Role of food of animal origin as source of AMR in humans

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NOT REPRESENTING THE DUTCH DELEGATION

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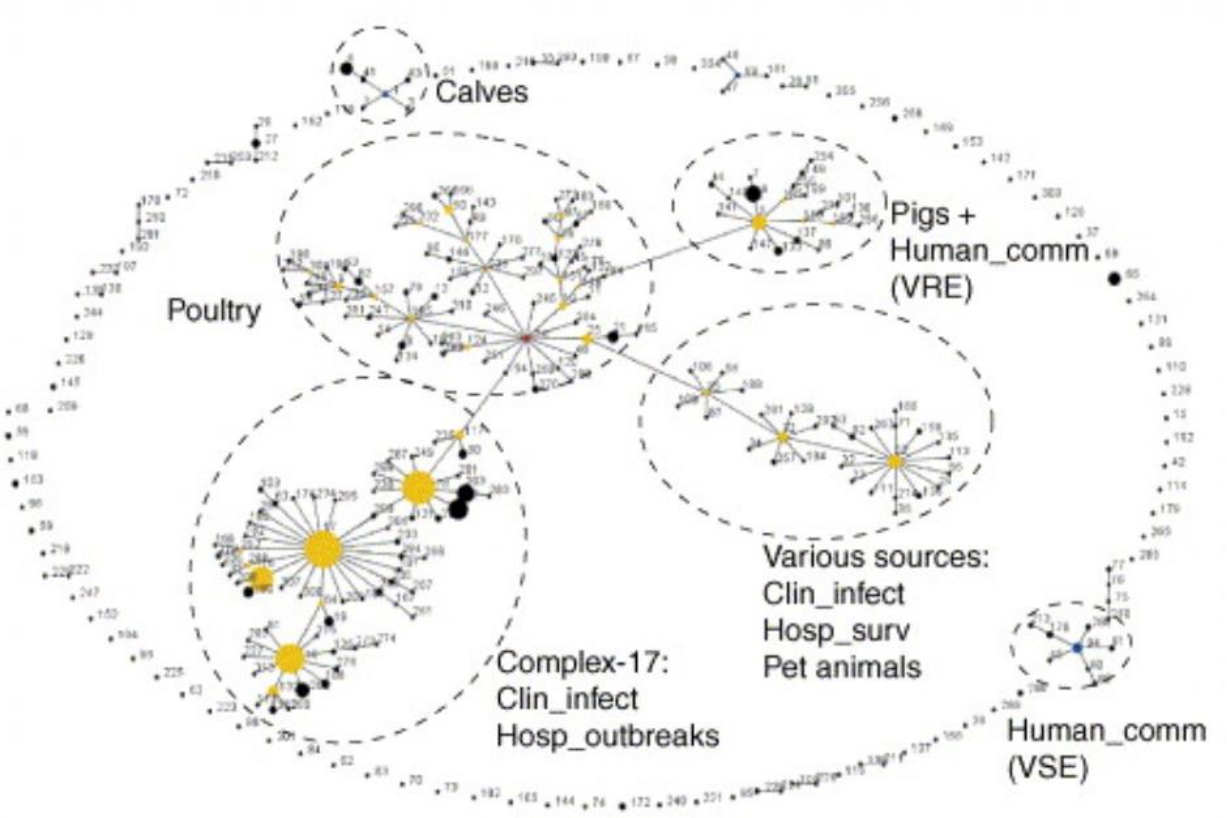
Outline

- What is the presence and the scientific evidence for transfer
- Interventions
- Treshold of resistance in food?
- Conclusions and data gaps

What are the concerns?

- Gram negatives (Enterobacteriaceae)
  - ESBL producing
  - carbapenemases producing (CPE)
- Livestock Associated Methicillin Resistant *S. aureus*
- Enterococci

Enterococcus faecium



Human illness source attribution methods

Methodologies for attribution of human illness to specific sources

Approaches	Methods
Microbiological approaches	Microbial subtyping
	Comparative exposure assessment
Epidemiological approaches	Analysis of sporadic cases
	Analysis of data from outbreak investigations
Intervention studies	
Expert elicitation	

Problems….

- Exposure does not lead to immediate respons/symptoms
- Epidemiological approach is difficult (compare with *Salmonella*)

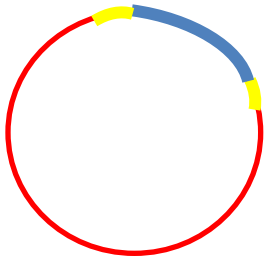
- Effect in humans of AMU intervention in animals under-explored and difficult because of parallel interventions
- Microbiological approach: typing is complex

ESBLs

1. ESBL gene

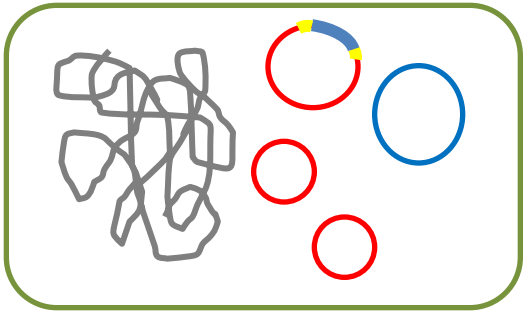
Gene(s)

2. Mobile elements
   - Plasmid
   - Insertion sequence
   - Transposons



Plasmid(s)

3. *E. coli* carrier/host



Single strain

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Journal of Antimicrobial Chemotherapy

Molecular relatedness of ESBL/AmpC-producing *Escherichia coli* from humans, animals, food and the environment: a pooled analysis

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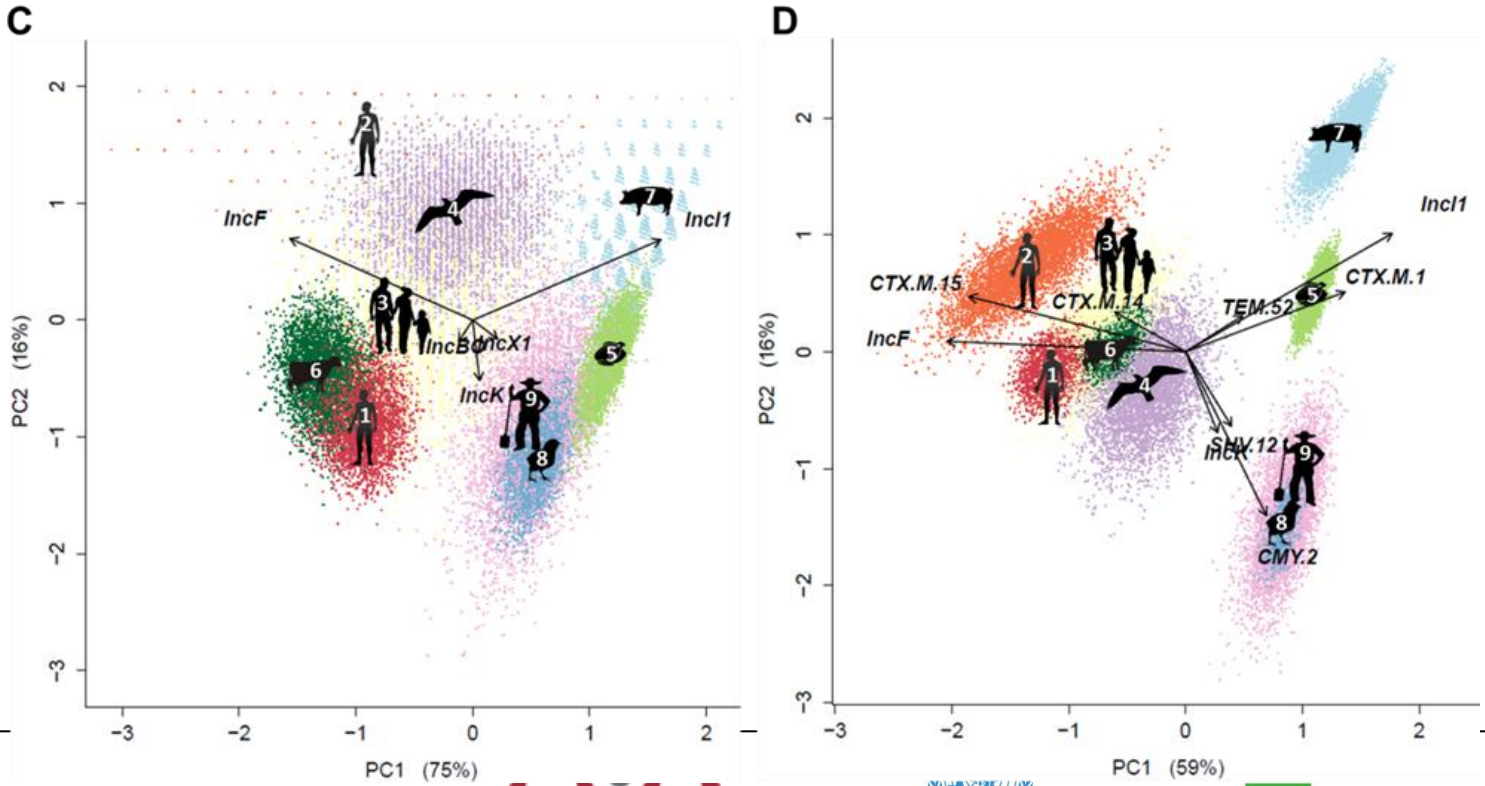
Background: In recent years, ESBL/AmpC-producing *Escherichia coli* (ESBL/AmpC-EC) have been isolated with increasing frequency from animals, food, environmental sources and humans. With incomplete and scattered evidence, the contribution to the human carriage burden from these reservoirs remains unclear.

Results-Proximity of reservoirs in terms of plasmid replicon types and ESBL/AmpC genes

Panel 2. Meta-analysis of plasmid replicon profiles from 808 *E.coli* isolates in the Netherlands. Human (H-), animal (A-), food (F-) and the environment (E-) reservoirs represented by silhouettes with the following numbers: 1-H-clinical UTIs, 2-H-clinical blood, 3-H-general population, 4-A-wild bird, 5-F-chicken meat, 6-A-veal calves, 7-A-pig, 8-A-broilers, 9-H-farmers/family in broiler farm.
A) Proportion of plasmid replicon types over total number of plasmids collated per reservoir.
B) Pairwise PSIs for plasmid replicon types between reservoirs. Cells are shaded gradually according to PSI values (from 0 [no similarity in gene profiles] to 1 [identical profiles])
C) PCA on the bootstrapped samples of plasmid replicon relative frequencies per reservoir. Only the most discriminatory plasmids are plotted. Higher dispersion of point clouds indicates less confidence in the clustering and vice versa.
D) PCA on the bootstrapped samples of plasmid replicon profiles (from 808 isolates) and of gene profiles (from the complete isolate meta-collection, n=3646) per reservoir. Only the most discriminatory plasmids and genes are plotted. Higher dispersion of point clouds indicates less confidence in the clustering and vice versa.



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Conclusions from this Dutch study

- Limited similarity between farm animals and humans in clinical settings or general population
- Farmers/family members very similar to animal reservoirs (ESBL transmission from animals to people)
- Environmental reservoirs sharing many similarities with human clinical samples (water samples-treatment plants/wild birds)
- Chicken meat isolates distant from the broiler reservoir (unknown country of origin of the samples)
- Human to human attribution overall highly relevant
- Animal human attribution in the 1-10% range for some specific livestock associated genes and animal species (sectors)

QMRA Exposure estimates meat/animals species

Category	exposure per contaminated portion (No. ESBL EC/portion)	fraction of contaminated portions	exposure per portion (No. ESBL EC/portion)	total number of consumed portions	total exposure (No. ESBL EC)
Beef	**1.88E+1**	1.46E-2	2.75E-1 (1)	3.29E+9	**9.05E+8 [77.5%]**
Chicken	1.75E+0	6.85E-2	1.20E-1 (2)	1.75E+9	**2.09E+8 [17.9%]**
Pork	2.44E+0	3.05E-3	7.44E-3 (4)	7.12E+9	**5.29E+7 [4.5%]**
Veal	3.56E+0	1.35E-2	4.81E-2 (3)	2.81E+7	**1.35E+6 [0.1%]**
Mutton/lamb	N.a.	0.00E+0	0.00E+0 (5)	5.22E+7	0.00E+0 [0%]
Mean (^{m}) or sum (^{s})	6.15E+0^{m}	1.55E-2^{m}	9.55E-2^{m}	1.22E+10^{s}	1.17E+9^{s}

total exposure Dutch population: 900 million per year

Evers et al., PlosOne 2017

EU-funded project on AMR

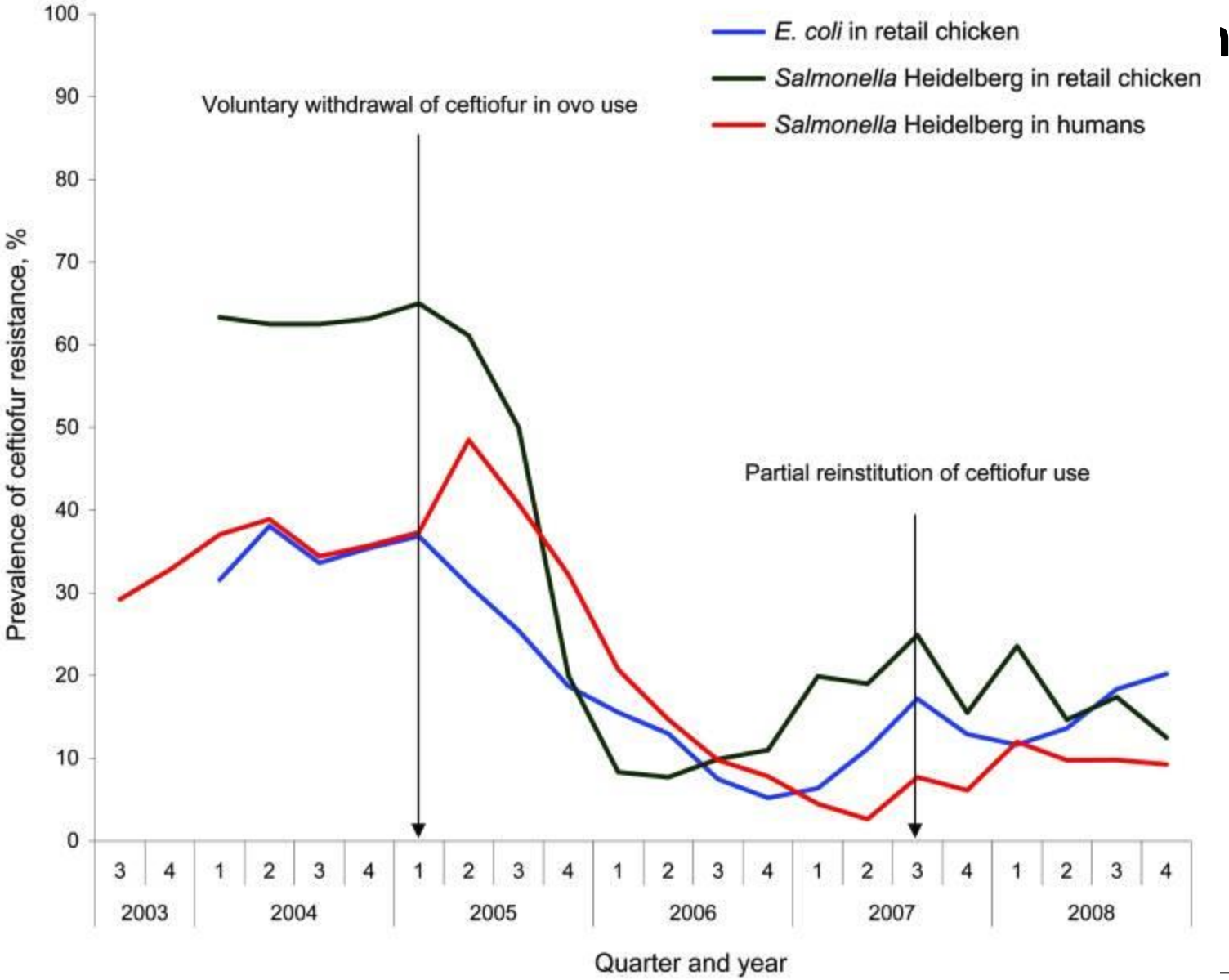
EFFORT: Ecology from **F**arm to **F**ork **O**f microbial drug **R**esistance and **T**ransmission

What is the relative attribution of food of animal origin to AMR exposure of humans and what effect will interventions have?

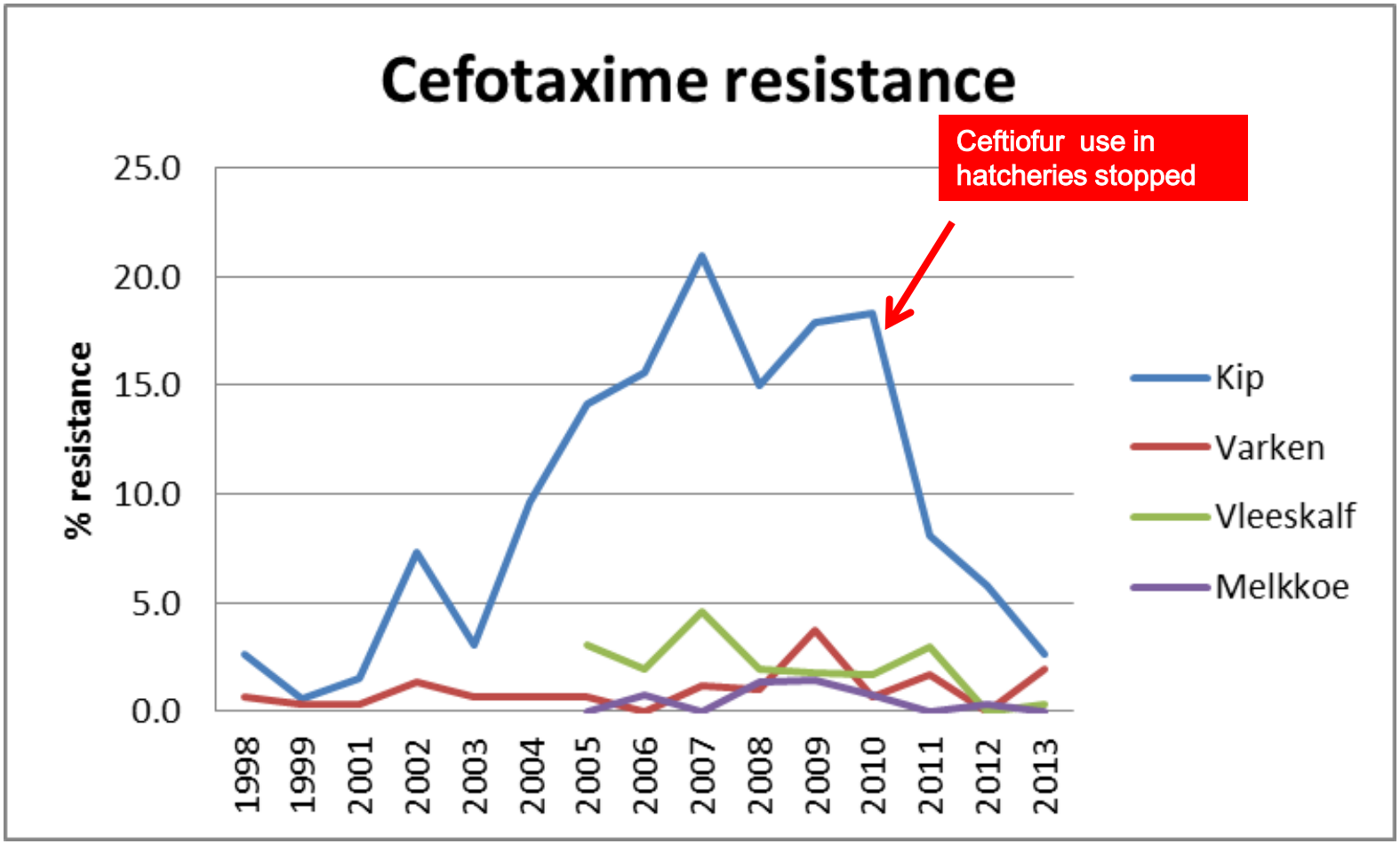
EFFORT
AGAINST ANTIMICROBIAL RESISTANCE

What are the interventions?

- Reduce the driving force: AMU
  - Overall and specifically the CIA
- AMU reduction in primary production (and humans)
- Assume that the total number of *E. coli* is rather constant in the gut, the proportion R/total becomes relevant: you can influence this on farm
- In the slaughterhouse the proportion R/total is 'frozen' and the aim is to reduce the total count with general hygiene/inactivation techniques


E. coli in retail chicken
Salmonella Heidelberg in retail chicken
Salmonella Heidelberg in humans
Voluntary withdrawal of ceftiofur in ovo use
Partial reinstitution of ceftiofur use
Prevalence of ceftiofur resistance, %
100
90
80
70
60
50
40
30
20
10
0
3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4 1 2 3 4
2003
2004
2005
2006
2007
2008
Quarter and year

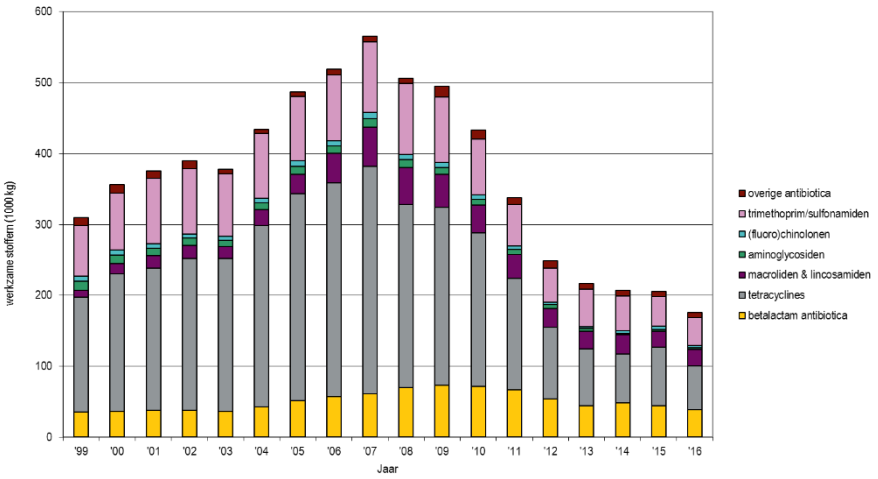
Effect of reduction of 3e-gen cephalosporins



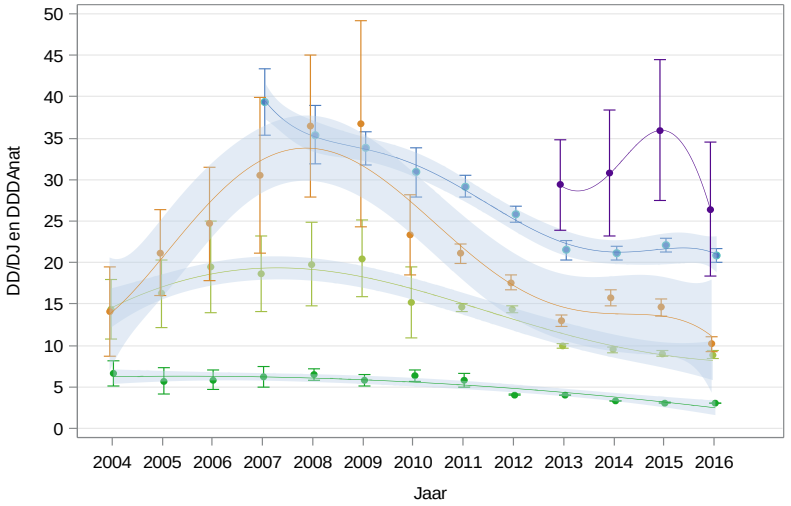
thanks to Dik Mevius

Effect of AMU reduction policy in the Netherlands

Sales data of antimicrobials in the Netherlands



DDD/AY for different sectors



- 68.9% reduction (2007-2016)
- Fluoroquinolones and 3rd/4th-gen cefalosporines usage reduced to a minimum
- 68% reduction in use of colistin (2011-2015)

Purple: turkeys
Blue: veal
Orange: broilers
Light green: pigs
Dark green: dairy

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Maran, 2016

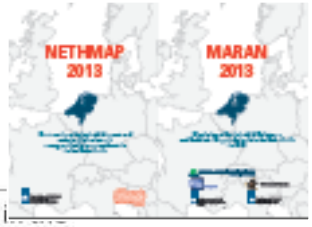
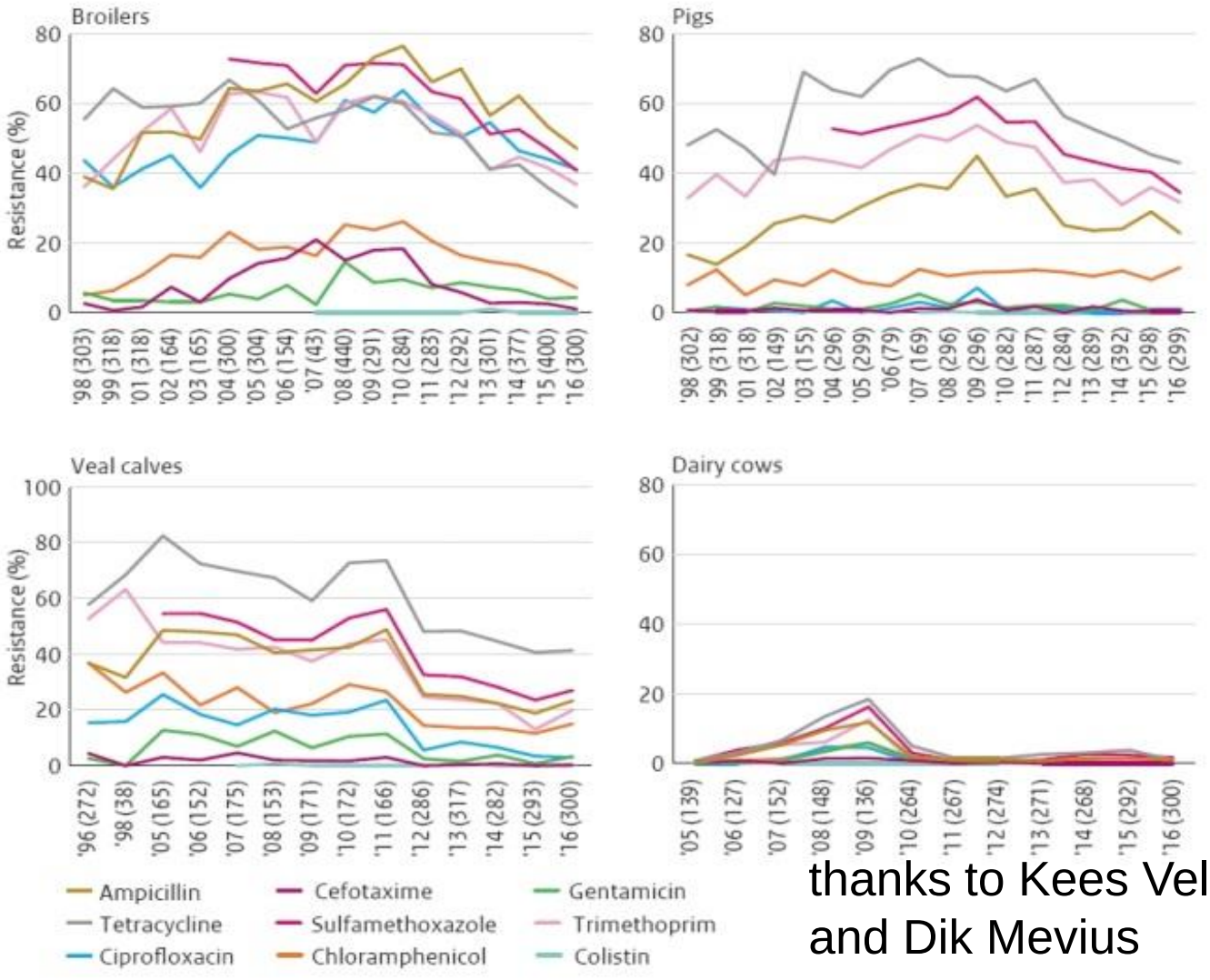


Figure Eco01 Trends in resistance (%) of *E. coli* isolated from broilers, slaughter pigs, veal calves and dairy cattle in the Netherlands from 1998-2016.



thanks to Kees Veldman and Dik Mevius

Effect in humans of reduced AMU in animals

Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis

Karen L Tang, Niamh P Caffrey, Diego B Nóbrega, Susan C Cork, Paul E Ronksley, Herman W Barkema, Alicia J Polachek, Heather Ganshorn, Nishan Sharma, James D Kellner, William A Ghali

Summary

Background Antibiotic use in human medicine, veterinary medicine, and agriculture has been linked to the rise of antibiotic resistance globally. We did a systematic review and meta-analysis to summarise the effect that interventions to reduce antibiotic use in food-producing animals have on the presence of antibiotic-resistant bacteria in animals and in humans.

Methods On July 14, 2016, we searched electronic databases (Agricola, AGRIS, BIOSIS Previews, CAB Abstracts, MEDLINE, Embase, Global Index Medicus, ProQuest Dissertations, Science Citation Index) and the grey literature. The search was updated on Jan 27, 2017. Inclusion criteria were original studies that reported on interventions to reduce antibiotic use in food-producing animals and compared presence of antibiotic-resistant bacteria between intervention and comparator groups in animals or in human beings. We extracted data from included studies and did meta-analyses using random effects models. The main outcome assessed was the risk difference in the proportion of antibiotic-resistant bacteria.

Findings A total of 181 studies met inclusion criteria. Of these, 179 (99%) described antibiotic resistance outcomes in animals, and 81 (45%) of these studies were included in the meta-analysis. 21 studies described antibiotic resistance outcomes in humans, and 13 (62%) of these studies were included in the meta-analysis. The pooled absolute risk reduction of the prevalence of antibiotic resistance in animals with interventions that restricted antibiotic use commonly ranged between 10 and 15% (total range 0–39), depending on the antibiotic class, sample type, and bacteria under assessment. Similarly, in the human studies, the pooled prevalence of antibiotic resistance reported was 24% lower in the intervention groups compared with control groups, with a stronger association seen for humans with direct contact with food-producing animals.

Interpretation Interventions that restrict antibiotic use in food-producing animals are associated with a reduction in the presence of antibiotic-resistant bacteria in these animals. A smaller body of evidence suggests a similar association in the studied human populations, particularly those with direct exposure to food-producing animals. The implications for the general human population are less clear, given the low number of studies. The overall findings have directly informed the development of WHO guidelines on the use of antibiotics in food-producing animals.

Funding World Health Organization.

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See Comment page e307

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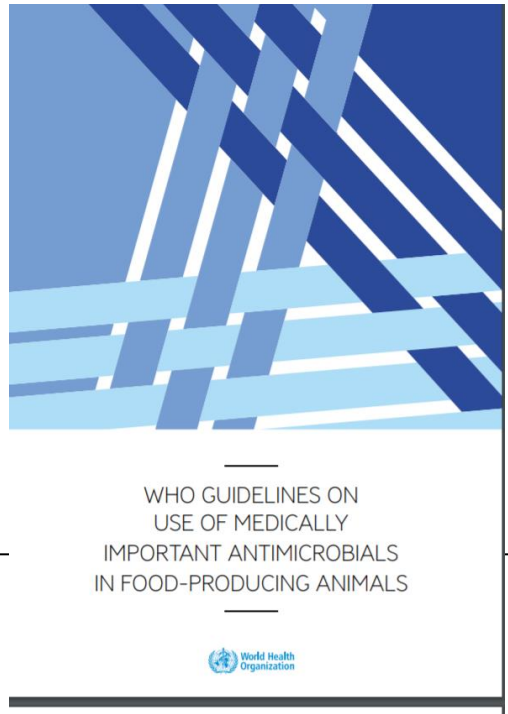
Interventions in LMIC

These guidelines apply universally, regardless of region, income and setting, however, the GDG acknowledged that implementation of these guidelines in low and middle-income countries may require special considerations. These include assistance with animal health management to reduce the need for antimicrobials, including improvements in disease prevention strategies, housing and husbandry practices. Furthermore, many countries may need technical and laboratory capacity building assistance for conducting the recommended bacterial culture and antimicrobial sensitivity testing. FAO and OIE may be able to assist in implementation of these guidelines. Finally, the GDG emphasized the need for countries to conduct surveillance and monitoring of antimicrobial usage in food-producing animals to monitor and evaluate the implementation of these guidelines.



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Aquaculture

- Surveillance systems use different drug/bug combinations (*Aeromonas* spp) – integrated surveillance……
- OIE-Aquatic Animal Health Code: *Salmonella* spp., *Vibrio parahaemolyticus*, *Listeria monocytogenes*

SECTION 6.	ANTIMICROBIAL USE IN AQUATIC ANIMALS
Chapter 6.1.	Introduction to the recommendations for controlling antimicrobial resistance
Chapter 6.2.	Principles for responsible and prudent use of antimicrobial agents in aquatic animals
Chapter 6.3.	Monitoring of the quantities and usage patterns of antimicrobial agents used in aquatic animals
Chapter 6.4.	Development and harmonisation of national antimicrobial resistance surveillance and monitoring programmes for aquatic animals
Chapter 6.5.	Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in aquatic animals

- Data are very limited

Trade – tresholds for resistance?

- Economics are (maybe) the strongest incentive for action
- Absence can be required for certain resistance mechanisms (e.g. carbapenemase producers)
- Existing resistance mechanisms:
  - Total counts and R/total counts?
  - For each class of antimicrobial?
  - Assign ‘weight’ to resistance mechanism?
- Technically a huge challenge

Residues and persistance of antimicrobials

- Chemical half life time of amoxicillin?
  a. < 1 day
  b. 3 days
  c. >20 days
- Chemical half life time of tetracyclines?
  a. < 1 day
  b. 3 days
  c. >20 days

Healthy humans and environment

- How can we collect more evidence –based data?
- WHO Tricycle project: collecting data on ESBL-Ec from food chain, environment, diseased and healthy humans

Conclusions

- The attribution of AMR in humans from food of terrestrial animals is difficult to estimate
- ESBLs: 1-10% of the plasmids/genes in humans has animal similarity
- Aquaculture data are scarce, attribution is unknown and difficult to include in integrated surveillance
- Interventions in AMU are effective to reduce AMR in animals, effect in humans not quantified yet (WHO-Guideline)
- Economics are a driving force for action, consider tresholds
- Big data gap in dosis-response in humans
- Differences in chemical persistance of antimicrobials may influence the selection of resistance, the environment is therefore crucial to include

"The Triumph of Death" by Flemish painter Pieter Breugel in his mid-16th-century reflects the social upheaval and terror that followed plague.

Image courtesy Museo del Prado, Madrid


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