Antibiotic Resistance
The European perspective

Dik Mevius
Antibiotic Resistance Surveillance EU

**Legal Basis:**
- Target organisms:
  - Salmonella, Campylobacter and other organisms of PH-concern (e.g. MRSA)
  - E. coli, enterococci (indicator or sentinel organisms)
- EFSA-guidelines

**Broth microdilution**
- (NEN-EN-ISO 16256:2012 ≅ CLSI)
- No clinical MIC-breakpoints
- EUCAST ECOFF’s
Indicator organisms (E. coli)

- Provide optimum information about acquired resistance in populations and associations with antibiotic usage or interventions
  - Sampling can randomized
  - No isolation rates or species/serotype influences on R%

- Currently under debate in EC to make this mandatory
  - Isolates from faecal samples taken at/close to slaughter
  - and meat
European reports
Resistance from 1998 - 2011
(E. coli as commensal in the GI-tract) (MARAN-2012)
Expressed as multi-drug resistance
Antibiotic usage in humans and animals in Europe
ESAC versus ESVAC

Figure 1. Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg of live mass 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.
Antibiotic use in animals in NL (Source FIDIN)

90% oral administration by group/flock mediation

Increase up to 2007 was the basis for mandatory reduction policy of the government of 20/50%
Animal versus human use in kg

van Geijlswijk, et al, TvD, 2009
What does this mean

- Dutch food-producing animals are an ideal environment for multidrug resistant organisms

- Risk??
  - Animal health?
    - Yes, if they cause infections
  - Public health?
    - Yes if:
      - Food-borne pathogens
      - Zoonotic organisms
      - Transferable genes
Relation between resistance in animals and humans?

- In spite of long term differences in usage, the resistance levels in Dutch Health care are low!
- So does a relation with resistance in animals exist?
  - Unfortunately, yes
    - MRSA!
    - ESBLs!
EARSS-net 2010 report (ECDC) on MRSA and ESBLs in invasive infection in hospitals
Extended Spectrum Beta-lactamases (ESBLs)

- Enzymes that inactivate beta-lactam antibiotics
  - Penicillin, ampicillin, amoxicillin
  - All cefalosporins

- Consequence for infections with ESBL-producers:
  - Impaired treatment, increased risk for patients

- Genes are transferable on plasmids (E. coli/Salmonella)
  - Transmission of ESBLs also via the food-chain!!!
Types of Beta-Lactamases

- **Beta-Lactamase**
  - Penicillinase $bla_z$ (S. aureus)
  - TEM-1, SHV-1 (Enterobacteriaceae)

- **ESBLs**
  - TEM-derivatives, SHV-2 and derivatives, CTX-M, OXA, PER, VEB, GES

- **AmpC-group (CMY, DHA etc)**

- **Carbapenemases (KPC, OXA, IMP, VIM, NDM)**
  - > 1000 variants known
  - EU: CTX-M-1, TEM-52 dominant in poultry
  - US: CMY-2
Cefotaxime resistance in E. coli (MARAN)

Cefotaxime R% in E. coli

- Dairy cattle
- Veal calves
- Pigs

Dairy cattle: Green circles
Veal calves: Blue diamonds
Pigs: Black triangles


R%:
- 0
- 5
- 10
- 15
- 20
- 25

Increased detection of extended spectrum beta-lactamase producing Salmonella enterica and Escherichia coli isolates from poultry
Cindy Dierikx, Alieda van Essen-Zanderbergen, Kees Veldman, Hilde Smith, Dik Mevius

β-Lactamases among extended-spectrum β-lactamase (ESBL)-resistant Salmonella from poultry, poultry products and human patients in The Netherlands
Henrik Hasman, Dik Mevius, Kees Veldman, Inger Olesen and Frank M. Aarestrup
ESBL-genes and plasmids in Broiler isolates
(Dierikx et al. 2010)

Humans:
CTX-M15, 14/9, 3…..

100% farms positive, 96% of the animals
Transmission in the Poultry production pyramid

Vertical transmission and recirculation in all layers of the pyramid

Broilers app. 100% positive in one week!!
Distribution in Europe in poultry

CMY

ESBL + CMY

Map of Europe with arrows indicating distribution patterns.
Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains

M. A. Leverstein-van Hall¹,2, C. M. Dierikx¹, J. Cohen Stuart¹, G. M. Voets¹, M. P. van den Munde³, A. van Essen-Zandbergen¹, T. Platteel¹,4, A. C. Fluit¹, N. van de Sande-Bruinisma², J. Scharinga¹, M. J. M. Bonten¹,5 and D. J. Mevius³,4; on behalf of the national ESBL surveillance group a

1) Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, 2) Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, 3) Department of Bacteriology and TSEs, Central Veterinary Institute of Wageningen UR, Lelystad, 4) SALTRO, Primary Health Care Laboratory, Utrecht, 5) Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht and 6) Department of Infectious Diseases & Immunology, Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands

<table>
<thead>
<tr>
<th>Level of genetic typing</th>
<th>% of human isolates with poultry associated genetic element a</th>
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<tbody>
<tr>
<td>ESBL genes (blaCTX-M-1, blaTEM-52, blaSHV-12, blassHV-2 and blaCTX-M-2)</td>
<td>35% (see Table 1)</td>
</tr>
<tr>
<td>blaCTX-M-1 and blaTEM-52 genes</td>
<td>30% (23.7% blaCTX-M-1; 6.2% blaTEM-52)</td>
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<tr>
<td>blaCTX-M-1 and blaTEM-52 genes on IncI plasmid</td>
<td>20% (14.2% blaCTX-M-1; 6.2% blaTEM-52)</td>
</tr>
<tr>
<td>blaCTX-M-1 and blaTEM-52 genes on IncI plasmid belonging to complex CC7 or CC3 and CC5 resp.</td>
<td>19% (12.6% blaCTX-M-1; 6.2% blaTEM-52)</td>
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<tr>
<td>blaCTX-M-1 and blaTEM-52 genes on IncI plasmid belonging to complex CC7 or CC3 and CC5 resp. in a poultry-associated MLST strain (ST10, ST58 or ST117)</td>
<td>11% (9.5% blaCTX-M-1; 2.0% blaTEM-52)</td>
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Association with humans

Extended-Spectrum β-Lactamase Genes of *Escherichia coli* in Chicken Meat and Humans, the Netherlands

Ilse Overdevest, Ina Willemsen, Martine Rijnsburger, Andrew Eustace, Li Xu, Peter Hawkey, Max Heck, Paul Savelkoul, Christina Vandenbroucke-Grauls, Kim van der Zwaluw, Xander Huijsdens, and Jan Kluytmans

**Figure 1.** Distribution of extended-spectrum β-lactamase genes in chicken meat (A), human rectal swabs (B), and human blood cultures (C), the Netherlands. Values in parentheses are no. positive.
Conclusion:

- Yes an animal attribution is apparent
- Poultry meat was considered to be the most likely source

84 – 100% of poultry meat pos for ESBLs
Pork/beef incidentally pos
## ESBLs in other animals in The Netherlands

<table>
<thead>
<tr>
<th>Animal species</th>
<th>ESBLs-Prevalence</th>
<th>ESBL subtypes detected</th>
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<tbody>
<tr>
<td>Companions</td>
<td></td>
<td></td>
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<tr>
<td>Wilde eend</td>
<td>Anas platyrhynchos</td>
<td>CTX-M-1, 2, 9, 14, 15, 22, 80, OXA-1</td>
</tr>
<tr>
<td>Rotsduif</td>
<td>Columbia livia</td>
<td>TEM-30, 52, 58, OXA-1</td>
</tr>
<tr>
<td>Kemphaan</td>
<td>Philomachus pugnax</td>
<td>CMY-2, 39 (qnr)</td>
</tr>
<tr>
<td>Tureluur</td>
<td>Tringa totanus</td>
<td></td>
</tr>
<tr>
<td>Kokmeeuw</td>
<td>Chroicocephalus ridibundus</td>
<td>CTX-M-1, 2</td>
</tr>
<tr>
<td>Veal calves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zilvermeeuw</td>
<td>Larus argentatus</td>
<td></td>
</tr>
<tr>
<td>Zwarte zwaan</td>
<td>Cygnus atratus</td>
<td></td>
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<tr>
<td>Grote mantelmeeuw</td>
<td>Larus marinus</td>
<td></td>
</tr>
<tr>
<td>Jan van Gent</td>
<td>Morus bassanus</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>17 (22%)</td>
</tr>
<tr>
<td>Slaughter pigs</td>
<td></td>
<td></td>
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<tr>
<td>Dairy cows</td>
<td>11% individual animals</td>
<td>CTX-M-1, 2</td>
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<tr>
<td>Turkeys</td>
<td>50% flocks</td>
<td>CTX-1, 15, CMY-2</td>
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Is poultry the source or part of the problem??
Measures implemented by the government
2008 memoranda of understanding signed

■ Mandatory reduction of antibiotic usage of 20% in 2012 and 50% in 2013 (compared to 2009)
  • New target = 70%
  • All antibiotic use on farms registered
    • Mandatory since 2012
  • Preventive use not legal
  • Restrictions on use of FQ and Cefs
  • Independent control institute
    • Animal Drug Authority (SDa, [www.autoriteitdiergeneesmiddelen.nl](http://www.autoriteitdiergeneesmiddelen.nl))
      » Tasks
        » Report usage data publically,
        » Define targets for usage
        » Identify frequent users
        » Control measures to improve usage
BENCHMARK INDICATORS

ACTION LEVEL
Direct measures necessary to reduce antibiotic usage

SIGNALING LEVEL
Please be aware

TARGET LEVEL
No direct measures necessary to reduce antibiotic usage
Broilers usage data 2011 in (N = 737)

$\text{ADDD/Y} \approx \text{nr of treatment days per year on each farm}$

Median -20%

Germany NRW 50 ADDDs

Denmark 3 ADDDs

P75

Behandeldagen/year

Frequentie
Is it all about targets and control??

- **Not only**
  - Stimulate the responsibility of both farmers and vets to control and improve the health status of the animals without strategic usage of preventive antibiotics
  - ADDD’s are a tools to visualize the effects of measures aimed at:
    - Infection control
    - Improved management, climate etc.
    - Feed quality
    - Drinking water
    - Housing density
    - Other preventive measures…
Ceftiofur use in Dutch poultry

- **Not licenced in poultry in EU because no MRL for poultry**
  
  >> administration in poultry only legal according to the cascade rule

- **Used in:**
  
  - **Reproduction animals (GP, P) (until 2010 in NL, other EUMSs??)**
    - In day-old chicks SC injection
    - In-ovo
  
  - **Broilers hatcheries**
    - Spray in NL and B (until March 2010)
Cefotaxime resistance in E. coli

Ban of ceftiofur use at hatcheries
Impact of withdrawal of in ovo use of ceftiofur in Québec

Voluntary withdrawal in Québec*

Percentage of ceftiofur resistance

Year and quarter

Dutil et al.
Trends in Sales of antibiotics in NL

*sales 2012 are estimated, based on preliminary data of the first half year

(FIDIN/LEI 2012)
www.maran.wur.nl
Sales of antibiotics for animals (mg) per kg biomass produced (PCU) in Europe

2007

2010

Antibiotic use in mg/PCU in 19 EU Member States
Will we succeed?

Antibiotic reduction

- Most likely, yes!!

Antimicrobial resistance

- Why?
  - Global problem
  - More determinants than antibiotic usage
  - May need structural changes in animal husbandry practices

Will it be enough??
Thanks to Manon Houben, PorQ