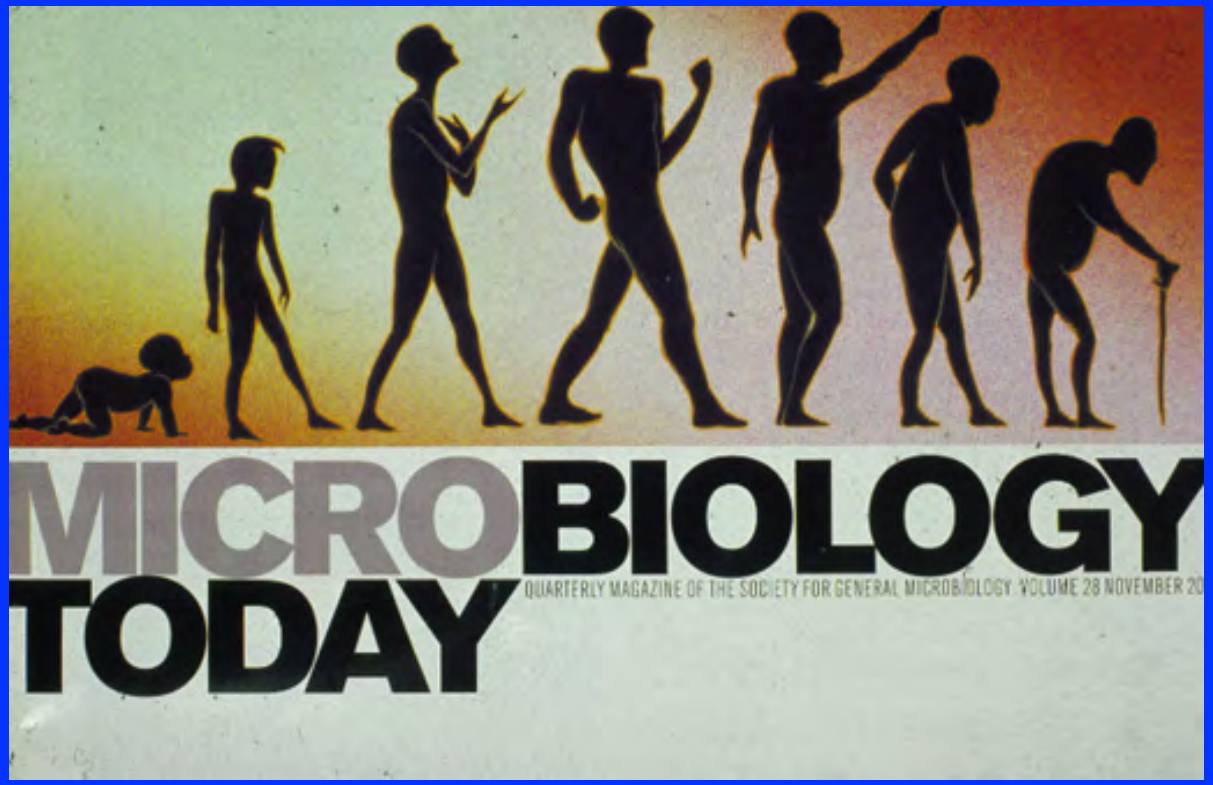
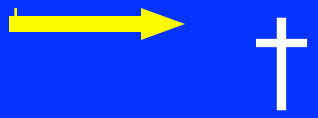
ANTIBIOTIC RESISTANCE OVERVIEW – ARE WE HEADING TOWARDS A POST ANTIBIOTIC ERA?

NIELS HØIBY



KMA-RH: en antibiotikapolitik skal sikre effektiv behandling og forhindre resistensudvikling fra vugge



Optimal antibiotika behandling

- Forebyggelse af resistensudvikling - hos den ætiologiske bakterie

Korrelation mellem forbrug af penicillin og resistensudvikling hos Pneumokokker i Europa

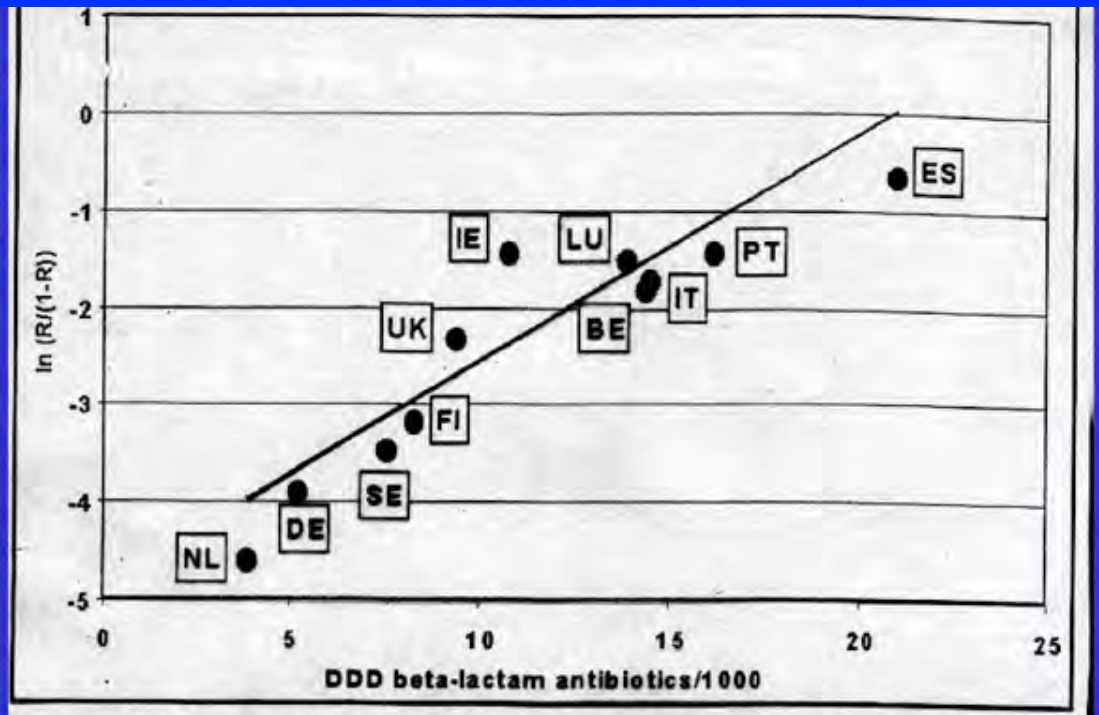
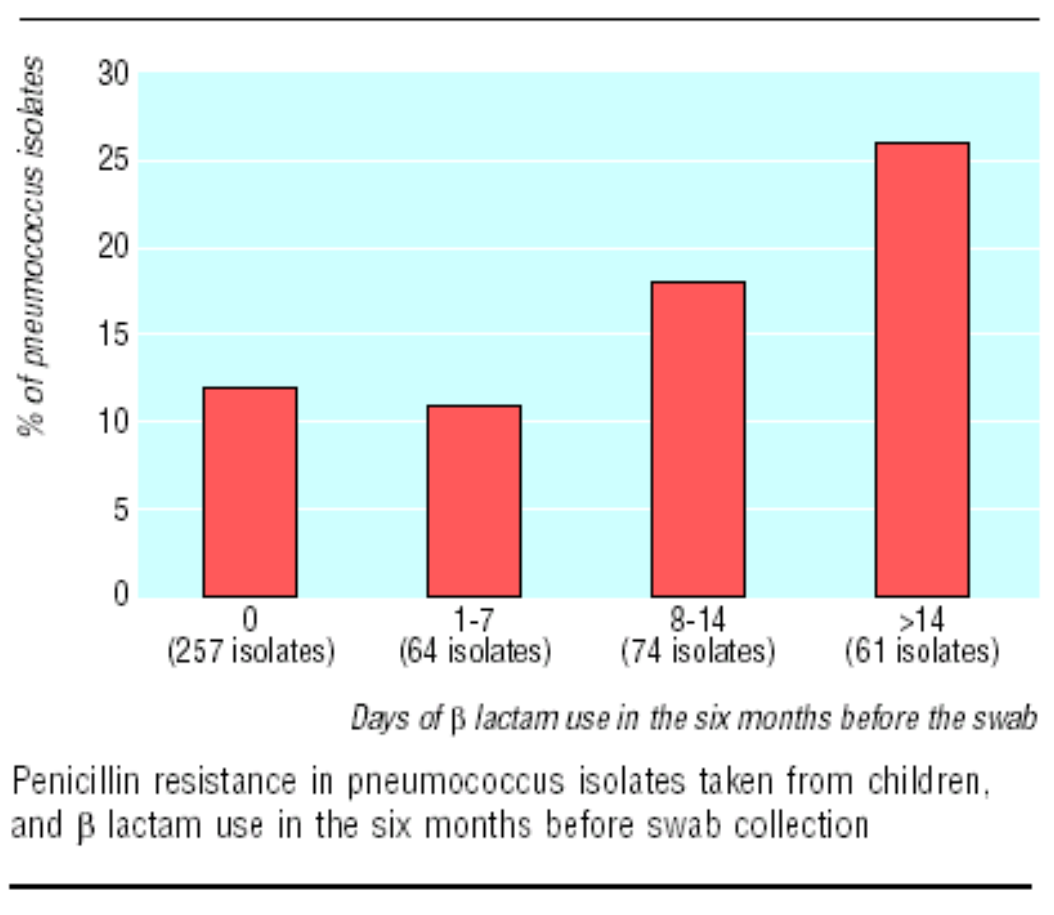


Figure 2. The logodds of resistance to penicillin among invasive isolates of *Streptoccus pneumoniae* (PNSP; ln(R/[1-R])) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries; antimicrobial resistance data are from 1998 to 1999 and antibiotic sales data are from 1997. DDD = defined daily dose; BE = Belgium; DE = Germany; FI = Finland; IE = Ireland; IT = Italy; LU = Luxembourg; NL = the Netherlands; PT = Portugal; ES = Spain; SE = Sweden; UK = United Kingdom.

Resistensudvikling efter antibiotika



Penicillin resistance in pneumococcus isolates taken from children, and β lactam use in the six months before swab collection

- Antal dage i løbet af 6 måneder hvor børn har fået behandling med beta-lactam antibiotika
- Penicillin-resistens hos Pneumokokker (N=456) efter penicillin behandling af forskellig varighed
- VUGGESTUE-BØRNEHAVEINFEKTIONERNE!

International spredning af en multiresistent klon af *S. pneumoniae* med mennesker. Det samme gør sig gældende med resistente zoonotiske bakterier (*E. coli, Salmonella spp.*) som spredes via menneskers tarmflora/fæces og med fødevarer

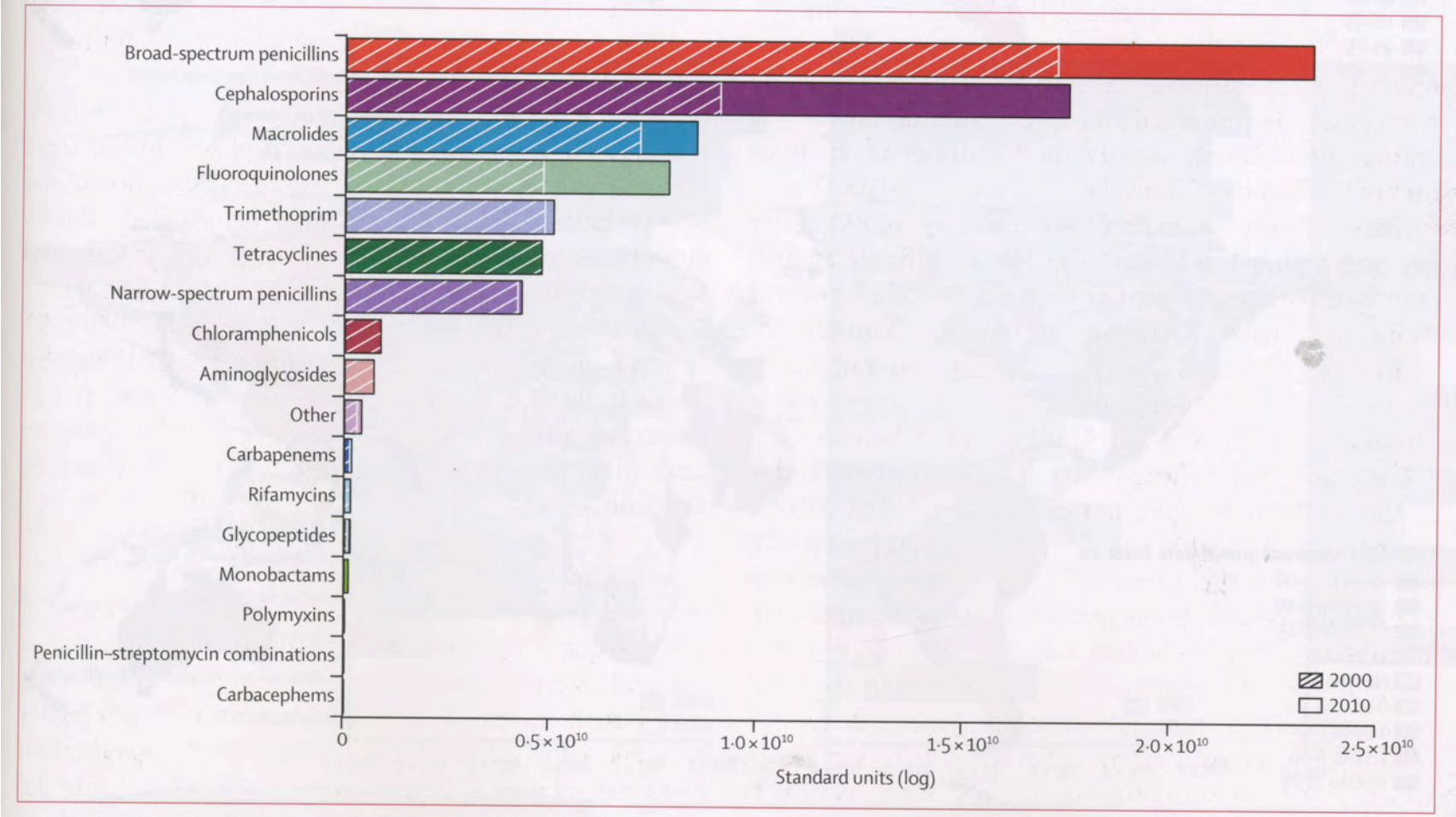


***Figure* 1: Global antibiotic consumption by class in 2000 and 2010**
Standard units are defined as a single dose unit (ie, pill, capsule, or ampoule).

Van Boeckel et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect. Dis. 14.742-50; 2014

Stichele et al: Hospital consumption of antibiotics in 15 European countries: results of the ESAC retrospective data collection (1997-2002). JAC 58:159-167; 2006

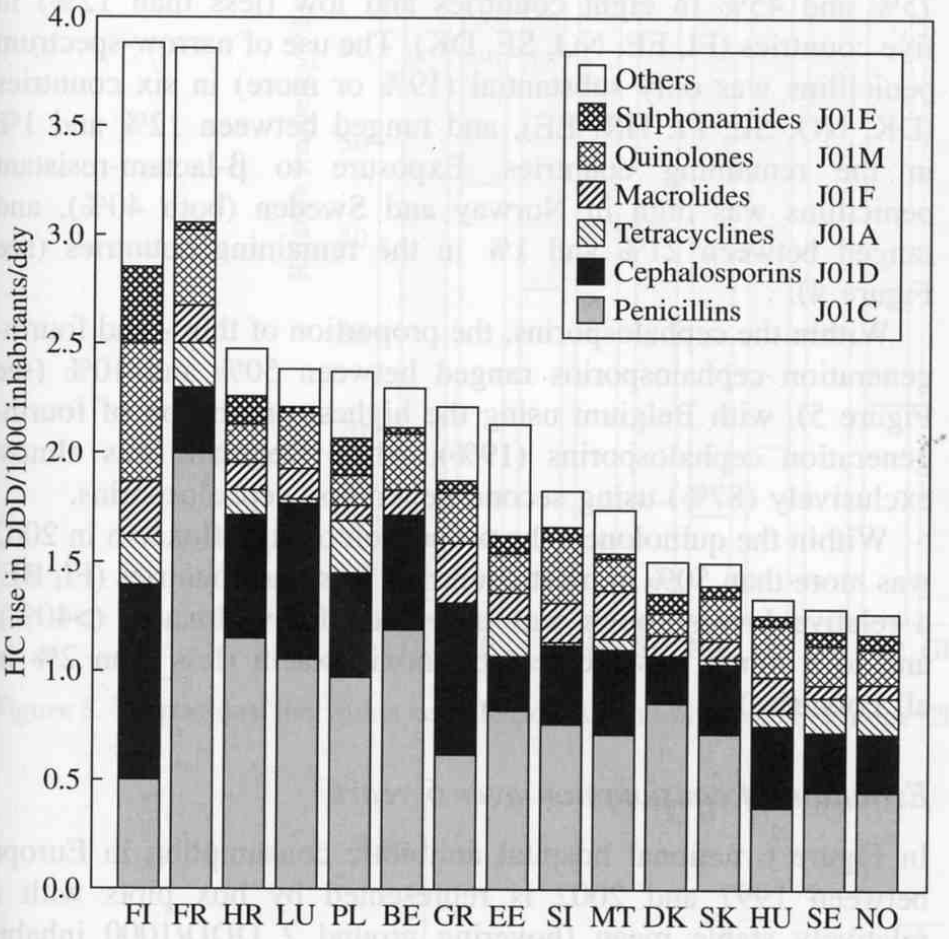


Figure 1. Antibiotic use and distribution over main classes in hospital care (HC) in Europe (2002). *Note*: data from Finland include primary healthcare centres and nursing homes.

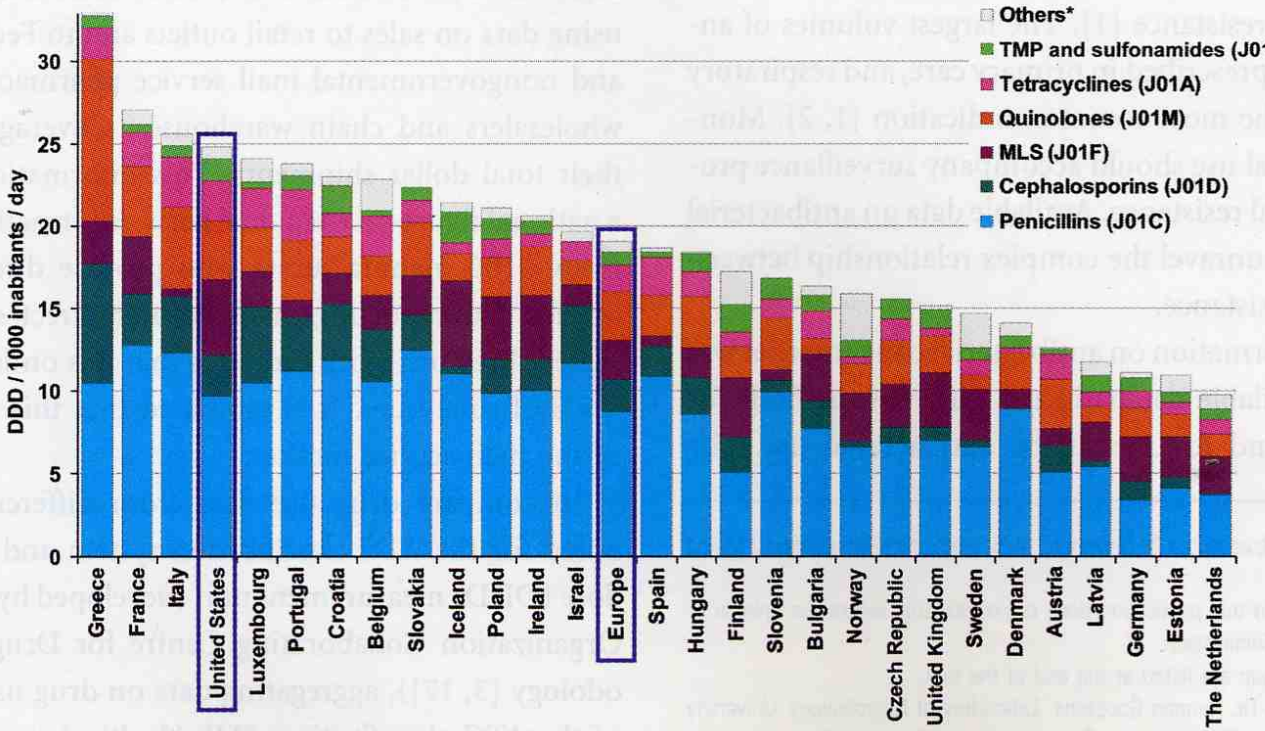


Figure 1. Total outpatient antibacterial use in the United States and 27 European countries in 2004 (total use for Greece, Iceland, and Bulgaria, 2002 data for Poland, and 2003 data for Italy). DDD, defined daily dose; MLS, macrolides, lincosamides, and streptogramins; TMP, trimethoprim. *Includes amphenicols (J01B), aminoglycosides (J01G), combinations of antibacterial agents (J01R), and other antibacterial agents (J01X).

Goossens et al. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European countries. CID 44:1091-95; 2007

Figure 5.1. Total consumption of antimicrobial agents in humans in primary health care vs hospital care, Denmark. DANMAP 2014

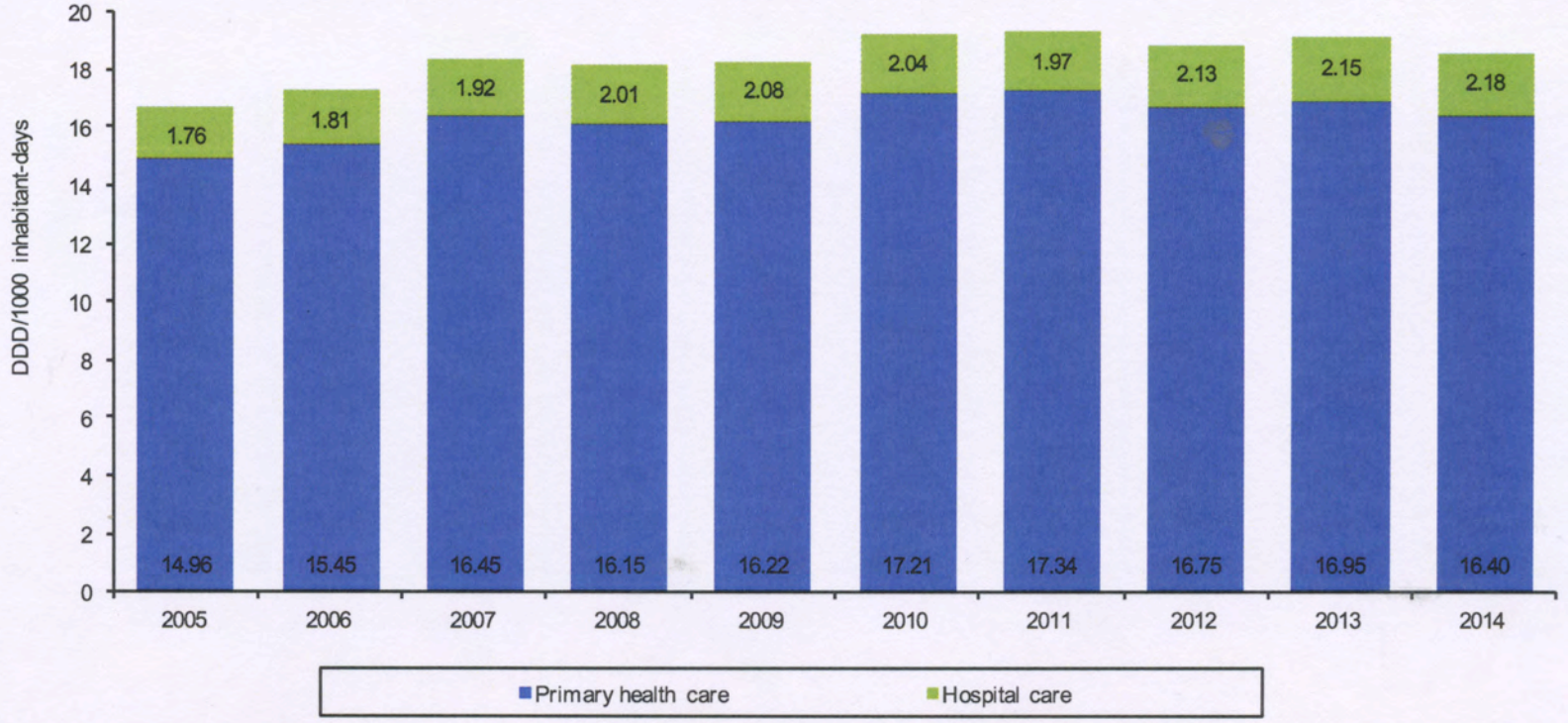


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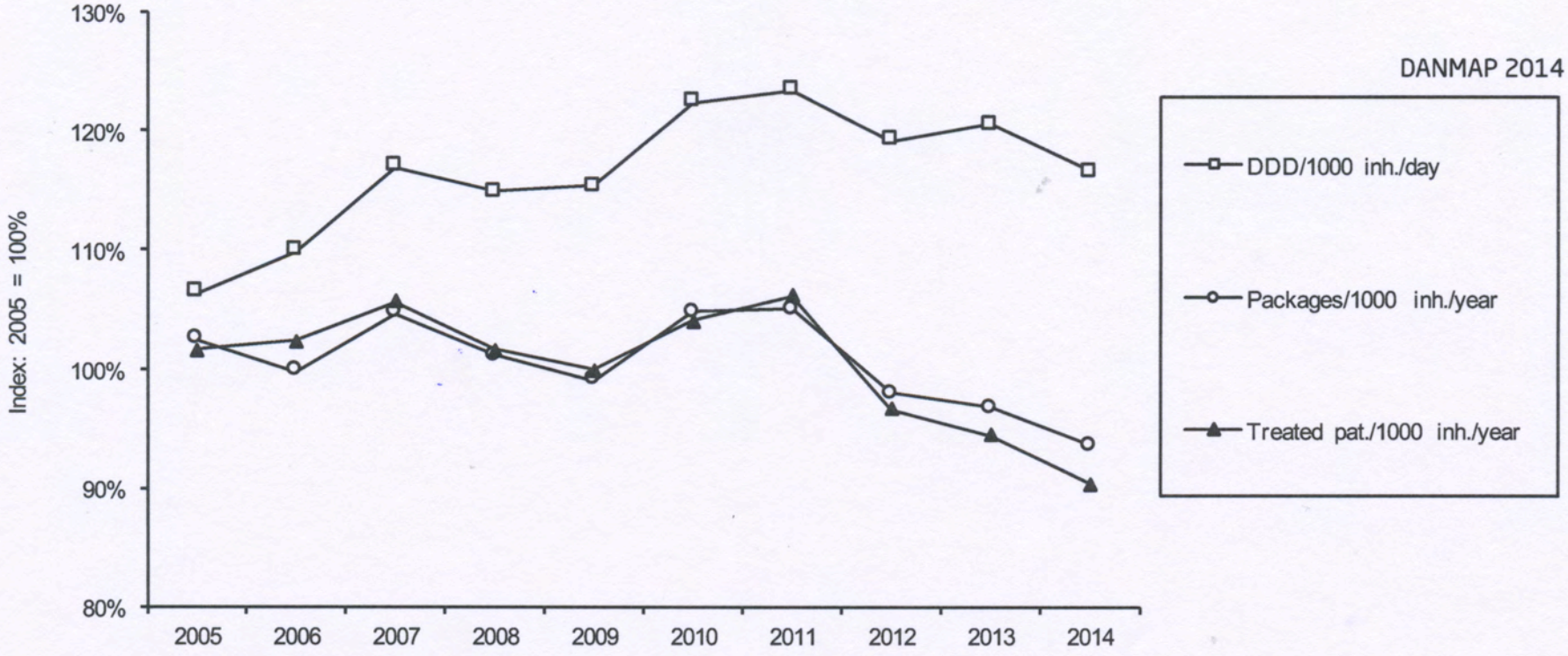
Figure 5.5. Indicators of antimicrobial consumption (J01) in primary health care, Denmark



DANMAP 2014

Muscat et al. Patterns of antibiotic use in the community in Denmark. Scand. J. Infect. Dis. 38:597-603; 2006 (questionary to 3000 persons in 2003, Copenhagen, Frederiksborg, Fyn, Aarhus)

VUGGESTUE/BØRNEHAVE-SMITTE-RESPIRATIONSVEJSINFEKTIONER

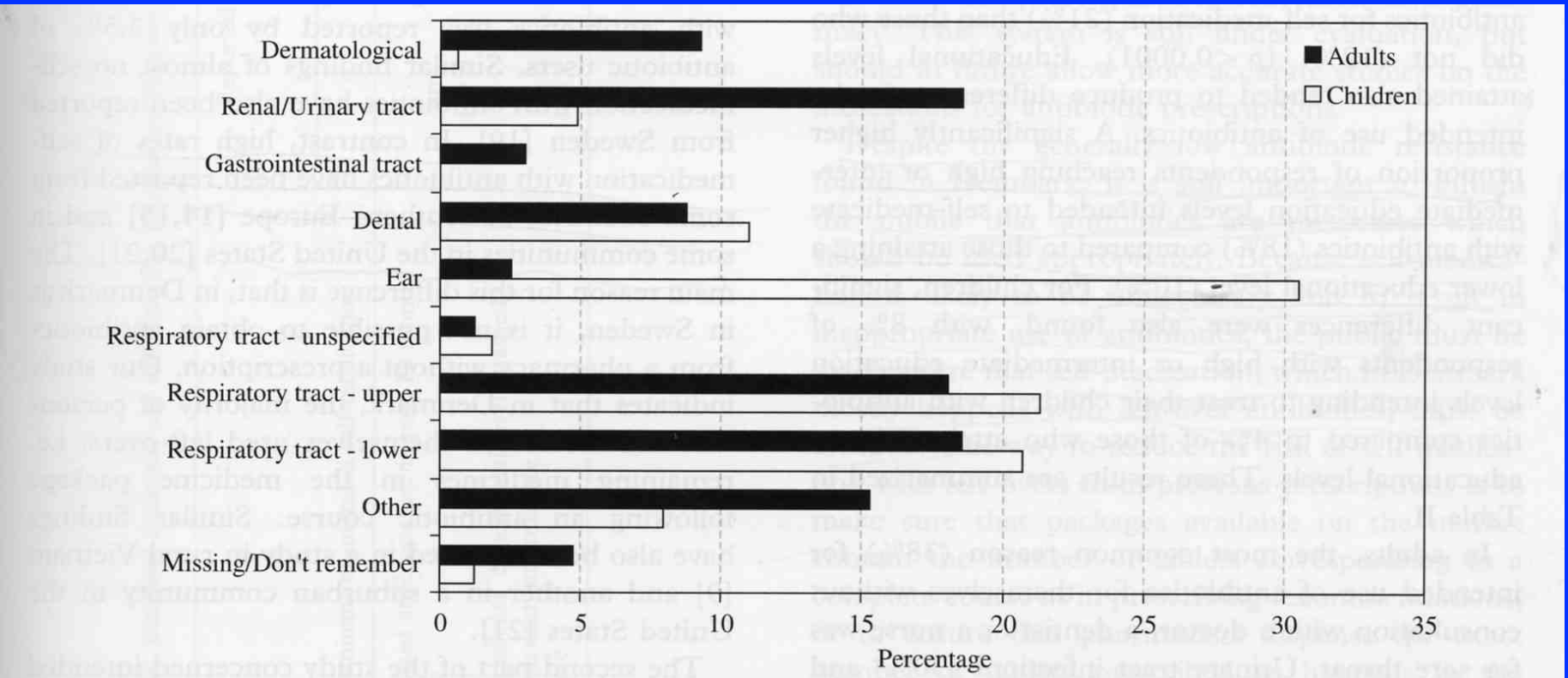


Figure 1. Reported reasons for using prescribed antibiotics in adults ($n = 399$) and children ($n = 164$) grouped by site of infection. There may be more than 1 site of infection per person.

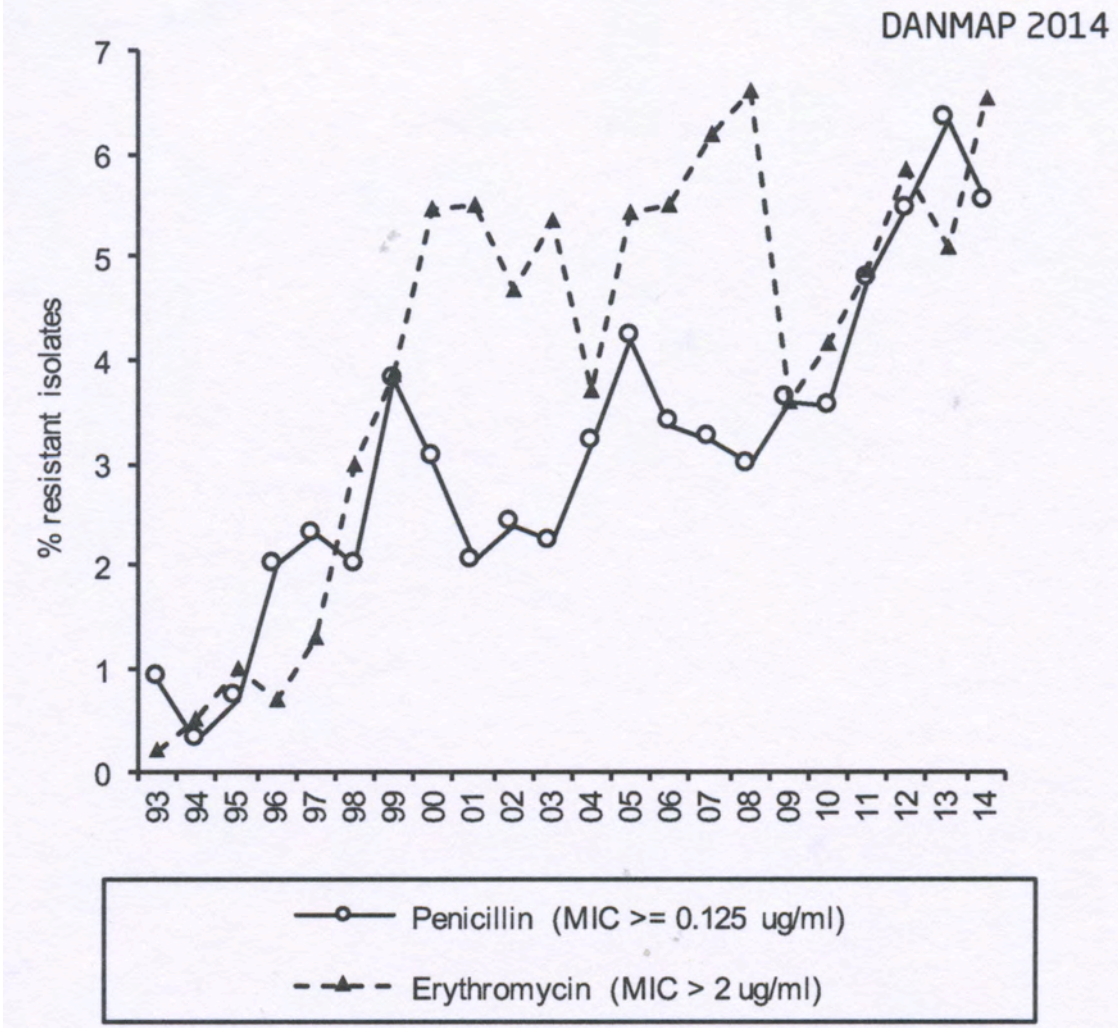
Antibiotikaresistens i Danmark

- Sjældent MRSA (methicillin-resistente *S. aureus, 1-2%*)
- Sjældent penicillin-, macrolid- og tetracyklin-resistente *S. pneumoniae*
- Sjældent plasmid associeret extended spectrum β-lactamase (ESBL), aminoglycosid og florquinolon resistens - men stigende!
- Sjældent *S. pyogenes Gr. A* resistens
- Sjældent *H. influenzae* resistens

MEN

- Ofte β-lactamase producerende *S. aureus*
- Ofte ampicillin-, sulfa- og trimethoprim resistens i *E. coli*
- Ofte MRSE (methicillin-resistente *S. epidermidis*)
- Ofte β-lactamase producerende *M. catarrhalis*

Figure 8.8. Nonsusceptibility (%) in *Streptococcus pneumoniae* blood and spinal fluid isolates from humans, Denmark

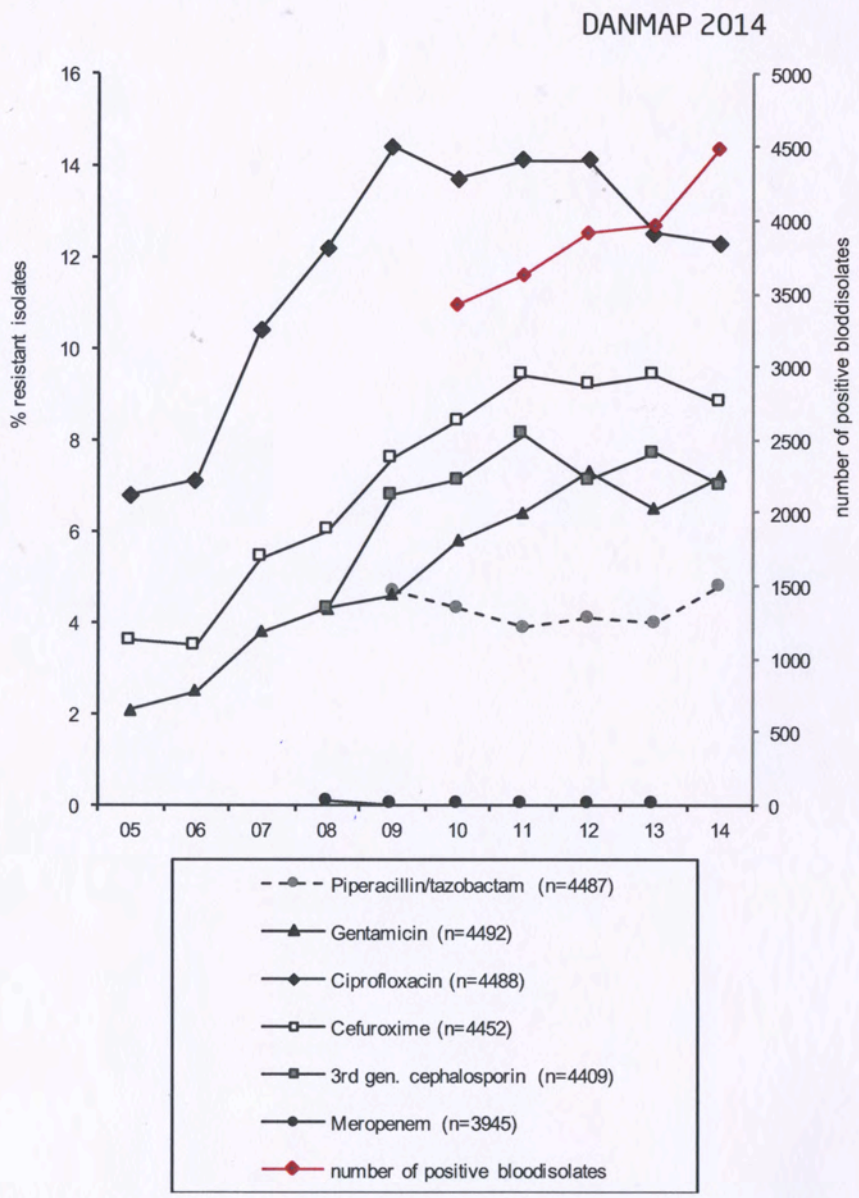


DANMAP 2014
1 stamme var højresistent (MIC>2µg/ml), resten var intermediær resistente (MIC 0,1,-1,0 µg/ml), hvor klinisk effekt kan opnås med højere beta-lamtamantibiotika dosis

Resist. Blodisol. 2014, DANMAP	S. aureus	E. coli	K. pneumoniae	P. aeruginosa
Methicillin	2,9%	x	x	x
Ampicillin	77%	45%	100%	x
Pip-tazo	2,9%	5%	8%	-4%
Sulfonamider	x	32%(urin)	19%(urin)	x
Mecillinam	x	8%	8%	x
Cefuroxim	2,9%	9%	12%	x
Ceftazidim o.a.	2,9%	7%	8%	≈4%
Meropenem	(2,9%- lav MIC)	<1%	<1%	≈4%
Gentamicin	2%(kanamycin)	7%	5%	2%
Ciprofloxacin	x	12%	7%	≈4%
Erythromycin	8%	x	x	x
Tetracyklin	5%	x	x	x
Fucidin	15%	x	x	x
Rifampicin	<1%	x	x	x
Linezolid	0%	x	x	x

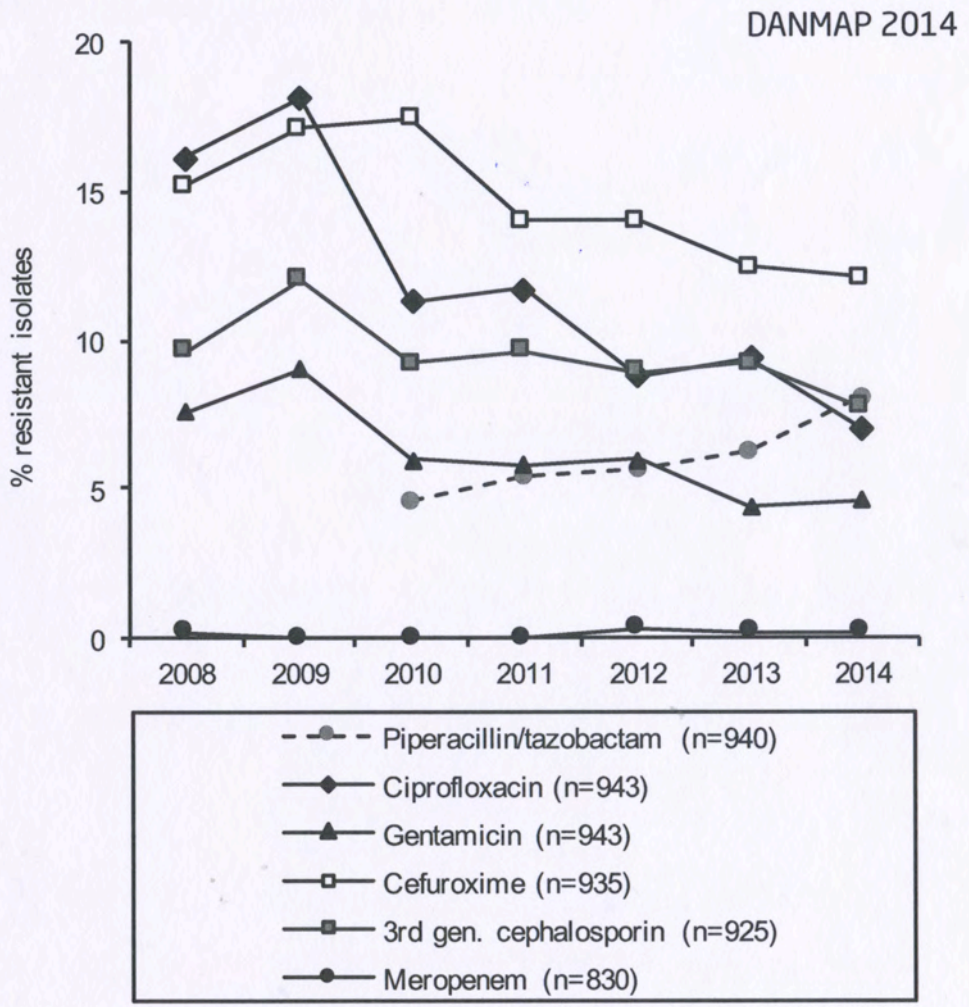
DANMAP 2014

Figure 8.1. Resistance (%) in *Escherichia coli* blood isolates from humans, Denmark



Note: The number (n) in parentheses represents the number of isolates

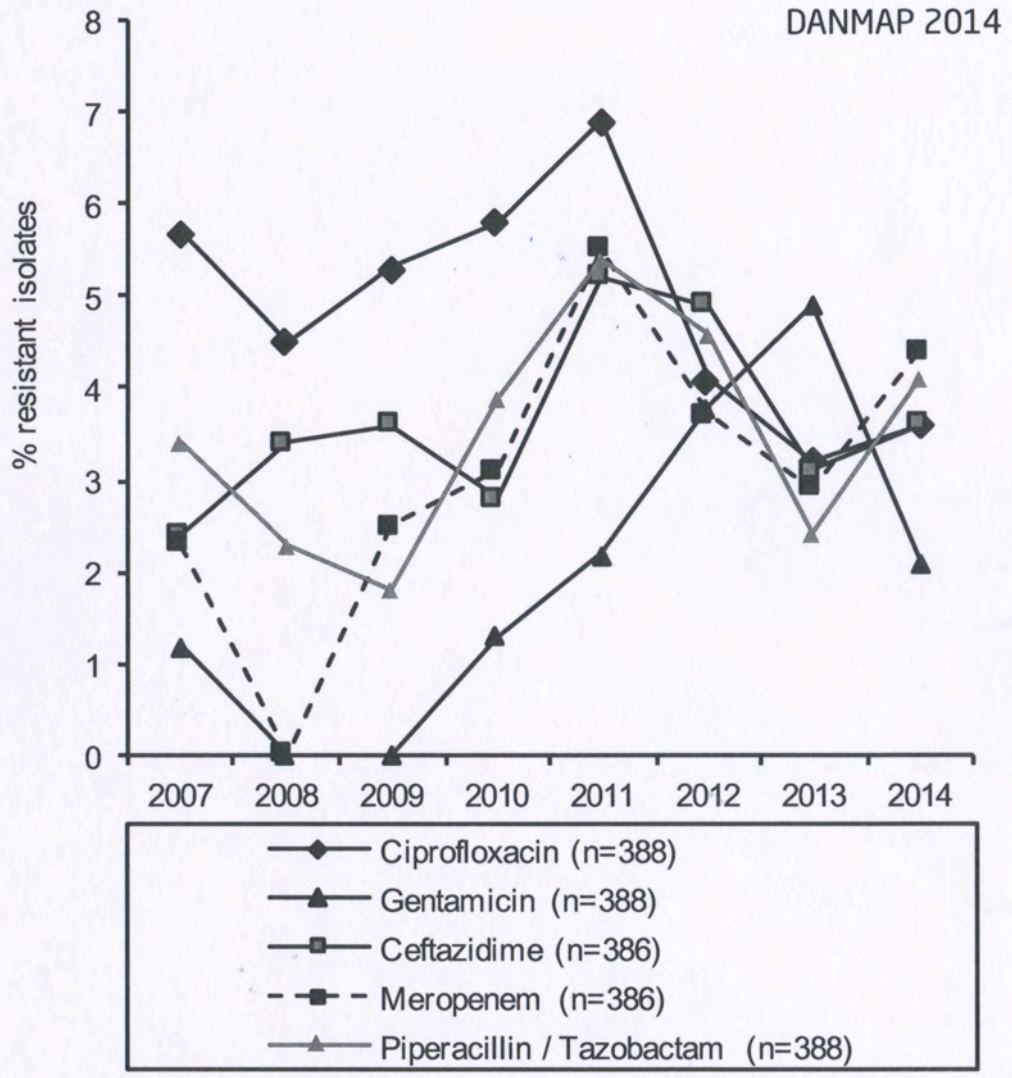
Figure 8.4. Resistance (%) in *Klebsiella pneumoniae* blood isolates from humans, Denmark



Note: The number (n) in parentheses represents the number of isolates tested for susceptibility in 2014.

DANMAP 2014

Figure 8.7. Resistance (%) in *Pseudomonas aeruginosa* blood isolates from humans, Denmark



Note: The number (n) in parentheses represents the number of isolates tested for susceptibility in 2014.

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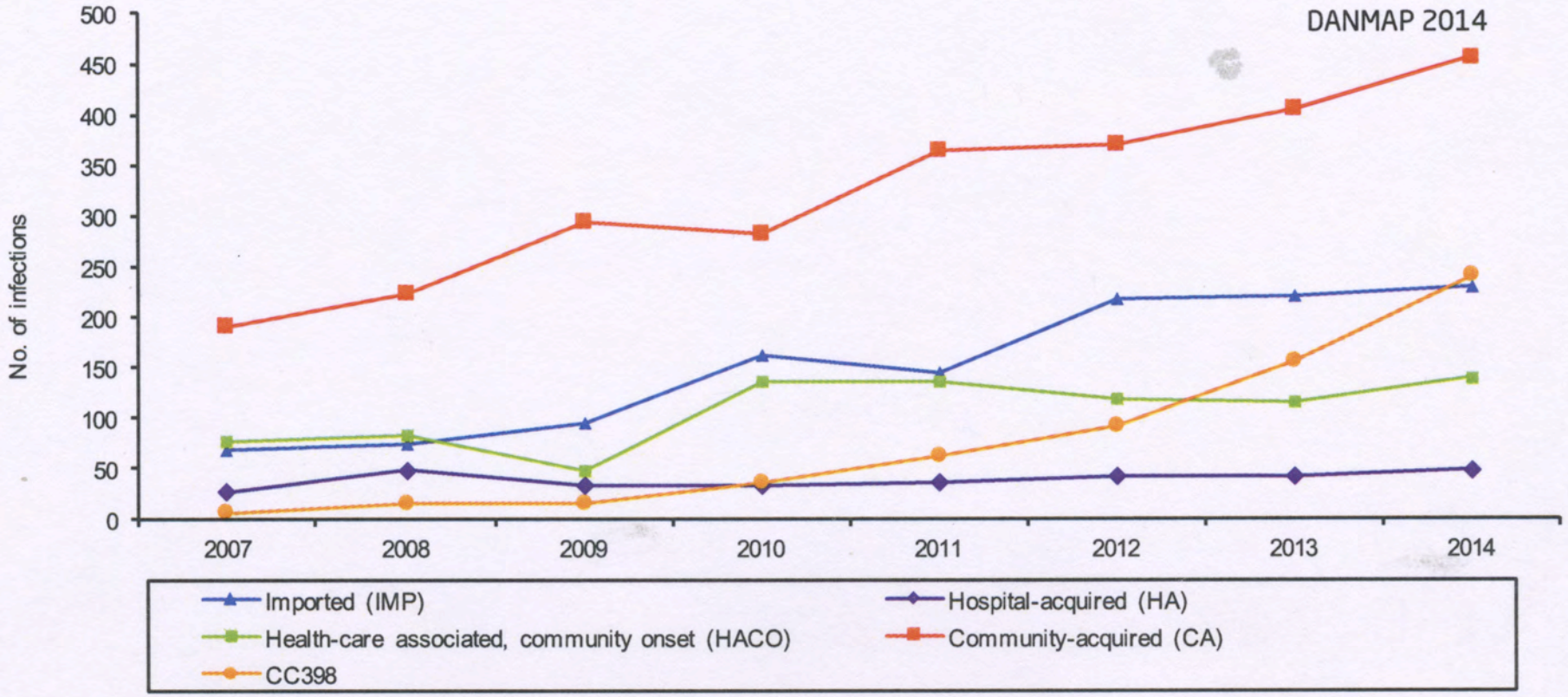
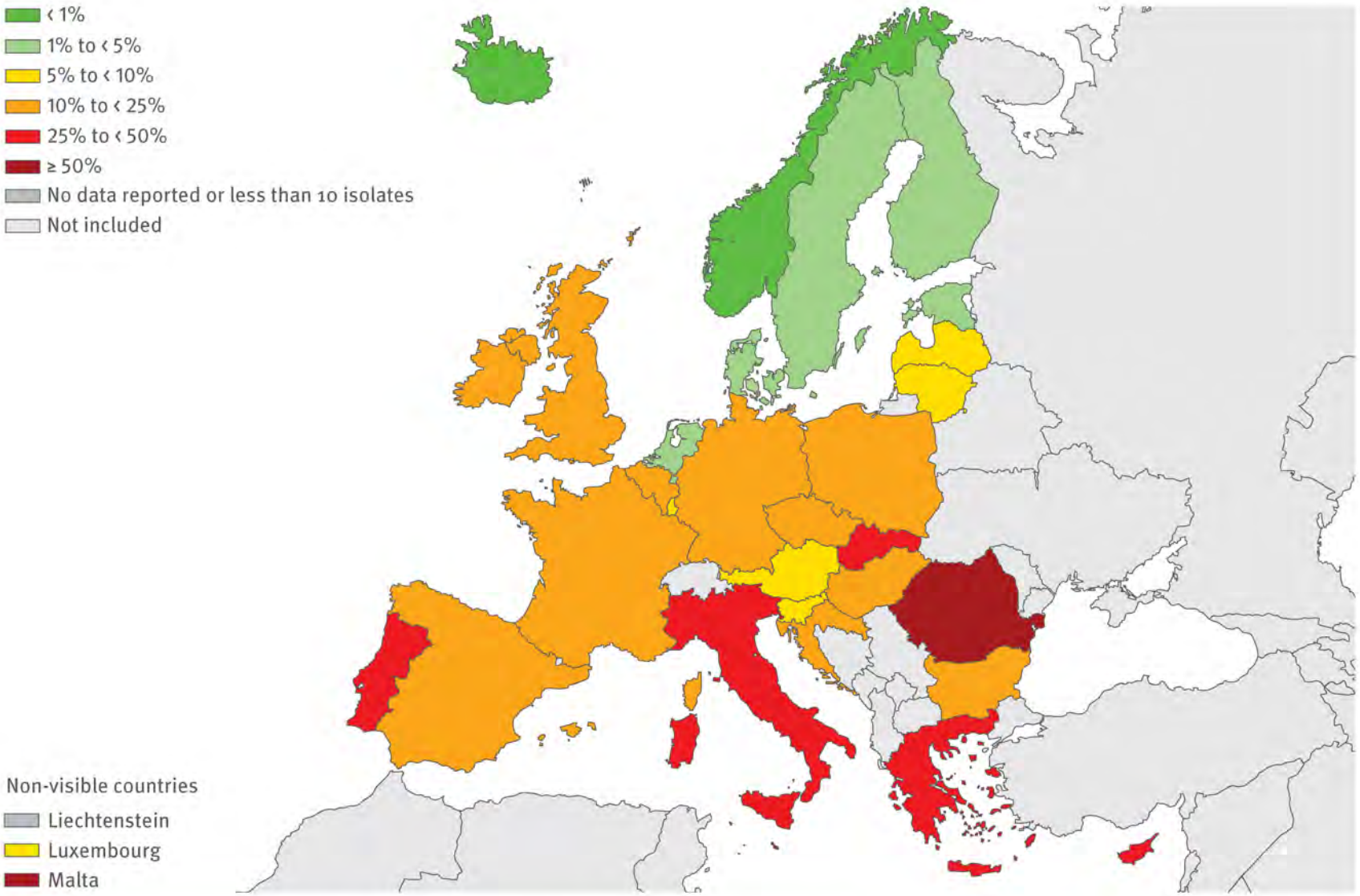
Figure 8.10. Number of MRSA infections according to epidemiological classification, Denmark

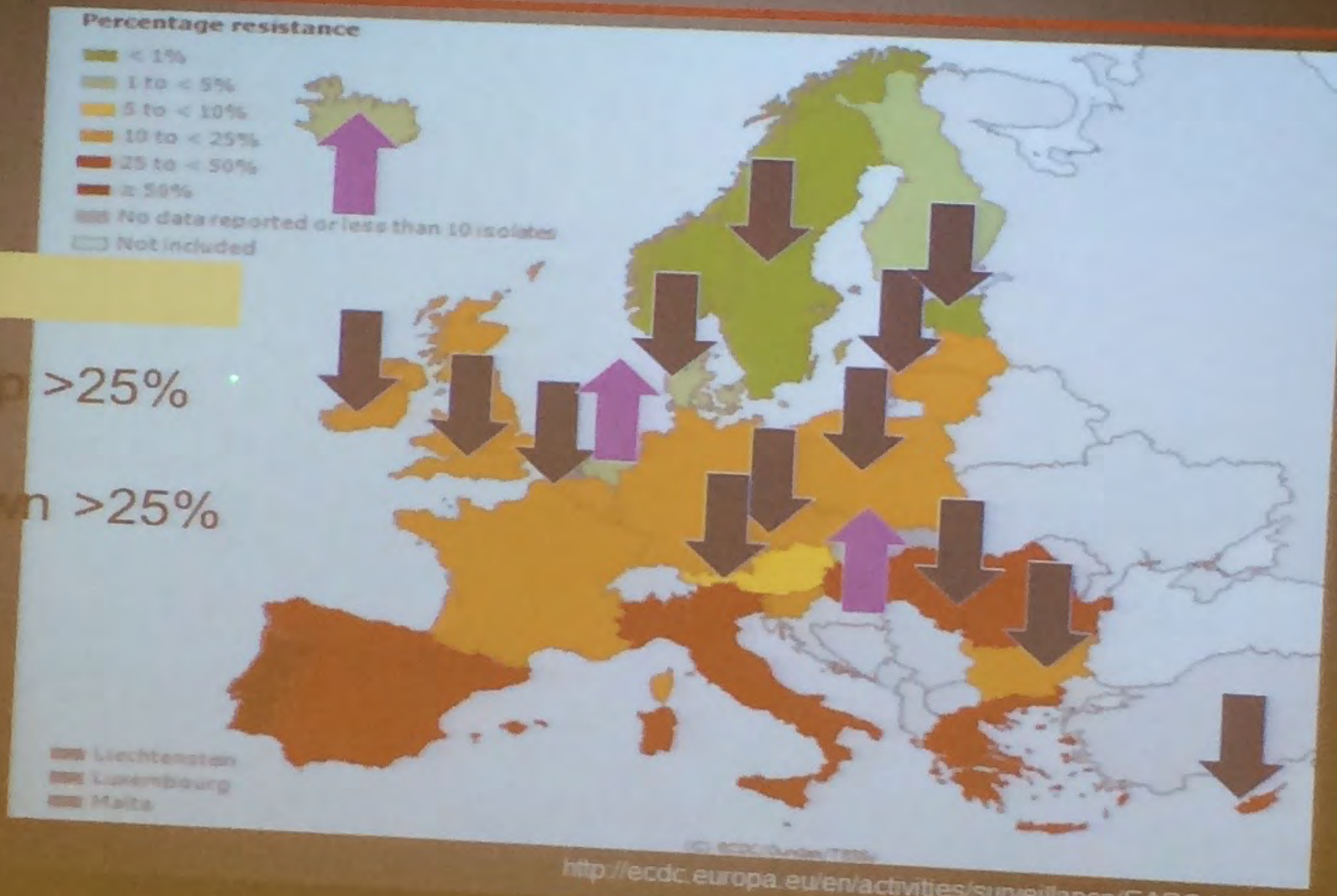


Staphylococcus aureus. Percentage (%) of invasive isolates resistant to meticillin (MRSA), by country, EU/EEA countries, 2013



Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2013. Stockholm: ECDC, 2014

MRSA as % of *S. aureus* bacteraemias 2013



Up >25%

Down >25%

http://ecdc.europa.eu/en/activities/surveillance/EARS-Net

Table 8.3. Resistance (%) in isolates from *S. aureus* bacteraemia cases, Denmark DANMAP 2014

Antimicrobial agent	2005 %	2006 %	2007 %	2008 %	2009 %	2010 %	2011 %	2012 %	2013 %	2014 %
Methicillin	1.6	1.4	0.6	1.3	1.6	1.4	1.4	1.2	1.7	2.9
Penicillin	78	80	78	77	77	75	77	74	76	77
Erythromycin	5	5	4	5	7	5	7	6	7	8
Clindamycin	4	4	3	4	6	4	6	6	6	8
Tetracycline	3	3	2	3	2	3	2	2	3	5
Fusidic acid	10	10	9	9	9	13	13	14	15	15
Rifampicin	<1	<1	<1	<1	<1	<1	<1	<1	0	<1
Norfloxacin	3	2	1	2	2	3	4	4	5	6
Kanamycin	2	1	<1	1	1	1	<1	1	2	2
Linezolid	nt	nt	nt	0	0	0	0	0	0	0
Mupirocin	0	0	<1	<1	<1	<1	<1	<1	<1	<1
Trimethoprim-sulfamethoxazole	nt	nt	nt	nt	nt	nt	<1	1	1	1

Note: nt = not tested. In web annex table A8.1 the distribution of MICs and resistance for all tested antimicrobial agents are shown.

Antimicrobial Resistance of *Staphylococcus aureus* Strains Acquired by Pig Farmers from Pigs

Anne Oppliger,[a] Philippe Moreillon,[b] Nicole Charrière,[a] Marlyse Giddey,[b] Delphine Morisset,[b] and Olga Sakwinska[b]*

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Carriage of animal-associated methicillin-resistant *Staphylococcus aureus* (MRSA) clonal complex 398 (CC398) is common among pig farmers. This study was conducted (i) to investigate whether pig farmers are colonized with pig-specific *S. aureus* genotypes other than CC398 and (ii) to survey antimicrobial resistance of *S. aureus* isolates from pigs and pig farmers. Forty-eight *S. aureus* isolates from pig farmers and veterinarians and 130 isolates from pigs collected in Western Switzerland were genotyped by *spa* typing and amplified fragment length polymorphism (AFLP). Antimicrobial resistance profiles were determined for representative sample of the isolates. The data obtained earlier on healthy *S. aureus* carriers without exposure to agriculture were used for comparison. The genotype composition of *S. aureus* isolates from pig farmers and veterinarians was similar to isolates from pigs with predominant AFLP clusters CC398, CC9, and CC49. The resistance to tetracycline and macrolides (clarithromycin) was common among the isolates from farmers and veterinarians (52 and 21%, respectively) and similar to resistance levels in isolates from pigs (39 and 23%, respectively). This was in contrast to isolates from persons without contact with agriculture, where no (0/128) isolates were resistant to tetracycline and 3% of the isolates were resistant to clarithromycin. MRSA CC398 was isolated from pigs ($n = 11$) and pig farmers ($n = 5$). These data imply that zoonotic transmission of multidrug-resistant *S. aureus* from pigs to farmers is frequent, and well-known MRSA transmission merely represents the tip of the iceberg for this phenomenon. We speculate that the relatively low frequency of MRSA isolation is related to lower antimicrobial use in Switzerland compared to, for example, the Netherlands.

Oppliger et al. Appl. Environm. Microbiol. 78:8010-14; 2012

MRSA er ikke multiresistente – de er faktisk lette at behandle, afgørende er det at den empiriske behandling er dækkende!

Table 8.6. Resistance (%) in CC398 MRSA and other MRSA cases, Denmark

pigs

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Clonal complex	CC398 %	other CC %	All cases %
Erythromycin	41	33	35
Clindamycin	89	23	33
Tetracycline	99	21	33
Fusidic acid	1	17	14
Rifampicin	0	<1	<1
Norfloxacin	28	27	27
Kanamycin	7	30	26
Linezolid	0	<1	<1
Mupirocin	0	<1	<1
Trimethoprim-sulfamethoxazole	1	3	3
Number of tested isolates	316	1616	1932

In web annex table A8.2 the distribution of MICs and resistance for all tested antimicrobials are shown.

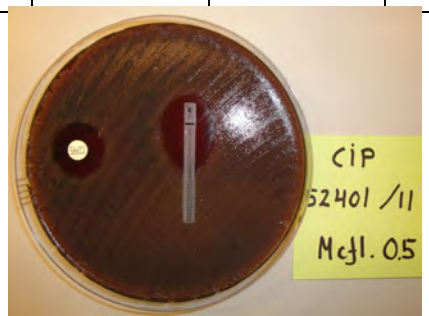
MSSA MICs MSSA MICs MRSA MICs MRSA MICs

E-test, Rosco diffusionszone og kløverblad (*Sarcina lutea* og i kryds *S. aureus*) på MSSA og MRSA *Staphylococcus aureus*
25-08-2014

17.10.11

McFarland 0,5,udsået med vatpind	**E-test µg/ml 52401/11**	**Rosco målt i mm 52401/11**	**E-test µg/ml 52232/11/11**	**Rosco målt i mm 52232/11**	**MRSA µg/ml E-test 51812/11**	**MRSA Rosco målt i mm 51812/11**	**MRSA µg/ml E-test 54793/11**	**MRSA Rosco målt i mm 54793/11**
XM Cefur 60µg	0,75/0,094µg/ml	45/32mm	0,75/0,125µg/ml	45/30mm	3µg/ml	26mm	2,0/0,5µg/ml	40/25mm
PTc Pip + Tazo 100µg+10µg	1,5µg/ml	26mm	0,75/0,094µg/ml	40/32mm	16µg/ml	22mm	2,0µg/ml	26mm
PP Piperacillin	1,5µg/ml	Ingen tablet	0,094/0,5µg/ml	Ingen tablet	64µg/ml	Ikke udført	24µg/ml	Ikke udført
MP Mero 10µg	0,047µg/ml	45/35mm	0,32/0,094µg/ml	45/35mm	0,38µg/ml	35/32mm	0,125µg/ml	40/32mm
Tz Cefta 30µg	6,0/3,0µg/ml	32/24mm	6,0/3,0µg/ml	31/23mm	16µg/ml	18mm	12/6,0µg/ml	25/19mm
TX Ceftrix 30µg	3,0/0,25µg/ml	37/28mm	3,0/0,38µg/ml	35/25mm	>32µg/ml	18mm	>32/2µg/ml	32/18mm
XL Am+Cl 30µg+15µg	0,5µg/ml	40/32mm	0,19/0,064µg/ml	41/32mm	2µg/ml	26mm	1,0µg/ml	36/30mm
ME Methi	Ingen E-test	38/25mm	Ingen E-test	38/30mm	Ingen E-test	22mm	Ingen E-test	27/23mm
Cefpodoxime 10µg	Ingen E-test	35/23mm	Ingen E-test	34/22mm	Ingen E-test	Ikke udført	Ingen E-test	Ikke udført
PG Penicillin 5µg	0,38µg/ml	18mm	0,023µg/ml	44/32mm	16µg/ml	0	8µg/ml	0
	Bloddyrkning, 140811-6240 P:0, ellers følsom		Bloddyrkning, 111045-1098 følsom for alt		Næsepodning, 191287-1868 P:0, M:0, ellers følsom		Perineum podning, 101246-0828 P:0, M:0, Azithromycin:1, Clinda:1	

1



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Journal of Antimicrobial Chemotherapy

Spread of multidrug-resistant *Enterococcus* to animals and humans: an underestimated role for the pig farm environment

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Objectives: The aim of this study was to discover the potential role of the pig farm environment in the spread of multidrug-resistant (MDR) *Enterococcus* strains, including high-risk clones, to animals and humans.

Methods: *Enterococcus* isolates were recovered from a variety of samples ($n=82$; swine, feed/medicines/antiseptics and pig farm facilities) from six Portuguese farms, most using antibiotics. Antimicrobial susceptibility/conjugation assays were performed by standard procedures, bacterial identification/screening of antibiotic resistance genes were performed by PCR and clonality was determined using PFGE/multilocus sequence typing.

Results: *Enterococcus* isolates resistant to antibiotics ($n=473$) were recovered from samples of different origin (swine, feed/antiseptics, animal residues and pig farm facilities), but only the clinically relevant species *Enterococcus faecium* ($n=171$) and *Enterococcus faecalis* ($n=78$) were included for further comprehensive molecular analysis. Isolates resistant to vancomycin, ampicillin, tetracyclines, erythromycin and aminoglycosides were better recovered in Slanetz–Bartley medium with these antibiotics present than in media not supplemented with antibiotics ($P<0.05$). *E. faecium* was more frequently resistant to ampicillin, ciprofloxacin or nitrofurantoin and *E. faecalis* to tetracyclines, chloramphenicol or aminoglycosides ($P<0.05$). Glycopeptide and erythromycin resistance rates were similar in both species. The transfer of resistance to several antibiotics, including vancomycin and ampicillin, was demonstrated. Clones associated with human infections were detected in different samples from the same farm [*E. faecium* from sequence type (ST) 78 lineage and *E. faecalis* ST16; manure, waste lagoons, faeces and drinking water] and in geographically distant farms [*E. faecium* clonal complex (CC) 5; *E. faecalis* CC21 and ST16].

Conclusions: The pig farm environment has an underestimated potential role in the transmission of MDR *Enterococcus* to animals and, possibly, to humans. The continuous contact of swine with MDR *Enterococcus* by different routes (e.g. feed, dust, air and rooms) might decrease the impact of restrictive antibiotic use policies and reinforces the need for different and preliminary interventions at the husbandry management level.

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MINIREVIEW

Public Health Risks of Multiple-Drug-Resistant *Enterococcus* spp. in Southeast Asia

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Enterococci rank as one of the leading causes of nosocomial infections, such as urinary tract infections, surgical wound infections, and endocarditis, in humans. These infections can be hard to treat because of the rising incidence of antibiotic resistance. Enterococci inhabiting nonhuman reservoirs appear to play a critical role in the acquisition and dissemination of antibiotic resistance determinants. The spread of antibiotic resistance has become a major concern in both human and veterinary medicine, especially in Southeast Asia, where many developing countries have poor legislation and regulations to control the supply and excessive use of antimicrobials. This review addresses the occurrence of antibiotic-resistant enterococci in Association of Southeast Asian Nations countries and proposes infection control measures that should be applied to limit the spread of multiple-drug-resistant enterococci.

Appl. Envir. Microb. 81:6090-97; 2015

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Journal of Antimicrobial Chemotherapy

Multiple hospital outbreaks of *vanA Enterococcus faecium* in Denmark, 2012–13, investigated by WGS, MLST and PFGE

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Objectives: In Denmark, the incidence of vancomycin-resistant *Enterococcus faecium* (VREfm) has increased since 2012. The aim of this study was to investigate the epidemiology and clonal relatedness of VREfm isolates in Danish hospitals in 2012–13 using WGS. The second aim was to evaluate if WGS-based typing could replace PFGE for typing of VREfm.

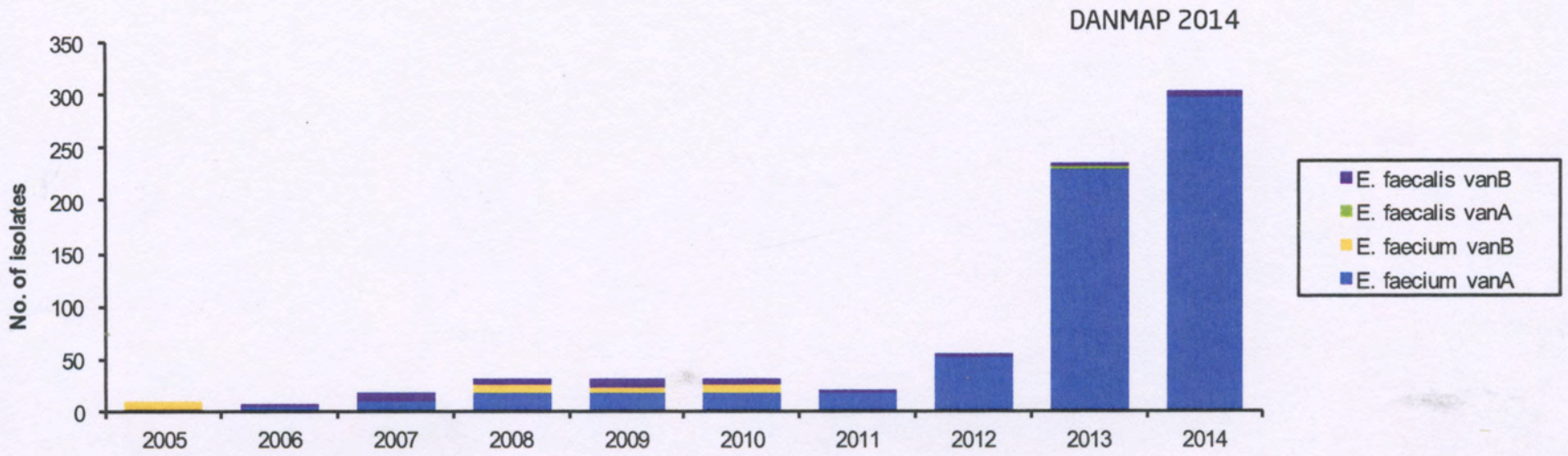
Methods: A population-based study was conducted including all VREfm isolates submitted for national surveillance from January 2012 to April 2013. All isolates were investigated by WGS, MLST and PFGE.

Results: One-hundred and thirty-two isolates were included. The majority of the isolates were from clinical samples (77%). Gastroenterology/abdominal surgery (29%) and ICUs (29%) were the predominant departments with VREfm. Genomics revealed a polyclonal structure of the VREfm outbreak. Seven subgroups of 3–44 genetically closely related isolates (separated by <17 SNPs) were identified using WGS. Direct or indirect transmission of VREfm between patients and intra- and inter-regional spreading clones was observed. We identified 10 STs. PFGE identified four major clusters (13–43 isolates) and seven minor clusters (two to three isolates). The results from the typing methods were highly concordant. However, WGS-based typing had the highest discriminatory power.

Conclusions: This study emphasizes the importance of infection control measures to limit transmission of VREfm between patients. However, the diversity of the VREfm isolates points to the fact that other important factors may also affect the VREfm increase in Denmark. Finally, WGS is suitable for typing of VREfm and has replaced PFGE for typing of VREfm in Denmark.

Keywords: surveillance, resistance, typing methods

Figure 1. Numbers of vancomycin resistant *Enterococcus faecium* and *Enterococcus faecalis* isolates from clinical samples and van genes, Denmark



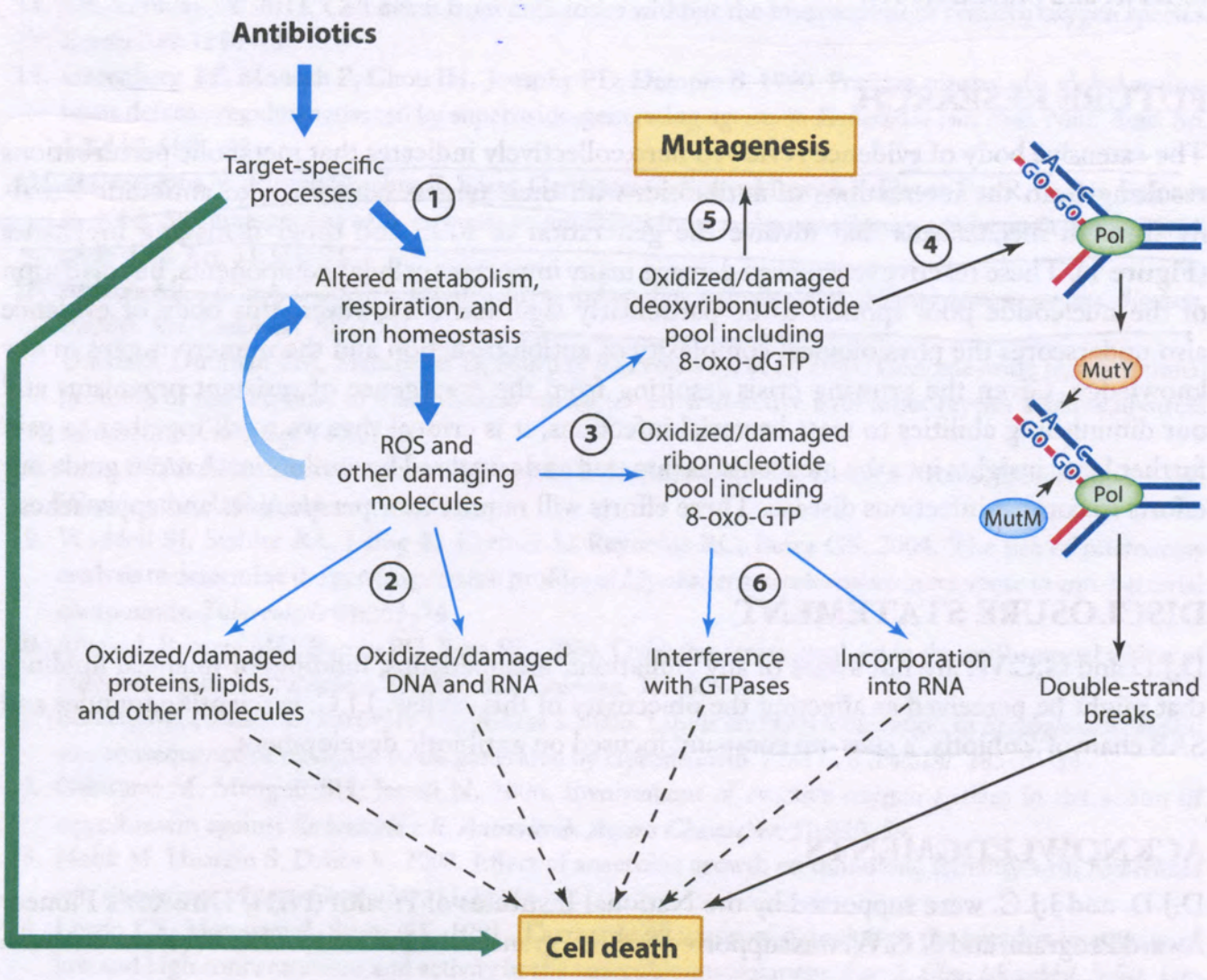
Optimal antibiotika behandling

- Forebyggelse af resistensudvikling - hos den ætiologiske bakterie
- Forebyggelse af resistensudvikling - normalfloraen er meget vigtig pga. horisontal genoverførsel vha. konjugation og transformation!

Udvikling af resistens under antibiotika behandling

- Gennemgang af 173 studier med 14.000 patienter, 8 antibiotika klasser, 225 individuelle behandlingsregimer
- Forekomst af resistente mikroorganismer
  - 4% af alle mikroorganismer (sjældent)
  - 6% af alle infektioner
  - Hyppigere når der benyttes monoterapi med penicillin og aminoglycosid (p=0.0002)
  - Sjældnere med imipenem (p=0.03), aztreonam (p=0.0001) og kombinationsterapi (p=0.001)

Fish et al. Pharmacother. 15:279-91,1995



Dwyer, Collins, Walker: Unraveling the physiological complexities of antibiotic lethality. Ann. Rev. Pharmacol. Toxicol. 55:1-20; 2015

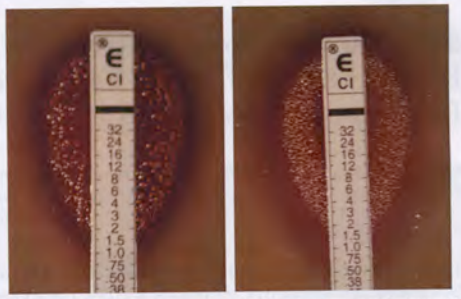


FIG 1 Characterization of the susceptibility to ciprofloxacin of the bacterial population and assignment of population MIC values. To distinguish between different sizes of the resistant subpopulations that grew in the inhibition zone, four descriptive entities were defined: (i) "double zone" if the resistant colonies exhibit a confluent growth, (ii) +++ if the number of colonies was higher than 100, (iii) ++ if the number of colonies was between 10 and 100, and (iv) + if fewer than 10 colonies were present. The descriptions of the two bacterial populations in this figure are thus as follows: in the left panel, the population MIC is 1.5 μg/ml, there is no double zone (dz−), and the size of the resistant subpopulation is +++; in the right panel, the population MIC is 1.5 μg/ml, a double zone is present until 12 μg/ml (dz 12), and resistant colonies in the inhibition zone are also present (+).

Jørgensen. K.M., Wassermann, T., Jensen, P.Ø., Wang, H., Molin, S., Høiby, N., Ciofu, O.: Sub-lethal ciprofloxacin treatment leads to rapid development of high-level ciprofloxacin resistance during long-term experimental evolution of Pseudomonas aeruginosa. Antimicrob. Agents Chemother.57:4215-4221; 2013.

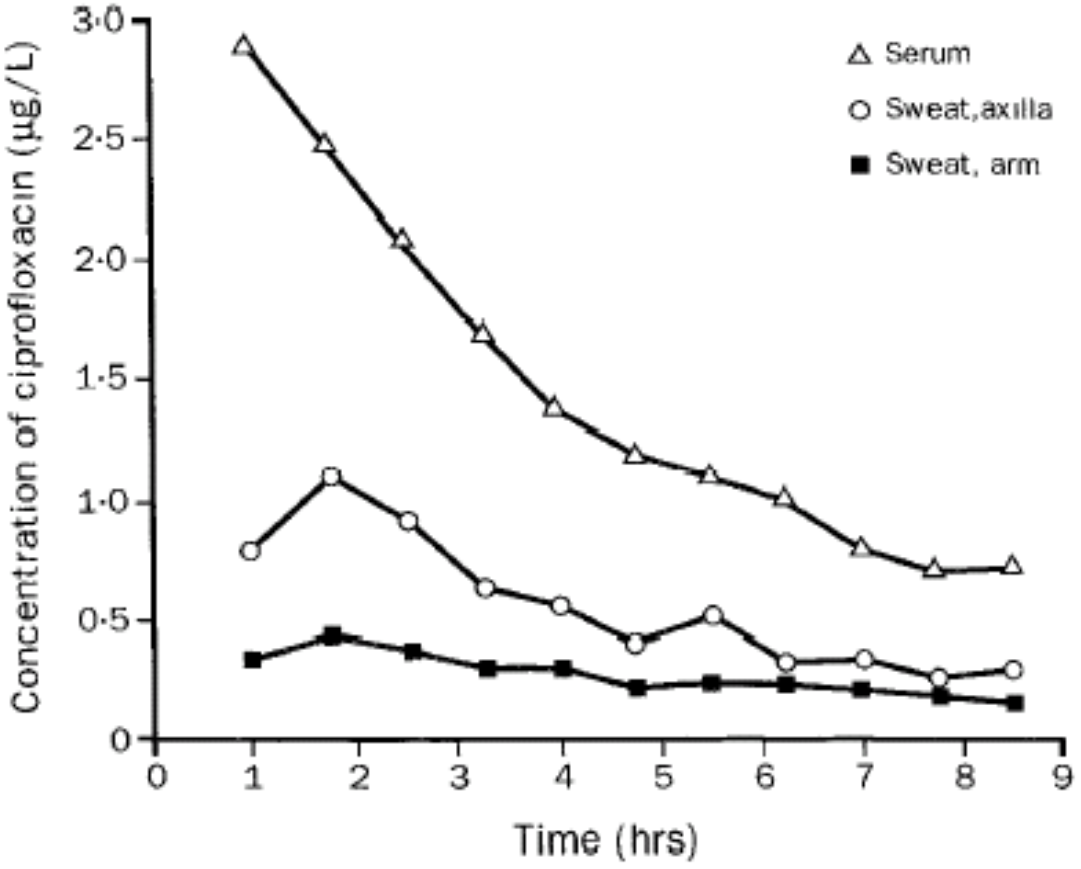
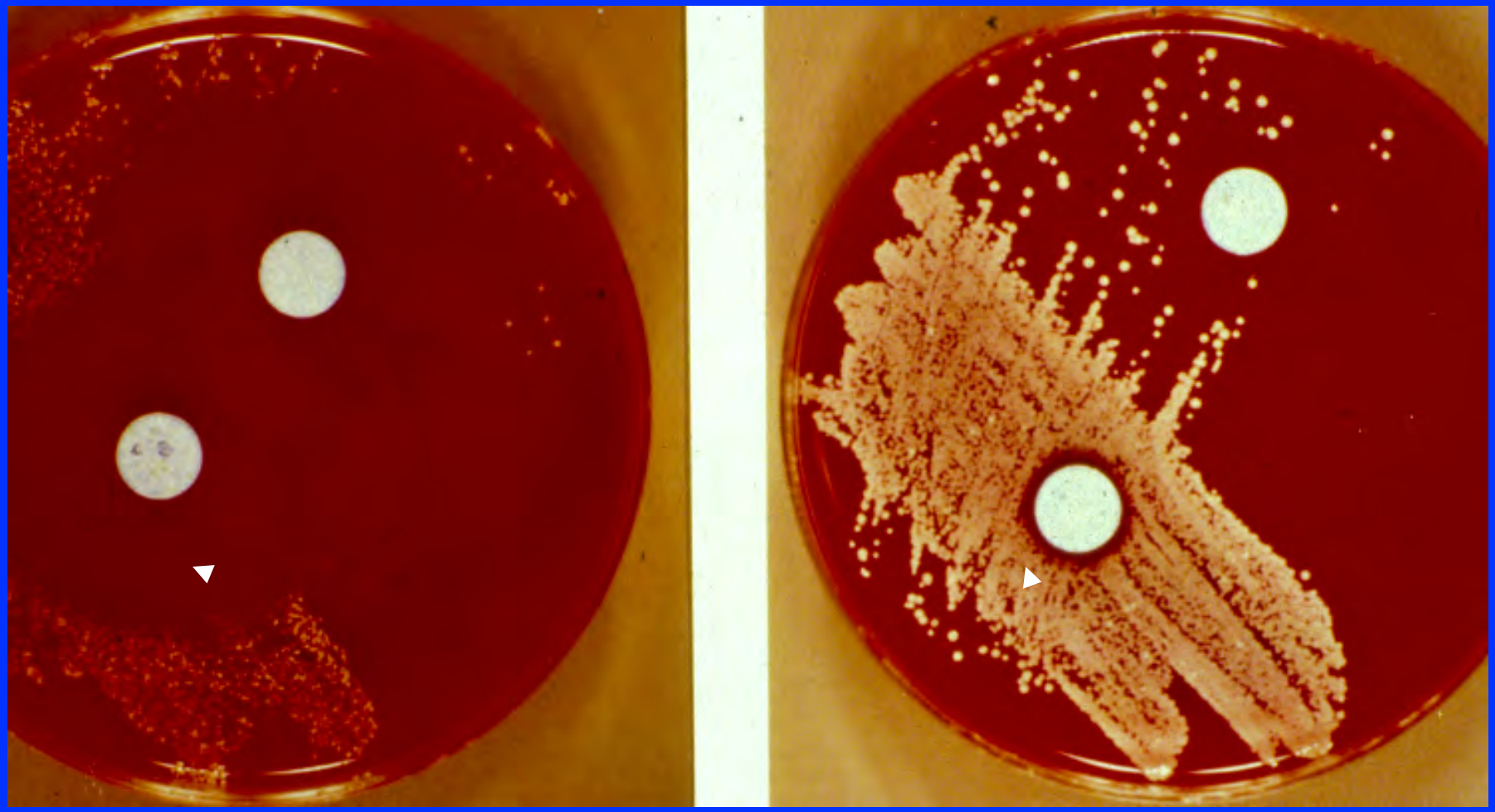


Figure: **Ciprofloxacin concentrations in serum and sweat**
Mean of ciprofloxacin concentrations in serum and sweat obtained from axilla and volar surface of the forearm after 750 mg orally in 6 normal persons. For comparison: MIC_{90} of bacterial species of the skin flora (µg/mL): *S aureus:* 0·5, *S epidermidis:* 0·25, *Propionibacterium* species: 0·50, *C jeikeium:* 1·0. No antibacterial activity of sweat was detectable before intake of ciprofloxacin.

Høiby et al. Lancet, 346:1235,1995



Ciprofloxacin og *S. epidermidis* fra axillen før og 3 dage efter start på behandling med ciprofloxacin p.o. til normal KMA læge

Høiby et al. Lancet 1997;349:167-9

Development of resistance to antibiotics occurs very rapid in the normal flora of the skin during therapy with antibiotics which are excreted into the sweat

MIC before treatment (µg/mL)	MIC of resistant strains (µg/mL)	Mean number of: Resistant strains per person (34 swabs)	Resistant isolates§ per person (axilla/nose)	Days to appearance of resistant isolates (axilla/nose)	Days to disappearance of last resistant isolates (axilla/nose)
0·13–0·38*	Intermediate 4–12† High >32‡	2·7 (range 2–3)	18/11 (range 3–32/3–24)	2·7/18‖ (range 1–7/8–34)	37/39** (range 7–62/20–62)

*Sensitive to all antibiotics tested. †Also resistant to methicillin. ‡Also resistant to methicillin, erythromycin, sulphonamide, trimethoprim, and gentamicin. §One swab may contain more than one resistant isolate. ‖After start of treatment. **After end of treatment.

S. epidermidis: Development of resistance to ciprofloxacin in isolates from 6 persons treated for 7 days. Molecular mechanism: Genta: *aac(6')-aph(2")*; Meth: *mecA*; Ery: *erm(C); C*ipro: mutations in *gyrA, parC, gyrB*
Whole genomes sequenced by Anders Rhod Larsen & Andreas Petersen, SSI

Høiby et al. Lancet 1997, 349,167-9

Fluoroquinolones and the Risk for Methicillin-resistant *Staphylococcus aureus* in Hospitalized Patients[1]

Stephen G. Weber,* Howard S. Gold,* David C. Hooper,† A.W. Karchmer,* and Yehuda Carmeli*

To determine whether fluoroquinolone exposure is a risk factor for the isolation of *Staphylococcus aureus* and whether the effect is different for methicillin-resistant *S. aureus* (MRSA) versus methicillin-susceptible *S. aureus* (MSSA), we studied two case groups. The first case group included 222 patients with nosocomially acquired MRSA. The second case group included 163 patients with nosocomially acquired MSSA. A total of 343 patients admitted concurrently served as controls. Outcome measures were the adjusted odds ratio (OR) for isolation of MRSA and MSSA after fluoroquinolone exposure. Exposure to both levofloxacin (OR 5.4; $p < 0.0001$) and ciprofloxacin (OR 2.2; $p < 0.003$) was associated with isolation of MRSA but not MSSA. After adjustment for multiple variables, both drugs remained risk factors for MRSA (levofloxacin OR 3.4; $p < 0.0001$; ciprofloxacin OR 2.5; $p = 0.005$) but not MSSA. Exposure to levofloxacin or ciprofloxacin is a significant risk factor for the isolation of MRSA, but not MSSA.

Fluoroquinolones are among the most commonly prescribed classes of antimicrobial drugs in both the hospital and in the community. Ciprofloxacin, one of the first fluoroquinolones to gain extensive clinical use, was originally heralded for its activity against a broad range of pathogens, including MRSA (7). However, by the early 1990s, many MRSA isolates from clinical specimens were found to be resistant to ciprofloxacin (8). The next generation of fluoroquinolones, including levofloxacin, was introduced during the second part of the 1990s and promised improved activity against gram-positive pathogens. Unfortunately, screening of large numbers of staphylococcal bloodstream isolates as part of the SENTRY Antimicrobial Surveillance Program demonstrated resistance to many of the newest fluoroquinolones as well (9).

Several recent investigations offer preliminary evidence that suggests that the fluoroquinolones themselves

Resistensudvikling hos *E. coli* i tarmfloraen under peroral ampicillinbehandling – selektion for multiresistens på plasmider

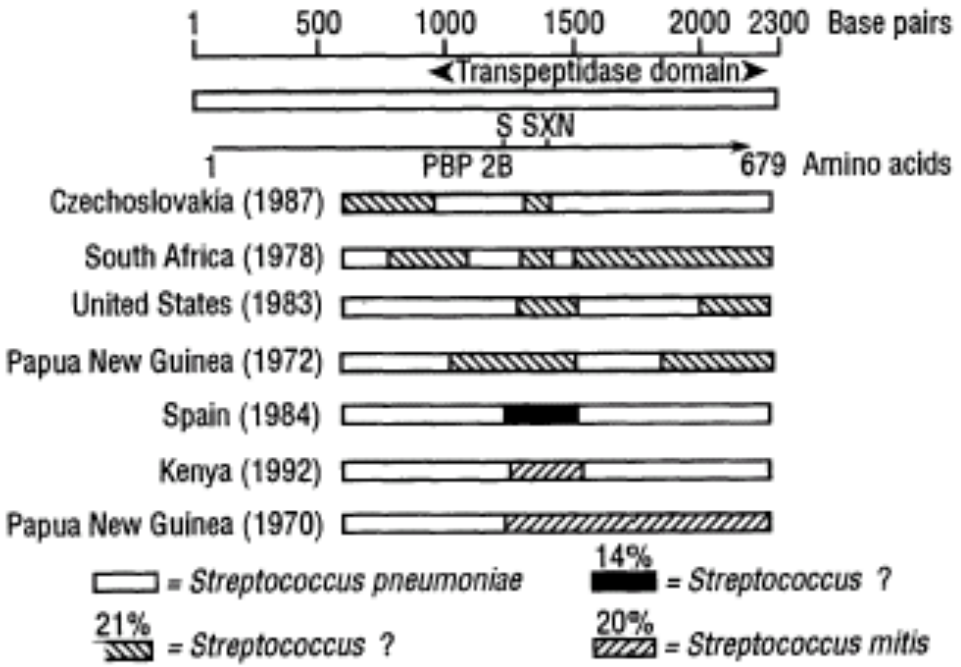
::

	Før beh.	Dag 1 og 2	Dag 3-5	Dag 6-8	Dag 9-11	Efter 11 dage
Antal *E. coli* stammer	**22**	10	6	4	3	**4**
Resistent for Ap (%)	**9**	20	50	50	100	**100**
Multiresistent (%)	**18**	40	50	50	100	**100**
Konjugativ resistens (%)	18	20	50	50	100	100
Stammer med plasmider (%)	86	70	83	75	100	100
Strammer med plasmider større end 12 Mdal (%)	73	60	67	75	100	100

Laufs et al. Excerpta Medica ICS 477:74,1979

Resistensudvikling i orale streptokokker og overførsel af resistensen til Pneumokokker ved transformation af frigivet DNA

Fig. 2. Mosaic PBP 2B genes in penicillin-resistant pneumococci. The divergent regions in the PBP 2B genes of seven resistant pneumococci from different countries are shown. These regions have been introduced from at least three sources, one of which appears to be *S. mitis*. The approximate percent sequence divergence of the divergent regions from the PBP 2B genes of susceptible pneumococci is shown. The figure was drawn from data in (*20, 21*).



Resistensoverførsel ved transformation i *S. mutans*, som laver biofilm på tænder (plaques) er styret af et quorum-sensing peptid pheromone signal system og er 10-600 x hyppigere end i planktonisk voksende bakterier

Spratt. Science 1994;264:388-93
Li et al. J. Bact. 183:897-908; 2001

	Risiko for svælgfloraen			Risiko for colonfloraen		
	Høj	Moderat	Lav	Høj	Moderat	Lav
Orale antibiotika	Tetra	V-pen	Clinda	Tetra	Ery	V-pen
		bac/piv-Amp	Metro			bac/piv-Amp
		Ery	Kinol			Clinda
						Metro
						Kinol
Parenterale antibiotika		Ery	G-pen		G-pen	Thien
		Amp	Pip		Amp	Clinda
			Aztreonam		Pip	Metro
			Cefoxitin		Aztreonam	
			Ceftriaxon		Cefoxitin	
			Clinda		Ceftriaxon	
			Metro			

Antibiotikaforkortelser som i Tabel 1, endvidere: V-pen: V-penicillin, bac/piv-Amp: bacampicillin og pivampicillin, som absorberes bedre end almindeligt ampicillin.

- Risiko for resistensudvikling i de aerobe fakultative bakterier i normalfloraen under eller efter behandling med forskellige antibiotika i standarddosering

(modificeret efter Nord et al 1986)

(Sllivan, Edlund, Nord. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect. Dis. 1:101-114; 2001)

(Rashid, Weintraub, Nord. Effect of new antimicrobial agents on the ecological balance of human midroflora.Anaerobe 18:249-53; 2012)

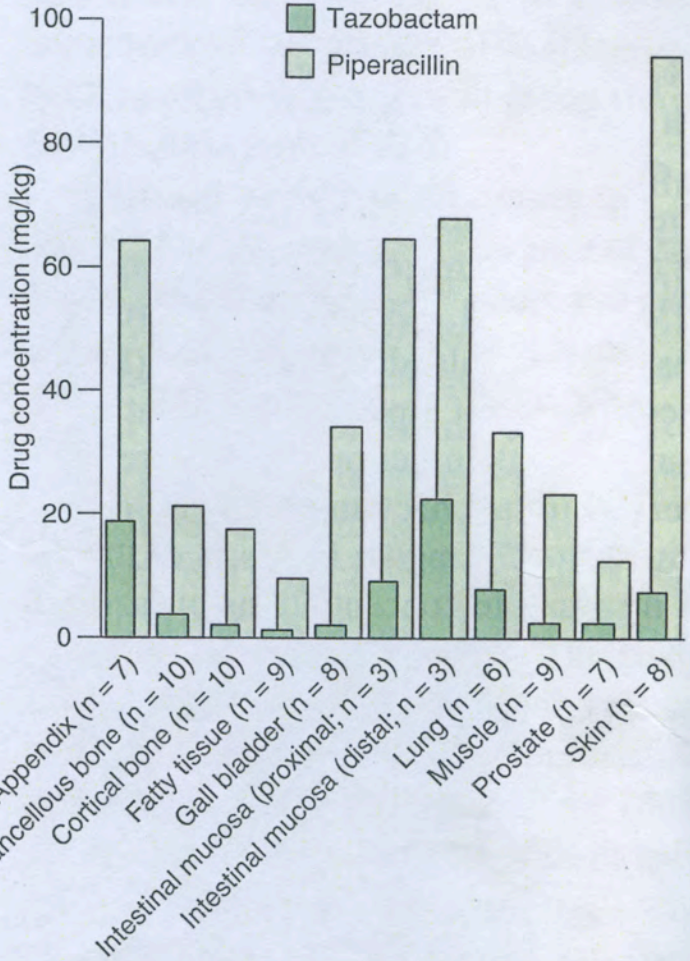
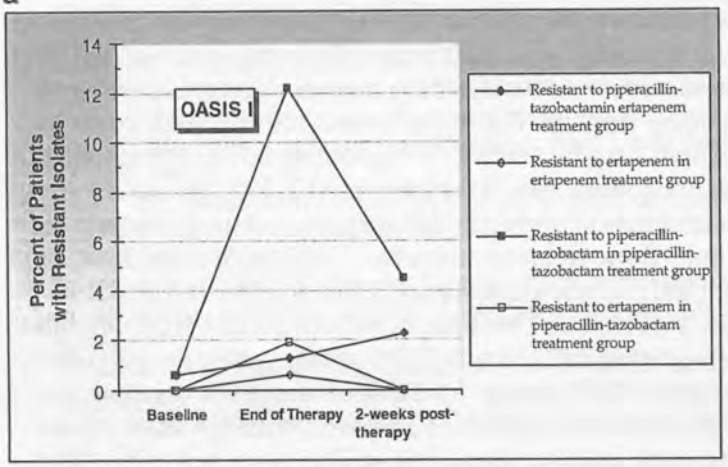


Fig. 4. Mean concentrations of piperacillin and tazobactam in various tissues after intravenous administration of piperacillin/tazobactam 3/0.375 or 4/0.5g in patients. Samples were taken approximately 60 to 120 minutes after drug administration (after Incavo et al. 1993; Kinzig et al. 1992; Sörgel & Kinzig 1993).

Drugs 47:520; 1994

a



b

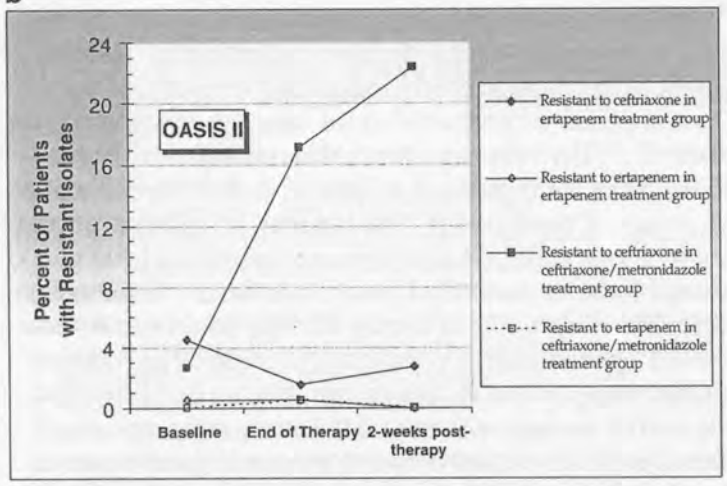


Fig. 1 Prevalence of resistant *Enterobacteriaceae* before and after therapy by treatment group. The figure displays the percentages of assessable patients in each treatment group from whom *Enterobacteriaceae* resistant to the study drug were isolated at the three time points when specimens for cultures were collected. The frequency of resistance at the specified time points is expressed as the number of patients with any resistant *Enterobacteriaceae* divided by the total number of patients assessable at that visit. Panel A displays results from OASIS I comparing piperacillin-tazobactam with ertapenem; panel B shows results from OASIS II comparing ceftriaxone/metronidazole with ertapenem. Note that the scales for the y-axes are different in the two panels

Patients and methods

Primary study design

Adults with intra-abdominal infections requiring surgery were eligible to enter open-label, randomized trials comparing ertapenem 1 g once a day either to piperacillin-tazobactam 13.5 g/day in 3–4 divided doses (OASIS I) or to ceftriaxone 2 g/day in 1–2 divided doses plus metronidazole 30 mg/kg/day in 2–4 divided doses (OASIS II). Most enrolled patients had community-acquired infections defined by clinical manifestations before or within 48 h of hospitalization. Patients who had received preoperative antimicrobial therapy for >24 h or more than a single dose of an antimicrobial regimen postoperatively were excluded unless they were failing treatment. The recommended duration of study therapy was 4–14 days. Nonstudy antimicrobial drugs were prohibited per protocol after the first day of the study except for the use of vancomycin or teicoplanin in selected patients.

DiNubile et al. Bowel colonization with resistant gram-negative bacilli after antimicrobial therapy of intra-abdominal infections: observations from two randomized comparative trials of ertapenem therapy. Eur. J. Clin. Microbiol. Infect. Dis. 24:443-449; 2005

Epidemiol. Infect. (2014), **142**, 1437–1448.
doi:10.1017/S0950268813002380

Risk factors for *Clostridium difficile* infection in the community: a case-control study in patients in general practice, Denmark, 2009–2011

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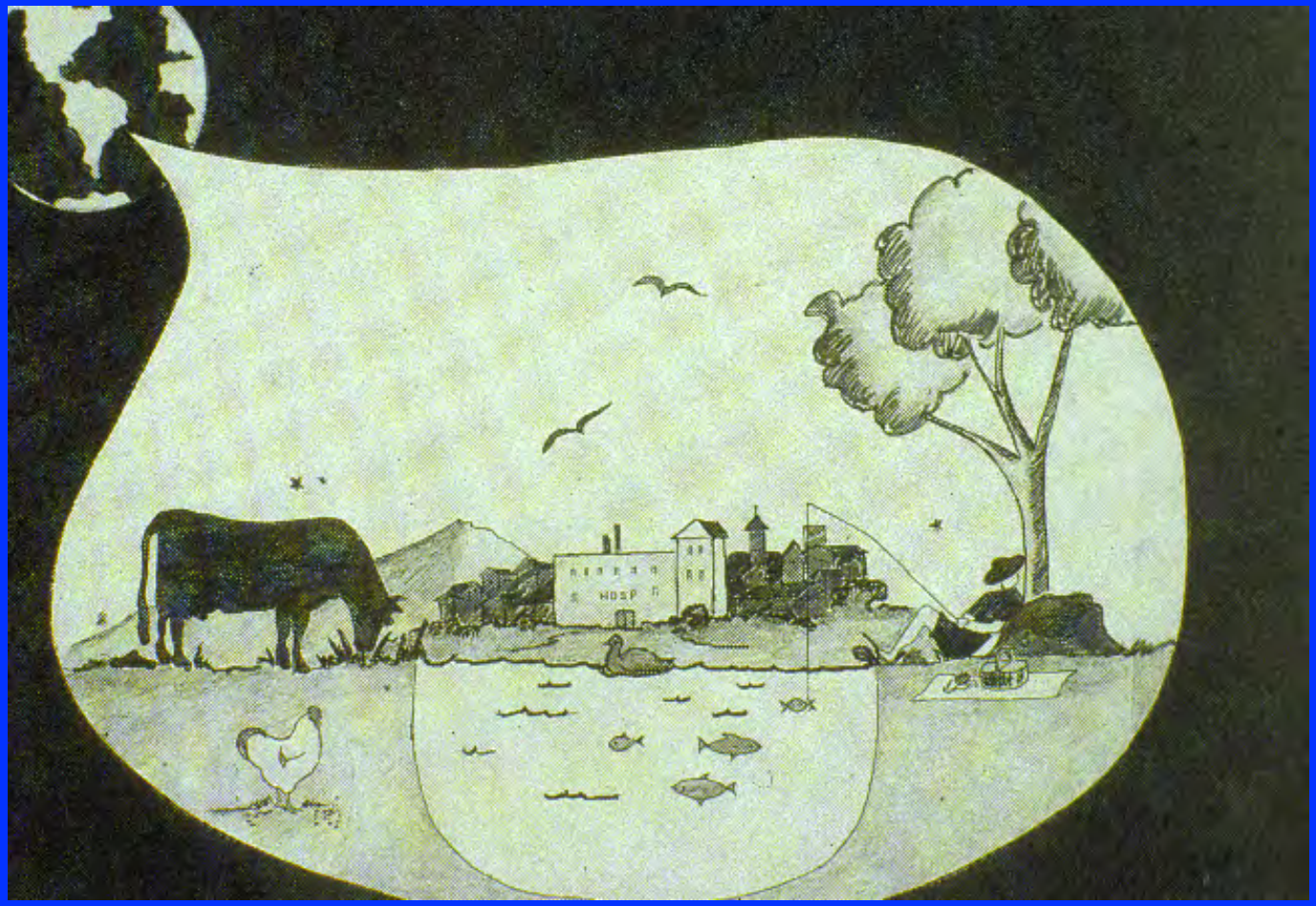
SUMMARY

To identify risk factors for *Clostridium difficile* infection (CDI) in Danish patients consulting general practice with gastrointestinal symptoms, a prospective matched case-control study was performed; cases ($N=259$) had positive cultures for toxigenic *C. difficile* and controls ($N=455$) negative cultures. Data were analysed by conditional logistic regression. In patients aged, ⩾2 years (138 cases), hospitalization [odds ratio (OR) 8·4, 95% confidence interval (CI) 3·1–23], consumption of beef (OR 5·5, 95% CI 2·0–15), phenoxymethylpenicillin (OR 15, 95% CI 2·7–82), dicloxacillin (OR 27, 95% CI 3·6–211), and extended spectrum penicillins (OR 9·2, 95% CI 1·9–45) were associated with CDI. In patients aged <2 years none of these were associated with CDI, but in a subgroup analysis contact with animals was associated with CDI (OR 8·1, 95% CI 1·0–64). This study emphasizes narrow-spectrum penicillins, and suggests beef consumption, as risk factors for CDI in adults, and indicates a different epidemiology of CDI in infants.

Optimal antibiotika behandling

- Antibiotika i landbruget - resistente bakterier i maden

Jens Hansens bondegård – fuld af antibiotika!



Det er nu et internationalt accepteret problem:

Collignon, P.: Resistant E. coli – we are what we eat. CID 49:202-4; 2009 (editorial)

Collignon et al.: WHO ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. CID 49:132-41; 2009

FOOD

EXPLORE
By the Numbers

Antibiotic Resistance

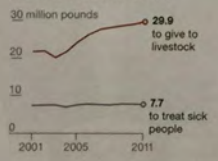
Since the 1950s farmers have fed antibiotic growth promoters (AGPs) to livestock. Overusing these substances can create superbugs, pathogens that are resistant to multiple drugs and could be passed along to humans. Mindful of that, companies such as Perdue Farms have stopped using the drugs to make chickens gain weight faster. Since Denmark banned AGPs in the 1990s, the major pork exporter says it's producing more pigs—and the animals get fewer diseases. Says Centers for Disease Control and Prevention epidemiologist Tom Chiller, "Antibiotics are miracle drugs that should only be used to treat diseases." —*Kelsey Nowakowski*

ANTIBIOTIC USE

80%

of all antibiotics sold in the U.S. are given to poultry and other livestock.

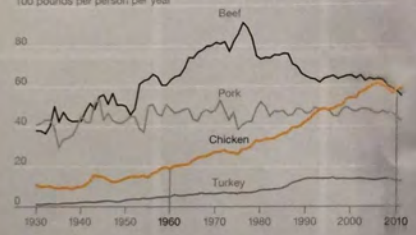
ANTIBIOTICS SOLD IN THE U.S.



THE POULTRY CASE STUDY

Americans today eat three times as much poultry as they did in 1960. Since most U.S. chickens are raised in large, crowded facilities, farmers feed them antibiotics to prevent disease as well as speed their growth.

MEAT CONSUMPTION IN THE U.S.
100 pounds per person per year



ANTIBIOTICS AS GROWTH PROMOTERS
They help chickens grow bigger faster, making the meat...

...cheaper for the consumer

In 1960 it took 63 days to grow a 3.4-pound broiler. **$3.24*** a pound

In 2011 it took 47 days to grow a 5.4-pound one. **$1.29** a pound

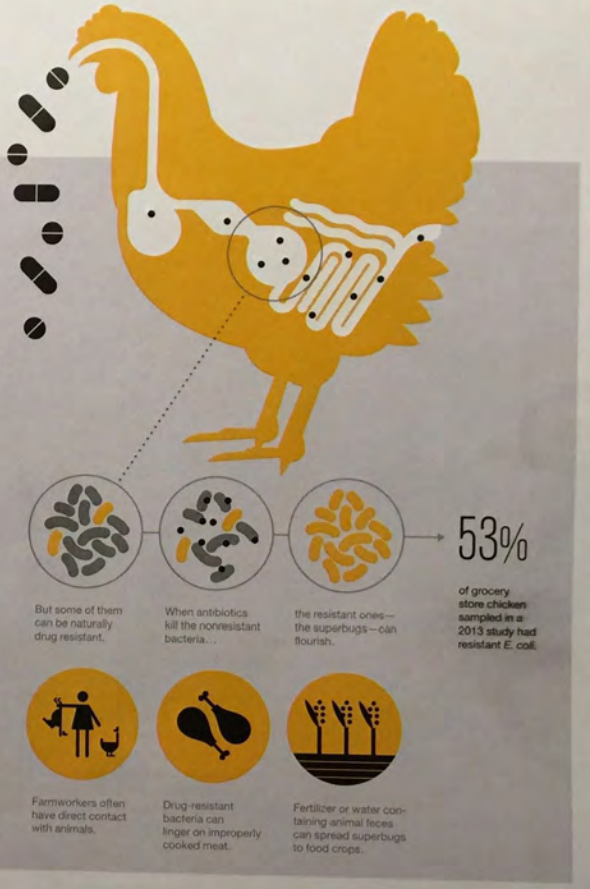
*2011 dollars, adjusted for inflation

COST OF ANTIBIOTIC-RESISTANT INFECTIONS TO U.S. HEALTH SYSTEM, 2013

$21-34 billion

The low-end figure is more than double the Centers for Disease Control and Prevention's 2013 budget.

HOW RESISTANCE DEVELOPS AND SPREADS



CASES OF ANTIBIOTIC RESISTANCE IN AMERICANS, 2013

2,049,400
Illnesses

23,000
Deaths

HOSPITALIZATION TIME

Resistant bacterial infections 12.7 nights

Nonresistant 6.4

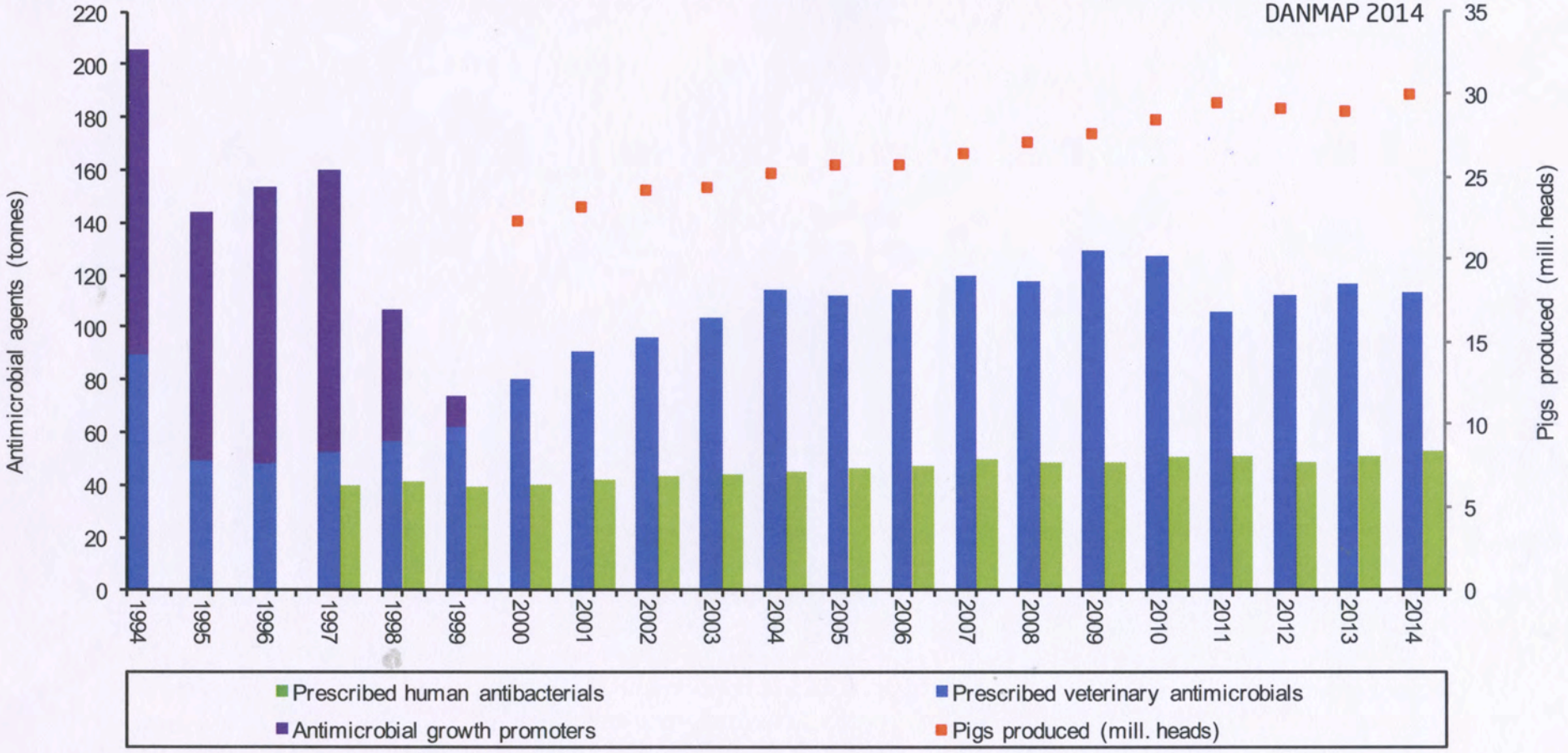
Resistant bacterial infections double risk of death compared with nonresistant infections.

Only 7 percent of some 400 antibiotic drugs given to livestock have been reviewed by the FDA.

GRAPHIC: ÁLVARO VALIÑO. SOURCES: NATURAL RESOURCES DEFENSE COUNCIL; CDC; USDA; ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS; NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM

National Geographic Magazine, March 2015

Figure 4.1. Prescribed antimicrobial agents for humans, and for animals compared with the number of pigs produced, Denmark



Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996-2000). Data from 2001-2014 originate from VetStat.

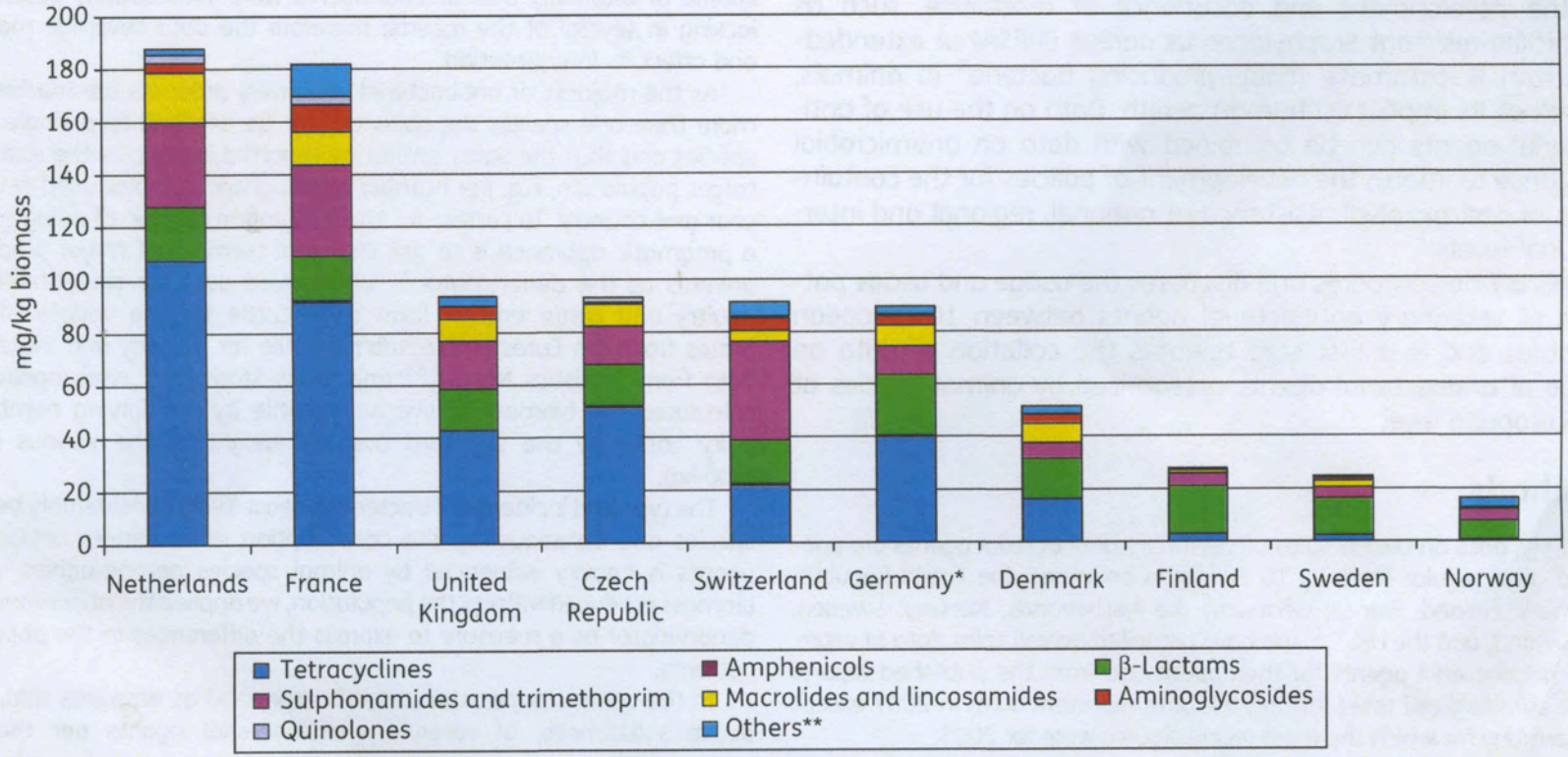


Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.

Grave et al.: Comparison of the sales of veterinary antibacterial agents between 10 European countries. JAC 65:2037-40; 2010

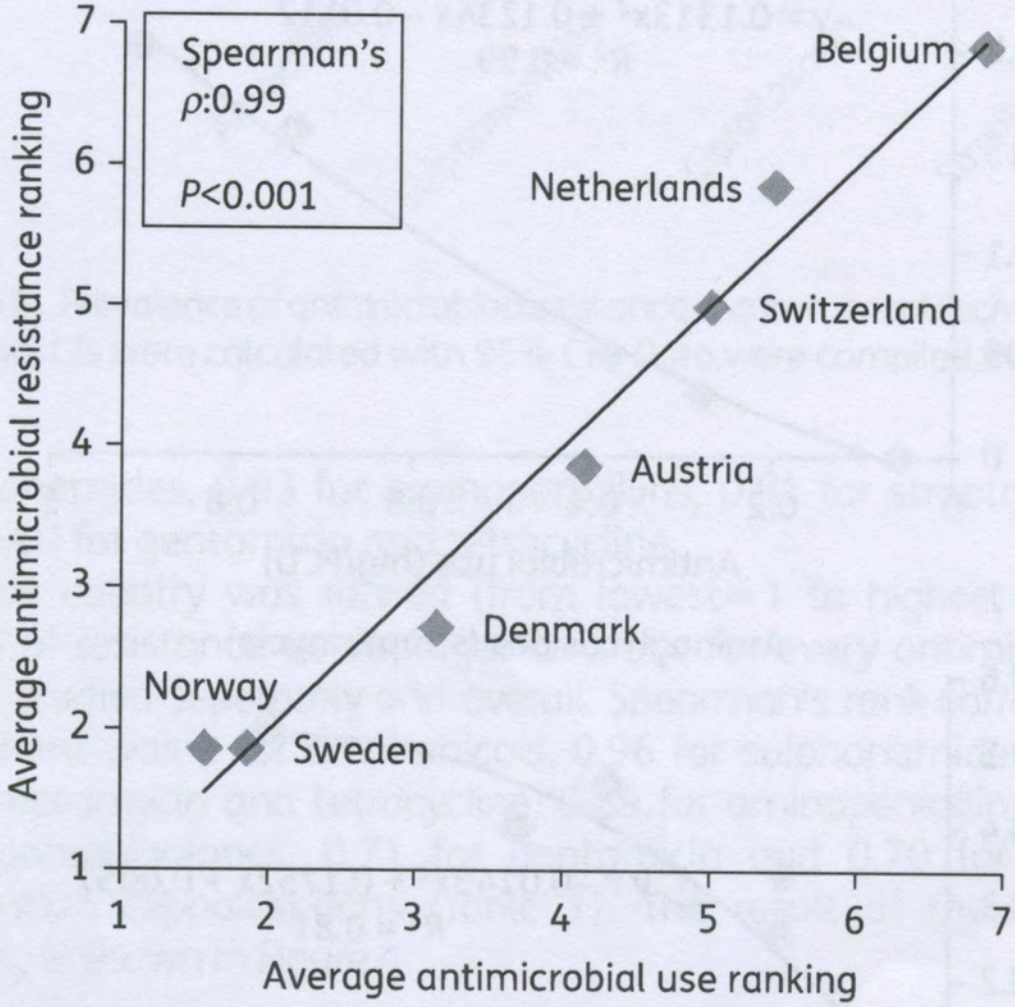


Figure 4. Spearman's rank correlation coefficient between average antimicrobial use ranking (lowest=1 to highest=7) of country and average antimicrobial resistance ranking (lowest=1 to highest=7) of indicator *Escherichia coli* isolates for all antimicrobial agents tested except amphenicols (not all countries provided usage data), for food-producing animals. Each symbol represents the data from a single country. A linear trend line is shown.

Chantziaras et al. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. JAC 69:827-34; 2014

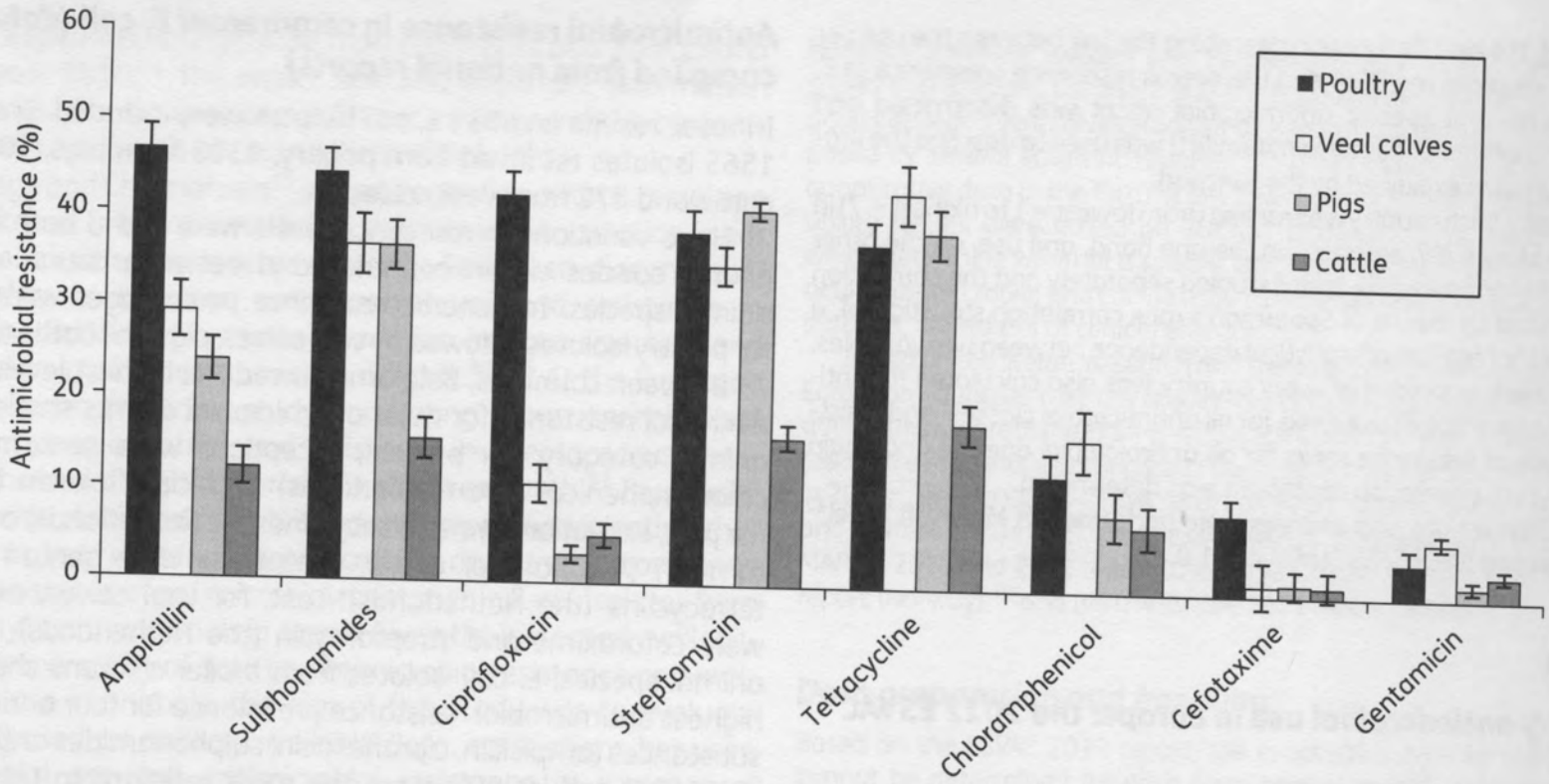
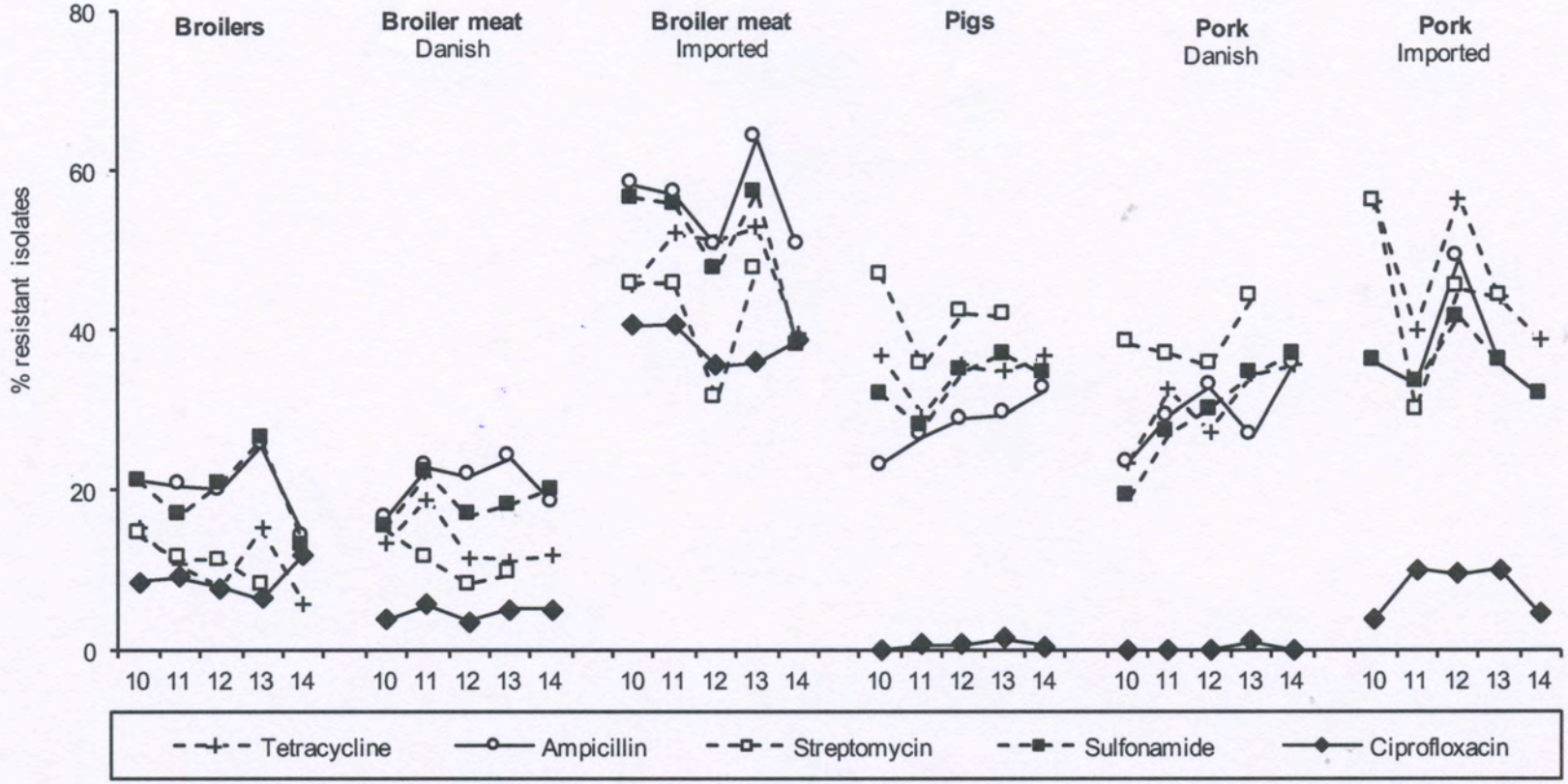


Figure 2. Prevalence of antimicrobial resistance in commensal *Escherichia coli* attributed to included antimicrobial agents, for the selected countries. Exact binomial CIs were calculated with 95% CIs. Data were compiled from various reports.[19,20,22,27,44,45]

Chantziaras et al. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. JAC 69:827-34; 2014

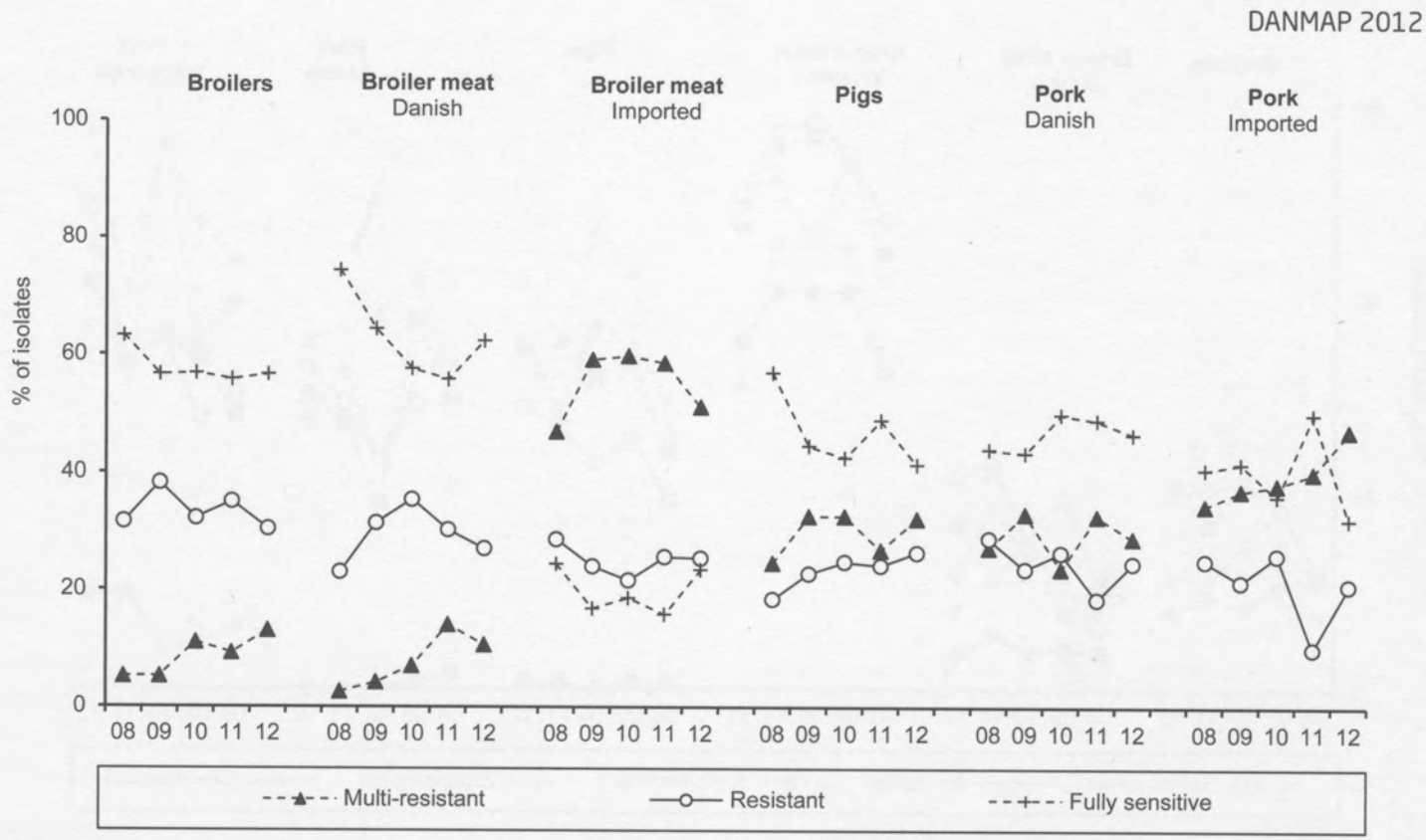
Figure 7.3. Resistance (%) in *Escherichia coli* from animals and meat of Danish and imported origin, Denmark DANMAP 2014



Note: The number of isolates varies between years (broilers: n = 115-191, Danish broiler meat: n = 116-197, imported broiler meat: n =136-177, pigs: n = 146-209, Danish pork: n = 68-93 and imported pork: n = 30-53). Isolates are not tested for resistance to streptomycin in 2014.

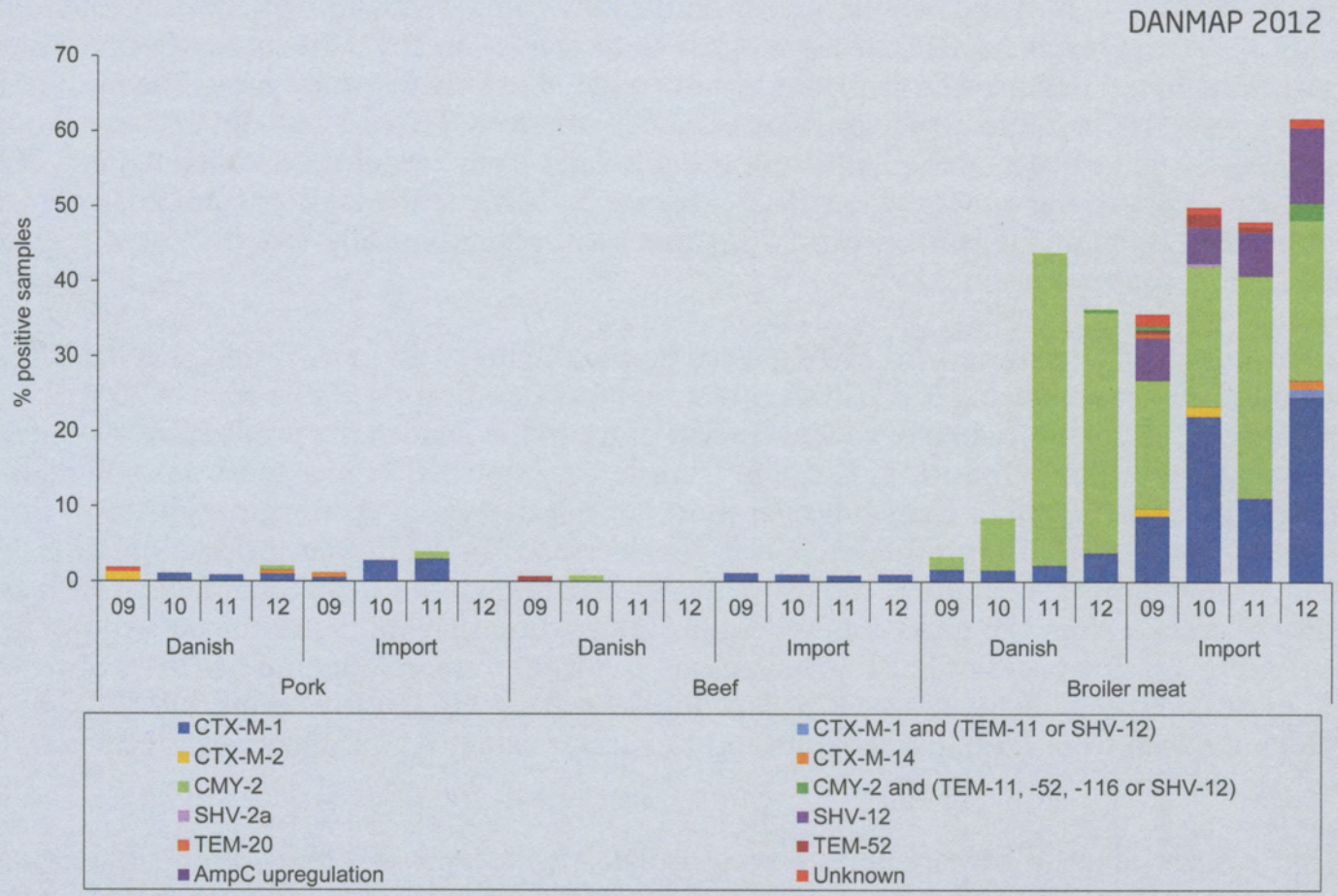
DANMAP 2014

Figure 7.6. Occurence (%) of multi-resistant and fully sensitive *Escherichia coli* [a] from animals and meat of Danish and imported origin, Denmark



DANMAP 2012

Figure 2. Occurrence (%) of ESBL *Escherichia coli* and genes in meat[a], Denmark



DANMAP 2012

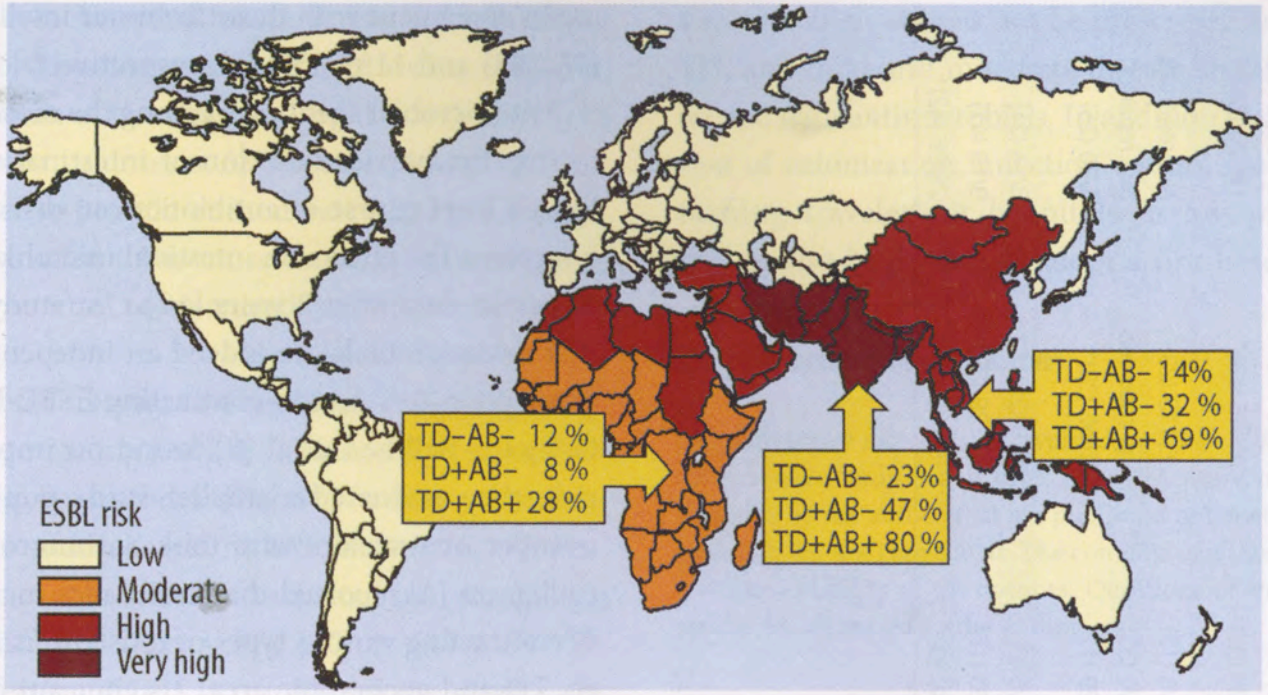


Figure 2. World map indicating the risk levels of contracting extended-spectrum beta-lactamase–producing *Enterobacteriaceae* (ESBL-PE) in different geographic regions as established in the present investigation. In the entire study population, 21% of the travelers contracted ESBL-PE; 11% in subgroup TD–AB– (travelers' diarrhea/antimicrobials), 21% in TD+AB–, and 37% in TD+AB+ contracted ESBL-PE. The respective subgroup analyses for the regions with highest risk (Africa, South Asia, and Southeast Asia) are given in the boxes with arrows. The ESBL-PE strains contracted were all *Escherichia coli*, except for 2 *Klebsiella oxytoca* and 1 *Escherichia hermannii*.

Kantele et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae (ESBL-PE). CID 60:837-46; 201

'Mere end 300 mio. rejsende besøger regioner med dårlig hygiejne hvert år'.

21% af 430 finske rejsende uden for skandinavien blev ESBL-PE. Højst i Sydøstasien (46%), og blandt dem, der havde diarré og også fik antibiotika, var det 80%. Ingen blev Carbapenem-producerende Enterobacteriaceae koloniseret.

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Journal of Antimicrobial Chemotherapy

Carbapenemase-producing Enterobacteriaceae and non-Enterobacteriaceae from animals and the environment: an emerging public health risk of our own making?

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Acquired carbapenemases pose one of the most pressing public health threats relating to antibiotic resistance. In most countries, the number of carbapenemase-producing bacteria from human clinical specimens is rising, and the epidemiological status of these multiresistant bacteria is progressively worsening. Furthermore, there is a growing number of reports of carbapenemases found either in bacteria isolated from non-human sources or in *Salmonella enterica* subsp. *enterica*, a zoonotic species. However, carbapenemases are not yet systematically sought in bacteria from non-human sources, reports of them are largely observational, and there is limited investigation of carbapenemase-positive bacteria in animals and possible links with people who may have acted as potential sources. Active surveillance and monitoring for carbapenem-resistant bacteria in the food chain and other non-human sources is urgently needed, with an enhanced and rigorous follow-up of all positive results. The carbapenems are currently our last good defence against multiresistant Gram-negative bacteria. Our ability to limit the rise and spread of carbapenemase producers, which occur only at basal levels in many countries at present, should serve as a key performance indicator for the success or failure of the efforts that have been called for by international organizations and governments to reduce the impact of antibiotic resistance.

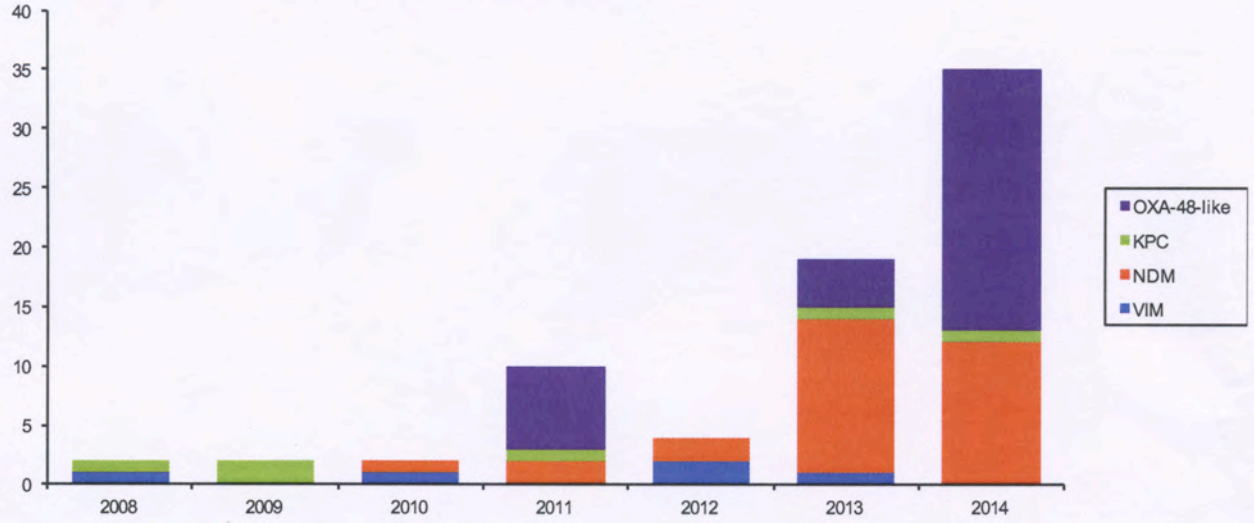
Textbox 8.2

Carbapenemase producing bacteria in Denmark, 2014

Background: Carbapenems comprise one of the only classes of antimicrobial agents that can be used for treatment of infections with multi-resistant Gram-negatives like *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Acinetobacter baumannii.* Treatment options for infections with carbapenem-resistant bacteria are often none or suboptimal. Resistance can be caused by the presence of various carbapenemases of which the most frequently occurring are *K. pneumoniae* carbapenemase (KPC), Oxacillinase (OXA), Verona integron-encoded metallo-β-lactamase (VIM), and New Delhi metallo-β-lactamase (NDM), and Imipenemase (IMP).

In recent years, Danish Departments of Clinical Microbiology (DCM) have on a voluntary basis submitted carbapenem resistant isolates for verification and genotyping to the Antimicrobial Resistance Reference Laboratory at Statens Serum Institut. The present textbox describes carbapenemase-producing *Enterobacteriaceae* (CPE), carbapenemase-producing *P. aeruginosa* and *Acinetobacter* ssp.

Figure 1. Numbers of carbapenemase-producing Enterobacteriaceae (CPE)

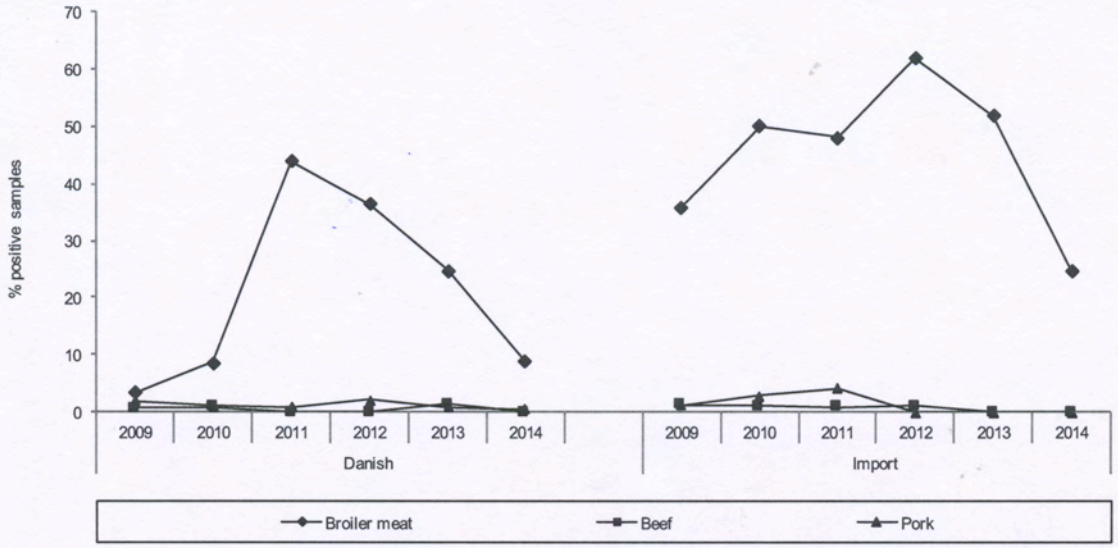


More than one isolate was included from the same patient, if the isolates belonged to different bacterial species and/or harboured different carbapenemases.

DANMAP 2014

continued ... Textbox 7.1

Figure 1. Occurrence (%) of samples with ESBL-producing *Escherichia coli* in meat, Denmark DANMAP 2014



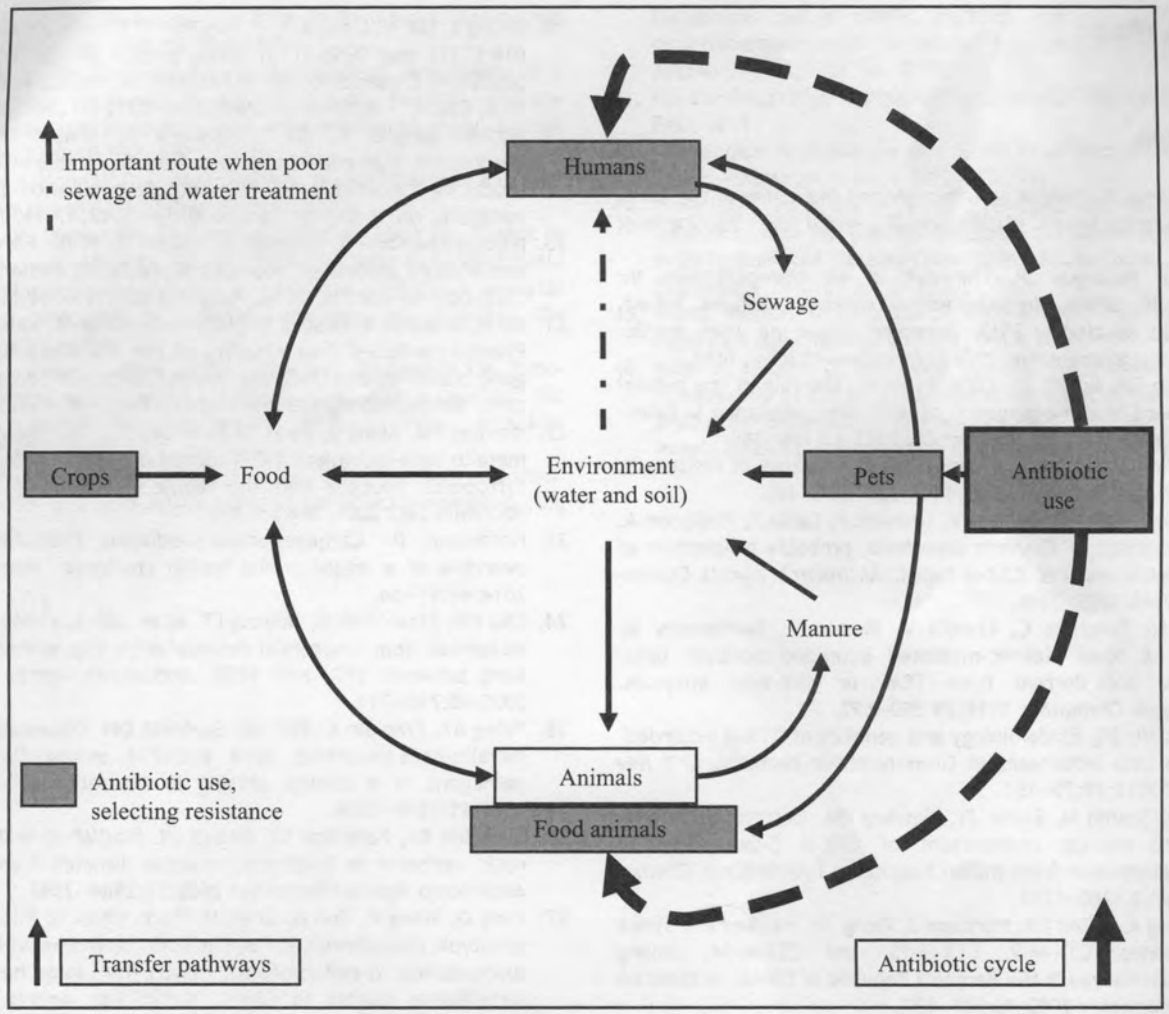


Figure 1. Principal transfer pathways for antibiotic resistance genes in humans, animals, food, and the environment. (Reproduced with permission from The Joint Working Group of Defra's Antimicrobial Resistance Co-ordination (DARC) and Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infections (ARHAI). ESBLs – a threat to human and animal health? https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215180/dh_132534.pdf [accessed 16.01.15]).

Hawkey. Multidruf-resistant Gram-negative bacteria: a product of globalization. J. Hosp. Infect. 89:241-47; 2015

Antibiotikaresistens i Danmark

- Sjældent MRSA (methicillin-resistente *S. aureus, 1-2%*)
- Sjældent penicillin-, macrolid- og tetracyklin-resistente *S. pneumoniae*
- Sjældent plasmid associeret extended spectrum β-lactamase (ESBL), aminoglycosid og florquinolon resistens - men stigende!
- Sjældent *S. pyogenes Gr. A* resistens
- Sjældent *H. influenzae* resistens

MEN

- Ofte β-lactamase producerende *S. aureus*
- Ofte ampicillin-, sulfa- og trimethoprim resistens i *E. coli*
- Ofte MRSE (methicillin-resistente *S. epidermidis*)
- Ofte β-lactamase producerende *M. catarrhalis*

- ZOONOTISKE RESERVOIR AF MULTIRESISTENTE BAKTERIER FRA DANMARK OG ISÆR UDLANDET ->MADEN -> MENNESKER

- MENNESKER: STORT ANTIBIOTIKAFORBRUG TIL BØRN I VUGGESTUER/BØRNEHAVER
- FØDEVAREINDUSTRIEN: STORT ANTIBIOTIKAFORBRUG TIL SVIN, KALVE, KYLLINGER OSV.

8 basale antibiotika spørgsmål

- Hvilken type patient?
- Hvilken bakterieart?
- Hvilken følsomhed/resistens?
- Tilstrækkelig penetration?
- PK/PD?
  - A: ß-lactam, glycopeptider, makrolider
    koncentration > MIC ≥50% doserings intervallet
  - B: aminoglykosider, fluokinoloner, colistin
    maksimal topkoncentration
- Påvirkes normalfloraen på slimhinder og hud?
- Behandlingsvarighed?
- Biofilm?