Herlev Hospital

REGION

Antibiotic resistance – does it matter in paediatric clinical practice ?

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Background

The Department of Clinical Microbiology at Herlev Hospital serves:

- 4 hospitals in the Capital Region (Herlev and Gentofte Hospital, Hillerød and Frederikssund Hospital) as well as ca 700 general practitioners

Number of samples received per year > 500,000 (bacteriology, mycology, parasitology, and virology)

Infection control team (6 ICN, 6 consultants in clinical microbiology)

Two large paediatric departments (e.g. neonatology, neurology, endocrinology , nephro-urology, pulmonology, cardiology, allergology….but no highly specialised surgery or oncology /haematology wards)

Regular clinical conferences with one of the consultants in clinical microbiology and paediatricians are held on a weekly basis

Data sources on multiresistant bacteria

DANMAP

Nationwide yearly report with surveillance data on resistant indicator bacteria in veterinary medicine, food, and human infections

Task force (Capital Region):

Hospital acquired infections plus

Certain resistant bacteria: MRSA, VRE

Statens Serum Institut

EPINYT newsletter on a weekly basis

(HAIBA)

Local data (Department of Clinical Microbiology, Herlev Hospital)

Surveillance of MRSA, ESBL *E. coli*, VRE

Specific data on a ward level can be extracted

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Short but not sweet

- **ESBL** **extended spectrum beta-lactamase producing**
- **MRSA** **methicillin resistant *Staphylococcus aureus***
- **PNSP** **Penicillin non-susceptible *Streptococcus pneumoniae***
- VRE vancomycin resistant enterococci
- KPC *Klebsiella pneumoniae* carbapenemase
- CPE carbapenemase producing *Enterobacteriaceae*
- MDRAB multidrug resistant *Acinetobacter baumannii*
- XDRAB Extreme DRAB

More than 600 beta-lactamases are out there

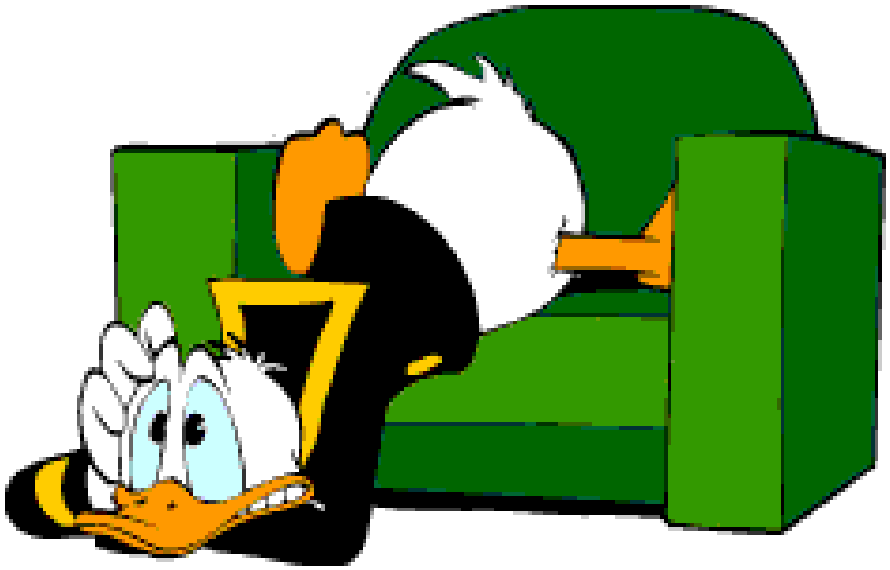
Table 1. Selected β-Lactamases of Gram-Negative Bacteria.

β-Lactamase	Examples	Substrates	Inhibition by Clavulanic Acid*	Molecular Class
Broad-spectrum	TEM-1, TEM-2, SHV-1	Benzylpenicillin (penicillin G), aminopenicillins (amoxicillin and ampicillin), carboxypenicillins (carbenicillin and ticarcillin), ureidopenicillin (piperacillin), narrow-spectrum cephalosporins (cefazolin, cephalothin, cefamandole, cefuroxime, and others)	+++	A
	OXA family	Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin	+	D
Expanded-spectrum	TEM family and SHV family	Substrates of the broad-spectrum group plus oxyimino-cephalosporins (cefotaxime, cefpodoxime, ceftazidime, and ceftriaxone) and monobactam (aztreonam)	++++	A
	Others (BES-1, GES/IBC family, PER-1, PER-2, SFO-1, TLA-1, VEB-1, and VEB-2)	Same as for TEM family and SHV family	++++	A
	CTX-M family	Substrates of the expanded-spectrum group plus, for some enzymes, cefepime	++++	A
	OXA family	Same as for CTX-M family	+	D
AmpC	ACC-1, ACT-1, CFE-1, CMY family, DHA-1, DHA-2, FOX family, LAT family, MIR-1, MOX-1, and MOX-2	Substrates of expanded-spectrum group plus cephamycins (cefotetan, cefoxitin, and others)	0	C
Carbapenemase	IMP family, VIM family, GIM-1, and SPM-1	Substrates of the expanded-spectrum group plus cephamycins and carbapenems (ertapenem, imipenem, and meropenem)	0	B
	KPC-1, KPC-2, and KPC-3	Same as for IMP family, VIM family, GIM-1, and SPM-1	+++	A
	OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, and OXA-48	Same as for IMP family, VIM family, GIM-1, and SPM-1	+	D

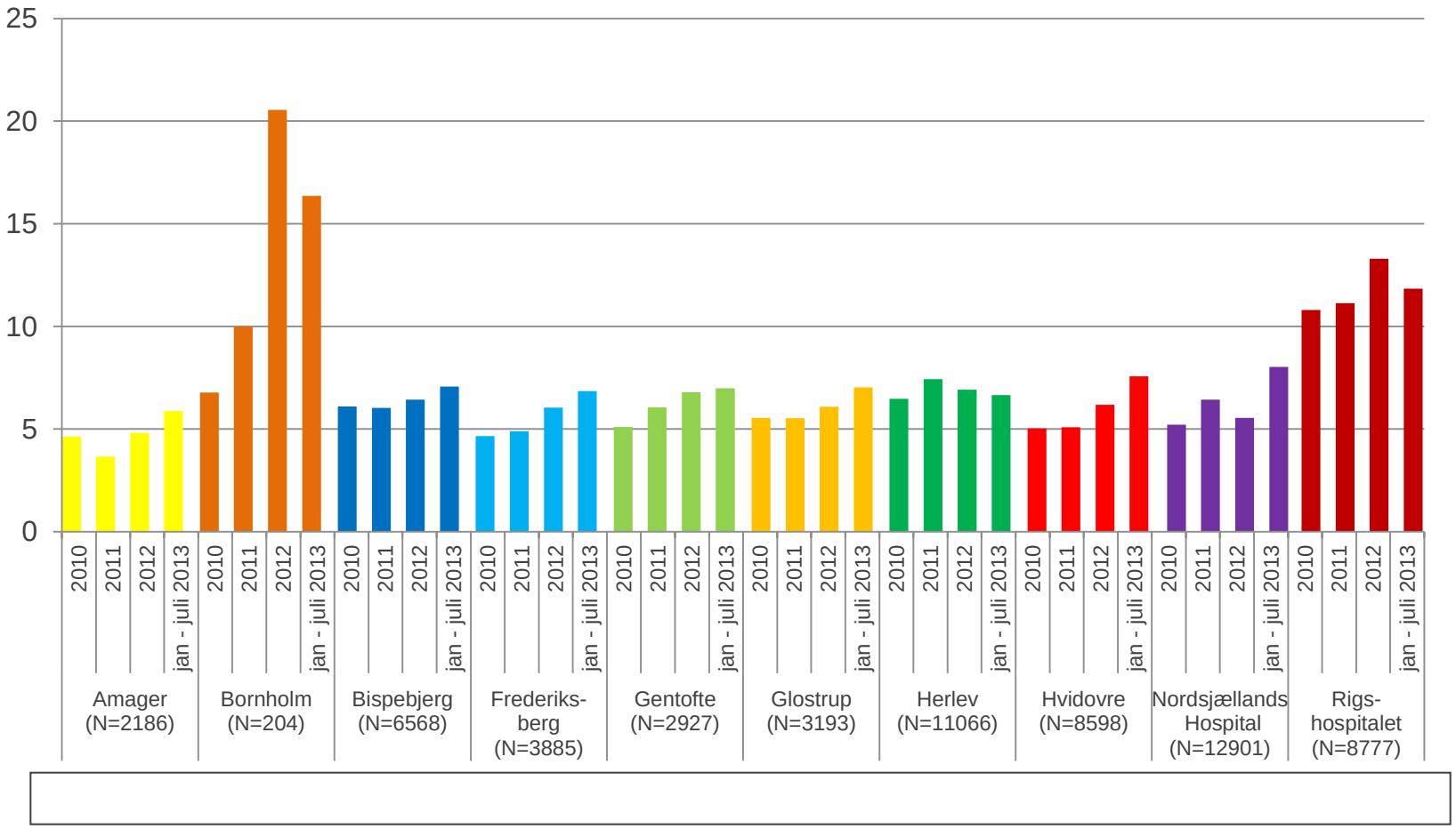
* Plus signs denote relative sensitivity to inhibition.

Detecting antibiotic resistance

A complicated matter for the clinical microbiologist - since many resistance mecanisms are not revealed by routine methods but demand specific testing, often with different combinations of antibiotic disks

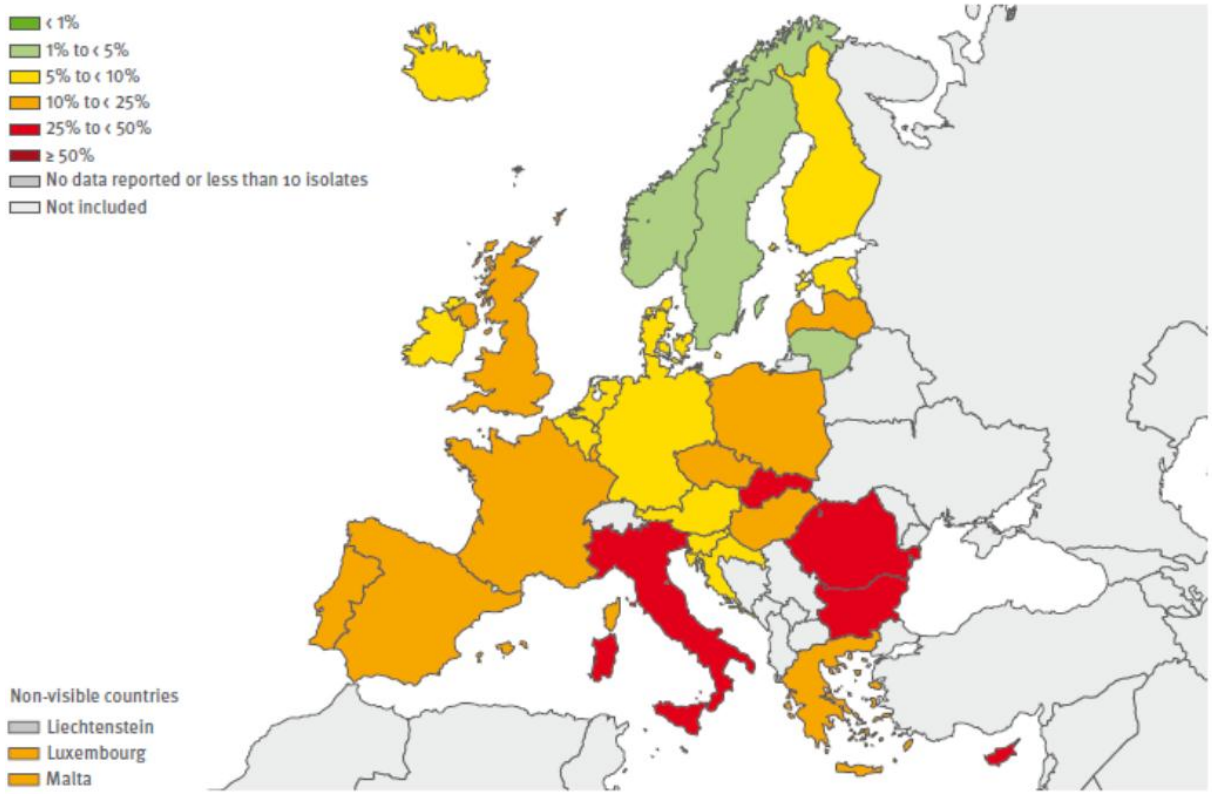


Cefuroxim resistance (%) in *E. coli* 2010-13



European data on ESBL *E. coli*

Figure 3.1. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country, EU/EEA countries, 2012



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No doubt that adult patients are facing increasing problems with resistant Gramnegative bacteria – but what about the children?

Data from DANMAP and The Task Force in the Capital Region are from all age groups, so no firm surveillance data for children or paediatric wards

Local data from one paediatric ward (Herlev Hospital):

In 2014, **19 children** were diagnosed with ESBL *E. coli* urinary tract infection/colonisation (i.e. 4-5 cases every three months)

(the total number of patients with ESBL *E. coli* isolated from urine samples at Herlev Hospital was **299**)

In 2011, the corresponding numbers were **2** and **171**

No bacteraemia episodes with ESBL *E. coli* in children.

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Neonatal wards in the Capital Region and MRSA

MRSA (methicillin resistant *Staphylococcus aureus*) strains are introduced from the community from time to time and cause small (or big) outbreaks:

In 2008, a major outbreak with CA-MRSA (spa type t127) occurred in a neonatal intensive care unit (32 children from 25 families). None of the children had clinical infection.

As a consequence, all neonates transferred between the four NICUs in the Capital Region are isolated and screened for MRSA on arrival in a new NICU.

In 2014, a smaller outbreak of CA-MRSA occurred in one of the paediatric wards (not an NICU). Five out of 6 mothers had mastitis. None of the children had clinical infection.

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MRSA outbreak in a NICU, 2008: 32 neonates

OPEN ACCESS Freely available online

PLOS ONE

First Outbreak with MRSA in a Danish Neonatal Intensive Care Unit: Risk Factors and Control Procedures

Benedicte Grenness Utke Ramsing[1]*, Magnus Arpi[2], Erik Arthur Andersen[1], Niels Knabe[1], Dorthe Mogensen[2], Dorte Buhl[2], Henrik Westh[3,4], Christian Østergaard[2,3]

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Abstract

Introduction: The purpose of the study was to describe demographic and clinical characteristics and outbreak handling of a large methicillin-resistant *Staphylococcus aureus* (MRSA) outbreak in a neonatal intensive care unit (NICU) in Denmark June 25th–August 8th 2008, and to identify risk factors for MRSA transmission.

Methods: Data were collected retrospectively from medical records and the Danish Neobase database. All MRSA isolates obtained from neonates, relatives and NICU health care workers (HCW) as well as environmental cultures were typed.

Results: During the 46 day outbreak period, 102 neonates were admitted to the two neonatal wards. Ninety-nine neonates were subsequently sampled, and 32 neonates (32%) from 25 families were colonized with MRSA (spa-type t127, SCCmec V, PVL negative). Thirteen family members from 11 of those families (44%) and two of 161 HCWs (1%) were colonized with the same MRSA. No one was infected. Five environmental cultures were MRSA positive. In a multiple logistic regression analysis, nasal Continuous Positive Airway Pressure (nCPAP) treatment ($p = 0.006$) and Caesarean section ($p = 0.016$) were independent risk factors for MRSA acquisition, whereas days of exposure to MRSA was a risk factors in the unadjusted analysis ($p = 0.04$).

Conclusions: MRSA transmission occurs with high frequency in the NICU during hospitalization with unidentified MRSA neonates. Caesarean section and nCPAP treatment were identified as risk factors for MRSA colonization. The MRSA outbreak was controlled through infection control procedures.

Citation: Ramsing BGU, Arpi M, Andersen EA, Knabe N, Mogensen D, et al. (2013) First Outbreak with MRSA in a Danish Neonatal Intensive Care Unit: Risk Factors and Control Procedures. PLoS ONE 8(6): e66904. doi:10.1371/journal.pone.0066904

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MRSA data 2014

At The Department of Clinical Microbiology , Herlev Hospital, 319 patients were diagnosed with MRSA (infection or colonization, 4 hospitals + GPs)

Thirteen children were diagnosed in relation to hospital contact:

2 refugee children

5 sporadic cases with CA-MRSA

6 neonates, outbreak at a neonatal ward (5 out of 6 mothers had mastitis)

MRSA is not a big issue in the hospital environment, except for small outbreaks mainly in the neonatal wards

But how about MRSA in the community ?

Trends over time: MRSA (source: Statens Serum Institut)

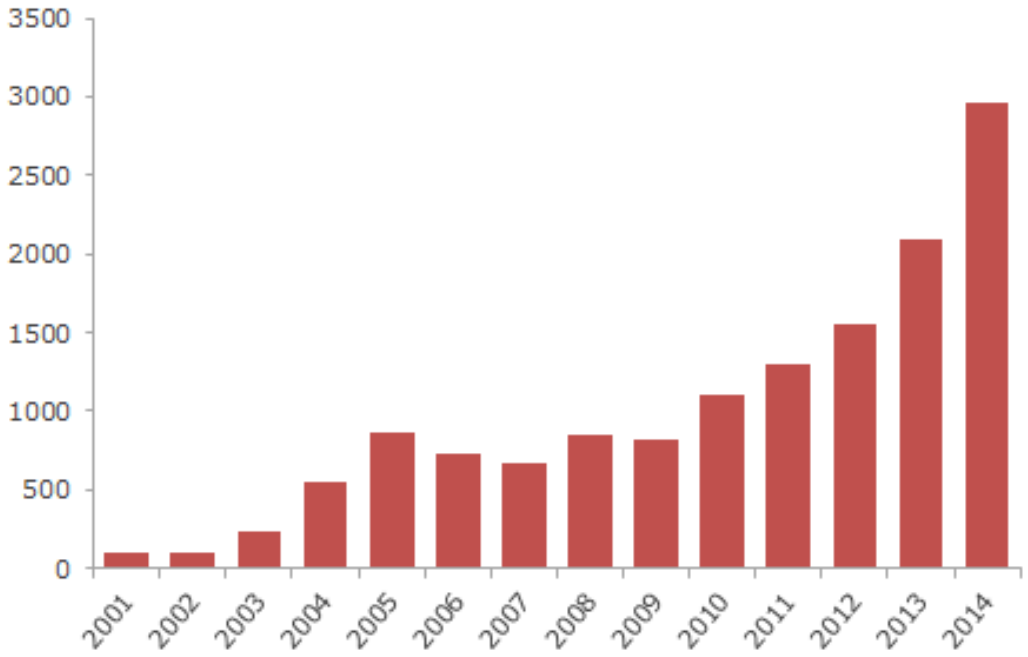
In 2002, 100 cases of MRSA were diagnosed in Denmark

In 2014, 2,965 cases of MRSA were diagnosed in Denmark

Rise from 2012 to 2013: 30 %

Rise from 2013 to 2014: 42 %

Figur 1. Antal MRSA-tilfælde fordelt på år, 2001-2014



Penicillin non-susceptible *Streptococcus pneumoniae*

S. pneumoniae from blood and CSF (national data, Statens Serum Institut)

6.3 % penicillin R or I

None were penicillin R, i.e. all isolates with decreased susceptibility were penicillin I

BSI with a respiratory tract infection can be treated with penicillin

Meningitis cases have to be treated with 3rd generation cephalosporins (pen I)

S. pneumoniae from respiratory samples (local data)

1 % penicillin R

10 % penicillin I

Respiratory tract infections (pen I) can be treated with penicillin

The general impression

Carbapenemase producing *Enterobacteriaceae* (CPE),

Klebsiella pneumoniae carbapenemase (KPC)

Multidrug-resistant *Acinetobacter baumannii* (MDRAB)

Vancomycin resistant enterococci (VRE)

are rarely seen, if at all, in the pediatric departments at Herlev and Hillerød Hospital

BUT: Highly specialised paediatric wards caring for children with complicated surgery, cancer and/or neutropenia, receiving multiple courses of broad-spectrum antibiotics can have different resistance problems

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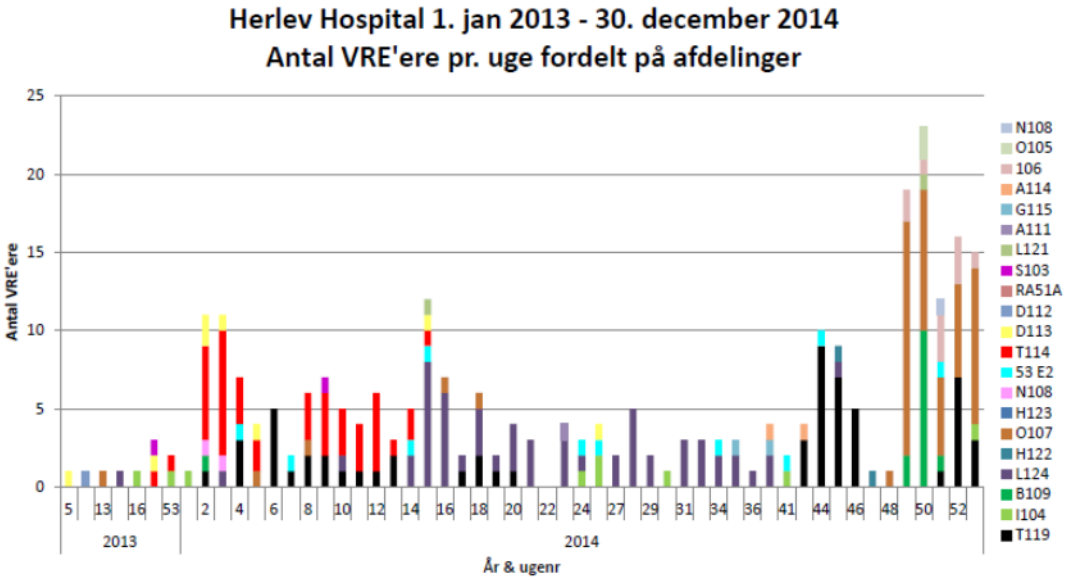
Vancomycin Resistant Enterococci (VRE): not a paediatric problem (yet)



Conclusion

CA-MRSA is a serious concern

ESBL *E. coli* and *K. pneumoniae* have to be followed closely

The occurrence of penicillin I *S. pneumoniae* in respiratory samples is on the rise but does not (yet) cause treatment problems

VRE, CPE and MDRAB are not (yet) a problem in relation to the general paediatric patient

The good news: No decreased penicillin susceptibility in haemolytic streptococci Group A and B

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Travel is a risk factor for colonisation with resistant bacteria in the gut

High Rates of Antimicrobial Drug Resistance Gene Acquisition after International Travel, the Netherlands

Christian J.H. von Wintersdorff, John Penders, Ellen E. Stobberingh, Astrid M.L. Oude Lashof, Christian J.P.A. Hoebe, Paul H.M. Savelkoul, and Petra F.G. Wolffs

We investigated the effect of international travel on the gut resistome of 122 healthy travelers from the Netherlands by using a targeted metagenomic approach. Our results confirm high acquisition rates of the extended-spectrum β-lactamase encoding gene bla_{CTX-M}, documenting a rise in prevalence from 9.0% before travel to 33.6% after travel ($p<0.001$). The prevalence of quinolone resistance encoding genes *qnrB* and *qnrS* increased from 6.6% and 8.2% before travel to 36.9% and 55.7% after travel, respectively (both $p<0.001$). Travel to Southeast Asia and the Indian subcontinent was associated with the highest acquisition rates of *qnrS* and both bla_{CTX-M} and *qnrS*, respectively. Investigation of the associations between the acquisitions of the bla_{CTX-M} and *qnr* genes showed that acquisition of a bla_{CTX-M} gene was not associated with that of a *qnrB* ($p = 0.305$) or *qnrS* ($p = 0.080$) gene. These findings support the increasing evidence that travelers contribute to the spread of antimicrobial drug resistance.

of whether it is a pathogen, have the potential to emerge in clinically relevant pathogens (*6*). Several of such HGT interactions between clinically relevant pathogens and environmental species have been described; for example, the plasmid-mediated quinolone resistance encoding *qnrA* gene originated from the chromosomes of the aquatic bacterium *Shewanella algae* (*7*). Another well-known example is the extended-spectrum β-lactamase (ESBL) encoding bla_{CTX-M} gene, which originates from chromosomal genes of environmental *Kluyvera* species (*8*) and has emerged as the most prevalent cause of plasmid-mediated ESBL.

Resistance reservoirs have unpredictable and immense potential for rendering antimicrobial drugs ineffective. The human gut microbiota warrants special attention because of its high density of microorganisms and high accessibility (*9*). The gastrointestinal tract is constantly exposed to numerous bacteria from the environment, e.g., food, water,

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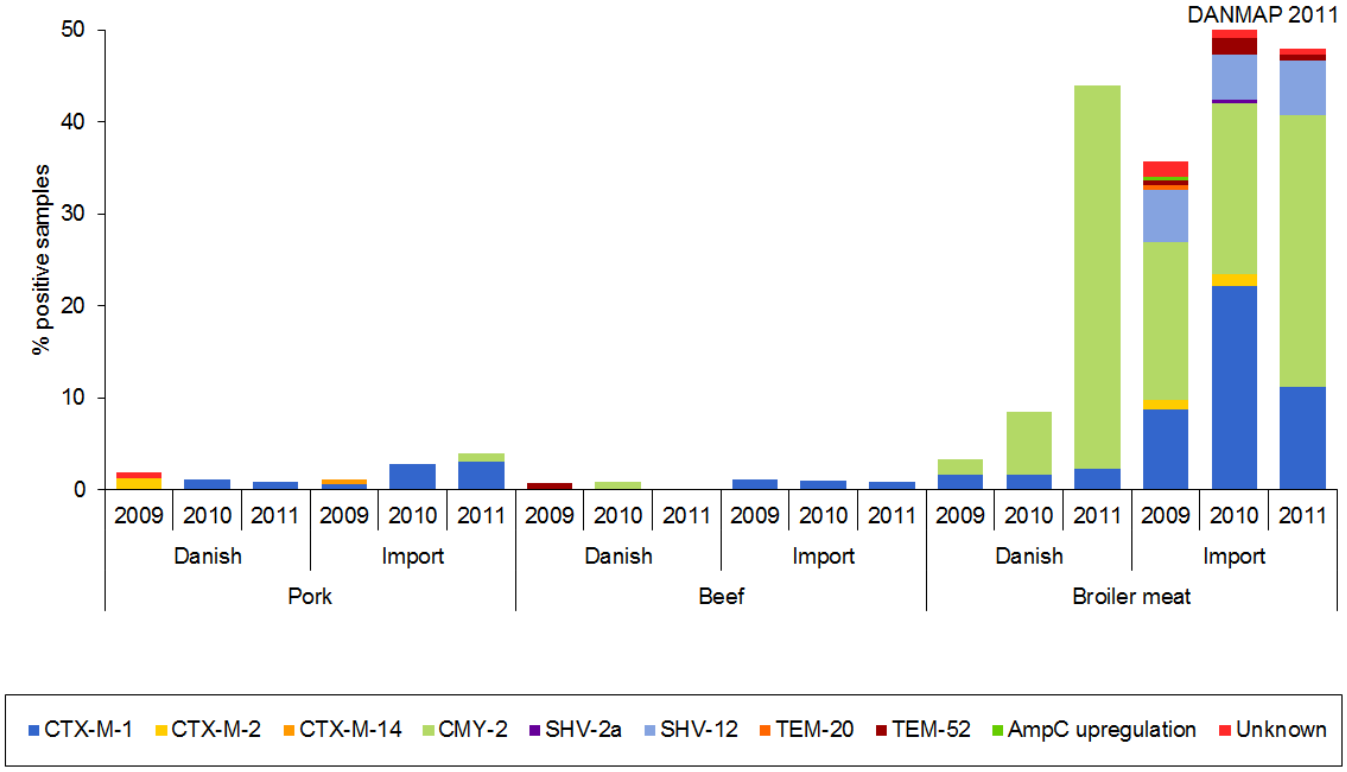
Enjoy your imported – or Danish - gourmet chicken…..

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



a) E. coli was isolated after selective enrichment with ceftriaxone (1 µg/ml). The genetic background for ESBL resistance was revealed by use of PCR, micro array and DNA sequencing

b) Each year approximately 1,000 samples are collected evenly distributed between the six categories of meat

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Guidelines for the use of antibiotics in the paediatric department at Herlev Hospital

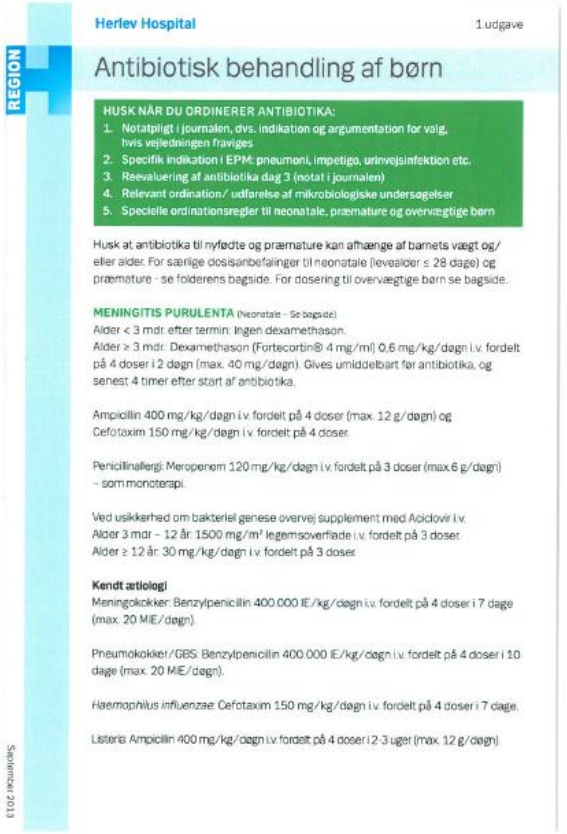
Old school choices:
Penicillin, ampicillin/amoxicillin, dicloxacillin, …

Sepsis treatment: Ampicillin + gentamicin

Meningitis: Ampicillin + cefotaxime

Urinary tract infections: Pivmecillinam

Cefuroxime and meropenem are only used
in case of allergy towards penicillins
(meropenem in case of meningitis)
As for the adult guidelines, recommendations are
based upon evaluation of all bacteraemia cases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Antibiotisk behandling af børn

HUSK NÅR DU ORDINERER ANTIBIOTIKA:
1. Notatpligt i journalen, dvs. indikation og argumentation for valg, hvis vejledningen fraviges
2. Specifik indikation i EPM: pneumoni, impetigo, urinvejsinfektion etc.
3. Reevaluering af antibiotika dag 3 (notat i journalen)
4. Relevant ordination/ udførelse af mikrobiologiske undersøgelser
5. Specielle ordinationsregler til neonatale, præmature og overvægtige børn

Husk at antibiotika til nyfødte og præmature kan afhænge af barnets vægt og/ eller alder. For særlige dosisanbefalinger til neonatale (levealder ≤ 28 dage) og præmature - se folderens bagside. For dosering til overvægtige børn se bagside.

MENINGITIS PURULENTA (Neonatale - Se bagside)
Alder < 3 mdr. efter termin: Ingen dexamethason.
Alder ≥ 3 mdr.: Dexamethason (Fortecortin® 4 mg/ml) 0,6 mg/kg/døgn i.v. fordelt på 4 doser i 2 døgn (max. 40 mg/døgn). Gives umiddelbart før antibiotika, og senest 4 timer efter start af antibiotika.

Ampicillin 400 mg/kg/døgn i.v. fordelt på 4 doser (max. 12 g/døgn) og
Cefotaxim 150 mg/kg/døgn i.v. fordelt på 4 doser.

Penicillinallergi: Meropenem 120 mg/kg/døgn i.v. fordelt på 3 doser (max 6 g/døgn) – som monoterapi.

Ved usikkerhed om bakteriel genese overvej supplement med Aciclovir i.v.
Alder 3 mdr – 12 år: 1500 mg/m² legemsoverflade i.v. fordelt på 3 doser.
Alder ≥ 12 år: 30 mg/kg/døgn i.v. fordelt på 3 doser.

Kendt ætiologi
Meningokokker: Benzylpenicillin 400.000 IE/kg/døgn i.v. fordelt på 4 doser i 7 dage (max. 20 MIE/døgn).

Pneumokokker/GBS: Benzylpenicillin 400.000 IE/kg/døgn i.v. fordelt på 4 doser i 10 dage (max. 20 MIE/døgn).

Haemophilus influenzae: Cefotaxim 150 mg/kg/døgn i.v. fordelt på 4 doser i 7 dage.

Listeria: Ampicillin 400 mg/kg/døgn i.v. fordelt på 4 doser i 2-3 uger (max. 12 g/døgn).

Skejnmøgn 2013

Fighting (multi) drug resistant microorganisms (MDRM)

- Access to fast and accurate **diagnostic testing**
- **Antibiotic stewardship** to diminish selection pressure and prevent transfer of antibiotic resistance between bacteria (horisontal resistance transfer)
- **Infection control measures** to prevent the transfer of MDRM between HCWs and patients and between patients: adherence to **guidelines** for managing patients carrying or infected with resistant microorganisms, also with a focus on cleaning procedures
- **Surveillance**: detecting outbreaks and tracking tendencies

Newsweek March 28th, 1994