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Advice on implementing measures under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products – Criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans

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Introduction

On 6 February 2019, the European Commission sent a request to the European Medicines Agency (EMA) for a report on the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans in order to preserve the efficacy of those antimicrobials.

The Agency was requested to provide a report by 31 October 2019 containing recommendations to the Commission as to which criteria should be used to determine those antimicrobials to be reserved for treatment of certain infections in humans (this is also referred to as 'criteria for designating antimicrobials for human use', 'restricting antimicrobials to human use', or 'reserved for human use only').

The Committee for Medicinal Products for Veterinary Use (CVMP) formed an expert group to prepare the scientific report. The group was composed of seven experts selected from the European network of experts, on the basis of recommendations from the national competent authorities, one expert nominated from European Food Safety Authority (EFSA), one expert nominated by European Centre for Disease Prevention and Control (ECDC), one expert with expertise on human infectious diseases, and two Agency staff members with expertise on development of antimicrobial resistance .

When addressing this request, the European Commission asked the Agency to, in particular:

- liaise with relevant European Union bodies (including EFSA and ECDC).
- take into account the work of relevant international organisations, bodies or organisations (such as OIE, WHO, FAO¹) and to organise a scientific workshop with those international organisations.
- consider examples of Third Countries with relevant experience in the establishment of criteria serving a similar purpose.

In addition, the Committee for Medicinal Products for Human Use (CHMP) and CVMP members were requested to collect information at Member State level on restrictions of antimicrobials and criteria used.

As requested by the European Commission in its mandate the criteria listed in article 107(6) of Regulation (EU) 2019/6 for the establishment of a list of antimicrobials that shall not be used or shall be used subject to certain conditions outside the terms of the marketing authorisation were also considered.

The expert group submitted their report to the CVMP on 29 August 2019.

The CVMP adopted the scientific advice on 10 October 2019.

Summary

The new legislative basis for the authorisation of veterinary medicines in the European Union (EU), Regulation (EU) 2019/6 on veterinary medicinal products, hereafter referred to as the Regulation, was published on 7 January 2019 (Official Journal of the European Union, 2019). The Regulation foresees the establishment of criteria for the designation of antimicrobials or classes of antimicrobials which are to be reserved for human use only.

This advice addresses the request from the European Commission to the European Medicines Agency (Agency) to provide recommendations to define the criteria that should be used to determine those antimicrobials to be restricted to human use as foreseen under Article 37(4) of the Regulation.

¹ OIE: World Organisation for Animal Health, WHO: World Health Organization, FAO: Food and Agriculture Organization of the United Nations

In the context of this advice, a scientific workshop with international organisations was organised in Brussels on 14 June 2019, in order to exchange views and share expertise for establishing the criteria to be used for designating antimicrobials to be reserved for human use only.

In order to recommend criteria for the designation of antimicrobials, a review of existing relevant work done at international level, by third countries and by the European Union Member States was performed. This review allows for the identification of possible criteria to be used for the designation of antimicrobials to be reserved for the treatment of certain infectious in humans and shows that very few countries have specific legislation for banning the use of certain antimicrobial/antimicrobial classes in veterinary medicine.

It is recognised that the designation of antimicrobials for human use only is the most severe risk management measure which should be used with discretion, and that other risk management measures exist that can be applied to preserve the efficacy of antimicrobials in human medicine.

It is concluded that antimicrobials or classes of antimicrobials designated to be only used in humans will be those that are of highest importance to human health, for which the risk the transfer of antimicrobial resistance from animals to humans is considered as significant and for which the importance to animal health is low.

In addition to the recommended criteria, it was also discussed how these criteria could be used in different scenarios based on authorisation status in the European Union: that is, when the antimicrobial/antimicrobial class is authorised in human medicine only, in veterinary medicine only, in both human and veterinary medicine or not authorised in either human or in veterinary medicine. Chapter 5 includes preliminary approaches which, following experience from its application, might need further refinement.

Recommendations

Among the possible criteria identified, it is recommended that the designation of antimicrobials as reserved for human use only should be based on the following three criteria:

1. High importance to human health

The antimicrobial or antimicrobial class meets this criterion if any of the following apply:

- It is either the sole or last-resort or an essential component of the limited few alternatives available in a patient management treatment approach for serious, life-threatening infections in humans which, if inappropriately treated, would lead to significant mortality or debilitating morbidity.
- Antimicrobial agents authorised in the European Union for the treatment of serious bacterial infections in patients with limited treatment options, indicating that it has been established that these agents address an unmet medical need related to drug resistance, should, by default, be considered for a restricted use to humans.

2. Risk of transfer of resistance

The antimicrobial/antimicrobial class meets this criterion if:

- Transmission of bacteria resistant to the antimicrobial/antimicrobial class or transmission of genes conferring resistance to the antimicrobial/antimicrobial class from non-human sources to humans is significant and linked to the use of the antimicrobial/antimicrobial class in animals;

- Data exist to show the actual emergence, dissemination and transmission of resistance to this antimicrobial/antimicrobial class following use in animals or, in case the antimicrobial is not authorised for animals, data exist to show the potential of emergence, dissemination and transmission of resistance.

Generally, the negative impact of the use of an antimicrobial in animals on public health will be highest if the resistance gene(s) selected by its use confer(s) resistance or cross-resistance to compounds that are critically important for human medicine, if transmission of resistance occurs vertically as well as horizontally, if zoonotic pathogens are involved, and if transmission of resistant bacteria or resistance genes takes place by different routes and/or is linked to a number of different animal species.

3. Low importance to animal health

The antimicrobial/antimicrobial class meets this criterion if:

- It is not essential to treat serious, life-threatening infections in animals, which if left untreated would lead to significant morbidity and/or mortality.
- Alternatives exist to the use of the antimicrobial/antimicrobial class for the treatment of serious life-threatening infections in animals.
- A ban on the use of the antimicrobial/antimicrobial class in animals would not result in a major impact on animal health and welfare, or human health, as alternative management strategies other than the use of antimicrobials exist to prevent, treat or control such infections.

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

Table of contents

1. Terms of reference and scope	7
2. Consideration of existing work	8
2.1. Criteria used for designation of antimicrobials of importance in human medicine	8
2.1.1. Criteria in human medicine at the international level.....	8
2.1.1.1. WHO Critically important antimicrobials for human medicine, 6 th Revision 2018: Ranking of medically important antimicrobials for risk management of antimicrobial resistance due to non-human use	8
2.1.1.2. The 21 st WHO Model List of Essential Medicines (2019).....	10
2.1.1.3. Health Canada (Government of Canada) - Categorization of Antimicrobial Drugs Based on Importance in Human Medicine (Version - April, 2009)	11
2.1.1.4. Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Center for Veterinary Medicine October 23, 2003	13
2.1.1.5. Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia, Version 1.0 (2018) (Commonwealth of Australia)	14
2.1.1.6. Ranking of the Importance of Antimicrobials against bacteria which affect human Health through Food Commodities (provisional translation). Last amended March 31, 2014. - Food Safety Commission of Japan.	15
2.1.1.7. Discussion and conclusions	16
2.1.2. Criteria in human medicine at Member State level	22
2.1.2.1. Existing recommendations on antimicrobials in human medicine	22
2.1.2.2. Discussion and conclusions	23
2.2. Criteria used for designation of antimicrobials of importance in veterinary medicine ...	24
2.2.1. Criteria in veterinary medicine at the international level	24
2.2.1.1. OIE list of Antimicrobials of veterinary importance	24
2.2.1.2. WHO Guidelines on use of medically-important antimicrobials	25
2.2.1.3. International (Third Country) position	26
2.2.2. Criteria in veterinary medicine at the European Union level.....	27
2.2.2.1. Criteria used for categorisation of antimicrobials.....	27
2.2.2.2. Existing recommendations on restriction of antimicrobials in animals	28
2.2.3. Criteria in veterinary medicine at member state level.....	30
2.2.3.1. Existing recommendations on antimicrobials in veterinary medicine	30
2.2.3.2. Discussion and conclusions	34
2.3. Summary and analysis (international, European Union, Member States)	34
3. Considerations for the selection of the criteria	36
3.1. Consideration of criteria for assessing the importance of antimicrobials in human health	36
3.1.1. Serious bacterial diseases.....	36
3.1.2. Available treatment alternatives	37
3.2. Resistance transfer, resistance linked to other antimicrobials	38
3.3. Consideration of criteria for assessing the importance of antimicrobials in animal health	40
3.3.1. Serious bacterial disease	40

3.3.2. Available treatment alternatives	42
3.4. Discussion	43
4. Criteria retained	43
4.1. High importance to human health.....	44
4.2. Risk of transfer of resistance.....	44
4.3. Low importance to animal health.....	44
5. Using the criteria.....	45
5.1. Antimicrobials only authorised in human medicine	45
5.2. Antimicrobials only authorised in veterinary medicine	47
5.3. Antimicrobials authorised in human and veterinary medicine	47
5.4. Antimicrobials not authorised in human and veterinary medicine.....	48
6. Annexes.....	50
Annex 1 – Summary table of antimicrobial rankings of importance for human medicine.....	50
Annex 2 – Scoring system reflecting the current use of antimicrobials in the Australian human medicine (ASTAG, 2018)	60
Annex 3 – Main pathogens/disorders for which antimicrobials are mostly used (RONAFA) (EMA/EFSA, 2017)	61
Annex 4 – References.....	64

1. Terms of reference and scope

The request from the European Commission to the EMA correlates to Article 37(3) of the Regulation related to decisions refusing marketing authorisations that states that “a marketing authorisation for an antimicrobial veterinary product shall be refused if the antimicrobial is reserved for the treatment of certain infections in humans (...)”.

The request for advice from the European Commission requires EMA to “establish clear and pertinent criteria to adequately designate those antimicrobials or groups of antimicrobials which are reserved for human use in order to preserve their efficacy” (pursuant Article 37(4)).

Founded on criteria related to this request, antimicrobials or groups of antimicrobials that should be reserved for human use will be designated by implementing acts (Article 37(5)).

The request also correlates to Article 107(5) that states that medicinal products which contain designated antimicrobials referred to in Article 37(5) and are reserved for human use shall not be used outside of the terms of the marketing authorisations. As a consequence, designation of antimicrobials reserved for humans will automatically lead to a complete prohibition for use in animals.

Article 152(1) indicates that existing products authorised in accordance with the previous legislation shall be deemed to be authorised according to the Regulation, with the exception of authorisations of veterinary medicinal products containing antimicrobials which have been reserved for human use only. It is understood that the criteria to be defined in the delegated act in accordance with Article 37(4) are not limited to antimicrobials that have not yet been authorised for the veterinary market but will also be applied to existing veterinary products.

The request is further linked to Article 118(1) of the Regulation which states that third countries will also have to respect the restrictions imposed on the use of antimicrobials in animals in the European Union. The prohibition on use of antimicrobials designated in accordance with Article 37(5) will also apply to animals or products of animal origin exported from third countries to the Union.

In the context of this advice, considerations on possible impacts of the designation of antimicrobials reserved for human use were limited to health issues.

Finally, the request also refers to Article 107(6). This article relates to the establishment of a list of antimicrobials which may not be used outside the terms of the marketing authorisation or should be used subject to certain conditions only. For this list, no delegated acts are foreseen, only implementing acts. The article provides criteria that shall be taken into account by the Commission when adopting those implementing acts:

- a) risks to animal or public health if the antimicrobial is used outside the terms of the marketing authorisation
- b) risk for animal or public health in case of development of antimicrobial resistance
- c) availability of other treatments for animals
- d) availability of other treatment for humans
- e) impact on aquaculture and farming if the animal affected by the condition receives no treatment

The list of antimicrobials that will be established based on Article 107(6) will be a separate list but will include antimicrobials that should be reserved for human use according to Article 37(5).

The off-label use of antimicrobials in animals includes usage of antimicrobials authorised for humans and animals. As the criteria a-e) may lead to a complete restriction of the use of antimicrobials outside

the terms of the marketing authorisation, they need also to be considered in the reflection on the criteria for the designation of antimicrobials reserved for human use.

According to the Regulation, 'antimicrobials' include antibiotics, antivirals, antifungals and antiprotozoals. The criteria for the designation of antimicrobials to be reserved for treatment of certain infections in humans have been developed primarily with antibacterial substances in mind, but in principle could also be applied to other types of antimicrobials.

2. Consideration of existing work

2.1. Criteria used for designation of antimicrobials of importance in human medicine

Antimicrobials are life-saving medicines, but their effectiveness is compromised by increasing antimicrobial resistance levels leading to increased morbidity and mortality. Governments around the world have recognised the growing issues of antimicrobial resistance, where many of the same classes of antimicrobials used to treat and prevent infections in human medicine are also used in animals. Inappropriate use of antimicrobials across human health, animal health and agriculture globally is responsible for accelerating the development of antimicrobial resistance.

While the efficacy of all antimicrobials is important, some antimicrobials are deemed more critical than others, based on being preferred options for the treatment of serious infections in humans, and the availability or lack of alternative treatment options. If antimicrobial resistance emerges to an antimicrobial agent used to treat a specific infection for which there are no treatment alternatives, the consequences to health outcomes are significant and potentially life threatening. The human sector, the agricultural sector, and the environment are all essential parts of "One Health", where antimicrobial management in any one sector can affect antimicrobial resistance levels in the other sectors.

Various international organisations and countries have developed criteria for specifying or ranking the importance of antimicrobials or antimicrobial classes for human medicine. These were developed for use in risk management strategies related to antimicrobial use in human healthcare settings and animal use. Prioritising antimicrobials that are critically important for humans is a valuable tool for aiding an evidence-based approach to risk management.

In this part 2 of the text the terminology of the authoring organisations is maintained.

2.1.1. Criteria in human medicine at the international level

2.1.1.1. WHO Critically important antimicrobials for human medicine, 6th Revision 2018: Ranking of medically important antimicrobials for risk management of antimicrobial resistance due to non-human use

Purpose: The document (WHO, 2019a) is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.

The ranking of medically important antimicrobials was based on two criteria as defined below.

Criterion 1 (C1): *The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.*

Explanation: It is evident that antimicrobials that are the sole or one of few alternatives for the treatment of serious bacterial infections in humans occupy an important place in medicine. While

severity of illness may relate to the site of infection (e.g. pneumonia, meningitis) or the host (e.g. infant, immunosuppressed), serious infections are overall more likely to result in increased morbidity or mortality if left untreated because no effective antibacterial agents are available. It is of prime importance that the efficacy of such antibacterial agents be preserved, as loss of efficacy in these drugs due to the emergence of resistance would have a significant impact on human health, especially for people with life-threatening infections. This criterion does not consider the likelihood that these pathogens may be transmitted, or have been transmitted, from non-human sources to humans.

Criterion 2 (C2): *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.*

Explanation: Antimicrobial agents used to treat diseases caused by bacteria that may be transmitted to humans from non-human sources are considered of higher importance since these infections are most amenable to risk-management strategies related to non-human antimicrobial use. The organisms that cause disease need not be drug-resistant. However, the potential for transmission shows the path for acquisition of resistance now or in the future. The evidence for a link between non-human sources and the potential to cause human disease is greatest for certain bacteria (e.g. non-typhoidal *Salmonella*, *Campylobacter* spp., *Escherichia coli*, *Enterococcus* spp., and *Staphylococcus aureus*). Commensal organisms from non-human sources (animals, water, food, or the environment) may also transmit resistance determinants to human pathogens; the commensals themselves may also be pathogenic in immunosuppressed hosts. It is important to note that the transmission of such organisms or their genes need not be demonstrated; rather, it is considered sufficient that the potential for such transmission exists.

Based on these two criteria above WHO developed the list of all antimicrobial classes used in human medicine and categorised antimicrobials into three groups of critically important, highly important, and important:

Critically important: Antimicrobial classes which meet both C1 and C2.

Highly important: Antimicrobial classes which meet either C1 or C2.

Important: Antimicrobial classes which meet neither C1 nor C2.

Prioritization within the critically important category

Antimicrobials within the critically important category are further prioritized to assist in allocating resources towards agents for which risk-management strategies are needed most urgently.

Prioritization criterion 1 (P1): Large number of people in the community or in certain high-risk populations (e.g. patients with serious infections in health care settings), who are affected by diseases for which there are very limited antimicrobial choices.

Prioritization criterion 2 (P2): High frequency of use of the antimicrobial class for any indication in human medicine or in certain high-risk groups (e.g. patients with serious infections in health care settings), since use may favour selection of resistance.

Prioritization criterion 3 (P3): The antimicrobial class is used to treat infections in people for which there is extensive 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.

Explanation: The first two prioritization criteria (P1 and P2) relate to the first Criterion (C1) used to categorise antimicrobials. The first prioritization criterion (P1) relates to the number of people that

might need therapy and the second prioritization criterion (P2) relates to the frequency of and the intensity of antimicrobial use in humans. The third prioritization criterion (P3) relates to the second Criterion (C2) which is used to classify antimicrobials and relates to the amount of evidence already available that shows transmission of resistant bacteria, or their genetic elements, is occurring relatively frequently.

Table 1. Summary of categorisation and prioritisation of critically important antimicrobials (Extract from Table 3 of WHO (2019a))

Antimicrobial class	Criterion / Prioritization Factor				
	C1	C2	P1	P2	P3
CRITICALLY IMPORTANT ANTIMICROBIALS					
<i>Highest Priority Critically Important Antimicrobials</i>					
Cephalosporins (3 rd -, 4 th - and 5 th -generation)	Yes	Yes	Yes	Yes	Yes
Glycopeptides	Yes	Yes	Yes	Yes	Yes
Macrolides and ketolides	Yes	Yes	Yes	Yes	Yes
Polymyxins	Yes	Yes	Yes	Yes	Yes
Quinolones	Yes	Yes	Yes	Yes	Yes
<i>High Priority Critically Important Antimicrobials</i>					
Aminoglycosides	Yes	Yes	No	Yes	Yes
Ansamycins	Yes	Yes	Yes	Yes	No
Carbapenems and other penems	Yes	Yes	Yes	Yes	No
Glycylcyclines	Yes	Yes	Yes	No	No
Lipopeptides	Yes	Yes	Yes	No	No
Monobactams	Yes	Yes	Yes	No	No
Oxazolidinones	Yes	Yes	Yes	No	No
Penicillins (antipseudomonal)	Yes	Yes	No	Yes	No
Penicillins (aminopenicillins)	Yes	Yes	No	Yes	Yes
Penicillins (aminopenicillins with beta-lactamase inhibitors)	Yes	Yes	No	Yes	Yes
Phosphonic acid derivatives	Yes	Yes	Yes	Yes	No
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Yes	Yes	Yes	Yes	No

2.1.1.2. The 21st WHO Model List of Essential Medicines (2019)

Purpose: To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, three different categories were developed – the Access, Watch, Reserve (AWaRe) classification of antibiotics. This approach to classification of antibiotics was developed to emphasize the importance of their appropriate use (WHO, 2019b).

Group 1 - ACCESS GROUP ANTIBIOTICS

This group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. Selected Access group antibiotics are recommended as essential first or second choice empiric treatment options for infectious syndromes reviewed by the WHO Model List of Essential Medicines Expert Committee and are listed as individual medicines on the Model Lists to improve access and promote appropriate use. They are essential antibiotics that should be widely available, affordable and quality assured.

Group 2 - WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the critically important antimicrobials for human medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the Model List.

Group 3 - RESERVE GROUP ANTIBIOTICS

This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Reserve group antibiotics should be treated as “last resort” options. Selected Reserve group antibiotics are listed as individual medicines on the Model Lists when they have a favorable risk-benefit profile and proven activity against “Critical Priority” or “High Priority” pathogens identified by the WHO Priority Pathogens List, notably carbapenem resistant *Enterobacteriaceae*. These antibiotics should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

2.1.1.3. Health Canada (Government of Canada) - Categorization of Antimicrobial Drugs Based on Importance in Human Medicine (Version - April, 2009)

Purpose: Pre-defined criteria were established to group antimicrobials into different categories based on the implications of resistance to these drugs for human medicine. The categorisation provides a rationale for priority setting and identifying the level of detail required for risk assessments related to antimicrobial resistance (Health Canada, 2009).

Criteria: The principal criteria were the **indication** and the **availability** of alternative antimicrobials for the treatment of infections in human medicine. The use of antimicrobials in veterinary medicine was not considered during this categorisation, but would be part of a separate human health risk assessment process. The extent of use in human medicine was not considered but could be applicable to prioritizing antimicrobials within a category or during a risk assessment process. It was noted that for the sake of simplicity, antimicrobial agents were typically categorised according to their chemical class. However, some of the individual agents in a particular class may not fall in the same category as other substances of the same class and such exceptions were treated on a case-by-case basis.

Indication: Includes the use of antimicrobials in human medicine and the spectrum of activity as well as the efficacy. Antimicrobials that are preferred for the treatment of serious bacterial infections were considered more important than those not used for this purpose. It was noted that development and increasing antimicrobial resistance, including cross- and co-resistance to other classes of antimicrobials, could alter the usefulness and hence the indications of a substance.

Availability of alternative antimicrobial drugs: Antimicrobials with limited or no alternatives for treatment of infections, or where alternatives available were within the same class, were considered more important than others. Antimicrobials used generally as last resort treatments were considered more important. Acquired resistance, including multidrug resistance, affects the efficacy of the antimicrobial and limits the availability of effective alternative antimicrobials.

A table was provided of the general principles of the criteria for antimicrobial categorisation. The antimicrobial agents were grouped into four categories.

Table 2. Application of criteria for antimicrobial categorisation

Category	Preferred option for treatment of serious human infections*	No or limited alternatives available
I – Very High Importance	Yes	Yes
II – High Importance	Yes	No
III – Medium Importance	No	No/Yes
IV – Low Importance	Not applicable	Not applicable

* Serious infections are considered those which if left untreated would lead to significant morbidity requiring emergency care including hospitalization and/or mortality.

1. Category I: Very High Importance

These antimicrobials were considered of very high importance to human medicine since they met the criteria of being essential for the treatment of serious bacterial infections and limited or no availability of alternative antimicrobials for effective treatment in case of emergence of resistance to these agents. Antimicrobial classes specified in this category included: carbapenems, 3rd- and 4th-generation cephalosporins, fluoroquinolones, glycopeptides, glycylicyclines, ketolides, lipopeptides, monobactams, nitroimidazoles (metronidazole), oxazolidinones, penicillin- β -lactamase inhibitor combinations, polymyxins (colistin), and therapeutic agents for tuberculosis (e.g. ethambutol, isoniazid, pyrazinamide and rifampin).

2. Category II: High Importance

Antimicrobials in this category consisted of those that could be used to treat a variety of infections including serious infections and for which alternatives are generally available. Bacteria resistant to these antimicrobials were generally susceptible to Category I drugs which could be used as the alternatives. Antimicrobial classes specified in this Category included: aminoglycosides (except topical agents), 1st and 2nd-generation cephalosporins (including cephamycins), fusidic acid, lincosamides, macrolides, penicillins, quinolones (except fluoroquinolones), streptogramins, and trimethoprim/sulfamethoxazole.

3. Category III: Medium Importance

Antimicrobials in this category were for treatment of bacterial infections for which alternatives are generally available. Infections caused by bacteria resistant to these drugs can, in general, be treated by Category II or I antimicrobials. Antimicrobial classes specified in this category included: aminocyclitols, aminoglycosides (topical agents), bacitracins, fosfomycin, nitrofurans, phenicols, sulphonamides, tetracyclines, and trimethoprim.

4. Category IV: Low Importance

Antimicrobials in this category were currently not used in human medicine. Antimicrobial classes specified in this category included: flavophospholipols (Bambermycin), and Ionophores.

2.1.1.4. Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Center for Veterinary Medicine October 23, 2003

Guidance to the Industry #152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Ranking of antimicrobial drugs according to their importance in human medicine (Appendix A)

Purpose: To describe a process as part of the pre-approval safety evaluation of veterinary medicinal products for ranking antimicrobial drugs with regard to their relative importance in human medicine. FDA recommends this ranking be considered when completing the *hazard identification* and the *consequence assessment* portions of the qualitative risk assessment outlined in this guidance document (FDA, 2003).

The possible importance rankings were defined as follows:

Critically Important: Antimicrobial drugs which meet BOTH criteria 1 and 2 below.

Highly Important: Antimicrobial drugs which meet EITHER criteria 1 or 2 below.

Important: Antimicrobial drugs which meet EITHER criterion 3 and/or 4 and/or 5.

Criteria: In developing criteria for ranking antimicrobial drugs with regard to their importance in human medicine, the FDA considered broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance. The criteria are ranked from most to least important, e.g. criterion 1 is the most important.

1. Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease

The Infectious Disease Society of America (IDSA) guidelines on the treatment of diarrhea and other sources such as the Sanford Guide detail the drugs typically used in the treatment of food-borne diseases.

2. Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease

- A. Includes antimicrobials like vancomycin and linezolid for MRSA infections. Although they are not the "sole" therapy, they are one of only a few alternatives.
- B. This would also include a drug like polymyxin where it is one of few alternatives for multi-drug resistant *Pseudomonas aeruginosa* infections.
- C. Rifampin is not only a drug used to treat TB but also it is an essential part of the treatment regimen as the cure rate is lower without it.
- D. Serious diseases are defined as those with high morbidity or mortality without proper treatment regardless of the relationship of animal transmission to humans. For example, rifampin is an essential drug to treat disease caused by *Mycobacterium tuberculosis* (high morbidity and mortality if untreated) even though this is a human pathogen. Gonorrhea occurs only in humans and is not lethal but can result in sterility if left untreated (high morbidity).

3. Antimicrobials used to treat enteric pathogens in non-food-borne disease

Enteric pathogens may cause disease other than food-borne illness. For instance, *E. coli*, which causes food-borne disease, is also capable of causing diseases as diverse as urinary tract infections and neonatal meningitis.

4. No cross-resistance within drug class and absence of linked resistance with other drug classes

- A. Absence of resistance linked to other antimicrobials makes antimicrobials more valuable. An example is quinolone resistance in pneumococci, which currently does not appear linked to penicillin resistance. On the other hand, penicillin resistance appears to be linked to macrolide, tetracycline, and trimethoprim-sulfamethoxazole resistance in pneumococci.
- B. Cross-resistance within antimicrobial classes and absence of linked resistance may change over time and will need to be updated periodically.
- C. In this context, “cross-resistance” refers to the transmission of resistant determinants between bacterial species or genera and does not refer to transmission of resistant organisms between animals and humans. This is addressed in the release assessment part of the guidance.

5. Difficulty in transmitting resistance elements within or across genera and species of organisms

- A. Antimicrobials to which organisms have chromosomal resistance would be more valuable compared to those antimicrobials whose resistance mechanisms are present on plasmids and transposons.
- B. This does not refer to “ease of transmissibility” from animals to humans of the resistant pathogen as this is addressed elsewhere in the guidance in the release assessment.

2.1.1.5. Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia, Version 1.0 (2018) (Commonwealth of Australia)

Purpose: To provide information to regulators and users of antibacterials on their importance in the treatment of infections in animals and humans, and the seriousness of the consequences should resistance emerge or be amplified (ASTAG, 2018).

The Antibacterial Importance Ratings categorises each antibacterial as either of ‘High’, ‘Medium’ or ‘Low’ importance for the mitigation of antibacterial resistance.

Low Importance: There are a reasonable number of alternative antibacterials in different classes available to treat or prevent most human infections even if antibacterial resistance develops.

Medium Importance: There are some alternative antibacterials in different classes available to treat or prevent human infections, but less than for those rated as Low Importance.

High Importance: These are essential antibacterials for the treatment or prevention of infections in humans where there are few or no treatment alternatives for infections. These have also been termed “last resort” or “last line” antibacterials.

The potential for all antibacterials to select for resistance is recognised, not just to the agent itself, but also cross-resistance (to agents from the same or similar classes), and the co-selection of resistance (linked resistances in the same bacterial strain to unrelated antibacterial classes). Cross-resistance is more immediate and a primary consideration for antibacterial classes that might be shared between human and animal health.

In general, it is expected that antibacterials with a High rating would have restricted use in animals producing food for human consumption (which includes cattle, pigs, poultry, sheep, and some horses). The use of antibacterials with High ratings in animals will be considered appropriate when national stewardship guidelines are available, or in ‘exceptional circumstances’. For the purposes of this document, exceptional circumstances are defined as:

Based on culture and susceptibility testing, there are no effective alternate agents and the animal is not destined for human consumption.

It is important that all antibacterials are used appropriately regardless of their importance rating because, when resistance emerges to Low and Medium Importance agents, High Importance agents will be required more often. This will accelerate the development of resistance in these agents.

As part of the 'Antibacterial Importance Ratings categories' a legend is provided with a scoring system of antimicrobials under the descriptions of 'prophylactic use', 'therapeutic use' and 'restriction on use' that reflect the current use of the antimicrobials in Australian human medicine (see Annex 2).

2.1.1.6. Ranking of the Importance of Antimicrobials against bacteria which affect human Health through Food Commodities (provisional translation). Last amended March 31, 2014. - Food Safety Commission of Japan.

Purpose: As basic material to be used in risk assessment of foodborne antimicrobial resistant bacteria, the Food Safety Commission of Japan introduced a ranking of antimicrobials according to their importance for the treatment of human infections with antimicrobial-resistant bacteria through food commodities (Food Safety Commission of Japan, 2014). The ranking was developed based on reference materials and documents submitted to the Ministry of Agriculture in Japan. It was meant to complement the consequence assessment used in the hazard identification. The ranking focusses on a risk assessment of foodborne antimicrobial-resistant bacteria. Various organisations in Japan (e.g. Japanese Society of Chemotherapy, Japanese Association of Infectious Diseases, Food Safety Commission of Japan, etc.) collected and analyzed information on human antimicrobials, including:

- antimicrobial activity and biological characteristics of target pathogens,
- pharmacokinetic/pharmacodynamic modelling in humans for a given antimicrobial,
- amount and frequency of use,
- administration route and dosage,
- mechanisms and emergence of antimicrobial resistance.

In order to rank Japanese human antimicrobials based on their importance to human medicine, four points were considered for each antimicrobial:

- availability of alternative antimicrobials for human therapy on the occasion/s of antimicrobial-resistant bacteria.
- antimicrobial activity and spectrum against target pathogens for human diseases.
- severity of human diseases caused by target pathogens requiring antimicrobial treatment.
- mechanism/s by which bacteria develop resistance to the antimicrobial.

Based on the above, the following criteria were developed for ranking antimicrobials:

I: Critically important

An antimicrobial which could be the only one to work specifically against a certain human disease, or when there is hardly any alternative for the drug.

(e.g. 15-ring macrolides, fluoroquinolones, 3rd- and 4th-generation cephalosporins, etc.)

II: Highly important

There are some effective alternative drugs available in a case where antimicrobial-resistant bacteria against the corresponding antimicrobial have been selected, but the number of these drugs is extremely low compared to those ranked as III.

(e.g. streptomycin, 2nd-generation cephalosporins, erythromycin, etc.)

III: Important

There are abundant, effective alternative drugs available either for the same or different types of antimicrobials, even if antimicrobial-resistant bacteria have been selected against the corresponding antimicrobial.

(e.g. kanamycin, sulfonamides, 1st-generation cephalosporins, etc.)

2.1.1.7. Discussion and conclusions

In total, six sources of international documents could be identified that detail criteria for ranking antimicrobials based on importance to human medicine. In all cases, predefined criteria, based on consultation with experts, were used to establish an antimicrobial categorisation system.

The purpose of the various categorisation systems included their use either as part of the antimicrobial risk assessment process of veterinary medicinal products or foodborne pathogens, or to improve antimicrobial stewardship/prudent use in humans and animals.

Several aspects of the criteria and subsequent categorisation are not fully explained. For instance, the questions posed to the experts are not listed. Also, the indications are not listed for the antimicrobials to further understand which serious infections the antimicrobials are reserved for. Also, it is unclear as to whether the WHO Critically Important Antimicrobials list was considered and to what extent. Bacterial resistance is mentioned in the description of the categories but not specified for each antimicrobial class. In the description of the various criteria, both the importance of the antimicrobial to human medicine and antimicrobial resistance are mentioned. However, the balance between these two aspects is not stated in the final categorisation of antimicrobials. For example, for certain antimicrobial classes, antimicrobial sub-classes or individual molecules of that class are included in different categories, but this approach could be questioned where bacterial resistance genes code for entire antimicrobial classes (e.g. ESBL genes, *cfp* gene, *mec* genes, etc).

Examining the criteria selected and used by various third parties, in order of priority, reveals a number of common aspects that allows ranking the criteria based on their importance:

Top priority criterion: A common criterion stated as a top priority was the specification of antimicrobials that are considered vital to human medicine. Various descriptions are used to convey the importance of these antimicrobials including essential, "last resort", limited or no alternatives for serious infections (life-threatening) or medical cases where there is antimicrobial resistance or multi-resistance to these antimicrobials. One third party stated that the designation of these essential antimicrobials should be tailored to highly specific patients and settings, when all alternatives have failed. Only one third party stated a one of the top priorities that antimicrobials used for the treatment of foodborne enteric pathogens.

Second priority criterion: A common theme for the second priority of antimicrobials important for human medicine was specifying those that are important for treatments, but where limited alternatives are available, in case of antimicrobial resistance. One third party stated these antimicrobials should be those used to treat either zoonotic infections or bacteria acquiring resistance genes from non-human sources, whereas this was stated as a top priority from another third party

Third priority criterion: Common statements for the third criterion included antimicrobials that are used either commonly or are widely available for bacterial infections. These antimicrobials include those for which there are several alternatives, including treatment options for resistant bacteria. Only one third party stated these antimicrobials as used to treat enteric pathogens in non-food-borne disease, whereas this was either a top priority or second priority from other third parties.

Apart from these three top criteria, other criteria stated included:

- Antimicrobials not currently used in human medicine
- No cross-resistance within an antimicrobial class and absence of linked resistance with other antimicrobial classes
- Difficulty in transmitting resistance elements within or across genera and species of organisms

Table 3. Summary of criteria used by third parties for designation of antimicrobials of importance in human medicine

	WHO	WHO	Canada	USA	Australia	Japan
Source document	WHO (AGISAR): Critically Important Antimicrobials for Human Medicine 6 th Revision, 2018 (WHO, 2019a)	21 st WHO List of Essential Medicines, 2019 (WHO, 2019b)	Health Canada: Categorization of Antimicrobial Drugs Based on Importance in Human Medicine, 2009 (Health Canada, 2009)	FDA: Guidance for industry #152, 2003 (FDA, 2003)	Importance Ratings and Summary of Antibacterial Uses in Human and Animal Health in Australia, Version 1.0, 2018 (ASTAG, 2018)	Ranking of the Importance of Antimicrobials against bacteria which affect Human Health through Food Commodities, 2014 (Food Safety Commission of Japan, 2014)
Objectives	Intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that all antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.	To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance	Purpose of this document is to assist the microbiological safety assessment of pre- and post-market evaluation of veterinary antimicrobials. This also provides a rationale for priority setting and identifying the level of detail required for risk assessments related to antimicrobial resistance.	Appendix describes a process for ranking antimicrobial drugs with regard to their relative importance in human medicine. FDA recommends this ranking be considered when completing the hazard identification and the consequence assessment portions of the qualitative risk assessment outlined in this guidance document.	Document is intended to provide information to regulators and users of antibacterials on their importance in the treatment of infections in animals and humans, and the seriousness of the consequences should resistance emerge or be amplified.	Food Safety Commission of Japan introduced the ranking for use in the “Assessment Guideline for the Effect of Food one Human Health Regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals”.

	WHO	WHO	Canada	USA	Australia	Japan
Criterion (Priority order) 1	Antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people.	Antibiotics that should be treated as “last resort” options, but tailored to highly specific patients and settings, when all alternatives have failed (e.g. serious, life-threatening infections from multi-drug resistant bacteria)	Essential for the treatment of serious bacterial infections and limited or no availability of alternative antimicrobials for effective treatment in case of emergence of resistance to these agents.	Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease	High Importance: Essential antibacterials for the treatment or prevention of infections in humans where there are few or no treatment alternatives for infections. These have also been termed “last resort” or “last line” antibacterials.	Critically important: An antimicrobial which could be the <u>only one</u> to work specifically against a certain human disease, or when there is <u>hardly any alternative</u> for the drug.
2	Antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from non-human sources, (2) bacteria that may acquire resistance genes from non-human sources.	Antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications.	Could be used to treat a variety of infections including serious infections and for which alternatives are generally available. Resistant bacteria are still susceptible to other antimicrobials.	Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease.	Medium Importance: There are some alternative antibacterials in different classes available to treat or prevent human infections, but less than for those rated as Low Importance.	Highly important: There are <u>some</u> effective alternative drugs available in a case where antimicrobial-resistant bacteria against the corresponding antimicrobial have been selected, but the number of these drugs is extremely low compared to those ranked as Important.

	WHO	WHO	Canada	USA	Australia	Japan
3	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.	Antibiotics that should be widely available, as 1 st or 2 nd choice options, affordable and quality-assured.	Treatment of bacterial infections for which alternatives are generally available. Resistant bacteria are still susceptible to other antimicrobials.	Antimicrobials used to treat enteric pathogens in non-food-borne disease.	Low Importance: There are a reasonable number of alternative antibacterials in different classes available to treat or prevent most human infections even if antibacterial resistance develops.	Important: There are <u>abundant</u> , effective alternative drugs available either for the same or different types of antimicrobials, even if antimicrobial-resistant bacteria have been selected against the corresponding antimicrobial.
4	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.		Antimicrobials not currently used in human medicine.	No cross-resistance within drug class and absence of linked resistance with other drug classes.		
5	The antimicrobial class is used to treat			Difficulty in transmitting		

	WHO	WHO	Canada	USA	Australia	Japan
	infections in people for which there is evidence of transmission of resistant bacteria (e.g. non-typhoidal <i>Salmonella</i> and <i>Campylobacter spp.</i>) or resistance genes (high for <i>E. coli</i> and <i>Enterococcus spp.</i>) from non-human sources.			resistance elements within or across genera and species of organisms.		

2.1.2. Criteria in human medicine at Member State level

Members of the Agency's Committee on Medicinal Products for Human Use (CHMP) were requested to provide information on the work known at Member State level on the ranking of antimicrobial agents based on their importance for human medicine. Information was received from the following countries: Germany, Portugal, Ireland and France, which is summarised below. It is worth noting that there may be legislation or national action plans restricting use of certain antimicrobials in those European Union Member States that did not provide a response to the EMA request.

2.1.2.1. Existing recommendations on antimicrobials in human medicine

In **France**, the agency for human products (ANSM), in 2013², established a list of critically important antimicrobials for humans, which was updated in 2015³. This list is intended to prioritise antimicrobials according to their importance in humans. No consideration was given to the use in animals. Two categories were identified:

Category 1: Antimicrobials that are particular generators of bacterial resistance:

amoxicillin/clavulanic acid combinations, cephalosporins in particular 3rd-and 4th-generations, other cephalosporins: ceftriaxone. Of more concern for the oral route are: fluoroquinolones, temocillin*

Category 2: Last resort antimicrobials:

daptomycin, glycopeptides**, linezolid and tedizolid (against Gram-positive bacteria), colistin injectable, penems**, fenicoles, tigecycline (against Gram-negative bacteria), fosfomycin injectable (against Gram-positive and Gram-negative bacteria).

*selection pressure linked to an un-optimised dose; **particular generator of bacterial resistance

In **Ireland**, a ranking of antimicrobial agents based on the importance for human use exists. The information is taken from the Irish Department of Health and Department of Agriculture's One Health Report on antimicrobial use and antimicrobial resistance. The report is mostly based on surveillance data for 2016, with the exception of carbapenemase producing *enterobacteriaceae* (CPE) data for 2017 in humans (for details see section 1.6, page 18 of that report)⁴.

Most important antimicrobials are carbapenems (meropenem, ertapenem), polymyxins (colistin) and oxazolidinones (linezolid and tedizolid).

Very important antimicrobials are 4th-generation cephalosporins (cefepime), 5th-generation cephalosporins (ceftaroline), monobactams (aztreonam), fluoroquinolones (ciprofloxacin, levofloxacin), glycylycylines (tigecycline), lipopeptides (daptomycin) and aminoglycosides (amikacin).

Important antimicrobials are 3rd-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime), macrolides (azithromycin, clarithromycin), glycopeptides (vancomycin, teicoplanin), phosphonic acid derivatives (fosfomycin), antimicrobials used to treat mycobacterial infections.

In **Germany**, to date there is no official ranking of antimicrobial substances based on importance for human use.

In **Portugal**, to date there is no official ranking of antimicrobial substances based on importance for human use. However, the Portuguese national competent authority performs an epidemiologic surveillance of the consumption of certain antimicrobial substances in human medicine used in

² http://ansm.sante.fr/content/download/56371/725211/version/1/file/Rapport_Antibiotiques-Critiques_Novembre2013.pdf

³ <http://ansm.sante.fr/content/download/85395/1077521/version/1/file/ATBC-antibiotiques-critiques-actualisation2015.pdf>

⁴ <https://health.gov.ie/wp-content/uploads/2019/01/One-Health-Report-on-Antimicrobial-Use-Antimicrobial-Resistance.pdf>

hospitals (carbapenems, fluoroquinolones, cephalosporins) and the community (penicillins, other beta-lactam antimicrobials, macrolides, lincosamides and streptogramins, quinolones, beta-lactamase sensitive penicillins, combinations of penicillins, 3rd- and 4th-generation cephalosporins, fluoroquinolones), the results of which are made publically available every month on the Infarmed's website.

In addition, according to the National Pharmacy and Therapeutics Commission (CNFT), a list of recommendations for the proper use of antimicrobials in humans is provided: All prescriptions of antimicrobials must have a written justification. All health institutions must have a local antimicrobial stewardship program that is responsible for auditing and if necessary, intervening in the prescription of antimicrobials, and having the power to change the antimicrobial. For use of carbapenems and quinolones, the antimicrobial stewardship program team must check all prescriptions during the first 96 hours. Quinolones, due to their side effects as well as their direct association with selection of resistant microorganisms, should be restricted to treatment of infections where there is no other alternative, or to serious infections where alternatives are less effective (e.g. *Legionella pneumophila*). Moreover, the CNFT has issued a specific guideline on the use of antimicrobials. In that document, among other points, the CNFT recommends that each local pharmacy commission, together with the local antimicrobial stewardship program team, define the antimicrobials that are to be restricted and the criteria for its use. In addition, 'stop orders' and intravenous to oral recommendations are provided.

2.1.2.2. Discussion and conclusions

Based on the limited information provided, it would appear that, to date, in human medicine there are some recommendations on prioritisation of the use of specific antimicrobial substances or classes at Member State level. Portugal informed on a recommendation to restrict quinolones to treatment of infections where there is no other alternative or to serious infections where alternatives are less effective. Reasons given for this recommendation are the side effects of this antimicrobial class as well as their direct association with selection of resistant microorganisms. Pertinent to the Portuguese recommendation, a recent European Commission decision⁵ is of note: due to the serious, disabling and potentially permanent side effects of quinolone and fluoroquinolones the marketing authorisation of medicines containing cinoxacin, flumequine, nalidixic acid, and piperimidic acid was suspended in March 2019. Furthermore, the use of the remaining fluoroquinolone antimicrobials was restricted, i.e. they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);
- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antimicrobial medicines commonly recommended for these infections cannot be used.

In addition, Portugal, Ireland and France reported either on the surveillance of the consumption of certain antimicrobial substances or on rankings based on the importance of antimicrobials for humans. Ireland allocates antimicrobials to three different categories: 'most important', 'very important', 'important'. In France, antimicrobials were denoted as 'last resort antimicrobials' or as 'particular inducers of bacterial resistance', some of which were considered to be 'of more concern for the oral

⁵ <https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products>

route'. The criteria used for the selection of antimicrobials were not defined or explicitly mentioned, i.e. there is no information available detailing the underpinning criteria for these categories.

2.2. Criteria used for designation of antimicrobials of importance in veterinary medicine

As on the human side, international organisations, the European Union and several Member States have developed rankings for antimicrobials by taking into account their importance for the veterinary sector. These rankings were developed with the purpose to provide an appropriate balance between animal health needs, human health needs and public health considerations. The different categorisations aim to prioritise risk management measures such as limiting their use in animals to preserve their effectiveness both in human and veterinary medicine.

Recommendations have been made on the international and European level by addressing in the first place the restriction or prohibition of growth promotion use, an overall reduction in use of all antimicrobial classes as well as the promotion of responsible and prudent use principles. For certain antimicrobial classes that are critically important, both for human and animal health, more specific recommendations are made on the conditions of use in particular for use in food-producing animals e.g. not to use these classes as first line treatments, as preventive treatment (prophylaxis), for disease control (metaphylaxis) or for off-label use.

2.2.1. Criteria in veterinary medicine at the international level

2.2.1.1. OIE list of Antimicrobials of veterinary importance

Following two WHO/FAO/OIE workshops 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 in 2019 (OIE, 2019). The OIE list is based on a questionnaire sent to all OIE member countries.

Purpose: To identify antimicrobials that are critically important in veterinary medicine to complement the identification of critically important antimicrobials used in human medicine. Criteria for the identification of these antimicrobials of critical importance in animals should be established. The overlap of critical lists for human and veterinary medicine should provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.

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 antimicrobials agents. This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.

- If both these criteria are fulfilled the compound or class is regarded as a veterinary critically important antimicrobial agent (VCIA).
- If one of these criteria are fulfilled the compound or class is regarded as a veterinary highly important antimicrobial agent (VHIA).
- If none of these criteria are fulfilled the compound or class is regarded as a veterinary important antimicrobial agent (VIA).

The OIE list of antimicrobial agents of veterinary importance includes recommendations on antimicrobial usage.

The basic recommendation states that “any use of antimicrobial agents in animals should be in accordance with the OIE standards on the responsible and prudent use laid down in the Chapter 6.9 of the Terrestrial Animal Health Code and in the Chapter 6.3 of the Aquatic Animal Health Code. The responsible and prudent use of antimicrobial agents does not include the use of antimicrobial agents for growth promotion in the absence of risk analysis.”

Among the VCIA in the OIE list, some are considered to be critically important both for human and animal health; this is currently the case for fluoroquinolones, the 3rd- and 4th-generation cephalosporins and colistin. These antimicrobial classes should not be used for prevention or as a first line treatment and their use should ideally be based on the results of bacteriological tests. Off-label use should be limited and reserved for instances where no alternatives are available.

The OIE also recommend that classes in the WHO category of highest priority critically important antimicrobials should be the highest priorities for countries in phasing out use of antimicrobial agents as growth promoters.

A specific recommendation is available for antimicrobial classes or sub classes used only in human medicine:

“Recognising the need to preserve the effectiveness of the antimicrobial agents in human medicine, the OIE advises that careful consideration should be given regarding their potential use (including extra-label/off-label use) / authorisation in animals.” (OIE, 2018; OIE, 2019)

2.2.1.2. WHO Guidelines on use of medically-important antimicrobials

In 2017, WHO published guidelines on use of medically-important antimicrobials in food-producing animals (WHO, 2017). These guidelines were developed by the Guideline Development Group (GDG) using the WHO guideline development process and are based on two systematic literature reviews and one meta-analysis 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.

Purpose: These guidelines present evidence-based recommendations and best practice statements on use of medically important antimicrobials in food-producing animals, based on the WHO Critically Important Antimicrobials List. They aim primarily to help preserve the effectiveness of medically important antimicrobials, particularly those antimicrobials judged to be critically important to human medicine and also help preserve the effectiveness of antimicrobials for veterinary medicine, in direct support of the WHO global action plan on AMR.

The recommendations and best practice statements of the WHO guidelines on use of medically important antimicrobials in food-producing animals are summarised here after.

Recommendation 1: Overall antimicrobial use

We recommend an overall reduction in use of all classes of medically important antimicrobials in food-producing animals. Strong recommendation, low quality evidence.

Recommendation 2: Growth promotion use

We recommend complete restriction of use of all classes of medically important antimicrobials in food-producing animals for growth promotion. Strong recommendation, low quality evidence

Recommendation 3: Prevention use (in the absence of disease)

We recommend 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. Strong recommendation, low quality evidence.

Recommendation(s) 4: Control and treatment use (in the presence of disease)

Recommendation 4a

We suggest 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. Conditional recommendation, very low quality evidence.

Recommendation 4b

We suggest 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. Conditional recommendation, very low quality evidence

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.

Best practice statement 1

Any new class of antimicrobials or new antimicrobial combination developed for use in humans will be considered critically important for human medicine unless categorised otherwise by WHO.

Best practice statement 2

Medically important antimicrobials that are not currently used in food production should not be used in the future in food production including in food-producing animals or plants.

2.2.1.3. International (Third Country) position

A review was undertaken to investigate whether third countries (outside the European Union) had completely restricted the use of certain antimicrobials (or classes of antimicrobials) in animals. The primary regions assessed (by direct contact with, and examination of relevant documents published by, formal regulatory bodies) were the United States of America, Canada, Australia, New Zealand, South Africa and Japan. In all cases, a variety of regulatory steps have been undertaken to collect data and conduct on-going surveillance of antimicrobial use and antimicrobial resistance patterns in order to more precisely define the nature and extent of the antimicrobial resistance problem. In addition, many jurisdictions have attempted to provide all stakeholder groups with proposed timelines for key decisions to be made once appropriate data have been collated, or scientific committees have concluded their deliberations. As an example, in September 2018, the FDA Centre for Veterinary Medicines (CVM) published a position paper on “Supporting Antimicrobial Stewardship in Veterinary Settings – Goals for Fiscal Years 2019-2023”⁶. This exercise outlined the pre-review and post-approval surveillance and monitoring steps that the CVM would conduct in the coming years to promote antimicrobial stewardship and acknowledged the roles all stakeholders needed to adopt to stem the development of antimicrobial resistance. Similar guidance programmes were also adopted in other jurisdictions, along with generic recommendations on prudent use principles, particularly involving the use of critically important antimicrobials.

⁶ <https://www.fda.gov/media/115776/download>

In addition to the various regulatory agencies, professional bodies such as national veterinary associations have also published guidance notes to promote conscientious oversight and evidence-based, responsible decision making in prescribing practices in order to safeguard animal, public and environmental health.

Whilst acknowledging all the above action steps and guidance notes, there was no evidence that the regulatory agencies specified had (to date) taken the step to legally restrict the use of a specific antimicrobial (or antimicrobial family) to human use exclusively but the relevant authorities in both Argentina and Uruguay have taken a decision to restrict the use of colistin to human use only. However, it is unknown if applications for authorisations relating to specific antimicrobials for use in animals have been declined in third countries (as a policy decision). In addition, it is unknown if any of the action steps or reviews currently being undertaken will lead to such restrictions in these major markets in the near future. Certain sub-restrictions do exist at present in veterinary clinical practice, such as the ban on the use of fluoroquinolones in poultry in certain jurisdictions, and partial restrictions that apply to the use of 3rd- and 4th-generation cephalosporins in the USA.

2.2.2. Criteria in veterinary medicine at the European Union level

2.2.2.1. Criteria used for categorisation of antimicrobials

2.2.2.1.1. AMEG

In July 2017, the European Commission asked the EMA to update its advice regarding the categorisation of antimicrobials and the early hazard characterisation published in 2014 (EMA/AMEG, 2014). Regarding the categorisation of antimicrobials, the European Commission requested that the AMEG review and update the original classification giving consideration to, in particular: the categorisation of aminoglycosides and penicillins; the need for further refinements of the criteria for the categorisation; improved communication of the categorisation; and, the need for additional categorisation for antimicrobials categorised by the World Health Organization (WHO) and OIE. The EMA is expected to finalise this advice by December 2019.

Although the revised AMEG advice is still in draft form, the updated draft criteria are as follows:

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

The updated draft categorisation considers all classes of antimicrobials and includes additional criteria such as the availability of alternative antimicrobials in veterinary medicine. The refined classification now comprises four categories, from A to D, each of them labelled with a key action word for more clarity.

- Category A ("Avoid") includes antimicrobial classes not currently authorised in veterinary medicine in the European Union. For these medicines, in the absence of established maximum residue limits for foodstuffs of animal origin, their use in food-producing animals is not allowed, and they may be

given to individual companion animals only under exceptional circumstances in compliance with the prescribing “cascade”⁷.

- Category B (“Restrict”) comprises quinolones, 3rd- and 4th-generation cephalosporins and polymyxins. Use of these antimicrobials in animals should be restricted to mitigate the risk to public health. They should be considered only for treatment of clinical conditions when there are no alternative antimicrobials in categories C or D that could be effective. Especially for this category, use should be based on the results of antimicrobial susceptibility testing, whenever possible.
- Category C (“Caution”) covers antimicrobials for which, in general, alternatives in human medicine exist in the European Union, but in veterinary medicine there are only few alternatives in certain indications. Antimicrobial classes that may select for resistance to a substance in Category A through specific multi-resistance genes have also been placed in this category. Category C antimicrobials should only be used when there are no antimicrobial substances in Category D that would be effective.
- Category D (“Prudence”) is the lowest risk category. Antimicrobials belonging to this category can be used in animals in a prudent manner. This means that unnecessary use and unnecessarily long treatment periods should be avoided and class treatment should be restricted to situations where individual treatment is not feasible.

2.2.2.2. Existing recommendations on restriction of antimicrobials in animals

2.2.2.2.1. European Union guidelines for the prudent use of antimicrobials in veterinary medicine

In 2015, the European Commission published a Notice on Guidelines for the prudent use of antimicrobials in veterinary medicine (Official Journal of the European Union, 2015), which sets out measures to be considered by Member States when developing and implementing national strategies to combat antimicrobial resistance.

These guidelines include information on possible actions that may be implemented at the European Union level to facilitate appropriate use, such as referrals and summary of product characteristics harmonisation and gives the principles for the prudent use of antimicrobials.

Recommendations are available for critically important antimicrobials that are only authorised for human use (e.g. carbapenems and tigecycline). In particular, it is stated that the off-label use of products containing such antimicrobials in non-food-producing animals should be avoided and strictly limited to very exceptional cases and where no other antimicrobials would be effective. Off-label use of such products may be necessary to avoid the suffering of diseased animals and should take into consideration ethical and public health concerns. The use of critically important antimicrobials should be limited to cases where no other alternative is available.

In the annex of this guideline examples of actions implemented by Member States are provided as well as a summary of EMA/CVMP recommendations on responsible use.

2.2.2.2.2. EMA/CVMP recommendations

The Committee for Medicinal Products for Veterinary Use (CVMP) of the European Medicines Agency has made recommendations on the use of antimicrobials, most of which belong to those classified as

⁷ Article 11 of Directive 2001/82/EC and Articles 107, 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.

critically important antimicrobials for human use, namely (fluoro)quinolones, 3rd- and 4th-generation cephalosporins, macrolides, aminoglycosides, aminopenicillins and their beta-lactamase inhibitor combinations as well as less critical classes such as pleuromutilins, lincosamides and streptogramins (EMA/CVMP/AWP, 2013; EMA/CVMP/AWP, 2018b; EMA/CVMP/AWP, 2019, DRAFT; EMA/CVMP/SAGAM, 2011; EMEA/CVMP/SAGAM, 2007; EMEA/CVMP/SAGAM, 2009b). In certain cases, the recommendations have resulted in referrals or recommendations to be further implemented, e.g. a referral on veterinary medicinal products containing systemically administered 3rd- and 4th-generation cephalosporins in food-producing animals. Other recommendations related to 3rd- and 4th-generation cephalosporins have resulted in the deletion of the target species poultry from the product information as well as to a prohibition of off-label use in poultry, which in the product information of relevant veterinary medicinal products is reflected as the contraindication "Do not use in poultry" (EMA/CVMP, 2012).

In addition, specific precautionary phrases have been included in the summary of product characteristics for products containing fluoroquinolones and 3rd- and 4th-generation cephalosporins that are administered systemically, i.e. "The antimicrobial should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials/first line treatment."

The CVMP has also made recommendations on the risk of transfer of resistant bacteria i.e. MRSA (meticillin-resistant *Staphylococcus aureus*), MRSP (meticillin-resistant *Staphylococcus pseudintermedius*), the risk of antimicrobial resistance transfer from companion animals and on the off-label use of antimicrobials in veterinary medicine (EMA/CVMP/AWP, 2015; EMA/CVMP/AWP, 2018a; EMEA/CVMP/SAGAM, 2009a; EMEA/CVMP/SAGAM, 2011). All these recommendations⁸ are based on the considerations of the CVMP experts on antimicrobials (CVMP Antimicrobials Working Party (AWP), formerly known as Scientific Advisory Group on Antimicrobials (SAGAM)).

2.2.2.2.3. EMA advice on colistin

In December 2014, the CVMP recommended the restriction of the indications for use of colistin to treatment of enteric infections caused by susceptible non-invasive *E. coli* only, that any indications for prophylactic use should be removed and that the treatment duration should be limited to the minimum time necessary for the treatment of the disease and not exceed 7 days. In April 2016, the CVMP recommended the withdrawal of the marketing authorisations for all veterinary medicinal products for oral use containing colistin in combination with other antimicrobial substances.

Following the discovery of a new horizontally transferable colistin resistance mechanism (*mcr-1* gene) in 2015 (Liu et al., 2015), the European Commission requested the EMA to update its previous advice on the impact of and need for colistin use for human and animal health (EMA, 2013). Since then, seven additional *mcr* homologues (*mcr-2 to -8*) have been identified in *Enterobacteriaceae*. Colistin-resistance may be spread *via* passing on chromosomal genes to daughter colonies (vertical transmission) or *via* mobile genetic elements (horizontal transmission).

The updated recommendation (EMA/AMEG, 2016) advises that:

- European Union Member States should minimise sales of colistin for use in animals, to achieve a 65% reduction in European Union-wide sales; Reduction in use of colistin should be achieved without an increase in the use (in mg/PCU) of fluoroquinolones, 3rd- and 4th-generation cephalosporins or overall consumption of antimicrobials.

⁸ <https://www.ema.europa.eu/en/veterinary-regulatory/research-development/scientific-guidelines/safety-residues/safety-residues-antimicrobials>

- Colistin be added to a more critical category of medicines, reserved for treating clinical conditions for which there are no effective alternative treatments.

2.2.2.2.4. EMA advice on tigecycline

In April 2013, the European Commission requested advice from the European Medicines Agency on the impact of the use of antibiotics in animals on public and animal health and measures to manage the possible risk to humans (EMA/AMEG, 2013).

The first question in this Commission request was related to tigecycline, an antimicrobial currently not authorised in veterinary medicine. A summary of the answer given by the EMA is provided here-after:

“Tigecycline, an antibiotic of the glycylicycline class, is not currently approved for use in animals. The extent of off-label use of this antibiotic in veterinary medicine cannot currently be quantified, although there is some anecdotal evidence of the use in dogs and cats of tigecycline products authorised for human use. The Agency advised that currently no need is foreseen for the authorisation of tigecycline for use in animals. If the need for an approval of tigecycline as a veterinary medicine should ever arise in the future, authorisations should only be considered on the basis of a positive benefit-risk assessment which would take into account the risk of transfer of resistance to humans. However, based on the current situation, it is unlikely that a marketing authorisation could be granted in light of the need for this antibiotic in human medicine.”

2.2.3. Criteria in veterinary medicine at member state level

CVMP members were requested to provide information on existing national legislation on prohibiting or restricting antimicrobials for use in animals and the work done at member state level on ranking of antimicrobial agents based on importance for human use. In response to that request, information was received from the following countries: Germany, Portugal Belgium, United Kingdom, Netherlands, Finland, Denmark, Romania, Spain, Sweden, France, Hungary, Czechia and Poland. The following summarises information received from those Member States that replied to EMA’s query. It is worth noting that there may be legislation or national action plans on prohibiting or restricting antimicrobials in those European Union Member States that did not provide a response to the EMA request.

2.2.3.1. Existing recommendations on antimicrobials in veterinary medicine

In **Germany** no legal provisions banning the use of certain antimicrobials or classes of antimicrobials in animals exist. However, since March 2018 there are legal provisions in place prohibiting the off-label use of fluoroquinolones and 3rd- and 4th-generation cephalosporins in cattle, pigs, chickens, turkeys, dogs and cats (Regulation on Veterinary Medicine Pharmacies; §12b TÄHAV, Verordnung über tierärztliche Hausapotheken⁹). These antimicrobial classes can only be used off-label if a veterinary medicinal product is authorised for the respective target animal species but for another indication and on the condition that animal health and welfare is considered to be jeopardised in that particular case. The reason(s) for off-label use must be documented. In addition, antimicrobial susceptibility testing (if feasible) is a prerequisite for any use of fluoroquinolones and 3rd- and 4th-generation cephalosporins in cattle, pigs, chickens, turkeys, dogs, cats and horses.

Portugal reported that there is no national legislation banning or restricting the use of some antimicrobials or classes of antimicrobials in animals.

⁹ https://www.gesetze-im-internet.de/t_hav/BJNR021150975.html

According to the Royal Decree on the use of antimicrobials for veterinary use in **Belgium** (chapter VI¹⁰), which came into force on July 2016, the use of critical important antimicrobials, i.e. 1st- to 3rd-generation fluoroquinolones as well as 3rd- and 4th-generation cephalosporins in food-producing animals, is subject to the condition of antimicrobial susceptibility testing (if feasible), demonstrating that the causative bacterial pathogen is not susceptible to less important antimicrobials. Veterinary medicinal products for use in equines and veterinary medicinal products for intramammary use are exempted from that rule. In addition, exemptions are possible in cases of an emergency, when animal health welfare is jeopardised.

The **United Kingdom** does not have any national legislation restricting the use of specific antimicrobials/classes in animals. There are various voluntary restrictions in place from livestock bodies and quality assurance schemes e.g. the poultry sector stopped the use of 3rd- and 4th-generation cephalosporins and colistin, and restricted the use of fluoroquinolones (and macrolides in the meat sector)¹¹, the 'Red Tractor' quality assurance scheme restricts the use of high priority critically important antimicrobials (3rd- and 4th-generation cephalosporins, fluoroquinolones, colistin) in pigs, sheep and cattle¹².

In the **Netherlands**, the legislation lays down some rules related to the use of antimicrobials in animals, for example mandatory antimicrobial susceptibility testing before the prescription of 3rd- and 4th-generation cephalosporins and fluoroquinolones, prohibition of preventive use of antibiotics in farm animals, prescription and administration of antimicrobials in livestock farming only by veterinarians after clinical inspection of the animals on the farm, and the obligation for veterinarians and farmers to register the prescription and administration of antimicrobials in a designated (central) data base. Additional restrictions on the use of antimicrobials in livestock are included in the private quality system (not legally binding but compulsory for participation in the quality system): ban on the use of 3rd- and 4th-generation cephalosporins in pig farming and ban on the use of 3rd- and 4th-generation cephalosporins for dry cow therapy.

In **Finland**, a national Decree entered into force in 1999 and listed antimicrobials, which are prohibited for use in all animal species, or are allowed to be used in animals only in accordance with the terms of the (veterinary) marketing authorisation. Since the listing consists primarily of antimicrobials for which no veterinary marketing authorisation exists, the use of those antimicrobials is, in practice, not allowed in animals. The listing was at the time compiled at the national authority level, in co-operation with human infectious diseases experts and veterinary authorities. Later on, some additions were inserted. Only the contents for the most relevant parts of the Decree as well as the listing have been provided for the development of this advice. Use of a veterinary medicinal product containing the substances listed in the following is allowed only and strictly according to the terms of the marketing authorisation (or other permit granting the right to release the veterinary medicinal product for consumption): avoparcin, vancomycin and teicoplanin; virginiamycin; 3rd- and 4th-generation cephalosporins; rifampicin and rifabutin; moxifloxacin, ofloxacin, levofloxacin and gatifloxacin (except for local treatment of eye inflammation in equines and companion animals); tigecycline; mupirocin; telitromycin; daptomycin; linezolid; quinupristin and dalfopristin; carbapenems; monobactams; temocillin; lipoglycopeptides (telavancin) and neoglycosides.

Since 2010 **Denmark** has regulated the consumption of antimicrobials for pigs through the so-called Yellow Card initiative (Danish Veterinary and Food Administration, 2013). If an established limit is

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http://www.afsca.be/productionanimale/animaux/medicamentsveterinaires/_documents/2016_07_21_KB21juli2016_AR21juillet2016_BS_MB.pdf

¹¹ <https://www.britishpoultry.org.uk/bpc-antibiotic-stewardship-report-2018/>

¹² https://assurance.redtractor.org.uk/contentfiles/Farmers-6935.pdf?_id=636643269105341095

exceeded at a pig farm, the Danish Veterinary and Food Administration can order the farmer to lower the consumption to a level below the limit. In 2016, the Yellow Card initiative was extended so that certain types of antimicrobials are regulated separately by allocation of a multiplication factor to adjust the use. This is the case for 3rd- and 4th-generation cephalosporins and fluoroquinolones and colistin (included in 2017).

By means of an Executive Order, further restrictions are laid down on the use of fluoroquinolones for production animals. Fluoroquinolones may only be used, if a sensitivity test has shown that no other antimicrobials are effective for the treatment. Furthermore, conditions are set for the use of preparations for dry cow treatment and broad-spectrum antimicrobials for the treatment of mastitis in cows. Antimicrobials for dry cow treatment may only be used after detection of pathogenic microorganisms in a milk sample from the individual cow. If antimicrobials other than simple penicillins are used for the treatment of mastitis in cattle, a milk sample must be taken for bacteriological examination and sensitivity testing prior to treatment. When the results of the laboratory tests show that the treatment selected is not optimal, the veterinarian must correct the treatment.

Romania reported the promotion of prudent use of antimicrobials in animals according to a national guideline published on the NSVFSA (National Sanitary Veterinary and Food Safety Authority) website in 2016. In addition, in 2018, national legislation on biosecurity in poultry holdings (Ord. 21/05.03.2018¹³) included special requirements for the prudent use of antimicrobials. Between 2016 and 2018, NSVFSA has developed and carried out the strategy for combating antimicrobial resistance in veterinary medicine (strategy approved by the order of the president of NSVFSA).

Spain has no specific legislation banning or restricting the use of some antimicrobials or classes of antimicrobials in animals. Nevertheless, Spain follows the criteria and measures endorsed by the AMEG relating to restrictions on use.

In **Sweden**, since 2013 the national regulation on the use of veterinary medicinal products (Swedish Board of Agriculture, SJVFS 2019: 32¹⁴) includes general restrictions regarding the use of veterinary medicinal products in animals as detailed below:

In accordance with the cascade (Article 10 of Directive 2001/82/EC), and in case where there is no veterinary medicinal product available for treatment of the current condition in animals, the veterinarian may prescribe medicines that are approved only for use in humans, provided they do not contain any of the substances listed in Annex 1 (aztreonam, ceftarolin, daptomycin, doripenem, ertapenem, etambutol, imipenem, isoniazid, linezolid, meropenem, mupirocin, rifabutin, rifampicin (the restriction does not apply to the treatment of horses with infection caused by *Rhodococcus equi*), teicoplanin, tigecycline, vancomycin) of the national regulation.

The regulation includes a possibility to make exceptions to these rules if there are exceptional reasons and the veterinarian in the individual case is authorised by the Swedish Board of Agriculture to perform such treatment.

Apart from the restrictions mentioned above, the regulation includes restrictions regarding the use of 3rd- and 4th-generation cephalosporins and fluoroquinolones in all animal species: The veterinarian may only prescribe these antimicrobials when microbiological examination and susceptibility testing shows that no other type of antimicrobials will be effective. In cases where such an antimicrobial is used, the veterinarian should justify and record the choice of the antimicrobial.

Restriction of antimicrobial use in animals in **France**: French law foresees to list critically important antimicrobials that are reserved for human use (Public Health Code Article L. 5144-1-1). In accordance

¹³ <http://legislatie.just.ro/Public/DetaliuDocument/198867>

¹⁴ <https://lagen.nu/sjvfs/2019:32>

with subsequent decrees (16 March 2016¹⁵, 18 March 2016¹⁶), two lists of critically important antimicrobials are established:

- Antimicrobials for which the prescription in veterinary medicine is subject to certain conditions: 3rd-generation cephalosporins (cefoperazone, ceftiofur, cefovecin), 4th-generation cephalosporins (cefquinome), fluoroquinolones (danofloxacin, enrofloxacin, marbofloxacin, orbifloxacin, pradofloxacin). Conditions include a mandatory examination by the veterinarian and antimicrobial susceptibility testing.
- Antimicrobials for which the prescription and delivery to animals is prohibited: 3rd- and 4th-generation cephalosporins (ceftriaxone, cefixim, cefpodoxime, cefotiam, cefotaxime, ceftazidime, cefepime, cefpirome, ceftobiprole), other cephalosporins (ceftarolin), fluoroquinolones (levofloxacin, lomefloxacin, pefloxacin, moxifloxacin, enoxacin), carbapenems (meropenem, ertapenem, doripenem, imipenem and inhibitor), phosphorus acid (fosfomycin), glycopeptides (vancomycin, teicoplanin, telavancin, dalbavancin, oritavancin), glycolcyclines (tigecycline), lipopeptides (daptomycin), monobactams (aztreonam), oxazolidinones (cycloserin, linezolid, tedizolid), riminofenacins (clofazimine), penicillins (piperacillin, piperacillin and inhibitor, temocillin, ticarcillin, ticarcillin and inhibitor), sulfones (dapson), antimicrobials against tuberculosis and leprosy (rifampicin, rifabutin, capreomycin, isoniazid, ethionamid, pyrazinamide, ethambutol, clofazimin, dapson and ferrous oxalate).

A list of human antimicrobials that are permitted under specific conditions of use was also established: fluoroquinolones (ciprofloxacin, ofloxacin, norfloxacin). These antimicrobials can be used topically against eye infections in companion animals and equines.

In **Hungary** at present there is no legislation, which would ban or restrict the use of any antimicrobials in animals.

In **Poland** there is no national legislation banning or restricting the use of some antimicrobials in animals.

In the late nineties (1998), and in line with the antimicrobials policy of the **Czech Republic**, a list of antimicrobials that should only be used under a prudent regimen was established: 3rd-generation cephalosporins (ceftiofur, cefoperazon, cefovecin), 4th-generation cephalosporins (cefquinom), ansamycins (rifaximin), aminoglycosides (gentamicin, kanamycin), (fluoro)quinolones (difloxacin, enrofloxacin, flumequine, ibafloxacin, marbofloxacin, orbifloxacin, pradofloxacin). Veterinary medicinal products containing these antimicrobials can be used only in cases where for the same purpose of use (indication) no other veterinary medicinal product, in which such limitation was not set, is not available and when the susceptibility against the active substance of the product of concern has been established¹⁷.

The list of concerned antimicrobial substances/classes was established by veterinarians in agreement with colleagues from the human sector in 1998 and the list has since then been continuously updated. The following reasons for inclusion are given: The active substance is essential for the treatment of serious infections in human medicine (e.g. treatment of tuberculosis: rifaximin: first line, kanamycin: second line). An increase in resistance was proven in relation to the use of products containing this active substance, and/or resistance can arise during the treatment course and could lead to treatment failure (e.g. (fluoro)quinolones, ansamycins). Use of the active substance leads to the selection of resistant strains (e.g. use of 3rd- and 4th-generation cephalosporins lead to the selection of bacteria carrying extended spectrum beta-lactamases (ESBLs)).

¹⁵ <https://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000032251629&categorieLien=id>

¹⁶ <https://www.legifrance.gouv.fr/eli/arrete/2016/3/18/AGRG1526116A/jo>

¹⁷ <http://uskvbl.cz/cs/registrace-a-schvalovani/registrace-vlp/seznam-vlp/aktualne-registrovane-vlp/vyhledavaci-formula-vlp>

2.2.3.2. Discussion and conclusions

Most of the Member States rely on the existing European Union recommendations on antimicrobial use in animals and have no specific legislation in place at the national level.

For Member States having specific legislation restricting antimicrobial use, these apply mainly to fluoroquinolones and 3rd- and 4th-generation cephalosporins. In some cases, other antimicrobial classes such as ansamycins, colistin, aminoglycosides and antimicrobials not currently authorised in animals are included. Restrictions include the requirement of AST showing that less important antimicrobials will not be effective, the obligation to report on the results, strict use according to the terms of the marketing authorisation, and/or prohibitions on off-label use.

Of those who responded to the EMA request, only two Member States have specific legislation prohibiting the use of some antimicrobial classes.

- In Sweden, a list of antimicrobials that should not be used in animals is available; however exceptions are permitted in very specific conditions.
- In France, a list of antimicrobials that cannot be used at all in animals is available.

The antimicrobials listed by these Member States include antimicrobials or antimicrobial classes not currently authorised in animals.

Criteria used for designating these antimicrobials are rarely stated. When stated, the criteria relate to the transfer of antimicrobial resistance from animals to humans and the importance of the antimicrobial to treat serious diseases in humans.

2.3. Summary and analysis (international, European Union, Member States)

A review of existing categorisations in human and veterinary medicine available from international organisations, third countries, the European Union, and European Union Member States can identify trends of principle criteria that could be generally retained for the establishment of criteria according to this mandate, even if the purpose of the existing categorisations may be different.

The main criteria that have been used in human medicine are:

- the importance of the antimicrobial to humans

The importance of the antimicrobial for human medicine is one of the main criteria that is retained in the majority of cases. Various descriptions are used to convey the importance of these antimicrobials including essential, "last resort", serious infections (life-threatening) or medical cases where there is antimicrobial resistance or multi-resistance to these antimicrobials.

- the availability of treatment alternatives

In addition to specifying those antimicrobials that are important for treatments, it is also considered in general whether there are no or few effective treatment alternatives available. More specifically, consideration is given to the availability of treatment alternatives against zoonotic infections, infections due to bacteria acquiring resistance genes from non-human sources, enteric pathogens in non-food-borne disease, and antimicrobial resistant or multi-resistant bacteria.

- availability and frequency of use

Consideration is given to whether or not antimicrobials are used commonly or are widely available for certain bacterial infections. In their approach to categorisation, some organisations also took into

consideration the number of people affected, as well as the amount and frequency of use of the antimicrobial.

- the transfer of antimicrobial resistance

A further main criterion is the potential of transmission of resistant bacteria or resistance genes from animals to humans. For this criterion, the resistance linked to other antimicrobials (i.e. co or cross resistance), the possibility of transmitting resistance elements within or across bacterial genera or species as well as the evidence of non-human to human transmission are typically taken into account when evaluating this criterion.

The primary objective of all existing recommendations on categorisations is that they are to be used either as part of the antimicrobial risk assessment within the marketing authorisation process of veterinary medicinal products or to improve antimicrobial stewardship or prudent use in humans and animals. Only a few specific recommendations are made regarding the use of antimicrobials in human medicine. According to the 20th WHO Model List of Essential Medicines (WHO, 2019b), antimicrobials are allocated to key access, watch, and reserve groups for the purpose of assisting in the development of tools for antibiotic stewardship at local, national and global levels, and to reduce antimicrobial resistance. Some Member States established rankings based on the importance of antimicrobials that should be considered when using antimicrobials prudently.

Some of the most restrictive measures on antimicrobial use in human medicine relate to the potential for side effects, rather than risk of antimicrobial resistance: for example, the CHMP of the EMA has published advice that fluoroquinolones should only be used under certain conditions due to their serious, disabling and potentially permanent side effects.

Restrictions are also imposed on certain antimicrobials which are thought to address an unmet medical need, and for which the indication granted clearly states that they should be used for the treatment of serious infections in patients with limited therapeutic options due to the pattern of resistance.

Criteria used for veterinary medicine include:

- the importance of the antimicrobial to animals

This is the main criterion taken into account to address the need of having antimicrobials available to treat animal diseases in general and to treat serious animal diseases in particular.

- the availability of treatment alternatives

In addition to specifying those antimicrobials that are important for treatments in animals, the absence of alternative antimicrobial treatment for serious animal diseases is also considered or whether antimicrobials are available in veterinary medicine with lower antimicrobial resistance risk to animal and public health

- the transfer of antimicrobial resistance

The knowledge of factors influencing the likelihood and possible consequence of antimicrobial resistance transfer from animals to humans are reflected, thereby considering more specifically individual mechanisms of resistance such as genes associated with mobile multi-resistance, e.g. 'cfr'.

- if the antimicrobial is authorised for use as a veterinary medicine
- the importance of the antimicrobial to human medicine according to the WHO ranking

For this criterion, the European Union situation is specifically taken into account.

While the OIE categorisation considers only the importance of the antimicrobial for animals to complement the identification of such antimicrobials used in human medicine (WHO list), the AMEG categorisation combines human and animal related criteria to balance between animal health needs, human health needs, and public health considerations.

In general, the different categorisations have the objective of aiding the development of risk management strategies such as limiting the use of antimicrobials in animals, based on public health concerns. Both WHO and OIE have recommendations regarding the antimicrobials that are only authorised in human medicine. WHO states that these antimicrobial classes should not be used in animals in the future, whereas, according to OIE, careful consideration should be given regarding their potential use in animals, including extra-label or off-label use, and authorisation. Only a few recommendations relate to the total ban of some antimicrobial classes in animals, e.g. colistin has been restricted to human use only in Argentina and Uruguay. Certain sub-restrictions exist in the USA, such as the ban of fluoroquinolones for use in poultry, and partial restrictions apply to the use of 3rd- and 4th-generation cephalosporins. Complete restriction of the use of an antimicrobial or a class of antimicrobials in animals was identified in two European countries (Sweden and France), and these are mostly limited to antimicrobials that are only authorised in humans even though other antimicrobials within the same class may be authorised in animals.

3. Considerations for the selection of the criteria

When reviewing the approach to categorisation of antimicrobials worldwide, three major criteria are regularly quoted: the importance of the antimicrobial/antimicrobial class for human and veterinary medicine, the availability of treatment alternatives, and the potential for transfer of antimicrobial resistance. According to the Regulation (Article 107(6)) similar criteria are proposed to be taken into account for the restriction of use of antimicrobials outside the terms of the marketing authorisation, i.e. the availability of other treatments for humans or for animals, the risk for animal or public health in case of development of antimicrobial resistance. Thus, these criteria are considered most important to be selected as criteria for the purpose of this mandate.

3.1. Consideration of criteria for assessing the importance of antimicrobials in human health

3.1.1. Serious bacterial diseases

Serious, i.e. life-threatening or medically debilitating, bacterial infections may be acquired in the community, in hospitals, and in other health care facilities and are associated with high mortality, if not treated promptly and effectively. Inappropriate or ineffective initial empirical treatment (and further modifications if needed), is also more likely to result in debilitating morbidity¹⁸.

Seriousness of the bacterial infection may be related to several factors, starting with the characteristics of the bacterium responsible for the infection (e.g. resistance, virulence). Increasing antimicrobial resistance has led to focus on optimisation of antibiotic therapy, with simultaneous goals of improving patient outcomes and minimising antimicrobial resistance, i.e. the contribution of that therapy to making the available antibiotics no longer effective. Another factor to take into consideration is bacterial virulence, i.e. the potential for the bacterium to produce bacterial toxins, cell surface proteins that mediate bacterial attachment, cell surface carbohydrates and proteins that protect the bacteria, hydrolytic enzymes or other features that may contribute to its pathogenicity such as the

¹⁸ Debilitating morbidity: For the purpose of applying Criterion 1, morbidity refers to the consequences and complications (other than death) that may result from a disease. Debilitating morbidity leads to long-term or permanent dysfunction.

Panton-Valentine leucocidin, a pore-forming toxin secreted by strains of community-acquired methicillin-resistant *S. aureus*.

Seriousness of the infection may also be related to patient characteristics. Certain populations such as critically ill patients, immunocompromised patients or neonates have clinical features that render them more at risk for infections with multidrug-resistant bacteria or life-threatening infections. Critically ill patients have an increased risk of developing infections and infectious complications, sometimes followed by death. Infections remain one of the most serious concerns in the critical care setting, where multidrug-resistant bacteria jeopardise effective empiric therapy. In immunocompromised patients, the patterns of infection, aetiology and organ involvement are different and the possible aetiologies of infections range from common bacterial pathogens that can affect all types of patients to opportunistic pathogens that are clinically significant only for immunocompromised hosts. An additional challenge is that antimicrobial therapy is often more complex in immunocompromised patients because of the need to rapidly initiate empiric therapy and the frequency of drug toxicity and drug interactions.

The concept of seriousness of the infection plays a central role for a correct therapeutic choice and for determining the availability of alternative antimicrobials for the treatment of these infections in human medicine.

3.1.2. Available treatment alternatives

When considering the availability of treatment options for serious bacterial infections, several aspects that can influence the efficacy of the antimicrobial should be considered, such as the site of infection, the host and the bacterial characteristics.

Additional factors that can be taken also into account are the extent of use of the antimicrobial/antimicrobial class in human medicine and/or whether it is used with high frequency in certain high risk groups where curative first choice treatment is essential.

Site of infection

Limited treatment alternatives can be due to the pharmacokinetic properties of antimicrobial and the ability to distribute to the site of infection. For certain of infections (e.g. osteomyelitis), an appropriate distribution of the antimicrobial to the site of infection is critical with infection at some sites such as infective endocarditis or bacterial meningitis defining *per se* a life-threatening infection.

Host

The heterogeneity of antimicrobial pharmacokinetics and pharmacodynamics (e.g. resistance, virulence) in special populations such as critically ill patients (e.g. admitted to an intensive care unit) or paediatric or elderly patients might potentially affect outcomes. Because of the extensive variability and possibly altered pharmacokinetics, as well as the lack of robust clinical studies and/or the safety profile of the antimicrobial agent in these patient populations, the choice of the appropriate antimicrobial agent or the choice of an appropriate dose is a complicated process, that could lead to fewer or no effective antimicrobial alternatives.

For example, in critically ill patients, dysfunction of organ systems (e.g. dysfunction of the cardiovascular and renal systems) can result in significant changes in pharmacokinetics that influence drug and dosing considerations. Absorption, distribution, metabolism and excretion may all be affected by the various disease states that define critical illness.

The availability of appropriate dosing recommendations and/or the safety profile in the paediatric population, in particular in neonates and preterm neonates, is scarce leading to few safe and effective antimicrobial options for this vulnerable population.

Moreover, impairment of the immune system, either associated with elderly patients, immunosuppression by chemotherapy or after trauma or tissue damage decreases the ability to fight infection, also restricting the antibiotic options.

Bacterial characteristics

Limited treatment alternatives can be due to bacterial resistance phenotype(s) of the strain causing infection. Acquired resistance, including multi-drug resistance, limits the availability of effective alternative antimicrobials: for example acquisition of resistance relating to the production of extended-spectrum beta-lactamase or carbapenemase is commonly identified in *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* spp. causing nosocomial infections, as well as in other organisms associated with community-acquired infections, such as *Escherichia coli*, *Salmonella enterica* and *Campylobacter* spp. If resistance emerges to an antimicrobial agent used to treat specific serious infections for which there are no or limited treatment alternatives, the consequences to health outcomes are significant and potentially life threatening. It is noteworthy to mention that not all infections due to multidrug-resistant bacteria require treatment with last-resort antimicrobials.

Antimicrobial agents thought to address an unmet medical need in human medicine

A new antimicrobial agent that belongs to a new class that has a unique mechanism of action can be assumed to be a candidate to address an unmet clinical need (EMA/CHMP, 2013). New agents of existing classes that are active against organisms resistant to other members of the same class are also potential candidates for the treatment of serious infections in patients with limited therapeutic options. These could be standalone agents or they may be present in combination with a molecule (e.g. beta-lactam agent plus beta-lactamase inhibitor) that protects them against one or more bacterial mechanisms of resistance. In these situations, a marketing authorisation for the treatment of serious infections due to selected organisms in patients with limited treatment options is usually granted after considering whether the antimicrobial addresses an unmet medical need in terms of the pattern of resistance in human medicine.

In the case of tuberculosis, existing treatments cannot effectively combat the disease because of reduced efficacy against multidrug-resistant (MDR-TB)¹⁹, pre-extensively drug-resistant (pre-XDR-TB)²⁰ and extensively drug-resistant (XDR-TB)²¹, imposing a heavy burden on patients, families and healthcare systems (WHO, 2018). New tuberculosis medicines that can overcome drug resistance may also be approved for restricted indications as part of appropriate combination regimens for pulmonary drug-resistant tuberculosis when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Overall, antimicrobial agents authorised in the European Union for the treatment of serious bacterial infections in patients with limited treatment options, indicating that it has been established that these agents address an unmet medical need related to drug resistance, should, by default, be considered for a use restricted to humans.

3.2. Resistance transfer, resistance linked to other antimicrobials

Acquisition of antimicrobial resistance occurs by gene mutation in one of the target genes or acquisition of antibiotic resistance genes carried by mobile genetic elements such as plasmids, transposons, insertion sequences, and integrative conjugative elements. Once acquired, antimicrobial

¹⁹ Multi-drug resistant tuberculosis (MDR-TB) is defined as a form of tuberculosis caused by bacteria that are resistant to treatment with at least two of the first-line anti-tuberculosis medications (drugs), isoniazid and rifampin.

²⁰ Pre-extensively drug resistant tuberculosis (pre-XDR-TB) is defined as tuberculosis with resistance to isoniazid and rifampicin and either a fluoroquinolone or a second-line injectable agent but not both.

²¹ Extensively drug resistant tuberculosis (XDR-TB) is defined as multi-drug resistant pulmonary tuberculosis (MDR-TB) plus resistance to at least one fluoroquinolone and a second-line injectable agent (amikacin, capreomycin or kanamycin).

resistance genes can be transferred to the cell progeny, known as vertical transmission, or to other bacteria of the same or different species, known as horizontal transmission, when associated with mobile genetic elements. In addition to the broad range of bacterial hosts, and potential rapid spread of the mobile genetic elements carrying resistance genes, often the acquisition of resistance also increases the likelihood of co-resistance to other compounds, since multiple resistance genes can be located on these mobile genetic elements. Moreover, it is important to know whether a resistance gene confers resistance to other antimicrobials of the same or different classes, known as cross-resistance. If there is (complete) cross-resistance within a class or between different classes, then the use of one substance in animals might confer resistance to another substance of the same or a different class in humans. This is of particular concern for antimicrobial agents which are to be restricted for the treatment of serious infections in humans.

Transmission of resistant bacterial pathogens or commensal strains as well as of resistance genes from animals to humans can take place through a variety of routes, including direct contact between humans and animals, transmission of bacteria via food, and indirect transmission via emissions in the environment. The evidence for a link between antimicrobial resistance in animals and the transmission of antimicrobial resistance to humans is greatest for certain zoonotic bacterial pathogens (e.g. non-typhoidal *Salmonella* spp., *Campylobacter* spp., Shiga-toxin producing *Escherichia coli*, and some *Staphylococcus aureus* clones). Commensal organisms from non-human sources (animals, water, food, or the environment) such as *E. coli* and enterococci may also transmit resistance determinants to human pathogens.

Evaluation of the impact of transmission of resistance between animals and humans

Different aspects need to be taken into consideration when evaluating the impact of the transmission of resistant bacteria or resistance genes between animals and humans.

The similarity of resistance genes or resistant bacteria is used to demonstrate the link between animals and humans, either considering: i) resistance gene level, defined as a similar resistance gene detected in bacterial isolates of animal and human origin; ii) mobile genetic elements, defined as a similar mobile genetic element carrying a resistance gene detected in bacterial isolates of animal and human origin; iii) drug-resistant bacterial strain, defined as a similar bacterium harbouring a resistance gene (either chromosomally or mobile genetic element-encoded) of animal and human origin.

A greater impact from transmission of resistance between animals and humans is expected to occur associated with the following events:

1. Transmission of resistance through zoonotic pathogenic bacteria (e.g. *Salmonella* spp., *Campylobacter* spp., MRSA, *E. coli* (VTEC/STEC)).

2. Transmission of resistance through successful clone(s). Defined as transmission of resistance through a multidrug-resistant clone that demonstrates a higher greater ability to spread to other hosts, e.g. *E. coli* ST131, monophasic *Salmonella Typhimurium* ST34 and MRSA ST398.

3. Transmission of resistance through horizontal transfer. Defined as the transfer of a resistance gene from one cell to another by means of mobile genetic elements (plasmids, conjugative transposons, integrative conjugative elements (ICE)), phage or membrane vesicles. Among those, plasmids, conjugative transposons and ICEs are of higher relevance for the transmission of resistance genes between different bacteria. The presence of mechanisms for self-transferability, a broad range of hosts and a small size confers a higher potential for spread to a plasmid harbouring a resistance gene. ICEs, more recently recognised as important vehicles for resistance gene transfer between different bacteria, can reside either on the chromosome or on plasmids.

4. Co-selection of resistance. Defined as the selection of multiple antibiotic resistances (or resistance gene(s)) when an antimicrobial compound is administered. Co-selection may occur when different antimicrobial resistance genes are genetically linked in a bacterium. The consumption of a particular antimicrobial therefore selects for resistance not only to that particular antimicrobial but to the other genetically-linked resistances which are also present. Thus, use of a particular antimicrobial might (through co-selection) select for resistance to a different antimicrobial. The possibility of co-selection increases with the number of resistance genes present in a bacterium. The genetic linkage of the gene with other resistance genes on a mobile genetic element or its location in a genetic environment together with other resistance genes in such a way that there is a potential for mobilisation (e.g. Insertion Sequence-elements or resistance islands) increases the likelihood for dissemination.

5. Transmission route. The impact of transmission from non-human sources is also influenced by the transmission route (food, contact, environment or combinations of these). If contact with animals is the main transmission route, the number of persons exposed to the resistant bacteria is limited to those in contact with animals, whereas exposure through food potentially affects a larger number of persons and can cause outbreaks. Therefore, the risk associated with the use of a veterinary medicinal product in companion animals for the population at large might be different from that in food-producing animals. On the other hand, contact between companion animals and their household members can be very close, therefore increasing the likelihood of transfer. We can consider that the risk on the population level will be lower if transmission occurs by direct and indirect contact with animals only, increases when there is also exposure via the environment, and is highest when it can be also transmitted through the consumption of food.

6. Prevalence of resistance. The impact of the transfer of resistance determinants between animals and humans is also influenced by the prevalence of resistance in bacteria from animals and humans. If the prevalence in animals is much higher than in humans, the potential contribution of animals to the resistance in humans is greater than when the prevalence of resistance in humans is already very high, while it is still low in animals.

3.3. Consideration of criteria for assessing the importance of antimicrobials in animal health

3.3.1. Serious bacterial disease

Antimicrobial agents are essential medicines for maintaining human or animal health and welfare. One very significant difference that exists between the use of antimicrobials in humans and animals relates to the multitude of species that have to be treated in veterinary medicine (OIE, 2019). Thus, from the outset, the identification of antimicrobials that are essentially needed to treat bacterial infections in animals is a challenging task. Among the vast variety of bacterial infections that occur in veterinary medicine, the highest importance for antimicrobial availability relates to clinically serious diseases that, if left untreated, would lead to significant morbidity and/or mortality. Omission of antimicrobial treatment would result in unacceptable suffering or even death, which is not acceptable from an animal health and welfare perspective. Another consequence would be the potential spread of causative bacteria, which, depending on their properties, could constitute a very significant risk for subsequent infections to in-contact animals and/or humans or on food safety and security (Rushton et al., 2014). In such a situation, the only treatment option left to the veterinarian would be slaughter or euthanasia. In practice, and bearing in mind the high incidence of spread of certain infectious diseases amongst intensively reared animals, the practical logistics of a slaughter policy would be hugely problematic, even before effects on food supply were considered.

In order to identify serious bacterial infections for which antimicrobial treatment is considered indispensable, criteria such as prevalence, incidence, morbidity, mortality, contagiousity and zoonotic potential should be considered. Other criteria such as the extent of use, the intended use (first line treatment ...) may be elements to take into account.

For **food-producing animals** the main pathogens or disorders for which antimicrobials are mostly used have been reflected in the RONAFA report (please see annex 3 for more details) (EMA/EFSA, 2017). These encompass pathogens or disorders for which certain antimicrobials are important as treatments of life threatening diseases (e.g. post-partum septic metritis in cows, streptococcal meningitis in pigs, colisepticemia in poultry, pneumonia in foals) as well as bacterial infections which have high prevalence for that antimicrobials are important because they are extensively used (e.g. bovine or swine respiratory disease).

Depending on the target animal species, production type, production category or level, husbandry conditions, etc. a huge diversity of bacterial diseases requiring antimicrobial treatment exists. Among the multiplicity of bacterial infections, those affecting almost all food-producing animals are related to infections of the gastrointestinal tract, respiratory tract, urogenital tract, musculoskeletal system and septicaemia as well as mastitis. Depending on the geographical region and climate conditions, differences in the prevalence and incidence may occur across the European Union. Sufficient antimicrobial products seem to be available at least for the major food-producing species cattle, chickens, and pigs. In these species reported off-label use concerned antimicrobial veterinary medicines already approved for the respective target animal species but used for another indication or at other doses (EMA/CVMP/AWP, 2018a). This situation is different in particular for other major food-producing species, e.g. salmon and sheep as well for minor food-producing species (e.g. goat, fish, horse, rabbits, bees etc.) since for these animal species considerably fewer antimicrobial products are authorised.

Many different bacterial pathogens are involved in infections affecting food-producing animals. For some of them, antimicrobial resistance is widespread and treatment of diseases caused by such organisms would require treatment options other than first line antimicrobials e.g. multi-resistant *E. coli* causing gastrointestinal infections. That said, diseases caused by multi-resistant bacteria that would require treatment with last resort antimicrobials that are authorised for human medicine only are expected to be of minor relevance. Further, in the absence of MRLs, their use is not allowed in food-producing animals.

Antimicrobial-resistant bacteria and resistance conferring mobile genes from food-producing animals can affect human populations differently. For example, caretakers or farm workers in food-producing animal facilities can receive direct transmission of antimicrobial resistant mobile genes as well as clonal transmission of antimicrobial-resistant bacterial strains (de Been et al., 2014). Other human populations can potentially acquire antimicrobial-resistant bacteria or genes from food-producing animal products or indirectly from environmental sources where animal waste products have been applied (e.g. crop production, groundwater).

For **companion animals**, the issue of availability of antimicrobials to treat serious bacterial diseases has particular nuances that need to be considered both in terms of the risks posed for antimicrobial resistance, and the practical application of any restrictions applied. The role of companion animals within the European Union society, and the nature of the bond between owner and pet are the first facets that need to be recognised, and taken into account, with regard to any restriction on antimicrobial prescribing practices. In contrast to food-producing species, treatment for serious bacterial diseases in companion animals is invariably on an individual basis and does not involve mass medication of large numbers of animals. Hence, treatment of companion animals overall leads to less exposure to antimicrobials and to a lower selection pressure. As such, it is likely true (though not yet

proven by scientific data) that treatment of single pet animals in households containing healthy human individuals, is significantly less likely to contribute to antimicrobial resistance at a population level as compared to mass oral medication of an entire flock or herd.

In line with the principles of Good Veterinary Practice, any decision to implement antimicrobial therapy must take account of disease severity, the animal's overall clinical condition and the likelihood of resolution without the need for such intervention.

A variety of serious bacterial infections can affect a multitude of organ systems in companion animals; the causal pathogen can likewise vary from case to case (typically more so than in food animal practice), as can the severity and duration or chronicity of infection. Examples of serious infections that typically require antimicrobial therapy include deep pyoderma, otitis externa, non-healing surgical wounds, urinary tract infections (both upper and lower tract), cholangio-hepatitis, osteomyelitis and respiratory tract infections. Though limited in scope, examples of specific pathogens of prime concern in companion animal practice include *Staphylococcus aureus*, *Staphylococcus pseudintermedius*, *Enterococcus faecalis*, "*Enterobacteriales*" and *Pseudomonas aeruginosa*. However, as immunosuppression is a common event in companion animal medicine (e.g. FIV/FelV infection in cats, cytotoxic chemotherapy etc.), even opportunistic pathogens can cause overwhelming infection and sepsis in pets; appropriate therapy is essential to save the animal's life, though fortunately such pathogens are often susceptible to first line antimicrobials.

It should be noted that antimicrobials are not routinely administered to companion animals with gastrointestinal bacterial infections; only a few exceptions exist such as dogs with systemic manifestations of salmonellosis (rather than cases with uncomplicated gastrointestinal signs alone).

The closeness of the contact on a daily basis between pet and pet owner underpins the very real risk of zoonotic transmission of pathogens in cases such as exudative *P. aeruginosa* infections (otitis externa and pyoderma) and urinary tract infections caused by gram negative coliforms. There is a significant risk that failure to promptly and appropriately treat such infections could lead to such pathogen transmission to humans. Antimicrobial susceptibility testing is always recommended, and widely performed, in most Member States in which initial infections in companion animals fail to respond to first line treatment. In cases in which Antimicrobial susceptibility testing identifies that a more critically important antimicrobial may be indicated (e.g. 3rd-generation cephalosporin or a fluoroquinolone), it must be recognised that pet owners in the European Union are historically most unlikely to accept adoption of alternative pathways such as non-treatment (poor welfare) or euthanasia (pet-human bond broken, loss of a "family member").

3.3.2. Available treatment alternatives

In general, and as has been described for the human sector, similar aspects such as site of infection, host, bacterial characteristics and unmet medical need have to be considered when evaluating the availability of treatment options of a bacterial infection. Nevertheless, the evaluation of alternatives for animals is more complex compared to human medicine, due to the huge variety of target animal species, their different serious bacterial diseases as well as the differing prevalence of antimicrobial resistance in causative bacterial pathogens.

A further aspect of particular importance for animals is the route of administration. Not every pharmaceutical form is applicable for all target animal species: e.g. in species such as fish, poultry, and food rabbits, antimicrobial formulations other than those that can be administered by the oral route are generally not feasible.

It should also be taken into account when there is low availability of alternatives, the impacts of restricting one class on the use of an alternative should be considered. Restricting availability of

alternatives may lead to over-reliance on a few antimicrobial classes and might hasten development of resistance to these few antimicrobial classes.

It is of note that according to Commission Regulation (EU) No 37/2010 the antimicrobial substances chloramphenicol, dapsone (sulfone), dimetridazole, metronidazole, ronidazole (nitroimidazoles), nitrofurans (including furazolidone) are prohibited for use in food-producing animals since no MRL can be established. Consequently, for food-producing animals, these antimicrobials cannot be taken into consideration as treatment alternatives.

The availability of authorised vaccines (or other ancillary measures) to prevent specific bacterial diseases in animals could form part of any future strategy on restricted classifications. Likewise, bacterial desensitisation vaccines can be attempted in companion animals with relapsing pyoderma.

For cutaneous, ear and ocular infections, the availability of topical agents (e.g. shampoos, drops and creams, particularly those not related to existing systemic antimicrobial classes) should equally represent part of the decision tree.

When identifying the availability of antimicrobial alternatives for prevention and treatment of serious bacterial diseases in animals, the authorisation status of medicinal products in the European Union should also be taken into account, i.e. whether the antimicrobial(s) is (are) authorised for the (i) respective target animal species, (ii) for another target animal species (food-producing vs companion animal), (iii) for humans only, or, if no antimicrobial treatment alternative is available at all (unmet medical need). Thus, the authorisation status of medicinal products in the European Union can be used as a starting point when using the criteria selected: antimicrobials only authorised in human medicine, antimicrobials only authorised in veterinary medicine, antimicrobials authorised in human and veterinary medicine, antimicrobials not authorised in human and veterinary medicine (please see details in chapter 7).

3.4. Discussion

The aspects described above are the most important and eligible criteria to fulfil the purpose of this request for advice. When applying the criteria, the challenge is how to weigh the criteria against each other to find an appropriate balance between animal health needs, human health needs and public health considerations. Depending of the antimicrobial/antimicrobial class, the information available to evaluate the criteria may be very limited (antimicrobials not yet authorised) or more extensive (antimicrobials already authorised). Applying the criteria for any potential situation in human and animal medicine may lead to great complexity in the decision process where conclusions built on a simple “yes or no basis” may not be possible in any case.

As the designation on antimicrobials for human use only constitutes a very strong risk management measure, the impact on animal health if the substance is banned needs also to be taken into account. This aspect is likewise related to the Regulation as a criterion to be taken into account for the restriction of use of antimicrobials outside the terms of the marketing authorisation i.e. impact on aquaculture and farming if the animal affected by the condition receives no treatment. Moreover, when applying the criteria it has to be kept in mind that a prohibition or restriction of one antimicrobial/antimicrobial class could lead to an increase in use of other restricted classes authorised for the same indications.

4. Criteria retained

An antimicrobial/antimicrobial class reserved for human use should be designated as such based on the criteria described in the points below.

4.1. High importance to human health

The antimicrobial/antimicrobial class meets this criterion if any of the following apply:

- It is either the sole/last-resort or an essential component of the limited few alternatives available in a patient management treatment approach for serious, life-threatening infections in humans which, if inappropriately treated, would lead to significant mortality or debilitating morbidity.

Limited treatment alternatives can be due to antimicrobial resistant phenotype/s of the bacteria causing infection, including multidrug resistance that impact either individual patient treatment or public health (e.g. extended-spectrum beta-lactamase-producing and/or carbapenem-resistant *Klebsiella pneumoniae*, multi-drug resistant *Pseudomonas aeruginosa*, multidrug-resistant *Acinetobacter* spp., as well as organisms causing infections in the community such as *Escherichia coli*, *Salmonella enterica*, and *Campylobacter* spp., which have shown resistance to many antimicrobial/antimicrobial classes). Limited alternatives can also be a consequence of site of infection (e.g. osteomyelitis), the type of patient (e.g. immunocompromised patients) and the safety profile for certain patients' groups (e.g. paediatric and elderly patients). Virulence of the bacterial strains is also relevant including high-virulent bacteria which cause community-acquired infections (e.g. community-acquired MRSA harbouring the Panton–Valentine leukocidin gene) as well as those virulence-enriched strains of low-virulent bacterial species involved in hospital-acquired infections (such as those caused by *Enterococcus* spp. in particular *E. faecium*), for which it is important to secure last-resort treatment options.

- Antimicrobial agents authorised in the European Union for the treatment of serious bacterial infections in patients with limited treatment options, indicating that it has been established that these agents address an unmet medical need related to drug resistance, should, by default, be considered for a restricted use to humans.

4.2. Risk of transfer of resistance

The antimicrobial/antimicrobial class meets this criterion if:

- Transmission of bacteria resistant to the antimicrobial/antimicrobial class or transmission of genes conferring resistance to the antimicrobial/antimicrobial class from non-human sources to humans is significant and linked to the use of the antimicrobial/antimicrobial class in animals.
- Existence of data to show the actual emergence, dissemination and transmission of resistance or, in case the antimicrobial is not authorised for animals, data exist to show the potential of emergence, dissemination and transmission of resistance.

Generally, the impact of the use of antimicrobial in animals will be highest if the resistance selected by its use confer resistance or cross-resistance to compounds that are critically important for human medicine, if transmission of resistance occurs by vertical as well as horizontal transmission, if transmission of resistance involves zoonotic pathogens, and if transmission can take place by different routes and/or is linked to a number of different animal species.

4.3. Low importance to animal health

The antimicrobial/antimicrobial class meets this criterion if:

- The antimicrobial/antimicrobial class (present either within an authorised veterinary medicinal product, or within a human authorised medicinal product that is used in compliance with the cascade) is not essential to treat a serious, life-threatening infection in animals, which if left untreated would lead to significant morbidity and/or mortality.

- Alternatives exist to the use of the antimicrobial/antimicrobial class for the treatment of serious life-threatening infections in animals.
- A ban on the use of the antimicrobial / antimicrobial class in animals would not result in a major impact on animal health and welfare, or human health, as alternative management strategies other than the use of antimicrobials exist to prevent, treat or control such infections.

Since there is a goal to encourage the development of new antimicrobials, the availability of alternative treatments should not be a reason to prevent a new antimicrobial from use in animals if the substance has been found not to be of importance to human health.

5. Using the criteria

Reserving an antimicrobial or a class of antimicrobials for human use only is the most severe risk management measure that can be taken. Antimicrobials or classes of antimicrobials designated to be only used in humans will be those that are of highest importance to human health, for which the risk the transfer of resistance from animals to humans is considered as significant and for which the importance to animal health is low.

The designation of antimicrobials to be reserved for human use only should be considered as one of the potential measures to preserve human health.

Other possibilities to restrict the use of antimicrobials to prevent infections should always be considered:

- Possibility to limit the use outside the terms of the marketing authorisation under Article 107(6)
- Restriction of the use in the marketing authorisation
- Establishing conditions for using the antimicrobial such as: "the antimicrobial should be considered only for the treatment of clinical conditions when there are no alternative antimicrobials of lower importance that could be clinically effective".

In any case, the limitation of the use of antimicrobials in animals should not be considered as the only way to preserve the efficacy of antimicrobials to treat human diseases. Prevention of infectious diseases, biosecurity, herd management etc. are also important tools.

The three criteria defined previously are intended to be applied to all antimicrobials or classes of antimicrobials regardless of authorisation status: that is, the antimicrobial may be authorised for use in both human and veterinary medicine, authorised for use in human or veterinary medicine only or not yet authorised for use in human and veterinary medicine.

However, depending on the specific case, application of the criteria may be adapted taking into account data available.

Sections 5.1 - 5.4 include preliminary approaches which, following experience from its application, might need further refinement.

5.1. Antimicrobials only authorised in human medicine

1. High importance to human health: Information is available on whether there are no or few alternatives for the treatment of serious infections in humans either at the community or at hospital level which, if inappropriately treated, would lead to significant mortality or debilitating morbidity.

There are up-to-date data to assess the relevance of the antimicrobial/antimicrobial class to human health in terms of extent of use and/or frequency of use in high-risk groups (e.g. ECDC data such as data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), the European Antimicrobial Resistance Surveillance Network (EARS-Net) etc.).

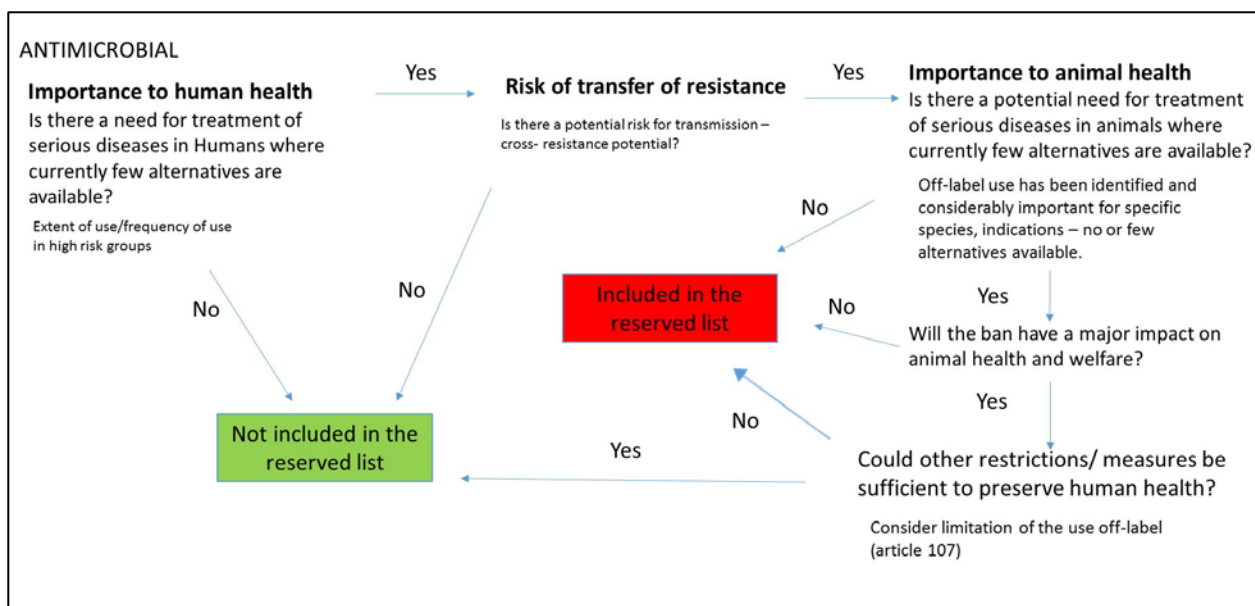
Antimicrobial agents authorised in the European Union for the treatment of serious infections in patients with limited treatment options addressing an unmet medical need related to drug resistance should, by default, be considered for a restricted use to humans.

2. Risk of transfer of resistance: As the antimicrobial is not authorised in animals, few data may be available on the link between the use in animals and the impact on resistance. In this case, the potential risk for transmission of resistance (including the potential for cross-resistance) should be assessed.
3. Low importance to animal health: The need for the treatment of serious diseases in animals where currently few alternatives are available is the key issue that should be considered in determining the consequences of the ban to animal health.

Existing significant and documented off-label use of human products should be considered in order to assess if the restriction to human use will have a significant impact on animal health and welfare.

In any case, it should be assessed if restricting the use of the antimicrobial for a particular species/indication under Article 107(6) would be sufficient to protect human health.

Figure 1. Antimicrobial only authorised in human medicine



5.2. Antimicrobials only authorised in veterinary medicine

1. High importance to human health: since the antimicrobial is not or no longer authorised in human medicine, it can generally be considered that alternatives are preferred for treating serious infections in humans. Often, these molecules present higher toxicity than available alternatives in humans.

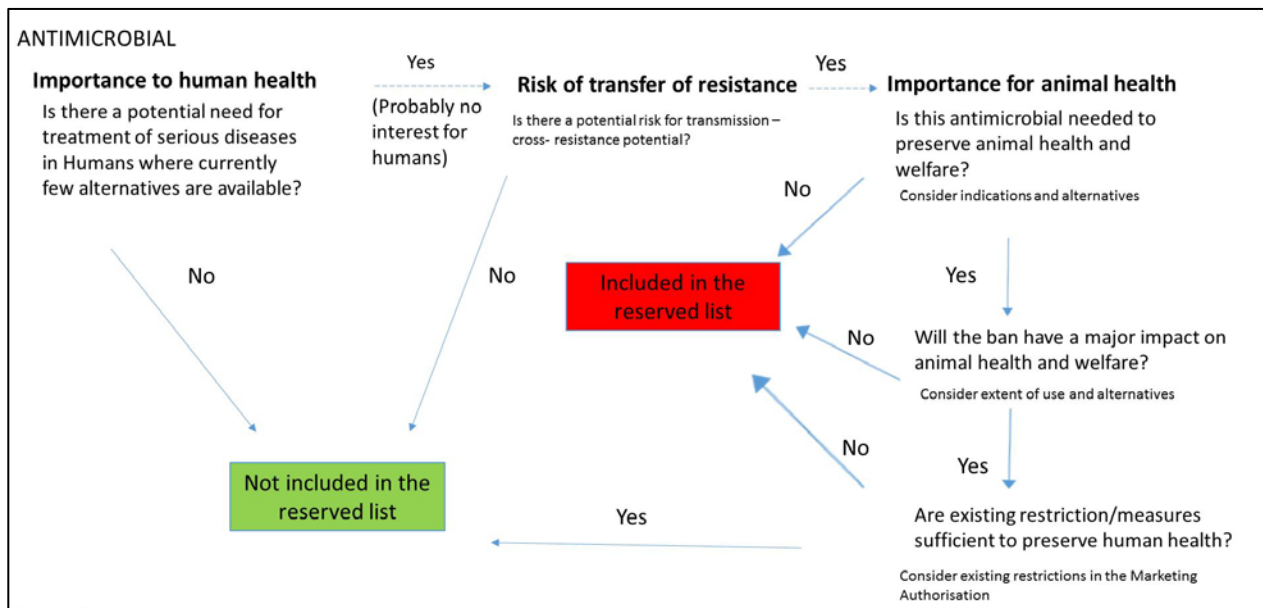
The potential need for these antimicrobials or other molecules/derivatives of the same class with lower toxicity for the treatment of serious diseases in humans when few alternatives are available should nevertheless be considered.

2. Risk of transfer of resistance: Data on antimicrobials only authorised in animals are available to assess the risk of transfer of resistance. For new molecules/derivatives of the same class the potential for cross-resistance and risk for transmission of resistance should be assessed.
3. Low importance to animal health: Information is available and up-to-date to assess the importance to animal health such as (ESVAC data, indication by species, existing alternatives). The existing OIE and AMEG categorisation of importance in veterinary medicine can be taken into account.

The impact on animal health and welfare, food safety and security if the antimicrobial is banned also needs to be considered.

In any case, it should be assessed if existing restrictions/measures are sufficient to protect human health.

Figure 2. Antimicrobial only authorised in veterinary medicine



5.3. Antimicrobials authorised in human and veterinary medicine

1. High importance to human health: Information is available on whether there are no or few alternatives for the treatment of serious infections in humans either at the community or at hospital level which, if inappropriately treated, would lead to significant mortality or debilitating morbidity.

There are up-to-date data to assess the relevance of the antimicrobial/antimicrobial class to human health in terms of extent of use and/or frequency of use in high-risk groups (e.g. ECDC data such

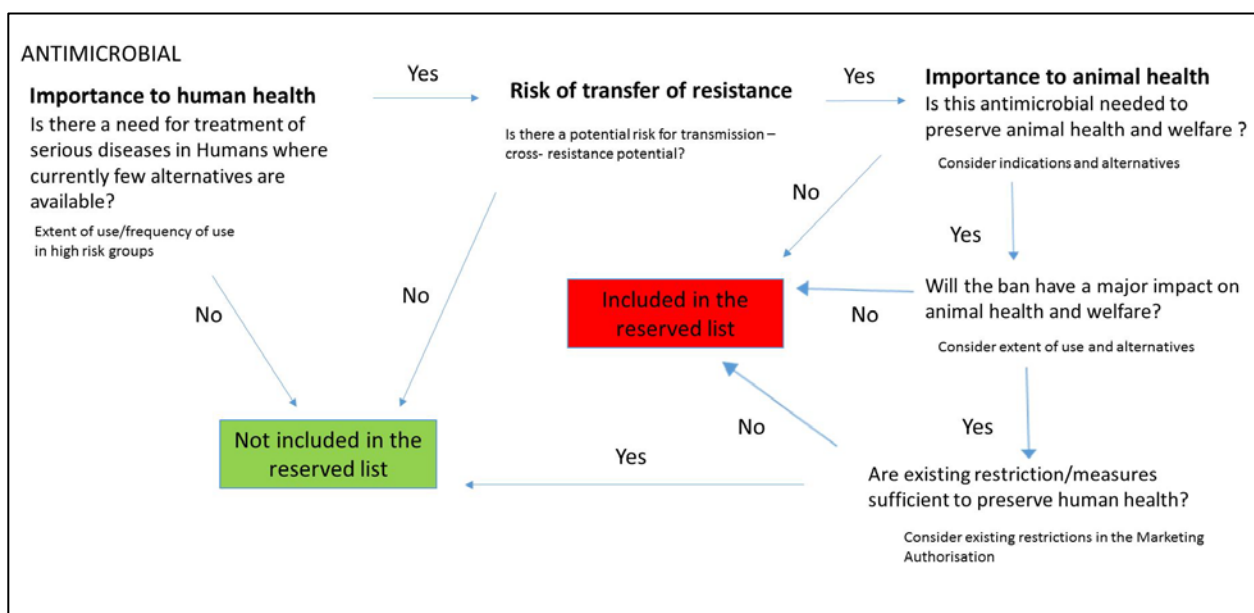
as data from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), the European Antimicrobial Resistance Surveillance Network (EARS-Net) etc.).

2. Risk of transfer of resistance: Data are available and enable the assessment of the risk of transfer of resistance and cross-resistance.
3. Low importance to animal health: Information is available and up-to-date to assess the importance to animal health such as (ESVAC data, indication by species, existing alternatives etc.). The existing OIE and AMEG categorisation of importance in veterinary medicine can be taken into account.

The impact on animal health and welfare, food safety and security if the antimicrobial is banned also needs to be considered.

In any case, it should be assessed if existing restrictions/measures are sufficient to protect human health.

Figure 3. Antimicrobial authorised in human and veterinary medicine



5.4. Antimicrobials not authorised in human and veterinary medicine

1. High importance to human health: Since the antimicrobial is not or no longer authorised in human medicine, its potential for the treatment of serious infections in humans should be considered.

In the specific case that an antimicrobial was authorised in the past in human medicine, it can generally be considered that alternatives are preferred for treating life-threatening infections in humans or toxicity issues prevented its use. The possibility of reintroducing this antimicrobial or of other molecules/derivatives of the same class with lower toxicity for treatment of serious diseases in humans when few alternatives are available should be considered.

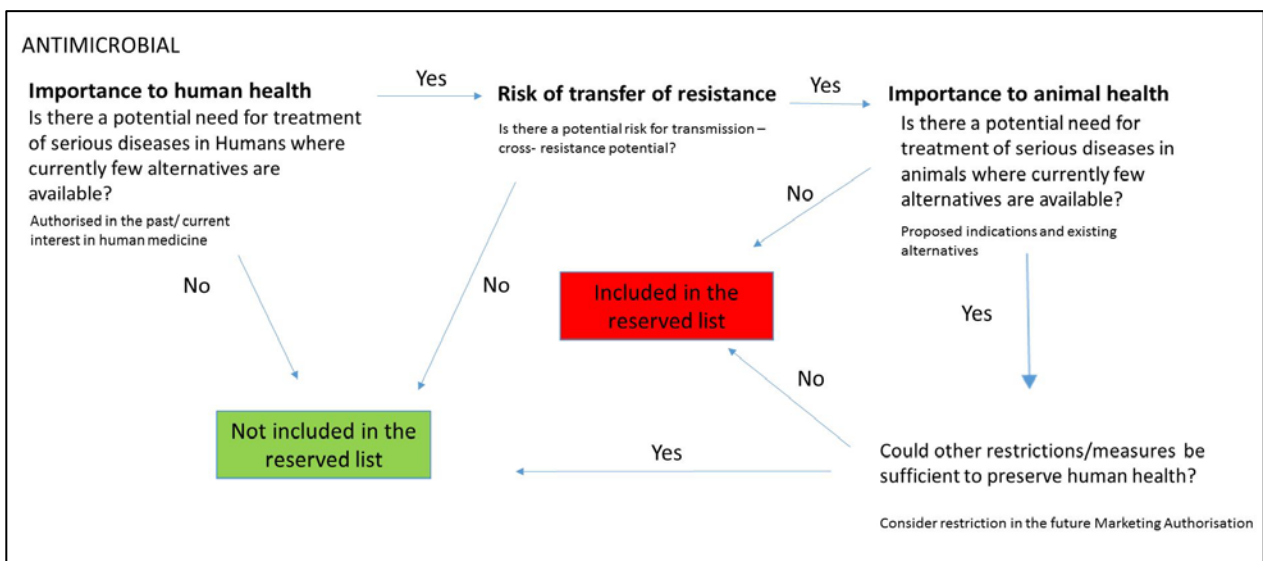
2. Risk of transfer of resistance: A minimum data set would be needed to assess the potential risk of transfer of resistance. In the specific case where an antimicrobial was used in the past in human medicine, data may be available. For new molecules/derivatives of a previous authorised class the potential risk of cross-resistance and transmission of resistance from animals to humans should be assessed.

3. Low importance to animal health: The potential therapeutic indication(s) for these antimicrobials should be taken into account to determine if, for the targeted infection in animals, alternative treatments are available. Since there is a goal to encourage the development of new antimicrobials, the availability of alternative treatments should not be a reason to prevent a new antimicrobial from use in animals if the substance has been found not to be of high importance to human health.

In any case, it should be assessed if potential restrictions/measures could be sufficient to protect human health.

For any intended future submission of an application for the establishment of maximum residue levels or a marketing authorisation for a new antimicrobial for veterinary use, a specific process should be put in place in order to assess the antimicrobial against the criteria for the designation of antimicrobials to be reserved for human use.

Figure 4. Antimicrobial not authorised in human and veterinary medicine



6. Annexes

Annex 1 – Summary table of antimicrobial rankings of importance for human medicine

Table 4. Cross-section overview of antimicrobial rankings of importance for human medicine, by various international (non-European Union) organisations

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
Cephalosporins	1st-generation cefazolin cefalexin cefadroxil cefapirin cefazedone (WFM) cefazaflur (WFM) cefradine (WFM) cefroxadine (WFM) ceftezole (WFM) cefaloglycin (WFM) cefacetrile (WFM) cefalonium (VM Only) cefaloridine (WFM) cefalotin (WFM) cefatrizine (WFM)	Highly Important	ACCESS	High Importance	Important	Medium Importance	Important
	2nd-generation cefaclor cefotetan cefoxitin cefprozil cefuroxime cefuroxime axetil cefamandole (WFM) cefminox (WFM) cefonicid (WFM) ceforanide (WFM) cefotiam (WFM) cefbuperazone (WFM) cefuzonam (WFM) cefmetazole (WFM) carbacephem (WFM)	Highly Important	ACCESS	High Importance	Important	Medium Importance	Highly Important, except for oxacephem
	3rd-generation cefcapene cefdaloxime	CIA Highest	WATCH	Very High Importance	Critically Important	High Importance	Critically Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	cefdinir cefditoren cefetamet cefixime cefmenoxime cefodizime cefotaxime ceftiofur (VM only) cefpimizole cefpodoxime cefteteram ceftamere ceftibuten ceftiofur (VM only) ceftiolene ceftizoxime ceftriaxone Antipseudomonal: ceftiofur (also VM) ceftazidime cepheids are occasionally classed with 3 rd -Gen cephalosporins: oxacepheids: latamoxef (moxalactam) (WFM)	Priority					
4th-generation	cefclidine cefepime ceftuprenam cefoselis ceftozopran ceftirome ceftquinome (VM only) cepheids are occasionally classed with 4 th -Gen cephalosporins: oxacepheids: flomoxef	CIA Highest Priority	RESERVE	Very High Importance	Highly Important	High Importance	Critically Important
5th-generation	ceftobiprole ceftaroline ceftolozane	CIA Highest Priority	RESERVE	Not categorised	Not categorised	High Importance	Not categorised
Glycopeptides	vancomycin	CIA	WATCH	Very High	Highly Important	High	Critically Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	teicoplanin telavancin ramoplanin decaplanin dalbavancin oritavancin bleomycin (anti-tumor) avoparcin (VM only)	Highest Priority		Importance		Importance	
Macrolides	14-member erythromycin troleandomycin roxithromycin clarithromycin dirithromycin oleandomycin	CIA Highest Priority	WATCH	High Importance	Critically Important	Low Importance	Critically Important, except Erythromycin – highly important
	15-member azithromycin boromycin flurithromycin tulathromycin (VM only) gamithromycin (VM only)	CIA Highest Priority	WATCH	High Importance	Critically Important	Low Importance	Critically Important
	16-member tylosin (VM only) carbomycin A kitasamycin (VM only) spiramycin josamycin miocamycin midecamycin rokitamycin tilmicosin (VM only) tildipirosin (VM only) tylvalosin (VM only)	CIA Highest Priority	WATCH	High Importance	Critically Important	Low Importance	Important
Ketolides	telithromycin (WFM) cethromycin solithromycin	CIA Highest Priority	Not categorised	Very High Importance	Not categorised	Not categorised	Not categorised
Polymyxins	polymyxin B polymyxin E (colistin)	CIA Highest Priority	RESERVE	Very High Importance	Highly Important	High Importance	Critically Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)	
(Fluoro) Quinolones	1st-generation	cinoxacin (WFM) flumequine (VM only) nalidixic acid (WFM) oxolinic acid (VM only) pipemidic acid (WFM) piromidic acid (WFM) rosoxacin (WFM)	CIA Highest Priority	WATCH	High Importance	Important	Not categorised	Important
	2nd-generation	ciprofloxacin ofloxacin enoxacin (WFM) fleroxacin (WFM) lomefloxacin (WFM) nadifloxacin (WFM) norfloxacin (WFM) pefloxacin (WFM) rufloxacin (WFM)	CIA Highest Priority	WATCH	Very High Importance	Critically Important	High Importance	Critically Important
	3rd-generation	levofloxacin balofloxacin (WFM) grepafloxacin (WFM) pazufloxacin (WFM) sparfloxacin (WFM) temafloxacin (WFM) tosufloxacin (WFM)	CIA Highest Priority	WATCH	Very High Importance	Critically Important	High Importance	Critically Important
	4th-generation	besifloxacin delafloxacin gatifloxacin finafloxacin gemifloxacin moxifloxacin clinafloxacin (WFM) garenoxacin (WFM) prulifloxacin (WFM) sitafloxacin (WFM) trovafloxacin (WFM) alatrofloxacin (WFM) nemonoxacin	CIA Highest Priority	WATCH	Very High Importance	Critically Important	High Importance	Critically Important
	<u>Vet Only</u>	danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin	CIA Highest Priority	WATCH	Very High Importance		High Importance	Critically Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	orbifloxacin pradofloxacin sarafloxacin (WFM)						
Aminoglycosides	-mycin (Streptomyces) Aminocyclitols	streptomycin neomycin framycetin paromomycin ribostamycin kanamycin amikacin arbakacin bekanamycin dibekacin tobramycin spectinomycin hygromycin B apramycin (VM only) puromycin nourseothricin	Important	ACCESS	Medium Importance	Highly Important	Low (neomycin, framycetin, streptomycin, streptomycin, capreomycin, paromomycin) Medium (gentamicin, tobramycin, apramycin) High (amikacin) Critically important (arbakacin) Highly Important (kanamycins of which the antimicrobial activity against antimicrobial-resistant bacteria has been improved (except for arbakacin), gentamicins, sisomicins and streptomycins) Important (astromicins, fradiomycins and wild-type kanamycins)
	-micin (Micromonospora)	gentamicin netilmicin sisomicin isepamicin verdamicin astromicin	CIA High Priority	ACCESS	High Importance	Highly Important	Low (neomycin, framycetin, streptomycin, streptomycin, capreomycin, paromomycin) Medium (gentamicin, tobramycin, apramycin) High (amikacin) Critically important (arbakacin) Highly Important (kanamycins of which the antimicrobial activity against antimicrobial-resistant bacteria has been improved (except for arbakacin), gentamicins, sisomicins and streptomycins)

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
							Important (astromicins, fradiomycins and wild-type kanamycins)
	Neoglycoside	plazomicin	CIA High Priority	RESERVE	Not categorised – assumed Very High Importance	Not categorised – assumed Critically Important	Not categorised – assumed Critically Important
Ansamycins	Rifamycins	rifampicin rifabutin rifapentine rifaximin rifalazil	CIA High Priority	Not categorised	Very High Importance	Highly Important	High Importance
	Lipiarmycins	fidaxomicin	CIA High Priority	Not categorised	Very High Importance	Highly Important	High Importance
Carbapenems & other penems	imipenem meropenem ertapenem doripenem panipenem (WFM) biapenem (WFM) tebipenem faropenem (WFM) ritipenem	CIA High Priority	WATCH	Very High Importance	Highly Important	High Importance	Critically Important (carbapenems) Highly Important (other penems)
Glycylcyclines	tigecycline	CIA High Priority	RESERVE	Very High Importance	Not categorised	High Importance	Critically Important
Fluorocyclines	eravacycline	CIA High Priority		Very High Importance			
Lipopeptides	daptomycin surfactin	CIA High Priority	RESERVE	Very High Importance	Not categorised	High Importance	Critically Important
Monobactams	aztreonam tigemonam (WFM) carumonam (WFM) nocardicin A (WFM)	CIA High Priority	RESERVE	Very High Importance	Important	High Importance	Critically Important
Oxazolidinones	eperezolid	CIA	RESERVE	Very High	Highly Important	High	Critically Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	linezolid posizolid radezolid ranbezolid sutezolid tedizolid	High Priority		Importance		Importance	
Carboxypenicillins	ticarcillin carbenicillin (WFM) carindacillin (WFM) temocillin (WFM)	CIA High Priority	WATCH	High Importance	Highly Important	High Importance	Highly Important
Ureidopenicillins	piperacillin azlocillin (WFM) mezlocillin (WFM)	CIA High Priority	WATCH	High Importance	Highly Important	Medium Importance	Highly Important
Aminopenicillins	amoxicillin ampicillin hetacillin (WFM) bacampicillin (WFM) metampicillin (WFM) talampicillin (WFM) epicillin (WFM)	CIA High Priority	ACCESS	High Importance	Highly Important	Low Importance	Highly Important
Phosphonic Acid Derivatives	fosfomycin	CIA High Priority	RESERVE	Medium Importance	Not categorised	High Importance	Highly Important
Drugs used solely for Tuberculosis & Mycobacterial diseases	ethambutol isoniazid methaniazide para-aminosalicylic acid capreomycin cycloserine ethionamide prothionamide pyrazinamide thiocarlide bedaquiline	CIA High Priority	Not categorised	Very High Importance	Highly Important	High Importance	Critically Important
Amdinopenicillin (Group 4 penicillins)	mecillinam (WFM)	Highly Important	Not categorised	Not categorised	Not categorised	High Importance	Not categorised
Amphenicols	chloramphenicol azidamfenicol thiamphenicol florfenicol (VM only)	Highly Important	ACCESS	Medium Importance	Highly Important	Low Importance	Highly Important
Lincosamides	clindamycin	Highly	ACCESS	High Importance	Highly Important	Medium	Highly Important

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	lincomycin pirlimycin	Important				Importance	
Penicillins (β-lactamase sensitive)	benzylpenicillin (G) benzathine benzylpenicillin procaine phenoxymethylpenicillin (V) propicillin (WFM) pheneticillin (WFM) azidocillin (WFM) clometocillin (WFM) penamecillin (WFM)	Highly Important	ACCESS	High Importance	Highly Important	Low Importance	Highly Important
Penicillins (β-lactamase resistant)	cloxacillin flucloxacillin oxacillin nafcillin methicillin (WFM)	Highly Important	ACCESS	High Importance	Highly Important	Medium Importance	Highly Important
Pseudomonic Acid	mupirocin	Highly Important	Not categorised	Not categorised	Not categorised	Medium Importance	Critically Important
Riminofenazines	clofazimine	Highly Important	Not categorised	Not categorised	Not categorised	High Importance	Not categorised
Steroid antibiotics	fusidic acid	Highly Important	Not categorised	High Importance	Not categorised	High Importance	Important
Streptogramins	pristinamycin quinupristin/dalfopristin virginiamycin (VM only)	Highly Important	Not categorised	High Importance	Highly Important	High Importance	Highly Important
Sulfonamides, dihydrofolate reductase inhibitors and combinations	sulfaisodimidine sulfamethizole sulfadimidine sulfapyridine sulfafurazole sulfanilamide sulfathiazole sulfathiourea sulfamethoxazole sulfadiazine sulfamoxole sulfadimethoxine sulfadoxine sulfalene sulfametomidine sulfametoxydiazine	Highly Important	ACCESS	Category III: Medium Importance Category II: High Importance (trimethoprim/sulfamethoxazole) Category III: Medium Importance (trimethoprim)	C - Critically important (trimethoprim / sulfamethoxazole)	Low Medium (trimethoprim/sulfa combination)	Highly Important (trimethoprim/sulfamethoxazole) Important (sulphonamides)

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	sulfamethoxypyridazine sulfaperin sulfamerazine sulfaphenazole sulfamazone sulfacetamide sulfadicramide sulfametrole sulfanitran trimethoprim/sulfamethoxazole ormetoprim/sulfadimethoxine						
Sulfones	dapsone	Highly Important	Not categorised			High Importance	
Tetracyclines	doxycycline chlortetracycline clomocycline demeclocycline lymecycline meclocycline (WFM) metacycline minocycline omadacycline oxytetracycline penimepicycline rolitetracycline sarecycline tetracycline	Highly Important	ACCESS	Medium Importance	Highly Important	Low Importance	Highly Important (tetracyclines of which the duration of activity has been improved) Important (wild-type tetracyclines)
Cyclic polypeptides	bacitracin gramicidin thiostrepton (VM only)	Important	Not categorised	Medium Importance	Not categorised	Low Importance	Important
Nitroimidazoles	metronidazole tinidazole ornidazole	Important	ACCESS	Very High Importance	Highly Important	Medium Importance	Important
Nitrofuran	nitrofurantoin furazolidone (WFM) nifurtoinol	Important	ACCESS	Medium Importance	Not categorised	High Importance	Not categorised
Aminocoumarin	novobiocin coumermycin clorobiocin	Important	Not categorised			Low Importance	
Pleuromutilins	retapamulin (VM only)	Important	Not	Not categorised	Not categorised	Low	Not categorised

Antimicrobial class	Individual active substance	WHO Class (WHO, 2019a)	WHO Group (WHO, 2019b)	Canada (Health Canada, 2009)	USA (FDA, 2003)	Australia (ASTAG, 2018)	Japan (Food Safety Commission of Japan, 2014)
	tiamulin (VM only) valnemulin (VM only)		categorised			Importance	

CIA = Critically Important Antimicrobial;
VM only = Veterinary Medicine Only;
WFM = Withdrawn from Market

Annex 2 – Scoring system reflecting the current use of antimicrobials in the Australian human medicine (ASTAG, 2018)

P: Prophylactic use

0 = not recommended for prophylactic use;

1 = rarely used;

2 = moderate use;

3 = frequent or major use.

T: Therapeutic use

0 = not used for treatment;

1 = infrequently used for listed indications;

2 = moderate use for listed indications;

3 = used frequently for listed indications.

R = Restriction on use (Pharmaceutical Benefits Scheme or hospitals)

1. = readily available;

2. = some extra rules on use e.g. 'Restricted benefit' in the Pharmaceutical Benefits Scheme (PBS) or not listed on the PBS and therefore not subsidised;

3. = higher level of restriction e.g. needs an 'Authority required' prescription on the PBS or not listed on the PBS and therefore not subsidised; often restricted use in hospitals;

4. = use severely restricted (e.g. not available for prescription under PBS, available in major hospitals but only with permission from a microbiologist or infectious diseases consultant, or in a special clinic);

5. = not TGA (Therapeutic Goods Administration) registered but imported under the Special Access Scheme.

Annex 3 – Main pathogens/disorders for which antimicrobials are mostly used (RONAFA) (EMA/EFSA, 2017)

Poultry

broilers:

gastrointestinal disorders (such as coccidiosis, necrotic enteritis, dysbacteriosis);

respiratory diseases (including infections that are often followed by secondary infection with *E. coli*, such as infectious bronchitis, Newcastle disease, infectious laryngotracheitis);

locomotion-related diseases (bacterial arthritis - due to e.g. *E. coli*, *Staphylococcus aureus* or *Enterococcus* spp., and secondary bacterial infections connected with tenosynovitis, necrosis of the femur head);

septicaemia, omphalitis;

laying hens (much less use, in part due to the effects of withdrawal periods on eggs):

gastrointestinal disorders (such as enteritis caused by *E. coli*, avian intestinal spirochaetosis);

respiratory and locomotion-related diseases (caused by *E. coli* and *Mycoplasma*);

secondary bacterial infections connected, for example, with red mite infestation; taeniosis (in free range production systems);

turkeys:

respiratory diseases (caused by *Ornithobacterium* infection);

gastrointestinal disorders (caused by coccidiosis).

Pigs

suckling piglets:

locomotory infections (arthritis), neurological disorders and diarrhoea (caused by *E. coli*);

weaners:

diarrhoea, and respiratory diseases often associated with transport and stress when bringing together pigs originating from different farms or housing animals in holdings with inappropriate ventilation systems, and/or improper feeding strategies and insufficient biosecurity measures;

fatteners:

respiratory (e.g. Porcine Respiratory Disease Complex) and digestive disorders (e.g. proliferative enteropathy by *L. intracellularis*, swine dysentery, ileitis, *Salmonella* spp.);

sows:

urogenital disorders (e.g. leptospirosis), post-partum dysgalactia syndrome, *Actinobacillus pleuropneumoniae* in gilts.

Ruminants

dairy cattle:

mastitis (especially the dry cow treatment);

lameness/foot disease;
uterine problems (e.g. metritis);
surgery;

calves and veal:

respiratory diseases;
diarrhoea;

beef:

respiratory diseases (mainly at the beginning of the fattening period);
locomotory diseases (lameness, arthritis);
neonatal diarrhoea.

lambs in their first month of life:

enteritis/enterotoxaemia ('watery mouth');
Mannheimia spp. infections in case of motherless rearing;
Arthritis, especially in intensive goat farming);

growing fattening lambs:

respiratory diseases (e.g. *Mannheimia* spp. infections, especially during the end of housing period and first time on pasture);
lameness due to arthritis, including problems resulting of tick pyaemia or footrot;
infectious conjunctivitis;

ewes/does and adults:

bacterial abortion, e.g. *Chlamydia* spp., *Campylobacter* spp., *Listeria* spp., *Coxiella burnetii*;
post-partum disorders of the genital system;
diarrhoea due to clostridial infections;
bacterial mastitis and contagious agalactia;
lameness (e.g. footrot, scald, contagious ovine digital dermatitis);
tick-borne fever;
listeriosis.

Horses

use within racing yards with young horses at risk of disease or respiratory infections limiting grade performance;
respiratory diseases in stable and studs with large number of horses or horses frequently travelling to competitions stabled with a variety of horses;
wounds;
intrauterine treatment of broodmares treated for hypofertility;

some specific infections, such as from *Rhodococcus equi*;
perioperative antimicrobials.

Rabbits

breeding females:

respiratory and genital infections due to *Pasteurella multocida*, metritis and mastitis due to staphylococcal bacteria and others;

small kits before weaning:

enterotoxemia due to *Clostridium spiriforme*, colibacillosis, neonatal enteritis and staphylococcal infections;

fattening phase:

major cause of death in young rabbits immediately after weaning is due to intestinal disorders such as Enzootic Rabbit Enterocolitis, Colibacillosis, proliferative enteropathy caused by *Lawsonia intracellularis* bacteria, coccidiosis caused by *Eimeria* spp.

Bees

American foulbrood and European foulbrood, due to *Paenibacillus* larvae and *Melissococcus pluton*, respectively;

nosemosis type-A and type-C, due to *Nosema apis* and *Nosema ceranae*, respectively

Fish

salmon:

fry in the fresh-water phase (florfenicol and flumequine);

sea-bass and sea-bream:

juvenile early life stages for tenacibaculosis, photobacteriosis and vibriosis;

trout:

fry (early life stage) for rainbow trout fry syndrome (florfenicol, oxytetracycline), enteric redmouth diseases by *Yersinia ruckerii*, furunculosis (sulfadiazine-trimethoprim, florfenicol, oxytetracycline, 1st- and 2nd-generation quinolones).

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