Antimicrobial use and resistance: 
Background from a veterinary perspective

Prof. Dr. Jeroen Dewulf
Jeroen.Dewulf@UGent.be

Unit for Veterinary Epidemiology,
Faculty of Veterinary Medicine
Ghent University

Centre of excellence AMCRA
The epidemiology of antimicrobial resistance in animals

Transmission of resistance from animals to humans and vice versa
Epidemiology of antimicrobial resistance

May be divided into 4 steps:

1. Development of antimicrobial resistance
2. Selection of antimicrobial resistance
3. Persistence of antimicrobial resistance
4. Reduction of antimicrobial resistance
Epidemiology of antimicrobial resistance

Fase I:
Development of AR
Antimicrobial resistance genes are naturally present in the environment

• Development of antimicrobial resistance is independant of antimicrobial use

• Function of the genes is often unknown
Antibiotic resistance is ancient

Vanessa M. D’Costa1,2*, Christine E. King3,4*, Lindsay Kalan1,2, Mariya Morar1,2, Wilson W. L. Sung4, Carsten Schwarz3, Duane Froese5, Grant Zazula6, Fabrice Calmels5, Regis Debruyne7, G. Brian Golding4, Hendrik N. Poinar1,3,4 & Gerard D. Wright1,2

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes3,2. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics3. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Recent studies of modern environmental and human commensal microbial genomes have a much larger concentration of antibiotic resistance genes than has been previously recognized4-6. In addition, metagenomic studies have revealed diverse homologues of known resistance genes broadly distributed across environmental locales. This widespread dissemination of antibiotic resistance elements is inconsistent with a hypothesis of contemporary emergence and instead suggests a richer natural history of resistance. Indeed, estimates of the origin of natural product antibiotics range from 2 Gyr to 40 Myr ago7,6, suggesting that resistance should be similarly old. The discovery of genes encoding antibiotic resistance in the fossil record provides a direct and compelling example of the long-standing nature of this phenomenon. Our findings also serve as a cautionary reminder that antibiotic resistance is not only a modern phenomenon, but one that predates the antibiotic era and is deeply ingrained in the evolutionary history of bacteria.
Resistance can easily be transmitted
Epidemiology of antimicrobial resistance

Fase I:
Development of AR

Fase II:
Selection of AR resistance
Selection of resistance

- Selection of antimicrobial resistance is the result of:
  - Antimicrobial use!
  - Non-use risk factors (persistance and spread):
    - Stress
    - Feed
    - Hygiene
    - Housing
    - ...

Selection of resistance

Callens et al., 2011
Belgian broilers:

35 – 40% *E. coli* resistant for ceftiofur
60% of broilers carrier of ESBL

Persoons et al., 2010
ANTIMICROBIAL RESISTANCE *Escherichia coli* end fattening period

**Fattening Pigs:**

Callens et al., 2011
Epidemiology of antimicrobial resistance

Fase I: Development of AR

Fase II: Selection of AR resistance

Fase III: Persistence of AR resistance
Fattening pigs:

**ANTIMICROBIELE RESISTENTIE Escherichia coli** end of fattening period

![Graph showing antimicrobial resistance levels for Escherichia coli in fattening pigs. The graph indicates the percentage of resistant strains for various antibiotics, including Streptomycin, Sulfonamides, Tetracycline, Trimethoprim, Ampicillin, Chloramphenicol, Kanamycin, Flofenicol, Apramycin, Neomycin, Nalidixine, Amoxiclav, Cefiofur, Enrofloxacine, and Gentamicine. The data is from Callens et al., 2011.](image)
Belgian broilers

Persoons et al., 2010
Prevalence of MRSA in pigs
Epidemiology of antimicrobial resistance

Fase I: Development of AR

Fase II: Selection of AR resistance

Fase III: Persistence of AR resistance

Fase IV: Reduction of AR resistance
Reversion to susceptibility by reduced antimicrobial consumption
The epidemiology of antimicrobial resistance in animals

Transmission of resistance from animals to humans and vice versa
Transmission of antimicrobial resistance from animal-human: Literature data

Gentamicin resistance in clinical isolates of *Escherichia coli* encoded by genes of veterinary origin

Evidence for Natural Horizontal Transfer of *tetO* between Bacteria That Normally Colonize Humans and Bacteria That Normally Colonize Livestock

Urinary isolates of apramycin-resistant *Escherichia coli* and *Klebsiella pneumoniae* from Dublin

**Vancomycin resistant *Enterococcus faecalis* isolates from a Danish patient and two healthy human volunteers are possibly related to isolates from imported turkey meat**

Aminoglycoside Acetyltransferase 3-IV (*aacC4*) and Hygromycin B

4-1 Phosphotransferase (*hphB*) in Bacteria Isolated from Human and Animal Sources
Antimicrobial resistant *Salmonella* Typhimurium-transmission too human through food

<table>
<thead>
<tr>
<th></th>
<th>ABRP Varken</th>
<th>ABRP Kip</th>
<th>Amp varken/kip</th>
</tr>
</thead>
<tbody>
<tr>
<td>= ABP Varken</td>
<td>74,5%</td>
<td>94,1%</td>
<td>92,1%</td>
</tr>
<tr>
<td>= ABP Kip</td>
<td>53,6%</td>
<td>90,7%</td>
<td>79%</td>
</tr>
<tr>
<td>Amp varken/kip</td>
<td>48,5%/56,1%</td>
<td>35,3%/76,7%</td>
<td>50,3%</td>
</tr>
</tbody>
</table>

ABRP=antibioticum resistentie profiel; Amp=ampicilline resistentie;

Research scientific comity FASFC 2009
Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains

M. A. Leverstein-van Hall¹,², C. M. Dierikx³, J. Cohen Stuart¹, G. M. Voets¹, M. P. van den Munckhof¹,
A. van Essen-Zandbergen³, T. Platteel¹,⁴, A. C. Fluit¹, N. van de Sande-Bruinsma², J. Scharinga¹, M. J. M. Bonten¹,⁵
and D. J. Mevius³,⁶; on behalf of the national ESBL surveillance group*

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
Assessment of human exposure to cephalosporin resistant E.coli (CREC) from chicken through consumption of broiler meat

Probability of the exposure to CREC through consumption of a meal containing chicken meat and in function of 4 arbitrarily chosen infection doses.

<table>
<thead>
<tr>
<th>Infection doses (arbitrarily chosen)</th>
<th>10000 cfu</th>
<th>1000 cfu</th>
<th>100 cfu</th>
<th>10 cfu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure through insufficient heating of chicken meat preparations</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0,03%</td>
</tr>
<tr>
<td>Exposure through cross contamination (all types of chicken excl. chicken meat bought cooked / prepared)</td>
<td>0,39%</td>
<td>1,53%</td>
<td>3,26%</td>
<td>6,97%</td>
</tr>
<tr>
<td>Total exposure</td>
<td>0,39%</td>
<td>1,53%</td>
<td>3,26%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Research scientific comity FASFC 2011
Resistente bacteriën in groenten

Nederlandse wetenschappers hebben in groenten bacteriën gevonden die resistent zijn voor een groot aantal antibiotica.

De onderzoekers van de VUmc in Amsterdam vinden in zeven van de in totaal 120 onderzochte groentenmonsters een ESBL-houdende resistente bacterie. Dat zijn enzymen die bacteriën aanmaken waardoor ze resistent worden voor veel antibiotica.

De bacteriesoorten komen op grote schaal voor in menselijke en dierlijke darmen en luchtwegen.

Ook biologisch

De monsters waren afkomstig van vijftien verschillende groentensoorten die op of in de grond groeien. In taugé, radijs, lente-ui en pastinaak werd de bacterie aangetroffen.

In totaal waren zeven monsters ESBL-positief. Opmerkelijk genoeg waren vier van de zeven besmette monsters van biologische kweek.

Hoe de groenten besmet raken, is nog niet onderzocht. De meest waarschijnlijke hypothese is dat bemesting met dierlijke mest daarbij een rol speelt. Ook is het mogelijk dat de resistentie bacteriën al in de grond zaten.
Conclusions

- AMR is selected for by use of antimicrobials
- Once AMR is present it is difficult to get rid of again
- AMR may spread from animals to humans through food, direct contact and environment
- Lots of unknowns
Thank you for your attention

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