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Committee for Medicinal Products for Human Use (CHMP)

Categorisation of antibiotics in the European Union

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

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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[2] 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.

Since the original AMEG scientific advice (EMA/AMEG, 2014), the terms 'antimicrobial' and 'antibiotic' have been defined in the Regulation on veterinary medicinal products (EU) 2019/6. In accordance with these definitions, the AMEG's categorisation includes specifically antibiotics, defined under the new legislation as '*…any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious disease*'. Substances with primarily antifungal, antiprotozoal or antiviral activity (included in the definition of antimicrobials) and disinfectants are out of scope. The term 'antimicrobial' was used in discussion of the first AMEG categorisation to reflect the reference to the WHO's list of 'Critically Important Antimicrobials for Human Medicine'. In the interests of consistency with Regulation (EU) 2019/6 and the scope of the AMEG's categorisation, the term 'antibiotic' is now used, except when referring to other publications which use the term 'antimicrobial' or when this latter term is used in the context of the definitions in the new legislation.

During this current review, the AMEG considered additional criteria that could be taken into account for the categorisation of antibiotics. Hence in the updated categorisation proposal, more emphasis is placed on the availability of alternative antibiotics 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

[1] For the original AMEG scientific advice (2014) "antimicrobial" was 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 the context of that advice, antivirals, antiparasitics and disinfectants were excluded from the definition. In Regulation (EU) 2019/6, "antimicrobial" is defined as meaning 'any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals'. See also text box.
[2] Colistin is also known a polymyxin E.

the categories, in terms of level of risk, has been reversed compared to the first AMEG report. Further, those antibiotic 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. The Categorisation includes only antibiotic classes that have been authorised for human and/or veterinary use in the EU. With the exception of two individual substances and new antibiotics authorised in human medicine after publication of this updated advice, the Categorisation should be understood to operate at the level of antibiotic (sub)classes.

In the categorisation process, defined criteria, based on evidence and experts' considerations, have been applied to provide a rationale for the ranking.

The updated criteria on which the Categorisation is based are as follows:

1. If the (sub)class or group is authorised for use as a veterinary medicine in the EU

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 particular considering mechanisms where a single gene confers multiresistance (or resistance to several classes) (Tables 2 and 3).

4. The availability of alternative antibiotic (sub)classes in veterinary medicine with lower AMR risk to animal and public health (Table 4).

Based on supporting evidence included within the tables in this report and expert opinion, the AMEG has applied these criteria to place each antibiotic (sub)class in one of four different categories, from A to D. For communication purposes, key action words have been attributed to each category.

Category A ("Avoid") corresponds to Category 3 in the first AMEG report and includes antibiotic classes not authorised in veterinary medicine but authorised in human medicine in the EU. These classes may be used exceptionally in non-food producing animals in compliance with the prescribing "cascade"[3]. In the case of food-producing animals, these substances cannot be used under the prescribing "cascade" in the absence of established maximum residue limits. By default, any new antibiotic substance authorised for use in human medicine after the publication of the categorisation will be provisionally included in Category A regardless of the categorisation of its parent (sub)class.

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

These restricted antibiotics should only be used for the treatment of clinical conditions when there are no alternative antibiotics in a lower category that could be clinically effective. Especially for this category, use should be based on the results of antibiotic 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

[3] Article 10 and 11 of Directive 2001/82/EC and Articles 107, 112, 113 and 114 of Regulation (EC) 2019/6. Legislation includes provisions which, when no suitable authorised product is available and under exceptional circumstances, allow 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 – the "cascade". Individual substances that are not authorised for use in a veterinary medicine but are in antibiotic (sub)classes included in Categories B, C or D (e.g. azithromycin, which is in the macrolide class) may also only be administered under the "cascade".

[4] Quinolones: fluoroquinolones and other quinolones

(EMA/CVMP/AWP, 2018b) and aminopenicillins (EMA/CVMP/AWP, 2019, 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 antibiotics 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 antibiotics 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 antibiotic 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.

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

These antibiotics should only be used when there is no available substance in Category D that would be clinically 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 antibiotics 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 responsible 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 Regulation (EU) 2019/6 on veterinary medicinal products (Official Journal of the European Union, 2019) in relation to use of antibiotics for prophylaxis, metaphylaxis and under the "cascade".

The AMEG also considered the route of administration as a further criterion to refine the Categorisation. Owing to the complexity, given the variety of formulation/antibiotic class combinations authorised for the different animal species and husbandry conditions in Europe, it was decided to introduce the route of administration as a separate listing. The list below suggests routes of administration and types of formulation given in general order of preference in terms of their estimated impact on the selection of AMR. The list should be used together with the Categorisation when factoring AMR into prescribing decisions:

- Local individual treatment (e.g. udder injector, eye or ear drops);
- Parenteral individual treatment (intravenously, intramuscularly, subcutaneously);
- Oral individual treatment (i.e. tablets, oral bolus);
- Injectable group medication (metaphylaxis), only if appropriately justified;

- Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified;
- Oral group medication *via* feed/premixes (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified.

This categorisation does not directly translate into a treatment guideline for use of antibiotics in veterinary medicine but can be used as a tool by those preparing guidelines, for making decisions about prescribing under the "cascade" or when deciding on risk mitigation activities. 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 broiler chickens by medication of drinking water) and diversity of indications are all factors that must 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 nationally, regionally or even locally developed and implemented. Development and implementation of evidence-based national and regional treatment guidelines are encouraged.

It is recommended that this categorisation should be reviewed in the light of the data collated annually in the mandatory EFSA/ECDC monitoring programme for AMR in zoonotic and indicator bacteria (and at least within 5 years) and, if necessary, on the basis of new ad hoc scientific evidence or emerging information on changing patterns of antibiotic use and/or resistance trends.

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

Table 1. Summary of the AMEG Categorisation

AMEG Categories	Antibiotic class, subclasses	Example of antibiotic(s)
Category A (*"Avoid"*)	Amdinopenicillins	mecillinam, pivmecillinam
	Carbapenems	meropenem, doripenem
	Other cephalosporins§ and penems (ATC code J01DI), including combinations of 3rd-generation cephalosporins with beta-lactamase inhibitors	ceftobiprole, ceftaroline, ceftolozane-tazobactam, faropenem
	Glycopeptides	vancomycin
	Glycylcyclines	tigecycline
	Ketolides	telithromycin
	Lipopeptides	daptomycin
	Monobactams	aztreonam
	Oxazolidinones	linezolid
	Penicillins: carboxypenicillins and ureidopenicillins, including combinations with beta-lactamase inhibitors	piperacillin-tazobactam
	Phosphonic acid derivates	fosfomycin
	Pseudomonic acids	mupirocin
	Rifamycins (except rifaximin)	rifampicin
	Riminofenazines	clofazimine
	Streptogramins	pristinamycin, virginiamycin
	Sulfones	dapsone
	Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid, ethambutol, pyrazinamide, ethionamide
	Substances newly authorised in human medicine following publication of the AMEG categorisation.	To be determined.

AMEG Categories	Antibiotic class, subclasses	Example of antibiotic(s)
Category B (*"Restrict"*)	Cephalosporins: 3rd- and 4th-generation, except combinations with beta-lactamase inhibitors	ceftiofur, cefovecin, cefquinome
	Polymyxins	colistin, polymyxin B
	Quinolones: fluoroquinolones and other quinolones	enrofloxacin, ciprofloxacin, ofloxacin, oxolinic acid
Category C (*"Caution"*)	Aminoglycosides (except spectinomycin)	streptomycin, gentamicin
	Aminopenicillins in combination with beta-lactamase inhibitors	amoxicillin-clavulanic acid
	Amphenicols	florfenicol, thiamphenicol
	Cephalosporins: 1st- and 2nd-generation, and cephamycins	cefalexin, cefapirin
	Macrolides (not including ketolides)	tylosin, tulathromycin
	Lincosamides	clindamycin, lincomycin
	Pleuromutilins	tiamulin, valnemulin
	Rifamycins: rifaximin only	rifaximin
Category D (*"Prudence"*)	Aminopenicillins, without beta-lactamase inhibitors	amoxicillin, ampicillin
	Cyclic polypeptides	bacitracin
	Nitrofuran derivatives*	furazolidone
	Nitroimidazoles*	metronidazole
	Penicillins: Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)	cloxacillin
	Penicillins: Natural, narrow spectrum penicillins (beta-lactamase-sensitive penicillins)	benzylpenicillin, phenoxymethylpenicillin
	Aminoglycosides: spectinomycin only	spectinomycin
	Steroid antibacterials*	fusidic acid
	Sulfonamides, dihydrofolate reductase inhibitors and combinations	sulfadiazine, trimethoprim
	Tetracyclines	oxytetracycline, doxycycline

§ Other than 1st-, 2nd-, 3rd- and 4th-generation
* Authorised for companion animals only

The categorisation of antibiotic classes for veterinary use in the EU, with examples of active substances per class, is presented in the infographic available on EMA's website. A listing of routes of administration and types of formulation in order of preference in terms of their estimated impact on AMR is also included. Veterinarians are encouraged to consult this infographic as a source of information when deciding which antibiotic to prescribe to animals.

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), published a reflection paper on the

aminoglycosides in 2018 (EMA/CVMP/AWP, 2018b) and is in the process of finalising its considerations on the aminopenicillins (EMA/CVMP/AWP, 2019, DRAFT).

Following the discovery of *mcr-1*, a horizontally transferable resistance gene mediating resistance to colistin and 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 the use of colistin, published by the EMA in 2016, resulted in a reclassification of this substance to the higher risk category (category 2) of the AMEG Categorisation (EMA/AMEG, 2016).

In July 2017, the EC asked the EMA to update its advice published in 2014. Regarding the categorisation of antibiotics, 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 21st 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 antibiotics.

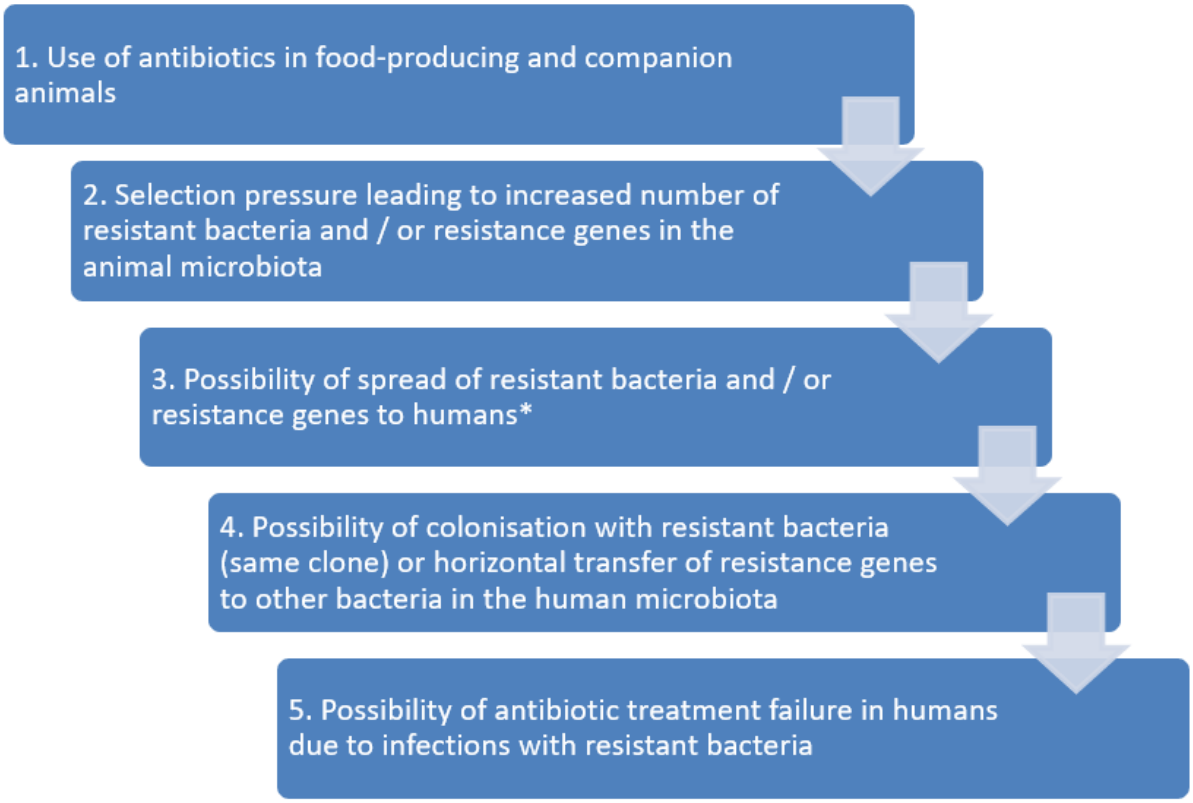
It should be noted that in its most recent request for advice, the EC also requested that the AMEG further elaborate on the 'early hazard characterisation' proposed in its 2014 advice as a means of assessing the risk to public health from AMR for new antimicrobials prior to submission of a marketing authorisation application. The AMEG response to this specific request is published in a separate document (EMA/AMEG, 2019).

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 antibiotics 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 antibiotics in food-producing and companion animals, resulting in a compromised antibiotic treatment in humans. Other routes for the development and spread of resistant bacteria and /or resistance genes to humans include use of antibiotics in humans, varying infection prevention and control/hygiene practices to prevent cross-transmission between humans, as well as environmental sources.

Figure 1. The chain of events that may follow from use of antibiotics in food-producing and companion animals resulting in compromised antibiotic treatment in humans*



* Other routes for the development and spread of resistant bacteria and/or resistance genes to humans include use of antibiotics in humans, varying infection prevention and control/hygiene practices to prevent cross-transmission between humans, as well as environmental sources.

Although lists can be useful tools during risk assessments, the categorisation of antibiotics according to AMR has certain limitations. This is mainly because co-selection between similar and also highly different classes of antibiotics, 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.

The AMEG acknowledged that there is a risk to animal health and welfare if sick animals cannot be treated and considered this risk while developing the categorisation of antibiotics.

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; WHO, 2019a).

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 6th Revision of Critically Important Antimicrobials for Human Medicine (WHO, 2019a), 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 is 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, 2017d). 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 (Aidara-Kane et al., 2018)

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 medicines

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 has updated the lists every two years.

Two lists are available: the current versions are the 21st WHO Essential Medicines List (EML) and the 7th WHO Essential Medicines List for Children (EMLc). Both lists were last updated in 2019 and can be found on the WHO website (WHO, 2019b; WHO, 2019c).

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

- ACCESS – first and second choice antibiotics for the empiric treatment of most common infectious syndromes, e.g. amoxicillin for bacterial pneumonia (mild to moderate);

- 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, e.g. macrolides, fluoroquinolones, and 3rd-generation cephalosporins; and
- RESERVE – antibiotics to be used mainly as 'last resort' treatment options, e.g. polymyxins and 4th- and 5th-generation cephalosporins.

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

Of the HPCIAs only polymyxins (e.g. colistin) and 4th- (e.g. cefipime) and 5th-generation cephalosporins (e.g. ceftaroline) 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

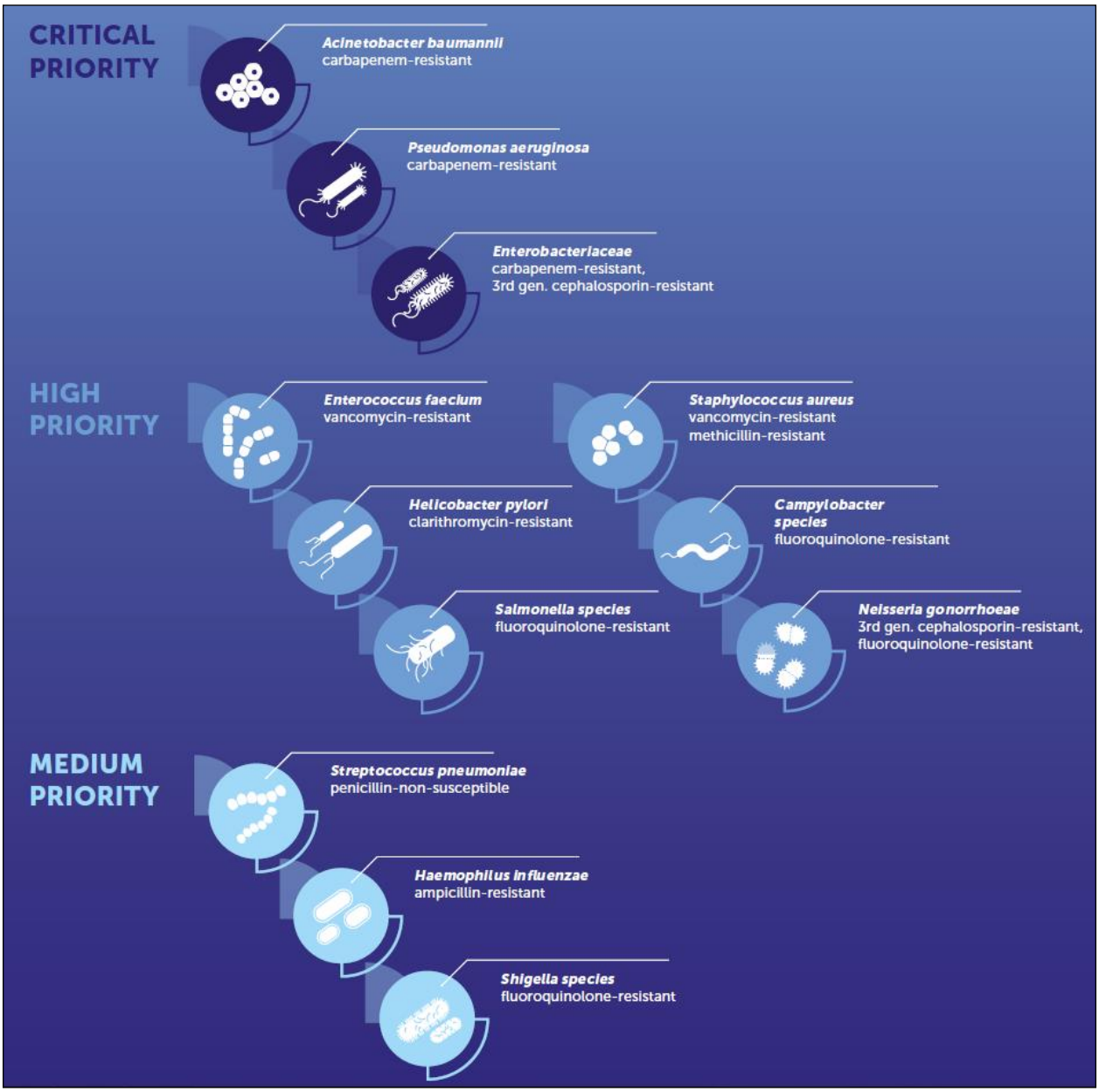
In 2016, WHO Member States mandated WHO to develop a global priority list of antibiotic-resistant bacteria to guide research and development (R&D) of new and clinically effective antibiotics. The main goal of this list is to prioritise funding and facilitate global R&D strategies.

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, 2017c). In the list, antibiotic-resistant bacteria are ranked in three groups according to the assessed priority for R&D of new and clinically effective antibiotics: priority 1 – critical, priority 2 – high, and priority 3 – medium (Figure 3) (WHO, 2017b).

Third-generation cephalosporin-resistant and/or carbapenem-resistant Enterobacterales and carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were listed among the antibiotic-resistant bacteria for which there is a critical need for new clinically 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 clinically effective antibiotics is of high priority.

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



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, 2018 and 2019 (OIE, 2019).

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 is 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).

The 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, 2019). 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 microbiological culture and antimicrobial susceptibility testing.

Antimicrobial (sub)classes used only in human medicine are not included in the OIE list. Recognising the need to preserve the clinical 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) and authorisation in animals.

3.3. Refinement of AMEG criteria

The first AMEG report considered only antibiotic 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 were 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, the CVMP's reflection paper recognises that in accordance with the categorisation criteria in the first AMEG report, all veterinary authorised aminoglycosides would be placed in Category 2. 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 antibiotics 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 antibiotic 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 antibiotic class in human medicine and the probability of AMR transfer), that could be considered to improve the categorisation of antibiotics include:

- **Criteria relating to antibiotic 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); pharmacokinetics, impact on gastrointestinal tract (lumen concentration, shedding of resistant bacteria/resistance genes etc.; importance of the antibiotics in veterinary medicine (e.g. OIE list); availability of antibiotic 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 antibiotics 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 potential reservoir of AMR following the administration of an antibiotic results from the exposure of the gut microbiota (flora), the route of administration is discussed extensively in section 3.3.1 of this report.
- **Indications for veterinary use and availability of alternative antibiotics of lesser risk:** The impact on animal health and welfare 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 and welfare. As routine, infection prevention and control measures should be implemented to improve animal health and reduce the need to resort to the use of antibiotics. Despite this, animals may become sick and those with clinical signs of bacterial infection that is impacting on their health and welfare in many cases need to be treated with antibiotics. In these circumstances, the importance of the substance for animal health is determined by the availability of alternative antibiotic treatment options for given indications in given species.

  From the perspective of protecting human health, the greater the availability of alternative antibiotic treatment options for veterinary indications, the more restrictions on veterinary use for a

given antibiotic can be tolerated without an adverse impact on animal health and welfare. Conversely, for those veterinary indications where the availability of alternative antibiotic treatment options is limited, restriction on veterinary use for a given antibiotic 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 antibiotic resistance risk to animal health. In addition, it should be considered that restriction of one antibiotic 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 antibiotic alternatives in veterinary medicine, and to identify if antibiotics of lower risk to both public and animal health are available for the same indication.

Applying this criterion to the categorisation of individual antibiotic (sub)classes relied on the expert judgement of AMEG members using information available in the form of the OIE list and the reflection papers on various antibiotic 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 antibiotic that affect the occurrence of AMR. These include: the type and formulation of the antibiotic agent; the dose; the total animal biomass, in particular the microbiota, exposed to the antibiotic (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 antibiotic 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 antimicrobial 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), with a potential benefit over in-feed administration related to antimicrobial resistance (Holmberg et al., 1987; Varga et al., 2009a; Varga et al., 2009b; Wu et al., 2019a). 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 of feed by diseased animals or seriously ill individuals not eating at all, 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 flora (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 opinion) 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). Notwithstanding that in intensively reared animals metaphylaxis may be appropriate in circumstances where there is potential for high morbidity (and sometimes mortality) due to rapidly spreading contagious disease, consideration should be given to the administration route/formulation used. Under the Regulation (EU) 2019/6 on veterinary medicinal products (Official Journal of the European Union, 2019) antimicrobial products for metaphylaxis and prophylaxis may be prescribed only for a limited duration to cover the period of risk (Article 105(6)). In addition, when

antibiotic medicinal products are used for prophylaxis, this is limited to use in individual animals only (Article 107(3)).

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 (i.e. tablets, oral bolus);
- Injectable group medication (metaphylaxis), only if appropriately justified;
- Oral group medication via drinking water/milk replacer (metaphylaxis), only if appropriately justified;
- Oral group medication *via* feed/premixes (EMA/EFSA, 2017) (metaphylaxis), only if appropriately justified.

This subsection 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. It is also acknowledged that these choices should be made taking note of the Summary of Product Characteristic for each given product.

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 antibiotics amplifies resistance (Levy, 2002; MacKenzie et al., 2007). In general, when there is a decrease in the exposure of animals to antibiotics a decrease in resistance is observed (Hanon et al., 2015). The same considerations are applicable to antibiotic usage in human medicine. Nevertheless, resistance can persist in the absence of antibiotic 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 antibiotic usage in human medicine (ECDC/EFSA/EMA, 2017). An example of such transfer is seen for livestock-associated *Staphylococcus aureus* (LA-MRSA), where whole genome sequencing of isolates 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 since the 1990s include *Salmonella* Typhimurium DT 104 (Mather et al., 2013; Threlfall, 2000), *E. coli* ST131 (Mathers et al., 2015), monophasic *Salmonella* Typhimurium (García et al., 2017; Hopkins et al., 2010a) LA-MRSA (Kinross et al., 2017) and ESBL and AmpC-producing *E. coli* (Ewers et al., 2012). Although molecular relatedness of ESBL/AmpC-producing *E. coli* from humans, food and the environment has been demonstrated in the Netherlands (Dorado-García et al., 2017) and there has also been evidence of the dissemination of cephalosporin resistance genes with common plasmid lineages in *E. coli* from farm animals and humans (de Been et al., 2014), *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). In contrast monophasic *S. Typhimurium* and LA-MRSA are zoonotic pathogens and their spread may have been facilitated by the use of antibiotics 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 antibiotic. 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 antibiotic might result in resistance to several substances within related classes of antibiotic 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 antibiotics, 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 antibiotic 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 (EMA/AMEG, 2014). 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 antibiotic (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 antibiotics 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: *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 antibiotic 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).

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

3.4.1. Consideration of antibiotic classes not taken into account in AMEG 1 advice[**] and those given further consideration[††]

Several antibiotic 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 antibiotics. For the additional antibiotic 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 antibiotics not covered by AMEG 1 advice (for details and references see Table 3)

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

Aminoglycosides: except spectinomycin	Enterobacterales
	Enterococcus spp.
		• Important antibiotics used alone, or in conjunction with other antibiotics 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 antibiotic;
		  • enzymatic modification of the drug;
		  • modification of the molecular target.

[**] 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 A3.

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• 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.
Aminoglycosides: spectinomycin only	Enterobacterales *Enterococcus* spp.	• Spectinomycin is occasionally used for the treatment of gonorrhoea in patients allergic to penicillins. Gonorrhoea is not transmitted to humans from non-human sources. Transfer of resistance genes from non-human sources unlikely. • Resistance to spectinomycin in Enterobacterales and Staphylococci is mainly by enzymatic drug modification *via* genes found on mobile elements. High-level resistance in *Neisseria* spp. is due to mutations in 16S rRNA.

Aminopenicillins	*Enterococcus* spp.
	Enterobacterales
		• 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 antibiotics 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 beta-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	Enterobacterales Staphylococci *Salmonella* spp. *Campylobacter* spp.	• Chloramphenicol second line antibiotic. • Broad spectrum including both Gram-positive and Gram-negative bacteria. • Antibotic 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 gene *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.

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• *optrA* also confers resistance to tedizolid.
Cephalosporins, 1st- and 2nd-generation, and cephamycins	Enterobacterales MSSA (Methicillin-susceptible *Staphylococcus aureus*)	• 1st-generation cephalosporins have good activity against Gram-positive bacteria, e.g. 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 beta-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 beta-lactamases.
Cyclic polypeptides	N/A	• Bacitracin mostly used topically for superficial skin infections caused by Gram-positive bacteria. • Several bacitracin resistance mechanisms exist, including: a) *bacA* gene, synonym to uppP, in b) efflux genes *bcrABC* genes or *vts*, 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 (excluding ketolides)	*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* spp. 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.

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• 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, ere, mph, mef, msr*). • The most common resistance mechanism is a target site modification mediated by at least 43 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	N/A	• Nitrofurantoin is one of the first choices of antibiotics for treating uncomplicated UTI in women, including treatment of UTIs with ESBL-producing Enterobacterales. • 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 (Clostridium) difficile (C. difficile).*

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• 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 (beta-lactamase-resistant penicillins)	MSSA (Methicillin-susceptible *Staphylococcus aureus*)	• Important antibiotics 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. • Found in many bacterial species, including MRSA.

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
Polymyxins	Enterobacterales	• 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 Enterobacterales, 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 acids	MRSA (Methicillin-resistant *Staphylococcus aureus*)	• Mupirocin first line antibiotic 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	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 *Staphylococcus aureus*)	• Streptogramin family of antibiotics 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 obsolete. • Resistance genes (e.g. *vat, vgb, erm, cfr, msr*, *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.

Antibiotic class‡‡	Hazard of potential zoonotic relevance	Overview of indications in human medicine and resistance mechanisms
		• *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	Enterobacterales *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.

N/A: not applicable

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 antibiotic favours the occurrence of resistance to other antibiotic 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 antibiotic 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.

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

Antibiotic 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
Amdinopenicillins	1	1	1	1	1	EMA/CVMP/AWP (2019, DRAFT) 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) Van Duijkeren et al. (2019)
Aminopenicillins including beta-lactamase inhibitors combinations	3	3	3	3	3	EMA/CVMP/AWP (2019, DRAFT)
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)

[§§] Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances are provided in Annex A2, Table A3.

Antibiotic 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
Carbapenems	3	3	3	2	2	Dortet et al. (2014) EFSA BIOHAZ Panel (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)
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	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) (Xu et al., 2018)
Glycopeptides	2	2	2	2	2	Braga et al. (2013) Rice (2012) Silveira et al. (2013)

Antibiotic 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
Glycylcyclines	2	1	2	1	1	EMA/AMEG (2013)
Ketolides	3	3	3	3	2	Clark and Langston (2003) Millan et al. (2004)
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 (not including ketolides)	3	3	3	3	2	Beier et al. (2019) EMA/CVMP/SAGAM (2011) Pyorala et al. (2014) Roberts (2008) Roberts (2011) Wu et al. (2019b)
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)

Antibiotic 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
						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) 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)

Antibiotic 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
						Sanchez Garcia et al. (2010)
Penicillins: Anti-staphylococcal penicillins (beta-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 (beta-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	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)

[***] 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)

Antibiotic 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
Polymyxins	3	1	2	3	3	EMA/AMEG (2016) Halaby et al. (2013) Monaco et al. (2014)
Pseudomonic acids	3	3	3	3	4	Desroches et al. (2013) 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	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)

Antibiotic 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
						Norström et al. (2009) Obaidat et al. (2018) Sala et al. (2016) Sousa et al. (2017) 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	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 section 3, taking as an additional criterion the availability of alternative antibiotics 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 in the EU*
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 particular considering mechanisms where a single gene confers multiresistance (or resistance to several classes) (Tables 2 and 3).*
4. *The availability of alternative antibiotic (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 section 3.3.1.

In this updated advice, all antibiotic classes that include substances that have been authorised for human and/or veterinary use in the EU were considered for categorisation and a summary of the evidence supporting the application of the criteria and the overall rationale for the categorisation has been added in Table 4. Supporting evidence is derived from published literature, reflection papers on individual antibiotic 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 antibiotic classes in Category A, the only consideration was the absence of authorisation of a substance from the class in a veterinary medicine in the EU. 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, except for two specific substances[11] and new antibiotics authorised in human medicine after the publication of this revision of the Categorisation. The latter will be provisionally included in Category A (see below). Examples of antibiotic substances and ATC/ATCvet codes included in each AMEG category are provided in Annex A2.

Otherwise, individual substances authorised as human medicines but not as veterinary medicines, but which belong to a class containing molecules that are authorised as veterinary medicines in the EU, 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", it cannot take account of all the principles to be considered and importantly the welfare of the

[11] Spectinomycin and rifaximin. Refer to Table 4 for rationale.

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 Regulation (EU) 2019/6 on veterinary medicinal products (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 37(5)). These substances shall not be used under the "cascade" to treat animals (Article 107(5)).
- 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 107(6))
- 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 107(3))
- 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 107(4)).

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 antibiotics, 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). National antimicrobial policy and other applicable legislative frameworks (e.g. the Water Framework Directive) (Official Journal of the European Communities, 2000) should also be taken into account.

4.1. Category A: "Avoid"

A number of the antibiotic (sub)classes listed are not authorised in veterinary medicine but are authorised in human medicine in the EU and these are presented as Category A.

The formal AMR risk assessment and risk management measures that accompany use of an authorised veterinary medicine are not available for use of these (sub)classes in animals. This might lead to an additional risk to public health (EMA/CVMP/AWP, 2018a).

Risk management measures: These antibiotic classes may only be used exceptionally in individual companion animals in compliance with the prescribing "cascade". Substances in these classes cannot be used for food-producing animals in the absence of established maximum residue limits.

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[12].

By default, any new antibiotic substance authorised for use in human medicine after the publication of the Categorisation will be provisionally included in Category A regardless of the categorisation of its parent (sub)class, pending evaluation by the AMEG. The spectrum of activity, indications and importance to human medicine of the new antibiotic may differ from other substances in the (sub)class.

In the event of a future Marketing Authorisation application for a veterinary medicinal product containing a substance in Category A, the benefits of use of the proposed veterinary medicine in animals will be 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.

It should be noted that different criteria will be applied to designate the antibiotics to be reserved for human treatment only in accordance with Article 37(5) of Regulation (EU) 2019/6. Substances fulfilling these criteria will be prohibited from use under the "cascade". The criteria have been determined under a separate Commission mandate (EMA/CVMP, 2019).

4.2. Category B: "Restrict"

Classes in the WHO's category of HPCIA (see section 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 (without beta-lactamase inhibitors) and polymyxins.

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

Risk management measures: These antibiotics should be considered only for the treatment of clinical conditions when there are no alternative antibiotics in Categories C or D that could be clinically effective. Especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible[13].

4.3. Category C: "Caution"

This category includes antibiotics 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.

[12] The provisions of the prescribing "cascade" (Articles 10 and 11 of Directive 2001/82/EC and Articles 107, 112, 113 and 114 of Regulation (EC) 2019/6) also apply to individual substances that are not authorised for use in veterinary medicine but are in (sub)classes included in Categories B, C and D.

[13] 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.'*

- The antibiotic selects for resistance to a substance in Category A through specific multiresistance genes.

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

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

4.4. Category D: "Prudence"

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

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

Risk management measures: These antibiotics are not devoid of negative impact on resistance development and spread. To keep the risk from use of these antibiotic 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.

Table 4. AMEG Categorisation table

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
Amdinopenicillins (e.g. mecillinam, pivmecillinam)	Multidrug-resistant (MDR) Enterobacterales	HIA	N/D	Not approved[18]	Not applicable	**N/A**	**A**	See section 4.1. For these antibiotics, if at any time in the future an approval is granted for use in veterinary medicine, the antibiotic class should then be categorised according the defined criteria
Carbapenems (e.g. meropenem, doripenem)	MDR Gram-negative bacteria (e.g. extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales)	CIA	N/D			**3**	**A**	
Other cephalosporins and penems (ATC code J01DI) and 3rd-generation cephalosporins with beta-lactamase inhibitors (e.g. ceftobiprole, ceftolozane-tazobactam)	Staphylococci (e.g. MRSA); MDR *Streptococcus pneumoniae*	HPCIA	N/D			**3**	**A**	
Glycopeptides (e.g. vancomycin)	Staphylococci (e.g. MRSA), MDR *Streptococcus pneumoniae,* MDR streptococci	HPCIA	N/D			**3**	**A**	
Glycylcyclines (e.g. tigecycline)	MDR Gram-negative bacteria, staphylococci (e.g. MRSA)	CIA	N/D			**3**	**A**	
Ketolides (e.g. telithromycin)	*Streptococcus pneumonia* infection	HPCIA	N/D			**1**	**A**	
Lipopeptides (e.g. daptomycin)	Staphylococci (e.g. MRSA), MDR *Enterococcus* spp., *Streptococcus pneumoniae*	CIA	N/D			**3**	**A**	

[14] Examples of ATC and ATCvet codes for the antimicrobial groups, subgroups and substances included in each AMEG category are provided in Annex A2, Table A3.
[15] WHO categorisation: HPCIA>CIA>HIA>IA
[16] OIE categorisation: VCIA>VHIA>VIA
[17] For polymyxins, the revision of 2016 advice (EMA/CVMP/CHMP/231573/2016) has been taken into account
[18] 'Approved' means approved in at least one Member State

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
Monobactams (e.g. aztreonam)	MDR Gram-negative bacteria, especially those producing metallo-beta-lactamases (MBL)	CIA	N/D			**3**	**A**	
Oxazolidinones (e.g. linezolid)	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, including combinations with beta-lactamase inhibitors (e.g. piperacillin-tazobactam)	MDR *Pseudomonas* spp., MDR Enterobacterales	CIA	N/D			**3**	**A**	
Phosphonic acid derivates (e.g. fosfomycin)	MRSA, penicillin-non-susceptible *S. pneumoniae*, MDR *E. coli (*and other susceptible Enterobacterales), MDR enterococci (e.g. VRE)	CIA	N/D			**3**	**A**	
Pseudomonic acids (e.g. mupirocin)	MDR staphylococci (e.g. MRSA)	HIA	N/D			**N/A**	**A**	
Rifamycins (except rifaximin) (e.g. rifampicin)	Mycobacterial diseases including tuberculosis. Adjunct treatment for prosthetic staphylococcal infections, prophylaxis for exposure to *N. meningitides*	CIA	VHIA			**1**	**A**	
Riminofenazines (e.g. clofazimine)	Leprosy, MDR *Mycobacterium tuberculosis*	HIA	N/D			**3**	**A**	

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
Streptogramins (e.g. pristinamycin, virginiamycin)	Staphylococci (e.g. MRSA), MDR *Enterococcus* spp. (e.g. VRE)	HIA	VIA			**N/A**	**A**	
Sulfones (e.g. dapsone)	Leprosy	HIA	N/D			**3**	**A**	
Drugs used solely to treat tuberculosis or other mycobacterial diseases (e.g. isoniazid, ethambutol)	Tuberculosis and other *Mycobacterium* spp. diseases	CIA	N/D			**3**	**A**	
Cephalosporins: 3rd- and 4th-generation, except combinations with beta-lactamase inhibitors (e.g. ceftiofur, cefquinome)	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 (Enterobacterales with confirmed or suspected resistance to antibiotics in Category C and D) Among few alternatives for treatment of respiratory tract infections where AMR to antibiotics in Category C and D has been confirmed	**2**	**B**	HPCIA in human medicine, where it is an essential class for treatment of severe and invasive infections such as acute bacterial meningitis. VCIA in veterinary medicine, where there are few alternatives for treatment of severe sepsis and respiratory tract infections in various animal species, where AMR to antibiotics in Categories D and C has been confirmed. Resistance is often transferrable (plasmid mediated, e.g. beta-lactamase genes).
Polymyxins (e.g. colistin, polymyxin B)	MDR *Pseudomonas aeruginosa,* MDR *Acinetobacter baumannii* and MDR Enterobacterales (*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 Categories C and D).	**2**	**B**	HPCIA in human medicine, where colistin is one of the few options for treatment of carbapenemase producing Enterobacterales, *Pseudomonas* spp. and *Acinetobacter* spp. Colistin is VHIA in veterinary medicine, where there are few alternatives for treatment of colibacillosis (e.g. weaning diarrhoea in pigs) caused by bacteria resistant to Category C and D antibiotics. Resistance can be caused by chromosomal mutations or can be transferrable (plasmid mediated e.g. *mcr* genes).

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
Quinolones: fluoroquinolones and other quinolones (e.g. enrofloxacin, oxolinic acid)	MDR Gram-negative bacteria, including Enterobacterales (e.g. *E.coli*, *Salmonella* spp. (invasive infection) and *Shigella* spp.) and *Pseudomonas aeruginosa*. Also *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 Categories C and D). Among few alternatives for treatment of severe (life threatening) sepsis in various animals (Enterobacterales with confirmed or suspected resistance to antibiotics in Categories C and D) Few alternatives for treatment of e.g. *Yersinia ruckeri, Aeromonas salmonicida* and *Flavobacterium* spp. in farmed fish (older quinolones)	**2**	**B**	HPCIA in human medicine, where it is an essential class for treatment of severe infections. VCIA in veterinary medicine, where there are few alternatives for treatment of infections with *E. coli* resistant to Category C and D antibiotics, severe sepsis and certain infections in fish. Both fluoroquinolones and other quinolones select for resistance in e.g. *Campylobacter* spp. and Enterobacterales (including *Salmonella* spp.). Resistance is usually caused by chromosomal mutations (single nucleotide and easily selected), but transferrable (plasmid mediated) mechanisms also occur.
Aminoglycosides (except spectinomycin) (e.g. streptomycin, gentamicin)	Enterococcal endocarditis, MDR Gram-negative bacteria (particularly Enterobacterales and *Pseudomonas* spp.), MDR tuberculosis	CIA/IA	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 alternatives for treatment of weaning diarrhoea; some alternatives are Category B. Few alternatives for treatment of infections with *Pseudomonas* spp. Few alternatives for MDR Enterobacterales; some alternatives are Category B.	**2**	**C**	Aminoglycosides/aminocyclitols, except for spectinomycin, are CIA in human medicine. Aminoglycosides are VCIA in veterinary medicine and one of few treatment options presenting a lesser risk for Pseudomonas infections in companion animals and horses and weaning diarrhoea due to Enterobacterales in pigs. There is a high potential for transmission of resistance determinants e.g. 16S mRNA methylases between animals and humans. Patterns of cross-resistance are complex. Due to the importance of aminoglycosides in veterinary medicine aminoglycosides other than spectinomycin are in Category C rather than in Category B.

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
								For spectinomycin there is no/limited cross-resistance to the other aminoglycosides and it is therefore in Category D. See also CVMP reflection paper on aminoglycosides (EMA/CVMP/AWP, 2018b).
Aminopenicillins in combination with beta-lactamase inhibitors (e.g. amoxicillin-clavulanic acid)	Enterobacterales	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**	CIA in human medicine. VCIA in veterinary medicine as there are few or no antimicrobial alternative treatments presenting a lesser risk available for certain indications in veterinary medicine. Use of amoxicillin-clavulanate selects for resistance towards penicillins and cephalosporins including the higher generation cephalosporins in both Gram-negative bacteria (ESBL) and in staphylococci (MRSA). Compared to aminopenicillins alone, amoxicillin-clavulanate has a wider spectrum and thereby a higher selection pressure for multidrug resistant organisms. Aminopenicillins with enzyme inhibitor are therefore in Category C rather than in Category D. (EMA/CVMP/AWP, 2019, DRAFT).
Amphenicols (e.g. florfenicol, thiamphenicol)	MDR Enterobacterales	HIA	VCIA	Approved for use in food-producing animals as formulations for use in group and individual animals, for systemic and local treatments. For use in companion animals as formulations for local treatments.	Few alternatives for treatment of e.g. *Aeromonas salmonicida* and *Flavobacterium* spp in farmed fish, one alternative in Category B. Among few alternatives for treatment of respiratory tract infections caused by	**N/A**	**C**	HIA in human medicine, but VCIA in veterinary medicine. Few or no antimicrobial alternative treatments presenting a lesser risk are available for certain indications in particular in farmed fish. Amphenicols select for the *cfr* and *optr*A resistance determinants that mediate

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
					bacteria resistant to alternatives in Category D.			resistance to oxazolidinones in MRSA and enterococci. Currently the *cfr* gene is considered to occur at a low prevalence in European animal isolates of e.g. LA-MRSA. Amphenicols are therefore in Category C rather than in D.
Cephalosporins, 1st- and 2nd-generation and cephamycins (e.g. cefalexin, cefapirin)	Enterobacterales, 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**	HIA in humans but VCIA in animals. Few antimicrobial alternative treatments presenting a lesser risk are available for indications such as skin infections with staphylococci in companion animals. These subclasses may select for resistance to penicillins and higher generation cephalosporins in both Gram-negative bacteria (ESBL, AmpC) and in staphylococci (MRSA). Due to available alternatives in human medicine and the importance for veterinary medicine these subclasses are Category C rather than in Category B.
Macrolides (not including ketolides) (e.g. tylosin, tulathromycin)	*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 antibiotics for treatment of haemorrhagic digestive tract disease in pigs (*Lawsonia intracellularis)*. Important for treatment of mycoplasma 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	**1**	**C**	WHO categorises macrolides as HPCIA. Macrolides are also classified as critically important for veterinary use (VCIA) and few or no antimicrobial alternative treatments presenting a lesser risk are available for e.g. infections with *Lawsonia* in pigs. The class selects for macrolide resistance in e.g. *Campylobacter* spp, a food borne zoonotic organism with comparatively high prevalence. Only serious cases, however, need treatment and proportion of case fatalities is low. Based

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
					in Category D. Some alternatives are Category B. Among few alternatives for treatment of foot-rot in sheep and goats.			on available knowledge and the group's expertise, it was concluded that, in the EU, the public health burden of infections with 3rd- and 4th-generation cephalosporin- and fluoroquinolone-resistant bacteria is higher than that for macrolide-resistant zoonotic bacteria. Recently, transferable resistance (*erm*-genes) has been described in *Campylobacter* spp. This implies a higher probability of emergence and spread. The *erm* genes are currently considered to be of low prevalence in animal isolates of *Campylobacter* and other food borne pathogens in the EU. On the basis of new scientific evidence, or emerging information on changing patterns of antibiotic use and/or resistance trends, the categorisation of this antibiotic class may need to be re-assessed. Altogether, macrolides are in Category C rather than in B.
Lincosamides (e.g. lincomycin, clindamycin)	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**	HIA in humans as alternative treatments exists. VHIA in veterinary medicine. Few or no alternatives of lesser risk for treatment of certain deep infections like osteomyelitis and severe skin conditions in companion animals. The *erm* genes that mediate cross resistance between macrolides, lincosamides and streptogramins are the most common mechanisms of resistance. Lincosamides select for the mobile *cfr* gene

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
								mediating resistance to oxazolidinones in MRSA. The prevalence of *cfr* genes is presently low in Europe, but due to the risk of imparting cross resistance to oxazolidinones, lincosamides are placed in Category C rather than in D.
Pleuromutilins (e.g. tiamulin, valnemulin)	*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**	IA for human medicine as presently only products for topical treatment are available. VHIA in veterinary medicine. There are few alternatives for treatment of e.g. swine dysentery in pigs. Pleuromutilin use in animals selects for the multidrug-resistance gene *cfr* in MRSA, including LA-MRSA, which is a hazard of zoonotic relevance. *cfr* mediates cross resistance to oxazolidinones. Pleuromutilins are therefore placed in Category C rather than in D.
Rifamycins: rifaximin only	Gastrointestinal infections	Rifaximin is not categorised individually by WHO and OIE.		Approved for use in food-producing species for local treatment.	None	**1**	**C**	Rifamycins are essential in human medicine for treatment of *Mycobacterium tuberculosis* (Mtb) infections. They are also CIA for treatment *of Staph. aureus* infections associated with prostheses. Rifamycins are VHIA in veterinary medicine. Although there is cross-resistance in the class, resistance is not horizontally transferable. Mtb is not treated in food animals and transfer of resistant Mtb organisms is not a potential zoonotic hazard in context of authorised local use of rifaximin in veterinary medicine. Use of rifaximin could select for cross-resistance to

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
								rifampicin in *Staph aureus* which may be a zoonotic hazard, although risk is low with appropriate hygiene measures and alternatives in human medicine are available. Resistance to rifamycins develops rapidly and responsible use is essential.
Aminopenicillins, without beta-lactamase inhibitors (e.g. amoxicillin, ampicillin)	*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 section 4.4. Aminopenicillins are CIA in human medicine and are commonly used first line antibiotics, but alternatives are available for most of the indications. Exceptions are infections with Listeria and with enterococci. In veterinary medicine aminopenicillins are VCIA, and important for treatment of infections in various animals, for example as first line treatment of urinary tract infections in companion animals and respiratory tract infections in pigs, when group treatment is warranted. Use of aminopenicillins selects for beta-lactam resistance. 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. Resistance is widespread in bacteria from both humans and animals. A range of different types of transferable resistance genes and mechanisms occur. Because of this, it is difficult to estimate to what extent use in animals may contribute to negative health effects in humans. The aminopenicillins

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
								class is thus placed in Category D rather than in C. See also CVMP reflection paper on Aminopenicillins (EMA/CVMP/AWP, 2019, DRAFT).
Cyclic polypeptides (e.g. bacitracin[19])	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**	
Nitrofuran derivatives (e.g. nitrofurantoin)	Enterobacterales (uncomplicated urinary tract infections)	IA	N/D	Approved for use in companion animals only.		**N/A**	**D**	
Nitroimidazoles (e.g. metronidazole)	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**	See section 4.4.
Penicillins: Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins) (e.g. cloxacillin)	*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 (beta-lactamase-sensitive penicillins) (e.g. benzylpenicillin, phenoxymethylpenicillin)	*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**	
Aminoglycosides: spectinomycin only	None, but spectinomycin is occasionally used for the treatment of gonorrhoea in	IA	VCIA	Approved for use in food-producing and companion animals. Formulations for use in group and individual	Oral treatment of enteric colibacillosis in neonatal lambs and piglets.	**2**	**D**	Spectinomycin is not classified as critically important or highly important for human medicine, but as important. In addition, the resistance mechanisms are different to those of most other

[19] Re-classification of bacitracin might be required if there is further evidence of co-selection of *mcr* genes.

Antibiotic classes, subclasses, substances[14]	Examples of important indications in human medicine	WHO[15]	OIE[16]	Use in veterinary medicine	Examples of indications where there are few alternatives in veterinary medicine	AMEG categorisation		Main rationale for categorisation
						previous	new[17]	
	patients allergic to penicillins			animals, for systemic and local treatments.				aminoglycosides. Therefore the risk to human health is lower compared to that of other aminoglycosides and spectinomycin is categorized in D instead of in C.
Steroid antibacterials (e.g. fusidic acid)	Staphylococci	HIA	VIA	Approved for use in companion animals, for use in individual animals for local treatment.		**N/A**	**D**	See section 4.4.
Sulfonamides, dihydrofolate reductase inhibitors and combinations (e.g. sulfadiazine, trimethoprim)	Enterobacterales, 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 (e.g. oxytetracycline, doxycycline)	*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 these are diseases with low incidence Fewer alternatives for vector-borne diseases in dogs and cats.	**1**	**D**	

For products containing a combination of antibiotics, the categorisation of the individual substance with the highest risk level should be taken into account for prescribing decisions.

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 its ranking of antibiotics 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 antibiotic classes which were not included in the previous ranking have also been categorised. According to the revised criteria applied for the new categorisation described in section 3.3, not only the importance of the antibiotic 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 alternative antibiotics in veterinary medicine to treat the infection under consideration, which may depend on the country and local epidemiological situation. 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 antibiotics in four different categories, from A to D. For communication purposes, key action words have been attributed to each category.

- Category A ("Avoid") corresponds to Category 3 in the first AMEG report and includes antibiotic (sub)classes not authorised in veterinary medicine but authorised in human medicine in the EU.
- Category B ("Restrict") corresponds to Category 2 in the first AMEG report, including (sub)classes 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 antibiotics, 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 antibiotic (sub)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 alternative antibiotics 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 (sub)classes included in this category is considered low, a number of the substances in this category are listed as WHO CIAs (aminopenicillins, natural penicillins).

This categorisation does not directly translate into a treatment guideline for use of antibiotics 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 broiler chickens by medication of drinking water) and diversity of indications are all factors that must 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. National antimicrobial policy and other applicable legislative frameworks (e.g. the Water Framework Directive (Official Journal of the European Communities, 2000)) should also be taken into account. Therefore, treatment guidelines need to be nationally, regionally or even locally developed and implemented. Development and implementation of evidence-based national and regional treatment guidelines are encouraged. The RONAFA report mentions the types of evidence that have been used as a basis for treatment guidelines and both this

and the European Commission's Guidelines for the prudent use of antimicrobials in veterinary medicine (giving practical examples) include examples of treatment guidelines in effect in EU member states.

- 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 risk analysis.
- This Categorisation may serve as a starting point for discussions on any new further risk assessments on request from the EC regarding the implementation of the Regulation (EU) 2019/6 on veterinary medicinal products (Official Journal of the European Union, 2019).
- The categories could be used to provide background for the consequence assessment of a risk assessment for antibiotic medicines.
- The Categorisation should also be considered as a guidance tool for assessing the importance of antibiotics when implementing prudent use measures.

For products containing a combination of antibiotics, the categorisation of the individual substance with the highest risk level should be taken into account for prescribing decisions.

The criticality of the need for use of an antibiotic 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 clinically 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 antibiotic class or substance in veterinary medicine but it may not be used as the sole basis 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.

Although the route of administration has not been retained as a ranking criterion for the categorisation of antibiotics, it is acknowledged that it can have an important impact on the overall exposure of the animal microbiota and hence the risk of AMR development (see 3.3.1). The route of administration should be considered alongside the Categorisation when making prescribing decisions.

6. Review of the AMEG Categorisation

The categorisation of antibiotics is a complex issue influenced by different factors such as medical practices, availability of medicines and guidelines for antibiotic 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 antibiotic drugs. As the categorisation is part of a dynamic process the relative importance of an antibiotic and its usage could evolve over time due to, for example, emergence of resistance, the availability of new drugs in the market, or due to identification of a new indication.

Commission Implementing Decision 2013/652/EC, implementing Directive 2003/99/EC, lays down detailed and harmonised rules for the monitoring and reporting of AMR in food-producing animals and food from a public health perspective, which are applicable from 2014 until the end of 2020. The collected AMR data are analysed and published annually in a joint report from EFSA and ECDC

(EFSA/ECDC, 2019). The EFSA has recently issued a scientific report further to a mandate received from the EC to review and propose updates of the harmonised monitoring technical specifications (EFSA, 2019) to be used for future years' surveillance. The data collected within this AMR monitoring programme may be used in time to inform reviews of the categorisation.

It is recommended that the AMEG categorisation should be reviewed in the light of the data collated annually in the mandatory EFSA/ECDC monitoring programme (and at least within 5 years) and, if necessary, on the basis of new ad hoc scientific evidence or emerging information on changing patterns of antibiotic use and/or resistance trends, in particular in respect of specific resistance genes noted in Table 4.

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, may 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

Antibiotic 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 Enterobacterales and *Pseudomonas* spp.) (MDR) tuberculosis	Enterobacterales *Enterococcus* spp.
Carbapenems and other penems	Multidrug-resistant (MDR) Gram-negative bacteria (e.g. Enterobacterales)	Enterobacterales
Cephalosporins, 3rd- and 4th-generation	Acute bacterial meningitis and disease due to *Salmonella* spp. in children Gonococcal infections	Enterobacterales
Ceftaroline and ceftobiprole[20]	MDR staphylococci (e.g. MRSA) Penicillin non-susceptible *Streptococcus pneumoniae* (PNSP)	MRSA
Cyclic esters[21]	ESBL (extended-spectrum beta-lactamases)-producing *E. coli* causing UTI MDR Gram-negative bacteria (IV formulation)	Enterobacterales
Fluoroquinolones and other quinolones	*Campylobacter* spp. Invasive *Salmonella* spp. infection MDR *Shigella* spp.	*Campylobacter* spp. Enterobacterales

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

Antibiotic class	Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)	Hazard of potential zoonotic relevance
	Pseudomonas aeruginosa, PNSP and MDR TB (tuberculosis) (intravenous/oral)	
Glycopeptides	MDR staphylococci (e.g. MRSA), PNSP	*Enterococcus* spp. MRSA
Glycylcyclines	MDR Gram-negative bacteria MDR staphylococci (e.g. MRSA)	MRSA Enterobacterales
Lipopeptides	MDR staphylococci (e.g. MRSA) MDR *Enterococcus* spp. PNSP	*Enterococcus* spp. 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)	Enterobacterales
Oxazolidinones	MDR staphylococci (e.g. MRSA) MDR *Enterococcus* spp. (e.g. VRE) MDR TB PNSP	*Enterococcus* spp. MRSA
Penicillins: Natural penicillins	Syphilis	None identified
Penicillins: Aminopenicillins including combinations with beta-lactamase inhibitors (e.g. amoxicillin + clavulanic acid)	*Listeria* spp. *Enterococcus* spp.	*Enterococcus* spp. Enterobacterales
Penicillins: carboxypenicillins and ureidopenicillins	MDR *Pseudomonas* spp. MDR Enterobacterales (temocillin)	Enterobacterales
Polymyxins	MDR Enterobacterales	Enterobacterales
Rifamycins	Mycobacterial diseases including tuberculosis	None identified
Riminofenazines	Leprosy MDR TB	None identified
Sulfones	Leprosy	None identified
Tetracyclines	*Brucella* spp.	*Brucella* spp.

Antibiotic class	Bacterial targets in human medicine (for which availability of class/substance is critically important due to few alternatives)	Hazard of potential zoonotic relevance
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

Annex 2 – Examples of antibiotic substances and ATC/ATCvet codes

Table A2. Examples of antibiotic substances authorised for veterinary use in the European Union

AMEG categories	Antibiotic classes, subclasses	Examples of antibiotics
B	Cephalosporins, 3rd- and 4th-generation, with the exception of combinations with β-lactamase inhibitors	cefoperazone cefovecin cefquinome ceftiofur
B	Polymyxins	colistin polymyxin B
B	Quinolones: fluoroquinolones and other quinolones	cinoxacin danofloxacin difloxacin enrofloxacin flumequine ibafloxacin marbofloxacin norfloxacin orbifloxacin oxolinic acid pradofloxacin
C	Aminoglycosides (except spectinomycin)	amikacin apramycin dihydrostreptomycin framycetin gentamicin kanamycin neomycin paromomycin streptomycin tobramycin
C	Aminopenicillins, in combination with beta-lactamase inhibitors	amoxicillin + clavulanic acid ampicillin + sulbactam
C	Amphenicols	chloramphenicol florfenicol thiamphenicol
C	Cephalosporins, 1st- and 2nd-generation, and cephamycins	cefacetrile cefadroxil cefalexin cefalonium cefalotin cefapirin cefazolin
C	Macrolides	erythromycin gamithromycin oleandomycin spiramycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin
C	Lincosamides	clindamycin lincomycin pirlimycin
C	Pleuromutilins	tiamulin valnemulin
C	Rifamycins: rifaximin only	rifaximin
D	Aminopenicillins, without beta-lactamase inhibitors	amoxicillin ampicillin metampicillin
D	Cyclic polypeptides	bacitracin
D	Nitrofuran derivatives	furaltadone furazolidone

AMEG categories	Antibiotic classes, subclasses	Examples of antibiotics
D	Nitroimidazoles	metronidazole
D	Penicillins: Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)	cloxacillin dicloxacillin nafcillin oxacillin
D	Penicillins: Natural, narrow-spectrum penicillins (beta-lactamase-sensitive penicillins)	benzathine benzylpenicillin benzathine phenoxymethylpenicillin benzylpenicillin penethamate hydriodide pheneticillin phenoxymethylpenicillin procaine benzylpenicillin
D	Aminoglycosides: spectinomycin only	spectinomycin
D	Steroid antibacterials	fusidic acid
D	Sulfonamides, dihydrofolate reductase inhibitors and combinations	formosulfathiazole phthalylsulfathiazole sulfacetamide sulfachlorpyridazine sulfaclozine sulfadiazine sulfadimethoxine sulfadimidine sulfadoxine sulfafurazole sulfaguanidine sulfalene sulfamerazine sulfamethizole sulfamethoxazole sulfamethoxypyridazine sulfamonomethoxine sulfanilamide sulfapyridine sulfaquinoxaline sulfathiazole trimethoprim
D	Tetracyclines	chlortetracycline doxycycline oxytetracycline tetracycline

Table A3. Examples of ATC and ATCvet codes. Note that some higher-level ATC codes appear in more than one (sub)class.

AMEG categories	Antibiotic classes, subclasses	Examples of ATC code(s)	Examples of ATCvet code(s)
A	Amdinopenicillins	J01CA08 (pivmecillinam), J01CA11 (mecillinam)	QJ01CA08 (pivmecillinam), QJ01CA11 (mecillinam)
A	Carbapenems	J01DH	QJ01DH
A	Other cephalosporins* and penems	J01DI54 (ceftolozane and beta-lactamase inhibitor)	QJ01DI54 (ceftolozane and beta-lactamase inhibitor)
A	Glycopeptides	J01XA	QJ01XA
A	Glycylcyclines	J01AA12 (tigecycline)	QJ01AA12 (tigecycline)
A	Ketolides	J01FA	QJ01FA
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 beta-lactamase inhibitors	J01CA03 (carbenicillin), J01CA09 (azlocillin), J01CA10 (mezlocillin), J01CA12 (piperacillin), J01CA13 (ticarcillin),	QJ01CA03 (carbenicillin), QJ01CA09 (azlocillin), QJ01CA10 (mezlocillin), QJ01CA12 (piperacillin), QJ01CA13 (ticarcillin), QJ01CR03 (ticarcillin

AMEG categories	Antibiotic classes, subclasses	Examples of ATC code(s)	Examples of ATCvet code(s)
		J01CR03 (ticarcillin and beta-lactamase inhibitor), J01CR05 (piperacillin and beta-lactamase inhibitor)	and beta-lactamase inhibitor), QJ01CR05 (piperacillin and beta-lactamase inhibitor)
A	Phosphonic acid derivates	J01XX01 (fosfomycin)	QJ01XX01 (fosfomycin)
A	Pseudomonic acids	D06AX09, R01AX06	QD06AX09, QR01AX06
A	Rifamycins (except rifaximin)	J04AB02 (rifampicin), J04AB03 (rifamycin), J04AB04 (rifabutin) and J04AB05 (rifapentine), J04AM02/J04AM05/J04AM06 (rifamycin combinations), A07AA13 (new code rifamycin)	QJ04AB02/QJ54AB02 (rifampicin), QJ04AB03/QJ54AB03 (rifamycin), QJ04AB04 (rifabutin) and QJ04AB05 (rifapentine), QJ04AM02/QJ04AM05/QJ04AM06 (rifamycin combinations), QA07AA13 (new code rifamycin)
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, with the exception of combinations with β-lactamase inhibitors	J01DD, J01DE	QJ01DD, QJ01DE
B	Polymyxins	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 (except spectinomycin)	J01GA, J01GB, A07AA (includes locally acting aminoglycosides), J04AB30 (capreomycin)	QJ01GA, QJ01GB, QJ51GA, QJ51GB, QJ51RG, QJ01RA97, QA07AA (includes locally acting aminoglycosides, QA07AA01 (neomycin))
C	Aminopenicillins, in combination with beta-lactamase inhibitors	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: rifaximin only	A07AA11 (rifaximin)	QA07AA11 (rifaximin)
D	Aminopenicillins, without beta-lactamase inhibitors	J01CA01 (ampicillin), J01CA04 (amoxicillin), J01CA51 (ampicillin, combinations)	QJ01CA01 (ampicillin), QJ01CA04 (amoxicillin), QJ01CA51 (ampicillin, combinations), QG01AG04/05/07 (different ampicillin combinations)
D	Cyclic polypeptides	J01XX10 (bacitracin)	QJ01XX10 (bacitracin), QA07AA93
D	Nitrofuran derivatives	J01XE, P01CC, A07AX03 (nifuroxazide), A07AX04 (nifurzide)	QJ01XE, QP51AC, QA07AX03 (nifuroxazide), QA07AX04 (nifurzide)
D	Nitroimidazoles	J01XD, P01AB	QJ01XD, QP51AA

AMEG categories	Antibiotic classes, subclasses	Examples of ATC code(s)	Examples of ATCvet code(s)
D	Penicillins: Anti-staphylococcal penicillins (beta-lactamase-resistant penicillins)	J01CF	QJ01CF, QJ51CF
D	Penicillins: Natural, narrow-spectrum penicillins (beta-lactamase-sensitive penicillins)	J01CE	QJ01CE, QJ51CE
D	Aminoglycosides: spectinomycin only	J01XX04	QJ01XX04
D	Steroid antibacterials	J01XC	QJ01XC
D	Sulfonamides, dihydrofolate reductase inhibitors and combinations	J01EA, J01EB, J01EC, J01ED, J01EE, A07AB	QJ01EA, QJ01EQ, QJ01EW, QP51AG, QJ51E, QJ51RE, QA07AB
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).

Annex 3 – References

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