EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

AMEG - Categorisation of antibiotics in the European Union

Anti**M**icrobial **E**xpert **G**roup

Joint EMA/FVE webinar on AMEG

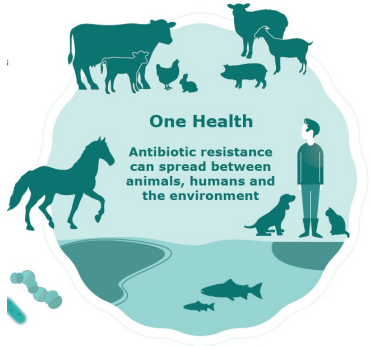
Presented by Gérard Moulin on 23 June 2021

AMEG Group - composition

The EMA-AMEG was created on request European Commission in April 2013

The AMEG is composed of representatives and experts from

- EMA's **CVMP** and CVMP Antimicrobials Working Party,
- EMA's **CHMP** and CHMP Infectious Diseases Working Party,
- **E**uropean **F**ood **S**afety **A**uthority **(EFSA),**
- **E**uropean **C**entre for **D**isease **P**revention and **C**ontrol **(ECDC),**



- **J**oint Interagency **A**ntimicrobial **C**onsumption and **R**esistance Analysis **(JIACRA)** working group.

https://www.ema.europa.eu/en/committees/working-parties-other-groups/cvmp/antimicrobial-advice-ad-hoc-expert-group-ameg

AMEG 2 - Categorisation of antibiotics in the EU

Background –

- The first AMEG categorisation was published in **2014**
- Included only antibiotics that met the WHO's C1 criterion (importance to human health)
- Noted that more in-depth risk profiling was needed for certain classes

2015: Identification of *mcr-1* plasmid-borne colistin-resistance gene in bacteria of food animal origin at a time of increasing importance of colistin in treatment of MDR infections in humans

2017: EC requested the EMA to update the advice from 2014

- Further refinement of the criteria
- Consideration of all antibiotic classes
- Communication

→ AMEG 2 Categorisation published December **2019**

Criteria considered in the categorisation

AMEG – Criteria refined:

- If the class is authorised for use in veterinary medicine in the EU
- Importance of the antibiotic class for human medicine (WHO ranking) taking into account the EU situation
- Likelihood *and possible consequences* of AMR transfer from treated animals to humans: *specific consideration given to mechanisms where a single gene confers multiresistance*
- *Availability of* ***alternative antibiotics in veterinary medicine*** *with lower AMR risk to* ***animal and public health*** *(OIE ranking, taking into account EU situation)*

New AMEG categories

4 Categories, **A to D**, replacing Categories 1 to 3

→ **ALL** antibiotic classes are now included

→ Allows **greater distinction in ranking** between substances and prevents too many antibiotics being placed in highest category

https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals

Category A: '*Avoid*'

Carbapenems, 5G cephalosporins, 3G cephalosporins+BLI, glycopeptides, glycylcyclines, ketolides, lipopetides, monobactams, oxazolidones, carboxy-/ureido- penicillins, phosphonic acid deriv, rifamycins (except rifaximin), riminofenazines, sulfones, antimicrobials solely to treat tuberculosis, amdinopenicillins, streptogramins, pseudomonic acid

- Antibiotic (sub)classes **not approved in veterinary medicine**
- Any new antibiotic authorised for human medicine after publication of the categorisation

Provided there are no Maximum Residue Limits established, these substances can only be used under the cascade in individual companion animals. Use is expected to be exceptional.

Category B: *'Restrict'*

3rd & 4th G cephalosporins, (fluoro) + quinolones, polymyxins

- WHO's **highest priority CIAs** (HPCIAs) (except Cat A substances and macrolides)

Should only be used in veterinary medicine when no alternative from category C or D could be clinically effective

Especially for this category, use should be based on susceptibility testing, whenever possible

Category C: '*Caution*'

Aminoglycosides, amphenicols, macrolides, lincosamides, rifaximin, pleuromutilins, 1st & 2nd G cephalosporins, aminopenicillins+b-lactamase inhibitor (amoxiclav combinations)

- Alternatives are available in human medicine for given indications
- There are **few or no alternatives for a given indication in veterinary** medicine from Category D
- and/or The antibiotic **selects for resistance to a substance in Category A** through specific multiresistance genes e.g. *cfr*

→ Higher AMR risk to human and/or animal health compared to Category D

Category C should only be used if a substance in D would not be effective

Category D: '*Prudence*'

Aminopenicillins (no inhibitor), penicillins - n/s and anti-staphylococcal, tetracyclines, sulfonamides/TMP, steroids (fusidic acid), cyclic polypeptides (bacitracin), nitrofurans, nitroimidazoles, spectinomycin

- There are alternative antibiotics in human and veterinary medicine for their given indications
- They do not select for resistance to Category A through specific multiresistance genes

→ Lower AMR risk for human and/or animal health

Responsible use principles apply: Unnecessary use and unnecessarily long treatment periods should be avoided and group treatment restricted to situations where individual treatment is not feasible

Route of administration

- Route of administration (RoA) may have an important impact on the AMR risk
- The AMEG has prepared a listing of preferred RoA and formulations, based on a simple literature review
- There is insufficient evidence to rank every <Antibiotic group + formulation> combination and this would produce a complex categorisation

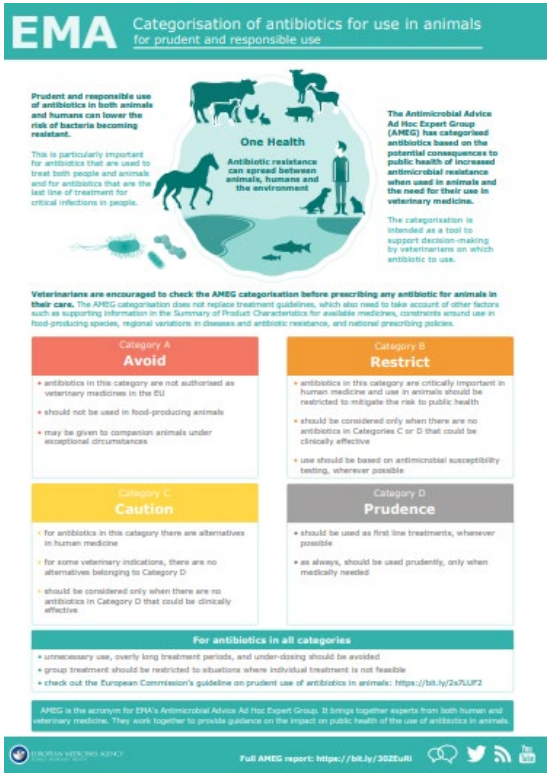
Preferred RoA/formulation

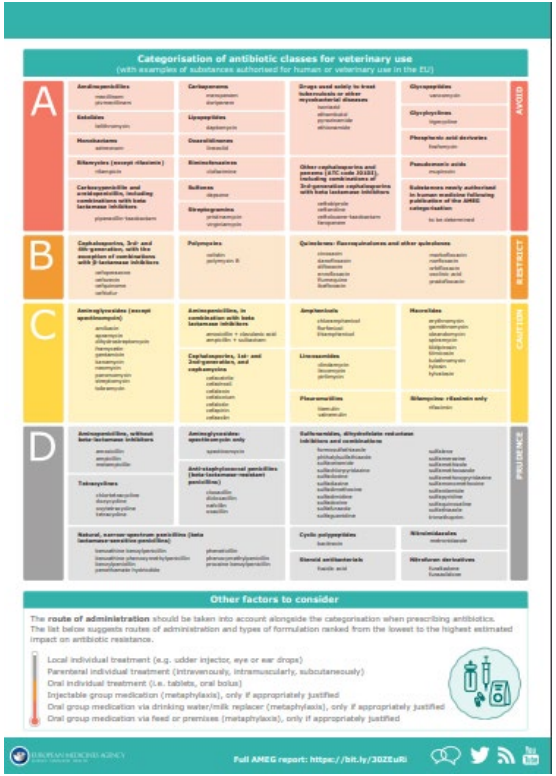
(from lower to higher effect on AMR selection)

Local individual treatment (e.g. udder injector, eye or ear drops)
Parenteral individual treatment (intravenously, intramuscularly, subcutaneously)
Oral individual treatment (i.e. tablets, oral bolus)
Injectable group medication (metaphylaxis), only if appropriately justified
Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified
Oral group medication via feed or premixes (metaphylaxis), only if appropriately justified

The aim should be to use this RoA list together with the Categorisation when factoring AMR into prescribing decisions

Infographic – available in all EU languages





AMEG - Categorisation of antimicrobials

https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals#related-information-materials-section

Use of the AMEG categorisation

- Aims to **balance human and animal health needs and public health considerations** (WHO, OIE)
- The categorisation is **not a full AMR risk assessment**: guidance tool as part of a risk analysis
- Can be used to **prioritise AMR risk analysis work**
- Tool to assist **development of local treatment guidelines**
- Tool to assist **decision making under cascade**
- Categorisation can feed into advice on **delegated/implementing acts in the Veterinary Medicinal Products Regulation**

Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6)

List of antimicrobials to be reserved for the treatment of certain infections in humans *(Reserved list of antimicrobials) - (article 37)*

List of antimicrobials, which shall not be used in accordance with Articles 112-114 or which may be used in accordance with these articles subject to certain conditions (Article 107(6)) *(Cascade use of AMs) - (article 107)*

https://www.ema.europa.eu/en/veterinary-regulatory/overview/veterinary-medicines-regulation
https://eur-lex.europa.eu/eli/reg/2019/6/oj

VMP-Reg (Regulation (EU) 2019/6) – Current Status

List of antimicrobials to be reserved for the treatment of certain infections in humans *(Reserved list of antimicrobials) - (article 37)*

Delegated act - Criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans

- EMA advice published in October 2019
- Targeted Stakeholder consultation – Ended on 23 April 2021
- Draft DA published in Eur-Lex EUR-Lex - Ares(2021)2132280 - EN - EUR-Lex (europa.eu) – 25 April 2021

VMP-Reg (Regulation (EU) 2019/6) – Current Status

List of antimicrobials to be reserved for the treatment of certain infections in humans *(Reserved list of antimicrobials) - (article 37)*

Delegated act - **Criteria for the designation of antimicrobials** to be reserved for treatment of certain infections in humans

Three criteria:

- Criterion of high importance to human health
- Criterion of risk of transmission of resistance
- Criterion of non-essential need for animal health

Implementing act – List of antimicrobials reserved to Humans

- Mandate to EMA received in July 2019 - Work ongoing

VMP-Reg (Regulation (EU) 2019/6) – Current Status

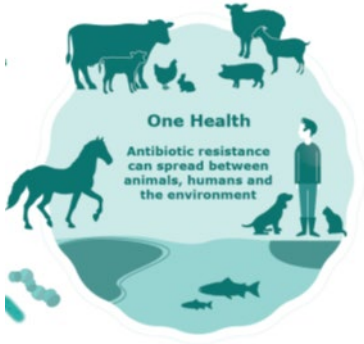
List of antimicrobials, which shall not be used in accordance with Articles 112-114 or which may be used in accordance with these articles subject to certain conditions (Article 107(6)) *(Cascade use of AMs) - (article 107)*

Implementing act

- Mandate to EMA received in February 2020 - Work is ongoing

AMEG Categorisation

- Recommendations
- Only Antibiotics
- Antibiotics only authorised in Humans not assessed
- Basis to take into account when drafting national guidelines
- Provide information for preferred choice of antimicrobials



VMP-Reg Lists

- Legislative constraints
- All Antimicrobials (Antibiotics, Antivirals, Antiprotozoals, Antifungals)
- No marketing authorisation and no off-label use are possible if they are in the Human Reserved list
- Restriction to cascade use

Both Human and Animal Health are taken into account

AMEG - Categorisation of antimicrobials

Thank you for your attention

Any questions?

Further information

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