EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Activities of the European Medicines Agency to minimize the risks arising from the use of antimicrobials in veterinary medicine

Fighting Antimicrobial Resistance: smart weapons against smart microorganism. Conference of the Italian Semester of Presidency

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An agency of the European Union

Outline

- The CVMP strategy on antimicrobials and recommendations on responsible use.
- Answers to the requests from the EC on use of antimicrobials animals and its impact on animal and public health.
- Sales of antimicrobials for veterinary use in the EU/EEA.
- Conclusions.

Antimicrobial resistance: the risk for public health

- Each year, about 25 000 patients die in the EU from an infection caused by multidrug-resistant bacteria.
- Antimicrobial Resistance (AMR) puts at risk the effective prevention and treatment of infections in humans and animals caused by an increasing range of bacteria.
- Increasing problem of diseases in humans for which there are few, if any, treatment options available.

Potential impact on public health of AMR

- No truly new antimicrobial classes have been introduced in recent years.
- Exposure of animals to antimicrobials increases the risk of selecting resistant bacteria, or of resistance determinants. The identification of Extended Spectrum Betalactamases (ESBLs) and carbapenem resistance in bacteria isolated from food producing species, including horses, is of concern.
- The precise impact on public health of use of antimicrobials in animals is as yet unknown.

CVMP strategy on antimicrobials 2011-2015*

- The CVMP strategy seeks to promote the continued availability of effective antimicrobials for use in animals whilst at the same time acting to minimise risks to animals or man arising from their use.
- Responsible use of antimicrobials is regarded a cornerstone to contain resistance for benefit of both animal and human health.
- Need for effective antimicrobial treatment for relevant indications in all species.

*Available from http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/01/WC500100649.pdf

Regulation of medicines and AMR

- Maximum Residue Limit
  - Disruption of the colonization barrier;
  - Increase in the population(s) of resistant bacteria in the human colon;
  - Detection of changes in the population of resistant bacteria;
  - Derivation of a microbiological ADI;
- Development of resistance
- Resistance relevant for clinical use

Guidelines available from: www.ema.europa.eu>veterinary regulatory>scientific guidelines>safety and residues>antimicrobials

3rd- and 4th-generation cephalosporins referral

- **Use of "XXX" may constitute a risk to public health due to spread of antimicrobial resistance.**
- "XXX" is intended for treatment of individual animals.
- Do not use for disease prevention or as a part of herd health programmes.
- Treatment of groups of animals should be strictly restricted to on-going disease outbreaks according to the approved conditions of use.

Fluoroquinolones

- "Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials."

- "Whenever possible, fluoroquinolones should only be used based on susceptibility testing."

European Commission request to the European Medicines Agency

- Subject: **Impact** of the **use of antibiotics in animals** on **public and animal health** and measures to manage the possible risk to humans.
- Experts from the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Medicinal Products for Human Use (CHMP).
- Other agencies to be consulted; EFSA and ECDC.
- Divided in four questions.

www.ema.europa.eu> Home> Special topics> Antimicrobial resistance

Preparation of the answers

Prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG) which is composed of experts from:

- CVMP (Committee for Medicinal Products for Veterinary Use);
- AWP (CVMP Antimicrobials Working Party);
- IDWP/CHMP (CHMP Committee for Medicinal Products for Human Use and Infectious Disease Working Party);
- European Food Safety Authority (EFSA);
- European Centre for Disease Prevention and Control (ECDC);
- JIACRA (Joint Interagency Antimicrobial Consumption and Resistance Analysis Report).

Colistin

- Toxic for humans but last-resort antibiotics for multidrug-resistant *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter.*
- The rapid emergence of resistance in humans after oral use in the Intensive Care Unit (ICU) for selective digestive tract decontamination shows that resistance in *Enterobacteriaceae* can emerge following oral use.
- Colistin used in veterinary medicine for over 50 years.
- From the information available, resistance has remained low in animals to date.

Colistin referral

- Referral recommendations endorsed by CVMP in December 2014.
- Measures that need to be taken to ensure the prudent use of colistin in food producing animals across the EU.
- Harmonised indications.
- Limitation of the duration of treatment up to 7 days.
- Warning sentences on prudent use.

Answer to the Question 2 from the EC (ranking of antibiotics)

"Advice on classes or groups of antibiotics ranked according to their relative importance for their use in human medicine, in particular considering whether these antibiotics are essential to treat multidrug-resistant infections in humans in the EU.

The Agency should take into account the existing work of the WHO on critical antibiotics and consider the need, advantages, disadvantages and feasibility of categorising antibiotics as for example first line, second line or last resort antibiotics."

Question 2. Category 1: Antimicrobials used in veterinary medicine where the risk for public health is currently estimated as low or limited

- **Certain penicillins, macrolides, tetracyclines and polymyxins** belong to this category. These antimicrobials are not devoid of negative impact on resistance development and spread.
- It is important to make sure that **responsible use principles are complied with in everyday practice**.
- **Unnecessary use** and, unnecessarily long treatment periods **should be avoided** and group treatment restricted to situations where individual treatment is not feasible.

Question 2. Category 2: Antimicrobials used in veterinary medicine where the risk for public health is currently estimated higher

- The risk to public health is **only acceptable provided that specific restrictions are placed** on their use (i.e. **fluoroquinolones**, and systemic use of **3rd- and 4th-generation cephalosporins**).
- These reserved antimicrobials should be included **in treatment guidelines only when there are no alternative antimicrobials** that could be used.
- **Penicillins** (effective against Enterobacteriaceae) and **aminoglycosides**: further risk profiling is needed.

Question 2 Category 3: Antimicrobials not approved for use in veterinary medicine

They may **only be used by way of exception** and only in **companion animals** (non-food producing species)

Carbapenems and other penems, cyclic esters (e.g. fosfomycin), glycopeptides, monobactams, oxazolidinones, penicillins: carboxy-penicillins and ureido-penicillins including β-lactamase inhibitors combinations:

- **Use in veterinary medicine should be kept at an absolute minimum** due to high risk for spread of resistance.

Question 2 Category 3: Antimicrobials currently not approved for use in veterinary medicine

They may **only be used by way of exception** and only in **companion animals** (non-food producing species)

Glycylcyclines;

- Glycylcyclines use in animals should be restricted. Currently no need for any approval of a veterinary medicinal product containing tigecycline is foreseen.

Ceftaroline and ceftobiprole, lipopeptides, riminofenazines, sulfones and drugs used solely to treat tuberculosis or other mycobacterial diseases:

- No specific concern identified yet (see disclaimer above).

Question 3 (new antibiotics)

"Advice what the possible impact could be on the treatment of resistant bacteria in humans of granting marketing authorisations for new classes of veterinary antibiotics, and whether there is a need to restrict or ban the use in animals of certain new classes of antimicrobials or antibiotic substances (especially those that are important in human medicine) that are currently not authorised.

It is stressed that the advice could discuss a positive impact (for example, better management of resistance in animals) or a negative impact (for example, increased risk of development of resistance in humans)."

Question 3 (new antibiotics)

The authorisation of completely new classes of antimicrobials for use in animals might decrease animal and public health risk related to antimicrobial resistance **provided co-selection** by earlier authorised products **is not implicated**.

Question 3 (new antibiotics)

- At the **time of first approval** for new antimicrobial substances/a new class of antimicrobials in veterinary medicine MAHs should have **plans in place to monitor susceptibility in zoonotic and indicator bacteria** through approved programmes.
- Based on the **outcome of antimicrobial resistance surveillance** and monitoring of usage, **a new risk assessment could be required** for all products of a specific antimicrobial class, encompassing both generic and reference products.

Question 3 (new antibiotics)

- A **declaration system** should be put in place in order to assess the extent and evolution of **off label use of human-only** authorised antimicrobials.
- Flexible tools to allow **banning or limitation of off label use in animals of certain antimicrobials**/classes authorised only in human medicine following an unfavourable hazard characterization or benefit-risk assessment should be included in future legislation.

Question 4 (risk mitigation options)

The EC has requested the European Medicines Agency to provide:

"Advice on the risk mitigation options [alternatives], including an assessment of costs and benefits, related with the use of certain classes of antibiotics or antibiotic substances that are critically-important in human medicine and are currently authorised as veterinary medicinal products."

Question 4 (risk mitigation options)

- Difficulties in estimating the impact of risk management measures are acknowledged.
- The potential for a **negative impact** on animal health when risk management measures are implemented must be considered. Therefore close attention may need to be paid to **husbandry conditions** when measures to reduce antimicrobial consumption are implemented.

Question 4 (risk mitigation options)

- Monitoring by **ESVAC** of changes in antimicrobial consumption, in particular of **fluoroquinolones and cephalosporins** as a means to measure impact of actions implemented.
- **More precise data by animal species**/livestock production categories in future ESVAC reports, including e.g. the use of DDDA (Defined Daily Dose Animals) and DCDA (Defined Cure Dose Animals).

Question 4 (risk mitigation options)

- Prescribers should **keep records of off-label use** to be provided at the request of the Authorities.
- **Authorities** should be encouraged to **collect data on off label use**.
- **Regular joint analyses of the evolution of antimicrobial resistance and sales/use** by the Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) EU expert group are recommended.

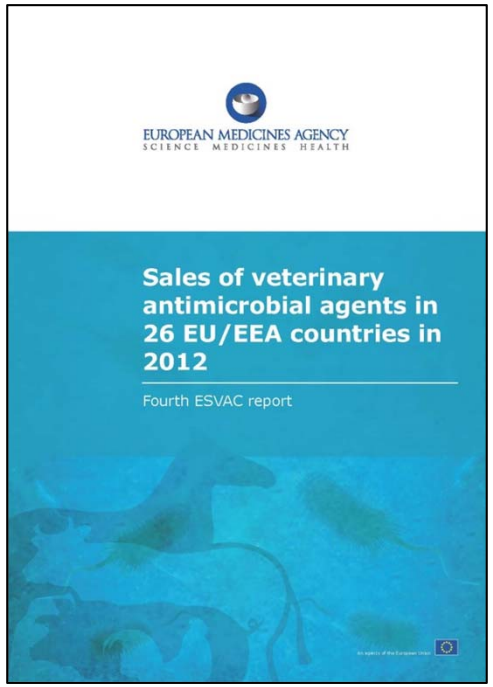
Question 4 (risk mitigation options)

Additional recommendations:

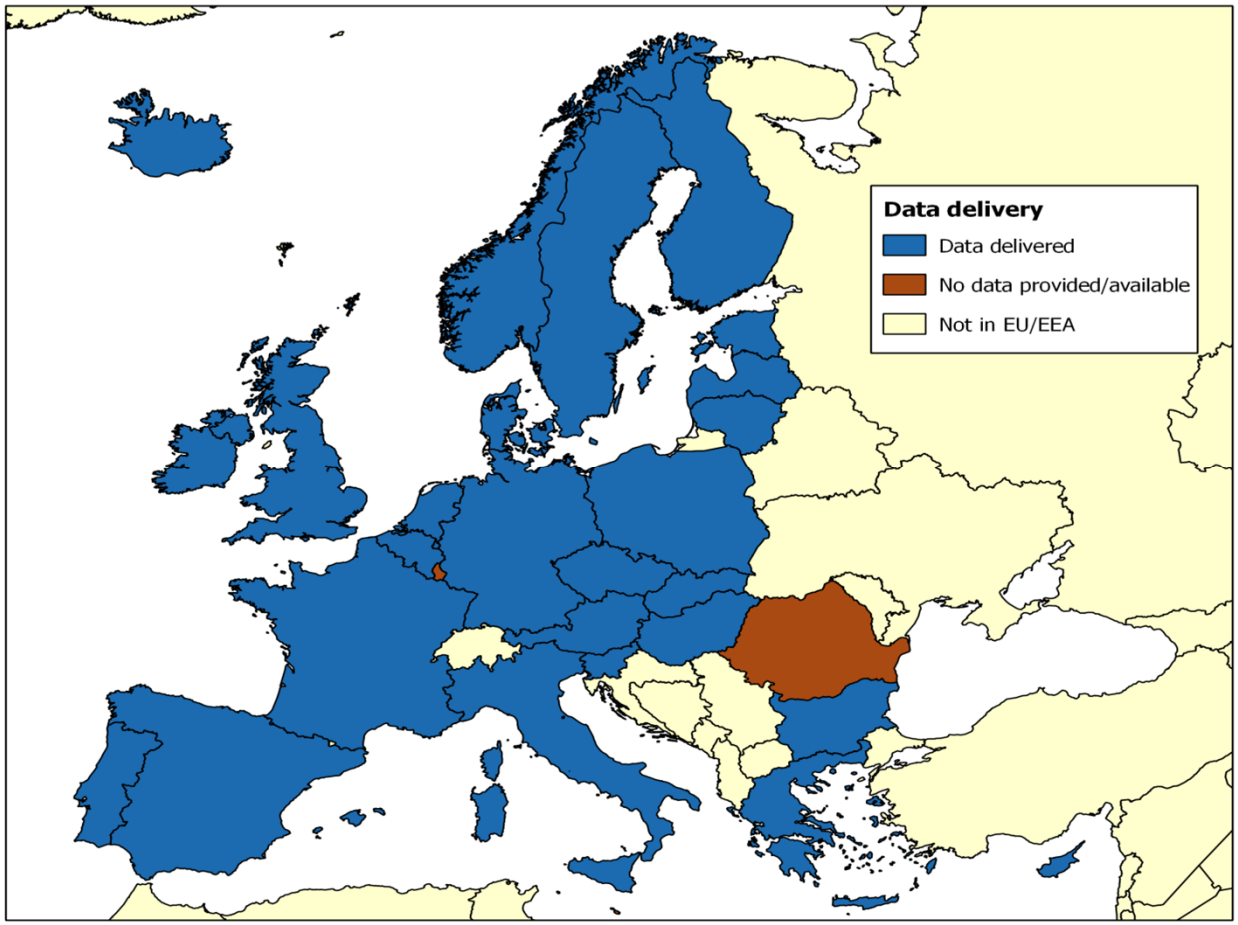
- **Reduction** of overall **antimicrobial consumption**.

Use of antimicrobials in the EU

- Use of antibiotics as growth promoters banned in the EU since 2006.
- ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) collects data on sales of antimicrobials for use in animals since 2009.



ESVAC collection of data



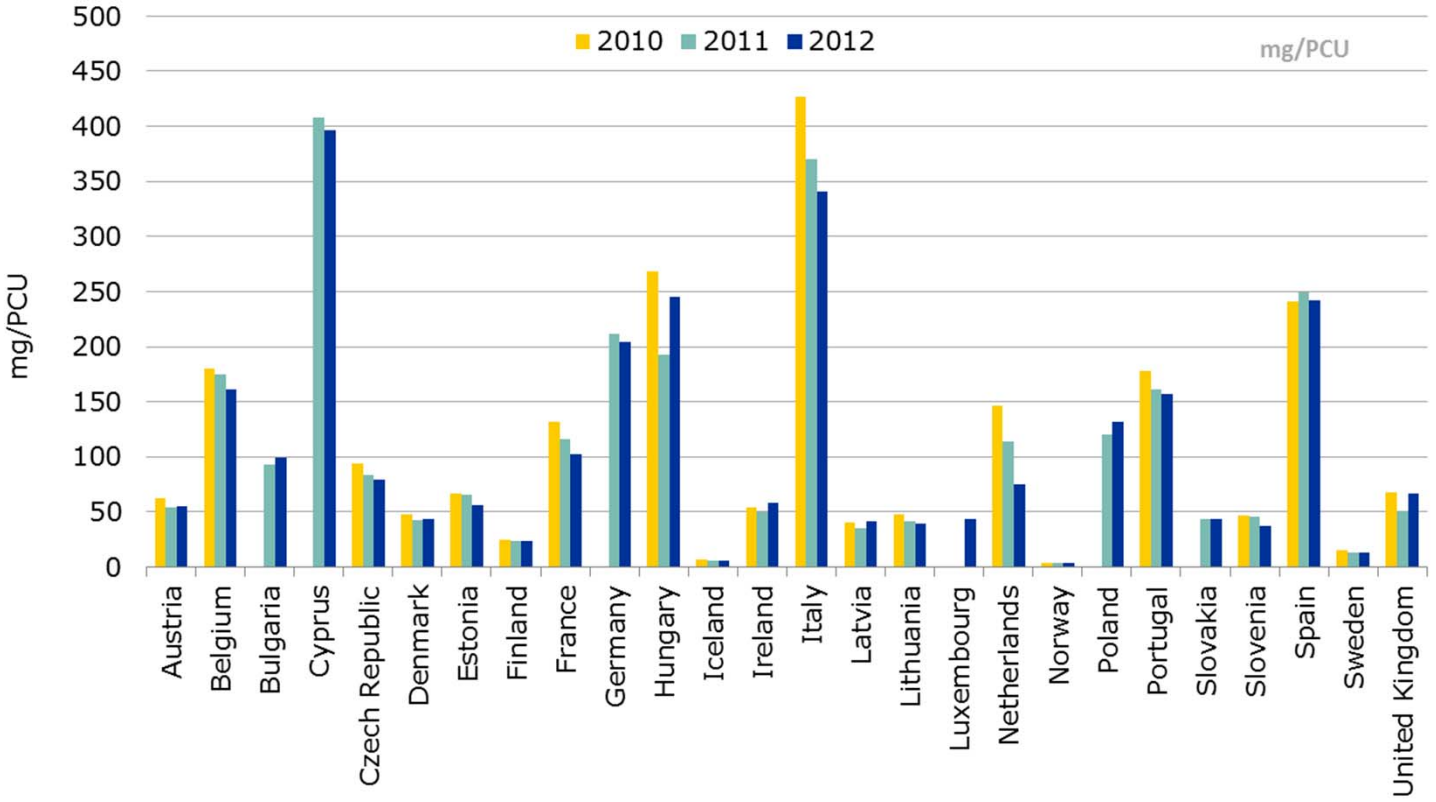
In 2014
26 of 29 EU/EEA countries had provided data for 2012 according to the ESVAC template

The ESVAC technical approach

- Data sets
  - Sales data provided at package level (name, pharmaceutical from, pack size ingredient(s) and strength(s). Calculated to express tonnes of active ingredient;
  - Animal population data from Eurostat, TRACES and national (horses).
- The main indicator applied to express the consumption of veterinary antimicrobials is mg active ingredient normalised by the population correction unit (mg/PCU):

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

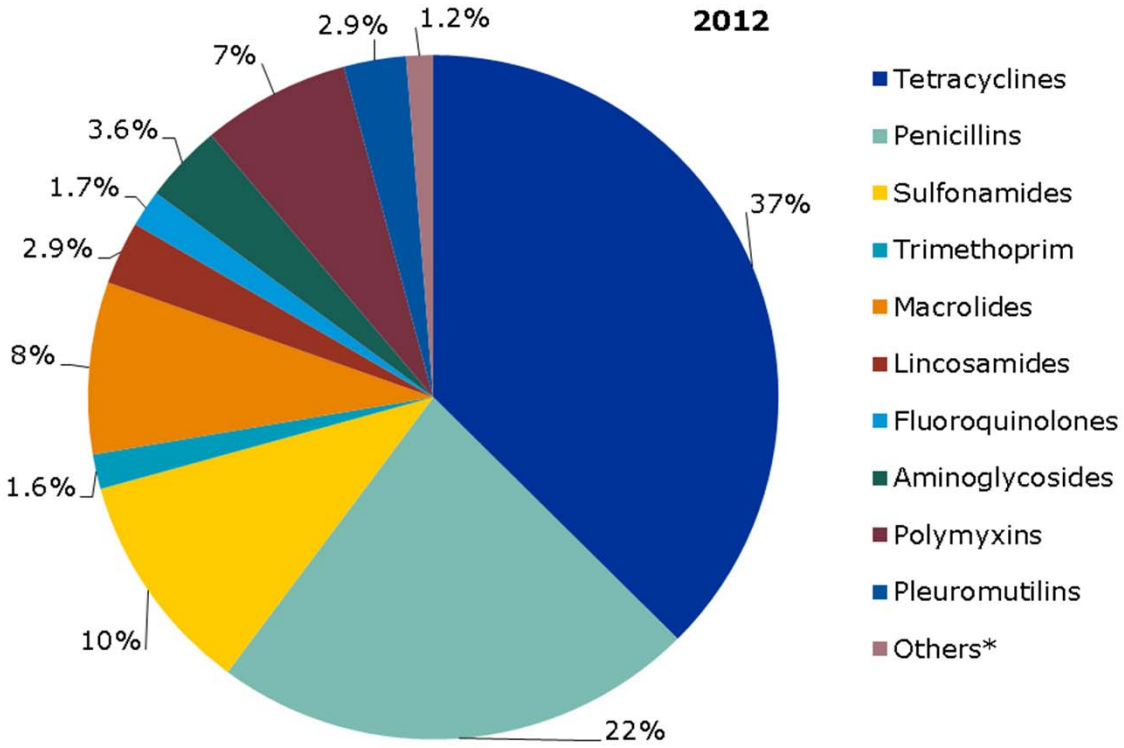
Total sales of veterinary antimicrobial agents for food-producing species, including horses, in mg/PCU, during 2010 to 2012, for 26 EU/EEA countries[1]



Covers 95% of the food producing animal population (measured as PCU)

[1] Note that substantial underreporting was identified for Spain for 2010, indicating that the sales have actually decreased from 2010 to 2012.

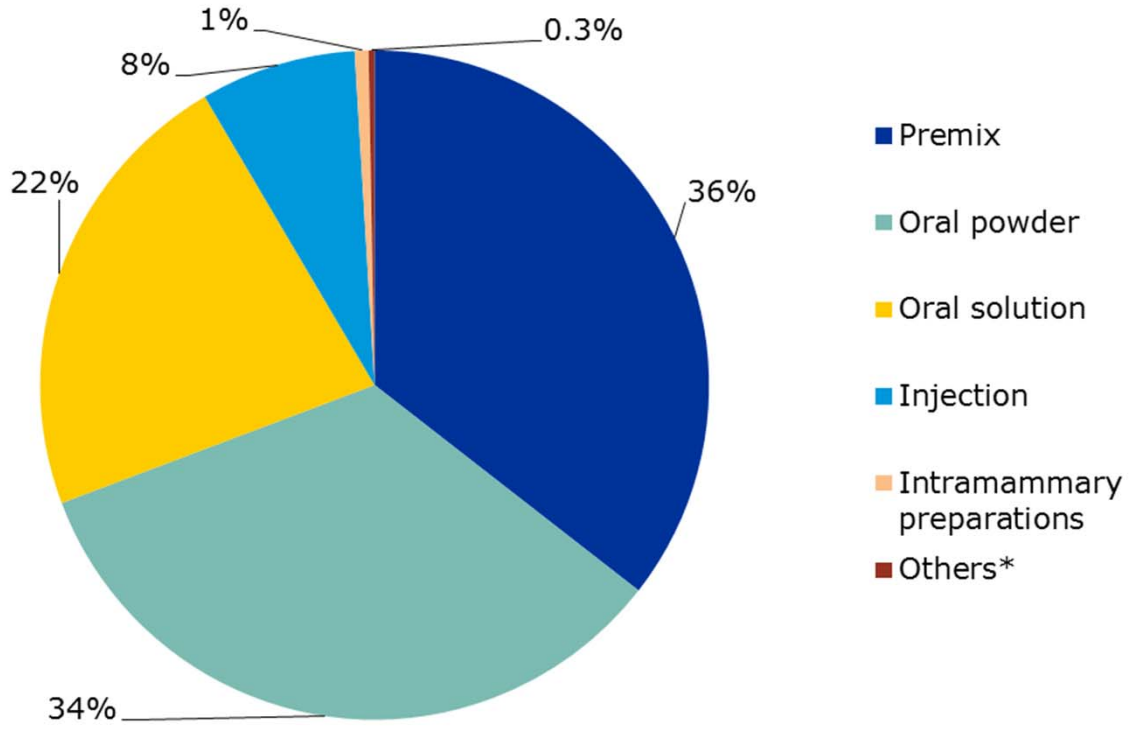
Sales of antimicrobial agents by antimicrobial class as percentage of the total sales for food-producing species (including horses), in mg/PCU, aggregated by 26 countries, for 2012



Overall sales patterns stable from 2011-2012

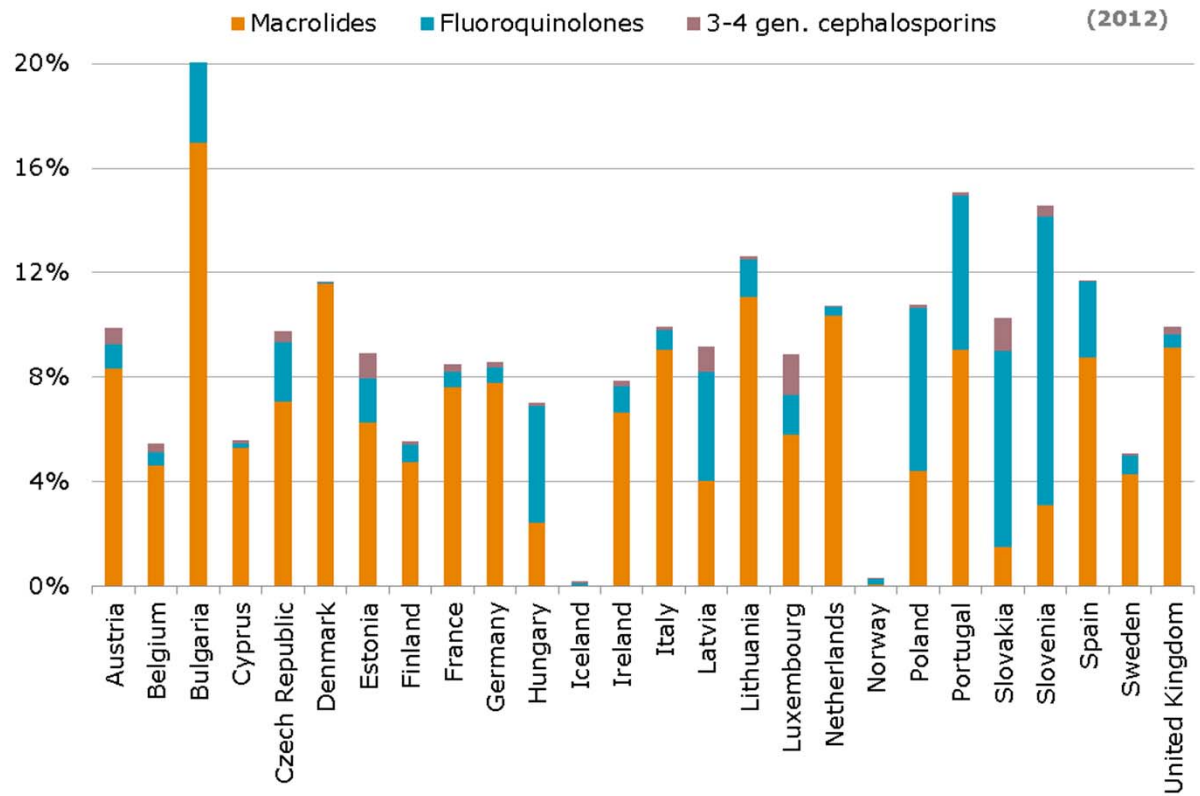
*Amphenicols, cephalosporins, other quinolones

Distribution of sales, in mg/PCU, by pharmaceutical forms of veterinary antimicrobials for food-producing animals (including horses) aggregated by the 26 EU/EEA countries for 2012

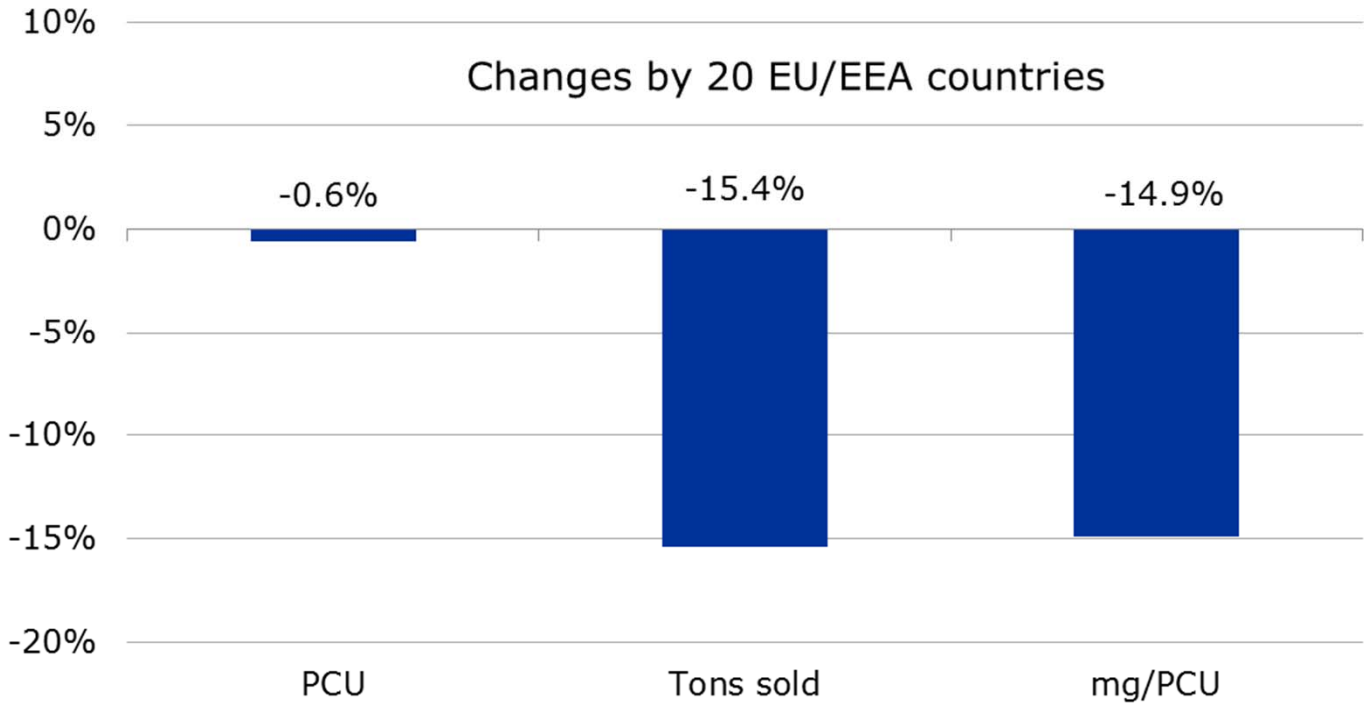


Distribution of sales of forms for group treatment and individual treatment stable compared to 2011

Proportion of the total sales of macrolides, fluoroquinolones and 3rd- and 4th-generation cephalosporins for food-producing species, in mg/PCU,–for 26 countries in 2012



Percentage changes in sales of veterinary antimicrobial agents for food-producing species, including horses, in mg/PCU, from 2010 to 2012, aggregated by 20 EU/EEA countries[1]



PCU stable

[1] Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Hungary, Iceland, Italy, Ireland, Latvia, Lithuania, the Netherlands, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom.

Other EMA ongoing activities on AMR

- Pilot collecting data on consumption in pigs.
- Establishment of DDDAs (Defined Daily Doses Animals) for pigs, broilers and cattle.
- Shorlty publication of the ECDC/EFSA/EMA first joint report on the integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals.

Conclusions

- Guidance on authorisation of antimicrobials for veterinary use take into account the impact of antimicrobial resistance in animal and public health.
- Recommendations have been made on responsible use of some critically important antimicrobials.
- Collecting data on consumption of antimicrobials in animals increases awareness of consumption and it's patterns and can be used as a **very powerful driver for responsible use of antimicrobials**.

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