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Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antimicrobials

Draft

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Summary assessment and recommendations

The first Antimicrobial Advice *ad hoc* Expert Group (AMEG) categorisation considered the risk to public health from antimicrobial resistance (AMR) due to the use of antimicrobials in veterinary medicine. The work focussed on antimicrobials included in the World Health Organisation's (WHO) list of critically important antimicrobials[1] (CIAs). The categorisation was based primarily on the need for a particular antimicrobial (sub)class in human medicine, and the risk for spread of resistance from animals to humans.

The categorisation was published in 2014 (EMA/AMEG, 2014) wherein the AMEG proposed to classify the 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.

The categorisation for colistin was reviewed in an updated advice published by the European Medicines Agency (EMA) in 2016 (EMA/AMEG, 2016).

In July 2017, the European Commission (EC) asked the EMA to update its 2014 advice regarding the categorisation of antimicrobials to take account of experience gained, in particular the reflection papers recently published by the EMA on the use of aminoglycosides and aminopenicillins in animals in the European Union, the risk of resistance development associated with their use and potential consequential impacts on human and animal health.

During this review, the AMEG considered additional criteria that could be taken into account for the categorisation of antimicrobials. Hence in the updated categorisation proposal, more emphasis is placed on the availability of alternative antimicrobials in veterinary medicine. In addition, the ranking has been refined with the addition of a further (fourth) category. To harmonise with other lists, the order of the categories, in terms of level of risk, has been reversed compared to the first AMEG report. Further, those antimicrobial classes which were not considered in the 2014 AMEG advice have been considered in this updated advice, and ranked according to the updated categorisation proposal.

A separate listing is provided which suggests routes of administration and types of formulation which, in general, are preferred in terms of their estimated impact on the selection of AMR.

The AMEG proposes to classify the antimicrobials in four different categories, from A to D. For communication purposes, key action words have been attributed for each category.

Category A ("Avoid") corresponds to Category 3 in the first AMEG report, and includes antimicrobial classes not currently authorised in veterinary medicine in the EU. In the absence of established maximum residue limits for foodstuff of animal origin, use of these classes of AM in food-producing animals is prohibited and they may only be administered to individual companion animals exceptionally, in compliance with the prescribing "cascade".

Category B ("Restrict") corresponds to Category 2 in the first AMEG report, including the substances listed as highest priority CIAs (HPCIAs) by the WHO with the exception of macrolides and those classes

[1] 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.

included in Category A. Thus, this category includes quinolones, 3rd- and 4th-generation cephalosporins and polymyxins. For these antimicrobials, the risk to public health resulting from veterinary use needs to be mitigated by specific restrictions.

These restricted antimicrobials should only be used for the treatment of clinical conditions when there are no alternative antimicrobials in a lower category that could be effective. Especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible.

In the first AMEG scientific advice (EMA/AMEG, 2014), aminoglycosides and the subclass of penicillins, aminopenicillins, were temporarily placed in Category 2, pending more in-depth risk profiling. The Committee for Medicinal Products for Veterinary Use (CVMP)'s reflection papers on aminoglycosides (EMA/CVMP/AWP, 2018b) and aminopenicillins (EMA/CVMP/AWP, 2018a),in draft) recognise that in accordance with the categorisation criteria in the first AMEG report, all veterinary authorised aminoglycosides and amoxicillin-clavulanate combinations would be placed in Category 2. However, as the use of these antimicrobials in veterinary medicine was considered to present a lower risk to human health compared to quinolones and 3rd- and 4th-generation cephalosporins, the CVMP recommended that a further stratification of the original AMEG categorisation should be considered. Further, it was suggested that the addition of an intermediate category would improve the utility of the categorisation as a risk management tool by avoiding the counterproductive outcome of too many antimicrobials being placed in the higher risk category.

Category C ("Caution") has been added as an intermediate category, taking account of the considerations above. This category includes individual antimicrobial classes listed in different categories by WHO, including the HPCIA macrolides. For those substances proposed for inclusion in this category, there are in general alternatives in human medicine in the EU but there are few alternatives in veterinary medicine for certain indications.

Antimicrobial classes that may select for resistance to a substance in Category A through specific multiresistance genes have also been placed in this category.

These antimicrobials should only be used when there is no substance in Category D that would be effective.

Category D ("Prudence") is the lowest risk category. While the risk to public health associated with the use in veterinary medicine of substances included in this category is considered low, a number of the substances in this category are listed as WHO CIAs (aminopenicillins, natural penicillins and isoxazolylpenicillin). It is acknowledged that these antimicrobials are not devoid of negative impact on resistance development and spread, in particular through co-selection. Therefore, while there are no specific recommendations to avoid use of Category D substances, there is a general recommendation that prudent use principles should be adhered to in everyday practice to keep the risk from use of these classes as low as possible. Unnecessary use and unnecessarily long treatment periods should be avoided and group treatment should be restricted to situations where individual treatment is not feasible.

The risk management measures applied to the individual AMEG categories should be seen as complementary to the provisions in the new regulation on veterinary medicines (Official Journal of the European Union, 2019) in relation to use of antimicrobials for prophylaxis, metaphylaxis and under the "cascade".

This categorisation does not directly translate into a treatment guideline for use of antimicrobials in veterinary medicine, but can be used as a tool by those preparing guidelines. In veterinary medicine,

the variety of animal species, the different routes of administration (from intramammary treatment of individual cows to treatment of many hundreds of fish by in-feed medication) and diversity of indications are all factors that have to be taken into account for treatment guidelines. Further, types of production systems, the presence of different diseases and occurrence of antimicrobial resistance may differ between regions. Therefore, treatment guidelines need to be regionally or even locally developed and implemented. Development and implementation of evidence-based national and regional treatment guidelines are encouraged.

A summary table specifying the categorisation for each class or subclass of antimicrobials is provided below.

Table 1. Summary of the AMEG categorisation

AMEG Categories	Antimicrobial class, subclasses, substances
Category A (*"Avoid"*)	• Amidinopenicillins • Carbapenems and other penems • Cephalosporins, Other cephalosporins and penems (ATC code J01DI) • Glycopeptides • Glycylcyclines • Lipopeptides • Monobactams • Oxazolidinones • Penicillins: carboxypenicillins and ureidopenicillins combinations with β-lactamase inhibitors • Phosphonic acid derivates (e.g. fosfomycin) • Pseudomonic acid • Riminofenazines • Streptogramins • Sulfones • Drugs used solely to treat tuberculosis or other mycobacterial diseases
Category B (*"Restrict"*)	• Cephalosporins, 3rd- and 4th-generation • Polymyxins (e.g. colistin) • Quinolones (fluoroquinolones and other quinolones)
Category C (*"Caution"*)	• Aminoglycosides and aminocyclitol • Aminopenicillins in combination with β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid) • Amphenicols (florfenicol & thiamphenicol) • Cephalosporins, 1st- and 2nd-generation and cephamycins • Macrolides • Lincosamides • Pleuromutilins • Rifamycins
Category D (*"Prudence"*)	• Aminopenicillins, without β-lactamase inhibitors • Cyclic polypeptides (bacitracin) • Nitrofuran derivatives (e.g. nitrofurantoin)* • Nitroimidazoles* • Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins)

AMEG Categories	Antimicrobial class, subclasses, substances
	• Penicillins: Natural, narrow spectrum penicillins (β-lactamase-sensitive penicillins) • Steroid antibacterials (fusidic acid)* • Sulfonamides, dihydrofolate reductase inhibitors and combinations • Tetracyclines (* Authorised for companion animals only)

After this AMEG scientific advice is finally adopted in 2019, an infographic and other communication materials for the specific purpose of publicising the categorisation will be developed by the EMA.

2. Introduction

2.1. Background

The European Commission (EC) requested in April 2013 a scientific advice from the European Medicines Agency (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 scientific advice was prepared by the Antimicrobial Advice *ad hoc* Expert Group (AMEG) and a response to the EC request was published by the EMA in December 2014 (EMA/AMEG, 2014).

One of the questions requested a ranking of classes or groups of antibiotics according to the relative importance for their use in human medicine. When the categorisation of antimicrobials (answer to question 2) was published, the necessity of further, more in-depth risk-profiling of aminoglycosides and aminopenicillins was highlighted. The Committee for Medicinal Products for Veterinary Use (CVMP), with the scientific input of its Antimicrobials Working Party (AWP), is in the process of finalising its considerations on these classes of antimicrobials.

Following the discovery of *mcr-1*, a horizontally transferable resistance gene identified in bacteria of food animal origin (Liu et al., 2015), the EC requested a re-assessment of the earlier advice on the impact of the use of colistin products in veterinary medicine on public and animal health. The updated advice on colistin, published by the EMA in 2016, resulted in a reclassification of this substance to the higher risk category (category 2) of the AMEG classification (EMA/AMEG, 2016).

In July 2017, the EC asked the EMA to update its advice published in 2014. Regarding the categorisation of antimicrobials, the EC requested that the AMEG review the original classification and update as necessary taking account of the following specific points:

- 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 World Health Organisation (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).

2.2. Scope of the response

The scope of the present document is limited to addressing the European Commission's request to update the 2014 advice on the categorisation of antimicrobials.

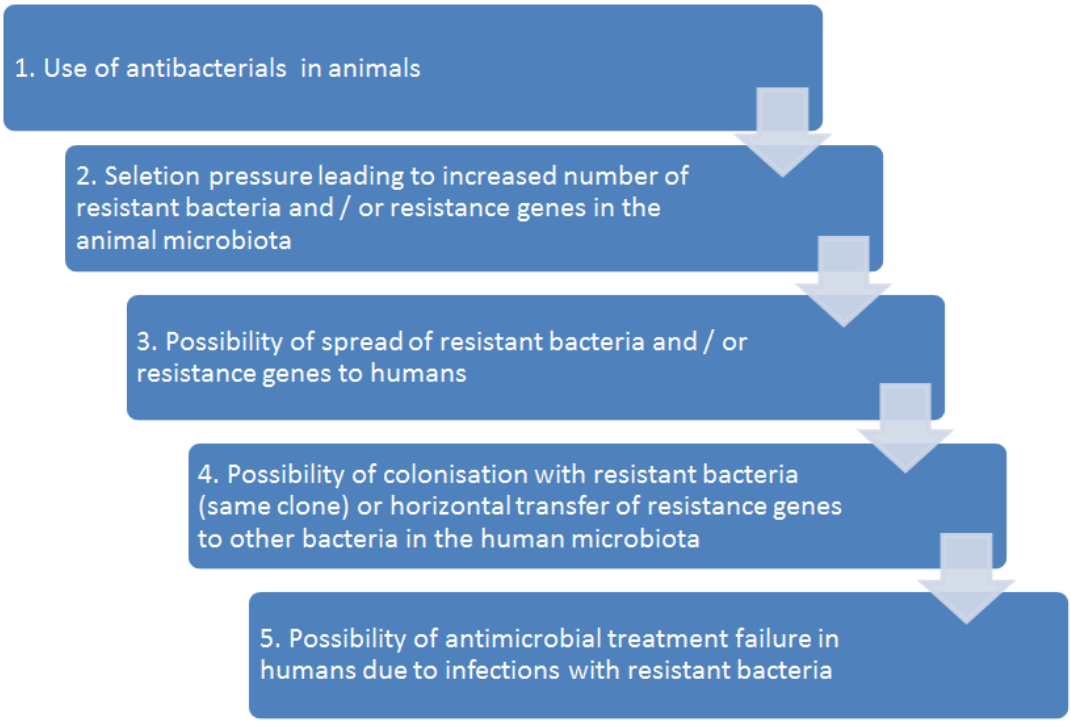
It should be noted that in its most recent request for advice, the EC also requested that the AMEG further elaborate on the 'early hazard characterisation' proposed in its 2014 advice as a means of assessing the risk to public health from AMR for new antimicrobials prior to submission of a marketing authorisation application. The AMEG response to this specific request is published in a separate document (EMA/682199/2017).

3. Considerations for the response

3.1. Risk to public health

The risk to public health from the development, emergence and spread of resistance consequent to use of antimicrobials (AMs) in veterinary medicine is dependent on multiple risk factors (Graveland et al., 2010; Persoons et al., 2011). Figure 1 summarises the chain of events that may follow from use of antimicrobials in animals resulting in a compromised antimicrobial treatment in humans.

Figure 1. The chain of events that may follow from use of antimicrobials in animals resulting in compromised antimicrobial treatment in humans



Although lists can be useful tools during risk assessments, the categorisation of AMs according to AMR has certain limits. This is mainly because co-selection between similar and also highly different classes of antimicrobials, may be present. As an example, co-selection exists between similar compounds such as amoxicillin and 3rd-generation cephalosporins (Persoons et al., 2012). Another example is tetracyclines, which facilitate spread of MRSA in livestock (Price et al., 2012). In other words, restrictions on one class alone might not have the desired impact because of co-selection of AMR.

3.2. Consideration of other recent work on classification of antimicrobials and pathogens

3.2.1. WHO

3.2.1.1. WHO list of Critically important antimicrobials

Following two tripartite WHO/FAO/OIE consultations on non-human antimicrobial usage and antimicrobial resistance (WHO, 2003; WHO, 2004), WHO has published a list of critically important antimicrobial agents for human medicine (WHO, 2005; WHO, 2007; WHO, 2011; WHO, 2012; WHO, 2016; WHO, 2017a).

The ranking identifies three categories: Critically Important Antimicrobials (CIA), Highly Important Antimicrobials (HIA) and Important Antimicrobials (IA).

Furthermore, a prioritisation has been performed among CIAs to identify the Highest Priority Critically Important Antimicrobials (HPCIA).

The HPCIA category includes quinolones, 3rd and higher generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

As noted in the 5th Revision of Critically Important Antimicrobials for Human Medicine (WHO, 2017a), these lists are intended *"to be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance mainly due to non-human use".*

"The use of this 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."

3.2.1.1.1. The WHO list is built on two criteria

- **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 non-human sources, or (2) bacteria that may acquire resistance genes from non-human sources.

If both of these criteria are fulfilled the compound or class is regarded as CIA.

If one of these criteria are fulfilled the compound or class is regarded as HIA.

If none of these criteria are fulfilled the compound or class is regarded as IA.

The list of CIAs and HIAs, which meet WHO Criterion 1, is presented with comments specific to the EU in the Annex (Table A1).

3.2.1.1.2. Criteria of prioritisation among the CIA

Antimicrobials within the critically important category are further prioritised by WHO.

The following three criteria are used for prioritisation:

- ***Prioritization criterion 1:*** *High absolute number of people, or high proportion of use in patients with serious infections in health care settings affected by bacterial diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans.*
- ***Prioritization criterion 2:*** *High frequency of use of the antimicrobial class for any indication in human medicine, or else high proportion of use in patients with serious infections in health care settings, since use may favour selection of resistance in both settings.*
- ***Prioritization criterion 3:*** *The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria (e.g. non-typhoidal Salmonella and Campylobacter spp.) or resistance genes (high for E. coli and Enterococcus spp.) from non-human sources.*

Antimicrobial classes that meet all three prioritization criteria (1, 2, and 3) are considered the *highest priority critically important antimicrobials*.

3.2.1.2. WHO Guidelines on use of medically- important antimicrobials in food-producing animals

In 2017, WHO published guidelines on use of medically-important antimicrobials in food-producing animals (WHO, 2017e). These guidelines were developed by the Guideline Development Group (GDG) using the WHO guideline development process and are based on two systematic reviews using standard methods and narrative literature reviews by topic experts. The GDG used the GRADE (grading of recommendations, assessment, development and evaluation) approach to appraise and use the evidence identified to develop recommendations. The main recommendations are summarised in Figure 2.

Figure 2. Recommendations in the WHO guidelines on use of medically important antimicrobials in food-producing animals[2]

Recommendations
1 The GDG recommends an overall reduction in use of all classes of medically important antimicrobials in food-producing animals.
2 The GDG recommends complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion.
3 The GDG recommends complete restriction of use of all classes of medically important antimicrobials in food-producing animals for prevention of infectious diseases that have not yet been clinically diagnosed. *Specific considerations: when a veterinary professional judges that there is a high risk of spread of a particular infectious disease, use of antimicrobials for disease prevention is justified, if such a judgement is made on the basis of recent culture and sensitivity testing results.*
4 a – The GDG suggests that antimicrobials classified as critically important for human medicine should not be used for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals. b – The GDG suggests that antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease. *To prevent harm to animal health and welfare, exceptions to recommendations 4a and 4b can be made when, in the judgment of veterinary professionals, bacterial culture and sensitivity results demonstrate that the selected drug is the only treatment option.*

3.2.2. WHO essential substances

The WHO Model Lists of Essential Medicines include medicines needed to treat common infections in humans, taking account of their clinical efficacy and safety and cost-effectiveness. Since 1977, WHO updates the lists every two years.

Two lists are available: the current versions are the 20th WHO Essential Medicines List (EML) and the 6th WHO Essential Medicines List for Children (EMLc). Both lists were last updated in March 2017 and can be found on the WHO website (WHO, 2017b).

As part of the 2017 review, a new categorisation of antibacterials into three groups was proposed:

[2] https://aricjournal.biomedcentral.com/articles/10.1186/s13756-017-0294-9

- ACCESS – first and second choice antibiotics for the empiric treatment of most common infectious syndromes;
- WATCH – antibiotics with higher resistance potential whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups; and
- RESERVE – antibiotics to be used mainly as 'last resort' treatment options.

The WATCH group includes the majority of the highest priority antimicrobials on the list of CIAs for Human Medicine.

Of the HPCIAs only polymyxin E (colistin) and 4th-generation cephalosporins (e.g. cefipime) are placed in the Reserve Group.

3.2.3. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics

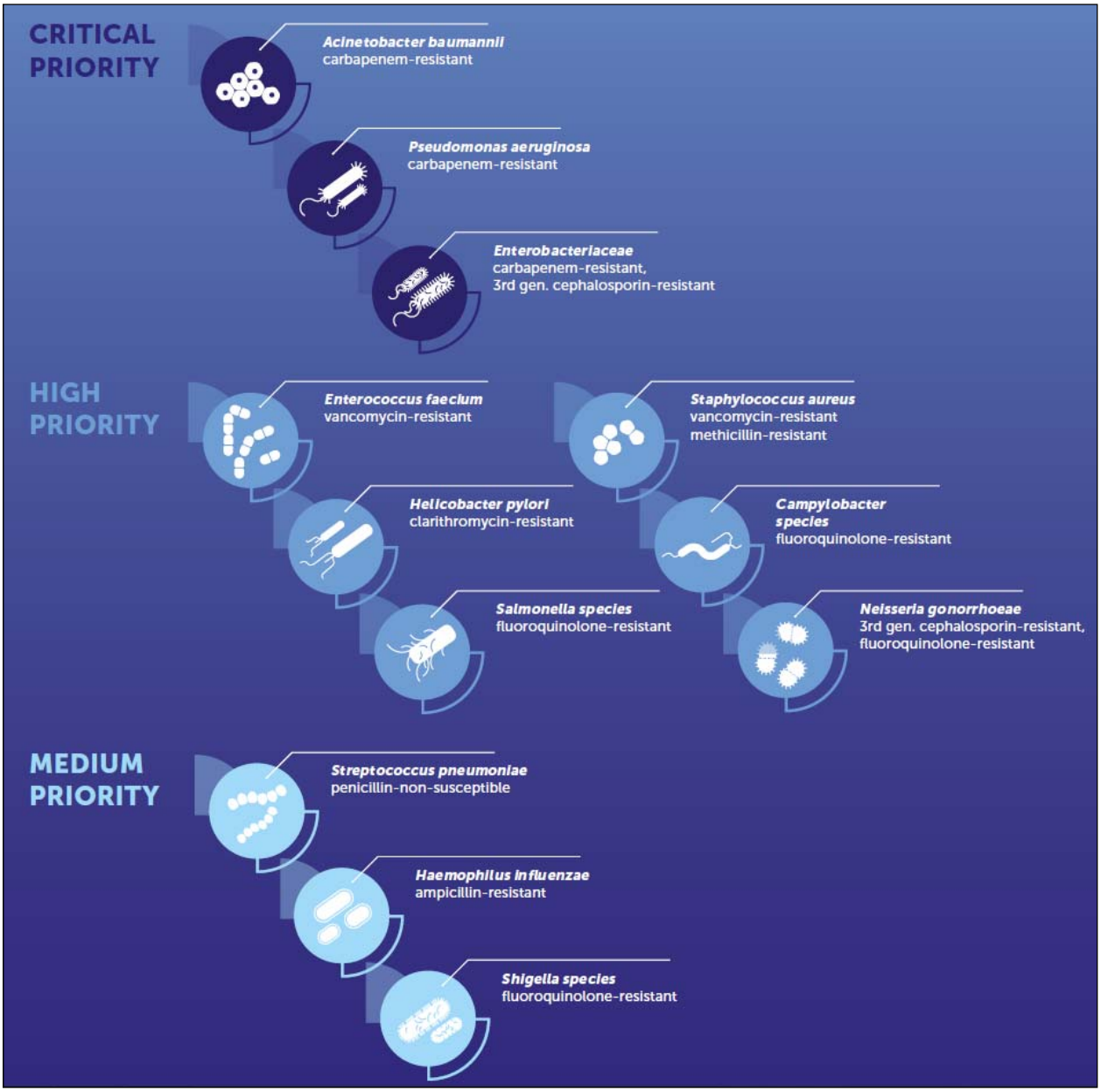
In 2016, WHO Member States mandated WHO to develop a global priority list of antimicrobial-resistant bacteria to guide research and development (R&D) of new and effective antibiotics. The main goal of this list is to prioritise funding and facilitate global R&D strategies.

The global priority list was developed by applying a multi-criteria decision analysis (MCDA) technique, which allows the evaluation of different alternatives according to multiple criteria, incorporating both expert opinion and evidence-based data in a transparent, explicit, and deliberative fashion. The list was developed in five steps: (a) selection of the antibiotic-resistant bacteria to be prioritised, (b) selection of criteria for prioritisation (all-cause mortality, healthcare and community burden, prevalence of resistance, 10-year trend of resistance, transmissibility, preventability in hospital and community settings, treatability and current pipeline), (c) data extraction and synthesis, (d) scoring of alternatives and weighting of criteria by experts (this was done blindly, i.e. based only on the characteristics of the antibiotic-resistant bacteria, but without knowing the names of these bacteria), and (e) finalisation of the ranking.

WHO published a global priority list in December 2017 (Tacconelli et al., 2018; WHO, 2017d). In the list, antibiotic-resistant bacteria are ranked in three groups according to the assessed priority for R&D of new and effective antibiotics: priority 1 – critical, priority 2 – high, and priority 3 – medium (Figure 3) (WHO, 2017c).

Third-generation cephalosporin-resistant and/or carbapenem-resistant Enterobacteriaceae and carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were listed among the antibiotic-resistant bacteria for which there is a critical need for new effective antibiotics. Vancomycin-resistant *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), as well as fluoroquinolone-resistant *Campylobacter* spp. and *Salmonella* spp., were listed among antimicrobial-resistant bacteria for which R&D of new effective antibiotics is of high priority.

Figure 3. Prioritization of pathogens to guide research and development of new antibiotics (WHO, 2017d)



3.2.4. OIE List of Antimicrobials of Veterinary Importance

Following two tripartite WHO/FAO/OIE consultations on non-human antimicrobial usage and antimicrobial resistance (WHO, 2003; WHO, 2004), the OIE published a list of antimicrobial agents of veterinary importance in 2007. This list was updated in 2013, 2015 and 2018 (OIE, 2018).

The OIE list is based on a questionnaire sent to all OIE member countries

- **Criterion 1.** Importance of the antimicrobial based on answers by OIE member countries. This criterion was met when a majority of the respondents (more than 50%) identified the importance of the antimicrobial class in their response to the questionnaire.

- **Criterion 2.** Treatment of serious animal diseases and availability of alternative antimicrobial agents. This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.

If both these criteria are fulfilled the compound or class is regarded as a veterinary critically important antimicrobial agent (VCIA).

If one of these criteria are fulfilled the compound or class is regarded as a veterinary highly important antimicrobial agent (VHIA).

If none of these criteria are fulfilled the compound or class is regarded as a veterinary important antimicrobial agent (VIA).

OIE list includes recommendations for antimicrobials that are considered as critically important for both human and animal health (fluoroquinolones, 3rd-and 4th-generation cephalosporins and colistin) (OIE, 2018). These recommendations include that these antimicrobials should not be used for prevention or as a first line treatment and that their use should ideally be based on the results of bacteriological tests.

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, the OIE advises that careful consideration should be given regarding their potential use (including extra-label/off-label use) / authorisation in animals.

3.3. Refinement of AMEG criteria

The first AMEG report considered only antimicrobial classes that fulfilled the WHO's criterion 1 ('the antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people'), with the EU situation being taken into account. These classes are listed in Table A1 in Annex 1 to this report. The AMEG categorisation was based on three main criteria as follows: (i) the relative importance of the antimicrobial class for human medicine according to the WHO ranking, (ii) the likelihood of transfer of resistance, and (iii) if the class was authorised for use in a veterinary medicine in the EU. For the indicated antimicrobial classes, three categories were agreed by the AMEG:

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

Criteria (i) and (ii) above are used to categorise classes or sub-classes as Category 1 or Category 2 antimicrobials. For Category 1 classes or subclasses of antimicrobials, prudent use is recommended. For Category 2 classes or subclasses, restrictions on use are needed. Category 3 included classes that are currently not authorised in veterinary medicines.

An objective of the current exercise is to review and update, as appropriate, the original AMEG categorisation (to consider additional criteria and/or refine the existing criteria). There are several reasons for undertaking this review.

Firstly, with regard to the aminoglycosides (AGs), the CVMP's reflection paper recognises that in accordance with the categorisation criteria in the first AMEG report, all veterinary authorised AGs would be placed in Category 2. However, their use in veterinary medicine was considered to have a

lower risk to human health compared with quinolones and 3rd- and 4th-generation cephalosporins. Therefore, it was suggested that a further stratification of the AMEG's categorisation should be considered. Likewise, for the aminopenicillins, the CVMP's (draft) risk profiling suggests that a further stratification would be needed to enable a distinction in the ranking between the Category 2 substances and amoxicillin-clavulanate combinations, and between the latter and the straight aminopenicillins. The addition of an intermediate category is expected to improve the utility of the categorisation as a risk management tool by avoiding the counterproductive outcome of too many antimicrobials being placed in a single 'higher risk' category with no possibility for prioritisation between them and where formal restrictions are necessary.

In addition, further thought was given to the criterion on the likelihood of transfer of resistance. It was questioned if the scoring of the factors taken into consideration for this criterion could be integrated to provide a reliable qualitative assessment. It was also proposed that further consideration should be given to specific mechanisms of resistance/genes that might have particularly important consequences for human health. These elements are discussed in section 3.4.

Also, with experience gained following application of the original AMEG categorisation, it was considered that additional criteria should be taken into account. When considering the chain of events leading from antimicrobial use in veterinary medicine to consequences on public health arising from AMR, possible criteria, in addition to those used in the first AMEG report (the importance of the antimicrobial class in human medicine and the probability of AMR transfer), that could be considered to improve the categorisation of antimicrobials include:

- **Criteria relating to antimicrobial class:** Chemical properties; Pharmacological properties; Spectrum of activity (e.g. narrow versus broad; associated hazards); Mechanisms of resistance (e.g. location) / co / cross resistance.
- **Criteria relating to conditions of use:** Animal species; indications (e.g. treatment versus prophylaxis or metaphylaxis); dose and duration; route of administration (e.g. different category for different route of administration); impact on gastrointestinal tract (lumen concentration, shedding of resistant bacteria/resistance genes etc.; importance of the antimicrobials in veterinary medicine (e.g. OIE list); availability of antimicrobial alternatives in veterinary medicine.
- **Criteria relating to prevalence of resistance:** Pathogens, commensals, zoonoses, frequency of resistance, transfer of resistance or mutations.
- **Criteria relating to environmental aspects:** Degradability of antimicrobials in animals and animal waste, persistence of antimicrobial resistance genes and antimicrobial resistant bacteria in manure or slurry, evidence of environmental transfer.

After considering the different potential criteria listed above, the following two were selected for more detailed consideration:

- **Route of administration:** According to the mandate the AMEG agreed to further consider the route of administration as a criterion to refine the categorisation. As the largest reservoir of AMR following the administration of an antimicrobial results from the exposure of the gut flora, the route of administration is discussed extensively in Chapter 3.3.1 of this report.
- **Indications for veterinary use and availability of alternative antimicrobials of lesser risk:** The impact on animal health may be considered as part of the approach to categorisation.

Consideration of the risk to public health has to be balanced with the importance of the substance for animal health. The importance of the substance for animal health is determined to a great extent by the availability of alternative treatment options for given indications in given species.

From the perspective of protecting human health, the greater the availability of alternative treatment options for veterinary indications, the more restrictions on veterinary use for a given AM can be tolerated without an adverse impact on animal health. Conversely, for those veterinary indications where the availability of alternative treatment options is limited, restriction on veterinary use for a given AM has the potential to impact negatively on animal health. This is notwithstanding the fact that proportionate restrictions should be placed on the use of such classes also for the management of the AMR risk to animal health. In addition it should be considered that that restriction of one antimicrobial class could lead to an increase in use of other restricted classes authorised for the same indications.

The objective, therefore, is to consider the importance and availability of antimicrobial alternatives in veterinary medicine, and to identify if antimicrobials of lower risk to both public and animal health are available for the same indication.

Applying this criterion to the categorisation of individual AM (sub)classes relied on expert judgement of AMEG members using information available in the form of the OIE list and the reflection papers on various antimicrobial classes published by the CVMP/SAGAM/AWP.

3.3.1. Impact of the route of administration on antimicrobial resistance

There are different factors directly related to the administration of an antimicrobial that affect the occurrence of AMR. These include: the type and formulation of the antimicrobial agent; the dose; the total animal biomass exposed to the antimicrobial (i.e. individual treatment versus mass medication); the treatment interval and the treatment duration. The formulation determines the route of administration but relatively little attention has been given to the association between the antimicrobial formulation and the rise of multidrug-resistant (MDR) organisms.

Across the EU as a whole, approximately 90% of all antimicrobials prescribed to livestock are given *via* the oral route (EMA/EFSA, 2017; EMA/ESVAC, 2017; Filippitzi et al., 2014; Timmerman et al., 2006). Administration of antimicrobial agents through either bulk animal feed or the drinking water supply, rather than by injection, has major economic and ergonomic advantages. In addition, potential unwanted effects of injection such as carcass damage or residues at an injection site are avoided. In some situations (e.g. commercial chicken production, aquaculture) oral administration to the whole group of animals is almost always the only feasible option. Furthermore, the withdrawal time (the minimum period between the last administration of a veterinary medicinal product to an animal and the production of foodstuffs from that animal which under normal conditions of use is necessary to ensure that such foodstuffs do not contain residues in quantities harmful to public health) is in general longer for VMPs administered by injection compared to VMPs administered orally.

However, for orally administered antimicrobials there are several opportunities for incorrect intake of dose and for the antimicrobial to present an AMR selection pressure before the agent reaches the target tissue at a concentration able to inhibit or kill the microorganism involved in an infection.

For in-feed medication, adequate mixing and homogenous distribution of the AM relies on the particle size and electrostatic properties of the premix, as well as the final composition of the feed and the mixing equipment used (Peeters, 2018). Further, the same equipment may also be used for the

production, storage and/or transport of both medicated and unmedicated feed, with the potential carry-over of antimicrobial residues (Filippitzi et al., 2016). Oral administration *via* drinking water can be more precisely dosed compared to medication administered in food (Filippitzi, 2018). Although for medication delivered via this route or in milk, the final concentration can still be highly variable and may be further influenced by factors such as water hardness, pH, temperature, light (Luthman and Jacobsson, 1983) and complex formation (with e.g. Ca^{++} in the milk replacer diet). It may, therefore, be difficult to control dosing so that it is consistent with the Summary of Product Characteristics (SPC) of the VMP.

Other factors contributing to variable intake of oral group medications include a relatively poor control over intake due to hierarchy in the flock/group, a lower intake by diseased animals, uncertain duration of therapy and potential for cross contamination of feed.

Of utmost importance with respect to the selection and containment of resistance is that oral antimicrobials may induce changes in the digestive tract microbiota, starting from the oropharynx and ending in the faeces, and by consequence in the environment. This is well documented for different antimicrobial agents in animals and humans (Crémieux et al., 2003; Sørum and Sunde, 2001).

The difference between oral and injectable formulations concerning the selection and spread of AMR in the faecal flora alone is shown to be extremely high. e.g. in a randomised controlled study in rodents the increase in the number of resistant coliforms in the group treated orally with ampicillin was 10,000 fold higher than in the group treated intravenously. The impact of oral versus intravenous administration of tetracycline on the carriage of resistant enterococci was over a 100 fold and it was suggested that this lower but significant difference may in part be due to biliary excretion of tetracycline. (Zhang et al., 2013). Similar findings demonstrating substantial benefits of injectables over oral administration in relation to development of antimicrobial resistance in the digestive tract have been published in controlled studies in other animal species (Bibbal et al., 2007; Chantziaras et al., 2017; Checkley et al., 2010; Wiuff et al., 2003). On a larger scale, microbiome studies have shown oral antimicrobials to have detrimental and persistent effects on the gut (Zaura et al., 2015). For this reason, and also due to high livestock densities that facilitate rapid exchange of multi-resistance within and between production cycles (Heuer et al., 2002), the routine use of oral (group) medication has been questioned (Catry, 2017).

Further considerations relevant for the selection pressure in the digestive tract, such as accompanying diet, absorption, reabsorption, passage rate, biodegradation and the luminal volume have recently been reviewed (Volkova et al., 2017).

Selection of AMR may also be pronounced after injection (Wiuff et al., 2003) given that certain antimicrobials administered parenterally can be actively excreted in the gut, *via* bile, where a similar selection pressure for AMR can be expected. Further research is needed into the impact on the selection of AMR in gastrointestinal microbiota by newer antimicrobial substances with long half-lives that are administered as a single injection (e.g. certain macrolides) (Zaheer et al., 2013). Rectal or sublingual administration to bypass the first pass effect (Steinman et al., 2000) and thereby also the selection pressure in the vast majority of the digestive tract without certain disadvantages of injectables, seems attractive from a research and development point of view.

The "Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety" (RONAFA report) stated that oral administration of antimicrobials in livestock is of particular concern in terms of promoting the development of AMR due to the high exposure of gastrointestinal commensal bacteria, and the

sometimes prolonged duration of treatment or exposure, especially for products administered in feed (EMA/EFSA, 2017). The purely preventative use of oral group treatments without clinical signs present (prophylaxis) should therefore be actively discouraged. Unjustified metaphylaxis is also of major concern. These issues are directly addressed in the new veterinary medicines regulation (Official Journal of the European Union, 2019).

The general consensus guidance to optimise antimicrobial drug use in both human and veterinary medicine is to give an appropriate dose for a minimum period of time (Thomas et al., 1998; Zhao and Drlica, 2001). In order to limit exposure of the microbiome, the antimicrobial selection pressure should be as local and short as possible, in line with current PK/PD strategies (Lees et al., 2018). The duration of therapy must be as short as possible but without jeopardising clinical recovery. It has been suggested that this may be achieved in practice by continuing therapy up until two days after symptoms have resolved (Chardin et al., 2009).

A suggested listing of routes of administration and formulations, ranked in order from those with in general lower effect on the selection of AMR to those that would be expected to have higher impact on resistance, is proposed as follows:

- Local individual treatment (e.g. udder injector, eye or ear drops);
- Parenteral individual treatment (intravenously, intramuscularly, subcutaneously);
- Oral individual treatment (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 medication *via* feed/premixes or top dressing (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified.

This subchapter is based on a simple review of literature. The conclusions drawn and proposed order of ranking should be confirmed by a systematic review followed by a meta-analysis in which clinical efficacy and microbiological impacts should be studied as outcomes.

Given that antimicrobials in each (sub)class are available in a number of different formulations and for administration by different routes, the AMEG chose not to include the route of administration as an additional criterion for the categorisation. It was the view of the group that to consider the relative AMR risk for all the different formulation/antimicrobial class combinations within the categorisation would be highly complex and difficult to evidence. Nevertheless, when factoring AMR risk into prescribing decisions, the aim should be to use the list above together with the AMEG categorisation to select both the formulation/route of administration and class that will have the least impact on the selection of AMR.

3.4. Transmission of antimicrobial-resistant bacteria or resistance determinants between animals and man

The likelihood of spread of AMR between animals and humans depends on a number of factors that influence either the spread of organisms exhibiting such resistance or the spread of resistance genes. Four different criteria defining the risk for spread are discussed below. The resistance to a particular substance/class has highest risk for spread if all four criteria are fulfilled.

The likelihood of spread varies over time and depends on the "bug-drug" combination. The level of detection also depends on the sampling frame, origin of samples and the methods used for sampling, for culture and for susceptibility testing. Whether the criteria are fulfilled for a certain substance or class may therefore need to be modified over time if new data become available from studies conducted under different conditions, or in the event that the relevant resistance mechanisms of the bacteria under investigation are proven to have evolved and reorganised.

Exposure to antimicrobials amplifies resistance (Levy, 2002; MacKenzie et al., 2007). In general, when there is a decrease in the exposure of animals to antimicrobials a decrease in resistance is observed (Hanon et al., 2015). The same considerations are applicable to antimicrobial usage in human medicine. Nevertheless resistance can persist in the absence of antimicrobial use (Enne et al., 2001). If this is the case (or in cases of co-resistance), reduction of consumption of a certain substance, in both veterinary and human medicine, will not necessarily lead to consequent reduction in AMR.

It should also be realised that although the transmission of AMR from animals to humans is undoubtedly highly important and is of particular relevance to this document, spread of AMR from humans to animals can also occur as a consequence of antimicrobial usage in human medicine (ECDC/EFSA/EMA, 2017). Examples of such transfer have been documented in relation to the appearance of decreased susceptibility to carbapenems in *Salmonella* spp., and *E. coli* in pigs and poultry in Germany (Fernández et al., 2018; Fischer et al., 2017). Similarly epidemiological evidence as well as whole genome sequencing of LA-MRSA from pigs and associated human cases in Norway clearly indicates that primary introduction to sow farms occurred through human-to-animal transmission (Grøntvedt et al., 2016). Studies have also documented transfer of MRSA from farmers to dairy cows in Sweden (Unnerstad et al., 2018).

Several highly successful clones of MDR bacteria that have spread EU-wide and in some cases worldwide in recent years include *E. coli* ST131 (Mathers et al., 2015), monophasic *Salmonella* Typhimurium (García et al., 2017; Hopkins et al., 2010a) and LA-MRSA (Kinross et al., 2017). Of these *E. coli* ST131 is an almost strictly human pathogen and its spread has been for the most part in the human population (Mathers et al., 2015), whereas monophasic *S. Typhimurium* and LA-MRSA are zoonotic pathogens and their spread may have been facilitated by the use of antimicrobials in food animals (EFSA, 2010; Grøntvedt et al., 2016).

Aspects of evolution and organisation of the resistance mechanisms are presented below according to four criteria to describe the likelihood of spread:

1) The presence of a chromosomal mutation contributing to the development of resistance to a clinically-relevant antimicrobial. Such mutations may occur randomly, and may give rise to both high level or low level resistance e.g. mutational resistance to fluoroquinolones in *Campylobacter* spp. (high level) or *Salmonella* spp. (low level). Alternatively, a series of stepwise mutations may be required before resistance reaches a level regarded as of therapeutic importance. Stability of the mutation(s) in the chromosome is also required for a critical level of spread of organisms exhibiting such resistance, whereby mutational resistance passes from the parent to the daughter bacterial colonies (clonal spread). A single mutational event giving rise to resistance to a particular antimicrobial might result in resistance to several substances within related classes of antimicrobial agents.
2) Organisation of non-chromosomal resistance genes into horizontally-transferable elements (Carattoli, 2009), enabling localisation on DNA outside the bacterial chromosome (e.g. conjugative or mobilisable plasmids, transposons, integron-gene cassettes). The likelihood of further spread is variable, dependent on the plasmid, the presence or absence of genes

mediating plasmid transfer, the presence of unrelated transferable plasmids which can mediate the transfer of plasmids without the necessary transfer-related genes by mobilisation, and whether horizontal plasmid/gene transfer is limited to one type of organism or if it crosses borders between related or distinct bacterial species.

3) Other factors such as: (a) the incorporation of plasmid- or transposon/integron-mediated resistance into the bacterial chromosome in discrete 'resistance islands', which may require mobilisation by other plasmids or by bacteriophages for horizontal transfer either within or between bacterial species; (b) presence of plasmid addiction systems. Such systems involve plasmid-mediated genes encoding toxin-antitoxin proteins where they serve to stabilise the plasmid within a bacterial population and, in the case of plasmids which code for resistance to a range of antimicrobials, lessen their chances of loss when antibiotic selection pressure is withdrawn. Such systems are becoming increasingly identified in plasmids belonging to a wide range of incompatibility groups, and have an important role in the maintenance of such plasmids in host bacteria.
4) The presence of a cluster of resistance genes will enable more efficient spread by co-selection. This process allows resistance spread for substance A when the unrelated substance B is used, because of linkage of resistance genes and subsequent co-transfer.

In the first AMEG report, for each antimicrobial class, influencing factors including those above were assigned a numerical score and crudely integrated to give a qualitative estimate of the overall probability of resistance transfer. For this updated report, the AMEG agreed that these values (see 3.4.2 for explanation), although individually informative for each factor, are not 'mathematically scaled' and that there is no validation that they can be combined to predict the probability of resistance transfer. The qualitative assessment (high, medium, low) based on this information has therefore been removed from the tables in this updated advice. While the AMEG agreed that a qualitative estimate of the overall probability of resistance transfer should not be incorporated into the approach to categorisation of individual AM (sub)classes, the AMEG was of the view that account should be taken of specific resistance genes associated with certain classes where transmission of these specific resistance genes could have important consequences for human health (that is, where these are mobile and confer multi-resistance to antimicrobials that are 'last resort' or used solely in human medicine). Resistance mechanisms are documented in Table 2 and where particularly relevant for the final categorisation they are discussed in the 'rationale' column for each class in Table 4.

It was agreed that the criterion should be amended as follows: ~~*The*~~ *Knowledge of factors influencing the likelihood and possible consequences of AMR transfer from animals to humans. In the new categorisation individual mechanisms of resistance have been considered more specifically for e.g. those genes associated with mobile multiresistance.*

In addition to the factors listed above, that for the most part relate only to genetic mechanisms, there are many other factors that may affect the probability of transfer of resistant bacteria or its determinants from animals to humans which reflect the conditions of use of the antimicrobial substance, e.g. dosing route and regimen, volume of usage, animal husbandry conditions. These must be taken into consideration for a full public health risk assessment (Codex Alimentarius, 2009; Codex Alimentarius, 2011).

For bacteria that may be foodborne there are a number of additional factors to consider such as consumption habits, environmental factors and the processes between slaughter and intake of food (Codex Alimentarius, 2009; Codex Alimentarius, 2011).

612 Tables 2 and 3 below list the classes/substances under assessment, adding information on the
613 bacterial hazards of zoonotic potential and the various resistance mechanisms.

614

3.4.1. Consideration of AM classes not taken into account in AMEG 1 advice[‡] and those given further consideration[§]

Several antimicrobial classes were not considered in the first advice from AMEG or have been given further consideration for this updated advice to provide a complete categorisation of antimicrobials. For the additional antimicrobial classes, the hazard of potential zoonotic relevance as well as an overview of indications in human medicine and resistance mechanisms are provided in Table 2.

Table 2. Overview of indications in human medicine and relevant mechanisms of resistance for antimicrobials not covered by AMEG 1 advice (for details and references see Table 3)

Antimicrobial class[**]	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
Amidinopenicillins	Enterobacteriaceae	• Narrow spectrum of activity. • One of the first choices for uncomplicated urinary tract infections (UTI). • Important antimicrobials and should be preserved, since effectiveness of other oral antibiotics is declining. • Only mutational resistance described. • No description of successful clones of relevance to animals.

Aminoglycosides	Enterobacteriaceae
	Enterococcus spp.
		• Important antimicrobials used alone, or in conjunction with other antimicrobials for the treatment of serious Gram-negative infections.
		• Can also be used in combination for Gram-positive infections (*S. aureus*, streptococci and enterococci), such as endocarditis.
		• Also used as part of first-line therapeutic regimens for infections with multidrug-resistant *Mycobacterium tuberculosis* and as part of treatment combinations for non-tuberculous mycobacteria.
		
		• Three main mechanisms of resistance are:
		  • reduction of the intracellular concentration of the antimicrobial;
		  • enzymatic modification of the drug;

[‡] For substances considered in the first AMEG report, Table 2 of that report (reproduced here in Annex 1, Table A1) includes information on indications in human medicine and the hazards of potential zoonotic relevance.
[§] Aminoglycosides and Aminopenicillins have been included in the table as further consideration of their categorization was requested by the EC in its 2017 mandate. The information on Polymyxins has been updated in view of the AMEG's revised advice, 2016. Expanded information has been provided on Macrolides.
[**] Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances are provided in Annex A2, Table A2.

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• modification of the molecular target. • Resistance genes often located on mobile elements thereby facilitating spread between different bacterial species and between animals and humans. • Same resistance genes found in isolates from humans and animals.
Aminopenicillins	*Enterococcus* spp. Enterobacteriaceae	• Aminopenicillins and their inhibitor combinations are one of the limited therapeutic options for infections caused by *Listeria monocytogenes* and *Enterococcus* spp. • Among the most commonly used antimicrobials in the EU for the treatment of various infections, e.g. respiratory tract, abdominal, soft tissue and urinary tract infections. • Main mechanisms of bacterial resistance to aminopenicillins are: • alterations in penicillin-binding proteins (PBP) mediated by the *mec* genes ; • hydrolysis by β-lactamases. • presence of efflux pumps/ alterations in expression of outer membrane proteins. • Use can create selection pressure leading to emergence of resistance and possible transmission of drug-resistant bacteria or resistance genes from non-human sources to humans.
Amphenicols	Enterobacteriaceae Staphylococci *Salmonella* spp. *Campylobacter* spp.	• Chloramphenicol second line antimicrobial. • Broad spectrum including both Gram-positive and Gram-negative bacteria. • Antimicrobial which is mainly used in low and middle income countries for treatment of typhoid. • Chromosomal mutations as well as horizontal gene transfer. • Predominant mechanism of resistance enzymatic inactivation (cat). • Resistance can also be due to exporter genes (*cmlA*, *fexA*, *fexB*, and *floR)*, as well as the MDR ene *cfr* that confers resistance to phenicols as well as lincosamides, oxazolidinones, pleuromutilins, and streptogramin A. • ABC transporter gene, *optrA*, confers resistance to phenicols and oxazolidinones, in *Enterococcus* and *Staphylococcus* spp. • Both *cfr* and *optrA* confer transferable resistance to linezolid. • *optrA* also confers resistance to tedizolid.
Cephalosporins, 1st- and 2nd-	Enterobacteriaceae	• 1st-generation cephalosporins have good activity against Gram-positive bacteria, e.g.

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
generation, and cephamycins	MSSA (Methicillin-susceptible *Staphylococcus aureus*)	for treatment of MSSA and streptococci. • Modest activity against Gram-negative bacteria. • Use in humans include skin and soft tissue infections, streptococcal pharyngitis, bacteraemia, endocarditis and others. • 2nd - generation cephalosporins have less activity against Gram-positive bacteria and more towards Gram-negative bacteria. • Cephamycins have also anaerobic activity. • 1st- and 2nd-generation cephalosporins recommended and most used antibiotics for surgical prophylaxis. • Resistance mainly due to β-lactamases (ESBLs and AmpC) and decreased ability to bind to penicillin-binding proteins (PBPs) (e.g *mec*A). • ESBL genes often located on plasmids. • *ampC* genes commonly located on the chromosome but may also be found on plasmids. • Some of these *ampC* genes are expressed inducibly; others constitutively. • Cephamycins (cefoxitin and cefotetan) not hydrolyzed by majority of ESBLs but by AmpC-type β-lactamases.
Cyclic polypeptides (bacitracin)	N/A	• Bacitracin mostly used topically for superficial skin infections caused by Gram-positive bacteria. • Four bacitracin resistance mechanisms: a) *bacA* gene, renamed to uppP, in *S. aureus, S. pneumoniae*, *E. faecalis*, b) *bcrABC* genes, c) overproduction of undecaprenol kinase, d) mutations inhibiting synthesis of exopolysaccarides. • *bcrAB*D operon located on plasmids in *C. perfringens* and *E. faecalis* as part of a MDR encoding conjugative plasmid associated with high-level resistance to bacitracin in *E. faecalis* in chickens. • *E. faecalis* isolates in humans and chickens shown to have homology and thus point to zoonotic potential.
Macrolides	*Campylobacter* spp., *Staphylococcus aureus*	• In humans, macrolides are used to treat atypical community-acquired pneumonia, *H. pylori* infection (as part of triple combination therapy), *Chlamydia* infections, acute non-specific urethritis, shigellosis, salmonellosis, campylobacteriosis, and pertussis. Macrolides are also a useful alternative for treatment in patients allergic to penicillins and cephalosporins. • Mechanisms of resistance include modification of the target, drug inactivation and drug

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		efflux. Resistance conferred by chromosomal mutations as well as horizontal transfer of resistance genes (*erm*, *vga*, *lnu*, *lmr*, *cfr*). • The most common resistance mechanism is a target site modification mediated by at least 32 different rRNA methylases (*erm* genes) described in 34 bacterial genera, which reduces the binding of the macrolides, lincosamides and streptogramin B to the ribosomal target site. • Many of the *erm* genes have been identified in Gram-positive, Gram-negatives and anaerobic bacteria and can be horizontally transferred (associated with conjugative or non-conjugative transposons, which tend to reside on the chromosomes). Macrolide-resistant *Campylobacter* spp. can be transmitted from animals to humans via food of animal origin.
Lincosamides	MRSA (Methicillin-resistant *Staphylococcus aureus*)	• In humans, lincosamides (clindamycin) used to treat infections caused by anaerobic and Gram-positive bacteria, e.g. staphylococci (including MSSA, MRSA and coagulase-negative staphylococci) and streptococci. • Mechanisms of resistance include modification of the target, drug inactivation and drug efflux. • Resistance conferred by chromosomal mutations as well as horizontal transfer of resistance genes (*erm*, *vga*, *lnu*, *lmr*, *cfr*). • Most common resistance mechanism is target site modification mediated by *erm* genes described in numerous bacterial genera, which are frequently associated with mobile genetic elements, e.g. transposons and can be horizontally transferred. • Homology between animal and human isolates demonstrated. • MDR *cfr* confers resistance not only to lincosamides but also to phenicols, streptogramin A, pleuromutilins and oxazolidinones.
Nitrofuran derivatives (e.g. nitrofurantoin)	N/A	• Nitrofurantoin is one of the first choices of antimicrobials for treating uncomplicated UTI in women, including treatment of UTIs with ESBL-producing Enterobacteriaceae. • Resistance either via chromosomal mutations and also plasmid-mediated via efflux genes, e.g *oqxA/B*, which confer MDR, including to nitrofurantoin.
Nitroimidazoles	*C. difficile*	• Nitroimidazoles, mainly metronidazole and tinidazole, mostly used to treat infections caused by anaerobic bacteria. • Metronidazole considered first line therapy in the paediatric population for *Clostridioides*

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		(Clostridium) difficile (C. difficile). • In the adult population can be used for treatment of mild to moderate infections with *C. difficile* when first line therapy not available. • Nitroimidazoles also used for the treatment of certain intestinal parasites (e.g. *Giardia lamblia, Entamoeba histolytica*). • Metronidazole classified as an essential medicine by WHO and important to preserve, since widely used in humans, including surgical prophylaxis in penicillin-allergic patients. • Resistance reported worldwide but mechanisms have not been extensively studied. • *nim* genes encoding resistance in *Bacteroides* spp. found on plasmids which are highly transferable between *Bacteroides* spp. in the ecosystem, animals and humans. • *C. difficile* has mobile genetic elements that can horizontally transfer resistance; homology in genetic sequences between animals and humans. • Successful *C. difficile* clones, such as ribotype 078n found in animals and humans.
Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins)	MSSA (Methicillin-susceptible *Staphylococcus aureus*)	• Important antimicrobials for treatment of methicillin-susceptible staphylococci and syphilis. • Resistance due to importation of *mec* genes leading to changes in penicillin binding protein 2 (PBP2) and to lesser degree due to mutations in the other penicillin binding proteins. • Horizontal transfer of resistance. Predominant mechanism in staphylococci including LA-MRSA mediated by *mecA* gene. Changes in PBP2 can also be mediated by *mecC* as well as *mecB*. • *mec* gene situated in the SCC med cassette that can be transferred between *S. aureus* and coagulase-negative staphylococci. • Assessment for probability of resistance transfer and likelihood of zoonotic transfer based on *mecA*- positive staphylococci • Risk for zoonotic transfer predominantly an occupational hazard.
Pleuromutilins	MRSA (Methicillin-resistant *Staphylococcus aureus*)	• Pleuromutilins only used topically for treatment of bacterial skin infections, e.g. *S. aureus*. • Resistance derives from chromosomal mutations. • In addition, resistance genes (e.g. *vga*, *cfr*) are located on mobile genetic elements. • The *cfr* gene mediates resistance not only to pleuromutilins, phenicols, lincosamides and streptogramin A, but also to oxazolidinones.

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• Found in many bacterial species, including MRSA.
Polymyxins (e.g. colistin)	Enterobacteriaceae	• Polymyxins, most notably colistin, are antibiotics that have re-emerged for treatment of multidrug-resistant Gram- negative infections, e.g. MDR *Pseudomonas aeruginosa, Acinetobacter baumannii* and Enterobacteriaceae, usually when alternative effective therapeutic options are limited or non-existent. • Chromosomal colistin resistance increasing in most EU/EEA countries. • Resistance also due to plasmid-mediated *mcr* gene reported globally from animals, food products, the environment and as well in human clinical and non-clinical (screening) specimens. • Presence of horizontally transferable colistin resistance in food animals, food products, the environment, paired with high rates of *in vitro* transfer between bacteria, worrisome for human medicine, as presence confers full resistance to colistin, rendering bacteria pandrug-resistant and likely resulting in poor patient outcomes. • Further studies needed to evaluate direct transfer of *mcr* genes from food animals and food to humans.
Pseudomonic acid	MRSA (Methicillin-resistant *Staphylococcus aureus*)	• Mupirocin first line antimicrobial available for decolonisation of *Staphylococcus aureus* (MSSA and MRSA) in humans and therefore, needs to be preserved. • *Stapylococcus aureus* decolonisation shown to significantly reduce morbidity and mortality in patient who undergo certain types of surgery. • Clonal transfer, including Livestock Associated (LA)-MRSA and horizontal gene transfer (mupA, mupB) shown.
Steroid antibacterials (fusidic acid)	MRSA (Methicillin-resistant *Staphylococcus aureus*)	• Fusidic acid mainly used for combination therapy in humans (systemic treatment) of staphylococcal infections or topically for treatment of skin or eye infections. • Mutational resistance (*fusA)*, genes on mobile elements (*fusB, fusC*), as well as spread of resistance through successful clones of staphylococci described.
Streptogramins	Enterococcus spp. (glycopeptide-resistant *E. faecium*) and MRSA (Methicillin-resistant	• Streptogramin family of antimicrobials consists of mixture of two groups of substances acting synergistically: streptogramin A and streptogramin B. Quinupristin-dalfopristin and pristinamycin could theoretically be alternatives in human medicine to treat glycopeptide-resistant enterococci and MRSA infections, but are presently considered

Antimicrobial class**	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
	Staphylococcus aureus)	obsolete. • Resistance genes (e.g. *erm*, *cfr*, *vga*, *lsa*, *sal(A)*) described and some of these in multiple bacterial species including staphylococci and enterococci. • Clonal transfer (LA-MRSA) as well as horizontal transfer of genes described. MDR genes: cfr, *lsaA* and *lsaE* of particular concern. • *cfr* gene mediates resistance not only to streptogramin A, phenicols, lincosamides and pleuromutilins, but also to oxazolidinones, • Found in many bacterial species, including MRSA.
Sulfonamides, dihydrofolate reductase inhibitors and combinations	Enterobacteriaceae, *Staphylococcus aureus*	• These combinations used for the treatment of UTIs, bronchitis, otitis media, pneumonia, staphylococcal (MSSA and MRSA) skin infections and the prevention and treatment of *Pneumocystis (Carinii) Jiroveci* pneumonia and traveller's diarrhoea. • Resistance to both has spread extensively and rapidly. Mainly due to the horizontal spread of resistance genes, expressing drug-insensitive variants of the target enzymes dihydropteroate synthase and dihydrofolate reductase, for sulfonamide and trimethoprim, respectively. • Chromosomal resistance as well as transfer by mobile genetic elements (*sul1*, *sul2*, *sul3*, *dfr*). • *sul1* gene is part of class 1 integrons and thus often associated with other resistance genes.

3.4.2. Mechanisms for transfer of resistance genes and resistant bacteria

Based on the literature review summarised in table 2, and with reference to Table 3 of the first AMEG report, the information available on various ways of transfer of resistance were defined and scored (Table 3) based on the criteria below:

Transmission of resistance through successful clone(s). Defined as the vertical transfer of a resistance gene through the parent to the daughter bacterium in a successful, highly disseminated drug-resistant clone of bacteria through a bacterial population, e.g. *E. coli* ST131 clone, MRSP CC(71) clone, MRSA ST398 clone. Probability (1 to 3):

1. no vertical transmission of gene described as associated with a particular successful drug-resistant clone;
2. gene is exclusively on the core bacterial chromosome in a particular successful drug-resistant clone (e.g. ST131);
3. gene is not only on a mobile genetic element, e.g. plasmid, but is also part of a highly-transmissible, successful drug-resistant clone (e.g. ST131)

Horizontal transmission Defined as a transfer of resistance gene by means of mobile genetic elements. Probability (1 to 3):

1. no mobile genetic element described;
2. gene is exclusively on the core bacterial chromosome but can be mobilised;
3. gene is on a mobile genetic element, e.g. plasmid, transposon.

Co-selection of resistance. Defined as a type of resistance where use of one antimicrobial favours the occurrence of resistance to other antimicrobial classes or sub-classes with a different spectrum. In this table, co-selection is limited to situations when different resistance genes are co-located on one mobile genetic element or are located in a genetic environment together with other resistance genes in such a way that there is a potential for mobilisation (e.g. IS-elements or resistance islands). A special case when one gene mediates resistance to several unrelated antimicrobial classes is also included. Probability (1 to 3):

1. no linkage of the gene with other resistance genes has been described, nor is it located in a genetic environment favouring mobilisation of the former gene and other resistance genes;
2. **either** linkage of the gene with other resistance genes on a mobile genetic element **or** location of the gene in a genetic environment favouring mobilisation of the gene together with other resistance genes have been described;
3. **both** linkage of the gene with other resistance genes on a mobile genetic element **and** location of the gene in a genetic environment favouring mobilisation of the gene together with other resistance gene has been described.

Transmission of resistance through zoonotic or commensal food-borne bacteria. Defined as transmission of resistance through zoonotic pathogens (e.g. *Salmonella* spp., *Campylobacter* spp., MRSA, *E. coli* (VTEC/STEC) or transmission of resistance through commensal food-borne bacteria (e.g. *E. coli*, *Enterococcus* spp.). Probability (1 to 3):

1. no transmission of resistance through zoonotic pathogens or commensal food-borne bacteria;
2. **either** transmission of resistance through zoonotic pathogens **or** through commensal food-borne bacteria;
3. **both** transmission of resistance through zoonotic pathogens **and** through commensal food-borne bacteria.

Similarity of resistance: Genes: defined as a similar resistance gene detected in bacterial isolates of animal and human origin; Mobile genetic elements: defined as a similar resistance-conferring mobile genetic element detected in bacterial isolates of animal and human origin; Drug-resistant bacteria: defined as a similar bacterium harbouring a resistance gene (either chromosomally or mobile genetic element-encoded) of animal and human origin. Probability (1 to 3):

1. unknown resistance similarity;
2. resistance genes have been shown to be similar between animals and humans;
3. **both** resistance genes **and** mobile genetic elements have been shown to be similar between animals and humans;
4. resistance genes, mobile genetic elements and drug-resistant bacteria have **all** been shown to be similar between animals and humans.

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663 **Table 3.** Classification of antimicrobial classes according to their likelihood for transfer of resistance genes and resistant bacteria via different mechanisms.
664 For definitions of criteria for the different columns please see above.

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
Amidinopenicillins	1	1	1	1	1	EMA/CVMP/AWP (2018a) Frimodt-Moller (2017) Kahlmeter and Poulsen (2012) Poulsen et al. (2013) Thulin et al. (2015) Thulin et al. (2017)
Aminoglycosides	3	3	3	3	3	Chen et al. (2007) Davis et al. (2010) Deng et al. (2011) Du et al. (2009) EMA/CVMP/AWP (2018b) Gonzalez-Zorn et al. (2005) Hopkins et al. (2010b) Liu et al. (2008)
Aminopenicilins including β-lactamase inhibitors combinations	3	3	3	3	3	EMA/CVMP/AWP (2018a)
Amphenicols	3	3	3	3	4	Long et al. (2006) Schwarz et al. (2004) Shen et al. (2013) Wang et al. (2015) Zhao et al. (2016)
Carbapenems and other penems	3	3	3	2	2	Dortet et al. (2014) EFSA BIOHAZ Panel

[††] Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances are provided in Annex A2, Table A2.

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
						(2013) Le Hello et al. (2013)
Cephalosporins: 1st - and 2nd-generation and cephamycins	3	3	3	3	3	Gazouli et al. (1996) Knothe et al. (1983) Mulvey et al. (2005)
Cephalosporins: 3rd-and 4th-generation	3	3	3	3	4	Catry et al. (2010) EFSA BIOHAZ Panel (2011) EMA/CVMP (2012) EMEA/CVMP/SAGAM (2009) Kluytmans et al. (2012) Liebana et al. (2013)
Cephalosporins: Other cephalosporins and penems (ATC code J01DI)	1	1	1	1	1	Casapao et al. (2012) Curcio (2014) Pillar et al. (2008) Steed and Rybak (2010)
Cyclic polypeptides (bacitracin)	3	3	3	3	4	Chancey et al. (2012) Charlebois et al. (2012) Chen et al. (2016) Han et al. (2015) Manson et al. (2004) Olsen et al. (2012) Poulsen et al. (2012) Wang et al. (2014)
Glycopeptides	2	2	2	2	2	Braga et al. (2013) Rice (2012) Silveira et al. (2013)
Glycylcyclines	2	1	2	1	1	EMA/AMEG (2013)

Antimicrobial classes, subclasses, substances††	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
Lincosamides	3	3	3	3	3	EMA/CVMP/SAGAM (2011)
Lipopeptides	1	1	1	1	1	Bayer et al. (2013) Kelesidis and Chow (2014) Kelesidis (2015)
Macrolides (including ketolides)	3	3	3	3	2	EMA/CVMP/SAGAM (2011) Pyorala et al. (2014) Roberts (2008) Roberts (2011)
Monobactams	3	3	3	3	2	Catry et al. (2010) EFSA BIOHAZ Panel (2011) EMA/CVMP (2012) EMEA/CVMP/SAGAM (2009) Kluytmans et al. (2012) Liebana et al. (2013)
Nitrofurantoins	3	3	3	3	3	Chen et al. (2012) García et al. (2017) Giske (2015) Ho et al. (2016) Li et al. (2013) Liu et al. (2013) Liu et al. (2018) Osei Sekyere (2018) Perez et al. (2013) Sandegren et al. (2008)
Nitroimidazoles	3	3	3	3	4	Álvarez-Pérez et al. (2014)

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
						Álvarez-Pérez et al. (2017) Andrés-Lasheras et al. (2018) Baines et al. (2008) Brazier et al. (1999) Dingsdag and Hunter (2017) Freeman et al. (2015) Knetsch et al. (2014) Kuijper and Wilcox (2008) Löfmark et al. (2005) Miyamoto et al. (2013) Nguyen and Vedantam (2011) Nikolich et al. (1994) Shoemaker et al. (2001) Snydman et al. (2016) Peng et al. (2017) Pirš et al. (2013) Snydman et al. (2015)
Oxazolidinones	3	3	2	1	2	Bonilla et al. (2010) Diaz et al. (2012) Endimiani et al. (2011) Gu et al. (2012) Liu et al. (2012) Mendes et al. (2014) Sanchez Garcia et al. (2010)

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins)[‡‡]	3	2	2	2 [§§]	4	Becker et al. (2018) Peeters et al. (2015) Price et al. (2012) Ward et al. (2014)
Penicillins: Natural, narrow-spectrum penicillins (β-lactamase-sensitive penicillins), carboxypenicillins and ureidopenicillins	3	1	2	2	2	Bush and Jacoby (2010) Jacoby (2012) U.S. National Library of Medicine (last accessed: 2018)
Phosphonic acid derivates (e.g. fosfomycin)	3	3	2	1	1	Karageorgopoulos et al. (2012) Oteo et al. (2009) Pérez et al. (2014) Wachino et al. (2010)
Pleuromutilins	2	3	2	3	4	Hauschild et al. (2012) Kadlec and Schwarz (2009) Kadlec et al. (2010) Kehrenberg and Schwarz (2006) Kehrenberg et al. (2009) Mendes et al. (2011) Shen et al. (2013) Wendlandt et al. (2013b)
Polymyxins (e.g. colistin)	3	1	2	3	3	EMA/AMEG (2016) Halaby et al. (2013) Monaco et al. (2014)
Pseudomonic acid	3	3	3	3	4	Desroches et al. (2013)

[‡‡] The assessment is based on the most frequent gene coding for resistance against antistaphylococcal penicillins (*mecA*)
[§§] Foodborne transmission has been implicated but is at the present time considered to be very rare (EFSA risk assessment)

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
						Hurdle et al. (2005) Kadlec et al. (2012) Malik et al. (2005) Patel et al. (2009) Rahman et al. (1989) Rossi et al. (2016) van Duijkeren et al. (2011) Wendlandt et al. (2013a) Werckenthin et al. (2001)
Quinolones (Fluoroquinolones and other quinolones)	3	3	2	3	2	Aldred et al. (2014) EMA/CVMP (2010) EMEA/CVMP/SAGAM (2007) Poirel et al. (2008)
Rifamycins	2	3	2	2	2	Arlet et al. (2001) Floss and Yu (2005) Tupin et al. (2010)
Riminofenazines	1	1	1	1	1	Grosset et al. (2012) Hartkoorn et al. (2014)
Steroid antibacterials (fusidic acid)	3	3	3	1	4	Bulajic et al. (2017) Chen et al. (2010) Chen et al. (2014) Clark et al. (2015) Loeffler et al. (2008) Nemeghaire et al. (2014) Norström et al. (2009) Obaidat et al. (2018) Sala et al. (2016) Sousa et al. (2017)

Antimicrobial classes, subclasses, substances[††]	Transmission of resistance through successful clone(s)	Horizontal transmission of resistance	Co-selection of resistance	Transmission of resistance through zoonotic or commensal food-borne bacteria	Similarity of resistance	References
						Ugwu et al. (2015)
Streptogramins	3	3	3	2	3	EMA/CVMP/SAGAM (2011) Hershberger et al. (2004) Pyorala et al. (2014) Simjee et al. (2006) Wendlandt et al. (2012) *See also pleuromutilins*
Sulfonamides, dihydrofolate reductase inhibitors and combinations	3	3	3	3	3	Estrada et al. (2016) Hennequin et al. (2018) Hsu et al. (2014) Sköld (2000) Sköld (2001) Vila-Costa et al. (2017)
Sulfones	1	1	1	1	1	Veziris et al. (2013)
Tetracyclines	3	3	3	3	4	Butaye et al. (2003) Butaye et al. (2006) Chopra and Roberts (2001)
Drugs used solely to treat tuberculosis or other mycobacterial diseases (e.g. isoniazid)	2	2	2	2	2	Ando et al. (2014) Bernardes-Genisson et al. (2013) Gagneux (2012)

4. Categorisation

The new AMEG categorisation builds on the conclusions of the first AMEG report and takes into account recent information and assessments. The criteria for the categorisation have been refined as discussed in Chapter 3, taking as an additional criterion the availability of alternative antimicrobials in veterinary medicine with lower AMR risk to animal and public health. Considering use of the new criterion and taking account of the recommendations included in the reflection papers recently published by the EMA on the use of aminopenicillins and aminoglycosides, an additional category has been included, so that there are now four categories, A to D. For consistency with other existing classifications at the international level, the order of the categories, in terms of level of risk, has now been reversed with the lowest risk category last.

The updated criteria are as follows:

1. *If the (sub)class or group is authorised for use as a veterinary medicine*
2. *The importance of the (sub)class or group to human medicine according to the WHO ranking and taking into account the EU situation (Tables 2 and 4).*
3. *The <knowledge of factors influencing the> likelihood and possible consequences of AMR transfer from animals to humans. In the new categorisation individual mechanisms of resistance have been considered more specifically for e.g. those genes associated with mobile multiresistance e.g. 'cfr' (Tables 2 and 3).*
4. *The availability of alternative antimicrobial (sub)classes in veterinary medicine with lower AMR risk to animal and public health (Table 4).*

A discussion of the updated criteria is given in sections 3.3 and 3.4 of the report. With regard to the route of administration, this has not been included as a criterion for the categorisation for reasons discussed in 3.3.1. The exception is for steroid antibacterials (fusidic acid) where it was taken into account that this class is only administered locally in animals.

In this updated advice, all antimicrobial classes were considered for categorisation and a summary of the evidence supporting the application of the criteria and the overall rationale for the categorisation have been added in Table 4. Supporting evidence is derived from published literature, reflection papers on individual antimicrobial classes published by CVMP, and expert opinion, as documented in tables 2, 3 and 4 of this report. The categorisations of WHO and OIE, and further WHO documents were also taken into account. For classes in Category A, the only consideration was the absence of authorisation of a substance from the class in a veterinary medicine. The final categorisation for other (sub)classes was based on the judgement of the AMEG in weighting the remaining three criteria, although the key considerations for each category are stated in sections 4.1 to 4.4, below.

The categorisation should be understood to operate at the level of (sub)classes. Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances included in each AMEG category are provided in Annex A2, Table A2.

Individual substances not authorised as veterinary medicine themselves, but which belong to a class containing molecules that are authorised as veterinary medicines, should be considered as having the same categorisation as the parent (sub)class. Although the categorisation may be used to help with

prescribing decisions made under the "cascade"[9], it cannot take account of all the principles to be considered and importantly the welfare of the individual animal(s). Therefore the categorisation does not override the complete rules of the prescribing "cascade" in which AMR risk is a factor to consider alongside other criteria as laid out in legislation.

Risk management measures to be applied to each category

It should be noted that under the new regulation on veterinary medicines (Official Journal of the European Union, 2019) certain important provisions are included regarding the use of antimicrobials in animals in order to address the risks to public and animal health from AMR:

- A list is to be established of antimicrobials (or groups of antimicrobials) to be reserved for treatment of certain infections in humans only (Article 32). These substances shall not be used under the "cascade" to treat animals (Article 111).
- A list is to be established of antimicrobials that shall not be used under the "cascade", or shall only be used under the "cascade" subject to conditions (Article 111)
- The use of antibiotic medicinal products for prophylaxis is limited to administration to individual animals only, in exceptional cases, when the risk of infection is very high and the consequences are likely to be severe (Article 111)
- Antimicrobial medicinal products shall only be used for metaphylaxis when the risk of spread of infection in the group of animals is high and where no appropriate alternatives are available (Article 111).

The risk management measures applied to the individual AMEG categories should be seen as being complementary to these provisions. As the categorisation is made at the level of (sub)classes of antimicrobials, risk management measures can be indicated at high level, only. These measures are stated *in italics* for each category below. Further examples of risk management measures that have been applied to certain classes of products (e.g. under CVMP referrals) are available in the Annex to the Commission's Guidelines for the prudent use of antimicrobials in veterinary medicine (European Commission, 2015). Restrictions on the use of certain antimicrobials may also be applied by individual member states on their territory.

4.1. Category A: "Avoid"

A number of the antimicrobial (sub)classes listed are not authorised in veterinary medicine and these are presented separately as Category A.

Risk management measures: In the absence of established maximum residue limits for foodstuff of animal origin, use of these classes of AM in food-producing animals is prohibited and they may only be administered to individual companion animals exceptionally, in compliance with the prescribing "cascade".

The extent of use of these classes, and hence overall selection pressure for AMR, would be low provided the restrictions detailed in the prescribing "cascade" are complied with.

[9] Articles 10 and 11 of Directive 2001/82/EC. The prescribing "cascade" is a provision in legislation which, when no suitable authorised product is available and under exceptional circumstances, allows a veterinarian to use a veterinary medicinal product outside of its authorised conditions of use, or to use an unauthorised medicine, according to given criteria.

In the event of a future Marketing Authorisation application for a veterinary medicinal product containing a substance in this category, the benefits of use of the proposed veterinary medicine in animals are considered alongside a risk assessment that takes account of the importance of the substance to human health and the risk of transfer of resistance of relevance for public health from treated animals to humans.

4.2. Category B: "Restrict"

Classes in HPCIA (see chapter 3.2.1.1. for WHO criteria) are included in Category B with the exception of macrolides and those (sub)classes which are not authorized in veterinary medicine in the EU.

Category B includes quinolones (fluoroquinolones and other quinolones), 3rd- and 4th-generation cephalosporins and polymyxins.

Risk to public health resulting from veterinary use needs to be mitigated by specific restrictions.

Risk management measures: These antimicrobials should be considered only for the treatment of clinical conditions when there are no alternative antimicrobials in categories C or D that could be effective. Especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible[10].

4.3. Category C: "Caution"

Antimicrobials for which there are alternatives in human medicine for their indications but which comply with one or both of the following criteria:

- For the veterinary indication under treatment, there are few or no alternatives belonging to Category D. Some examples of these indications are given in Table 4, alongside the relevant (sub)class.
- The antimicrobial selects for resistance to a substance in Category A through specific multiresistance genes

Antimicrobials placed in this category present a higher AMR risk for human and/or animal health than antimicrobials placed in Category D, as assessed by AMEG.

Risk management measures: These antimicrobials should only be used when there is no substance in Category D that would be effective.

4.4. Category D: "Prudence"

Category D includes antimicrobials where there are alternative treatments in human and veterinary medicine for their indications and that do not select for resistance to Category A through specific multiresistance genes.

[10] In accordance with the draft "Guideline on the summary of product characteristics for veterinary medicinal products containing antimicrobial substances" (EMA/CVMP/383441/2005-Rev. 1), the following recommendation is made for all antimicrobial products: *'Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target bacteria at farm level, or at local/regional level.'*

Antimicrobials placed in this category present a lower AMR risk than antimicrobials placed in Category C as assessed by AMEG and should be used where possible as first line treatments.

Risk management measures: These antimicrobials are not devoid of negative impact on resistance development and spread. To keep the risk from use of these antimicrobial classes as low as possible it is important that responsible use principles are complied with in everyday practice (EMA/EFSA, 2017; Official Journal of the European Union, 2015). Unnecessary use and unnecessarily long treatment periods should be avoided and group treatment restricted to situations where individual treatment is not feasible.

783 **Table 4.** AMEG Categorisation table
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Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
Amidinopenicillins	Multidrug-resistant (MDR) Enterobacteriaceae	HIA	N/D	Not approved[15]	Not applicable	**N/A**	**A**	See chapter 4.1. For these antimicrobials, if at any time in the future an approval is granted for use in veterinary medicine, the antimicrobial class should then be categorised according the defined criteria
Carbapenems and other penems	MDR Gram-negative bacteria (e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae)	CIA	N/D			**3**	**A**	
Cephalosporins: Other cephalosporins and penems (ATC code J01DI)	Staphylococci (e.g. MRSA); MDR *Streptococcus pneumoniae*	HPCIA	N/D			**3**	**A**	
Glycopeptides	Staphylococci (e.g. MRSA), MDR *Streptococcus pneumoniae, MDR streptococci*	HPCIA	N/D			**3**	**A**	
Glycylcyclines	MDR Gram-negative bacteria, Staphylococci (e.g. MRSA)	CIA	N/D			**3**	**A**	
Lipopeptides	Staphylococci (e.g. MRSA), MDR *Enterococcus* spp., *Streptococcus pneumoniae*	CIA	N/D			**3**	**A**	
Monobactams	MDR Gram-negative	CIA	N/D			**3**	**A**	

[11] Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances included in each AMEG category are provided in Annex A2, Table A2.
[12] WHO categorisation: HPCIA>CIA>HIA>IA
[13] OIE categorisation: VCIA>VHIA>VIA
[14] For polymyxins, the revision of 2016 has been taken into account
[15] Approved means approved in at least one Member State

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
	bacteria, especially those producing metallo-beta-lactamases (MBL)							
Oxazolidinones	Staphylococci (e.g. MRSA), MDR *Enterococcus* spp. (e.g. VRE), MDR Mycobacterium tuberculosis, MDR *Streptococcus pneumoniae*	CIA	N/D			**3**	**A**	
Penicillins: carboxypenicillins and ureidopenicillins combinations with β-lactamase inhibitors	MDR *Pseudomonas* spp., MDR Enterobacteriaceae	CIA	N/D			**3**	**A**	
Phosphonic acid derivates (e.g. fosfomycin)	MRSA, penicillin-non-susceptible *S. pneumoniae*, MDR *E. coli* (and other susceptible Enterobacteriaceae), MDR enterococci (e.g. VRE)	CIA	N/D			**3**	**A**	
Pseudomonic acid	MDR staphylococci (e.g. MRSA)	HIA	N/D			**N/A**	**A**	
Riminofenazines	Leprosy, MDR *Mycobacterium tuberculosis*	HIA	N/D			**3**	**A**	
Streptogramins	Staphylococci (e.g. MRSA), MDR *Enterococcus* spp. (e.g. VRE)	HIA	VIA			**N/A**	**A**	
Sulfones	Leprosy	HIA	N/D			**3**	**A**	
Drugs used solely to treat tuberculosis or other mycobacterial	Tuberculosis and other *Mycobacterium* spp. diseases	CIA	N/D			**3**	**A**	

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
diseases								
Cephalosporins, 3rd- and 4th-generation	Acute bacterial meningitis and disease due to *Salmonella* spp. in children, gonococcal infections	HPCIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in individual animals only, for systemic and local treatment (recommendations of restrictions apply)	Among few alternatives for treatment of severe (life threatening) sepsis in various animals (Enterobacteriaceae with confirmed or suspected resistance to antimicrobials in Category C and D) Among few alternatives for treatment of respiratory tract infections where AMR to antimicrobials in Category C and D has been confirmed	**2**	**B**	See chapter 4.2.
Polymyxins (e.g. colistin)	MDR *Pseudomonas aeruginosa, MDR Acinetobacter baumannii* and MDR Enterobacteriaceae (*Escherichia coli, Klebsiella pneumoniae*)	HPCIA	VHIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments (recommendations of restrictions apply).	Among few alternatives for treatment of colibacillosis (e.g. weaning diarrhoea in pigs) (*E. coli* with resistance to Category C and D).	**2**	**B**	
Quinolones (fluoroquinolones and other quinolones)	*Campylobacter* spp., *Salmonella* spp. invasive infection, MDR *Shigella* spp., *Pseudomonas aeruginosa, Streptococcus pneumoniae* and MDR tuberculosis	HPCIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatment (recommendations of restrictions apply).	Among few alternatives for treatment of diarrhoeas in piglets (*E. coli* with resistance to Category C and D). Among few alternatives for treatment of severe (life threatening) sepsis in various animals (Enterobacteriaceae with confirmed or suspected resistance to antimicrobials in Category C and D) Few alternatives for treatment of e.g. *Aeromonas salmonicida* and *Flavobacterium* spp. in farmed fish (older quinolones)	**2**	**B**	
Aminoglycosides and aminocyclitol	Enterococcal endocarditis, MDR Gram-negative bacteria	CIA/IA	VCIA	Approved for use in food-producing and companion animals. Formulations for use	Among few alternatives for treatment of weaning diarrhoea, some alternatives	**2**	**C**	Aminoglycosides, including streptomycin are critically important in human

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
	(particularly Enterobacteriaceae and *Pseudomonas* spp.), MDR tuberculosis			in group and individual animals, for systemic and local treatments.	are Category B. Few alternatives for treatment of infections with *Pseudomonas* spp. Few alternatives for MDR Enterobacteriaceae, some alternatives are Category B.			medicine. There is a high potential for transmission of AG-resistance determinants between animals and humans. But the risk to human health is lower compared to antimicrobials in Category B. Spectinomycin presents a lower risk than other AGs. See also CVMP reflection paper on Aminoglycosides (EMA/CVMP/AWP, 2018b).
Aminopenicillins in combination with β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid, co-amoxiclav)	Enterobacteriaceae	CIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.	Few alternatives for urinary tract infections in dogs, caused by bacteria that are resistant to alternatives in Category D and some in C Few alternatives for treatment of skin infections with staphylococci in dogs.	**2**	**C**	Aminopenicillins combined with beta-lactamase inhibitors are critically important in human medicine. Amoxicillin-clavulanate has a wider spectrum and thus it is likely that it has higher chance to select multidrug resistant organisms, ESBLs and AmpC compared to aminopenicillins alone. There are few or no antimicrobial alternative treatments presenting a lesser risk available for certain indications in veterinary medicine. See also CVMP reflection paper on Aminopenicillins (EMA/CVMP/AWP, 2018a).
Amphenicols (florfenicol & thiamphenicol)	MDR Enterobacteriaceae	HIA	VCIA	Approved for use in food-producing animals as formulations for use in group and individual animals, for	Few alternatives for treatment of e.g. *Aeromonas salmonicida* and *Flavobacterium* spp in	**N/A**	**C**	Antimicrobial class with high probability of resistance transfer. May lead to resistance to last resort

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
				systemic and local treatments. For use in companion animals as formulations for local treatments.	farmed fish, one alternative in Category B. Among few alternatives for treatment of respiratory tract infections caused by bacteria resistant to alternatives in Category D.			antimicrobials class. Several genes can code individually for resistance to amphenicols. Of special concern is the acquisition of either the *cfr* or *optr*A genes, since these also encode for resistance to antimicrobial classes of critical importance to human medicine (e.g. oxazolidinones, streptogramin A). However, currently the *cfr* or *optr*A genes are considered at a low prevalence in European animal bacterial isolates. Should this situation change to an increased prevalence then the classification of this antimicrobial class may need to be re-assessed. Few or no antimicrobial alternative treatments presenting a lesser risk are available for certain indications in veterinary medicine
Cephalosporins, 1st- and 2nd-generation and cephamycins	Enterobacteriaceae, MSSA, surgical prophylaxis	HIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in individual animals, for systemic and local treatments.	Few alternatives for treatment of skin infections with staphylococci in dogs	**N/A**	**C**	May lead to resistance to last resort antimicrobial class. However, few or no antimicrobial alternatives treatment presenting a lesser risk are available for certain indications in veterinary medicine.
Macrolides	*Legionella* spp., *Campylobacter* spp., invasive MDR *Salmonella* spp. and *Shigella* spp. infections	HPCIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.	Among few alternative antimicrobials for treatment of haemorrhagic digestive disease in pigs (*Lawsonia intracellularis)*. Important for treatment of mycoplasma	**1**	**C**	Antimicrobial class with high probability of resistance transfer. For the treatment of zoonotic pathogens (mainly *Campylobacter* spp.) in

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
					infections in pigs and poultry. Newer macrolides are among few alternatives for treatment of respiratory tract infections caused by bacteria that are resistant to alternatives in Category D. Some alternatives are Category B. Among few alternatives for treatment of foot-rot in sheep and goats.			humans, there are alternative antimicrobials such as fluoroquinolones, although fluoroquinolone resistance in *Campylobacter spp.* is high in most EU/EEA countries. The *erm* genes are considered to be of low prevalence in animal isolates of these pathogens in the EU. Should the occurrence of resistance increase the categorisation of this antimicrobial class may need to be re-assessed. Few or no antimicrobial alternative treatments presenting a lesser risk are available for certain indications in veterinary medicine.
Lincosamides	Staphylococci (e.g. MRSA)	HIA	VHIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.		**N/A**	**C**	Cross resistance between macrolides, lincosamides and streptogramins.
Pleuromutilins	*Staphylococcus* spp. (e.g. MRSA)	IA	VHIA	Approved for use in food-producing species for group and individual animal treatments.	Few or no alternatives for treatment of infections with *Brachyspira* spp. in pigs	**N/A**	**C**	Antimicrobial class with high probability of resistance transfer. May lead to resistance to last resort antimicrobials class especially to linezolid (oxazolidinone). However, few or no antimicrobial alternative treatments presenting a lesser risk is available in veterinary medicine.
Rifamycins	Mycobacterial diseases including tuberculosis	CIA	VHIA	Approved for use in food-producing species for local	Few treatment options for *Rhodococcus equi* pneumonia	**1**	**C**	Rifampin (rifampicin) continues to be part of the

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
	Adjunct treatment for prosthetic staphylococcal infections, prophylaxis for exposure to *N. meningitides*			treatment (intramammary formulations).	in horses (in combination with a macrolide)			essential combination antimicrobial treatment for *Mycobacterium tuberculosis* infections in human medicine. No hazard of zoonotic importance is identified, and extent of use in vet medicine is low. The concerns of its use in veterinary medicine are for the routine off-label use for oral treatment (and sometimes prophylaxis) of *Rhodococcus equi* infections in foals[16]. Resistance to rifampin develops rapidly and responsible use is essential.
Aminopenicillins, without β-lactamase inhibitors	*Streptococcus* spp., *Enterococcus* spp., *E. coli*, *Proteus mirabilis*	CIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.	Very important for treatment of many diseases in a broad range of animal species.	**2**	**D**	See chapter 4.4. CIA in human medicine due to high extent of use, although alternatives of last resort are available. AMR at high level in some organisms due to extensive use for many decades in both humans and animals. In case of further evidence indicates that veterinary use of aminopenicillins poses an added threat to public health due to animal-to-human resistance transfer, it could then be considered if a distinction in the categorisation should be

[16] List of substances essential for the treatment of *equidae*, Official Journal of the European Union. 2013. Commission Regulation (EU) No 122/2013 of 12 February 2013 amending Regulation (EC) No 1950/2006 establishing, in accordance with Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to veterinary medicinal products, a list of substances essential for the treatment of equidae. In http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1416502774573&uri=CELEX:32013R0122.

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
								made between straight aminopenicillins and narrow-spectrum penicillin See also CVMP reflection paper on Aminopenicillins (EMA/CVMP/AWP, 2018a). Narrow spectrum penicillins with a lower risk of AMR selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
Cyclic polypeptides (bacitracin)	Gram-positive bacteria (topical use)	IA	VHIA	Approved for use in food-producing animals. Formulations for use in group and individual animals, for local treatments.		**N/A**	**D**	See chapter 4.4.
Nitrofuran derivatives (e.g. nitrofurantoin)	Enterobacteriaceae (uncomplicated urinary tract infections)	IA	N/D	Approved for use in companion animals only.		**N/A**	**D**	
Nitroimidazoles	Anaerobic bacteria, intestinal parasites, *C. difficile*	IA	N/D	Approved use in companion animals. Formulations for use in individual animals for systemic treatment.	Among the few alternatives available for treatment of anaerobic infections in non-food producing animals.	**N/A**	**D**	
Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins)	*Staphylococcus aureus* (e.g. MSSA)	HIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in individual animals, for local treatments.		**1**	**D**	
Penicillins: Natural, narrow spectrum penicillins (β-lactamase-sensitive penicillins)	*Streptococcus* spp., *Enterococcus* spp.	CIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.		**1**	**D**	

Antimicrobial classes, subclasses, substances[11]	Examples of important indications in human medicine	WHO[12]	OIE[13]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[14]	
Steroid antibacterials (fusidic acid)	Staphylococci (e.g. MSSA)	HIA	VIA	Approved for use in companion animals, for use in individual animals for local treatment.		**N/A**	**D**	
Sulfonamides, dihydrofolate reductase inhibitors and combinations	Enterobacteriaceae, Staphylococci (e.g. MRSA)	HIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.	No alternatives for treatment of certain protozoal infections.	**N/A**	**D**	
Tetracyclines	*Brucella* spp.	HIA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual animals, for systemic and local treatments.	No alternatives for treatment of heartwater (*Ehrlichia ruminantium*) and anaplasmosis, although disease with low incidence Fewer alternatives for vector-borne diseases in dogs and cats.	**1**	**D**	

Abbreviations in Table 4:

WHO categorisation:

HPCIA: Highest Priority Critically Important Antimicrobials
CIA: Critically important Antimicrobials
HIA: Highly Important Antimicrobials
IA: Important Antimicrobials

OIE categorisation:

- VCIA: Veterinary Critically Important Antimicrobials
- VHIA: Veterinary Highly Important Antimicrobials
- VIA: Veterinary Important Antimicrobials

N/A: not applicable
N/D: not defined

5. Use of AMEG Categorisation

The AMEG has refined the ranking of the antimicrobials by adding an additional category. To harmonise with other lists, the order of the categories has been reversed compared to the first AMEG report. Additionally, in the current scientific advice, those antimicrobial classes which were not included in the previous ranking are also categorised. According to the revised criteria applied for the new antimicrobial categorisations described in chapter 3.3, not only the importance of the antimicrobial class in human medicine and knowledge of factors influencing the likelihood of resistance transfer are considered, but emphasis is now also placed on the importance and the availability of alternatives antimicrobials in veterinary medicine. These additional considerations make the methodology different from other categorisations made by international institutions (e.g. WHO, OIE) and thus the final ranking may differ. It should be noted that the proposed categorisation takes into account both the WHO and OIE lists of CIAs, thereby allowing an appropriate balance between animal health needs, human health needs and public health considerations.

The AMEG proposes to classify antimicrobials in four different categories, from A to D. For communication purposes, key action words have been attributed for each category.

- Category A ("Avoid") corresponds to Category 3 in the first AMEG report, and includes antimicrobial classes not currently authorised in veterinary medicine.
- Category B ("Restrict") corresponds to Category 2 in the first AMEG report, including substances listed as HPCIAs by the WHO with the exception of macrolides and those which are not authorised as veterinary medicines in the EU. For these antimicrobials, risk to public health resulting from veterinary use needs to be mitigated by specific restrictions.
- Category C ("Caution") was added in this report as an intermediate category. This category includes antimicrobial classes listed in different categories by WHO, including macrolides, which are listed by WHO as a HPCIA. For substances proposed for inclusion in this category, there are in general alternatives in human medicine in the EU but there are few alternatives in veterinary medicine for certain indications.
- Category D ("Prudence") is the lowest risk category. While the risk to public health associated with the use in veterinary medicine of substances included in this category is considered low, a number of the substances in this category are listed as WHO CIAs (aminopenicillins, natural penicillins and isoxazolylpenicillin).

This categorisation does not directly translate into a treatment guideline for use of antimicrobials in veterinary medicine, but can be used as a tool by those preparing guidelines. In veterinary medicine, the variety of animal species, the different routes of administration (from intramammary treatment of individual cows to treatment of many hundreds of fish by in-feed medication) and diversity of indications are all factors that have to be taken into account in treatment guidelines. Further, types of production systems, the presence of different diseases and occurrence of antimicrobial resistance may differ between regions. Therefore, treatment guidelines need to be regionally or even locally developed and implemented. Development and implementation of evidence-based national and regional treatment guidelines are encouraged.

- The categorisation itself is not a risk assessment but could be used as an independent guidance tool "e.g. for priority setting" as part of the risk analysis.

- This classification may serve as a starting point for discussions on any new further risk assessments on request from the EC regarding the implementation of the new veterinary regulation (Official Journal of the European Union, 2019).
- The categories could be used to provide background for the consequence assessment of a risk assessment for antimicrobial medicines.
- The categorisation should also be considered as a guidance tool for assessing the importance of antimicrobials when implementing prudent use measures.

Ideally, the criticality of use in veterinary medicine should be directly considered when creating treatment guidelines. For instance, there are situations where a substance could be approved and recommended as the first line treatment for a certain condition in a certain species where there are no effective alternatives even if the substance as such belongs to a category where the risk to public health is considered high. When risk to public health is considered in a benefit/risk perspective it could be that a higher risk level is found acceptable in case of a certain disease/species to be treated. Nevertheless, this reasoning has not been fully applied in this scientific advice due to lack of data on resistance in target animal pathogens.

This categorisation should be considered as one element when deciding on when/whether to use a certain class/substance in veterinary medicine but it may not be used as the sole base when creating treatment guidelines, for making decisions about prescribing under the "cascade" or when deciding on risk mitigation activities. It should not be interpreted as a recommendation for treatment guidelines.

Antimicrobial categorisation is a complex issue influenced by different factors such as the medical practices, availability and guidelines for antimicrobial therapy, which vary from country to country. Thus, for transparency of the categorisation process, defined criteria, based on evidence and experts' considerations, have been applied to provide a rationale for the ranking of antimicrobial drugs. As the categorisation is part of a dynamic process the relative importance of an antimicrobial and its usage could evolve over time due to changes in factors that determine the drug efficacy, e.g. emergence of resistance, the availability of new drugs in the market, or due to identification of a new indication. This categorisation should therefore be periodically (e.g. in 5 years) reviewed and, if necessary, revised on the basis of new scientific evidence or emerging information on changing patterns of antimicrobial use and/or resistance trends.

Annex 1 - The WHO list in an EU perspective

The list of substances and definitions for the WHO Criteria 1 and 2 are applicable for the EU. As indicated in the WHO list of critically important antimicrobials, "the implementation of the concept at the national level required that national considerations would be taken into account, and consequently lists may vary from country to country".

Some comments are added in Table 2, addressing specifically the EU situation.

Table A1 presents an amended version of the WHO list of CIAs and HIAs modified to consider EU particulars. To reduce the number of items in the list, the antimicrobials are mainly presented as classes although some unique characteristics for individual subclasses or substances are presented as appropriate. The list is not exhaustive as some classes/substances on the WHO list but of less importance for human medicine in EU are omitted. For each class/compound, examples among the most important infective agents are listed. These agents are bacteria causing infections against which there are few treatment alternatives. Depending on resistance pattern/s, a listed compound may be

the sole available treatment. Some of these bacteria (or their resistance genes) do have an animal reservoir and thus, in a sense, be zoonotic. In some cases resistance has been shown to spread between animals and humans, in other cases such transfer remains a theoretical possibility. Hazards ("bug/drug combinations", i.e. the bacteria when resistant against the antimicrobial in question) that might in theory have such a zoonotic potential are listed in a separate column.

Table A1. Hazard of zoonotic relevance as identified by AMEG for antimicrobials that fulfil WHO criterion 1

Antimicrobial class	Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)	Hazard of potential zoonotic relevance
Aminoglycosides	• Enterococcal endocarditis • Multidrug-resistant (MDR) Gram-negative bacteria (particularly Enterobacteriaceae and *Pseudomonas* spp.) • (MDR) tuberculosis	Enterobacteriaceae *Enterococcus* spp.
Carbapenems and other penems	• Multidrug-resistant (MDR) Gram-negative bacteria (e.g. Enterobacteriaceae)	Enterobacteriaceae
Cephalosporins, 3rd- and 4th-generation	• Acute bacterial meningitis and disease due to *Salmonella* spp. in children • Gonococcal infections	Enterobacteriaceae
Ceftaroline and ceftobiprole[17]	• MDR staphylococci (e.g. MRSA) • Penicillin non-susceptible *Streptococcus pneumoniae* (PNSP)	MRSA
Cyclic esters (e.g. fosfomycin)[18]	• ESBL (extended-spectrum beta-lactamases)-producing *E. coli* causing UTI • MDR Gram-negative bacteria (IV formulation)	Enterobacteriaceae
Fluoroquinolones and other quinolones	• *Campylobacter* spp. • Invasive *Salmonella* spp. infection • MDR *Shigella* spp. • *Pseudomonas aeruginosa*, PNSP and MDR TB (tuberculosis) (intravenous/oral)	*Campylobacter* spp. Enterobacteriaceae
Glycopeptides	• MDR staphylococci (e.g. MRSA), • PNSP	*Enterococcus* spp. MRSA
Glycylcyclines	• MDR Gram-negative bacteria • MDR staphylococci (e.g. MRSA)	MRSA Enterobacteriaceae
Lipopeptides	• MDR staphylococci (e.g. MRSA)	*Enterococcus* spp.

[17] Included in "Other cephalosporins and penems, ATC code J01DI" in other tables of the document.
[18] Included in "Phosphonic acid derivates" in other tables of the document.

Antimicrobial class	Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)	Hazard of potential zoonotic relevance
	• MDR *Enterococcus* spp. • PNSP	MRSA
Macrolides (including ketolides)	• *Legionella* spp. • *Campylobacter* spp. • Invasive MDR *Salmonella* spp. and *Shigella* spp. infections	*Campylobacter* spp. Invasive *Salmonella* spp.
Monobactams	• MDR Gram-negative bacteria, especially those producing metallo-beta-lactamases (MBL)	Enterobacteriaceae
Oxazolidinones	• MDR staphylococci (e.g. MRSA) • MDR *Enterococcus* spp. (e.g. VRE) • MDR TB • PNSP	*Enterococcus* spp. MRSA
Penicillins, Natural	• Syphilis	None identified
Penicillins: Aminopenicillins including combinations with β-lactamase inhibitors (e.g. amoxicillin + clavulanic acid)	• *Listeria* spp. • *Enterococcus* spp.	*Enterococcus* spp. Enterobacteriaceae
Penicillins: Carboxy-penicillins and ureido-penicillins	• MDR *Pseudomonas* spp. • MDR Enterobacteriaceae (temocillin)	Enterobacteriaceae
Polymyxins	• MDR Enterobacteriaceae	Enterobacteriaceae
Rifamycins	• Mycobacterial diseases including tuberculosis	None identified
Riminofenazines	• Leprosy • MDR TB	None identified
Sulfones	• Leprosy	None identified
Tetracyclines	• *Brucella* spp.	*Brucella* spp.
Drugs used solely to treat tuberculosis or other mycobacterial diseases (in particular, isoniazid, pyrazinamide, ethambutol and capreomycin)	• Tuberculosis and other *Mycobacterium* spp. diseases	None identified

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Annex 2 - ATC and ATCvet codes

Table A2. Examples of ATC and ATCvet codes

AMEG categories	Antimicrobial groups, subgroups and substances	Examples of ATC code(s)	Examples of ATCvet code(s)
A	Amidinopenicillins	J01CA08 (pivmecillinam), J01CA11 (mecillinam)	QJ01CA08 (pivmecillinam), QJ01CA11 (mecillinam)
A	Carbapenems	J01DH	QJ01DH
A	Other cephalosporins* and penems	J01DI	QJ01DI
A	Glycopeptides	J01XA	QJ01XA
A	Glycylcyclines	J01AA12 (tigecycline)	QJ01AA12 (tigecycline)
A	Lipopeptides	J01XX09 (daptomycin)	QJ01XX09 (daptomycin)
A	Monobactams	J01DF	QJ01DF
A	Oxazolidinones	J01XX08 (linezolid), J01XX11 (tedizolid)	QJ01XX08 (linezolid), QJ01XX11 (tedizolid)
A	Penicillins: Carboxypenicillins and ureidopenicillins, including combinations with β-lactamase inhibitors	J01CA03 (carbenicillin), J01CA09 (azlocillin), J01CA10 (mezlocillin), J01CA12 (piperacillin), J01CA13 (ticarcillin), J01CR03 (ticarcillin and β-lactamase inhibitor), J01CR05 (piperacillin and β-lactamase inhibitor)	QJ01CA03 (carbenicillin), QJ01CA09 (azlocillin), QJ01CA10 (mezlocillin), QJ01CA12 (piperacillin), QJ01CA13 (ticarcillin), QJ01CR03 (ticarcillin and β-lactamase inhibitor), QJ01CR05 (piperacillin and β-lactamase inhibitor)
A	Phosphonic acid derivates	J01XX01 (fosfomycin)	QJ01XX01 (fosfomycin)
A	Pseudomonic acid (mupirocin)	D06AX09, R01AX06	QD06AX09, QR01AX06
A	Riminofenazines	J04BA01 (clofazimine)	QJ04BA01 (clofazimine)
A	Streptogramins	J01FG	Q01FG, QJ01FG90 (virginiamycin)
A	Sulfones	J04BA02 (dapsone)	QJ04BA02 (dapsone)
A	Drugs used solely to treat tuberculosis or other mycobacterial diseases	J04AA, J04AC, J04AD, J04AK, J04AM	QJ04AA, QJ04AC, QJ04AD, QJ04AK, QJ04AM
B	Cephalosporins, 3rd- and 4th-generation	J01DD, J01DE	QJ01DD, QJ01DE
B	Polymyxins (e.g. colistin)	J01XB, A07AA10 (colistin), A07AA05 (polymyxin B)	QJ01XB, QJ51XB, QA07AA10 (colistin), QA07AA05 (polymyxin B), QA07AA98 (colistin, combinations with other antibiotics), QJ01RA95 (polymyxins, combinations with other antibacterials) QG51AG07 (ampicillin and colistin)
B	Quinolones: fluoroquinolones and other quinolones	J01MA, J01MB	QJ01MA, QJ01MB
C	Aminoglycosides and aminocyclitol	J01GA, J01GB, A07AA (includes locally acting aminoglycosides), J04AB30 (capreomycin)	QJ01GA, QJ01GB, QJ51GA, QJ51GB, QJ51RG, QJ01RA97, QA07AA (includes locally acting aminoglycosides, QA07AA01

AMEG categories	Antimicrobial groups, subgroups and substances	Examples of ATC code(s)	Examples of ATCvet code(s)
			(neomycin))
C	Aminopenicillins, in combination with β-lactamase inhibitors (e.g. amoxicillin-clavulanic acid, co-amoxiclav)	J01CR	QJ01CR
C	Amphenicols	J01BA	QJ01BA
C	Cephalosporins, 1st- and 2nd-generation, and cephamycins	J01DB, J01DC	QJ01DB, QJ01DC
C	Macrolides	J01FA	QJ01FA
C	Lincosamides	J01FF	QJ01FF
C	Pleuromutilins		QJ01XQ
C	Rifamycins	J04AB02 (rifampicin), J04AB03 (rifamycin), J04AB04 (rifabutin) and J04AB05 (rifapentine), J04AM02/J04AM05/J04AM06 (rifamycin combinations) A07AA11 (rifaximin), A07AA13 (new code rifamycin)	QJ04AB02/QJ54AB02 (rifampicin), QJ04AB03/QJ54AB03 (rifamycin), QJ04AB04 (rifabutin) and QJ04AB05 (rifapentine), QJ04AM02/QJ04AM05/QJ04AM06 (rifamycin combinations), QA07AA11 (rifaximin), QA07AA13 (new code rifamycin)
D	Aminopenicillins, without β-lactamase inhibitors	QJ01CA01 (ampicillin), QJ01CA03 (amoxicillin), QJ01CA51 (ampicillin, combinations)	QJ51CA01 (ampicillin), QJ51CA03 (amoxicillin), QJ51CA51 (ampicillin, combinations), QG51AG04/05/07 (different ampicillin combinations)
D	Cyclic polypeptides (bacitracin)	J01XX10 (bacitracin)	QJ01XX10 (bacitracin), QA07AA93
D	Nitrofuran derivatives (e.g. nitrofurantoin)	J01XE, P01CC, A07AX03 (nifuroxazide), A07AX04 (nifurzide)	QJ01XE, QP51AC, QA07AX03 (nifuroxazide), QA07AX04 (nifurzide)
D	Nitroimidazoles	J01XD, P01AB	QJ01XD, QP51AA
D	Penicillins: Anti-staphylococcal penicillins (β-lactamase-resistant penicillins)	J01CF	QJ01CF, QJ51CF
D	Penicillins: Natural, narrow-spectrum penicillins (β-lactamase-sensitive penicillins)	J01CE	QJ01CE, QJ51CE
D	Steroid antibacterials (fusidic acid)	J01XC	QJ01XC
D	Sulfonamides, dihydrofolate reductase inhibitors and	J01EA, J01EB, J01EC, J01ED, J01EE, A07AB	QJ01EA, QJ01EQ, QJ01EW, QP51AG, QJ51E, QJ51RE, QA07AB

AMEG categories	Antimicrobial groups, subgroups and substances	Examples of ATC code(s)	Examples of ATCvet code(s)
	combinations		
D	Tetracyclines	J01AA, J01RA08	QJ01AA, QJ51A, QJ51RA, QJ01RA90 (tetracyclines, combinations with other antibacterials), QJ01RA08

*Other than 1st-, 2nd-, 3rd- and 4th-generation

Disclaimer: This table is only indicative and should not replace the ATC/DDD Index (link) and ATCvet Index (link).

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