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

The JIACRA Report

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on behalf of the JIACRA expert working group

BfR-Symposium Antimicrobial Resistance in the Food Chain
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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

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

- 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

- 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

POTENTIAL RELATIONSHIPS INVESTIGATED

METHODS

Antimicrobial **consumption** in **humans**

*Antimicrobial **consumption** in **animals***

Antimicrobial **resistance** in **humans**

*Antimicrobial **resistance** in **animals***

POTENTIAL RELATIONSHIPS INVESTIGATED

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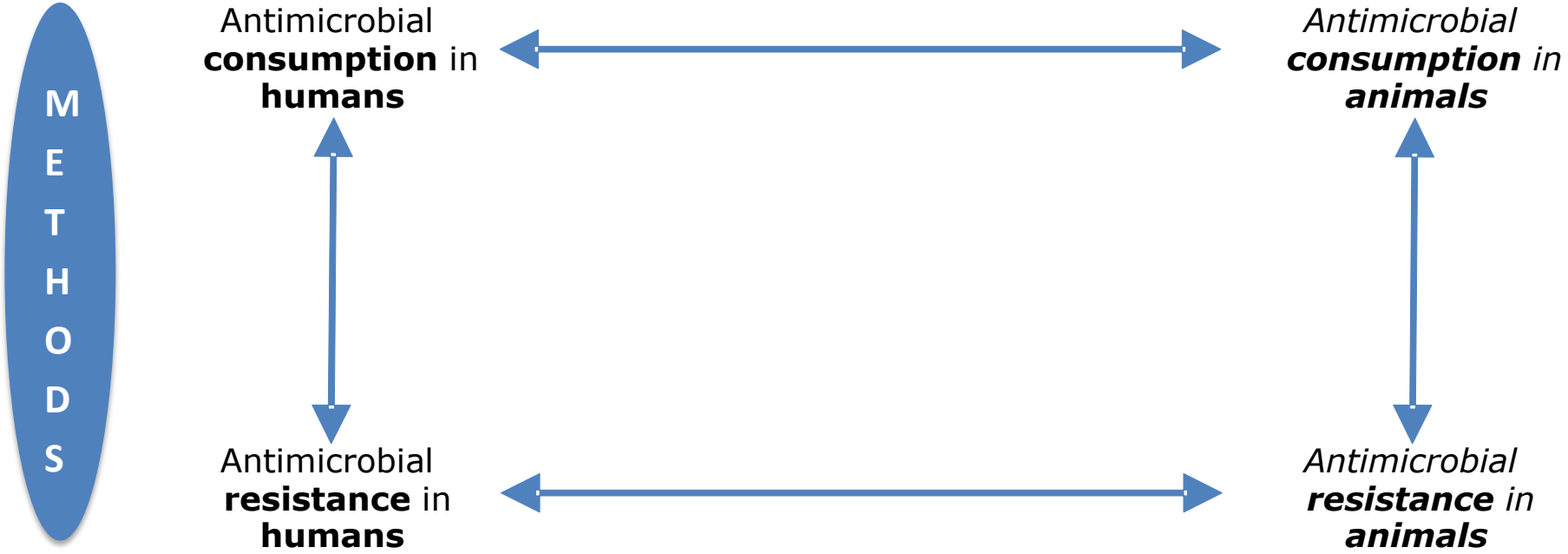
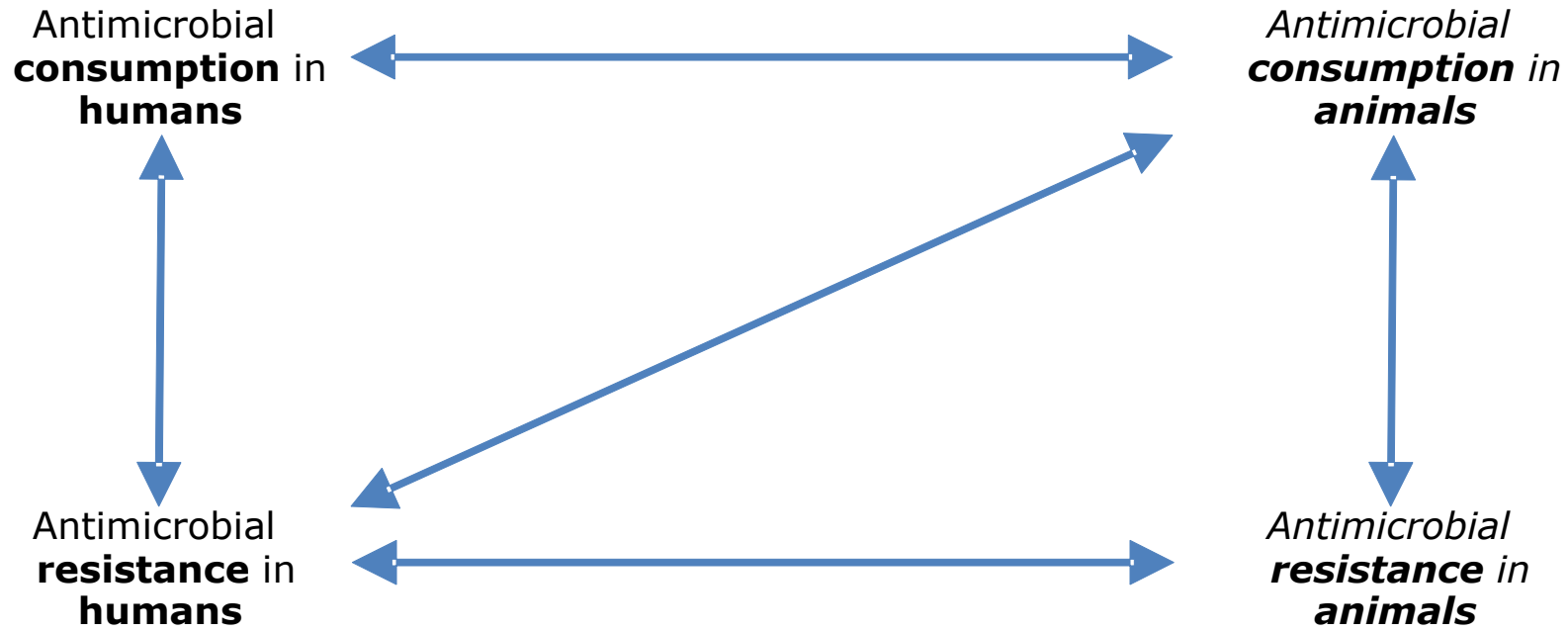
POTENTIAL RELATIONSHIPS INVESTIGATED



POTENTIAL RELATIONSHIPS INVESTIGATED

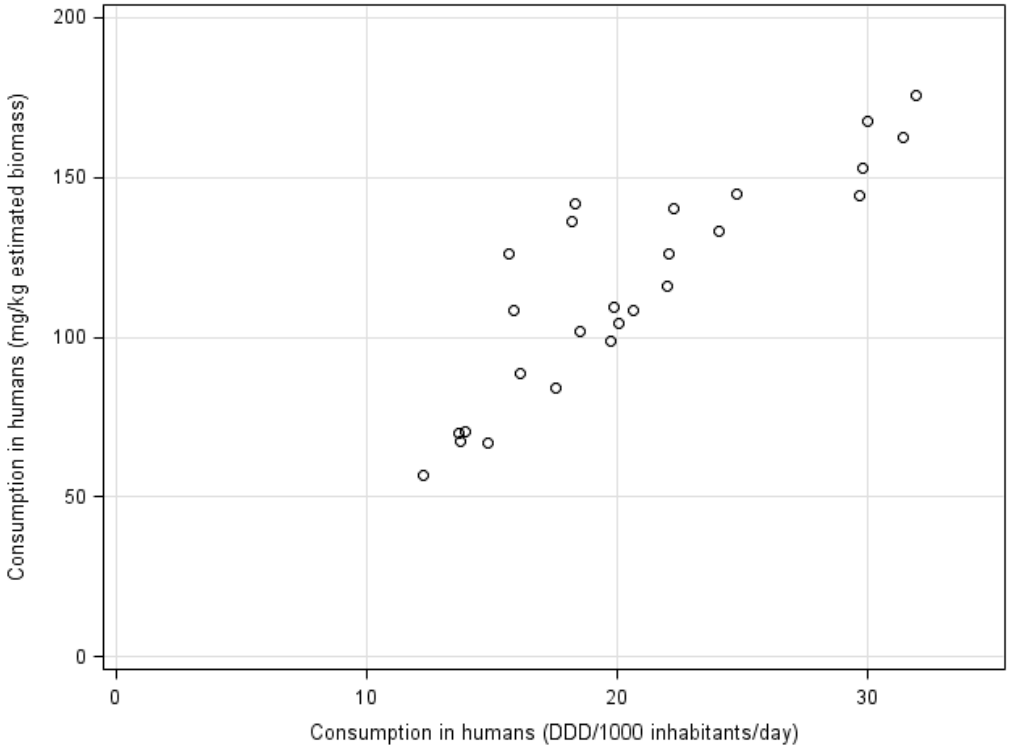
METHODS



REPORTING CONSUMPTION IN HUMANS

DDD/1000 inhabitants/day *vs.* mg/kg estimated biomass

METHODS

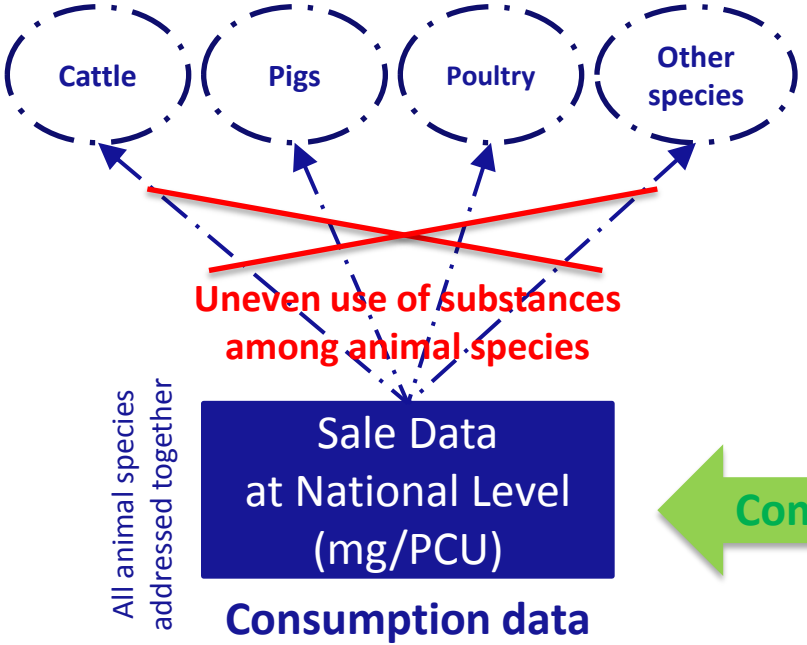


Spearman's rank correlation:
rho = 0.87; p-value < 0.0001

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

'Summary indicator' of resistance in animals

METHODS



COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

Antimicrobial consumption (mg/estimated biomass) *vs*. 'summary indicator' of Resistance

METHODS

- 'Summary indicators' of resistance
- Combining two or three animal species: Broilers / Pigs / Cattle
  - Weighted mean of 'Resistance per species'
  - PCU: weight to allow comparability between consumption data
  - Implicit Assumption: Excretion proportional to estimated biomass

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

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE

Modeling and Graphical Comparisons

METHODS

- Modeling the probability of resistance and consumption
- Logistic regression accounts for the true nature of data
  - Grouped data: group=country
  - Overdispersion
  - Small sample sizes: profile likelihood CLs
  - *Proc logistic* using SAS software
- Sensitivity analysis to 'influential points'

POSSIBLE RELATIONSHIPS INVESTIGATED

Antimicrobial **consumption** in **humans**

*Antimicrobial **consumption** in **animals***

Antimicrobial **resistance** in **humans**

*Antimicrobial **resistance** in **animals***

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

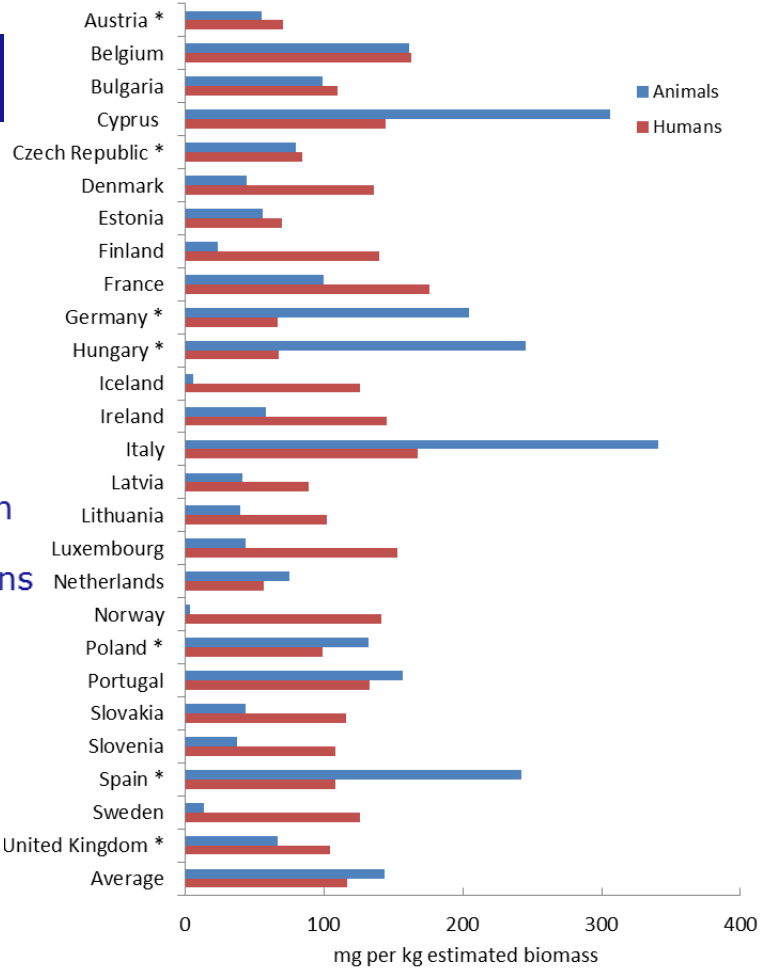
COMPARISON OF CONSUMPTION IN HUMANS AND FOOD-PRODUCING ANIMALS

	Total consumption in 2012 (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)

COMPARISON OF CONSUMPTION IN HUMANS AND FOOD-PRODUCING ANIMALS

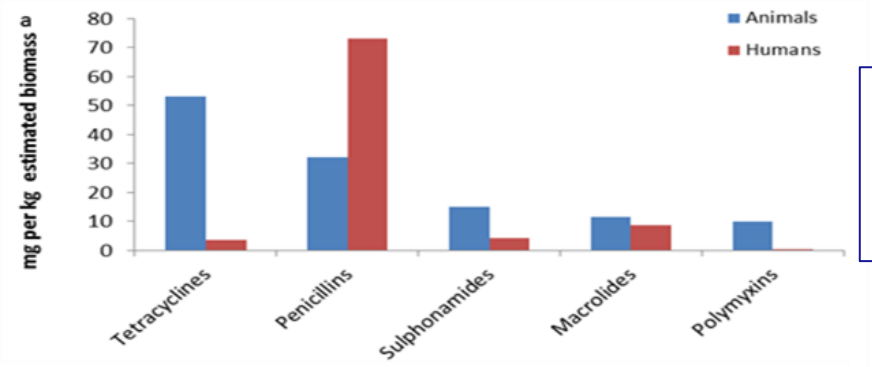
Comparison of biomass-corrected *consumption of antimicrobials* (milligrams per kilogram estimated biomass) in humans and animals by country in 26 EU/EEA countries in 2012

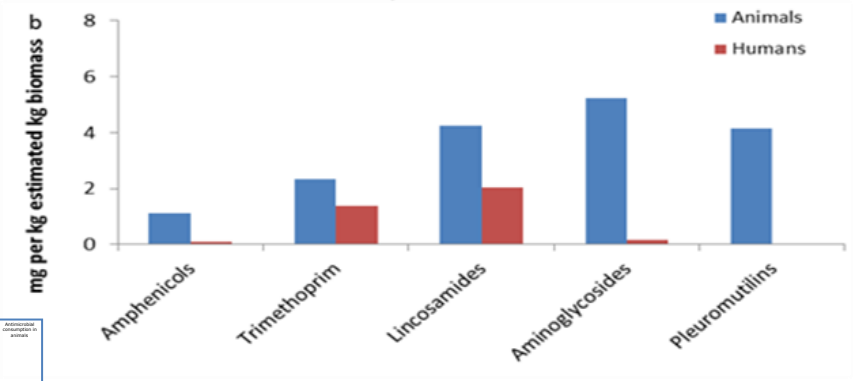
- 15 (/26) countries: animal consumption < human consumption
- 3 (/26) countries: similar consumptions for animals and humans
- 8 (/26) countries: animal consumption > human consumption



COMPARISON OF CONSUMPTION IN HUMANS AND FOOD-PRODUCING ANIMALS

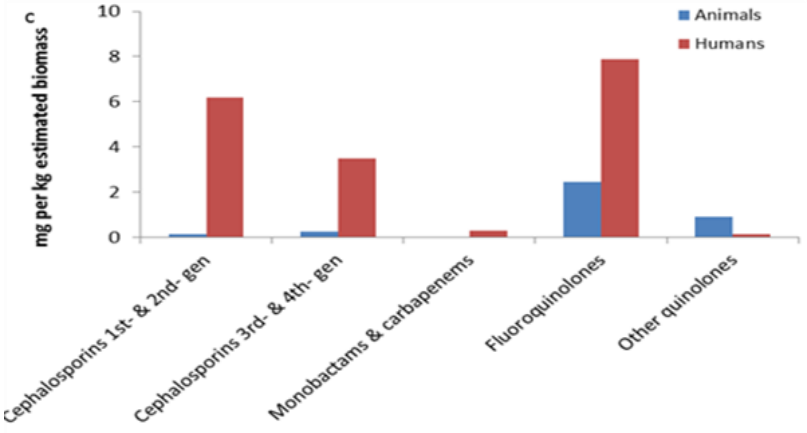
Selected antimicrobial classes - 26 EU/EEA countries in 2012





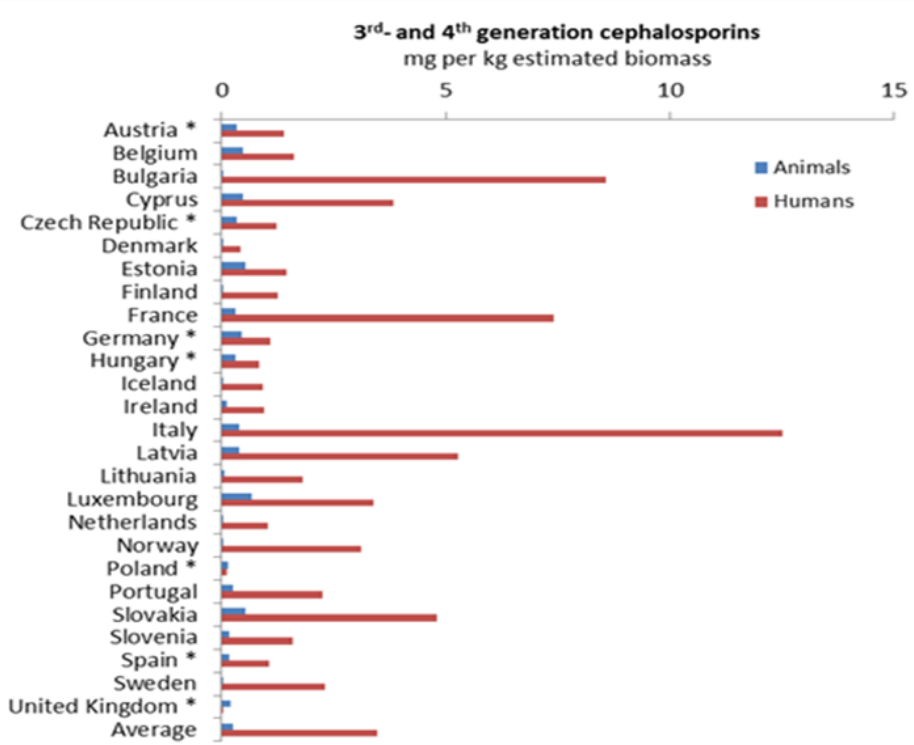
Highest selling AMs classes

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



COMPARISON OF CONSUMPTION IN HUMANS AND FOOD-PRODUCING ANIMALS

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

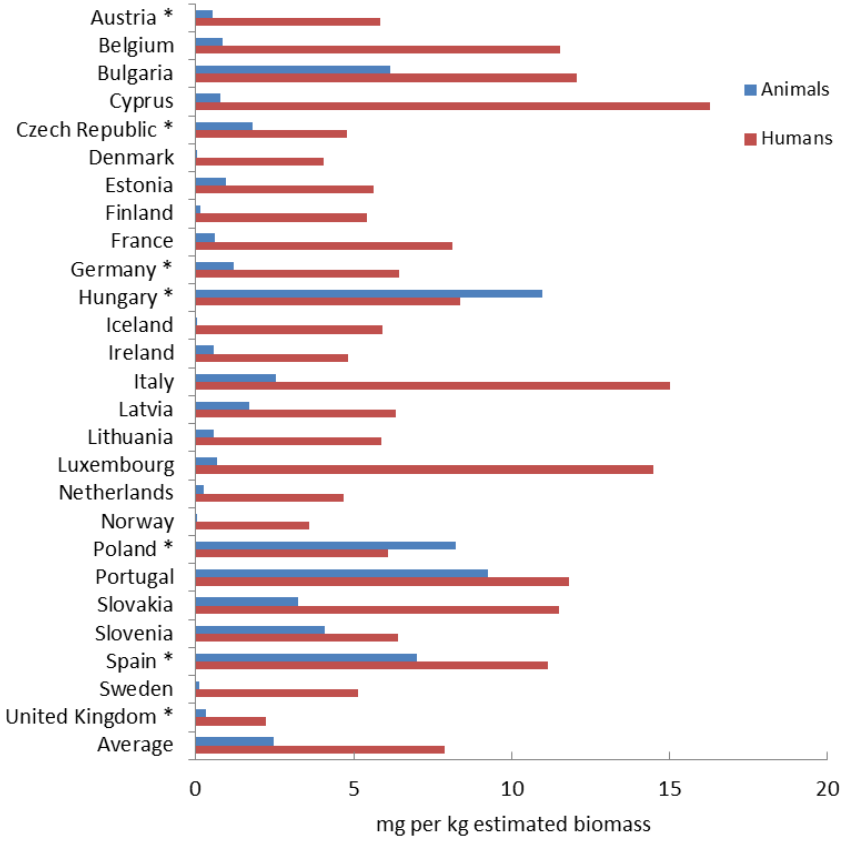


- Consumption of 3rd- and 4th-generation cephalosporins much lower for animals than for humans.
- This antimicrobial class is predominantly used in hospitals, and therefore the comparison may be misleading for countries not reporting (*) such hospital consumption.

COMPARISON OF CONSUMPTION IN 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.



POTENTIAL RELATIONSHIPS INVESTIGATED

Antimicrobial **consumption** in **humans**

*Antimicrobial **consumption** in **animals***

Antimicrobial **resistance** in **humans**

*Antimicrobial **resistance** in **animals***

COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN HUMANS

- Positive association between total consumption of 3rd- and 4th-generation **cephalosporins** and occurrence of resistance to 3rd-generation cephalosporins in *E. coli* from human BSIs
- Positive association between total consumption of **fluoroquinolones** and occurrence of fluoroquinolone resistance in *E. coli* from human BSIs
- No association between consumption of fluoroquinolones and the occurrence of fluoroquinolone resistance in *Salmonella* spp., *S.* Enteritidis and *S.* Typhimurium from cases of human infection

POTENTIAL RELATIONSHIPS INVESTIGATED

Antimicrobial **consumption** in **humans**

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Antimicrobial **resistance** in **humans**

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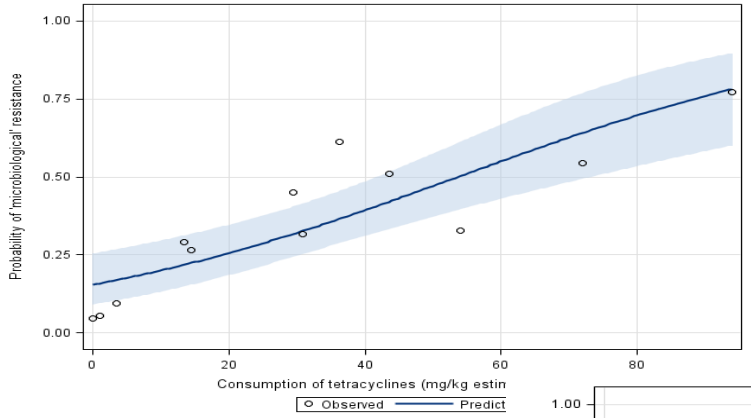
COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

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.



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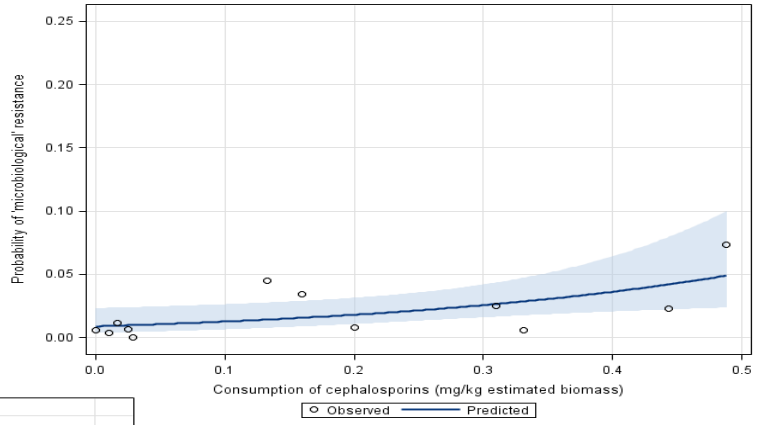
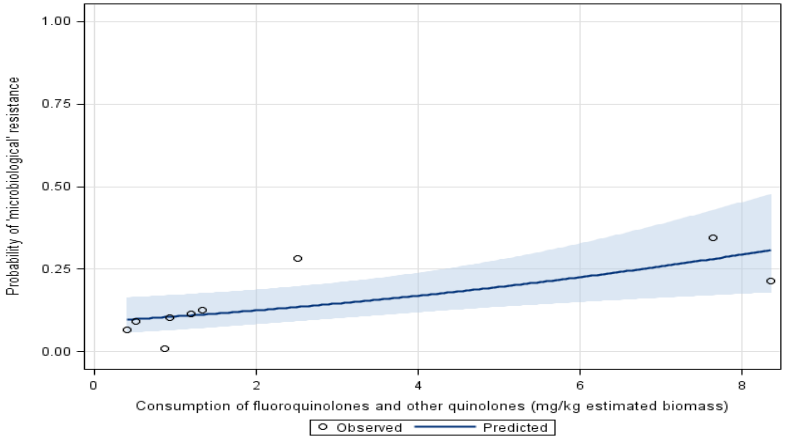


C.



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

POTENTIAL RELATIONSHIPS INVESTIGATED

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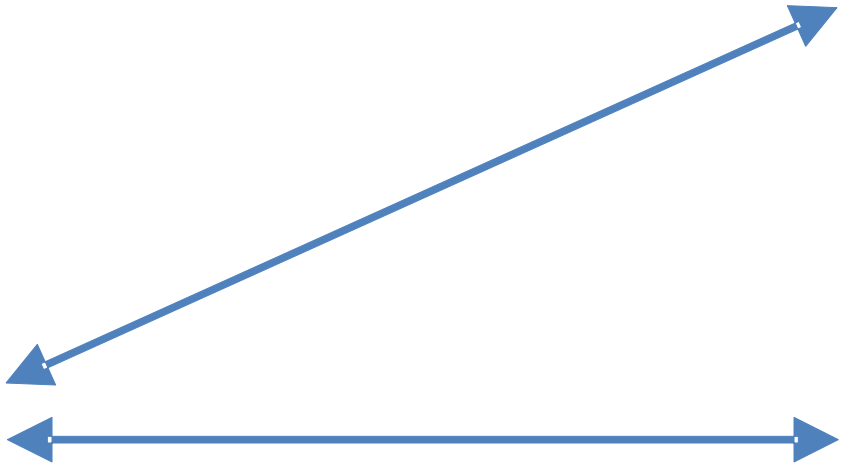
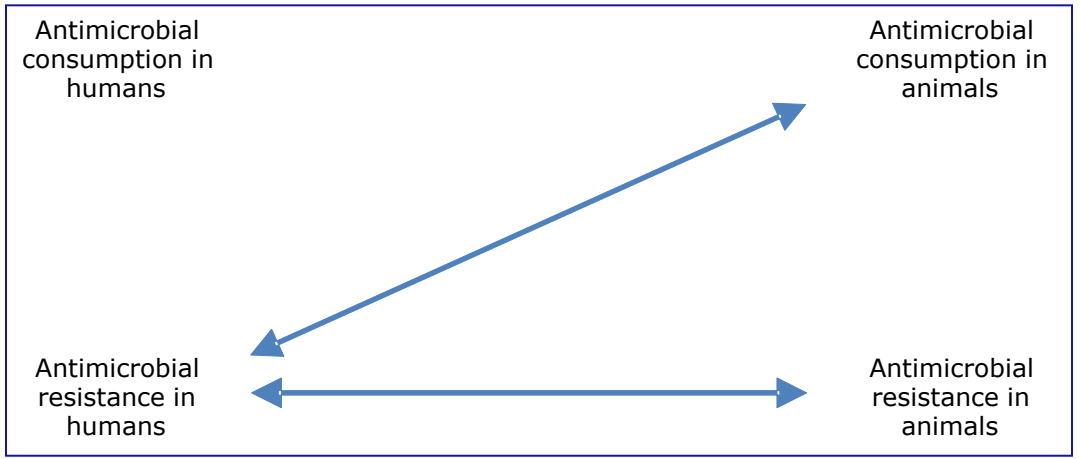
*Antimicrobial **consumption** in **animals***



Antimicrobial **resistance** in **humans**

*Antimicrobial **resistance** in **animals***

POTENTIAL RELATIONSHIPS INVESTIGATED



- For both ***cephalosporins*** and ***fluoroquinolones***, positive associations found **between occurrence of resistance** in indicator *E. coli* from **food-producing animals** and occurrence of resistance in *E. coli* from **humans**.

➔ Resistance in *E. coli* causing bloodstream infections in humans could be correlated with usage of antimicrobials in food-producing animals and in humans.

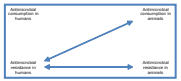
CONSUMPTION AND RESISTANCE : ANIMALS – HUMANS

- No associations between consumption of 3rd- and 4th-generation **cephalosporins** in food-producing animals and occurrence of resistance to this sub-class in selected bacteria from humans.

- Positive associations for consumption of **fluoroquinolones** in food-producing animals and occurrence of resistance in *E. coli* from humans, but not for *Salmonella* spp. and *Campylobacter* spp.

- Positive associations for consumption of **macrolides** in food-producing animals and the occurrence of resistance in *Campylobacter* spp. from human cases of infection.

- Positive associations for consumption of **tetracyclines** in food-producing animals and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp. from humans.



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!

CONCLUSIONS

- Marked variations between countries both in the overall consumption figures and for consumption of the 3rd- and 4th-generation 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 factors aside from antimicrobial consumption influence the occurrence of resistance

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]
Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report

Abstract

The ECDC, the EFSA and the EMA have for the first time jointly explored associations between consumption of antimicrobials in humans and food-producing animals, and antimicrobial resistance in bacteria from humans and food-producing animals, using 2011 and 2012 data currently available from their reference five EU monitoring networks. Combined data on antimicrobial consumption and corresponding resistance in animals and humans for EU MSs and reporting countries were analysed using logistic regression models for selected combinations of bacteria and antimicrobials. A summary indicator of the proportion of resistant bacteria in the main food-producing animal species was calculated for the analysis of resistant bacteria in food-producing animals and humans in 2012, both expressed in milligrams per kilogram of estimated biomass, revealed that overall antimicrobial consumption was higher in animals than in humans, although contrasting situations were observed between countries. The consumption of several antimicrobials extensively used in animal husbandry was higher in animals than in humans, while consumption of antimicrobials critically important for human medicine (such as fluoroquinolones and 3rd- and 4th-generation cephalosporins) was higher in humans. In both humans and animals, positive associations between consumption of antimicrobials and the corresponding resistance in bacteria were observed for most of the combinations investigated. In some cases, a positive association was also found between consumption of antimicrobials in animals and resistance in bacteria from humans. While highlighting findings of concern, these results should be interpreted with caution owing to current data limitations and the complexity of the AMR phenomenon, which is influenced by several factors besides antimicrobial consumption. Recommendations to address current data limitations for analyses of this type were identified. In any case, responsible use of antimicrobials in both humans and animals should be promoted.

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