Antimicrobial Resistance: EMA/AMEG categorisation in Veterinary Medicine in EU

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The priorities for legislators and institutions are:

1) the man

2) the environment in which he lives
No government or institution will allow man to die for:

✓ Workplace accidents (in Italy, 1,029 deaths in 2017 – INAIL data)

→ *Testo Unico sulla salute e sicurezza sul lavoro*, D.Lgs. n.81/2008 updated version of July 2018.

✓ Car accidents (in Italy, 3,378 deaths in 2017 – ISTAT data)

→ *Decreto sicurezza* (D.Lgs. 113/2018), Road Traffic Code amendments

✓ Antimicrobial Resistance (in EU 33,000 deaths/year – Ears-Net data
in Italy, 10,000 deaths/year - Ar-Iss data)

→ strategies to prevent and control antimicrobial resistance requiring
global European coordination and specific national strategies, able to
face local situations
→ strategies to prevent global warming

Zero risk does not exist...
A recent study published in *Nature Climate Change* suggest that a link between climate change and bacterial resistance exists.

Epidemiologist from Boston Children's Hospital and the University of Toronto found that **higher local temperatures** and **population densities** correlated to a greater level of antibiotic resistance among a number of common bacterial strains (*E. coli, K. pneumoniae, S. aureus*).

The strongest associations between temperature and resistances was found in **fluoroquinolones** and **beta-lactam antibiotics**, suggesting that warmer temperatures may affect the way bacteria respond to certain drug mechanisms.

*MacFadden et al., 2018*
Critically Important Antimicrobials (CIAs)

The concept of “critically important antimicrobials” was originally developed following recommendations from two expert workshops (Geneva, Switzerland, 2003; Oslo, Norway, 2004) organized by Food and Agriculture Organization of the United Nations (FAO), World Organization for Animal Health (OIE), and World Health Organization (WHO), to address public health consequences of antimicrobial agents use in food producing animals.

The workshops recommended that WHO should develop such a list of critically important antimicrobial agents in human medicine (CIAs) and that OIE should also develop a list of critically important antimicrobial agents in veterinary medicine (VCIAs).

The WHO CIA List was first developed in 2005, while the OIE VCIA List in 2007.

A third FAO/OIE/WHO expert meeting (Rome, Italy, 2007), considered WHO and OIE CIA lists and concluded that they should be revised on regular basis, in a collaborative and coordinated approach by FAO, OIE and WHO.
The World Health Organization (WHO) is a specialized agency of the United Nations that is concerned with international public health.

It was established on 7 April 1948, and is headquartered in Geneva, Switzerland.

Its current priorities include communicable diseases, in particular HIV/AIDS, Ebola, malaria and tuberculosis; the mitigation of the effects of non-communicable diseases such as sexual and reproductive health, development, and aging; nutrition, food security and healthy eating; occupational health; substance abuse; and driving the development of reporting, publications, and networking.

The WHO is financed by contributions from member states and outside donors.
The WHO CIA List was first developed in 2005, and then updated every 2 years.

During the first WHO Expert Meeting on CIA for Human Health (Canberra, Australia; 2005), participants categorized antimicrobial agents used in human medicine into three groups:

- Critically important
- Highly important
- Important

based on two criteria developed at the meeting:

**Criterion 1:** The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.

**Criterion 2:** The antimicrobial class is used to treat infections in people caused by either:
1. bacteria that may be transmitted to humans from nonhuman sources, or
2. bacteria that may acquire resistance genes from nonhuman sources.
The list was last updated in 2016 (5th revision of the CIA list).

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.
### CRITICALLY IMPORTANT ANTIMICROBIALS

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>C1</th>
<th>C2</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITICALLY IMPORTANT ANTIMICROBIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIGHEST PRIORITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins (3rd, 4th and 5th generation)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Macrolides and ketolides</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Quinolones</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>HIGH PRIORITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Ansamycins</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Carbapenems and other penems</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Glycylcyclines</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Monobactams</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Penicillins (natural, aminopenicillins, and antipseudomonal)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Phosphonic acid derivatives</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Drugs used solely to treat tuberculosis or other mycobacterial diseases</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

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**IMPORTANT ANTIMICROBIALS**

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>C1</th>
<th>C2</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic polypeptides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucolysinases</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mynapenemycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyxins</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources.*
The need to fight animal diseases at global level led to the creation of the Office International des Epizooties (OIE) in 1924.

In 2003, the Office became the World Organisation for Animal Health but kept its historical acronym OIE.

The OIE is the intergovernmental organisation responsible for improving animal health worldwide.

The OIE maintains permanent relations with nearly 75 other international and regional organisations and has Regional and sub-regional Offices on every continent. In 2018, it has a total of 182 Member Countries.

The day-to-day operation of the OIE is managed at the Headquarters situated in Paris, France.

The OIE's financial resources are derived principally from compulsory annual contributions backed up by voluntary contributions from Member Countries.
The OIE List of Antimicrobial agents of veterinary importance (VCIA) was first developed in 2007 and then was further updated in 2013, 2015 and 2018.
Criteria used for categorisation of veterinary important antimicrobial agents (OIE List)

On the basis of two criteria:
1. importance of the antimicrobial class
2. treatment of serious animal diseases and availability of alternatives

the following categories were established:

- **Veterinary Critically Important Antimicrobial Agents (VCIA)** - criteria 1 and 2
- **Veterinary Highly Important Antimicrobial Agents (VHIA)** - criteria 1 or 2
- **Veterinary Important Antimicrobial Agents (VIA)** - neither criteria 1 or 2

Antimicrobial classes/sub classes used only in human medicine are not included in the OIE List. Recognising the need to preserve the effectiveness of the antimicrobial agents in human medicine, careful consideration should be given regarding their potential use (including extra-label/off-label use)/authorisation in animals.
The wide range of applications and the nature of the diseases treated make cephalosporin third and fourth generation extremely important for veterinary medicine.

Cephalosporins are used in the treatment of septicemias, respiratory infections, and mastitis. Alternatives are limited in efficacy through either inadequate spectrum or presence of antimicrobial resistance.
The use of WHO list, in conjunction with the OIE list of antimicrobials of veterinary importance and the WHO Model Lists of Essential Medicines, will allow for prioritization of risk management strategies in the **human sector**, the **animal sector**, and in **agriculture**, through a coordinated One Health approach.
Which is the CIA list to be considered in Veterinary Medicine in EU?
The European medicines regulatory system is based on a network of around 50 regulatory authorities from the 31 EEA countries (28 EU Member States plus Iceland, Liechtenstein and Norway), the European Commission and EMA.
The European Commission is the Executive body of the EU responsible for proposing legislation, implementing decisions, upholding the Union's treaties and day-to-day running of the EU.
The European Medicines Agency (or EMA) is the EU regulatory body responsible for the scientific evaluation and supervision of medicine developed by pharmaceutical companies for use in the EU (= it ensures that medicines are safe and that they work as expected).

EMA’s main responsibility is the protection and promotion of public and animal health, by carrying out scientific evaluations of medicine for human and veterinary use.

The Agency also supervises the safety of medicines in the EU after they have been authorised. It can also give scientific opinions on medicines at the request of Member States or the European Commission.

It is located in London (UK) but will relocate to Amsterdam (NL) following the UK’s withdrawal from the EU on 30 March 2019 at the latest.
EMA and its scientific committees

There are 7 scientific committees that evaluate medicines at the EMA – 6 of these are for medicines for human use and one, the CVMP is for veterinary products.

The EMA Committees contain members nominated by the medicine regulatory authorities of the EU Member States (the ‘National Competent Authorities’)
Urgent restrictions before 2013:

EMA/186029/2010 - Article 35 referral for all veterinary medicinal products containing quinolones including fluoroquinolones intended for use in food-producing species (1 July 2010)

Conclusions:

variation of the MAs of products containing quinolones including fluoroquinolones intended for food producing species in order to amend the SPC and PL in those cases where there are not in line with the CVMP Reflection Paper.
EMA/967448/2011 - Article 35 referral for all veterinary medicinal products containing systemically administered (parenteral and oral) 3rd and 4th generation cephalosporins intended for use in food producing species (13 January 2012)

Conclusions:

Variations of the MAs for all veterinary medicinal products containing 3rd and 4th generation cephalosporins that are systemically administered (parenteral and oral) and intended for use in food producing species in order to amend the SPC and PL as recommended.

Amendments in the relevant sections of the summary of product characteristics

4.1 Target species

Delete, where applicable, poultry (poultry, chicken, etc) as target species.

4.2 Indications for use, specifying the target species

Delete, where applicable, all indications related to poultry (poultry, chicken, etc).

Add, where applicable, for products indicated for bovine metritis: The indication is restricted to cases where treatment with another antimicrobial has failed.

4.3 Contraindications

Add, to all products:
Do not use in poultry (including eggs) due to risk of spread of antimicrobial resistance to humans.

4.5 Special precautions for use

Add, to all products:
"Product name (to be completed nationally)" selects for resistant strains such as bacteria carrying extended spectrum beta lactamases (ESBL) and may constitute a risk to human health if these strains disseminate to humans e.g. via food. For this reason, "product name (to be completed nationally)" should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of such resistance. Whenever possible, "product name (to be completed nationally)" should only be used based on susceptibility testing.

"Product name (to be completed nationally)" 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 ongoing disease outbreaks according to the approved conditions of use.

Add, where applicable, for products indicated for bovine metritis:
Do not use as prophylaxis in case of retained placenta.

4.1.1 Withdrawal period(s)

Delete, where applicable, all withdrawal period(s) related to poultry (poultry, chicken, etc) as target species.
In April 2013, the European Commission (EC) requested advice from the European Medicines Agency (EMA) on the impact of the use of antibiotics in animals on public and animal health and measures to manage the possible risk to humans (4 Questions).
Antimicrobial Advice Ad Hoc Expert Group (AMEG)

AMEG was set up to answer four questions posed by the European Commission in April 2013 when it requested scientific advice from the EMA on the impact of the use of antibiotics in animals on public health and animal health and measures to manage the possible risk to humans.

The AMEG is an ad hoc group of 15 experts established jointly under the Committee for Medicinal Products for Veterinary Use (CVMP) and the Committee for Medicinal Products for Human Use (CHMP).

AMEG's tasks include:

• the categorisation of antimicrobials based on their risk to public health due to the development of antimicrobial resistance (AMR) following use in animals. Categorisation may have a significant impact on veterinarians' selection and use of antimicrobial medicinal products, and on national treatment guidelines;

• the development of an early hazard characterisation assessment. This is intended to address the risk to public health from AMR and will be assessed prior to the submission of a MAA. It will inform decisions on restricting or banning the use of a substance in food-producing species, and on the need to introduce risk management measures.
The response to Question 1 was published in July 2013 and includes advice from the Agency on the use of colistin and tigecycline in animals (EMA/443757/2013 - Antimicrobial resistance - European Medicines Agency provides advice on use of colistin and tigecycline in animals) as follows:

There is no available evidence on the transfer of resistance to colistin from animals to man but information on the subject is limited and more research and surveillance should be done. The advice recommends:

✓ **maintaining the responsible use of colistin in veterinary medicine** but restricting its use to the treatment of infected animals and those in contact with them, and to remove all indications for preventive (or prophylactic) use.

✓ **strengthening the systems for surveillance for resistance to colistin** in order to increase the likelihood of early detection of any rise. The benefit-risk balance for colistin to be re-evaluated if a substantial increase of resistance is detected.

Tigecycline, an antibiotic of the glycylcycline class, is not currently approved for use in animals; there is some evidence of off-label use in dogs and cats of tigecycline products authorised for human use. **The Agency advised that currently no need is foreseen for the authorisation of tigecycline for use in animals** and it is unlikely that a marketing authorisation could be granted in light of the need for this antibiotic in human medicine.
The answers to Question 2, 3 and 4 were provided in December 2014 in the publicly available document EMA/381884/2014 - Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals).

The answers were prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG).

AMEG has performed an evaluation on all human CIAs based on the degree of risk to man due to resistance development following use in animals.
The EMA/AMEG 2014 Categorisation

Question 4:
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.”

Preparation of the answers
The answers were prepared by the Antimicrobial Advice ad hoc Expert Group (AMEG). The AMEG is composed of representatives and experts from the European Medicines Agency (EMA) and its Committee for Medicinal Products for Veterinary Use and Antimicrobials Working Party (CVMP/AWP) and its Committee for Medicinal Products for Human Use and Infectious Disease Working Party (CHMP/DDWP), the European Food Safety Authority (EFSA), the European Centre for Disease Prevention and Control (ECDC) and the Joint Interagency Antimicrobial Consumption and Resistance Analysis Report (JIA CRA).
A stakeholders meeting was organised on 28 February 2014 and a public consultation launched with a

The AMEG proposes to classify antimicrobials from the WHO CIA list in three different categories:

- **Category 1** as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,
- **Category 2** as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and
- **Category 3** as antimicrobials not approved for use in veterinary medicine.

- **Category 1** as antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited,
- **Category 2** as antimicrobials used in veterinary medicine where the risk for public health is estimated higher and
- **Category 3** as antimicrobials not approved for use in veterinary medicine.

Category 1 includes some classes of antimicrobials that are listed as CIAs by WHO according to its criteria and for which use in veterinary medicine is extensive, but that nevertheless were considered to

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5 Overview of comments received on ‘Answers to the request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals’ (EMA/381844/2014), document reference EMA/598105/2014.

6 For this document “antimicrobials” is defined as “active substance of synthetic or natural origin which destroys microorganisms, suppresses their growth or their ability to reproduce in animals or humans”. In this context, antivirals, antiparasitics and disinfectants are excluded from the definition.

Answer to the Request for scientific advice on the impact on public health and animal health of the use of antibiotics in animals
EMA/381844/2014
The EMA/AMEG 2014 Categorisation

The **Category 1**, with low risk of resistance included different antimicrobials like macrolides (spiramycin, tylosin), penicillin with natural and narrow spectrum, polymyxins (e.g. colistin), rifamycins (rifaximin) and tetracyclines.

**Category 2**, with higher risk of resistance for humans, includes 3rd and 4th generation cephalosporins (ceftiofur, cefoperazone, cefquinome), fluoroquinolones (enrofloxacin, marbofloxacin), aminoglycosides and aminopenicillins including β-lactamase inhibitors (e.g. co-amoxiclav). The use of these antimicrobials in veterinary medicine is considered acceptable provided that specific restrictions are placed on their use like not being used as first choice antibiotic.

**Category 3** regards forbidden antimicrobials in veterinary medicine.

The AMEG categories take into account:

- the WHO categorisation of antimicrobials,
- the consumption of those antimicrobials in veterinary medicine,
- the hazards of zoonotic relevance in EU and
- the risk of resistance transfer to humans.

Data summary table

The antimicrobial classes have been classified as Category 1, 2 or 3 according to the risk to public health resulting from development of antimicrobial resistance.

Table 1: Summary table

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Hazard of zoonotic relevance (as detailed in Q2, Table 1)</th>
<th>Probability of resistance transfer (as detailed in Q2, Table 2)</th>
<th>Use in veterinary medicine (EMA/ESVAC, 2013) and information from Member States Marketing Authorisations</th>
<th>Concluding remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Antimicrobials used in veterinary medicine where the risk for public health is currently estimated low or limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides (including ketolides)</td>
<td>Canavibacter spp.</td>
<td>S. epidermidis spp.</td>
<td>High</td>
<td>Approved (including group medication)</td>
</tr>
<tr>
<td>Penicillins, Natural</td>
<td>None specific</td>
<td>High</td>
<td>Approved (including group medication)</td>
<td>Compliance with responsible use principles is necessary to reduce the risk of resistance transfer. Measures to reinforce responsible use principles are needed.</td>
</tr>
<tr>
<td>Penicillins: Narrow spectrum, β-lactamase-resistant penicillins</td>
<td>None specific</td>
<td>High</td>
<td>Approved (predominantly intramuscular formulations)</td>
<td>Compliance with responsible use principles is necessary to reduce the risk of resistance transfer. Measures to reinforce responsible use principles are needed due to risk for co-resistance.</td>
</tr>
<tr>
<td>Polymyxins (e.g., colistin)</td>
<td>Enterobacteriaceae</td>
<td>Low</td>
<td>Approved (including group medication)</td>
<td>See response to Question 1</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>None specific</td>
<td>High</td>
<td>Approved (limited use predominantly in horses and intramuscular formulations)</td>
<td>Compliance with responsible use principles is necessary to reduce the risk for resistance co-resistance.</td>
</tr>
</tbody>
</table>

The use of these antimicrobials is subject to specific conditions as detailed in Q2, Table 3.

Table 2: Hazard and probability of resistance transfer

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Hazard of zoonotic relevance (as detailed in Q2, Table 1)</th>
<th>Probability of resistance transfer (as detailed in Q2, Table 2)</th>
<th>Use in veterinary medicine (EMA/ESVAC, 2013) and information from Member States Marketing Authorisations</th>
<th>Concluding remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 2</td>
<td>Antimicrobials used in veterinary medicine where the risk for public health is currently estimated higher</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins, 3rd and 4th generation</td>
<td>Enterobacteriaceae</td>
<td>High</td>
<td>Approved (restrictions apply)</td>
<td>Compliance with existing restrictions is needed (see Question 4)</td>
</tr>
<tr>
<td>Fluoroquinolones and other quinolones</td>
<td>Canavibacter spp.</td>
<td>Enterobacteriaceae</td>
<td>High</td>
<td>Approved (including group medication, restrictions apply)</td>
</tr>
<tr>
<td>Class of antimicrobials for which a risk profiling is required before a final decision on its category can be made: Aminoglycosides</td>
<td>Enterobacteriaceae</td>
<td>Enterococcus spp.</td>
<td>High</td>
<td>Approved (including group medication)</td>
</tr>
<tr>
<td>Penicillins: Aminocyclines, including β-lactamase-resistant penicillins</td>
<td>Enterobacteriaceae</td>
<td>Enterococcus spp.</td>
<td>High</td>
<td>Approved (including group medication)</td>
</tr>
</tbody>
</table>

Answer to the Request for Scientific Advice on the Impact on Public Health and Animal Health of the Use of Antimicrobials in Animals

EPH/2013/H3/2014

Page 12/13
### Category 2

<table>
<thead>
<tr>
<th>Antimicrobials used in veterinary medicine where the risk for public health is currently estimated higher</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard of zoonotic relevance</strong></td>
</tr>
<tr>
<td>Lactamase inhibitors combinations (e.g., co-amoxiclav)</td>
</tr>
</tbody>
</table>

### Category 3

<table>
<thead>
<tr>
<th>Antimicrobials currently not approved for use in veterinary medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hazard of zoonotic relevance</strong></td>
</tr>
<tr>
<td>Carbapenems and other penems</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Cefotaxime and ceftobiprole</td>
</tr>
<tr>
<td>MRSA (Methicillin-resistant Staphylococcus aureus)</td>
</tr>
<tr>
<td>Cyclic esters (e.g., fosfomycin)</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Glycopeptides</td>
</tr>
<tr>
<td>Enterococcus spp., MRSA</td>
</tr>
</tbody>
</table>

### Antimicrobial class

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycyclines</td>
</tr>
<tr>
<td>Enterobacteriaceae, MRSA</td>
</tr>
<tr>
<td>Lipopeptides</td>
</tr>
<tr>
<td>Enterococcus spp., MRSA</td>
</tr>
<tr>
<td>Monobactams</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Oxazolidinones</td>
</tr>
<tr>
<td>Enterococcus spp., MRSA</td>
</tr>
<tr>
<td>Penicillins: carboxy-penicillins and ureido-penicillins including β-lactamase inhibitors combinations</td>
</tr>
<tr>
<td>Enterobacteriaceae, Enterococcus spp.</td>
</tr>
<tr>
<td>Rifamycines</td>
</tr>
<tr>
<td>None specific</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>None specific</td>
</tr>
<tr>
<td>Drugs used solely to treat tuberculosis or other mycobacterial diseases</td>
</tr>
<tr>
<td>None specific</td>
</tr>
</tbody>
</table>
Restrictions after 2014:

Polymyxins (e.g. colistin)

May 2014 - Referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing colistin as sole active substance for oral administration to food-producing species.

March 2015 – Adoption of EC Decision to restrict the indications (prophylactic use of oral colistin products in food-producing species excluded, salmonellosis claim deleted), target species (horse deleted), and duration of treatment (restricted to maximum 7 days) of the concerned products, as well as to add prudent use warnings to the product information.

May 2015 - Referral procedure under Article 35 of Directive 2001/82/EC for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally.

July 2016 - EC recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally.

July 2016 - following the discovery of mcr-1, a horizontal transferable resistance gene in bacteria of food animal origin, the impact of the current or future use of colistin products in veterinary medicine for animal health and welfare has been re-assessed:

- colistin moved from AMEG Category 1 of antimicrobials to Category 2, to be used as fluoroquinolones only as 2nd choice, after the Category 1 antimicrobials have not been effective. The opinion will be reviewed in 3-4 years.
- in 3-4 years the consumption should be reduced of 65-80% in the countries with the highest consumption, such as Italy and Spain, without increasing the use of fluoroquinolones, cephalosporins of 3rd and 4th generation and total consumption of antibiotics.
Currently in progress:


All veterinary-authorised AGs, including spectinomycin, would be placed in Category 2 (higher risk for public health), a further stratification is foreseen for some AGs, based on active substances and/or route of administration.
Aminopenicillins, especially those in association with clavulanic acid, have a similar spectrum to cephalosporins of 2nd and 3rd generation. They can also select and/or facilitate the development of bacteria with extended spectrum beta-lactamases (ESBLs), similar to cephalosporins of 3rd and 4th generation and fluoroquinolones. They are classified as CIA for humans (WHO) and as VCIA for animals (OIE) and for this they have been included by AMEG in Category 2.

Based on the assessment of the possible development of resistance and consequent impact on animal and human health, the CVMP suggests to AMEG to consider a further stratification of the current categorization, in order to review the priority among the substances currently present in Category 2 (fluoroquinolones, cephalosporins of 3rd and 4th generation and colistin, for which there are fewer alternatives) and the association amoxicillin-clavulanic acid, and between the latter and the aminopenicillins (amoxicillin, ampicillin). The association amoxicillin-clavulanic acid, having a broader spectrum, is indeed more likely to select multiresistant bacteria than single aminopenicillins.
Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union

Draft agreed by Antimicrobials Working Party (AWP) 24 May 2017
Adopted by CVMP for release for consultation 11 July 2017
Start of public consultation 25 July 2017
End of consultation (deadline for comments) 31 January 2018
Adopted by AWPR 19 September 2018
Adopted by CVMP 8 November 2018

Keywords: off-label use, antimicrobials, antimicrobial resistance, veterinary medicine

Reflection paper on antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products

Draft

Draft agreed by the Environmental Risk Assessment Working Party (ERAWP) 30 April 2018
Draft agreed by the Antimicrobials Working Party (AWP) 30 May 2018
Adopted by CVMP for release for consultation 8 November 2018
Start of public consultation 16 November 2018
End of consultation (deadline for comments) 31 August 2019

Comments should be provided using this template. The completed comments form should be sent to cvmpישראל@ema.europa.eu

Keywords: antibiotics, environmental fate, human health, animal health, risk assessment, antimicrobial resistance (AMR), antimicrobial resistance genes (ARGs)
### Category 1

<table>
<thead>
<tr>
<th>Class</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
<td>Erythromycin, Gamithromycin, Spiramycin, Tildipirosin, Tulathromycin, Tylosin, Tylvalosin, Tilmicosin</td>
</tr>
<tr>
<td><strong>Penicillins, Natural</strong></td>
<td>Benzylpenicillin, Benethamine penicillin, Penethamate (hydroiodide), Benzylpenicilline procaine, Benzathine penicillin</td>
</tr>
<tr>
<td><strong>Penicillins: Narrow spectrum, β-lactamase-resistant penicillins</strong></td>
<td>Cloxacillin, Dicloxacillin, Nafcillin, Oxacillin</td>
</tr>
<tr>
<td><strong>Rifamycins</strong></td>
<td>Rifaximin</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Chlortetracycline, Doxycycline, Oxytetracycline, Tetracycline</td>
</tr>
<tr>
<td>Category 2</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td><strong>Substances</strong></td>
</tr>
</tbody>
</table>
| Cephalosporins 3\(^{rd}\)- and 4\(^{rd}\)- generation | Ceftiofur  
Cefquinome |
| Fluoroquinolones and other quinolones | Danofloxacin  
Marbofloxacin  
Difloxacin  
Enrofloxacin  
Flumequin  
Oxolinic acid |
| Polymixins (e.g. colistin) | Colistin |
| Aminoglycosides | Amikacin  
(Dihydro)streptomycin  
Framycetin  
Gentamicin  
Kanamycin  
Neomycin  
Paromomycin (aminosidine)  
Apramycin  
Spectinomycin  
Tobramycin |
| Penicillins: Aminopenicillins including β-lactamase inhibitors combinations (e.g. co-amoxiclav) | Amoxicillin  
Ampicillin  
Amoxicillin + clavulanic acid |
## AMEG classification vs WHO classification

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>WHO 2016 classification</th>
<th>AMEG 2014 classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd- and 4th-generation cephalosporins</td>
<td>Highest priority CIAs (3rd- and higher-generation cephalosporins)</td>
<td>Category 2</td>
</tr>
<tr>
<td>Fluoroquinolones and other quinolones</td>
<td>Highest priority CIAs</td>
<td>Category 2</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Highest priority CIAs</td>
<td>Category 1</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Highest priority CIAs</td>
<td>Category 2</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>CIAs</td>
<td>Provisionally included in Category 2 (but no risk profiling has been provided) Category 2 confirmed by Reflection Paper EMA/CVMP/AWP/721118/2014 dt 21.06.2018</td>
</tr>
<tr>
<td>Certain penicillins (amoxicillin, ampicillin, metampicillin)</td>
<td>CIAs</td>
<td>Provisionally included in Category 2 (but no risk profiling has been provided) Category 2 confirmed by draft Reflection Paper EMA/CVMP/AWP/842786/2015 dt 13.09.2018</td>
</tr>
</tbody>
</table>
Classes of antibiotics included in the WHO, OIE and AMEG 2014 list of critically important antimicrobial agents
The EMA should address the following points:

1. Categorisation of antimicrobials
   - Categorisation of aminoglycosides and penicillins,
   - Further refinements of the criteria for the categorisation (e.g. including route of administration),
   - Improved communication of the categorisation,
   - Consideration of additional categorisation for antimicrobials categorised by the WHO as highly important and important (in addition to the critically important antimicrobials),
   - Consideration of other recent work of the WHO on classification of antimicrobials and pathogens (e.g. the 20th edition of the WHO Model List of Essential Medicines and the WHO Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics),
   - Consideration of any other relevant work in this area (e.g. OIE list of antimicrobial agents of veterinary importance).
The route of administration has been already used as refinement of the criteria for the EMA/AMEG Categorisation in 2014 (e.g. for rifamycins/rifaximin).

<table>
<thead>
<tr>
<th>Antimicrobial class</th>
<th>Summary of veterinary use in the EU</th>
<th>Risk management measures implemented by some countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td>Limited use in veterinary medicine.</td>
<td>Those recommended by responsible use.</td>
</tr>
</tbody>
</table>
|                     | • **Indications:**
|                     | Rifamixin is the only substance of the group authorised for use in food producing species with indications limited to intramammary or intrauterine use |
|                     | • **Pharmaceutical Form:** intramammary                                                          |
|                     | • **Species:** cattle.                                                                            |
| Comment: Rifampicin is included in the list of essential substances for horses for the treatment of *Rhodococcus equi* infections in equines. |

(from Table 8 EMA/381884/2014)
3.2 Particular issues to be considered before using critically important antimicrobials

Many of the antimicrobials used in animals are also used in humans. Some of these antimicrobials are critical (*) for preventing or treating life-threatening infections in humans. Special consideration is necessary to ensure the continued efficacy of such antimicrobials and to minimise the development of resistance.

Before using these antimicrobials in animals, consideration should be given to the following (in addition to the points already mentioned):

— These antimicrobials should only be used in situations where a veterinarian has assessed, on the basis of antimicrobial susceptibility testing and relevant epidemiological data, that there is no non-critically important effective antimicrobial available.

— In exceptional cases where the use of these antimicrobials under off-label use (cascade) is unavoidable and legally permissible, prescription and final use should be sufficiently justified and recorded. Such use should be based on clinical grounds, i.e. the prescribing veterinarian considers the use of a particular critically important antimicrobial necessary in order to avoid the suffering of diseased animals, and should also take into consideration ethical and public health concerns. The use of critically important antimicrobials should be limited to cases where no other alternative is available.

(*) http://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/


(*) In April 2013, the Commission requested advice from the European Medicines Agency on the impact of the use of antibiotics in animals on public and animal health. The response to this request should be used to identify the antimicrobials to be considered in this chapter.

Application of EMA/AMEG 2014 categorisation

EC letter to EMA, 2017

Dear Professor Razi,

Subject: Request for an update of the advice on the impact on public health and animal health of the use of antibiotics in animals (categorisation of antimicrobials and early hazard characterisation)

On request of the European Commission in April 2017, the European Medicines Agency (EMA) provided in 2014 the scientific advice on the impact on public health and animal health of the use of antibiotics in animals. This advice included a categorisation of critically important antimicrobials from the World Health Organisation list, based on their animal health impact.

Further updates of the list, including early hazard characterisation, were proposed.

You are in receipt of the revised categorisation and early hazard characterisation which need to be addressed at this stage; these points are reflected in the section II. ("Terms of reference") below.

With regard to the anticipated impact assessment, this problem statement indicates that:

- the revised categorisation may have a significant impact on the selection and use by veterinarians of antimicrobial medicinal products, on national treatment guidelines, ESVAC and JACRA;

- the early hazard characterisation may have an impact on the development and authorisation of new antimicrobials for veterinary use and on the revision of the draft CVMP guideline on assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals.
Application of EMA/AMEG 2014 categorisation

AEMPS; 2017

REFERENCIAS:


- EMA. 2014 Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals: 18 December 2014 EMA/381884/2014. Veterinary Medicines Division/CVMP/CHMP.

  http://apps.who.int/iris/bitstream/10665/77375/1/9789241504485_eng.pdf

- OIE LIST OF ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE
Application of EMA/AMEG categorisation

Eighth European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report, 2018

About the report

The eighth ESVAC report presents data on the sales of veterinary antimicrobial agents from 30 European countries in 2016, provided at package level according to a standardised protocol and template. In addition, it includes a chapter describing changes in consumption of veterinary antimicrobials for the years 2010-2016 (Chapter 2.8).

Chapter 2.8.2. focuses on the changes across time in each country. Explanations for the possible reasons for the changes across time in the various ESVAC participating countries have been provided by the ESVAC national contact points (NCs).

This chapter emphasises in particular certain classes/subclasses of antimicrobials included in Category 2 of the categorisation made by the EMA Antimicrobial Advice ad hoc Expert Group (AMEG) (see classification criteria in Annex 5). The AMEG categories take into account the World Health Organization (WHO) categorisation of antimicrobials, the consumption of those antimicrobials in veterinary medicine, the hazards of zoonotic relevance in Europe and the risk of resistance transfer to humans. The AMEG classification is published on the EMA webpage.

Category 2 of the AMEG categorisation includes those veterinary antimicrobials where the risk for public health is estimated to be higher than other classes of antimicrobials; fluoroquinolones, 3rd- and 4th-generation cephalosporins and polymyxins are included in this category. Macrolides are not included in Category 2 of the AMEG categorisation. Aminoglycosides and certain penicillins (aminopenicillins, i.e. amoxicillin, ampicillin and methampicillin) have been recently revised by the CVMP without suggesting a category for those groups of antimicrobials. A revision of the classification of AMEG is currently ongoing.
Application of EMA/AMEG categorisation


1.4.4.3 Sales of antibiotics of particular relevance to human health (mg/kg)

In VARSS reports, HP-CIAs are identified according to the categorisation by the Antimicrobial Advice ad hoc Expert Group (AMEG) of the EMA, and therefore include fluoroquinolones, 3rd and 4th generation cephalosporins and colistin (European Medicines Agency, 2014, 2016). Sales of HP-CIAs for food-producing animal species represented 0.28 mg/kg, a small proportion (0.8%) of the overall antibiotic sales. The sales decreased by 0.12 mg/kg (30%) between 2016 and 2017 and by 0.36 mg/kg (56%) since 2013 to 0.28 mg/kg in 2017. Between 2016 and 2017, sales of 3rd and 4th generation cephalosporins decreased by 0.03 mg/kg (21%), sales of fluoroquinolones decreased by 0.07 mg/kg (30%) and sales of colistin decreased by 0.017 mg/kg (94%) to very low levels (0.001 mg/kg), see Figure 1.5.
To conclude:

**The best choice:**
- **Cephalosporins 1\textsuperscript{st} - 2\textsuperscript{nd} generation:** cefacectile, cefadroxil, cefalexin, cefalonium, cefapyrin
- **Sulfonamides:** sulfadiazine, sulfadimethoxine, sulfadimidine, sulfadoxine, sulfaguanidin, sulfamethoxypyridazine, sulfquinoxaline...
- **Amphenicols:** florphenicol, thiamphenicol
- **Others:** bacitracin, fusidic acid
- **Lincosamides:** lincomycin, pirlimycin (prudent use recommended since 2011)

**The first choice:**
- **Macrolides:** erythromycin, gamithromycin, spiramycin, tildipirosin, tulathromycin, tylosin, tylvalosin, tilmicosin)
- **Penicillins, natural:** benzylpenicillin, benethamine penicillin, benethamate (hydroiodide), benzylpenicilline procaine, benzathine penicillin
- **Penicillins, narrow spectrum, \(\beta\)-lactamase-resistant penicillins:** cloxacillin, dicloxacillin, nafcillin, oxacillin
- **Rifamycins:** rifaximin
- **Tetracyclines:** chlortetracycline, doxycycline, oxytetracycline, tetracycline

**The second choice:**
- **Cephalosporins 3\textsuperscript{rd} - 4\textsuperscript{rd} generation (for systemic use):** ceftiofur, cefquinome
- **Fluoroquinolones and other quinolones:** danofloxacin, marbofloxacin, difloxac, enrofloxacin, flumequin, oxolinic acid
- **Polymixins (e.g. colistin):** colistin
- **Aminoglycosides:** amikacin, (dihydro)streptomycin, framycetin, gentamicin, kanamycin, neomycin, paromomycin (aminosidine), apramycin, spectinomycin, tobramycin
- **Penicillins, aminopenicillins including \(\beta\)-lactamase inhibitors combinations (e.g. co-amoxiclav):** amoxicillin, ampicillin, amoxicillin/clavulanic acid
Awaiting EMA/AMEG 2018 Categorisation...

...thank you for your attention!