

# **ECDC-EFSA-EMA Joint Opinion on Outcome Indicators on Surveillance of Antimicrobial Resistance and Use of Antimicrobials**

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**'One Health' Network on Antimicrobial Resistance**

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CCAB - Rue Froissart 36 – 1040 - Brussels

# BACKGROUND

- EC evaluation of 2011 5-year AMR action plan
  - 'called for further strengthening of monitoring and surveillance of AMR and AMR-related activities [...] developing indicators and instruments to monitor trends in resistant infections and antimicrobial consumption'
  
- Council conclusions June 2016
  - 'call upon MS to have in place before mid-2017 national action plans against AMR based on the 'One Health' approach and including measurable goals to reduce infections in humans and animals, the use of antimicrobials in the human and veterinary sectors and antimicrobials resistance in all domains'

## TERMS OF REFERENCE

- ECDC, EFSA and EMA have jointly established a list of harmonised outcome indicators to assist EU MSs in assessing their progress in reducing the use of antimicrobials and antimicrobial resistance (AMR) in both humans and food-producing animals.

# REQUIREMENTS (1)

- Maximum **15 indicators**, divided in:
  - Primary indicators (4) = monitoring essential points
  - Secondary indicators (11)= monitoring highly recommended points to assess progress made in Member States' plans
- Suitable to estimate **progress** made in **reducing AMR to key AMs** in accordance with WHO, AMEG and OIE definitions
- Robust, take into account 'One Health' approach to track and compare improvements in human/vet sectors

## REQUIREMENTS (2)

### ❖ Antimicrobial Resistance

- Bacteria
- Populations (human/animal)
- Antimicrobial substances
- Recommended protocol
- Reporting unit

### ❖ Antimicrobial Consumption

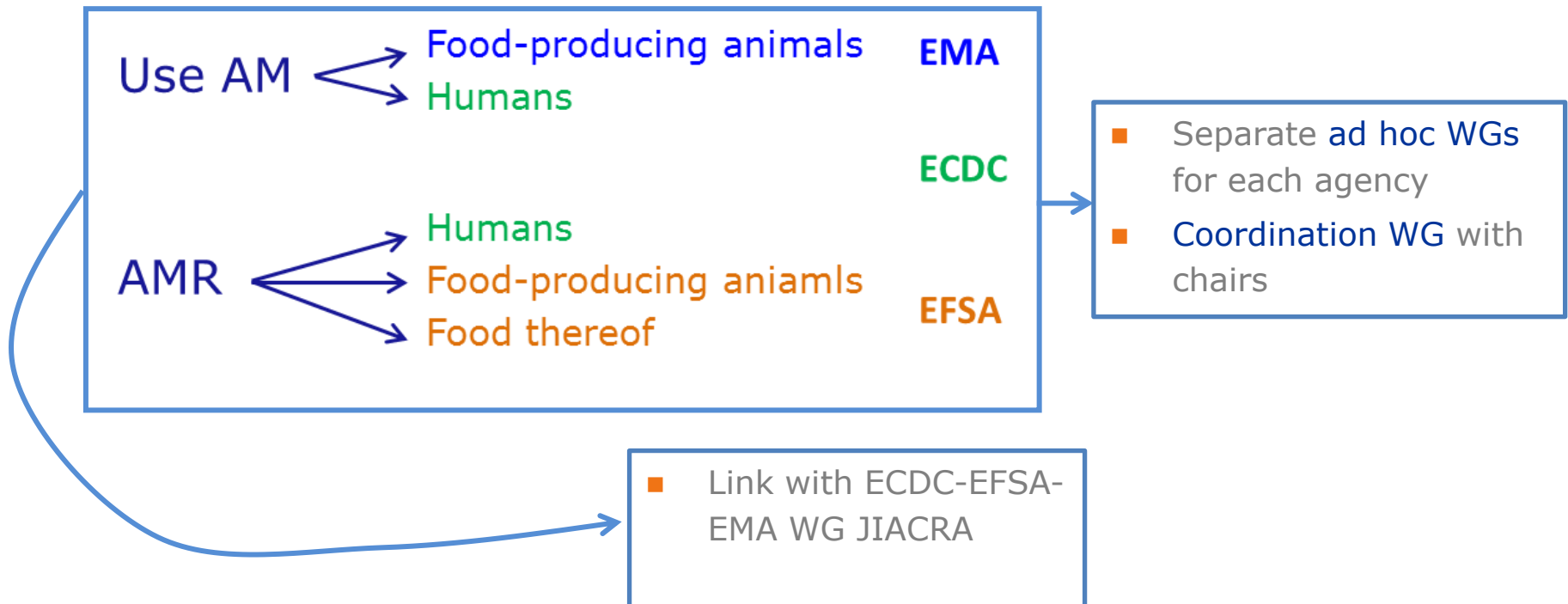
- Antimicrobial group
- Animal production sector
- At the community/hospital
- Reporting unit

■ Built where possible on **data already collected**

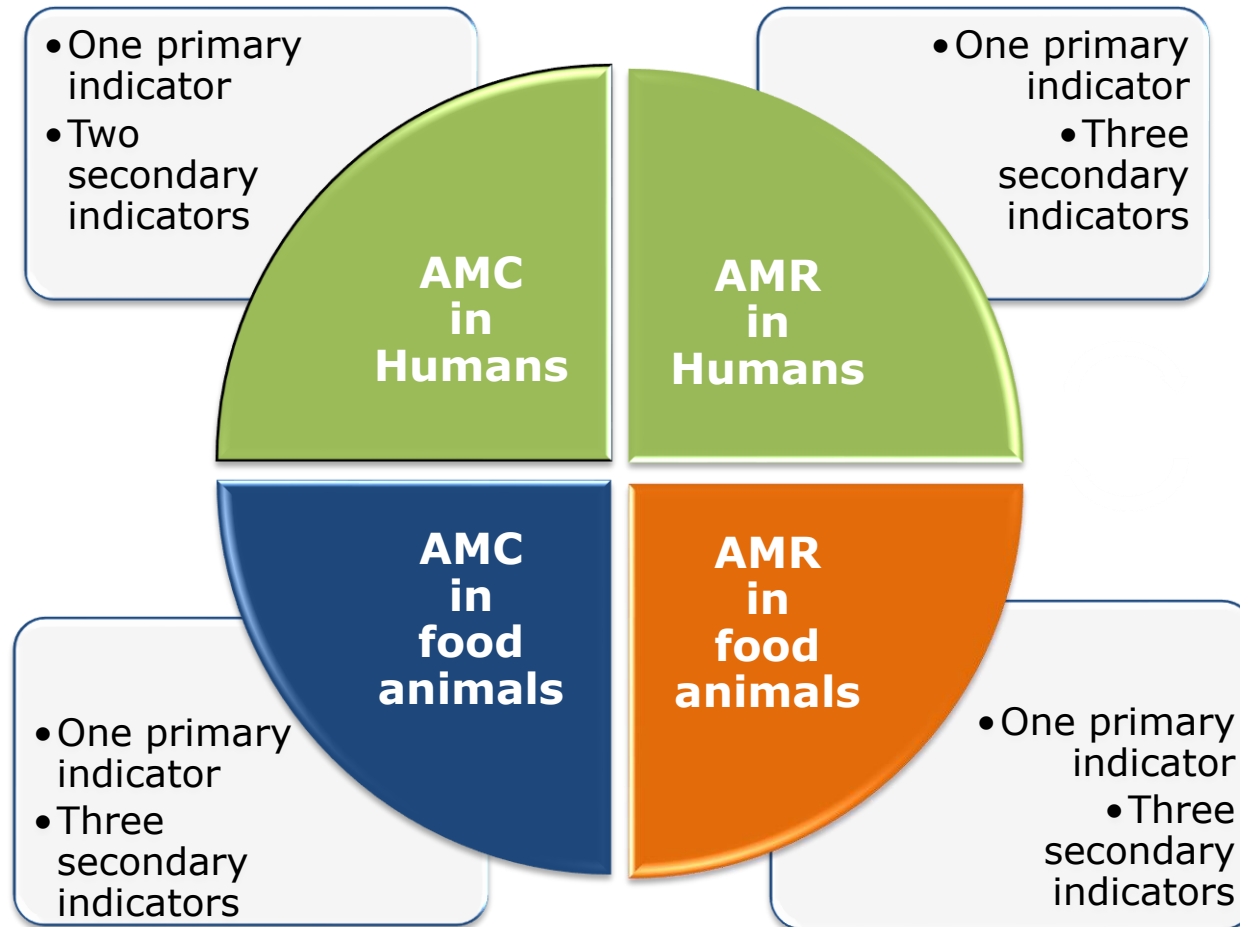
■ Remain relevant for **at least five years**

## PARTIES INVOLVED

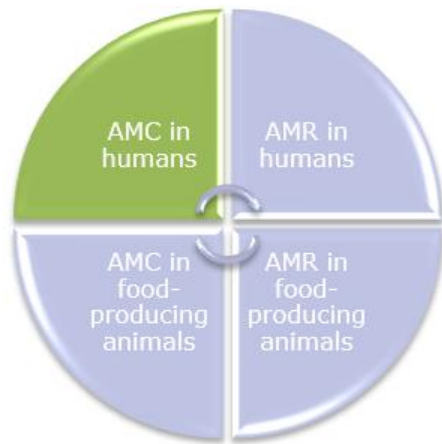
- EC mandate to be addressed jointly by ECDC-EFSA-EMA
- Adoption by respective bodies of the Agencies



# FOUR SECTORS AND 15 OUTCOME INDICATORS



# Indicators of antimicrobial consumption (AMC) in humans (ECDC)



## Primary indicator:

- Total consumption of all antimicrobials for systemic use (DDD per 1,000 inhabitants per day)

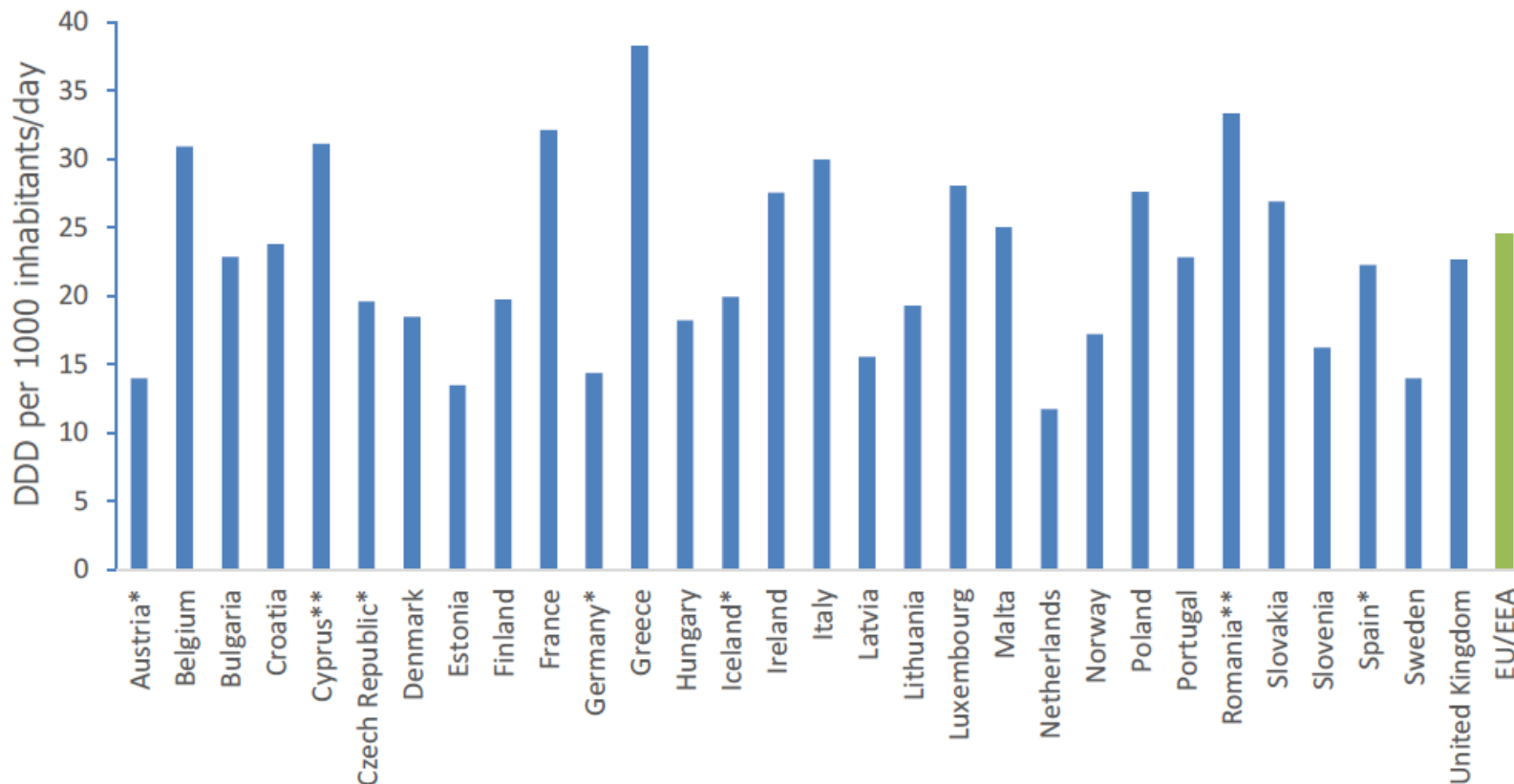
## Secondary indicators:

- Ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides and fluoroquinolones to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides;
- Consumption of glycopeptides, 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitors, linezolid, tedizolid and daptomycin (DDD per 1,000 inhabitants per day, and as proportion of the total hospital use)



# Example of calculation of indicators for AMC in humans

**Primary indicator:** Total consumption of all antimicrobials for systemic use, expressed in DDD per 1,000 inhabitants and per day, ESAC-Net, 2015



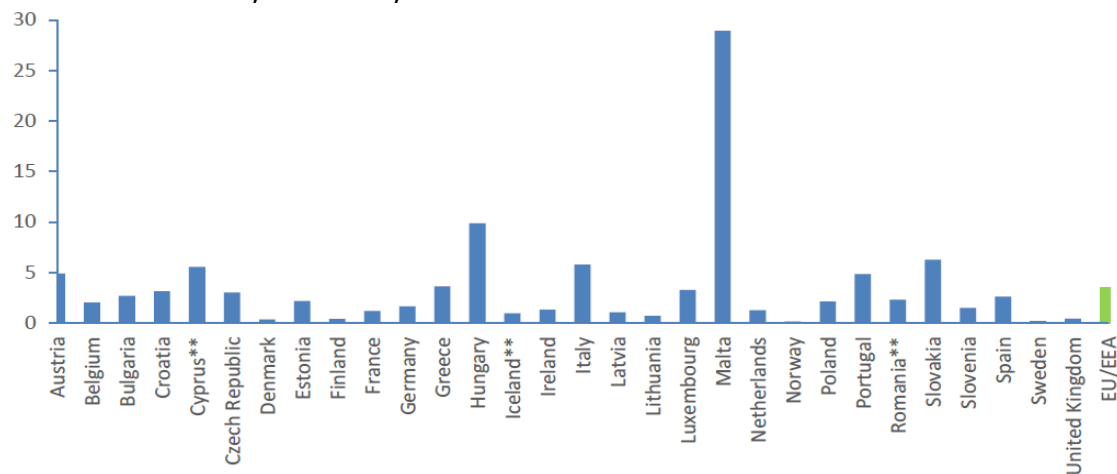
\*: Country reported only community data

\*\* : Country reported total care data (aggregated data for both sectors)

EU/EEA: EU/EEA population-weighted mean consumption

# Example of calculation of indicators for AMC in humans (continued)

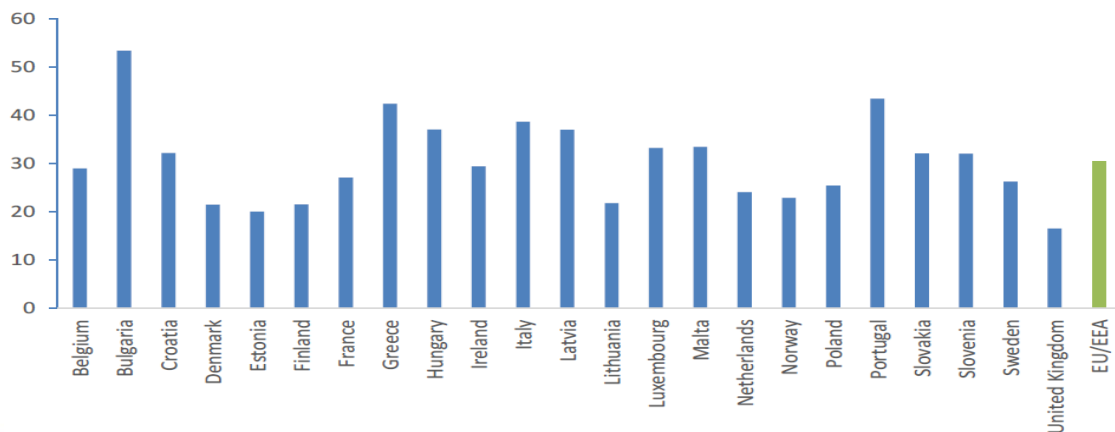
**Secondary indicator:** Ratio of community antimicrobial consumption of broad-spectrum to the consumption of narrow-spectrum antimicrobials<sup>†</sup>, ESAC-Net, 2015



<sup>†</sup> consumption of broad-spectrum penicillins, cephalosporins, macrolides and fluoroquinolones / consumption of narrow-spectrum penicillins, cephalosporins and macrolides

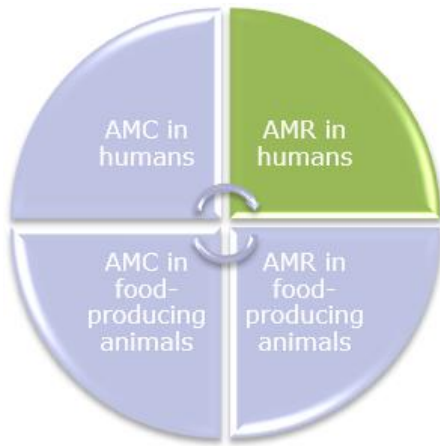
\*\* : Country reported total care data (aggregated data for both sectors) EU/EEA: EU/EEA population-weighted mean consumption

**Secondary indicator:** Proportion (%) antimicrobial consumption of selected hospital sector antimicrobials<sup>‡</sup> of the total hospital consumption of antibacterials for systemic use, ESAC-Net, 2015



<sup>‡</sup>glycopeptides, 3<sup>rd</sup>- and 4<sup>th</sup>-generation cephalosporins, monobactams, carbapenems, fluoroquinolones, polymyxins, piperacillin and enzyme inhibitors, linezolid, tedizolid and daptomycin

# Indicators of AMR in bacteria from humans (ECDC)



## Primary indicator:

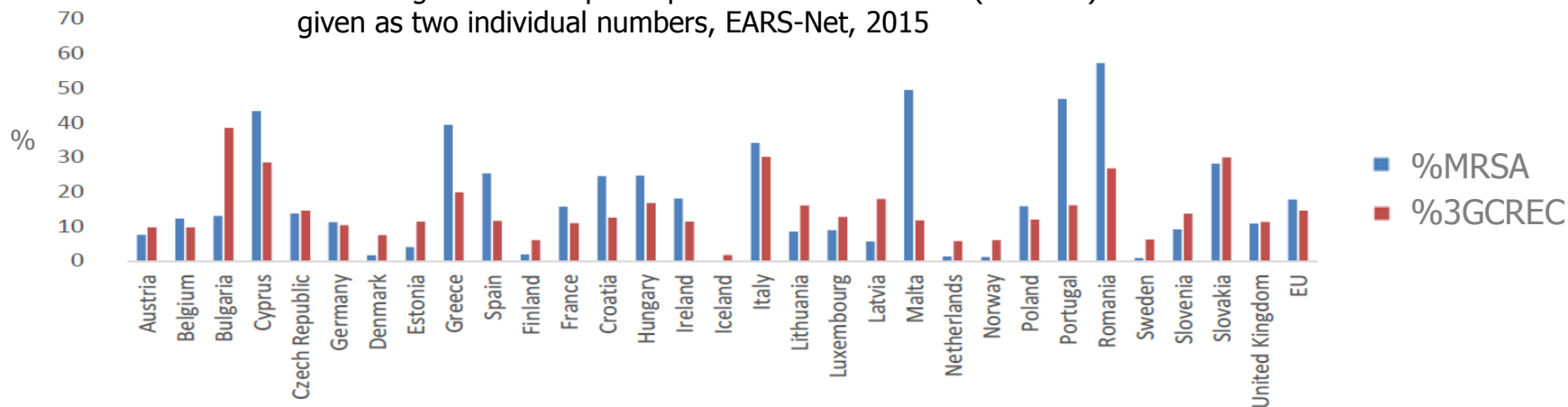
- Proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) and proportion of *E. coli* resistant to 3<sup>rd</sup>-generation cephalosporins (3GCR *E. coli*)

## Secondary indicators:

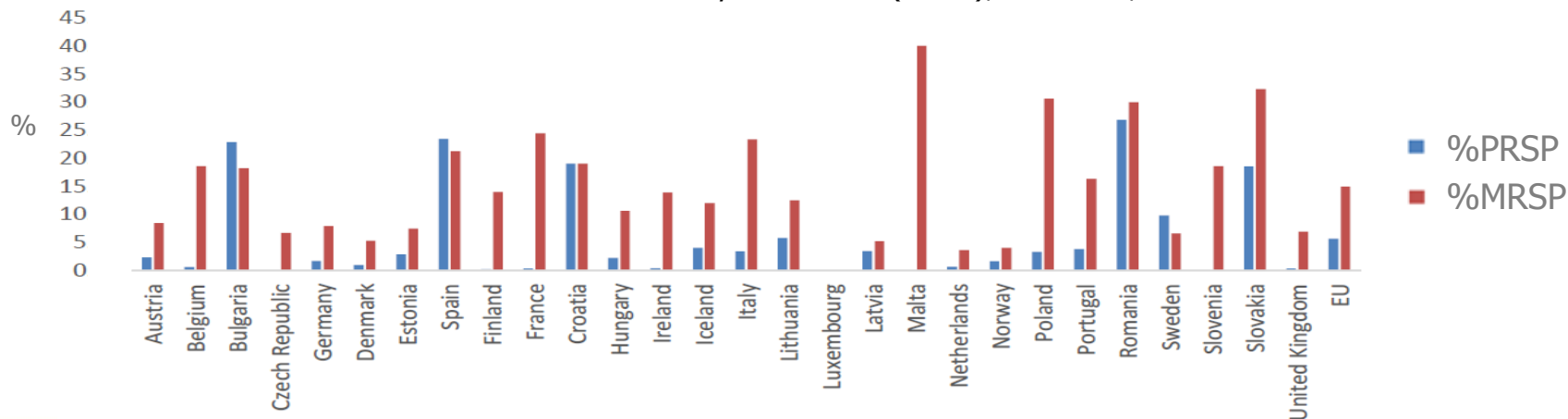
- Proportion of *K. pneumoniae* isolates with combined resistance to aminoglycosides, fluoroquinolones and 3<sup>rd</sup>-generation cephalosporins
- Proportion of penicillin-resistant *S. pneumoniae* and proportion of macrolide-resistant *S. pneumoniae*
- Proportion of carbapenem-resistant *K. pneumoniae*

# Example of calculation of indicators for AMR in bacteria from humans

**Primary indicator:** Proportion (%) of meticillin-resistant *Staphylococcus aureus* (MRSA) and 3rd-generation cephalosporin-resistant *E. coli* (3GCREC) given as two individual numbers, EARS-Net, 2015

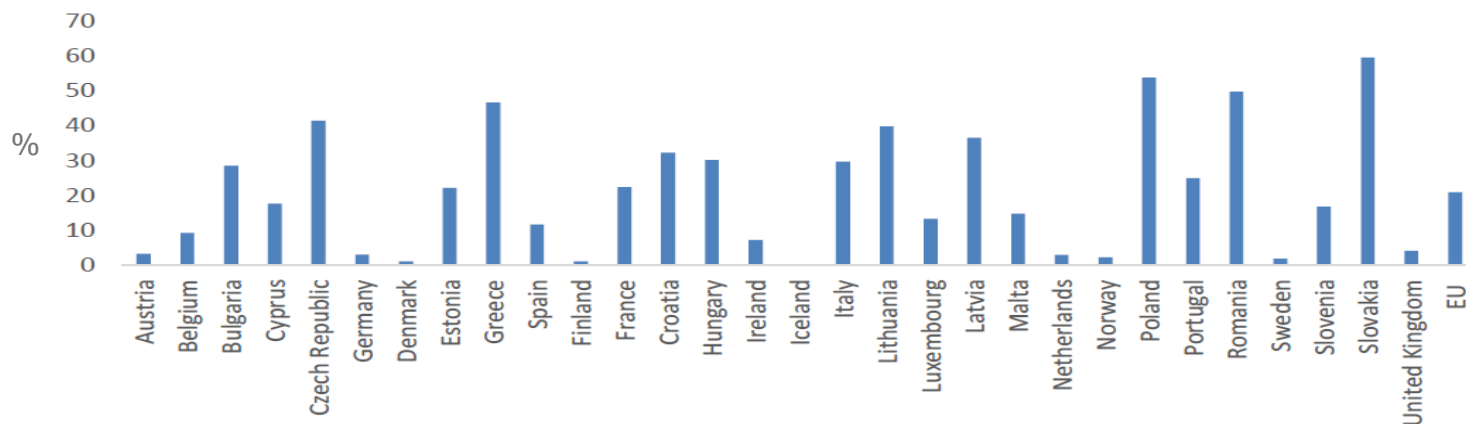


**Secondary indicator:** Proportion (%) of penicillin-resistant *Streptococcus pneumoniae* (PRSP) and macrolide-R resistant *S. pneumoniae* (MRSP), EARS-Net, 2015

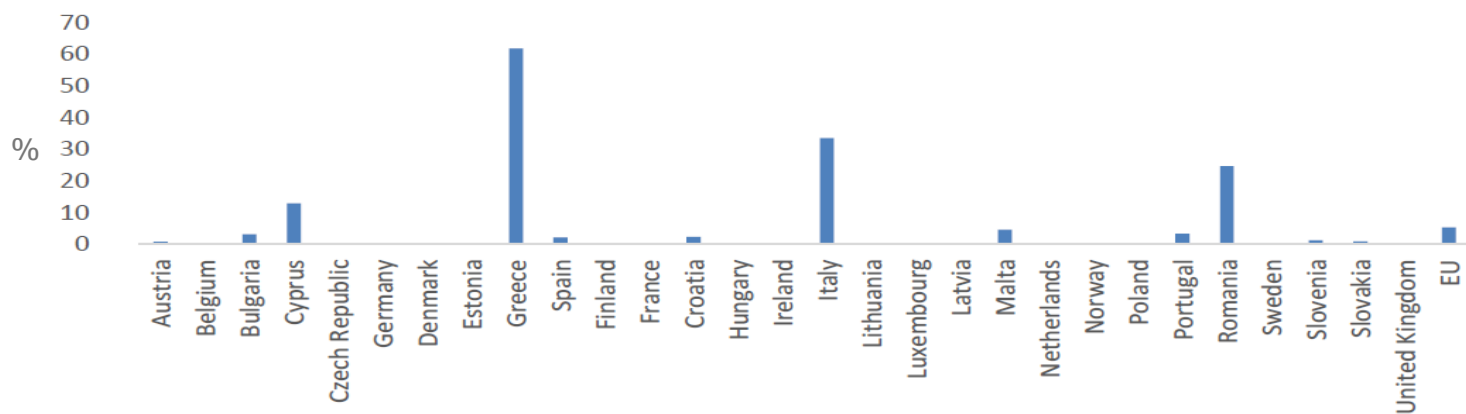


# Example of calculation of indicators for AMR in bacteria from humans (continued)

**Secondary indicator:** Proportion (%) of *Klebsiella pneumoniae* with combined resistance to aminoglycosides, fluoroquinolones and 3<sup>rd</sup>-generation cephalosporins, EARS-Net, 2015

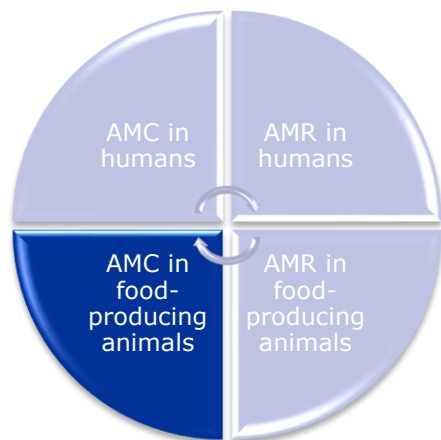


**Secondary indicator:** Proportion (%) of carbapenem-resistant *Klebsiella pneumoniae*, EARS-Net, 2015





# Indicators for AMC in food-producing animals (EMA)



## Primary indicator:

- Overall sales of AM in mg/PCU

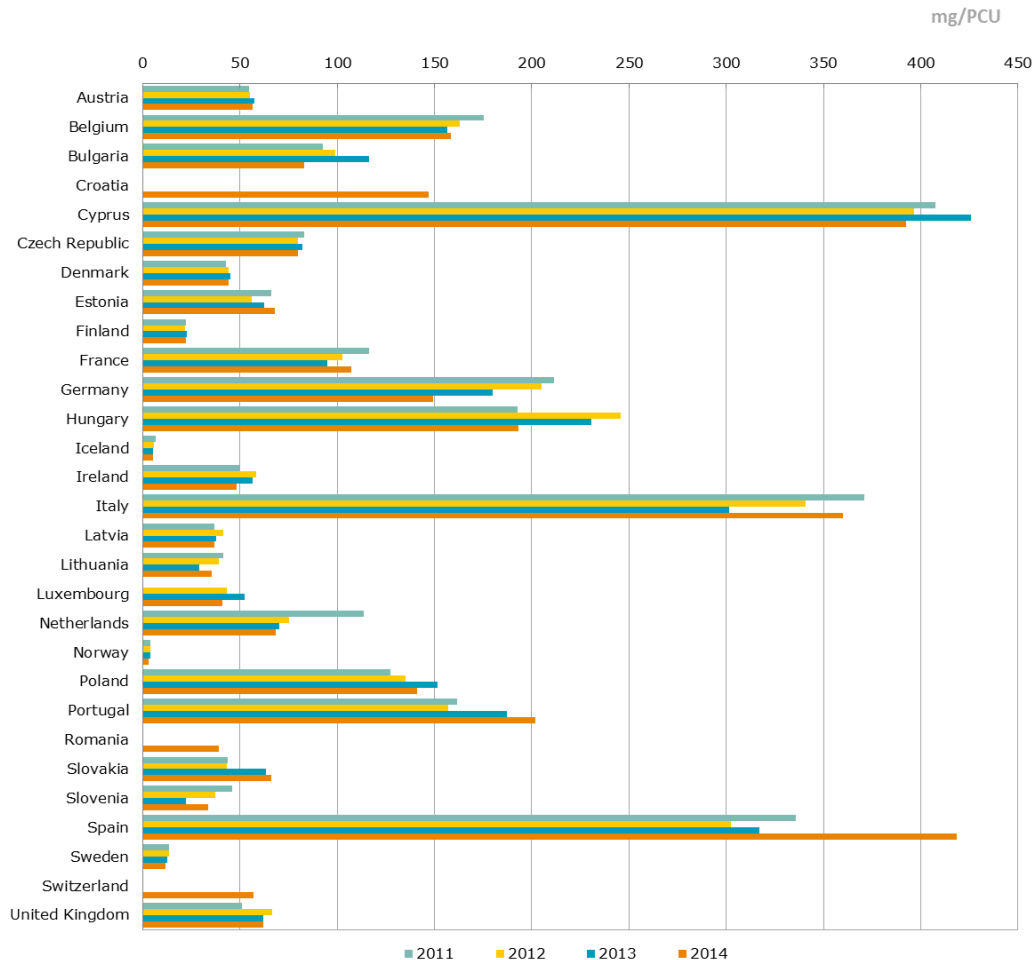
## Secondary indicators:

- Sales of 3/4G Cephalosporins (mg/PCU)
- Sales of all Quinolones, specifying the % of FQs and Qs (mg/PCU)
- Sales of Polymixins (mg/PCU)



# Example of calculation of indicators for AMC in food-producing animals

**Primary indicator:** Overall sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, from 2011 to 2014, for 29 European countries

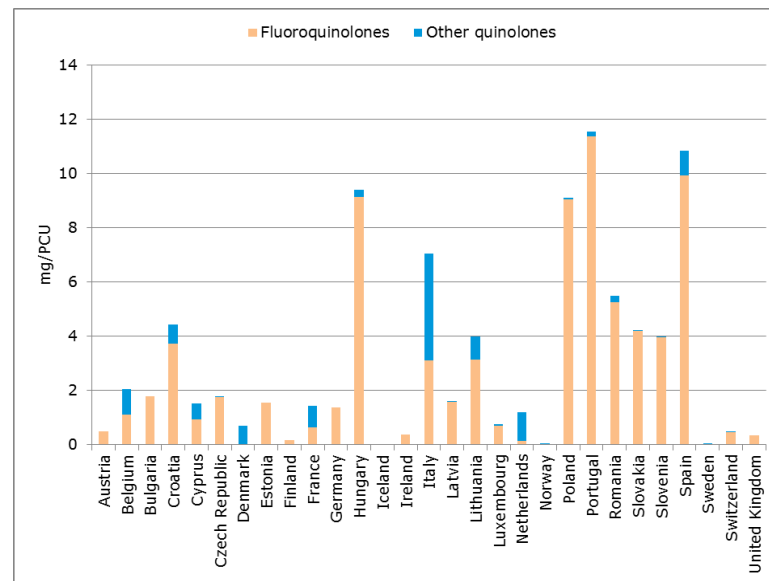
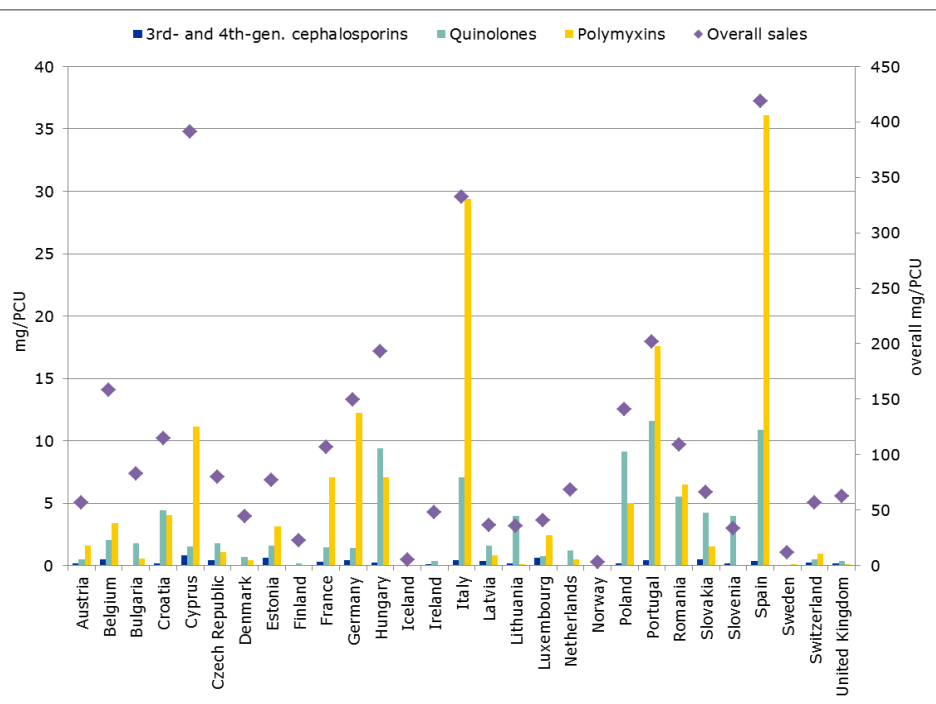




# Example of calculation of indicators for AMC in food-producing animals

**Secondary indicators:** Sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, overall (right Y-axis) and of **3rd- and 4th-generation cephalosporins**, **quinolones** and **polymyxins** (left Y-axis), for 2014, for 29 European countries.

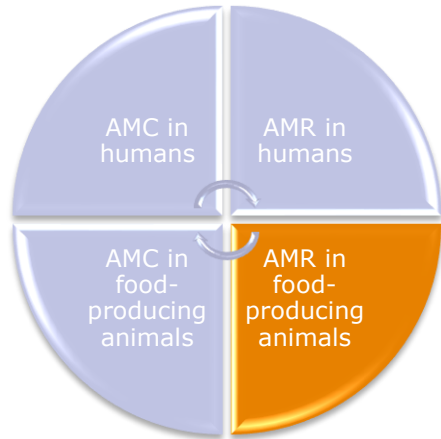
Sales of veterinary antimicrobial agents for food-producing species, in mg/PCU, **fluoroquinolones** and **other quinolones**, for 2014, for 29 European countries



Note the different axis scale for overall sales and those for HCIA's



# INDICATORS OF AMR IN FOOD-PRODUCING ANIMALS



- Indicator *E. coli*,
- Susceptibility to harmonised panel of substances,
- All animal species considered,
- Weighted mean by PCU,
- JIACRA II: negative association between total use and complete susceptibility.

## Primary indicator

- Proportion of *E. coli* completely susceptible to antimicrobials tested in the EU monitoring\*

## Secondary indicators

- Proportion of samples containing ESBL-/AmpC-producing *E. coli*\*
- Proportion of *E. coli* resistant to three or more antimicrobial classes\*
- Proportion of *E. coli* resistant to fluoroquinolones\*

- Use of information from the specific monitoring of proportion of samples harbouring ESBL-/AmpC-producing *E. coli*.

- Use of measures of MDR (different classes),
- Relevant to monitor the effect of reduced use,
- Useful when complete susceptibility is very low.

- Ciprofloxacin on WHO list highest priority CIAs,
- FQ resistance correlates consistently with usage.

\* All indicators are weighted for all food-producing animals (broilers, turkeys, pigs, calves)

# AMR, FOOD-PRODUCING ANIMALS

## How are they calculated?

- Same approach as that followed in JIACRA II report
  - Resistance data from EUSR AMR (EFSA and ECDC)
  - PCU data from ESVAC report (EMA)

$$I_X = \frac{R_{BRY} \cdot PCU_{BRY}}{PCU_y} + \frac{R_{TKY} \cdot PCU_{TKY}}{PCU_y} + \frac{R_{PGY} \cdot PCU_{PGY}}{PCU_y} + \frac{R_{CVY} \cdot PCU_{CVY}}{PCU_y}$$

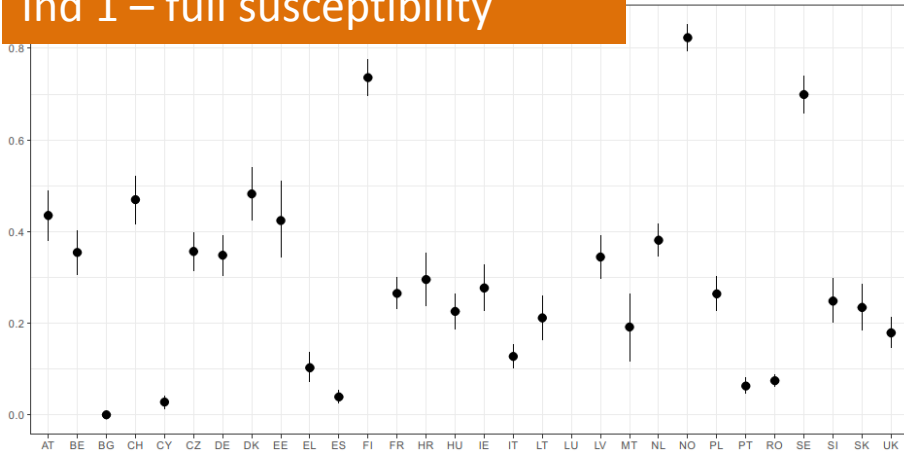
The diagram illustrates the calculation of the index  $I_X$  for the years 2014 and 2015. The equation is shown with terms for each year. The terms for 2014 are  $R_{BRY} \cdot PCU_{BRY}$  and  $R_{TKY} \cdot PCU_{TKY}$ , and the terms for 2015 are  $R_{PGY} \cdot PCU_{PGY}$  and  $R_{CVY} \cdot PCU_{CVY}$ . Each term is divided by  $PCU_y$ . The numerators are circled in blue, and the denominators are boxed in orange.

- Recommendation to include calculation of uncertainty
  - Example of methodology provided (including R code), based on MC simulation

# AMR, FOOD-PRODUCING ANIMALS

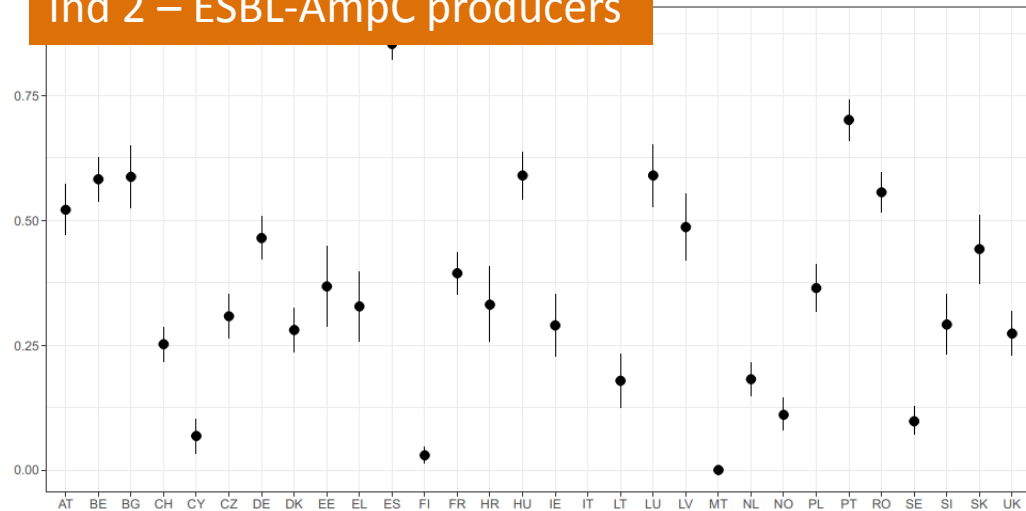
## Examples of calculations with 2014-2015 data

Ind 1 – full susceptibility



Not designed to compare countries

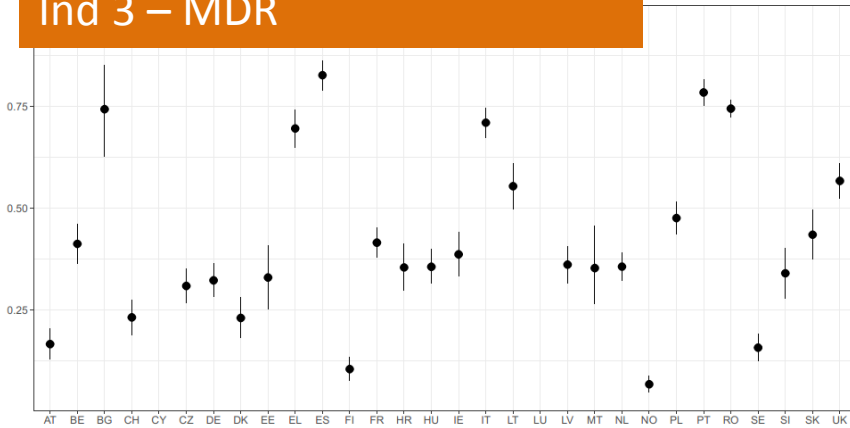
Ind 2 – ESBL-AmpC producers



# AMR, FOOD-PRODUCING ANIMALS

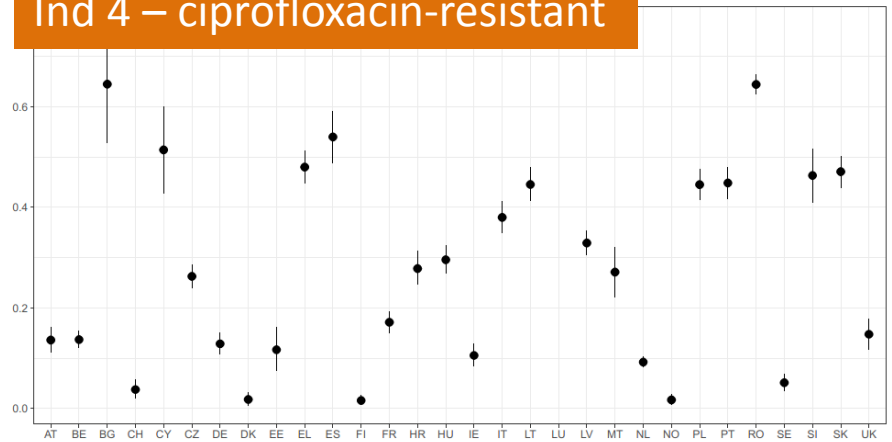
## Examples of calculations with 2014-2015 data

Ind 3 – MDR



Not designed to compare countries

Ind 4 – ciprofloxacin-resistant



# VALUE AND LIMITATION

## ■ Value

- Based on data already collected
- Summarising overall situation of AMC and AMR in humans and food-producing animals
- Tool for Member States to assess their progress
- Possible tool for risk managers to set targets

## ■ Limitation

- Summarising information = losing information
- Often not suitable to monitor the effects of targeted interventions in a specific sector (e.g. animal species)
- Apart from when proposed indicators are single indicators (human AMR indicators on MRSA), management decisions should never be based on these indicators alone but should take into account the underlying data and their analysis

## RECOMMENDATIONS (1)

- The chosen indicators should be **reconsidered at least every five years** to evaluate whether they still reflect the data available.
- Data on resistance should be **monitored on a continuous basis**, in order to follow up current AMR issues.
- In order to obtain information on resistance to macrolides in bacteria from livestock species, more data at the EU level on resistance to this class of antimicrobials in *Campylobacter* spp. and indicator species such as enterococci should be collected.
- Data on **AMC in animals** should in the future **be collected at farm level** and according to different production systems. Analysis should take into account differences in dosing between species and substances, e.g. using the **DDD<sub>vet</sub> system**.

## RECOMMENDATIONS (2)

- **Management decisions** should **never** be **based on these indicators alone** and during evaluation of the effectiveness of any national intervention, care has to be taken to use **appropriate statistical techniques**.
- Indicators in the different sectors should be **analysed together** within a MS.

# THANK YOU FOR YOUR ATTENTION!

## ACKNOWLEDGEMENTS

### Authors:

**ECDC:** Martin Cormican, Susan Hopkins, Vincent Jarlier, Jacqui Reilly, Gunnar Skov Simonsen, Reinhold Strauss, Olivier Vandenberg, Dorota Zabicka, Peter Zarb, Mike Catchpole, Ole Heuer, Elias Iosifidis, Dominique Monnet, Diamantis Plachouras and Klaus Weist.

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WORKING!