				26.5	19.4	21.4	16.3	1.0			15.3		
Gentamicin	0	[0-3.7]		1.0	25.5	72.4	1.0								
Streptomycin	51.0	[40.7-61.3]					45.9	3.1			9.2	41.8			
Ciprofloxacin	7.1	[2.9-14.2]	26.5	40.8	19.4	6.1		1.0	1.0	5.1					
Nalidixic acid	7.1	[2.9-14.2]						7.1	25.5	42.9	13.3	4.1	2.0	5.1	

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 46. Distribution of MICs and occurrence of resistance in Campylobacter jejuni *from broilers (n=82) and cattle (n=90), Denmark*

DANMAP 2008

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	128	>128
Tetracycline	Broilers	9.8	[4.3-18.3]			17.1	58.5	11.0	3.7		1.2		8.5			
	Cattle	3.3	[0.7-9.4]			83.3	13.3						3.3			
Chloramphenicol	Broilers	0	[0-4.4]						14.6	76.8	8.5					
	Cattle	0	[0-4.0]						84.4	15.6						
Erythromycin	Broilers	0	[0-4.4]				4.9	17.1	64.6	13.4						
	Cattle	0	[0-4.0]				20.0	62.2	17.8							
Gentamicin	Broilers	0	[0-4.4]		2.4	54.9	41.5	1.2								
	Cattle	0	[0-4.0]		7.8	71.1	21.1									
Streptomycin	Broilers	4.9	[1.3-12.0]					85.4	9.8		1.2		3.7			
	Cattle	1.1	[0.03-6.0]					97.8	1.1				1.1			
Ciprofloxacin	Broilers	12.2	[6.0-21.3]	6.1	45.1	32.9	2.4	1.2		1.2	11.0					
	Cattle	20.0	[12.3-29.8]	7.8	61.1	11.1					20.0					
Nalidixic acid	Broilers	12.2	[6.0-21.3]						1.2	51.2	26.8	8.5	1.2		11.0	
	Cattle	20.0	[12.3-29.8]						1.1	54.4	22.2	2.2		1.1	18.9	

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 47. Distribution of MICs and occurrence of resistance in Campylobacter jejuni *from broiler meat (Danish n=26; imported n=152), Denmark*

DANMAP 2008

Compound	Origin	% Resistant	95% Confidence interval	Distribution (%) of MICs												
				0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	>128
Tetracycline	Danish	11.5	[2.4-30.2]			80.8	7.7					3.8	7.7			
	Imported	49.3	[41.1-57.6]			36.2	5.3	7.9	1.3	0.7		0.7	48.0			
Chloramphenicol	Danish	0	[0-13.2]						84.6	15.4						
	Imported	0	[0-2.4]						57.9	20.4	15.8	5.9				
Erythromycin	Danish	0	[0-13.2]				42.3	50.0	7.7							
	Imported	6.6	[3.2-11.8]				37.5	42.8	11.2	2.0	0.7			5.9		
Gentamicin	Danish	0	[0-13.2]			84.6	15.4									
	Imported	0	[0-2.4]		3.3	69.7	27.0									
Streptomycin	Danish	3.8	[0.1-19.6]					96.2					3.8			
	Imported	2.6	[0.7-6.6]					96.1	1.3				2.6			
Ciprofloxacin	Danish	19.2	[6.6-39.4]	3.8	69.2	7.7					19.2					
	Imported	52.6	[44.4-60.8]	6.6	30.3	6.6	3.9			0.7	52.0					
Nalidixic acid	Danish	19.2	[6.6-39.4]						3.8	69.2	7.7				19.2	
	Imported	52.6	[44.4-60.8]						3.3	28.9	10.5	4.6		7.9	44.7	

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 48. Distribution of MICs and occurrence of resistance among Campylobacter jejuni *from human cases categorized as acquired domestically (n=185) or reported as associated with travel abroad (n=41), Denmark*

DANMAP 2008

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	17.3	[12.1-23.5]				66.5	11.9	2.7	1.6	0.5			16.8		
	Travel abroad reported	51.2	[35.1-67.1]				41.5	4.9	2.4					51.2		
Chloramphenicol	Domestically acquired	0	[0-2.0]							70.8	21.6	6.5	1.1			
	Travel abroad reported	0	[0-8.6]							58.5	22.0	17.1	2.4			
Erythromycin	Domestically acquired	1.6	[0.3-4.7]					35.7	50.3	11.9	0.5	1.1			0.5	
	Travel abroad reported	7.3	[1.5-19.9]					31.7	43.9	14.6	2.4				7.3	
Gentamicin	Domestically acquired	1.6	[0.3-4.7]			28.6	66.5	2.7	0.5	0.5		0.5	0.5			
	Travel abroad reported	2.4	[0.06-12.9]			22.0	68.3	7.3					2.4			
Streptomycin	Domestically acquired	2.2	[0.6-5.4]						96.2	1.6		0.5		1.6		
	Travel abroad reported	14.6	[5.6-29.2]						85.4				2.4	12.2		
Ciprofloxacin	Domestically acquired	28.1	[21.8-35.2]		28.6	35.7	4.3	2.7	0.5	1.1	1.6	25.4				
	Travel abroad reported	73.2	[57.1-85.8]		7.3	14.6	4.9				2.4	70.7				
Nalidixic acid	Domestically acquired	29.2	[22.8-36.3]							18.4	47.0	4.9	0.5	0.5	1.1	27.6
	Travel abroad reported	73.2	[57.1-85.8]							4.9	17.1	4.9			2.4	70.7

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

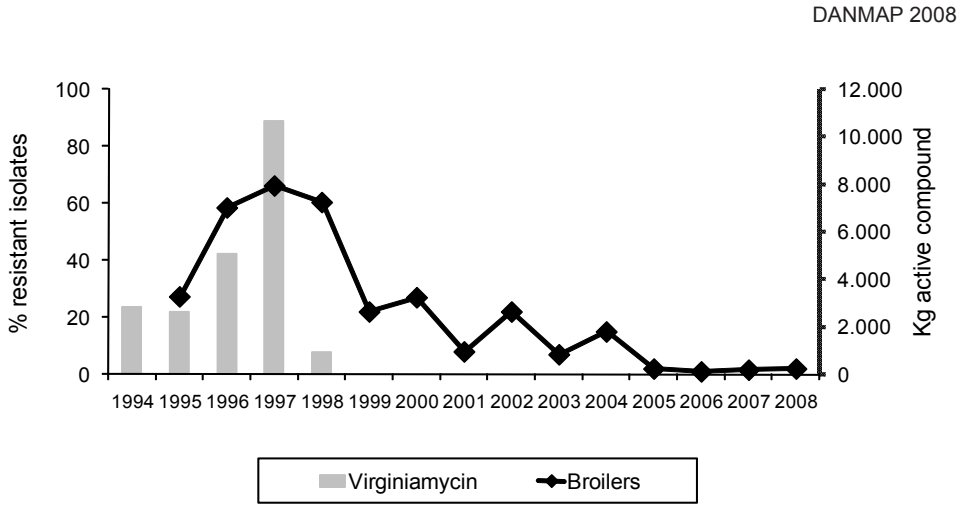

Figure 44. Trend in occurrence of resistance to streptogramins among Enterococcus faecium *from broilers the consumption of virginiamycin, Denmark, 1994-2008*

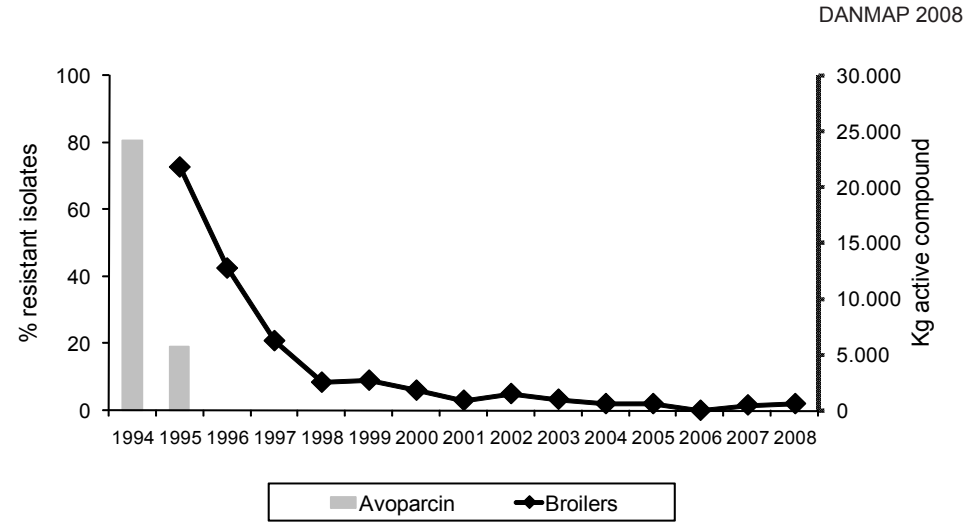

Figure 45. Trend in occurrence of resistance to vancomycin among Enterococcus faecium *from and the consumption of avoparcin, Denmark 1994-2008*

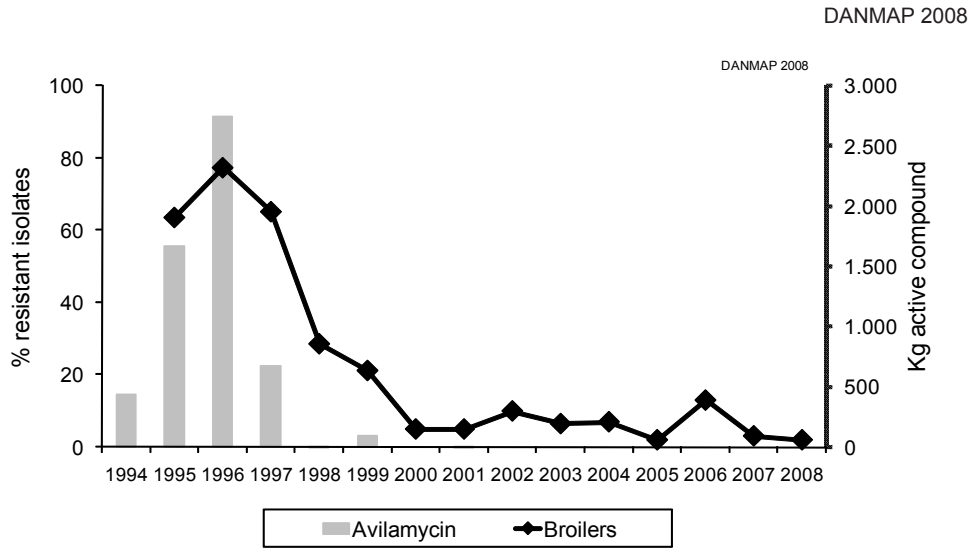

Figure 46. Trend in occurrence of resistance to avilamycin among Enterococcus faecium *from and the consumption of avilamycin, Denmark 1994-2008*

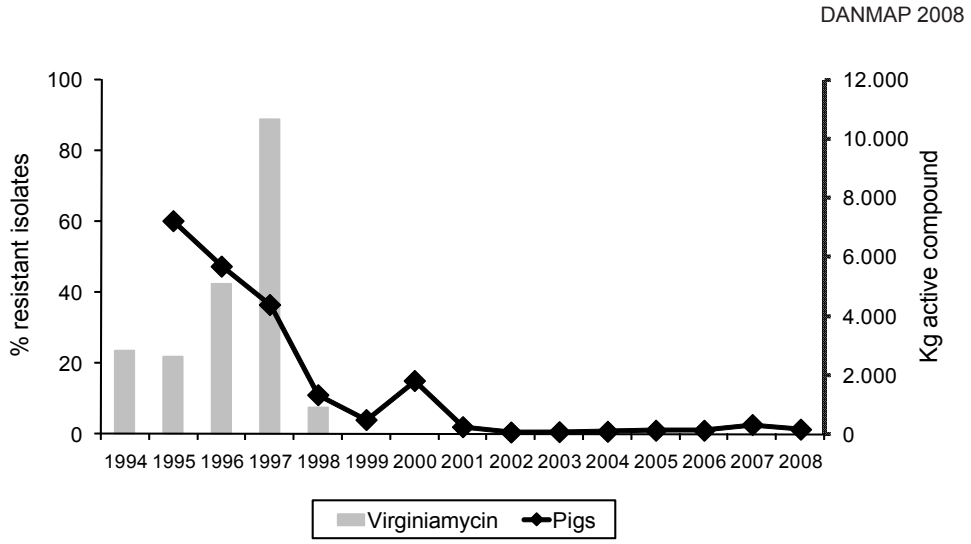

Figure 47. Trend in occurrence of resistance to streptogramins among Enterococcus faecium *from pigs and the consumption of virginiamycin, Denmark, 1994-2008*

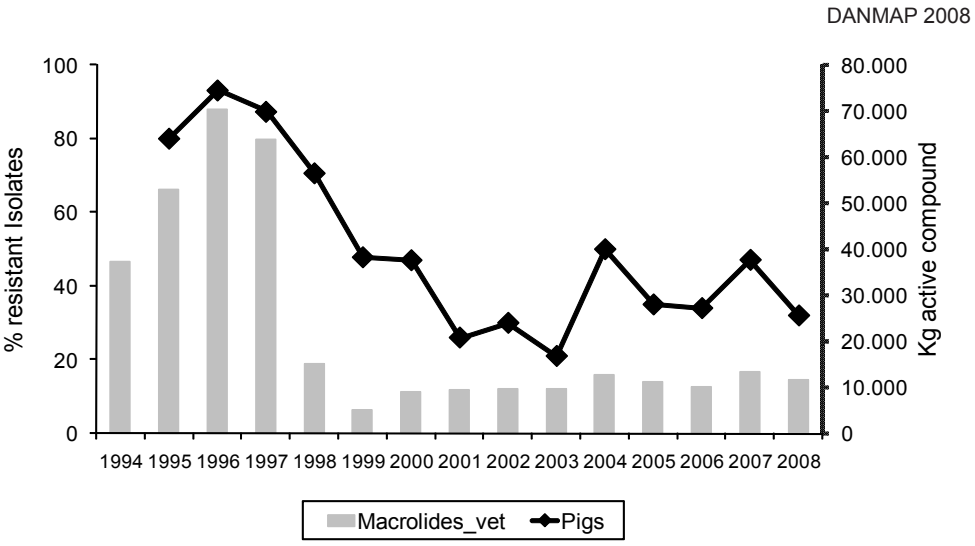

Figure 48. Trend in occurrence of resistance to erythromycin among Enterococcus faecium *from pigs and the consumption of erythromycin, Denmark, 1994-2008*

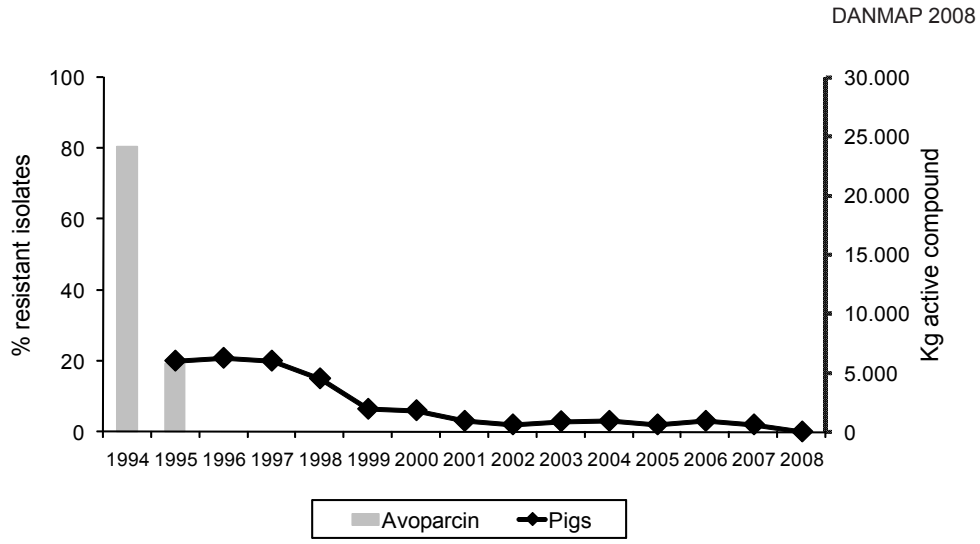

Figure 49. Trend in occurrence of resistance to vancomycin among Enterococcus faecium *from pigs and the consumption of avoparcin, Denmark, 1994-2008*

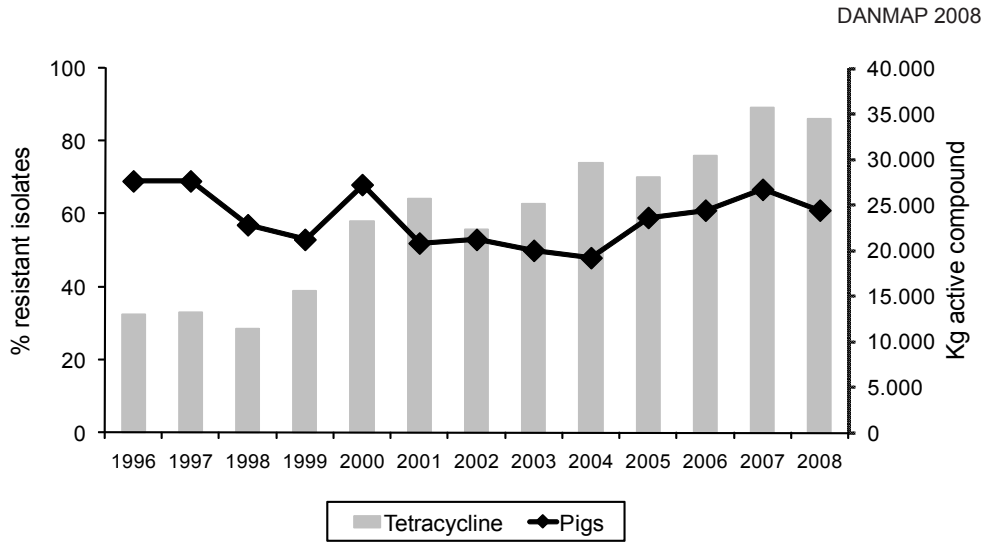

Figure 50. Trends in tetracycline resistance among Enterococcus faecium *from pigs and the consumption of tetracycline in pigs, Denmark, 1994-2008*

Table 49. Distribution of MICs and occurrence of resistance in Enterococcus faecalis *from broilers (n=49) and pigs (n=149), Denmark*

DANMAP 2008

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	4096	>4096
Tetracycline	Broilers	6.1	[1.3-16.9]							93.9						6.1							
	Pigs	83.9	[77.0-89.4]							16.1					12.8	71.1							
Tigecycline	Pigs	0	[0-2.4]	0.7	4.7	25.5	62.4	6.7															
Chloramphenicol	Broilers	0	[0-7.3]								4.1	34.7	61.2										
	Pigs	13.4	[8.4-20.0]									12.1	70.5	2.7	1.3	8.7	4.7						
Penicillin	Pigs	0	[0-2.4]								26.2	71.8	0.7	1.3									
Ampicillin	Broilers	0	[0-7.3]								100												
	Pigs	0	[0-2.4]								99.3	0.7											
Erythromycin	Broilers	10.2	[3.4-22.2]						22.4	30.6	36.7		2.0	2.0		6.1							
	Pigs	40.3	[32.3-48.6]						45.0	11.4	3.4				1.3	38.9							
Gentamicin	Broilers	0	[0-7.3]														100						
	Pigs	6.0	[2.8-11.2]											89.9	3.4				0.7	4.0	2.0		
Kanamycin	Broilers	0	[0-7.3]														93.9	4.1	2.0				
	Pigs	18.1	[12.3-25.3]														80.5	1.3					18.1
Streptomycin	Broilers	2.0	[0.05-10.9]														98.0						2.0
	Pigs	27.5	[20.5-35.4]													26.8	44.3		1.3	1.3	1.3		24.8
Vancomycin	Broilers	0	[0-7.3]								95.9	4.1											
	Pigs	0	[0-2.4]							48.3	47.0	4.7											
Avilamycin	Broilers	0	[0-7.3]								95.9	4.1											
	Pigs	0.7	[0.02-3.7]									99.3		0.7									
Flavomycin	Broilers	10.2	[3.4-22.2]									89.8		2.0		8.2							
Salinomycin	Broilers	2.0	[0.05-10.9]								77.6	20.4	2.0										
	Pigs	0	[0-2.4]								100												
Linezolid	Broilers	0	[0-7.3]							34.7	65.3												
	Pigs	0	[0-2.4]							22.8	76.5	0.7											

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.
Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 50. Distribution of MICs and occurrence of resistance in Enterococcus faecalis *from broiler meat (Danish n=50; imported n=144), beef (Danish n=59; imported n=38), pork (Danish n=72; imported n=125), Denmark*

DANMAP 2008

Compound	Food type	Origin	% 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	4096	>4096
Tetracycline	Broiler meat	Danish	26.0	[14.6-40.3]							74.0					10.0	16.0							
		Imported	66.7	[58.3-74.3]							32.6	0.7			0.7	12.5	53.5							
	Beef	Danish	18.6	[9.7-30.9]							81.4					1.7	16.9							
		Imported	21.1	[9.6-37.3]							73.7	5.3					21.1							
	Pork	Danish	18.1	[10.0-28.9]							76.4	5.6				1.4	16.7							
		Imported	32.0	[23.9-40.9]							66.4	1.6					32.0							
Tigecycline	Broiler meat	Danish	0	[0-7.1]		12.0	58.0	30.0																
		Imported	0	[0-2.5]		2.8	45.8	48.6	2.8															
	Beef	Danish	0	[0-6.1]		20.3	66.1	13.6																
		Imported	0	[0-9.3]		10.5	55.3	34.2																
	Pork	Danish	0	[0-5.0]		8.3	61.1	30.6																
		Imported	0	[0-2.9]	0.8	6.4	62.4	29.6	0.8															
Chloramphenicol	Broiler meat	Danish	0	[0-7.1]									38.0	62.0										
		Imported	8.3	[4.4-14.1]									14.6	74.3	2.8		3.5	4.9						
	Beef	Danish	1.7	[0.04-9.1]									37.3	59.3		1.7	1.7							
		Imported	2.6	[0.07-13.8]									23.7	73.7			2.6							
	Pork	Danish	1.4	[0.04-7.5]								1.4	26.4	70.8			1.4							
		Imported	4.8	[1.8-10.2]									21.6	72.0		1.6	3.2	1.6						
Penicillin	Broiler meat	Danish	0	[0-7.1]								44.0	56.0											
		Imported	0	[0-2.5]								46.5	52.8		0.7									
	Beef	Danish	0	[0-6.1]								37.3	62.7											
		Imported	0	[0-9.3]								34.2	63.2	2.6										
	Pork	Danish	0	[0-5.0]								34.7	65.3											
		Imported	0	[0-2.9]								56.0	44.0											
Ampicillin	Broiler meat	Danish	0	[0-7.1]								100												
		Imported	0	[0-2.5]								99.3	0.7											
	Beef	Danish	0	[0-6.1]								100												
		Imported	0	[0-9.3]								100												
	Pork	Danish	0	[0-5.0]								100												
		Imported	0	[0-2.9]								100												
Erythromycin	Broiler meat	Danish	12.0	[4.5-24.3]						56.0	20.0	12.0		2.0		2.0	8.0							
		Imported	50.7	[42.2-59.1]						27.1	11.8	10.4		2.1	4.2	1.4	43.1							
	Beef	Danish	5.1	[1.1-14.1]						61.0	23.7	10.2					5.1							
		Imported	10.5	[2.9-24.8]						50.0	31.6	7.9					10.5							
	Pork	Danish	8.3	[3.1-17.3]						51.4	29.2	11.1		1.4			6.9							
		Imported	8.0	[3.9-14.2]						48.0	28.0	14.4	1.6				8.0							
Gentamicin	Broiler meat	Danish	0	[0-7.1]											100									
		Imported	3.5	[1.1-7.9]											85.4	9.0				2.1	0.7	2.8		
	Beef	Danish	0	[0-6.1]											96.6	3.4								
		Imported	2.6	[0.07-13.8]											94.7	2.6						2.6		
	Pork	Danish	1.4	[0.04-7.5]											97.2	1.4					1.4			
		Imported	1.6	[0.2-5.7]											94.4	4.0					0.8	0.8		
Kanamycin	Broiler meat	Danish	0	[0-7.1]														98.0	2.0					
		Imported	21.5	[15.1-29.1]														77.1	0.7		0.7			21.5
	Beef	Danish	3.4	[0.4-11.7]														96.6						3.4
		Imported	7.9	[1.7-21.4]														92.1				2.6		5.3
	Pork	Danish	4.2	[0.9-11.7]														93.1	1.4		1.4			4.2
		Imported	4.0	[1.3-9.1]														94.4	1.6					4.0
Streptomycin	Broiler meat	Danish	4.0	[0.5-13.7]													18.0	76.0	2.0					4.0
		Imported	25.0	[18.2-32.9]													12.5	59.0	2.8	0.7	0.7	0.7		23.6
	Beef	Danish	3.4	[0.4-11.7]													37.3	57.6	1.7					3.4
		Imported	10.5	[2.9-24.8]													31.6	50.0	7.9					10.5
	Pork	Danish	6.9	[2.3-15.5]													36.1	56.9						6.9
		Imported	5.6	[2.3-11.2]													52.0	40.0	2.4			1.6		4.0
Vancomycin	Broiler meat	Danish	0	[0-7.1]							26.0	64.0	10.0											
		Imported	0	[0-2.5]							18.8	64.6	16.7											
	Beef	Danish	0	[0-6.1]							40.7	57.6	1.7											
		Imported	0	[0-9.3]							42.1	55.3	2.6											
	Pork	Danish	0	[0-5.0]							31.9	63.9	4.2											
		Imported	0	[0-2.9]							26.4	71.2	2.4											
Avilamycin	Broiler meat	Danish	0	[0-7.1]									100											
		Imported	0	[0-2.5]									97.9	2.1										
	Beef	Danish	0	[0-6.1]									100											
		Imported	0	[0-9.3]									97.4	2.6										
	Pork	Danish	0	[0-5.0]									100											
		Imported	0	[0-2.9]									99.2	0.8										
Salinomycin	Broiler meat	Danish	2.0	[0.05-10.6]								78.0	20.0	2.0										
		Imported	0	[0-2.5]								91.0	9.0											
	Beef	Danish	0	[0-6.1]								100												
		Imported	0	[0-9.3]								100												
	Pork	Danish	0	[0-5.0]								100												
		Imported	0	[0-2.9]								100												
Linezolid	Broiler meat	Danish	0	[0-7.1]							10.0	90.0												
		Imported	0	[0-2.5]							29.9	68.8	1.4											
	Beef	Danish	0	[0-6.1]							13.6	86.4												
		Imported	0	[0-9.3]							7.9	92.1												
	Pork	Danish	0	[0-5.0]							11.1	88.9												
		Imported	0	[0-2.9]							11.2	88.8												

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range. Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 51. Distribution of MICs and occurrence of resistance in Enterococcus faecium *from broilers (n=51) and pigs (n=145), Denmark*

DANMAP 2008

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	4096	>4096
Tetracycline	Broilers	7.8	[2.2-18.9]							88.2	3.9					7.8							
	Pigs	60.7	[52.2-68.7]							38.6	0.7		0.7		3.4	56.6							
Tigecycline	Pigs	0	[0-2.5]	0.7	3.4	80.7	11.7	3.4															
Chloramphenicol	Broilers	0	[0-7.0]								11.8	47.1	41.2										
	Pigs	0	[0-2.5]								3.4	32.4	60.0	4.1									
Penicillin	Pigs	9.7	[5.4-15.7]								25.5	17.2	2.8	44.8	9.0	0.7							
Ampicillin	Broilers	2.0	[0.05-10.4]								88.2	9.8	2.0										
	Pigs	9.0	[4.9-14.8]								46.2	44.8	7.6	0.7		0.7							
Erythromycin	Broilers	15.7	[7.0-28.6]						25.5	13.7	31.4	13.7	3.9	3.9		7.8							
	Pigs	31.7	[24.3-40.0]						14.5	3.4	26.9	23.4	3.4			28.3							
Gentamicin	Broilers	0	[0-7.0]														100						
	Pigs	0	[0-2.5]											97.9	2.1								
Kanamycin	Broilers	0	[0-7.0]														33.3	47.1	17.6	2.0			
	Pigs	23.4	[16.8-31.2]														22.8	43.4	9.7	0.7	0.7	22.8	
Streptomycin	Broilers	9.8	[3.3-21.4]														90.2					9.8	
	Pigs	43.4	[35.2-51.9]													54.5	2.1		4.1	15.2	11.0	13.1	
Vancomycin	Broilers	2.0	[0.05-10.4]								96.1	2.0				2.0							
	Pigs	0	[0-2.5]							88.3	8.3	3.4											
Quinupristin/-dalfopristin	Broilers	2.0	[0.05-10.4]						19.6	33.3	27.5	17.6		2.0									
	Pigs	1.4	[0.2-4.9]						13.8	4.8	51.7	28.3	1.4										
Avilamycin	Broilers	2.0	[0.05-10.4]								45.1	49.0		3.9	2.0								
	Pigs	0	[0-2.5]									95.9	3.4	0.7									
Salinomycin	Broilers	64.7	[50.1-77.6]								19.6	15.7	52.9	9.8	2.0								
	Pigs	0.7	[0.02-3.8]								99.3		0.7										
Linezolid	Broilers	0	[0-7.0]							23.5	76.5												
	Pigs	0	[0-2.5]							11.0	73.8	15.2											

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.

White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 52. Distribution of MICs and occurrence of resistance in Enterococcus faecium *from broiler meat (Danish n=81; imported n=115), beef (Danish n=23; imported n=15), pork (Danish n=15; imported n=16), Denmark*

DANMAP 2008

Compound	Food type	Origin	% 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	4096	>4096
Tetracycline	Broiler meat	Danish	8.6	[3.5-17.0]							91.4				2.5	2.5	3.7							
		Imported	44.3	[35.1-53.9]							54.8	0.9		0.9	1.7	2.6	39.1							
	Beef	Danish	13.0	[2.8-33.6]							87.0					8.7	4.3							
		Imported	0	[0-21.8]							100													
	Pork	Danish	13.3	[1.7-40.5]							86.7						13.3							
		Imported	12.5	[1.6-38.3]							87.5					6.3	6.3							
Tigecycline	Broiler meat	Danish	0	[0-4.5]		9.9	87.7	2.5																
		Imported	0	[0-3.2]		5.2	67.8	26.1	0.9															
	Beef	Danish	0	[0-14.8]			95.7		4.3															
		Imported	0	[0-21.8]			100																	
	Pork	Danish	0	[0-21.8]		6.7	86.7	6.7																
		Imported	0	[0-20.6]			100																	
Chloramphenicol	Broiler meat	Danish	0	[0-4.5]								4.9	46.9	46.9	1.2									
		Imported	0	[0-3.2]								1.7	15.7	70.4	12.2									
	Beef	Danish	0	[0-14.8]								4.3	30.4	65.2										
		Imported	0	[0-21.8]									6.7	93.3										
	Pork	Danish	0	[0-21.8]								6.7	53.3	33.3	6.7									
		Imported	0	[0-20.6]									56.3	43.8										
Penicillin	Broiler meat	Danish	1.2	[0.03-6.7]								70.4	19.8	7.4	1.2	1.2								
		Imported	13.9	[8.2-21.6]								36.5	23.5	7.8	18.3	5.2	8.7							
	Beef	Danish	0	[0-14.8]								47.8	43.5		8.7									
		Imported	0	[0-21.8]								46.7	46.7	6.7										
	Pork	Danish	6.7	[0.2-31.9]								33.3	46.7	6.7	6.7	6.7								
		Imported	0	[0-20.6]								50.0	43.8		6.3									
Ampicillin	Broiler meat	Danish	1.2	[0.03-6.7]								97.5	1.2	1.2										
		Imported	13.9	[8.2-21.6]								67.8	18.3	5.2		2.6	6.1							
	Beef	Danish	0	[0-14.8]								91.3	8.7											
		Imported	0	[0-21.8]								100												
	Pork	Danish	6.7	[0.2-31.9]								80.0	13.3	6.7										
		Imported	0	[0-20.6]								93.8	6.3											
Erythromycin	Broiler meat	Danish	18.5	[10.8-28.7]						27.2	8.6	12.3	33.3	4.9	6.2	3.7	3.7							
		Imported	53.0	[43.5-62.4]						10.4	10.4	18.3	7.8	5.2	1.7		46.1							
	Beef	Danish	8.7	[1.1-28.0]						43.5	13.0	21.7	13.0	8.7										
		Imported	6.7	[0.2-31.9]						26.7	6.7	46.7	13.3	6.7										
	Pork	Danish	26.7	[7.8-55.1]							13.3	20.0	40.0	20.0			6.7							
		Imported	31.2	[11.0-58.7]						6.3	12.5	12.5	37.5	25.0			6.3							
Gentamicin	Broiler meat	Danish	0	[0-4.5]											100									
		Imported	0	[0-3.2]											96.5	3.5								
	Beef	Danish	0	[0-14.8]											95.7	4.3								
		Imported	0	[0-21.8]											100									
	Pork	Danish	0	[0-21.8]											100									
		Imported	0	[0-20.6]											100									
Kanamycin	Broiler meat	Danish	0	[0-4.5]														37.0	45.7	16.0	1.2			
		Imported	8.7	[4.2-15.4]														23.5	38.3	25.2	4.3		8.7	
	Beef	Danish	4.3	[0.1-21.9]														43.5	30.4	17.4	4.3	4.3		
		Imported	0	[0-21.8]														33.3	46.7	20.0				
	Pork	Danish	0	[0-21.8]														26.7	33.3	40.0				
		Imported	6.2	[0.2-30.2]														31.3	31.3	31.3			6.3	
Streptomycin	Broiler meat	Danish	3.7	[0.8-10.4]													93.8	2.5			1.2	1.2	1.2	
		Imported	20.9	[13.9-29.4]													78.3	0.9	0.9		5.2	3.5	11.3	
	Beef	Danish	0	[0-14.8]													95.7	4.3						
		Imported	0	[0-21.8]													100							
	Pork	Danish	6.7	[0.2-31.9]													86.7	6.7			6.7			
		Imported	6.2	[0.2-30.2]													93.8						6.3	
Vancomycin	Broiler meat	Danish	0	[0-4.5]							61.7	30.9	7.4											
		Imported	0.9	[0.02-4.7]							80.9	13.9	4.3				0.9							
	Beef	Danish	0	[0-14.8]							91.3	8.7												
		Imported	0	[0-21.8]							86.7	13.3												
	Pork	Danish	0	[0-21.8]							86.7		13.3											
		Imported	0	[0-20.6]							93.8	6.3												
Quinupristin/dalfop	Broiler meat	Danish	3.7	[0.8-10.4]					1.2	39.5	16.0	30.9	8.6	2.5	1.2									
		Imported	7.0	[3.1-13.2]						23.5	12.2	38.3	19.1	4.3	2.6									
	Beef	Danish	0	[0-14.8]						43.5	13.0	34.8	8.7											
		Imported	0	[0-21.8]						53.3	13.3	33.3												
	Pork	Danish	0	[0-21.8]						26.7	6.7	60.0	6.7											
		Imported	0	[0-20.6]						37.5		50.0	12.5											
Avilamycin	Broiler meat	Danish	0	[0-4.5]									100											
		Imported	1.7	[0.2-6.1]									93.0	2.6	2.6		1.7							
	Beef	Danish	0	[0-14.8]									95.7	4.3										
		Imported	0	[0-21.8]									100											
	Pork	Danish	0	[0-21.8]									93.3	6.7										
		Imported	0	[0-20.6]									100											
Salinomycin	Broiler meat	Danish	50.6	[39.3-61.9]								19.8	29.6	50.6										
		Imported	19.1	[12.4-27.5]								38.3	42.6	19.1										
	Beef	Danish	4.3	[0.1-21.9]								95.7		4.3										
		Imported	0	[0-21.8]								100												
	Pork	Danish	0	[0-21.8]								100												
		Imported	0	[0-20.6]								100												
Linezolid	Broiler meat	Danish	0	[0-4.5]							1.2	90.1	8.6											
		Imported	0	[0-3.2]							7.0	86.1	7.0											
	Beef	Danish	0	[0-14.8]								91.3	8.7											
		Imported	0	[0-21.8]								93.3	6.7											
	Pork	Danish	0	[0-21.8]								100												
		Imported	0	[0-20.6]								100												

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.
Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 53. Distribution of MICs and occurrence of resistance in Enterococcus faecalis *from healthy humans (n=23), Denmark*

DANMAP 2008

Compound	% Resistant	[95% Condidence 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	13.0	[2.8-33.6]							87.0						13.0						
Tigecycline	0	[0-14.8]	4.3	4.3	4.3	60.9	26.1														
Chloramphenicol	4.3	[0.1-21.9]									8.7	82.6	4.3		4.3						
Ampicillin	0	[0-14.8]								100											
Erythromycin	8.7	[1.1-28.0]						39.1	26.1	21.7	4.3				8.7						
Gentamicin	4.3	[0.1-21.9]														95.7					4.3
Kanamycin	4.3	[0.1-21.9]														91.3	4.3				4.3
Streptomycin	0	[0-14.8]														100					
Vancomycin	0	[0-14.8]								52.2	47.8										
Avilamycin	0	[0-14.8]								78.3	21.7										
Flavomycin	0	[0-14.8]									95.7	4.3									
Salinomycin	0	[0-14.8]								100											
Linezolid	0	[0-14.8]							13.0	87.0											

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.
Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 54. Distribution of MICs and occurrence of resistance in Enterococcus faecium *from healthy humans (n=32), Denmark*

DANMAP 2008

Compound	% 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	3.1	[0.1-16.2]							96.9						3.1						
Tigecycline	0	[0-10.9]			28.1	65.6	6.3														
Chloramphenicol	0	[0-10.9]									6.3	90.6	3.1								
Ampicillin	0	[0-10.9]								100											
Erythromycin	25.0	[11.5-43.4]						34.4		12.5	28.1	25.0									
Gentamicin	0	[0-10.9]														100					
Kanamycin	3.1	[0.1-16.2]														21.9	53.1	21.9		3.1	
Streptomycin	0	[0-10.9]														100					
Vancomycin	0	[0-10.9]								96.9	3.1										
Quinupristin/dalfopristin	0	[0-10.9]						6.3	12.5		81.3										
Avilamycin	0	[0-10.9]								9.4	71.9	18.8									
Salinomycin	0	[0-10.9]								93.8	6.3										
Linezolid	0	[0-10.9]								62.5	37.5										

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.
Since isolates of poultry and human origin were tested in intervals of higher values than the cut-off value established by EUCAST for gentamicin CLSI clinical breakpoints is used to be able to compare results for prevalence.

Table 55. Distribution of MICs and occurrence of resistance in Escherichia coli *from broiler meat (Danish n=113; imported n=304), pork (Danish n=66; imported n=96), Denmark*

DANMAP 2008

Compound	Food type	Origin	% 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	Broiler meat	Danish	4.4	[1.5-10.0]								89.4	6.2				4.4						
		Imported	42.1	[36.5-47.9]								53.3	4.3	0.3		0.7	41.4						
	Pork	Danish	33.3	[22.2-46.0]								65.2		1.5		1.5	31.8						
		Imported	43.8	[33.6-54.3]								52.1	3.1	1.0			43.8						
Chloramphenicol	Broiler meat	Danish	0	[0-3.2]								2.7	37.2	60.2									
		Imported	14.5	[10.7-18.9]								1.0	30.6	53.0	1.0	5.3	3.0	6.3					
	Pork	Danish	6.1	[1.7-14.8]								1.5	34.8	56.1	1.5	3.0		3.0					
		Imported	7.3	[3.0-14.4]								3.1	30.2	59.4		5.2	1.0	1.0					
Florfenicol	Broiler meat	Danish	0	[0-3.2]								3.5	44.2	51.3	0.9								
		Imported	0.7	[0.08-2.4]								0.7	35.2	55.9	7.6	0.3	0.3						
	Pork	Danish	0	[0-5.4]								6.1	33.3	57.6	3.0								
		Imported	1.0	[0.03-5.7]								5.2	34.4	54.2	5.2	1.0							
Ampicillin	Broiler meat	Danish	10.6	[5.6-17.8]							8.0	37.2	40.7	3.5		0.9	9.7						
		Imported	48.0	[42.3-53.8]							2.0	18.4	27.0	4.6	0.3	0.3	47.4						
	Pork	Danish	28.8	[18.3-41.3]							3.0	25.8	40.9	1.5	1.5	1.5	25.8						
		Imported	30.2	[21.3-40.4]							3.1	22.9	37.5	6.3	1.0	2.1	27.1						
Ceftiofur	Broiler meat	Danish	0.9	[0.02-4.8]						96.5	2.7	0.9											
		Imported	7.6	[4.9-11.1]						92.4		0.7	1.0	3.3	2.6								
	Pork	Danish	0	[0-5.4]						100													
		Imported	1.0	[0.03-5.7]						96.9	2.1				1.0								
Cefotaxime	Broiler meat	Danish	0.9	[0.02-4.8]				96.5	2.7			0.9											
		Imported	7.6	[4.9-11.1]				92.1	0.3			0.7	1.3	5.6									
	Pork	Danish	0	[0-5.4]				100															
		Imported	1.0	[0.03-5.7]				94.8	4.2					1.0									
Sulfonamide	Broiler meat	Danish	11.5	[6.3-18.9]													88.5						11.5
		Imported	44.7	[39.1-50.5]													55.3						44.7
	Pork	Danish	30.3	[19.6-42.9]													69.7						30.3
		Imported	28.1	[19.4-38.2]													71.9						28.1
Trimethoprim	Broiler meat	Danish	2.7	[0.6-7.6]							97.3						2.7						
		Imported	31.6	[26.4-37.1]							68.4		0.3				31.3						
	Pork	Danish	24.2	[14.5-36.4]							75.8						24.2						
		Imported	25.0	[16.7-34.9]							74.0	1.0					25.0						
Apramycin	Broiler meat	Danish	0	[0-3.2]									80.5	16.8	2.7								
		Imported	0	[0-1.2]									79.3	18.8	2.0								
	Pork	Danish	0	[0-5.4]									77.3	19.7	3.0								
		Imported	0	[0-3.8]									70.8	26.0	3.1								
Gentamicin	Broiler meat	Danish	0	[0-3.2]						80.5	15.9	3.5											
		Imported	3.3	[1.6-6.0]						75.7	18.8	2.3	0.3	0.7	0.3	2.0							
	Pork	Danish	0	[0-5.4]						81.8	18.2												
		Imported	2.1	[0.3-7.3]						70.8	25.0	2.1			2.1								
Neomycin	Broiler meat	Danish	0	[0-3.2]								97.3	1.8	0.9									
		Imported	9.9	[6.8-13.8]								87.5	2.3	0.3	0.3	1.3	8.2						
	Pork	Danish	1.5	[0.04-8.2]								97.0	1.5				1.5						
		Imported	6.2	[2.3-13.1]								87.5	6.3			2.1	4.2						
Spectinomycin	Broiler meat	Danish	6.2	[2.5-12.3]											85.8	7.1	0.9	2.7	3.5				
		Imported	23.0	[18.4-28.2]											62.2	10.2	4.6	2.3	9.5	11.2			
	Pork	Danish	19.7	[10.9-31.3]											68.2	7.6	4.5	6.1	7.6	6.1			
		Imported	14.6	[8.2-23.3]											67.7	10.4	7.3	3.1	5.2	6.3			
Streptomycin	Broiler meat	Danish	8.0	[3.7-14.6]										90.3	1.8	6.2	0.9	0.9					
		Imported	32.9	[27.6-38.5]										60.2	6.9	7.9	5.3	7.9	11.8				
	Pork	Danish	31.8	[20.9-44.4]										65.2	3.0	10.6	10.6	4.5	6.1				
		Imported	39.6	[29.7-50.1]										58.3	2.1	6.3	7.3	12.5	13.5				
Ciprofloxacin	Broiler meat	Danish	3.5	[1.0-8.8]	69.0	27.4		1.8	1.8														
		Imported	33.2	[28.0-38.8]	44.4	22.4	1.0	2.0	15.1	8.2	1.3	0.7	0.3	4.6									
	Pork	Danish	1.5	[0.04-8.2]	81.8	16.7			1.5														
		Imported	6.2	[2.3-13.1]	64.6	29.2		3.1	2.1					1.0									
Nalidixic acid	Broiler meat	Danish	2.7	[0.6-7.6]									92.0	5.3				2.7					
		Imported	32.2	[27.0-37.8]									67.1	0.7		0.7	1.0	30.6					
	Pork	Danish	1.5	[0.04-8.2]									98.5					1.5					
		Imported	4.2	[1.1-10.3]									89.6	5.2	1.0		2.1	2.1					
Colistin	Broiler meat	Danish	0	[0-3.2]							100												
		Imported	3.9	[2.1-6.8]							94.1	2.0	3.9										
	Pork	Danish	0	[0-5.4]							100												
		Imported	1.0	[0.03-5.7]							97.9	1.0	1.0										

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 56. Distribution of MICs and occurrence of resistance in Escherichia coli *from beef (Danish n=63; imported n=40), Denmark*

DANMAP 2008

Compound	Food type	Origin	% 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	Beef	Danish	6.3	[1.8-15.5]								79.4	14.3				6.3						
		Imported	12.5	[4.2-26.8]								80.0	7.5				12.5						
Chloramphenicol	Beef	Danish	0	[0-5.7]								3.2	22.2	74.6									
		Imported	2.5	[0.06-13.2]									30.0	67.5				2.5					
Florfenicol	Beef	Danish	0	[0-5.7]									30.2	69.8									
		Imported	2.5	[0.06-13.2]									25.0	72.5				2.5					
Ampicillin	Beef	Danish	6.3	[1.8-15.5]							4.8	20.6	57.1	11.1		1.6	4.8						
		Imported	10.0	[2.8-23.7]								25.0	55.0	10.0			10.0						
Ceftiofur	Beef	Danish	0	[0-5.7]						100													
		Imported	0	[0-8.8]						100													
Cefotaxime	Beef	Danish	0	[0-5.7]				98.4	1.6														
		Imported	0	[0-8.8]				97.5	2.5														
Sulfonamide	Beef	Danish	6.3	[1.8-15.5]													93.7					6.3	
		Imported	15.0	[5.7-29.8]													85.0					15.0	
Trimethoprim	Beef	Danish	1.6	[0.04-8.5]							98.4						1.6						
		Imported	5.0	[0.6-16.9]							95.0						5.0						
Apramycin	Beef	Danish	0	[0-5.7]									87.3	11.1	1.6								
		Imported	0	[0-8.8]									90.0	5.0	5.0								
Gentamicin	Beef	Danish	0	[0-5.7]						88.9	9.5	1.6											
		Imported	0	[0-8.8]						82.5	15.0	2.5											
Neomycin	Beef	Danish	0	[0-5.7]								96.8	3.2										
		Imported	2.5	[0.06-13.2]								97.5					2.5						
Spectinomycin	Beef	Danish	0	[0-5.7]											96.8	3.2							
		Imported	5.0	[0.6-16.9]											87.5	5.0	2.5	2.5		2.5			
Streptomycin	Beef	Danish	7.9	[2.6-17.6]										90.5	1.6	1.6	1.6		4.8				
		Imported	15.0	[5.7-29.8]										85.0		2.5	5.0	5.0	2.5				
Ciprofloxacin	Beef	Danish	0	[0-5.7]	68.3	31.7																	
		Imported	5.0	[0.6-16.9]	75.0	20.0			2.5					2.5									
Nalidixic acid	Beef	Danish	0	[0-5.7]									100										
		Imported	5.0	[0.6-16.9]									95.0				2.5	2.5					
Colistin	Beef	Danish	0	[0-5.7]							100												
		Imported	0	[0-8.8]							100												

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 57. Distribution of MICs and occurrence of resistance in Escherichia coli *from broilers (n=114), cattle (n=97) and pigs (n=151), Denmark*

DANMAP 2008

	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	10.5	[5.6-17.7]								89.5				0.9	9.6						
	Cattle	4.1	[1.1-10.2]								76.3	19.6				4.1						
	Pigs	29.8	[22.6-37.8]								64.2	5.3	0.7		2.6	27.2						
Chloramphenicol	Broilers	0	[0-3.2]								9.6	62.3	28.1									
	Cattle	1.0	[0.03-5.6]								1.0	24.7	69.1	4.1		1.0						
	Pigs	0.7	[0.02-3.6]								4.0	39.7	54.3	1.3	0.7							
Florfenicol	Broilers	0	[0-3.2]								10.5	72.8	16.7									
	Cattle	1.0	[0.03-5.6]								1.0	25.8	68.0	4.1		1.0						
	Pigs	0	[0-2.4]								4.0	42.4	51.7	2.0								
Ampicillin	Broilers	12.3	[6.9-19.7]							15.8	36.8	34.2	0.9			12.3						
	Cattle	1.0	[0.03-5.6]							2.1	25.8	63.9	7.2			1.0						
	Pigs	19.2	[13.3-26.4]							3.3	38.4	37.1	2.0			19.2						
Ceftiofur	Broilers	0	[0-3.2]						97.4	2.6												
	Cattle	0	[0-3.7]						100													
	Pigs	0	[0-2.4]						99.3	0.7												
Cefotaxime	Broilers	0	[0-3.2]				99.1	0.9														
	Cattle	0	[0-3.7]				99.0	1.0														
	Pigs	0	[0-2.4]				98.7	1.3														
Sulfonamide	Broilers	11.4	[6.2-18.7]													88.6					11.4	
	Cattle	5.2	[1.7-11.6]													94.8					5.2	
	Pigs	24.5	[17.9-32.2]													75.5				1.3	23.2	
Trimethoprim	Broilers	4.4	[1.4-9.9]							95.6						4.4						
	Cattle	2.1	[0.3-7.3]							96.9	1.0					2.1						
	Pigs	17.9	[12.1-24.9]							81.5	0.7	0.7				17.2						
Apramycin	Broilers	0	[0-3.2]									70.2	27.2	2.6								
	Cattle	0	[0-3.7]									88.7	11.3									
	Pigs	0	[0-2.4]									89.4	9.3	1.3								
Gentamicin	Broilers	0.9	[0.02-4.8]						69.3	28.1	1.8				0.9							
	Cattle	0	[0-3.7]						94.8	5.2												
	Pigs	0.7	[0.02-3.6]						88.1	9.9	1.3		0.7									
Neomycin	Broilers	0.9	[0.02-4.8]								97.4	1.8				0.9						
	Cattle	0	[0-3.7]								99.0	1.0										
	Pigs	3.3	[1.1-7.6]								93.4	3.3			1.3	2.0						
Spectinomycin	Broilers	2.6	[0.5-7.5]											84.2	12.3	0.9	0.9	1.8				
	Cattle	1.0	[0.03-5.6]											88.7	8.2	2.1		1.0				
	Pigs	13.9	[8.8-20.5]											71.5	10.6	4.0	4.6	4.6	4.6			
Streptomycin	Broilers	7.9	[3.7-14.5]										89.5	2.6	3.5	3.5	0.9					
	Cattle	4.1	[1.1-10.2]										94.8	1.0	3.1			1.0				
	Pigs	26.5	[19.6-34.3]										70.2	3.3	6.0	7.3	8.6	4.6				
Ciprofloxacin	Broilers	12.3	[6.9-19.7]	78.1	9.6	0.9	5.3	6.1														
	Cattle	0	[0-3.7]	72.2	27.8																	
	Pigs	0.7	[0.02-3.6]	82.1	17.2			0.7														
Nalidixic acid	Broilers	12.3	[6.9-19.7]									86.8	0.9		3.5	3.5	5.3					
	Cattle	0	[0-3.7]									99.0	1.0									
	Pigs	0.7	[0.02-3.6]									98.0	1.3				0.7					
Colistin	Broilers	0	[0-3.2]							98.2	1.8											
	Cattle	0	[0-3.7]							99.0	1.0											
	Pigs	0	[0-2.4]							99.3	0.7											

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 58. Distribution of MICs and occurrence of resistance in Escherichia coli *from army recruits (n=75), Denmark*

DANMAP 2008

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	29.3	[19.4-41.0]							64.0	6.7			1.3	28.0					
Chloramphenicol	5.3	[1.5-13.1]								18.7	73.3	2.7	1.3		4.0				
Florfenicol	0	[0-4.8]								38.7	60.0	1.3							
Ampicillin	28.0	[18.2-39.6]						2.7	34.7	29.3	5.3	5.3	2.7	20.0					
Ceftiofur	1.3	[0.03-7.2]					96.0	2.7		1.3									
Cefpodoxime	2.7	[0.3-9.3]			9.3	54.7	26.7	6.7		1.3	1.3								
Sulfonamide	34.7	[24.0-46.5]												65.3					34.7
Apramycin	0	[0-4.8]								74.7	21	4.0							
Gentamicin	6.7	[2.2-14.9]						85.3	8.0	1.3			1.3	4.0					
Neomycin	9.3	[3.8-18.3]							86.7	4.0			2.7	6.7					
Spectinomycin	10.7	[4.7-19.9]										69.3	14.7	5.3	2.7	5.3	2.7		
Streptomycin	28.0	[18.2-39.6]								42.7	25.3	4.0		10.7	17.3				
Ciprofloxacin	13.3	[6.6-23.2]	86.7		1.3	5.3	1.3				5.3								
Nalidixic acid	13.3	[6.6-23.2]								85.3	1.3		1.3	1.3	10.7				

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 59. Distribution of MICs and occurrence of resistance in Staphylococcus hyicus *from pigs (n=31), Denmark*

DANMAP 2008

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	29.0	[14.2-48.0]				71.0						6.5	22.6				
Chloramphenicol	3.2	[0.08-16.7]						3.2	67.7	25.8				3.2			
Florfenicol	3.2	[0.08-16.7]					3.2	71.0	22.6					3.2			
Penicillin	67.7	[48.6-83.3]	32.3					3.2	3.2	35.5	9.7	16.1					
Erythromycin	35.5	[19.2-54.6]			64.5							35.5					
Cefoxitin	0	[0-11.2]				100											
Sulfonamide	0	[0-11.2]										71.0	22.6	6.5			
Trimethoprim	48.4	[30.2-66.9]				6.5	25.8	12.9	6.5				48.4				
Gentamicin	0	[0-11.2]			100												
Spectinomycin	29.0	[14.2-48.0]										51.6	19.4			29.0	
Streptomycin	48.4	[30.2-66.9]							45.2	6.5			9.7	38.7			
Ciprofloxacin	0	[0-11.2]		87.1	12.9												
Tiamulin	41.9	[24.5-60.9]			19.4	38.7						6.5	35.5				

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

Table 60. Distribution of MICs and occurrence of resistance in Escherichia coli *from cattle (n=45) and pigs (n=71), Denmark*

DANMAP 2008

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	Cattle	66.7	[51.0-80.0]								33.3				2.2	64.4						
	Pigs	60.6	[48.3-72.0]								29.6	7.0	2.8		5.6	54.9						
Chloramphenicol	Cattle	11.1	[3.7-24.1]									13.3	73.3	2.2			11.1					
	Pigs	14.1	[7.0-24.4]								1.4	62.0	21.1	1.4	1.4	4.2	8.5					
Florfenicol	Cattle	4.4	[0.5-15.1]									13.3	82.2				4.4					
	Pigs	1.4	[0.04-7.6]								7.0	71.8	16.9	2.8	1.4							
Ampicillin	Cattle	86.7	[73.2-94.9]								11.1	2.2				86.7						
	Pigs	42.3	[30.6-54.6]							7.0	36.6	14.1				42.3						
Ceftiofur	Cattle	4.4	[0.5-15.1]						95.6				2.2	2.2								
	Pigs	2.8	[0.3-9.8]						97.2					2.8								
Cefotaxime	Cattle	6.7	[1.4-18.3]				91.1	2.2	2.2				4.4									
	Pigs	2.8	[0.3-9.8]				95.8	1.4					2.8									
Sulfonamide	Cattle	57.8	[42.2-72.3]													42.2					57.8	
	Pigs	62.0	[49.7-73.2]													38.0				1.4	60.6	
Trimethoprim	Cattle	33.3	[20.0-49.0]							66.7						33.3						
	Pigs	40.8	[29.3-53.2]							59.2		1.4				39.4						
Apramycin	Cattle	11.1	[3.7-24.1]									71.1	17.8			11.1						
	Pigs	7.0	[2.3-15.7]									90.1	2.8			7.0						
Gentamicin	Cattle	11.1	[3.7-24.1]						60.0	28.9				8.9	2.2							
	Pigs	7.0	[2.3-15.7]						81.7	11.3			2.8	4.2								
Neomycin	Cattle	6.7	[1.4-18.3]								82.2	8.9	2.2			6.7						
	Pigs	18.3	[10.1-29.3]								80.3	1.4			4.2	14.1						
Spectinomycin	Cattle	28.9	[16.4-44.3]											62.2	4.4	4.4	6.7	11.1	11.1			
	Pigs	54.9	[42.7-66.8]											38.0	4.2	2.8	5.6	11.3	38.0			
Streptomycin	Cattle	62.2	[46.5-76.2]										37.8		15.6	22.2	13.3	11.1				
	Pigs	63.4	[51.1-74.5]										29.6	7.0	21.1	11.3	9.9	21.1				
Ciprofloxacin	Cattle	24.4	[12.9-39.5]	73.3	2.2		2.2	22.2														
	Pigs	15.5	[8.0-26.0]	77.5	7.0	4.2		9.9				1.4										
Nalidixic acid	Cattle	24.4	[12.9-39.5]									75.6					24.4					
	Pigs	12.7	[6.0-22.7]									83.1	2.8	1.4		1.4	11.3					
Colistin	Cattle	0	[0-7.9]							100												
	Pigs	0	[0-5.1]							100												

Vertical solid lines indicate EUCAST epidemiological cut-off values and vertical dotted lines indicate EUCAST clinical breakpoints or if not present, CLSI clinical breakpoints. Exceptions and further details can be found in appendix 2.
White fields represent the range of dilutions tested. MIC values equal to or lower than the lowest concentration tested are presented as the lowest concentration. MIC values greater than the highest concentration in the range are presented as one dilution step above the range.

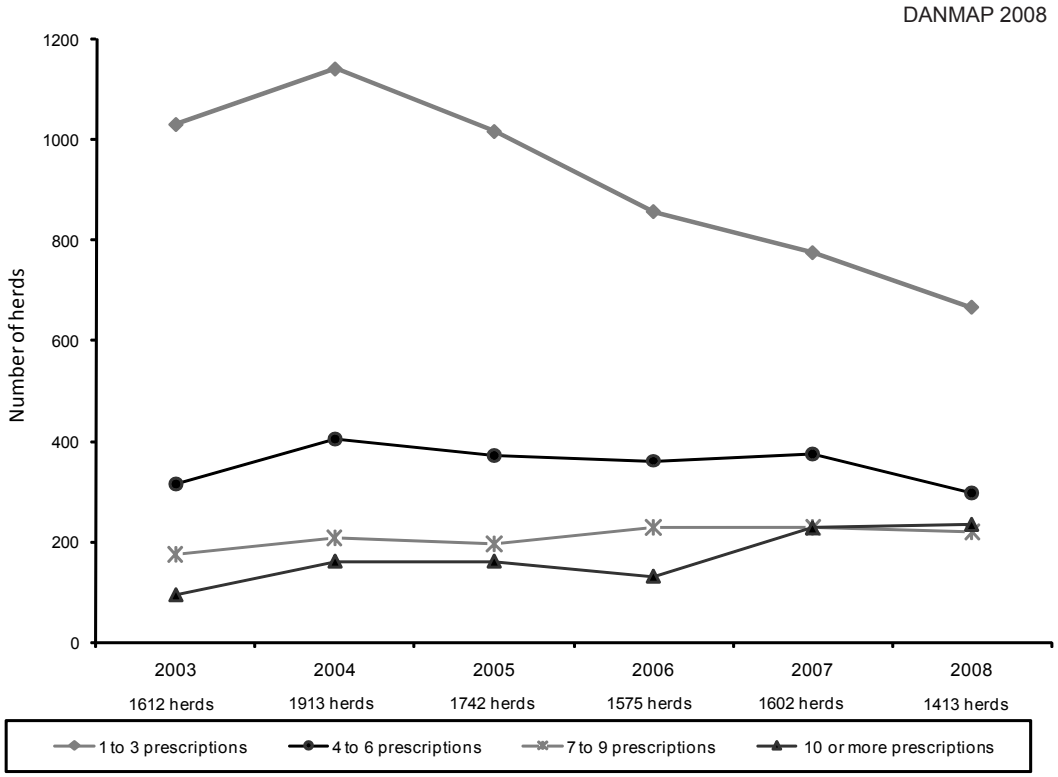

Figure 51. Number of herds using macrolides for oral use in weaning pigs, grouped by number of prescriptions per herds per year, Denmark 2003-2008
The total number of herds (N) receiving macrolides for oral use is shown below the x-axis.

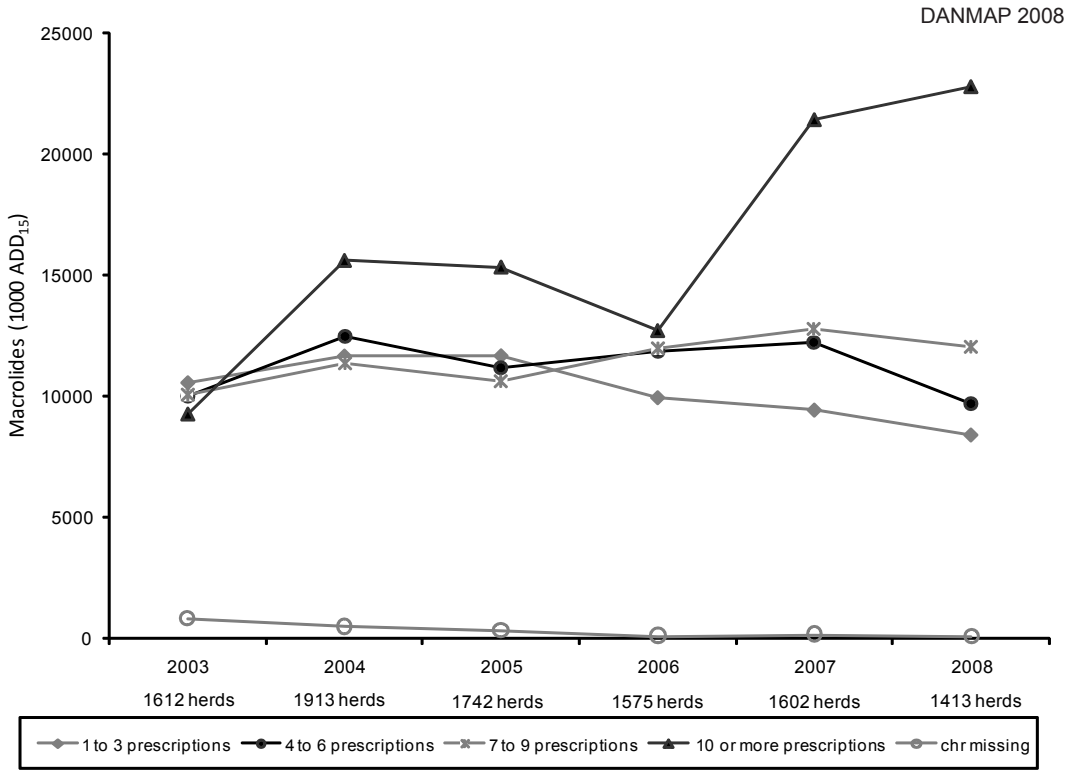

Figure 52. Amounts of macrolides for oral use in weaning pig herds, grouped by number of prescriptions per herd per year, Denmark 2003-2008
The total number of herds (N) receiving macrolides for oral use is shown below the x-axis.

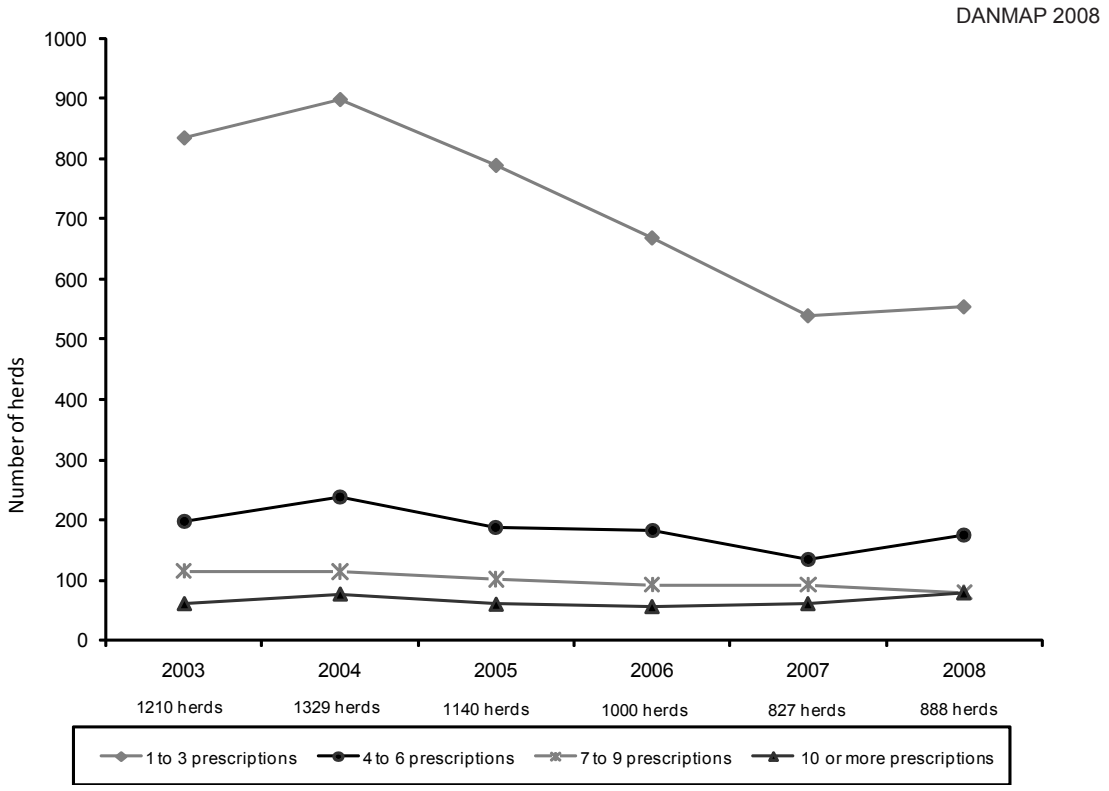

Figure 53. Number of herds receiving pleuromutilin drugs for oral use in weaning pigs, by number of prescriptions per herd per year, Denmark 2003-2008
The total number of herds (N) receiving tetracyclines for oral use is shown below the x-axis.

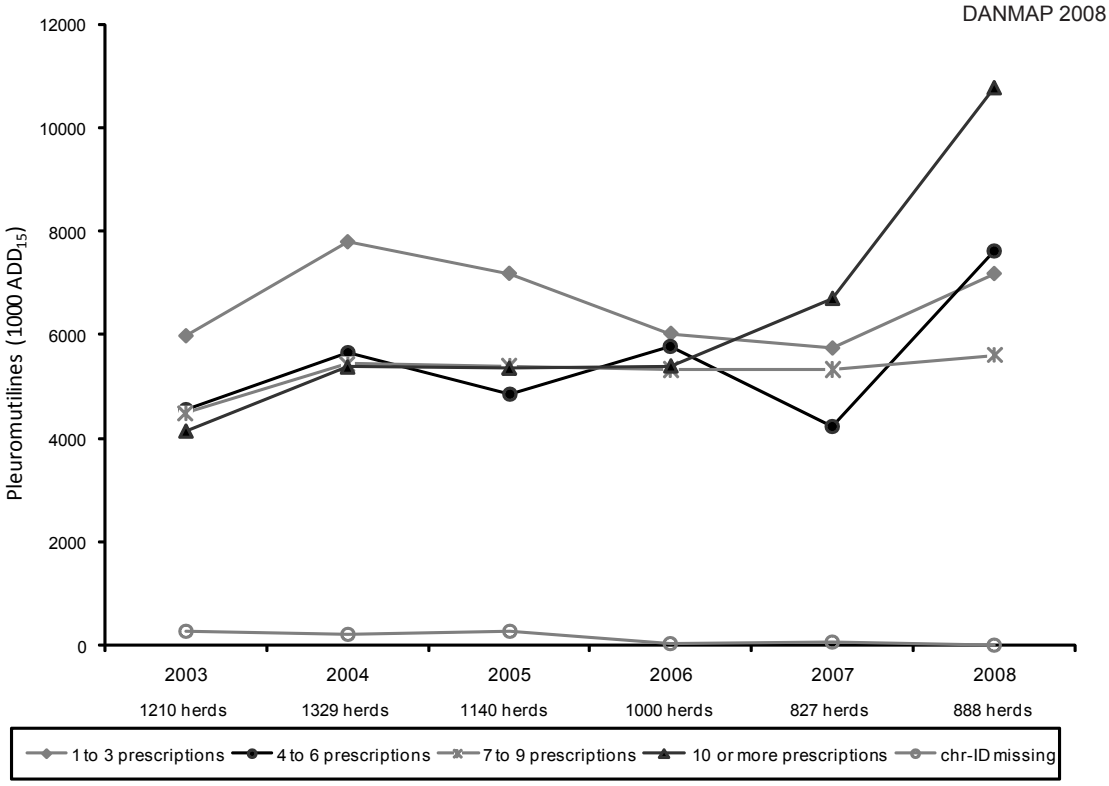

Figure 54. Amounts of pleuromutilins for oral use in weaning pig herds, grouped by number of prescriptions per herd per year, Denmark 2003-2008
The total number of herds (N) receiving pleuromutilins for oral use is shown below the x-axis.

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 specialise 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, because reorganisation of the hospital sector has resulted in regrouping hospitals that are distant geographically but under the same administration and therefore under 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 antimicrobials

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 2007, antimicrobials could only be purchased at the pharmacy or in medicated feed from the feed mills. The pharmacy either sells the medicines to vetenarians 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 and there is no direct economic encouragement for the veterinarian to sell drugs.

From April 2nd 2007, the monopoly of the pharmacy was suspended, and private companies can now on certain conditions (corresponding to the pharmacies) sell veterinary drugs to farmer on prescription.

In addition, price setting was liberalised in 2007, allowing 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 the pharmacies (88%), the drug selling companies (9%), 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 on a monthly basis. For most veterinarians, the registration of data is linked to the writing of invoices. 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 ADD_{xx} 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, ADD_{kg} is the dose needed to treat one kg animal. The ADD_{kg} is used to measure the consumption across age groups.

The length of the recommended treatment period may vary 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 (ADC_{kg}) or age group (ADC_{xx}), based on the corresponding ADD_{kg} or ADD_{xx}, respectively, for the relevant animal species and drug formulations. When no information of the applied treatment length in practice, a treatment course of 6 days is assumed.

Table 61. Antimicrobial agents used in humans and/or in animals in Denmark a)
Antimicrobial agents, which are only used in animals are mentioned in italics (animal growth promoters used before 1999 are mentioned in parentheses).
Antimicrobial agents, which are used both in humans and animals are underlined. DANMAP 2008

ATC/ATCvet codes	Therapeutic group	Names of antimicrobial agents 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*
J01DC	Second-generation cephalosporins	Cefuroxime
J01DD/*QJ01DD/QJ51DA*	Third-generation cephalosporins	Cefotaxime, ceftazidime, ceftriaxone, *cefoperazone, ceftiofur*
J01DE/*QJ51DA*	Fourth-generation cephalosporins	*Cefquinome, cefovecin*
J01DF	Monobactams	Aztreonam
J01DH	Carbapenems	Meropenem, ertapenem, doripenem
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*, *apramycin*
J01MA/*QJ01MA*	Fluoroquinolones	Ofloxacin, ciprofloxacin, moxifloxacin, *enrofloxacin*, *danofloxacin*, *marbofloxacin, difloxacin, ibafloxacin*
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

Antimicrobials used in humans / animals are presented in Table 61.

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 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

Table 62. Interpretation used for MIC-determination on bacterial isolates from animals, food and humans. Epidemiological cut-off values and clinical breakpoints recommended by EUCAST are marked in grey.

DANMAP 2008

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

Epidemiological cut-off values recommended by EUCAST was used for interpretation and are presented in grey fields. Other interpretation used was applied by DANMAP.

a) Clinical breakpoints was used for interpretation for enterococci to gentamicin where the EUCAST epid cut-off value was inappropriate due to differences in the dilution range tested at the different institutes.

b) Trade name is synercid. EUCAST epid cut-off value (>1) was not applied according to investigations presented in the DANMAP 2006 report p. 49-50.

c) CLSI clinical breakpoint was applied.

d) EUCAST epid cut-off values for S. aureus were applied except for chloramphenicol and erythromycin (S. hyicus cut-off values/clinical breakpoints presented) and gentamicin (CNS cut-off value/clinical breakpoint presented).

* CLSI clinical breakpoint. CLSI clinical breakpoints are presented, if EUCAST clinical breakpoints are not available.

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 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*) and from diagnostic submissions (*Staphylococcus hyicus* from pigs, *E. coli* O149 and *E. coli* F5 (K99) from diarrhoea pigs and cattle, respectively). 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 for pigs and cattle, and to the National Veterinary Institute, DTU for broilers. 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. For broilers samples representing all broiler houses are collected throughout the year, for cattle and pigs samples are collected once a month from January through November. The broiler, cattle and pig slaughter plants included in the surveillance programme account for 90-95 % 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, Technical University of Denmark 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 and 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 from the Laboratory of Swine Diseases, Danish Meat Association, Kjellerup. Accordingly, the programme achieves nationwide coverage for these pathogens.

Isolates from food

Danish *Salmonella* isolates from food originated from carcass swabs taken at the slaughter house after cooling. All other food samples are 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 consists of both Danish and imported foods. The food samples are 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. and *Campylobacter* spp. Antimicrobial susceptibility was performed on a sample of human faecal isolates submitted Statens Serum Institut (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.

***E. faecium*, *E. faecalis*, vancomycin-resistant enterococci and *E. coli*.** To monitor the level of resistance among individuals in the community 120 Army recruits were invited to participate in a study. A letter including information on the study together with a consent form was mailed to the selected individuals. They were asked to confirm their willingness to participate by returning the signed form. Faecal test tubes were mailed to the SSI. The study protocol has the approval of the scientific ethics committee for Copenhagen and Frederiksberg municipalities.

***Staphylococcus aureus*.** Until October 2006, all blood isolates from 15 of the 16 Danish counties were referred to the Staphylococcus reference laboratory at SSI on a voluntary basis. In October 2006, MRSA became a notifiable disease in Denmark and since then it has been mandatory to send all isolates to the Staphylococcus reference laboratory.

Invasive *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A streptococci), group 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*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, non-invasive *Streptococcus pneumoniae*, non-invasive *Streptococcus pyogenes*, invasive *E. faecium* and invasive *E. faecalis*.** Data was provided on all isolates recorded from either blood samples (*E. coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *E. faecium* and *E. faecalis*), urine samples (*E. coli)* or all non-invasive samples (*S. pyogenes* and *Streptococcus pneumoniae*) 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.

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**. Samples from pigs and poultry were examined by direct inoculation on selective agar (mCCD) followed by incubation in micro-aerophilic atmosphere for 1-5 days at 41.5°C. Samples from cattle were initialized by selective enrichment in Preston broth at a ratio of 1:10 incubated in microaerophilic atmosphere for 24 h at 41.5°C followed by inoculation of 10µ enrichment broth to mCCD agar incubated 1-5 days at 41.5°C.
Campylobacter-like colonies were identified by microscopy and oxidase activity. Species-identification was performed by catalase activity and the ability to hydrolyse indoxyl acetate and hippurate. All isolates of *C. jejuni* and *C. coli* were stored at -80°C

Escherichia coli from healthy animals (indicator *E. coli*). The material was inoculated directly onto Drigalski agar and incubated at 37°C overnight. For cattle and pigs, yellow colonies were inocultated onto CHROM Orientation agar and red colonies were identified as *E. coli* after incubation at 37°C overnight For poultry, yellow colonies were identified by catalase and oxidase activity, indole, citrate, methyl red and Voges-Proskauer reaction.

Enterococci. For samples 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. Three colonies with morphology typical of *E. faecalis* and *E. faecium* were sub-cultivated on blood agar. White colonies were identified by the following criteria: Motility, arginine dihydrolase and the ability to ferment mannitol, sorbitol, arabinose, raffinose and melibiose. All isolates of *E. faecium* and *E. faecalis* were stored at -80°C For samples from broiles, cloacal swabs were incubated overnight at 42°C in Enterococcus Selective Broth, prepared with a composition identical to that of Enterococcosel broth. Cultures were inoculated on Slanetz-Bartley agar and incubated for 48 h at 37°C followed by the same identification criteria as mentioned for isolates from pigs.

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

Isolates from food

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

***Campylobacter* spp**. was isolated according to the guidelines for microbiological examination of foods from the DVFA [NMKL No. 119, 3rd ed., 2007]. Further identification was performed at the National Food Institute, DTU, by microscopy, oxidase activity, catalase activity and the ability to hydrolyse indoxyl acetate and hippurate. All isolates of *C. jejuni* and *C. coli* were stored at -80°C

Indicator *E. coli* was 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 further identified by CHROM Orientation agar, and subsequently sent to the National Food Institute, DTU, for MIC-testing. All isolates were stored at -80°C

Enterococci was 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 48 hours, colonies typical of *E. faecium* and *E. faecalis* were sent to the National Food Institute, DTU, for further identification by the following criteria: Motility, arginine dihydrolase and the ability to ferment mannitol, sorbitol, arabinose, raffinose and melibiose. All isolates of *E. faecium* and *E. faecalis* were stored at -80°C

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. All *Staphylococcus aureus* blood isolates and methicillin-resistant *Staphylococcus aureus* (MRSA) in Denmark was referred to the Staphylococcus reference laboratory at SSI for confirmation of susceptibility results and typing. Sequencing of the *S. aureus* specific *spa* gene was used both for species conformation and typing purposes. Any *spa* negative isolates were confirmed as S. aureus by coagulase test. The *spa* typing [Harmsen D. *et. al.* J. Clin. Microbiol 2003; 41:5442-5448] and additional typing by multi locus sequence typing (MLST) was performed [Enright M.C *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].

Enterococci. Enterococci from army recruits were isolated and identified by the following procedure. Half gram of faeces suspended in 2 ml sodium chloride (0.9%) was spread on Slanetz agar and incubated for 2 days at 35oC. Ten µl of the suspension was furthermore added to 5 ml Enterococcosel broth and incubated overnight. Cultures were spread on Slanetz agar and incubated for 2 days at 35oC. Colonies showing morphology typical of *E. faecalis* or *E. faecium* were sub-cultivated on 5% blood agar and identified by API api20 strep tests (BioMérieux, France) and PCR according to Poulsen *et al*. and Dutka-Malen *et al*. [Poulsen RL *et al*., APMIS 1999; 107: 404-412 and Dutka-Malen S *et al.*, J. Clin. Microbiol., 1995; 33: 24-27].

Vancomycin-resistant enterococci. A selective method for isolation of vancomycin-resistant enterococci from army recruits was used. Ten µl of the faeces suspension was added to 5 ml Enterococcosel broth and incubated overnight. Cultures were spread on Bile Aesculin agar with 16 µg/ml vancomycin and incubated for 2 days at 35°C. Colonies showing morphology typical of *Enterococcus* spp. were sub-cultivated on 5% blood agar. The isolates were identified as enterococci by API api20 strep tests (BioMérieux, France) and PCR according to Poulsen et al. and Dutka-Malen *et al.* [Poulsen RL *et al*., APMIS 1999; 107: 404-412 and Dutka-Malen S *et al.,* J. Clin. Microbiol., 1995; 33: 24-27].

Escherichia coli. *E. coli* from army recruits were isolated and identified as follows: One-hundred µl of the diluted faecal sample was spread on the SSI Enteric Medium. Presumptive *E. coli* isolates were sub-cultured on 5% blood agar and identified by API 20Etest (BioMérieux, France).

ESBL-producing and ampC producing Enterobacteriaceae from army recruits. Half gram of faeces was suspended in 5 mL sodium chloride (0.9%). One-hundred µl of the suspension was spread on 2 SSI Enteric agar plates (SSI Diagnostica) supplemented with 2 mg/L cefotaxime and 2 mg/L ceftazidime, respectively. Both plates were incubated in ambient air for 18 hours at 35°C. Presumptive 3. generation cephalosporin resistant Enterobacteriaceae were sub-cultured on 5% blood agar. One colony per sample was further investigated. The isolates were identified using API 20E (BioMérieux, Marcy-l'Etoile, France) and retested for cefotaxime and ceftazidime using Etest. ESBL and/or ampC phenotype was tested using the Neosensitabs double disk method according to the producers guidelines (Rosco Diagnostica A/S). Based on the obtained phenotype, the presence of TEM, SHV, CTX-M, OXA, MOX, CIT, DHA, ACC, EBC and FOX beta-lactamase-geno-groups was studied using PCR.

Susceptibility testing of *Salmonella* spp., *Campylobacter* spp., indicator *E. coli, Enterococcus* spp. and the veterinary pathogens.

Antimicrobial susceptibility testing of *Salmonella* spp., *Campylobacter* spp., indicator *E. coli*, *Enterococcus* spp. and the veterinary pathogens was performed as microbroth dilution MIC with the Sensititre system (Trek Diagnostic Systems Ltd., UK). Inoculation and incubation procedures were in accordance with the CLSI guidelines. The following quality control strains were used for internal control of the MIC-testing: *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, Enterococcus faecalis ATCC 29212 and *Campylobacter jejuni* ATCC 33560.

An overview of the interpretation used for the MIC-values is presented in Table 62. Since 2007, the data was interpreted using EUCAST epidemiological cut-off values, and if not available, the EUCAST or CLSI clinical breakpoint was applied. Exceptions and further details are described by footnotes in Table 62. Data from previous years presented in this DANMAP report is not corrected for the change in interpretation (e.g. all data is presented with use of the interpretation applied for the year in question).

Since 1998, a performance test for susceptibility testing was carried out once a year or every second year as part of the DANMAP programme to ascertain the quality and comparability of susceptibility tests of the laboratories involved in presentation of data. In 2008 it was decided to end this activity. Today, all participating laboratories are accreditated by DANAK (the Danish national body for accreditation) to perform MIC-analysis, or awaiting an accreditation for the upcoming year. The accreditation makes demands on regularly participation in performance testings and evaluation of the achieved results.

All isolates from animals and foods were susceptibility tested at the National Food Institute, DTU, except

for broilers, where the testing was performed by 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.
Additional information on susceptibility testing is described in the next section.

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

Additional information on human isolates

Campylobacter spp. 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 number of isolates in these two groups.

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 an isolate was resistant to erythromycin), tetracycline, fusidic acid, rifampicin, norfloxacin, mupirocin 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 McFarland 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. 47:399-404]

Invasive *Streptococcus pneumoniae*. Screening for penicillin-resistant *S. pneumoniae* was performed using a 1 µg oxacillin tablet (Neo-Sensitabs®, A/S Rosco, Taastrup, 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 are those defined by the CLSI. Penicillin and erythromycin MIC's are 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 are those defined by Etest.

Invasive Streptococcus pyogenes (group A streptococci), group 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 are tested with 15 µg erythromycin disk (Oxoid) and 15 µg clindamycin disk (Oxoid, Greve, Denmark) on Danish Blood Agar (Resistensplade, SSI Diagnostika). Erythromycin MIC's are 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 are those defined by the CLSI. Resistant isolates are defined as both fully and intermediary resistant isolates.

***Escherichia coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, non-invasive *Streptococcus pneumoniae*, non-invasive *Streptococcus pyogenes*, invasive *E. faecium* and invasive *E. faecalis*.** In 2008, 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 (SRGA). The only material exception from SRGA was that the wildtype population of *E. coli* was deemed susceptible for ampicillin (and not intermediary susceptible).

In 2008, the DCM at Hillerød, 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. 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 due to an evaluation study presented in the DANMAP 2006 report, page 49-50.

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® at the National Food Institute, DTU. 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 value. 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, except for the data on Salmonella (carcass swabs), which were reported to and extracted from the laboratory database at the National Food Institute, DTU. For each bacterial isolate information is available on the food type, bacterial species, date of sampling, date of examination of the sample, the RFCA 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 (SQL database) 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.

Staphylococcus aureus. For MRSA, data on the characteristics of the isolates and the clinical/epidemiological information were obtained from the Danish MRSA register at SSI (mandatory reportable). In this database, patients were only registered the first time they were diagnosed with MRSA regardless of whether it was colonisation or infection. 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), imported infection (i.e. acquired outside Denmark), infection acquired in a Danish hospital, defined as diagnosed >48 hours after hospitalization with no sign of infection at admittance (HA-MRSA) or infection 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 hospitalisations 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*, *Streptococcus pyogenes* (group A streptococci), group 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, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, non-invasive *Streptococcus pneumoniae*, non-invasive *Streptococcus pyogenes*, invasive *E. faecium* and invasive *E. faecalis*.** Fourteen DCM provided data on resistance levels in *E. coli* blood and urine isolates, *Klebsiella pneumoniae, Pseudomonas aeruginosa,* non-invasive *Streptococcus pneumoniae*, non-invasive *Streptococcus pyogenes*, invasive *E. faecium* and invasive *E. faecalis*. 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.
Generally, resistance data were excluded if susceptibility to a certain antimicrobial agent 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. 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.

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