Integrated Analysis of Data on Resistance and Antimicrobial Consumption from the Human and Animal Sectors in Europe
The JIACRA Report

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Seminar on AMR, State Veterinary Administration,

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BACKGROUND

- Description of existing monitoring/surveillance systems
- 2011 and 2012 data from the EU MSs, IS, NO and CH
- Datasets used have been collected for purposes that were not *a priori* an integrated analysis

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

European Antimicrobial Resistance Surveillance Network (**EARS-Net**)

European Surveillance of Antimicrobial Consumption Network (**ESAC-Net**)

Food- and Water-borne Diseases Network (**FWD-Net**)

efsa
European Food Safety Authority

Scientific Network on Zoonoses Monitoring Data

EU Summary Report on AMR in zoonotic and indicator bacteria from humans, animals and food

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Surveillance of Veterinary Antimicrobial Consumption (**ESVAC**)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Surveillance of Veterinary Antimicrobial Consumption (**ESVAC**)

- Data on Sales of Veterinary Antimicrobials at package level
- All food-producing animal species
- Data not available by animal species
- Normalised data for the animal population that can be subjected to treatment
- Harmonised collection of data

European Food Safety Authority

Scientific Network on Zoonoses Monitoring Data

EU Summary Report on AMR in zoonotic and indicator bacteria from humans, animals and food

- Resistance in *Salmonella*, *C. jejuni* and *C. coli*, indicator commensal *E. coli* and enterococci
- Harmonised set of antimicrobials and protocols
- ECOFFs used to interpret resistance
- Monitoring performed on a voluntary basis in indicator bacteria

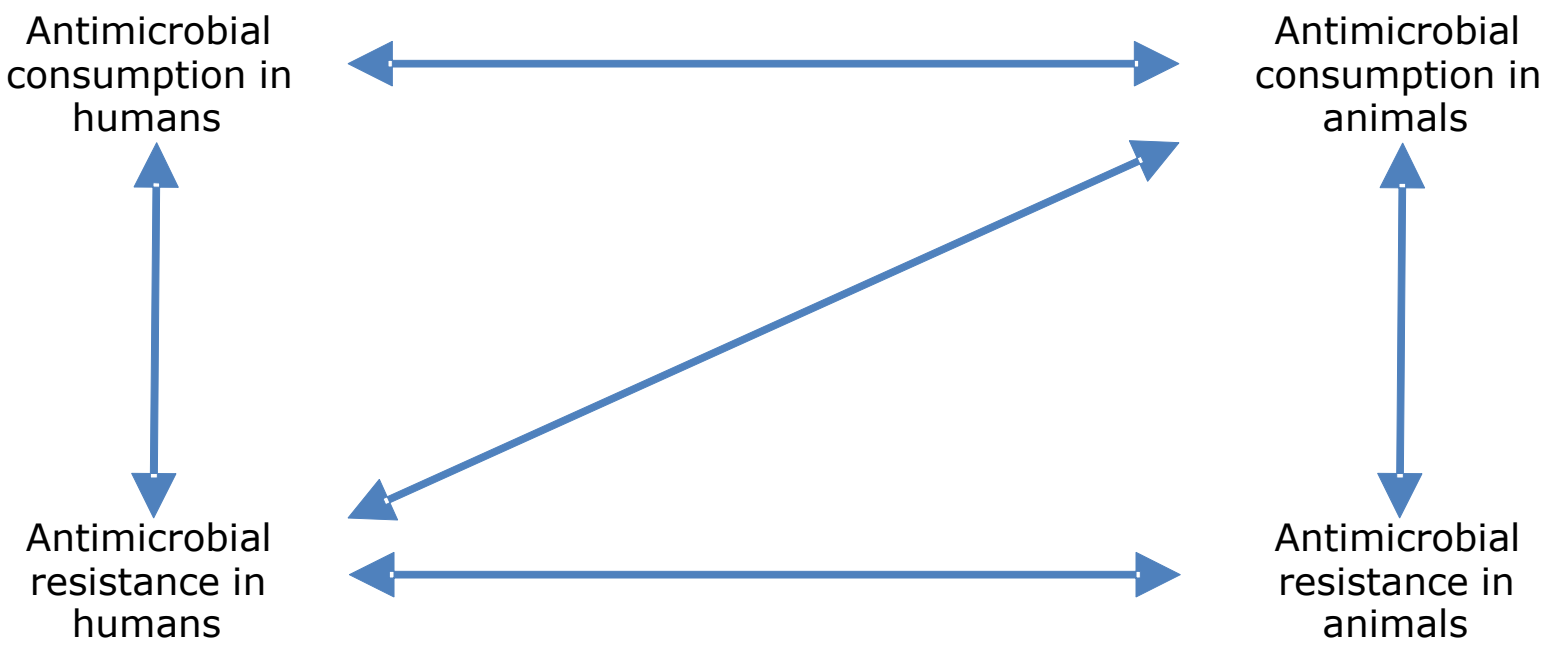
European Antimicrobial Resistance Surveillance Network (**EARS-Net**)

European Surveillance of Antimicrobial Consumption Network (**ESAC-Net**)

Food- and Water-borne Diseases Network (**FWD-Net**)

- ESAC-Net
  - Consumption data from the community (primary care) and from hospitals
  - Data collected at the package level
- EARS-Net
  - Invasive isolates from bloodstream infections (BSIs) in humans
  - Including *E. coli*
- FWD-Net
  - Clinical AST of *Salmonella* and *Campylobacter* from humans
  - Clinical breakpoints

POSSIBLE RELATIONSHIPS INVESTIGATED



COMPARISON OF CONSUMPTION IN HUMANS AND FOOD-PRODUCING ANIMALS

Total tonnes of active substance and estimated biomass

- In 2012, in the 26 EU/EEA countries, the amounts of active substance of antimicrobials sold equalled:
  - 3 400 tonnes in humans
  - 7 982 tonnes in food-producing animals
- Estimated biomass, expressed as 1000 tonnes:
  - 28 884 for humans
  - 55 421 for animals

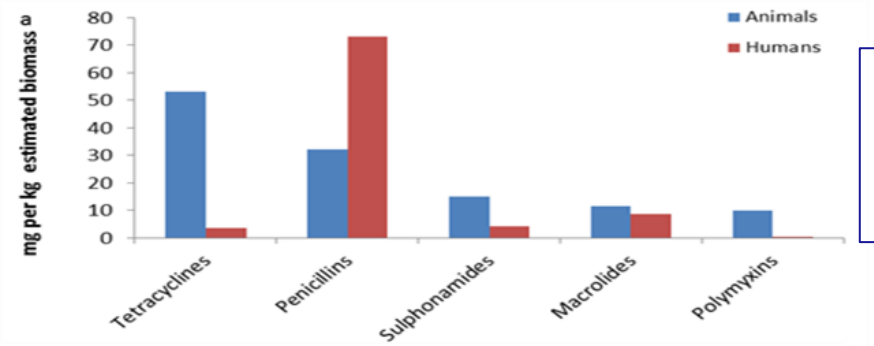
COMPARISON OF CONSUMPTION FOR HUMANS AND FOOD-PRODUCING ANIMALS

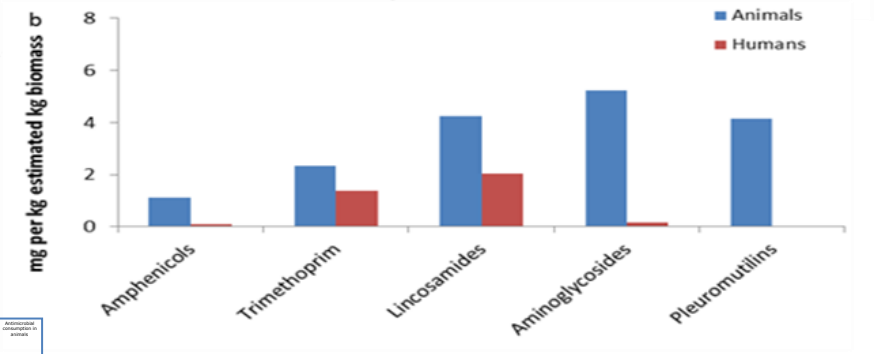
	Total consumption (expressed in mg/kg of estimated biomass)
In humans	116.4 mg/kg (range: 56.7 – 175.8 mg/kg)
In animals	144.0 mg/kg (range: 3.8 – 396.5 mg/kg)

- 15/26 countries:
  - animals < humans
- 3/26 countries:
  - similar for animals and humans
- 8/26 countries:
  - animals > humans

COMPARISON OF CONSUMPTION FOR HUMANS AND FOOD-PRODUCING ANIMALS

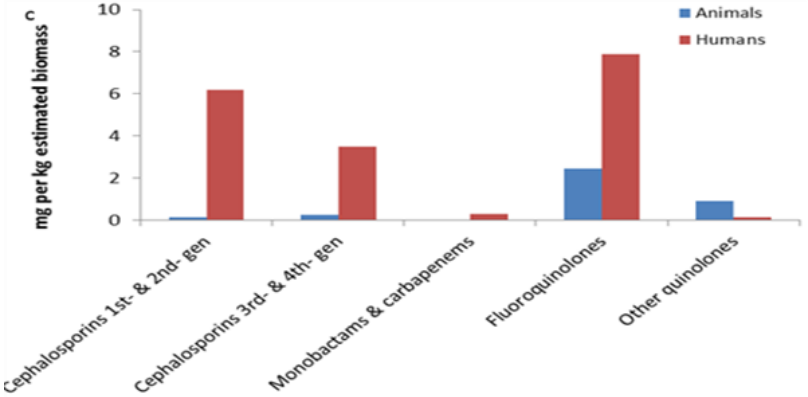
Selected antimicrobial classes - 26 EU/EEA countries in 2012





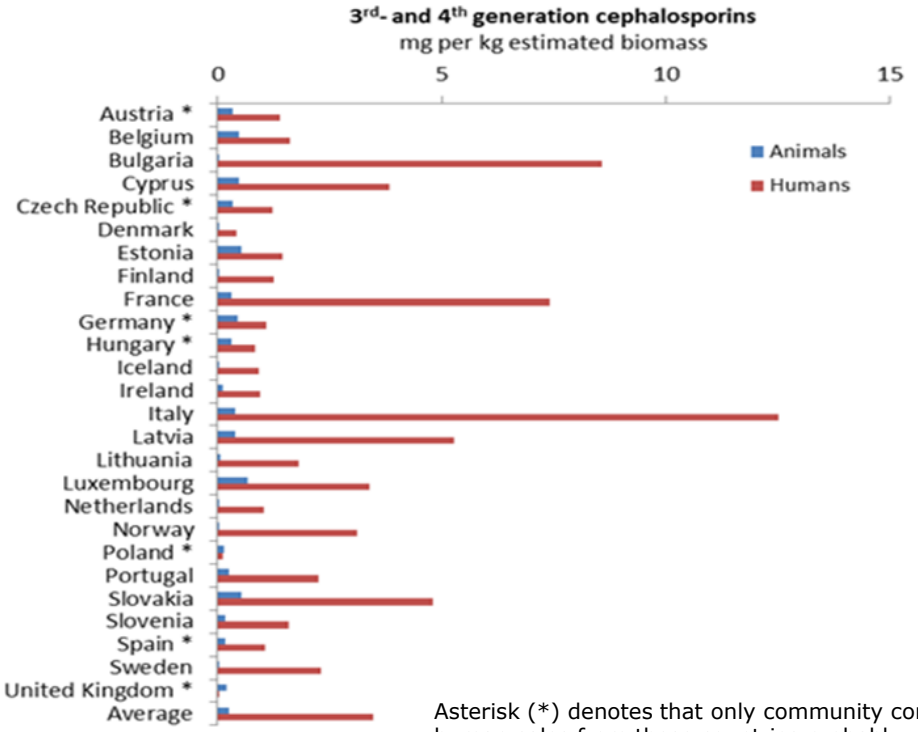
Highest selling AMs classes

- In human medicine: Pen, Macro, FQ
- In Food-producing animals: Tet, Pen, Su



COMPARISON OF CONSUMPTION FOR HUMANS AND FOOD-PRODUCING ANIMALS

3rd- and 4th-generation cephalosporins - 26 EU/EEA countries in 2012



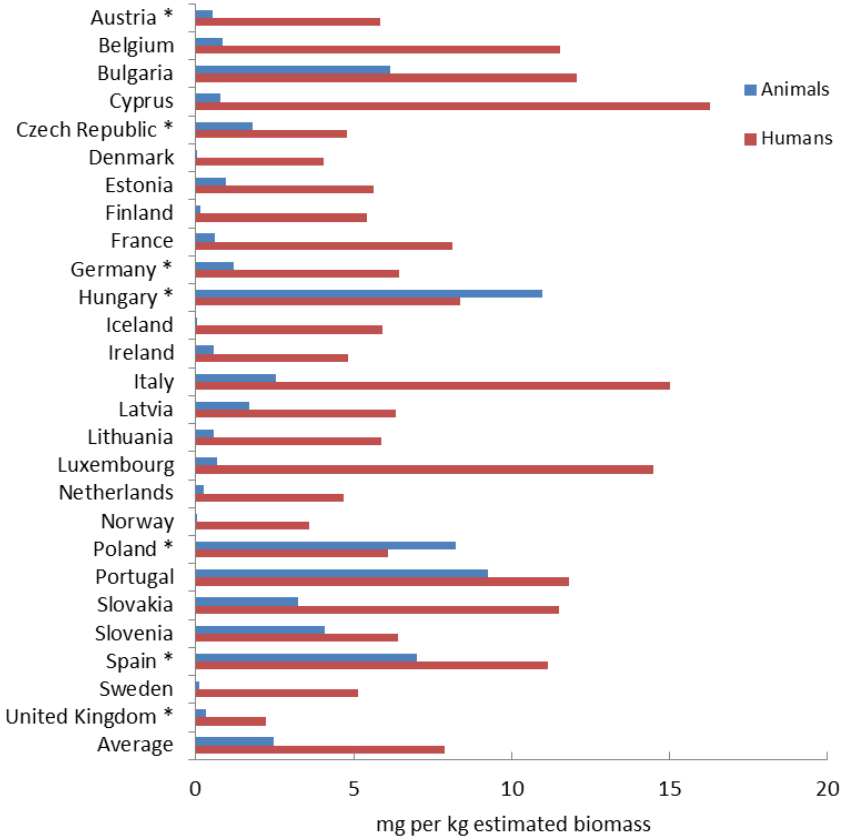
- Consumption of 3rd- and 4th-generation cephalosporins much lower for animals than for humans.
- This antimicrobial class is predominantly used in hospitals, and therefore the comparison may be misleading for countries not reporting (*) such hospital consumption.

Asterisk (*) denotes that only community consumption data were available for human medicine. Figures of human sales from these countries probably represent a considerable underestimate.

COMPARISON OF CONSUMPTION FOR HUMANS AND FOOD-PRODUCING ANIMALS

Population corrected consumption of *fluoroquinolones* in humans and food-producing animals by country in 26 EU/EEA countries in 2012

In most countries, the consumption of fluoroquinolones was lower for animals than for humans, but there was more variation between countries than for cephalosporins.



CONSUMPTION AND RESISTANCE (HUMANS) (HUMAN BACTERIA)

- **3-4th gen Cephs:** positive association for *E. coli* (BSIs)

- **Fluoroquinolones:** positive association for *E. coli* (BSIs). No association for *Salmonella* spp., *S.* Enteritidis or *S.* Typhimurium

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

Overview of data currently available in animals

Cattle | Pigs | Poultry | Others

No possible Comparison

All animal species addressed together

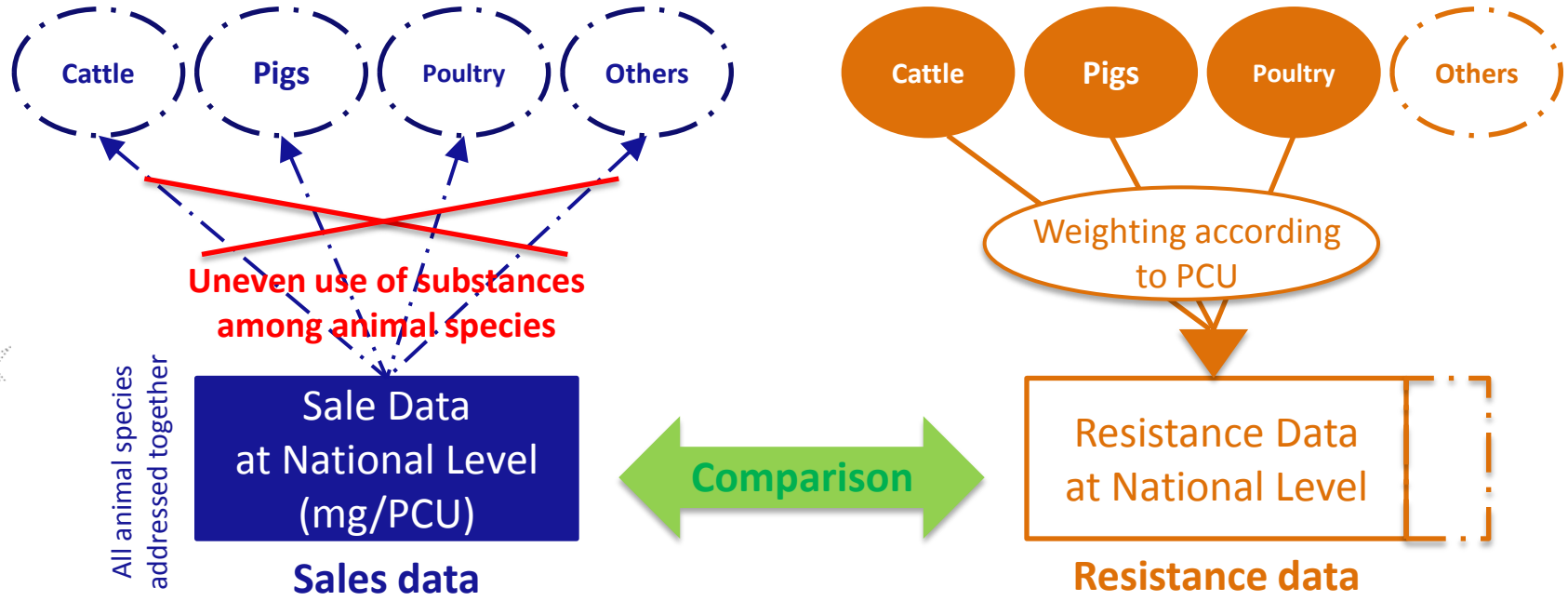
Sales Data
at National Level
(in mg/PCU)

Sales data

Resistance data

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

'Summary indicator' of resistance in animals

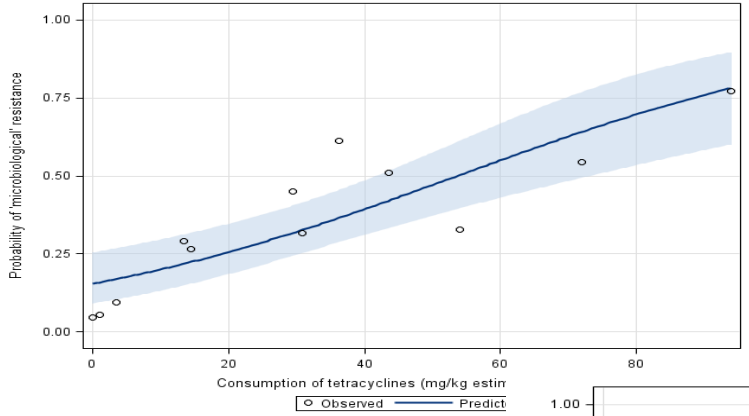


COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

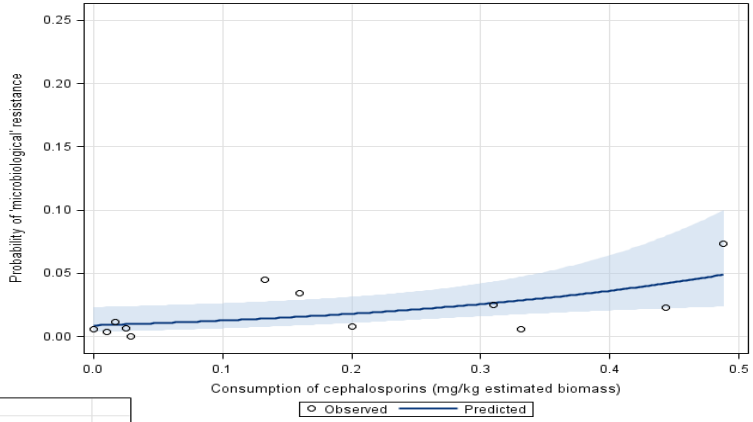
Bacteria	Antimicrobial class		*P*-value
Indicator *E. coli*	Tetracyclines		<0.05
	3rd gen. cephalosporins		<0.05
	Fluoroquinolones		<0.05
	Fluoroquinolones & quinolones		<0.05
C. jejuni* and *C. coli	Tetracyclines	*C. jejuni*:	<0.05
	Macrolides	*C. jejuni*: *C. coli*:	<0.05 <0.05
	Fluoroquinolones	*C. jejuni*:	<0.05
	Fluoroquinolones & quinolones	*C. jejuni*:	<0.05
***Salmonella* spp.**	Tetracyclines		<0.05
	3rd gen. cephalosporins		<0.05
	Fluoroquinolones		NS
	Fluoroquinolones and other quinolones		<0.05

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

A.



B.



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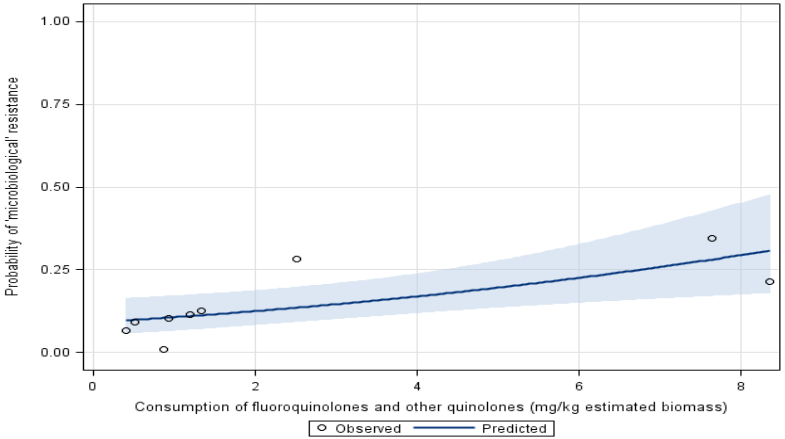
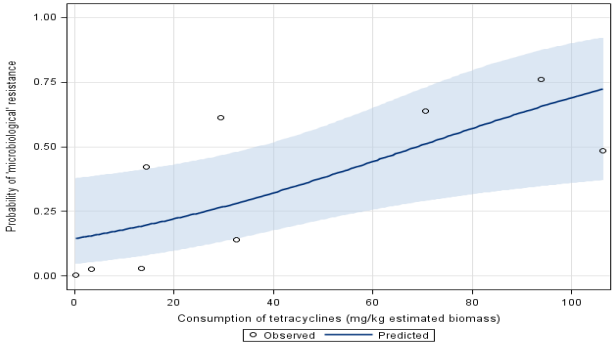


Indicator *E. coli*

A. Sales of TET – Resistance to TET
B. Sales of CEPH – Resistance to CTX
C. Sales of FQ and Q – Resistance to CIP

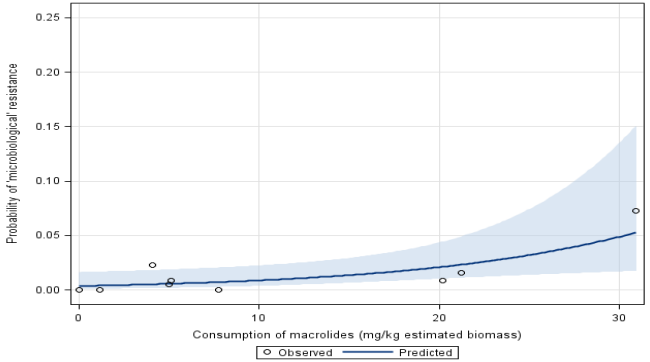
COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

Indicator *C. jejuni* –TET



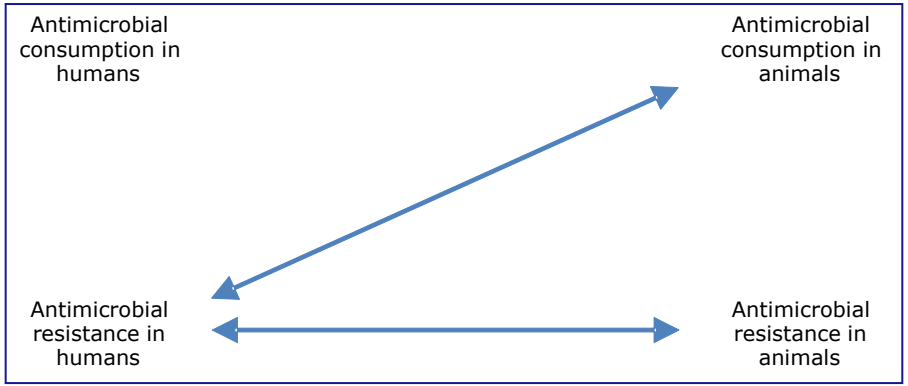
Countries included: AT, DE, DK, ES, FI, IT, NL + CH, NO
P<.05; OR=1.026; 95% PL CI: [1.006, 1.050]
Note: the association remains significantly positive after ignoring the point displayed on the middle right side of the graph: P<.05; OR=1.038; 95% PL CI: [1.012, 1.073]

Indicator *C. jejuni* –MACRO



Countries included: AT, DK, FI, DE, IT, NL, NO, ES, CH
P<.05; OR=1.091; 95% PL CI: [1.018, 1.176]

OTHER POSSIBLE RELATIONSHIPS INVESTIGATED



- For both ***cephalosporins*** and ***fluoroquinolones***: positive associations found between resistance in **indicator *E. coli*** from **FP-animals** and resistance in ***E. coli*** from **humans (BSIs)**.

Resistance in human *E. coli* correlated with usage of antimicrobials in FP-animals and in humans.

CONSUMPTION AND RESISTANCE (FP- ANIMALS) (HUMAN BACTERIA)

- **Cephs:** no association.
- **Fluoroquinolones:** positive association for *E. coli* (but not for *Salmonella* and *Campylobacter)*.
- **Macrolides:** positive association for *Campylobacter*.
- **Tetracyclines:** positive association for *Salmonella* and *Campylobacter*.

CONCLUSIONS

- Marked variations between countries both in the overall consumption figures, and for consumption of cephalosporins and fluoroquinolones
- Associations between consumption of selected antimicrobials and the occurrence of resistance in bacteria frequently observed
- Epidemiology of resistance is complex, and several other factors aside from antimicrobial consumption influence occurrence of resistance

LIMITATIONS

- Data on antimicrobial consumption in food-producing animals are not available by species
- Differences in systems for collection and reporting of data on antimicrobial consumption and resistance in bacteria from humans and animals have limited the potential for direct comparison
  - *e.g.* five-dilution difference between countries in the breakpoint applied for resistance to fluoroquinolones in *Salmonella* spp. from humans
- 'Ecological analyses' = hypotheses generating study
- Due to characteristics of data, interpretation criteria, and units of measurement, results should be interpreted with caution!

DISCUSSION POINTS FOR FUTURE ANALYSES

- To improve integrated analyses, more detailed and comprehensive data are required.
- Factors, such as
  - Antimicrobial Consumption Data per animal species
  - Resistance Data from all countries, in relevant animal species and food

  at a detailed level would be required.
- Other factors that would have to be considered are:
  - Resistance to other antimicrobials (co-selection phenomenon)
  - Travel
  - Imports of meat

AMR: A PUBLIC HEALTH PRIORITY IN EUROPE !

EU Action Plan: 7 areas - 12 actions

Human

1. Appropriate use

4. Prevention of infections

6. Development new antibiotics

9. Surveillance

Veterinary

2 & 3. Appropriate use

5. Prevention of infections

7. Need for new antibiotics?

10. Surveillance

8. International cooperation

11. Research & Innovation

12. Communication, education

ACKNOWLEDGEMENTS

- EU Member States and other reporting countries
- Surveillance/Monitoring networks involved
  - EARS-Net, ESAC-Net and FWD-Net
  - Scientific Network for Zoonosis Monitoring Data
  - ESVAC

THANK YOU FOR YOUR ATTENTION !

ECDC/EFSA/EMA first Joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals[1]
(JIACRA) Report

Abstract

EMA:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/01/WC500181485.pdf

EFSA:
http://www.efsa.europa.eu/en/efsajournal/doc/4006.pdf

ECDC:
http://ecdc.europa.eu/en/publications/publications/antimicrobial-resistance-jiacra-report.pdf

ANALYSES ON COMBINATIONS OF ANTIMICROBIALS AND BACTERIA

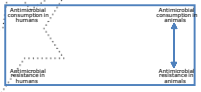
In Humans

Resistance data		Consumption data
Bacteria	Antimicrobial substances	Antimicrobial (sub-)classes
E. coli	Ceftriaxone Cefotaxime Ceftazidime Ciprofloxacin Ofloxacin Levofloxacin Meropenem Imipenem	3rd-and 4th-generation cephalosporins Fluoroquinolones Carbapenems
C. jejuni and *C. coli*	Tetracyclines Erythromycin Ciprofloxacin	Tetracyclines Macrolides Fluoroquinolones
Salmonella spp.	Tetracyclines Cefotaxime Ciprofloxacin	Tetracyclines 3rd- and 4th-generation cephalosporins Fluoroquinolones
K. pneumoniae	Meropenem Imipenem	Carbapenems

ANALYSES ON COMBINATIONS OF ANTIMICROBIALS AND BACTERIA

In Animals

Resistance data		Consumption data
Bacteria	**Antimicrobials used for testing**	**Antimicrobial (Sub-)classes**
Indicator *E. coli*	Tetracyclines	Tetracyclines
	Cefotaxime	3rd- and 4th-generation cephalosporins
	Ciprofloxacin	Fluoroquinolones
	Ciprofloxacin	Fluoroquinolones and other quinolones
C. jejuni and *C. coli*	Tetracyclines	Tetracyclines
	Erythromycin	Macrolides
	Ciprofloxacin	Fluoroquinolones
	Ciprofloxacin	Fluoroquinolones and other quinolones
Salmonella	Tetracyclines	Tetracyclines
	Cefotaxime	3rd-generation cephalosporins
	Ciprofloxacin	Fluoroquinolones
	Ciprofloxacin	Fluoroquinolones and other quinolones



‘summary indicator’ of Resistance

- Combining two or three animal species: Broilers / Pigs / Cattle
  - Weighted mean of ‘Resistance per species’
  - PCU: weight to allow comparability between sales data
  - Implicit assumption: Excretion proportional to the PCU

$$Ind_{Res} = \frac{1}{\mathrm{PCU}_{cattle} + \mathrm{PCU}_{fowl} + \mathrm{PCU}_{pigs}} . (\mathrm{PCU}_{cattle} . \mathrm{Res}_{cattle} + \mathrm{PCU}_{fowl} . \mathrm{Res}_{fowl} + \mathrm{PCU}_{pigs} . \mathrm{Res}_{pigs})$$

Graphical comparisons

- Logistic regression
- Grouped data: group=country
  - ‘Overdispersion’
    - Isolates are grouped into naturally occurring clusters. Isolates originating from the same country (the same domestic production sectors) are not independent, as they are exposed to many common factors that may produce the same outcome (antimicrobial susceptibility status).
  - Small sample sizes: Profile Likelyhood CLs
  - Sensitivity analysis to ‘influential points’