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

The JIACRA Report

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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

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- European Antimicrobial Resistance Surveillance Network (EARS-Net)
- European Surveillance of Antimicrobial Consumption Network (ESAC-Net)
- Food- and Water-borne Diseases Network (FWD-Net)

- Scientific Network on Zoonoses Monitoring Data
  - EU Summary Report on AMR in zoonotic and indicator bacteria from humans, animals and food

- 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
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- **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

Antimicrobial consumption in humans

Antimicrobial resistance in humans

Antimicrobial consumption in animals

Antimicrobial resistance in animals
POTENTIAL RELATIONSHIPS INVESTIGATED

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POTENTIAL RELATIONSHIPS INVESTIGATED

Antimicrobial consumption in humans

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Antimicrobial resistance in animals
REPORTING CONSUMPTION IN HUMANS

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

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

- Cattle
- Pigs
- Poultry
- Other species

Uneven use of substances among animal species

All animal species addressed together

Sale Data at National Level (mg/PCU)

Consumption data

Weighting according to PCU

Resistance Data at National Level

Resistance data
Antimicrobial consumption (mg/estimated biomass) vs. ‘summary indicator’ of Resistance

- ‘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

\[
Ind_{Res} = \frac{1}{PCU_{cattle} + PCU_{fowl} + PCU_{pigs}} \cdot (PCU_{cattle} \cdot Res_{cattle} + PCU_{fowl} \cdot Res_{fowl} + PCU_{pigs} \cdot Res_{pigs})
\]
COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE

Modeling and Graphical Comparisons

- 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
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

<table>
<thead>
<tr>
<th></th>
<th>Total consumption in 2012 (expressed in mg/kg of estimated biomass)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In humans</strong></td>
<td>116.4 mg/kg (range: 56.7 – 175.8 mg/kg)</td>
</tr>
<tr>
<td><strong>In animals</strong></td>
<td>144.0 mg/kg (range: 3.8 – 396.5 mg/kg)</td>
</tr>
</tbody>
</table>
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.
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.
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POTENTIAL RELATIONSHIPS INVESTIGATED

Antimicrobial consumption in humans

Antimicrobial resistance in humans

Antimicrobial consumption in animals

Antimicrobial resistance in animals
• 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

Antimicrobial resistance in humans

Antimicrobial consumption in animals

Antimicrobial resistance in animals
### COMPARISON OF ANTIMICROBIAL CONSUMPTION AND RESISTANCE IN ANIMALS

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Antimicrobial class</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indicator <em>E. coli</em></strong></td>
<td>Tetracyclines</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>3rd gen. cephalosporins</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones &amp; quinolones</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>C. jejuni and C. coli</strong></td>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Macrolides</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
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<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones and other quinolones</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
A. Sales of TET – Resistance to TET
B. Sales of CEPH – Resistance to CTX
C. Sales of FQ and Q – Resistance to CIP

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
Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA)

POTENTIAL RELATIONSHIPS INVESTIGATED

Antimicrobial consumption in humans

Antimicrobial resistance in humans

Antimicrobial consumption in animals

Antimicrobial resistance in animals
• 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. For example, a 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!

