Antibiotic Resistance – Linking Human and Animal Health

Henrik C. Wegener
Provost, Technical University of Denmark
Adjunct Professor, Univ. Cph.

DTU Food
National Food Institute
Disposition

• AMR in a One Health perspective
• National, regional and global examples of integrated surveillance systems
• Examples of “up-stream” interventions to prevent AMR emergence and spread
• Conclusions

“Prevention is better than (no available) cure”
AMR problems are all about negative externalities and tragedies of commons dilemmas'

A **negative externality** is an cost of a use decision by one set of parties on others who
did not have a choice and whose interests
were not taken into account.

"Tragedy of the commons" is a dilemma arising from the situation in which multiple individuals, acting independently and rationally consulting their own self-interest, will ultimately deplete a shared limited resource.

Societies’ approach to dealing with negative externalities and ToC dilemmas’ is by: **Regulation**
It’s about complex and unpredictable systems of – transmission,

Example: 100% of Vietnamese shrimp farms uses ciprofloxacin. Fluoroquinolone concentrations in sediments and surface waters reaches > 4,000 ug/kg (Thuy et al, 2011)

- Oral use
- Mass medication
- Low doses (AGP)
- Long term exposure
- Prophylaxis
- Long term carriage

Selective pressures favoring antibiotic resistance development

- Therapeutic use
  - High dose/short term
  - Clinical disease and short term carriage
And it’s about ... Pyramids and snowball effects
Up stream control of egg associated human salmonellosis in Denmark

Cases per 100,000 inhab.

88 89 90 91 92 93 94 95 97 99 '00 '01 '02 '03 '04 '05 '06 '07
Prevalence of *Salmonella* infected broiler flocks in Denmark

Pre-harvest testing, top down eradication, public-private partnership
And it’s about global spread...
It’s about the ever growing list of AMR pathogens

- **Salmonella**
  - Fluoroquinolone resistance, incl. plasmid mediated (qnr)
  - 3rd and 4th gen. cephalosporin resistance
- **E. coli**
  - Plasmidmediated quinolone resistance
  - 3rd. and 4th generation cephalosporin resistance
- **Campylobacter**
  - Fluoroquinolone resistance
  - Macrolide resistance
- **Enterococcus faecium/faecalis**
  - Vancomycin resistance
  - Synercid resistance
- **Staph. aureus**
  - Methicillin resistance
  - Multiple resistance

**How good is the evidence?**

Clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials, including:
- Infections that would not have otherwise occurred
- Increased frequency of treatment failures, sometimes death
- Increased severity of infections
And it’s about the way drugs are being used in modern agriculture

- Antimicrobial growth promotion & routine prophylaxis (e.g. Medicated Early Weaning and in-ovo injections), and the use of antibiotics as a main driver for cutting costs and/or increasing productivity

- Critically important antimicrobials for human health used in food animals

- Farmers access to antimicrobials without a prescription

- Veterinarians’ financial incentives to prescribe
National, regional and global initiatives to establish integrated surveillance
Integrated Surveillance of Zoonoses and AMR in Denmark

- Integrated surveillance of Zoonoses since 1994 (Danish Zoonosis Ctr.)
- Integrated surveillance of AMR since 1995 (DANMAP)
- Detailed surveillance of AMU since 2000 (VETSTAT)
- Strong intersectoral collaboration through the Danish Zoonosis Centre and the Danmap Steering Committee
The Danish Zoonosis Centre - a One Health Role Model

Ministry of Agriculture  Ministry of Education and Science  Ministry of the Environment  Ministry of Health

DK Veterinary and Food Administration  Danish Nature Agency  National Board of Health

National Veterinary Institute  Danish Zoonosis Centre Collection, collation, analysis, interpretation of data dissemination of information

Public Health Institute

National Food Institute

DZC Stakeholder Group: Industry, NGO’s, Academia, Unions and Prof. Associations
DANMAP Steering Committee - reporting to the Danish Zoonosis Centre and the National Antibiotic Council

Risk Assessment

Funded by MoA

National Food Institute
National Veterinary Institute

DANMAP Steering Committee

Funded by MoH

Public Health Institute

Risk Management

Danish Veterinary and Food Administration

Danish Board of Health

Danish Medicines Agency
DANMAP - Integrated Surveillance of Antimicrobial Resistance and Antimicrobial Usage in Denmark

Running costs: < 1,0 mio. US$/year
VETSTAT - National monitoring of veterinary antimicrobial usage in DK

Running costs: ~0.5 million € per year

For each record:
- Farm ID
- Animal species
- Age group
- Date
- Drug ID
- Drug quantity
- Disease category
- Prescriber ID

Medicated feed (5 %)

Coccidiostats

Thanks to D. Monnet
Resistance in *Campylobacter jejuni* – DANMAP 2010

Danish broilers

Danish broiler meat

Imported broiler meat

Domestically acquired

Travel abroad

- Tetracycline
- Erythromycin
- Ciprofloxacin
A regional Zoonosis/AMR Surveillance Network of EU Member States

Animal, food and feed monitoring → Foodborne outbreaks → EU

BSN Zoonoses

DSNs - Enter-Net - EuroTB

Communicable diseases

EFSA

Veterinary Laboratories Agency®

rivism

National Institute for Public Health and the Environment

DTU Food

National Food Institute

BfR

Bundesinstitut für Risikobewertung

ECDC

EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

National Food Institute, Technical University of Denmark
C. Jejuni in chicken and ciprofloxacin resistance, EU AMR survey 2009
Global Networks

WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

Develop harmonized schemes for monitoring AMR and AMU

Support WHO capacity-building activities for AMR and AMU monitoring (through WHO GFN).

Promote information sharing on AMR.

Provide expert advice on containment of AMR with a particular focus on Human Critically Important Antimicrobials.

Support and advise WHO on the design of pilot projects for conducting integrated surveillance of AMR.
Global Foodborne Infections Network

Building integrated zoonoses and AMR surveillance capacity globally

> 85 international training courses for > 140 countries

Currently: ~ 1.200 members from >160 countries
Quinolone resistance in *Salmonella* Schwarzengrund

Danish pigs

Danish Patients

Imported chicken meat in DK

Chicken meat in Thailand

Thai patients
Up-stream interventions to control AMR and their effects
Phasing out non-therapeutic use/growth promoter use in food animals in Denmark

Effect:
Reduced the total usage of antimicrobials in animals by ~50%
Banning Antimicrobial Growth Promoters effect on resistance to Vancomycin and Synercid in *E. faecium* in food animals

Source: DANMAP 99
Banning routine prophylactic usage and limiting vet’s profit from the sale of drugs (re. “perverse incentives”)

- New veterinary medicinal regulation adopted in 1995

**Effect:** Reduced the total usage of prescribed veterinary medicine by 30-40% from one year to the next
Preserving critically important drugs

- 1999 Voluntary terminating use of in-feed FQ’s
- 2002 Special regulatory requirement for prescribing fluoroquinolones; Documented need (no alternatives), District veterinary officer notified, and only administered by the veterinarian

**Effect:** Reduced usage of FQ’s and reduced levels of resistance in some FBP’s
Nalidixic acid resistance in *E. coli* from pigs in the EU 2009
Voluntary termination of the use of cephalosporins in swine

Danish swine producers introduced in the summer of 2010, a two year voluntary stop for the use of cephalosporins, in order to prevent the selection and spread of ESBL bacteria (*E. coli* and *Salmonella*) in swine production.

**Effect:** Imminent reduction in overall usage, awaiting AMR data the coming years.
Veterinary treatment guidelines

Based on data on resistance in common animal pathogens from diagnostic laboratories

Old narrow spectrum drugs given preference over newer and broader spectrum drugs

<table>
<thead>
<tr>
<th>Disease</th>
<th>Common Agent</th>
<th>Priority 1</th>
<th>Priority 2</th>
<th>Priority 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>L. intracellularis</td>
<td>Tiamulin</td>
<td>Tetracycline</td>
<td>Tylosin</td>
</tr>
<tr>
<td></td>
<td>S. hyodysenteria</td>
<td>Tiamulin (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>A. pleuropneumoniae</td>
<td>Penicillin (99%)</td>
<td>Amoxycillin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td></td>
<td>P. multocida</td>
<td>Penicillin (100%)</td>
<td>Amoxycillin</td>
<td>Ampicillin</td>
</tr>
</tbody>
</table>

Effect: Limited effect on amounts and patterns of use
The “Yellow Card” System
- monitoring of usage at herd level and follow up by the regulatory authorities

From the autumn 2010

Based on VETSTAT antibiotic usage monitoring data

The swine producers who are in the top end in terms of antibiotic usage (~1.250 farms) and their vet’s receive a “yellow card”.

If usage is not reduced within nine months of yellow card – the district vet’s office may impose sanctions to reduce usage.

Effect: ~ 20% reduction in 2011
Comparison of the sales of veterinary antibacterial agents between 10 European countries (Grave et al. 2010)
Different production systems – how low can we go?

Organic swine herds uses ~1/10th of the volumes used in comparable conventional herds in DK

Figure 11: Proportion of finisher pig herds within study herd type with registered consumption of different types of antimicrobial agents in 2007 (Source: Vetstat). Only antimicrobial agents prescribed for finishers is included.
Regulating the bug: Thresholds for certain resistant pathogens

- 0-tolerance for MR S. Typhimurium DT104 in food

**Effects:** Reduced consumer exposure to MR DT104 from domestically produced and imported food products

*Figure 7. Trends in resistance to selected antimicrobials among Salmonella Typhimurium isolated from poultry and pigs and from human cases, Denmark*
Stopping foodborne AMR at the border – non-discriminatory sampling and ”case-by-case risk assessment”

![Chart showing cases of susceptible, resistant, and multiple resistant cases, differentiated between Danish and imported cases. The chart indicates a higher number of resistant and multiple resistant cases in imported cases compared to Danish cases.]

- **Cases**
  - Susceptible
  - Resistant
  - Multiple resistant

- **Chart Legend**
  - Orange: Danish
  - Red: Imported

- **Note:** The chart highlights the importance of risk assessment at the border to control the entry of resistant Salmonella cases.
Conclusions - integrated surveillance

• Requires systematic sampling, harmonized laboratory methods, and good data management
• Requires detailed denominator data about the origin of the samples
• Requires sub-typing of bacterial isolates, and molecular characterization of resistance genes
• Requires detailed antimicrobial usage data
• Requires flawless collaboration and coordination, including sharing and comparing data
• Forms a solid basis for further detailed investigation of specific questions
Conclusions II
- AMR in a One Health perspective

• **Selection:** There is a direct but complex relationship between AMU and AMR in food animals however, other factors such as co-selection and clonal spread also play a part.

• **Transmission:** There is a direct but complex relationship between AMR in the food supply and AMR in foodborne human infections:

\[ R_{human} \approx X \cdot R_{domest. \text{ food/animals}} + Y \cdot R_{imported \text{ food}} + Z \cdot R_{travel \text{ abroad}} \]

• The relative impact of imported food stuffs and travel is increasing, calling for increased international collaboration.
Conclusions III
- up-stream interventions to reduce resistance

• It is possible to reduce resistance levels in the non-human reservoirs by reducing the selective pressure from antimicrobials in food animals.

• Banning non-therapeutic uses, and removing financial incentives for prescribing therapeutic drugs are effective interventions.

• Restricting the use of critically important drugs is effective.

• Reducing antimicrobial usage requires collaboration between experts, regulatory authorities and producers.

• Monitoring of the effects of interventions is essential.
Thank you for your attention

I’m just sitting here all by myself thinking off the future of integrated whole genome based microbial surveillance