



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## ESVAC collection of antimicrobial sales data

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EC workshop with EMA: Data collection on consumption of veterinary antimicrobials in Europe – achievements, challenges and way forward. Brussels, 26 April 2017

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# Outline

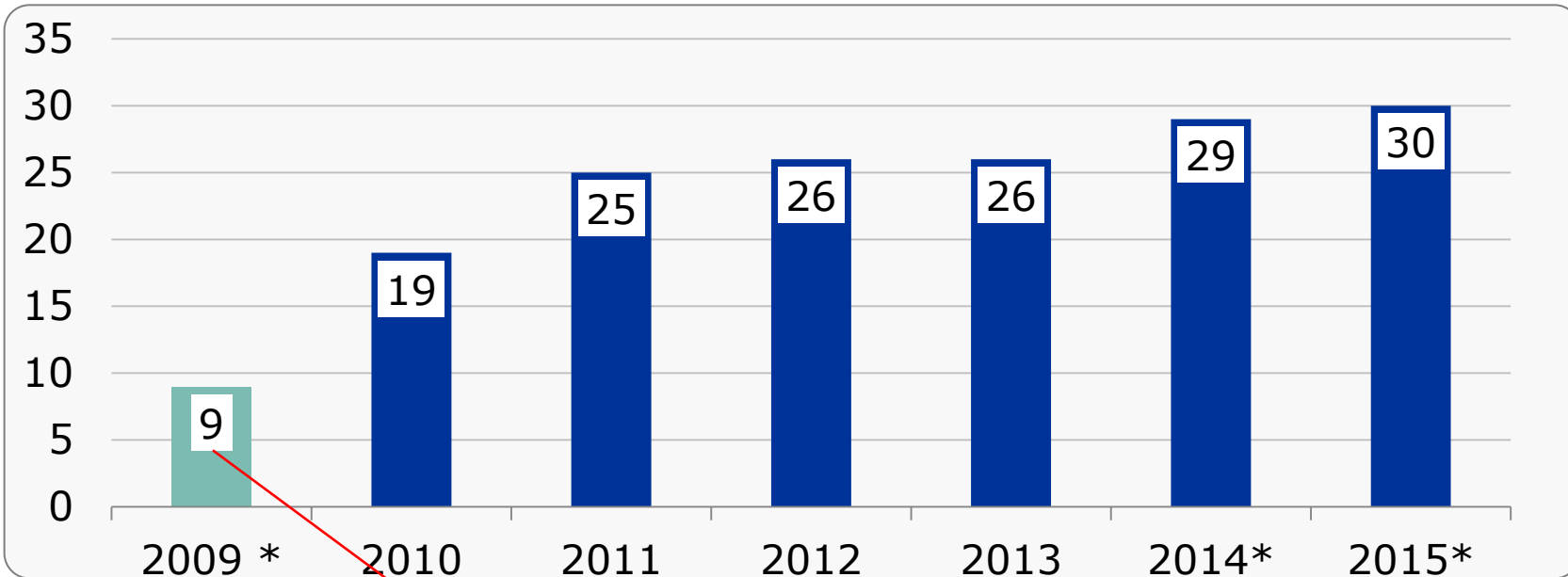
## ESVAC sales data

- ESVAC state of play
- Caveats of the ESVAC sales and denominator data

- Objectives

Purpose/why

- Examples of use of ESVAC sales data in the fight against AMR
  - Use at EU/EEA level
  - Use of sales data at national level
- Way forward



Before ESVAC – number of countries publishing data nationally

\* Switzerland included



Six reports published; 7th report will be published in October 2017

# Sales data for food-producing animals, including horses, represents

## Categories of veterinary antimicrobial agents included in the sales data

Antimicrobial agents for intestinal use

Antimicrobial agents for intrauterine use

Antimicrobial agents for systemic use

Antimicrobial agents for intramammary use

Antimicrobial agents for antiparasitic use<sup>1</sup>

<sup>1</sup> Solely sulfonamides

NOTE: Dermatological preparations and preparations for eyes and ears not included. Documented to be < 0.4% of sales in tonnes

NOTE: Tablets collected but excluded prior to the analysis as used almost solely for pets

- Numbers sold collected for each veterinary medicinal product (VMP) presentation
  - VMP presentation: Name, strength, form and pack size
  - Number VMP presentation in ESVAC database for 2014: 9,300 (tablets excluded)
- Weight (tonnes) of active ingredient sold per VMP calculated for each VMP

Strength x pack size x number packages

# Benefits and weaknesses of the sales data (numerator)

<b>Benefits</b>	<b>Weaknesses</b>
Relatively cheap to obtain	VMPs typically marketed/used for more than one animal species – sales data as such will usually not provide information on sales by animal species
Important for validation of by species data collected	Cannot correct for differences in dosing between antimicrobials, forms and species (use of DDDvet/DCDvet)

# Normalising sales data for population at risk of being treated with antimicrobials

- Number of animals – slaughtered and livestock not applicable as denominator (adding numbers broilers, dairy cattle etc.)
- Therefore, as a proxy for the size of the food-producing animal population (including horses) a population correction unit (**PCU**) was established



# Species included in the animal population data

Species/categories	Data source
Number slaughtered: cattle, goats, pigs, sheep, poultry, rabbits and turkey	Eurostat
Number livestock: dairy cows, sheep, sows and horses	Eurostat
Biomass fish	Eurostat
Number imported/exported: cattle, pigs, goat, sheep and poultry for slaughter or fattening	TRACES

Note that due to the limited availability of data on living goats in Eurostat at the time of establishment of PCU, this category is not included the PCU



# How the population correction unit (PCU) is calculated

Example pigs

Categories	PCU (1000 tonnes)
Number pigs slaughtered x standard estimated weight at treatment	
Number sows x standard estimated weight at treatment	
Number exported pigs (added)	
• For slaughter <sup>1</sup> x standard weight	(+)
• For fattening <sup>2</sup> x standard weight	(+)
Number imported pigs <sup>3</sup> (subtracted)	
• For slaughter x standard weight	(-)
• For fattening x standard weight	(-)
<b>Total PCU pigs per country X in year Y</b>	

<sup>2</sup> Because young animals are typically treated more frequently than other age classes

<sup>3</sup> Counted in numbers of animals slaughtered for importing country

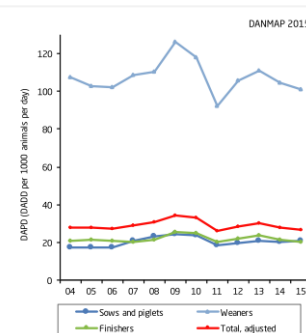
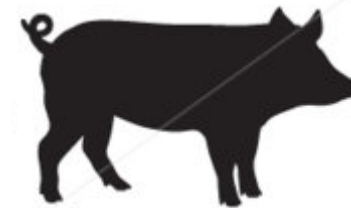


Figure 9: Antimicrobial consumption in the pig production, and the distribution on age groups, Denmark (source: (DANMAP, 2016) – see also original report)

# Strengths and weaknesses of the PCU model

	Strengths	Weaknesses
Harmonized across ESVAC participating countries	<ul style="list-style-type: none"><li>• Same animal (major) species/categories included</li><li>• Same data collection methodology (Eurostat and TRACES)</li></ul>	<ul style="list-style-type: none"><li>• Missing categories - e.g. living goat and suckling cows</li><li>• Clear criteria for which species/categories to be included missing</li><li>• Do not directly represent the country animal production</li></ul>
	<ul style="list-style-type: none"><li>• Weights used to calculate PCU standardized</li></ul>	<ul style="list-style-type: none"><li>• Documentation for the weights used is poor</li></ul>
Stable across years	<ul style="list-style-type: none"><li>• Reliable data to use for analysis</li></ul>	<ul style="list-style-type: none"><li>• All animal species/production categories included weighted the same – e.g. intensively versus extensively reared</li></ul>
Data sources public (Eurostat and TRACES)	<ul style="list-style-type: none"><li>• Analysis can be re-done at any time (update of historical data)</li></ul>	<ul style="list-style-type: none"><li>• Any changes in Eurostat and/or Traces have to be followed-up (e.g. broilers → chicken from 2008)</li></ul>

**NOTE: Discussions on revision of PCU are currently taking place**

# Main indicator to report sales of veterinary antimicrobials

- mg active ingredient normalised by the population correction unit (mg/PCU)

$$\frac{\text{Amount sold in tonnes} \times 10^9}{\text{PCU in kg}}$$

- Main outputs mg/PCU:
  - Total sales by year and country
  - Sales by antimicrobial class/sub-class by year and country
  - Sales by pharmaceutical form/administration route by year and country

# The objectives

- Given in terms of reference from EC (03.03. 2009):

In appendix to TOR:

Background document EMEA/507682/2008 (15.10.2008):

*“Considerations on monitoring on antibacterial drug usage in animals in the EU and EEA”\**

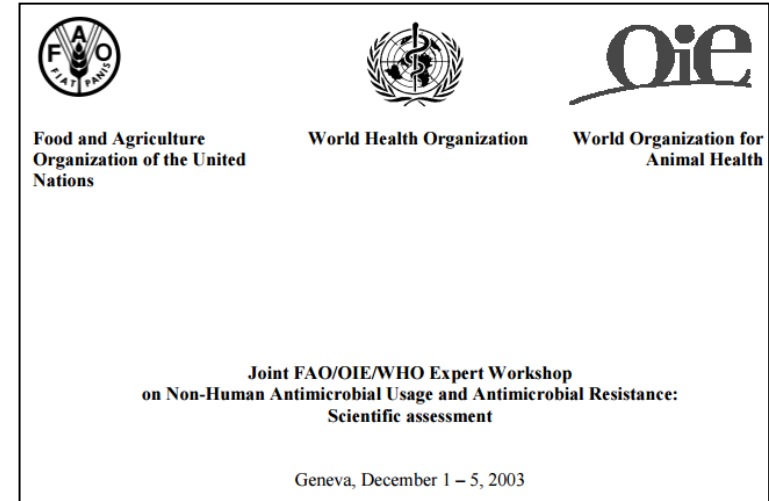
\*Main reference FAO/OIE/WHO document:

<http://www.oie.int/doc/ged/D454.PDF>

Geneva, December, 2003

# FAO/OIE/WHO: Purposes of surveillance of non-human antimicrobial usage and resistance\*

- Documentation of the situation
- Identification of trends
- Linkage of antimicrobial usage and antimicrobial resistance
- Basis for risk assessment
- Basis for interventions
- Evaluation of effectiveness of measures implemented
- Basis for focused and targeted research



Food and Agriculture  
Organization of the United  
Nations



World Health Organization



World Organization for  
Animal Health

Joint FAO/OIE/WHO Expert Workshop  
on Non-Human Antimicrobial Usage and Antimicrobial Resistance:  
Scientific assessment

Geneva, December 1 – 5, 2003

Are the sales data suitable for all these purposes?

[\\*http://www.oie.int/doc/ged/D454.PDF](http://www.oie.int/doc/ged/D454.PDF)

**Figure 21.** Spatial distribution of overall sales of antimicrobials for food-producing animals, in mg/PCU, for 29 countries, for 2014

Global picture





# Comparison across countries?

Observed difference between the countries on reported sales (mg/PCU) and on sales patterns should be interpreted with great care due to

- Variations between countries in the
  - composition of the animal population
  - production systems
- Variations of dosing for the various antimicrobial agents, forms and species
- Variations between countries in “type” of products marketed (and in prices)

May be categorized as high, medium and low users as in the EMA/CVMP/CHMP advice on colistin



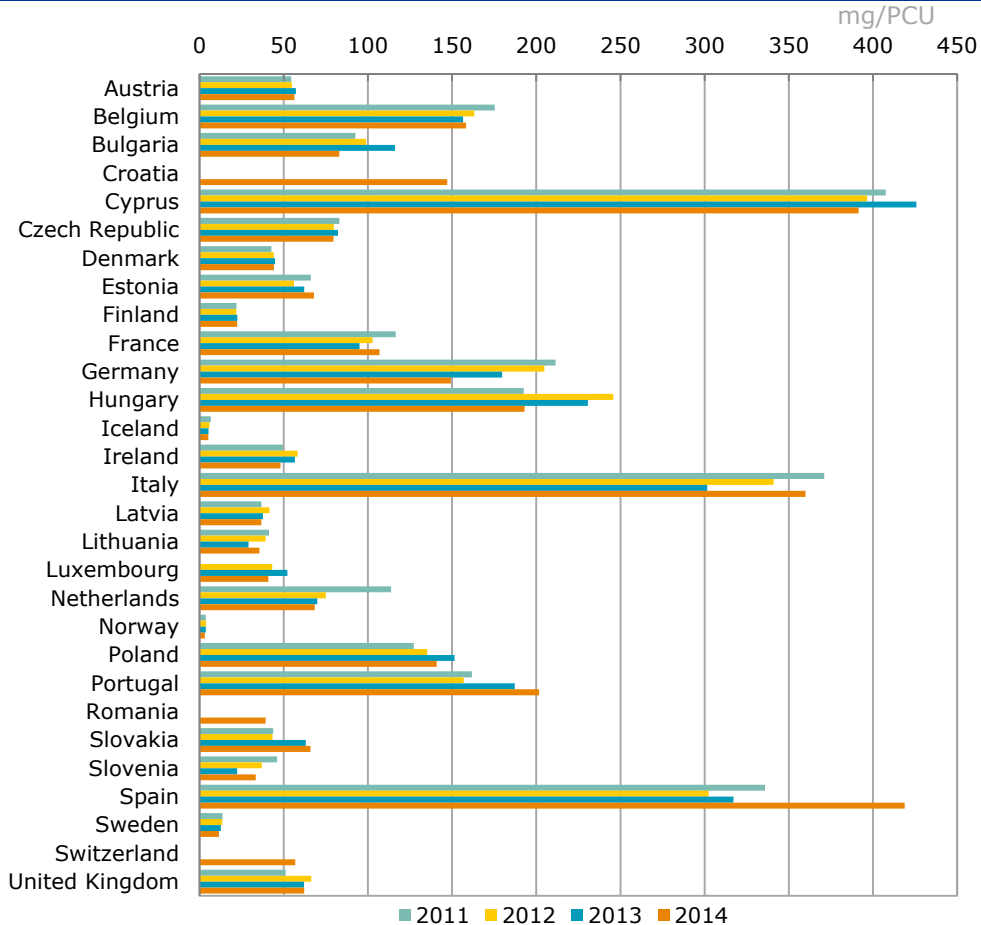
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27 July 2016  
EMA/CVMP/CHMP/231573/2016  
Committee for Medicinal Products for Veterinary use (CVMP)  
Committee for Medicinal Products for Human Use (CHMP)

Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health



# Identification of changes across years by country (trends)



- Preferably, comparison should cover at least 3 years

## To be considered in each case

- Animal population (PCU) stable or not?
- Changes in sales patterns - e.g. from low dose to high dose or vice versa?
- Change of data collection methodology?
- Are the data complete for all years?

# Basis for evaluation of effectiveness of management measures implemented (including following targets)

At EU/EEA level  
At national level

Always quantify  
before  
measures taken

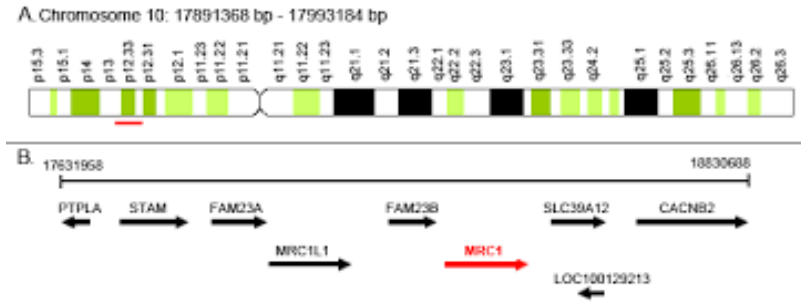
Implementation  
of management  
measures

Measure impact  
of measure



# EMA/CVMP/CHMP advice on colistin 2016

- Discovery of *mcr-1*, a horizontal transferable resistance gene in bacteria of food animal origin (Liu et al., 2015)



- The EC requested EMA to update the previous advice on the impact of and need for colistin use for human and animal health
- The advice should provide risk management options

# EMA/CVMP/CHMP advice - targets on colistin sales



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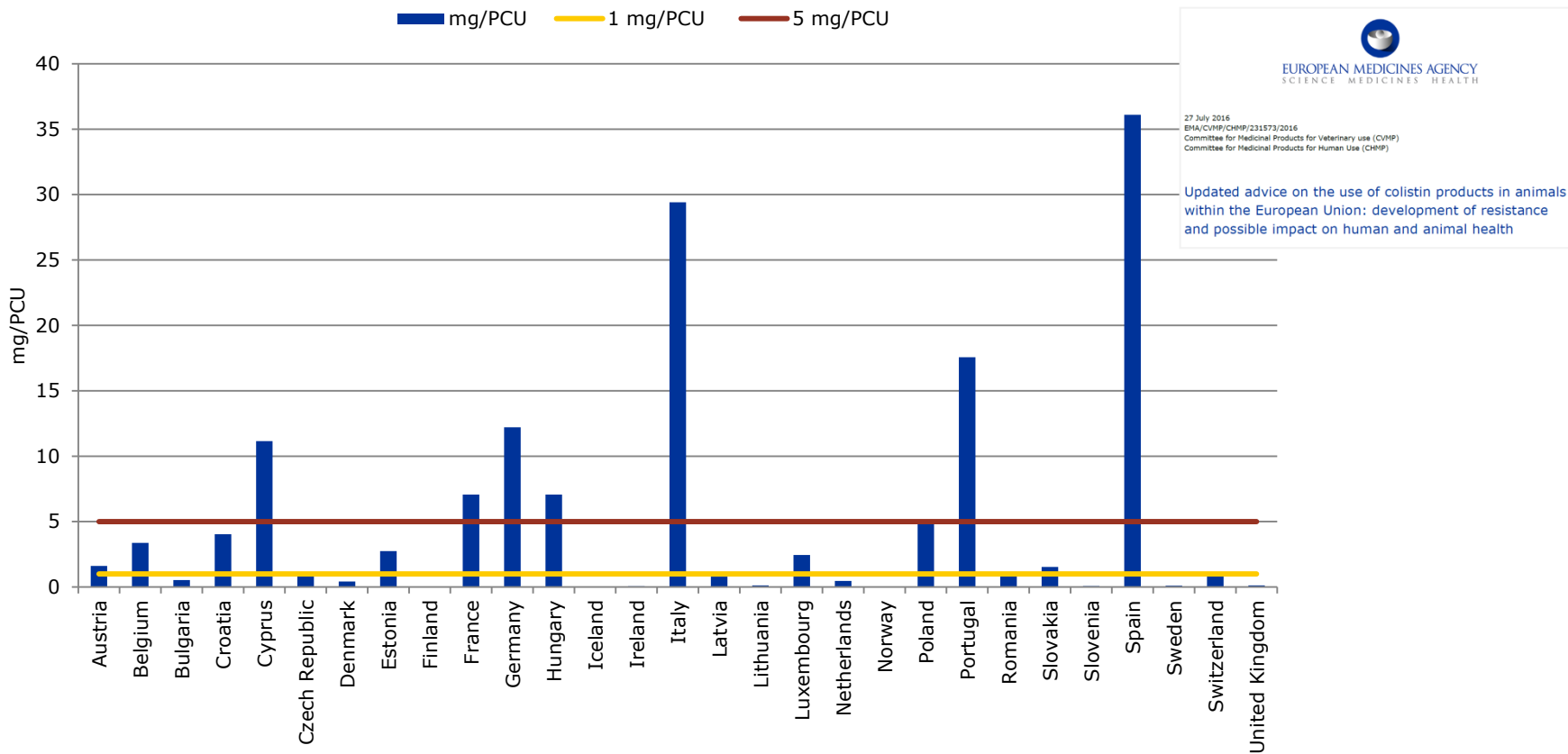
Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health

## 1. Executive summary

- For the current "high and moderate consumers" the target and desirable levels are set at **5 mg/PCU and 1 or below 1 mg/PCU**
- The above targets for reduction in sales of colistin should be achieved in a period of **three to four years.**

- ESVAC sales data supported the development of the Agency's advice on colistin, including setting targets
- These data important for the future assessment of impact of national risk mitigation measures to reduce sales of colistin for animal use

# Figure 4. Sales of colistin in for use in animals in mg/PCU in 2013 (ESVAC data), including the 5 and 1 mg/PCU levels\*



\*No sales reported in Finland, Iceland and Norway.

# Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Reports

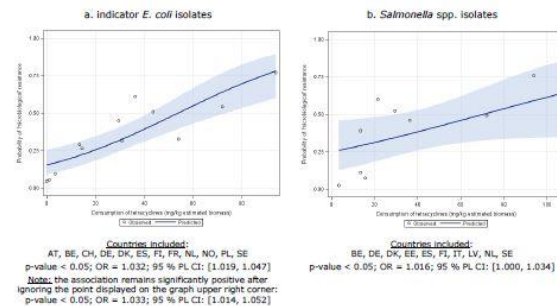
JIACRA I: Analysis of possible relationships between the sales of antimicrobial agents humans and food-producing animals and the occurrence of antimicrobial resistance in humans and food-producing animals

JIACRA II: Will also address co-resistance and information on fully-sensitive bacteria.

To be published: by summer 2017



Figure 7. Logistic regression analysis curves with OR estimates and 95 % profile-likelihood confidence intervals (PL CIs) of the national consumption of tetracyclines in food-producing animals and the probability of "microbiological" resistance to tetracyclines in (a) indicator *E. coli* isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs, (b) *Salmonella* spp. isolates (MIC > 8 mg/L) from cattle, domestic fowl and pigs and (c) *C. jejuni* isolates (MIC > 2 mg/L) from cattle and domestic fowl for the year 2012<sup>2</sup>—dots represent the countries included in the analysis.





## JIACRA II

- The EC has mandated ECDC, EFSA and EMA to establish a list of harmonised outcome indicators suitable for monitoring and detecting reductions of relevant magnitude in the levels of key drug-resistant microorganisms in humans, food-producing animals and food derived thereof, and in antimicrobial consumption in humans and food-producing animals
- These indicators would assist MSs to assess the progress made in the implementation of their action plans against AMR.
- **JIACRA II will provide information that will contribute to the rationale for the selection of appropriate indicators.**

A grey rounded rectangular callout box with a red arrow pointing from the text 'antimicrobial consumption' in the first bullet point to the box. The box contains the text 'ESVAC sales data' in a bold, sans-serif font.

ESVAC  
sales  
data



## Final reports of fact-finding missions carried in order to gather information on the prudent use of antimicrobials in animals

Denmark (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3642](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3642)

Germany (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3676](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3676)

Finland (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3715](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3715)

Netherlands (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3753](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3753)

Cyprus (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3759](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3759)

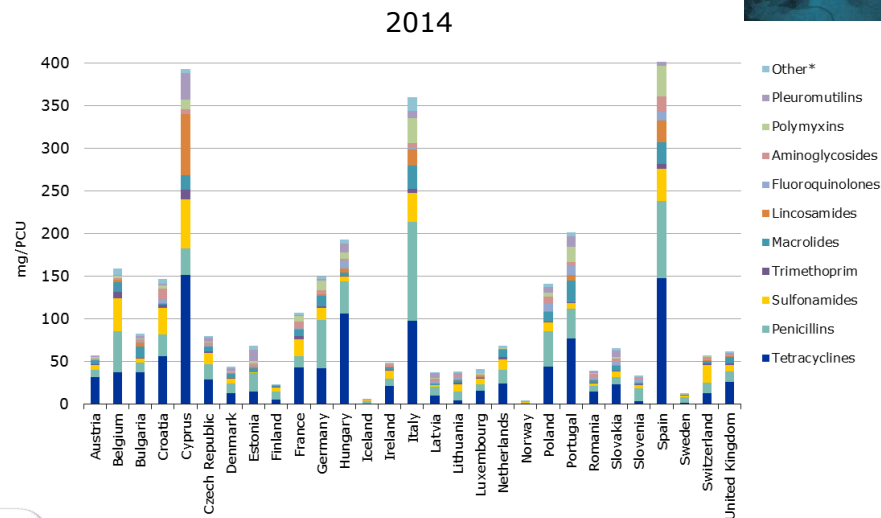
Slovenia (2016): [http://ec.europa.eu/food/audits-analysis/audit\\_reports/details.cfm?rep\\_id=3771](http://ec.europa.eu/food/audits-analysis/audit_reports/details.cfm?rep_id=3771)

For all the missions ESVAC sales data used as reference data



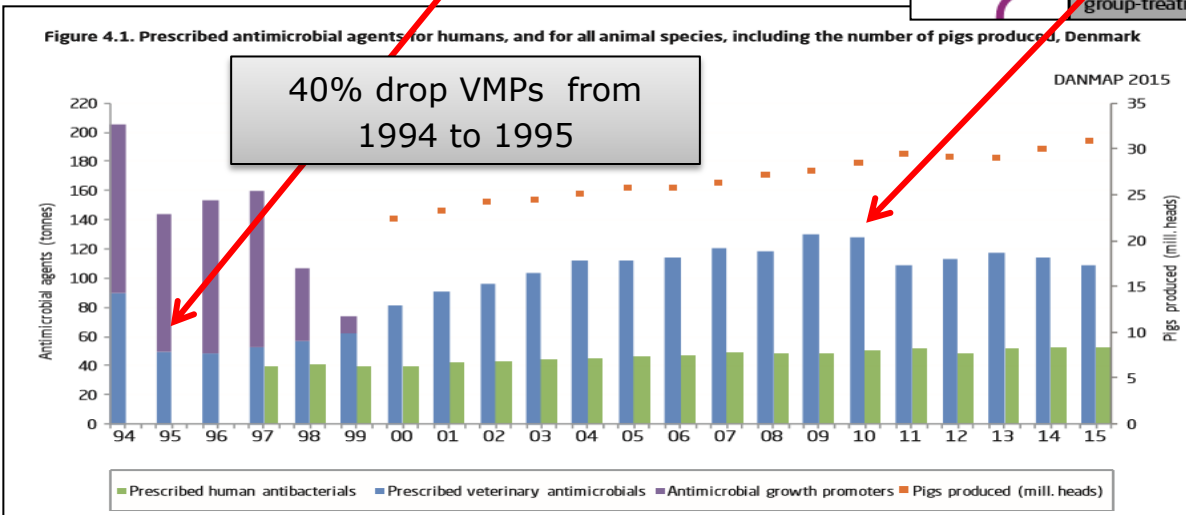
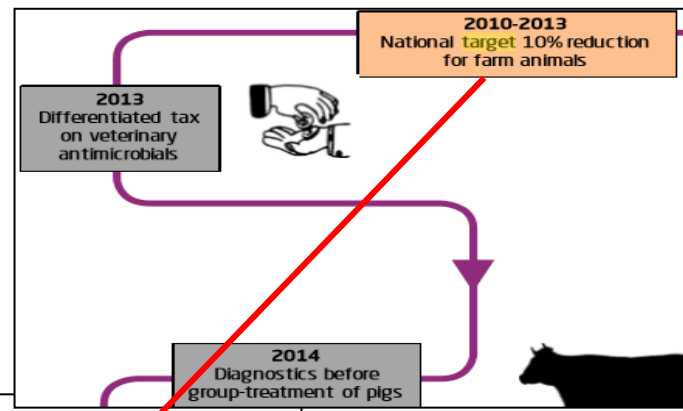
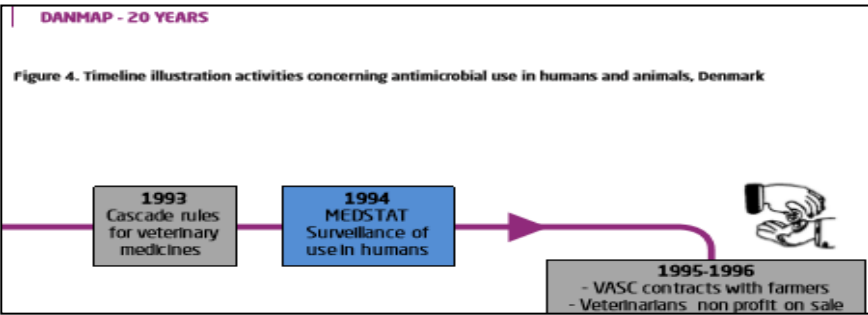
# Why variations in sales between the 29 countries

- Differences in the composition of the animal population, in the production systems in the various countries, variations in dosing used for the various antimicrobial agents and forms and prices.
- **This can only partly explain the differences in the sales observed between the 29 countries, so other factors must also be considered.**



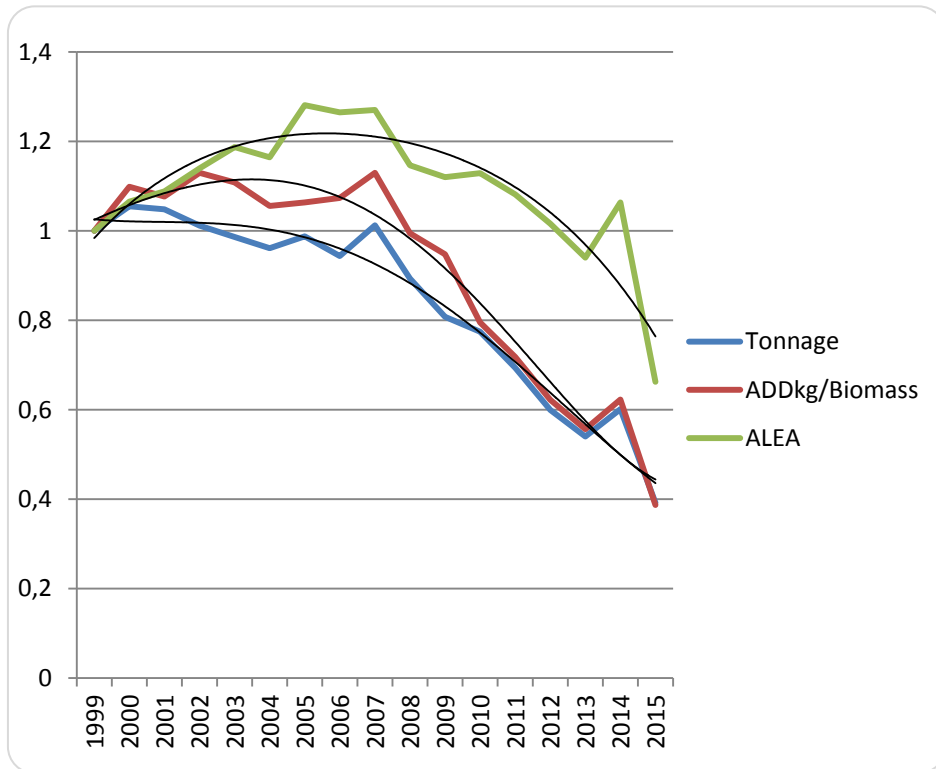
Fact finding missions looking among others for explanations

# Evaluation of measures- Denmark



Target was achieved

# France\*: Target - 25 % reduction of antimicrobial usage in 5 years from 2011



\*Provided by Gérard Moulin

## After 4 years:

- Tonnage - 28.4 %
- mg/kg body weight - 27.2 %
- ALEA - 20.1 %
- ADDkg/biomass - 29.7 %

**Target given in legislation: 25 % reduction in usage of 3<sup>rd</sup> 4<sup>th</sup> generation cephalosporins and Fluoroquinolones in 3 years from 2013**

## After 2 years :

- Cephalosporins - 21.3%
- Fluoroquinolones - 22.3%

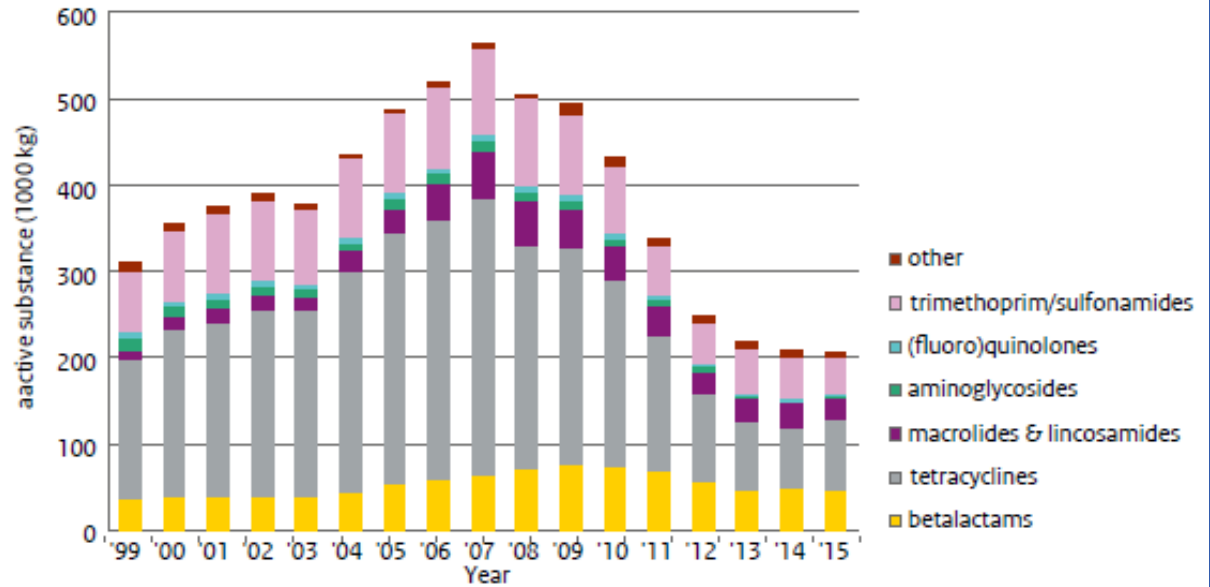
# Evaluation of national targets - Netherlands



Targets set by Dutch government: reduction of sales veterinary antimicrobials with 2009 as reference year:

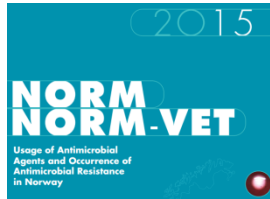
- 20% by 2011
- 50% by 2012
- 70% by 2015

Figure ABUse01 Antimicrobial veterinary medicinal product sales from 1999-2015 in kg (thousands).



From 2009 – 2015 sales reduced by 58.4%

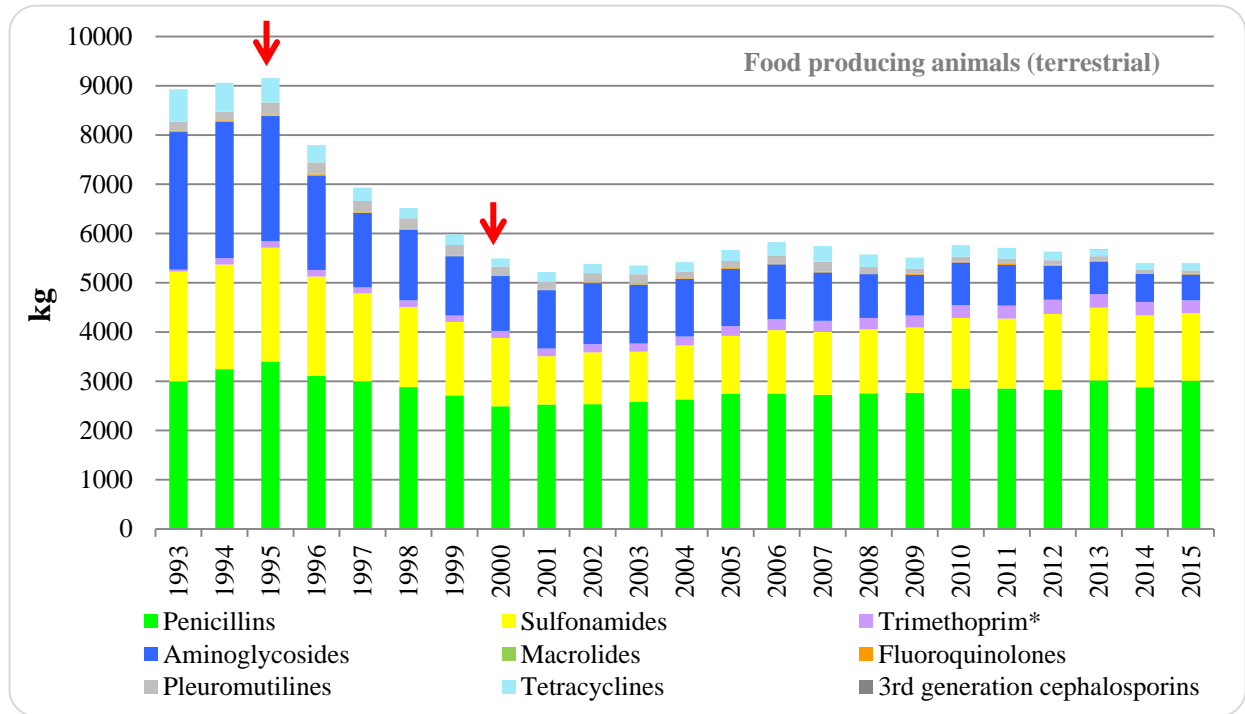
# Evaluation national targets - Norway



Targets set by Norwegian food animal industry: Sales to be reduced by 25 % in 5 years with 1995 as reference year

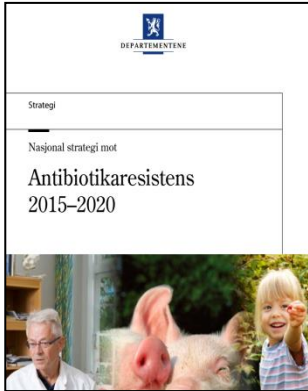
## Main actions

Therapeutic guidelines published and communicated on conferences regionally



- After 2 years (1997) 24% reduction
- After 5 years (2000) 40% reduction
- Relatively stable since then (varying between 36% and 43% lower)

# Evaluation national targets – Norway (cont.)



## **Governmental action plan AMR:**

Reduction of consumption of antimicrobials for terrestrial food producing animals by 10% by 2020 with 2013 as a reference year

- Therapeutic guidelines, awareness raising etc. not sufficient as tool for further reduction in Norway
- Antibiotic stewardship by use of on-farm level data (VetReg data) to identify high users suggested to be the way forward



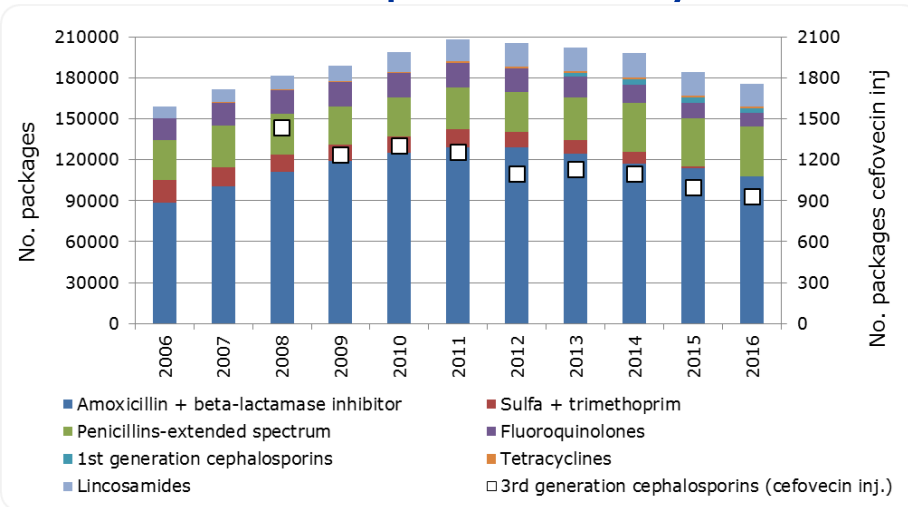
# Estimation of sales for dogs and cats – example Norway

## Estimated sales cats and dogs

Tablets, oral paste, oral solution and inj. VMP presentations approved for cats and/or dogs (only) included

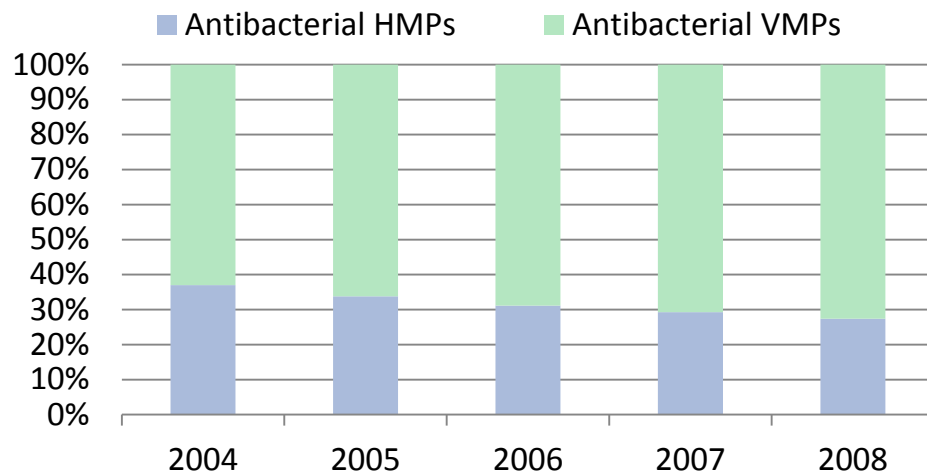
## Governmental action plan AMR:

Reduction of consumption of antimicrobials for companion animals by 30% by 2020 with 2013 as a reference year





## Prescription for dogs Norway - antibacterial human medicinal products (HMP) and veterinary medicinal products (VMP) 2004-2008\*



Proportion prescriptions of HMPs dogs

1987\*\* : 87 %

2004 : 37%

2008 : 27%

Antibacterial VMP presentations approved for dogs (and cats) only

2004 : 27

2008 : 29

2015 : 49

The increasing numbers of VMP presentations for dogs and cats since 2008 - likely decrease in prescription of HMPs

\* M. Kvaale et al. J Vet Pharmaol Therap, 2013; 36 (3):285-9

\*\* K.Grave et al. J Vet Pharmacol Therap 1992; 15: 45-52.





## Estimation of sales for dogs and cats – example Norway cont.

- Use of antimicrobial HMP assumed to be low as number of VMP presentations is assumed to cover the therapeutic needs
- Other injections (than ceftiofur) used - assumed to be low\*

Preliminary conclusion: For Norway, sales data assumed to be suitable to evaluate targets and effectiveness of prudent use guidelines for companion animals (dogs and cats)

\*ESVAC 6th report: "Data from Denmark and France for 2011 showed that approximately 0.1 % and 1.2 %, respectively, of the injectable antimicrobial VMPs sold were used for dogs and cats (E. Jacobsen and G. Moulin, unpublished data)".



## Summary

Both at EU/EEA level and nationally the sales data can be used for

- Documentation of the overall situation
- Identification of overall trends
- Linkage of antimicrobial sales and antimicrobial resistance (ecological analysis)
- As a basis for risk profiling
- To identify areas for interventions and evaluate effect of these
- For research

Estimation of sales data e.g. for some species (dogs and cats) and indications (dry cow treatment) suggested to be explored nationally

# Developments/way forward - sales data

- Maintain collection overall sales data
  - Sales data are needed in order to be able to
    - Present an overall global picture (as species data will not cover all sales/use)
    - For future validation (cross checking) of species data
- Continue to work together with the MSs in order to maintain and improve the validity of the data
- Refine PCU
  - Animal categories to be amended
  - Consider revision of animal weight at treatment used to calculate PCU



# Acknowledgement

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## European Medicines Agency staff members

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Thank you for your attention!



Norwegian Veterinary Institute

