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Advice on the designation of antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans - in relation to implementing measures under Article 37(5) of Regulation (EU) 2019/6 on veterinary medicinal products

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Introduction

According to Article 37(5) of Regulation (EU) 2019/6 ('the Regulation'), the European Commission shall adopt implementing acts designating antimicrobials or groups of antimicrobials to be reserved for the treatment of certain infections in humans. On 1 July 2019, the European Commission requested the European Medicines Agency to provide scientific recommendations on these 'designated antimicrobials'.

The EMA's scientific recommendations, together with the methodology used and the outcome of evaluations of different antimicrobial groups, are provided in this advice. Supplementary information, including supporting monographs prepared for antiviral and antifungal classes/substances and the ATC(vet) codes for substances included in each antimicrobial grouping are presented in the Annex.

The EMA has previously provided advice to the Commission in the context of the delegated act referenced under Article 37(4) of the Regulation, to establish the criteria to designate the antimicrobials to be reserved for humans [1]. Therefore, the CVMP considered that the expert group involved with this earlier advice should be requested also to assist in preparing the recommendations relating to the designated antimicrobials. This group consisted of experts from the European Network, EFSA, ECDC, EMA and external experts on human infectious diseases.

The CVMP appointed additional experts from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and from national authorities, who assisted by reviewing working documents prepared for the evaluation by the core expert group. The CVMP is grateful to all the experts for their participation.

The mandate and objectives of the expert group were agreed by the group itself and endorsed by the CVMP.

The expert group submitted their report to the CVMP on 21 January 2022.

The CVMP adopted the scientific advice on 16 February 2022.

Summary

Promoting the responsible use of antimicrobials in animals in order to reduce the risk of antimicrobial resistance to public health is one of the cornerstones of the Regulation (EU) 2019/6 on veterinary medicinal products ('the Regulation'), which came into application on 28 January 2022.

Article 37(5) of the Regulation mandates the designation of antimicrobials that shall be reserved for human use only, in order to preserve their efficacy for the treatment of certain critical infections in humans. These designated antimicrobials cannot be included in EU-authorized veterinary medicines (Articles 37(3) and 152(1) of the Regulation) or used to treat any animal¹ under the provisions of Articles 112, 113 and 114 of the Regulation i.e. outside the terms of the marketing authorisation (Article 107(5)). In addition, acknowledging the capacity for antimicrobial resistance (AMR) to disseminate and become a global public health concern, these designated antimicrobials must not be used in animals or their produce to be imported into the EU from third countries (Article 118 of the Regulation).

The provisions under Article 37(5) are part of a range of measures to tackle antimicrobial resistance that are laid down in the Regulation. Other measures include a ban on preventive use of antibiotics in groups of animals, restrictions on metaphylactic use of antimicrobials, a ban on the use of

¹ Regulation (EU) 2016/429, the Animal Health Law, defines 'animals' as vertebrate and invertebrate animals.

antimicrobials in veterinary medicinal products for promotion of growth and increasing yield and an obligation for Member States to collect data on the sales and use of antimicrobials in animals.

In 2019, the Agency provided to the European Commission recommendations on the criteria for designation of the antimicrobials to be reserved for humans [1]. Three main criteria were identified, which were subsequently formally laid out in Commission Delegated Regulation (EU) 2021/1760 [2]. In summary, these criteria relate to:

- A: High importance of the antimicrobial to human health to treat serious, life-threatening infections that have no or limited availability of alternative treatments.
- B: Risk of transmission of resistance to the antimicrobial from animals to humans, including cross-resistance or co-selection of resistance to other crucial antimicrobials.
- C: Non-essential need for the antimicrobial for animal health, meaning that the absence in veterinary medicine would not lead to a significant impact on animal health, animal welfare or public health.

An antimicrobial or a group of antimicrobials which meets all three of the criteria above shall be designated as reserved for the treatment of humans only.

In July 2019, the European Commission requested the European Medicines Agency to provide scientific recommendations on the designation of antimicrobials to be reserved for humans. Under the Regulation, 'antimicrobials' include antibiotics, antivirals, antiprotozoals and antifungals. The Commission's mandate advised that the recommendations should address antimicrobials both with or without a human and/or veterinary marketing authorisation, including those that may be developed in future.

Considering the number of individual substances in scope, and the mixed availability of supporting evidence relating to the criteria, different methodologies were used for the assessment of the different types of antimicrobials, as summarised below:

Antibiotics were addressed in their pharmacological (sub)classes as identified by AMEG, with a few exceptions for certain substances that were considered independently from their class due to individual characteristics. Considering the requirement that all three of the criteria in the delegated regulation should be met in order for an antimicrobial to be designated for use in humans only, a stepwise assessment was conducted: all classes were initially assessed against criterion A (high importance to human health); however, only those meeting this criterion were assessed against criterion B (risk of transmission of resistance), and only those meeting both criteria A and B were evaluated against criterion C (non-essential need for animal health).

The evaluation of the compliance of the antibiotics with the criteria for antimicrobials reserved for treatment of humans is provided in Section 3.1.

Antivirals are very important in human medicine as there are limited treatment options for specific viral diseases. Owing to their modes of action (see Section 2.6.), substances based on interferons and monoclonal antibodies were excluded from the scope of the review. At present, no antiviral agents are authorised in the EU in veterinary medicines. The potential risk from the use of antiviral substances in animals leading to the selection and dissemination of resistant viruses that could infect humans was assessed. As a first step, the zoonotic viruses that are known to occur in Europe and that could infect animal species that might be candidates for treatment with antivirals (food-producing, companion and other kept animals) were identified. In a second step, the frequency of the occurrence of the zoonotic disease in humans and the antivirals intended for human therapy of these viral zoonotic diseases were

considered. The antiviral classes identified were then assessed with regard to their mechanism of action (virus-specific or broad spectrum of activity). Antivirals that were assessed for recommendation to be reserved for use in humans were those used for human therapy of zoonotic diseases that are endemic or frequently occurring in the EU or those that, due to their spectrum of activity, may be active against such zoonotic viruses. Reports of use of these antivirals in veterinary medicine were identified along with any evidence for their effectiveness to treat animal diseases. It was then considered if these antivirals are essential in veterinary medicine for treatment of serious diseases in animals for which there are no alternatives before determining if they should be recommended to be reserved for humans.

The summary of the evaluation of the compliance of the important antivirals with the criteria for the designation of antimicrobials to be reserved for humans is provided in Section 3.2.

For antifungals, an initial review was made of the fungal diseases that are of greatest importance to human health, together with their global distribution. Consideration was then given to the zoonotic potential and epidemiology of these diseases to determine possible routes for transmission of antifungal resistance from treated animals to humans. Treatment guidelines, amongst other sources, were reviewed for preferred and last resort treatment options and it was considered if the same or similar antifungals are used in both human and veterinary medicine. Monographs were then prepared for the antifungal agents identified of highest importance to human health, addressing in more detail the three criteria to be met for the antimicrobials designated for treatment of humans only. It is of note that few antifungals are available and development of resistance to these agents in human medicine is of rising concern; however, little information is available on the extent of resistance, especially in veterinary fungal isolates.

A summary of the evaluation of compliance of the important antifungals with the criteria for the designation of antimicrobials to be reserved for humans is provided in Section 3.3.

Antiprotozoals include a diverse range of substances and their mode of action against specific protozoa is often poorly understood. Some are effective against a range of protozoa, whilst other individual agents have a more specific spectrum of activity. Hence, antiprotozoals are difficult to classify and were considered in the context of the disease they treat rather than in pharmacological groups. A similar approach was taken to their evaluation as that used for the initial review of the antifungals and the outcome is presented in a tabular format. The criterion of 'high importance to human health' was addressed through the discussion of the importance of the disease and its recognised treatments in humans as noted in published treatment guidelines (if available) and other sources, e.g. WHO's Essential Medicines List [3]. The possibility of a zoonotic reservoir for the important human protozoal diseases identified was then considered as this could represent a pathway for transmission of resistance if the same antiprotozoal is used to treat the infection in both animals and humans. There are few veterinary authorised antiprotozoals in the EU, other than for economically important diseases such as coccidiosis, hence use of medicines outside the terms of a marketing authorisation was also examined. For certain protozoal diseases (e.g. malaria), the occurrence of resistance is well documented, whereas for many others the evidence is limited, especially for veterinary isolates. This, and other evidence gaps e.g. in relation to the zoonotic potential of some diseases, hindered aspects of evaluation against the criteria. Detailed monographs were not prepared for individual classes or substances.

The evaluation of the compliance of important antiprotozoals with the criteria for the designation of antimicrobials to be reserved for humans is provided in Section 3.4.

The evidence used for the evaluation of antimicrobial classes against the criteria originated from various sources including peer-reviewed literature, textbooks and grey literature, the latter including EU surveillance and other reports published by ECDC, EFSA and EMA. For antibiotics, notice was paid to the categorisations made by the AMEG and by international organisations (WHO, OIE) also paying attention to their context and relevance to the criteria for antimicrobials designated for human use. When inadequate information was available in the public domain, the opinions of professional experts, e.g. infectious disease clinicians, microbiologists, have been sought. Considering, in particular, the lack of published data on the use of antimicrobials outside the terms of a marketing authorisation in animals, additional information on the treatment of serious infections in animals in the EU was solicited via an open call for data made by the Agency (see Section 4. of the Annex).

Recommendations for antimicrobials to be reserved for human use only according to Article 37(5)

It is recommended that the following antimicrobials and groups of antimicrobials should be reserved for the treatment of humans. See Section 2. Methodology for an explanation of the terms 'classes', 'subclasses' and 'groups', in the context of this advice.

Table 1. Recommendations on the antimicrobials to be reserved for human use

Antimicrobial classes, subclasses, substances	Location of the detailed evaluation
Antibiotics	
<i>Note: Except for five individual substances, reference is made to antibiotic classes with a single example given of a substance in each class.</i>	
Carboxypenicillins and ureidopenicillins, including their combinations with beta-lactamase inhibitors (e.g. piperacillin, piperacillin-tazobactam)	Table 12, page 34
Ceftobiprole and ceftaroline	Table 15, page 39
Combinations of cephalosporins with beta-lactamase inhibitors (e.g. ceftolozane-tazobactam)	Table 16, page 40
Siderophore cephalosporins (e.g. cefiderocol)	Table 17, page 41
Carbapenems, including carbapenems with beta-lactamase inhibitors (e.g. meropenem, meropenem-vaborbactam)	Table 18, page 42
Penems (e.g. faropenem)	Table 19, page 44
Monobactams (e.g. aztreonam)	Table 20, page 45
Phosphonic acid derivatives (e.g. fosfomicin)	Table 23, page 47
Glycopeptides (e.g. vancomycin)	Table 24, page 49
Lipopeptides (e.g. daptomycin)	Table 25, page 50

Antimicrobial classes, subclasses, substances	Location of the detailed evaluation
Oxazolidinones (e.g. linezolid)	Table 26, page 51
Macrocycles (e.g. fidaxomicin)	Table 29, page 54
Plazomicin	Table 34, page 58
Glycylcyclines (e.g. tigecycline)	Table 37, page 60
Eravacycline	Table 39, page 62
Omadacycline	Table 40, page 63
Antivirals <i>The following individual substances only</i>	
Amantadine Baloxavir marboxil Celgosivir Favipiravir Galidesivir Lactimidomycin Laninamivir Methisazone/metisazone Molnupiravir Nitazoxanide (also an antiprotozoal) Oseltamivir Peramivir Ribavirin Rimantadine Tizoxanide Triazavirin Umifenovir Zanamivir	Table 62, page 81
Antifungals	
None	Table 63, page 92
Antiprotozoals <i>The following individual substances only</i>	
Nitazoxanide (included due to antiviral properties)	Table 65, page 103

Further recommendations

- Endangered animal species that are kept for conservation purposes have special importance and a variety of antimicrobials are needed to treat the diverse diseases from which they may suffer. There is often restricted contact between these animals and humans, limiting the opportunity for transfer of resistant organisms. Thus, there are important factors to take into account for this

special group of animals in the context of the antimicrobials designated for human use only. This might be taken into consideration by the Commission.

- The recommendations on the antimicrobials to be reserved for human use were established based on current scientific knowledge. The recommendations should be reviewed, to consider both addition or deletion of classes/substances, in the light of new scientific evidence or emerging information. This information could include, in both human and veterinary medicine, the emergence of new diseases or changes in the epidemiology of existing diseases, changes in antimicrobial resistance and changes in availability and patterns of antimicrobial use.
- For new antimicrobial substances authorised for human use after publication of this advice, it is recommended that the Commission should request the Agency to evaluate them against the criteria for designation of antimicrobials to be reserved for human use only.
- It may be necessary periodically to review the methodologies used for the evaluation of antibiotics, antivirals, antifungals and antiprotozoals, presented in Sections 2.5. to 2.8. , in the light of scientific developments and experience gained.

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1. Terms of reference and scope

This report represents the advice of the Agency on implementing measures to be introduced under Article 37(5) of Regulation (EU) 2019/6 on veterinary medicinal products ('the Regulation') [4]. In this context, the request from the European Commission requires the Agency to provide scientific recommendations on the content of a list of antimicrobials to be reserved for use in human medicine, only.

This advice is linked to the *Advice on implementing measures under Article 37(4) of Regulation (EU) 2019/6 on veterinary medicinal products - Criteria for designating antimicrobials reserved for treatment of certain infections in humans* [1], as provided by the Agency to the European Commission in October 2019.

According to the Commission's mandate, both antimicrobials for which a marketing authorisation has already been granted and those without a marketing authorisation, including new antimicrobials and those to be developed in future, may be subject to evaluation under the criteria (Articles 37(5) and 152(1) of the Regulation). Article 37(3) states that a marketing authorisation for an antimicrobial veterinary medicinal product shall be refused if the antimicrobial is reserved for the treatment of humans in accordance with Article 37(5).

In addition, as described in Article 107(5), the antimicrobials designated to be reserved for human use shall not be used in accordance with Articles 112, 113 and 114 i.e. outside the terms of the marketing authorisation.

The designated antimicrobials or groups of antimicrobials will fall under the scope of Article 118(1) of the Regulation, which requires that operators in third countries shall not use these antimicrobials for animals or products of animal origin to be exported to the European Union.

The reservation of antimicrobials for human use is one of a range of measures to tackle antimicrobial resistance that are laid down in the Regulation. Other measures include a ban on preventive use of antibiotics in groups of animals, restrictions on metaphylactic use of antimicrobials, a reinforced ban on the use of antimicrobials for promotion of growth and increasing yield and an obligation for Member States to collect data on the sales and use of antimicrobials in animals.

Under the Regulation, 'antimicrobial' means any substance with a direct action on microorganisms used for treatment or prevention of infections or infectious disease, including antibiotics, antivirals, antifungals and antiprotozoals.

Coccidiostats and histomonostats that are regulated as feed additives in the EU under Regulation (EC) 1831/2003 are not addressed in this advice. Those anticoccidials that are regulated as veterinary medicinal products have been addressed in the section relating to antiprotozoals.

The Annex to the advice includes a summary analysis of an 'open call for data on the use of antimicrobials in animals', that was used to gain information on in-practice use of antimicrobials in veterinary medicine in order to support the advice.

2. Methodology

2.1. Background

It is recognised in the recitals to the Regulation that antimicrobial resistance is a major global public health threat that requires urgent action in accordance with a One Health approach. Hence a range of risk management measures aimed at tackling AMR are laid out, amongst them being provisions to reserve certain antimicrobials for use in humans only. This action is aimed to preserve as long as possible the efficacy of antimicrobials that are critical for the treatment of life-threatening infections in humans.

Article 37(4) of the Regulation allows the Commission to adopt a delegated act establishing the criteria for the designation of the antimicrobials to be reserved for human use. The Commission Delegated Regulation (EU) 2021/1760 on the criteria [2] was drafted by the Commission taking account of scientific advice from EMA [1] and following consultation with Member States and stakeholders. In the preamble to the delegated regulation, the Commission notes that various international organisations and countries have elaborated criteria for the ranking of antimicrobial classes for the purpose of developing risk management strategies relating to antimicrobial use, and mentions that these were taken into account in the Agency's advice to the Commission on the criteria for the designation of antimicrobials to be reserved for humans. It is also noted that the banning of the use of an antimicrobial in animals is one of the most severe risk management measures and should be done cautiously.

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

The Commission Delegated Regulation (EU) 2021/1760 includes three criteria to designate antimicrobials that shall be reserved for use in humans. In summary, these criteria lead to the identification of those antimicrobials:

- that are of high importance to preserve human health and that should therefore be considered for use in human medicine only (criterion A),
- whose use in animals could accelerate the spread of AMR by allowing transmission of resistance from animals to humans (criterion B), and
- that do not represent an essential need for animal health, and whose absence in veterinary medicine would not lead significant impact on animal health or major impact on animal welfare and public health (criterion C).

The criteria, as laid out in the Annex to the Commission Delegated Regulation, are presented in their entirety below. Antimicrobials that qualify to be designated to be reserved for treatment of humans **shall meet all three criteria, A, B and C**. If one of the three criteria is not met, the antimicrobial/antimicrobial group will not be reserved for treatment of humans.

Criteria from the Annex to the Commission Delegated Regulation (EU) 2021/1760 [2]

Part A: Criterion of high importance to human health

1. The antimicrobial or group of antimicrobials meets this criterion if any of the following applies:

(a) it is the sole or last-resort antimicrobial or group of antimicrobials available in a patient management treatment approach for serious, life-threatening infections in humans which, if inappropriately treated, would lead to significant debilitating morbidity or significant mortality;

(b) it is an essential component of the limited treatment alternatives available in a patient management treatment approach for serious, life-threatening infections in humans which, if inappropriately treated, would lead to significant debilitating morbidity or significant mortality;

(c) it is an antimicrobial or a group of antimicrobials, which is authorised in the Union for the treatment of serious microbial infections in patients with limited treatment options, indicating that the antimicrobial or the group of antimicrobials considered is recognised as addressing an unmet medical need related to antimicrobial resistance.

2. Factors considered responsible for limited treatment alternatives for patients, as referred to in point 1(b), include:

– the virulence and antimicrobial resistant phenotype(s) of the microorganisms causing infection, including multidrug resistance;

– the characteristics of the patients (for example, immunocompromised, paediatric, elderly) and disease (for example, site of infection concerned) under treatment;

– the proportion of patients requiring treatment and the impact on healthcare services.

Part B: Criterion of risk of transmission of resistance

1. The antimicrobial or group of antimicrobials meets this criterion if any of the following applies:

(a) for an antimicrobial or group of antimicrobials authorised for use in animals, scientific evidence, including epidemiological evidence where available, exists showing that:

– there is an actual emergence, dissemination and transmission of resistance to this antimicrobial or group of antimicrobials, or induction of cross-resistance or co-selection of resistance to other antimicrobials, and

– transmission of such resistance from animal sources to humans is significant and linked to the use of this antimicrobial or group of antimicrobial in animals, whether it occurs through microorganisms resistant to the antimicrobial or group of antimicrobials considered or through the transmission of genes conferring resistance to the antimicrobial or group of antimicrobials considered.

(b) for an antimicrobial or group of antimicrobials not authorised for use in animals, scientific evidence exists showing that:

– there is the potential for emergence, dissemination and transmission of resistance to this antimicrobial or group of antimicrobials or potential for inducing cross-resistance or co-selection of resistance to other antimicrobials, and

– this transmission from animal sources to humans would likely be significant and linked to the use of this antimicrobial or group of antimicrobials in animals, whether it would occur through microorganisms resistant to the antimicrobial or group of antimicrobials considered or through the transmission of genes conferring resistance to the antimicrobial or group of antimicrobials considered

2. Factors triggering significant transmission of resistance between animals and humans linked to the use of an antimicrobial or group of antimicrobials in animals include:

– use selects for resistance, cross-resistance or co-selection of resistance to antimicrobials that are crucial for human medicine;

– transmission of resistance occurs by vertical as well as horizontal transmission;

– transmission of resistance involves zoonotic pathogens;

– transmission can take place by different routes of exposure;

– transmission occurs through a number of different animal species.

Part C: Criterion of non-essential need for animal health

This criterion is met if any of the following apply:

1. The antimicrobial or group of antimicrobials meets this criterion if any of the following applies:

(a) there is no robust evidence of the need for the antimicrobial or group of antimicrobials in veterinary medicine;

(b) the antimicrobial or group of antimicrobials is used to treat serious, life-threatening infections in animals which, if inappropriately treated, would lead to significant morbidity or significant mortality, or would have a major impact on animal welfare or public health, but adequate alternative medicinal products are available for the treatment of those infections in the animal species concerned;

(c) the antimicrobial or group of antimicrobials is used to treat serious, life-threatening infections in animals which, if inappropriately treated, would lead to limited morbidity or limited mortality and there is scientific evidence showing an overriding public health interest in not using it.

2. The provisions laid down in point 1 apply when the antimicrobial or group of antimicrobials considered is either of the following:

(a) an antimicrobial or group of antimicrobials present within authorised veterinary medicinal products;

(b) an antimicrobial or group of antimicrobials present within medicinal products authorised for use in humans, that may be administered to animals outside the terms of their marketing authorisation.

Points regarding the application of the criteria

- The Commission Delegated Regulation also includes, in the recitals of the preamble, certain background of importance to the application of the criteria. In relation to Criterion C, in recital (9) of the delegated regulation, it is stated: *'When considering the use of alternative medicinal products instead of certain antimicrobial medicinal products, it is important that those products are adequate and available. Such alternatives should be authorised medicinal products in suitable formulations for the treatment of the disease in the animal species requiring treatment. Their use should result in a lower risk to public health in terms of antimicrobial resistance than the antimicrobial they aim to replace'*.
- Also of note, in relation to Criterion B, the term 'significant' is understood to mean that, in the Agency's view, there is sufficient evidence for transmission [or potential for transmission] of resistance to justify consideration of the need for risk mitigation, noting that Criteria A and C are also to be taken into account when considering if a substance should be reserved for human use.
- The scope of the antimicrobials designated for human use is understood to extend to **all** antimicrobial substances, **whether or not authorised for human medicine and/or veterinary medicine**, in or outside of the EU. Although the medicinal use of antimicrobial classes outside the EU may have been reviewed as part of the evaluations, compliance with criteria A and C has been assessed only in the context of circumstances in the EU.

Considering the number of individual substances in scope, and the mixed availability of supporting evidence relating to the criteria, different methodologies were used for the assessment of the different types of antimicrobials. The specific methodologies used to evaluate antibiotics, antivirals, antifungals and antiprotozoals against the criteria are addressed in Sections 2.5. , 2.6. , 2.7. and 2.8. of this advice, respectively.

2.3. Which substances are included within a particular 'group' of antimicrobials?

To assist with the identification of individual substances that belong to each group of antimicrobials considered, the related WHO ATC codes and ATCvet codes have been included in the supporting documentation (Annex 6.). However, the ATC classification [5] groups substances according to chemical, pharmacological and/or therapeutic groups, and in some instances the ATC groupings are inconsistent with those groupings considered to be pertinent for the development of recommendations on the antimicrobials to be reserved for human use. For example, some substances appear in more than one ATC grouping and have different codes if they are included in different pharmaceutical forms (e.g. for systemic or topical use) or have different therapeutic uses (e.g. nitroimidazoles, used as antibacterials or antiprotozoals). In addition, not all antimicrobial substances have ATC codes assigned and there is no complete international database of all antimicrobial substances available. Therefore, it is likely that there are some antimicrobials that have been omitted from specific mention in this report.

In most instances, antibiotics and antifungals have been evaluated in groups according to their pharmacological (sub)class. However, there may be exceptions. In some cases, individual substances were evaluated separately due to properties that set them apart from other antimicrobials in their pharmacological class. For example, eravacycline belongs to the tetracycline class but evades/overcomes a certain mechanism that confers resistance to most other tetracyclines. It has therefore been evaluated separately from other substances in the tetracycline class.

A different approach was taken to antivirals and antiprotozoals which, for methodological reasons explained below, were initially considered in groups relating to the important human diseases that they are used to treat.

For the reasons stated above, it is suggested that *antibiotics* not individually mentioned in the advice can be regarded as included in the same grouping as other molecules from the same pharmacological (sub)class that is used in this report. In many cases this can be based on the ATC coding; however, in some cases the grouping used for the recommendations on the antimicrobials to be reserved for humans is a sub-division of the lowest ATC grouping available (e.g. glycylicyclines are addressed separately from other tetracyclines although the ATC 4th level code is the same, J01AA).

For *antivirals*, it may be assumed that only those individual substances listed in Table 1 above are included in the recommendations on the antimicrobials to be reserved for human use.

At present, no antifungal or antiprotozoal groups are recommended to be reserved for human use only.

For *new antimicrobial substances* authorised for human use after publication of this advice it is recommended that the Commission should request the Agency to evaluate them against the criteria for designation of antimicrobials to be reserved for human use only. It should be noted that it may be necessary to consider these substances separately from their ATC group.

2.4. Data sources and open call for data

In order to formulate its recommendations, various data sources have been used e.g. peer-reviewed literature references, textbooks and grey literature: official reports from EU Agencies (e.g. EFSA, ECDC and EMA surveillance reports, scientific opinions, rapid risk assessments, EPARs); official reports from national institutions (e.g. national AMR surveillance reports); Summaries of Product Characteristics for authorised medicines and treatment guidelines published by professional bodies. The key references have been included in related parts of the report.

When inadequate data have been available in the public domain, the opinions of professional experts e.g. infectious disease clinicians, microbiologists, have been sought. In addition, an open call was made for data on the use of antimicrobials in animals (see below).

For antibiotics, attention has also been paid to the categorisations/lists from the AMEG, WHO and OIE, noting that the purpose of these lists, and hence the criteria on which they are based, differ in some aspects from the criteria established for the designation of antimicrobials to be reserved for humans. In addition, the evaluations have been conducted in the EU context and it should be considered that EU conditions in terms of disease prevalence, antimicrobial availability, etc. may differ from those in other global regions, such that international recommendations may not be fully applicable.

2.4.1. Open call for data on the use of antimicrobials in animals

Although data on the sales of veterinary antimicrobials in Europe have been collected through the ESVAC project since 2011, at present there is no official collection of data on how these antimicrobials are used in animals (species, indications, etc), and little published information in particular in relation to use of antimicrobials not authorised as VMPs [6]. Therefore, in order to support the Agency in the preparation of its scientific advice, interested parties were invited to submit information on the use and availability of antimicrobials in the EU to treat serious infections in animals, including outside the terms of a marketing authorisation, and to provide any scientific evidence of the impact on public and animal

health that the CVMP should consider. Throughout the report this data source is referred to as the 'open call for data'.

The open call for data was posted on 9 December 2019. Responses were accepted until 6 March 2020.

Background information and a partial summary report on the findings are presented in Section 4. of the Annex. Several limitations in this data source are discussed.

2.5. Methodology used to evaluate antibiotics

Grouping of antibiotics and identification of classes/substances not authorised for human or veterinary use in the EU

Considering the large number of individual antibiotic substances, they were addressed in their pharmacological (sub)classes as identified by the AMEG, with a few exceptions. Certain substances (e.g. eravacycline, minocycline, omadacycline, plazomicin) were considered separately from their AMEG class due to their individual importance or characteristics, e.g. novel tetracyclines that have been developed to overcome a specific antibiotic resistance mechanism, enabling them to be used to treat infections that are resistant to other molecules in the class.

The AMEG categorisation included only antibiotic classes that have been authorised for human and/or veterinary use in the EU. However, the mandate from the Commission specified that the scope of the advice should include antimicrobials for which a marketing authorisation has not yet been granted (including new antimicrobials or groups of antimicrobials remaining to be identified or developed in the future) (Article 37(3)). Therefore, a review of antibiotics authorised in third countries was performed as these may be developed in future for the EU market.

The search was performed using lists of antibiotics from international organisations, regulatory agency websites and information present in the literature [7-11]. Only substances that are in the scope of the Regulation and that have a potential to be used therapeutically in humans have been considered. The findings are presented in **Table 2** and **Table 3**. As there is no comprehensive worldwide database, the lists of antibiotics considered may not be exhaustive.

Table 2. Antibiotic classes from the WHO CIA, and OIE lists and the OIE Annual report on antimicrobials intended for use in animals, that are currently not used in humans and not authorised in veterinary medicine in the EU

Antimicrobial class	Substance	Where identified
Bicyclomycin (Bicozamycin)*		OIE [7]
Orthosomycins/Oligosaccharides*	Avilamycin	OIE [7]
	Evernimicin	WHO [11]
Quinoxalines*	Carbadox	OIE [7]
	Olaquinox	OIE [7]
	Quinocetol	OIE [8]
Thiopeptides	Thiostrepton	OIE [7]
	Nosiheptide	OIE [7]
Phosphoglycolipids/Moenomycins*	Bambermycin (Flavomycin)	WHO [11]

Antimicrobial class	Substance	Where identified
Elfamycins	Efrotomycin	OIE [8]
Aminocoumarins*	Novobiocin	OIE [7] WHO [11]

* These classes are included in Annex 2 to the WHO CIA list 6th Ed. as antimicrobial classes currently not approved for systemic use in human medicine, and therefore not included in the WHO CIA list.

The classes identified in **Table 2** were included in the evaluation. These classes have not been reviewed by AMEG.

Table 3. Other antibiotic substances not authorised in the EU but included in classes addressed in the AMEG categorisation

Substance not authorised in EU	Where identified	AMEG class
Enramycin/enduracidin	OIE [8]	Treated as cyclic polypeptide for this advice
Virginiamycin	OIE [8]	Streptogramins
Kitasamycin	OIE [8] OIE [7]	Macrolides
Avoparcin	OIE [8]	Glycopeptides
Kazugamycin	New Zealand Food Safety [10]	Aminoglycosides

For the purpose of the EU evaluation of antimicrobials to be designated for human use, the substances in Table 3 can be considered as included in the antimicrobial class used for the AMEG categorisation.

Stepwise assessment against the criteria

Considering the requirement that all three of the criteria in the delegated regulation shall be met in order for an antimicrobial to be designated for human use, it was agreed to conduct a stepwise assessment: all classes were initially assessed against criterion A (high importance to human health); however, only those meeting this criterion were assessed against criterion B (risk of transmission of resistance), and only those meeting both criteria A and B were evaluated against criterion C (non-essential need for animal health).

Table 4. Outcome of the stepwise assessment of antibiotic substances/(sub)classes

Antimicrobial substance/(sub)class	Criterion A	Criterion B	Criterion C
Natural, narrow spectrum penicillins (beta-lactamase-sensitive penicillins)	No	N/A	N/A
Antistaphylococcal penicillins (beta-lactamase-resistant penicillins)	Yes	Yes	No
Aminopenicillins, without beta-lactamase inhibitors	No	N/A	N/A
Aminopenicillins in combination with beta-lactamase inhibitors	Yes	Yes	No
Amdinopenicillins	No	N/A	N/A

Antimicrobial substance/(sub)class	Criterion A	Criterion B	Criterion C
Carboxypenicillins and ureidopenicillins, including their combinations with beta-lactamase inhibitors	Yes	Yes	Yes
1st- and 2nd-generation cephalosporins, and cephamycins	Yes	Yes	No
3rd- and 4th-generation cephalosporins, except combinations with beta-lactamase inhibitors	Yes	Yes	No
Ceftobiprole, Ceftaroline	Yes	Yes	Yes
Combinations of cephalosporins and beta-lactamase inhibitors	Yes	Yes	Yes
Siderophore cephalosporins	Yes	Yes	Yes
Carbapenems, including carbapenems with beta-lactamase inhibitors	Yes	Yes	Yes
Penems	Yes	Yes	Yes
Monobactams	Yes	Yes	Yes
Polymyxins	Yes	Yes	No
Cyclic polypeptides	No	N/A	N/A
Phosphonic acid derivates	Yes	Yes	Yes
Glycopeptides	Yes	Yes	Yes
Lipopeptides	Yes	Yes	Yes
Oxazolidinones	Yes	Yes	Yes
Pleuromutilins	No	N/A	N/A
Macrolides	Yes	Yes	No
Macrocycles	Yes	Yes	Yes
Ketolides	No	N/A	N/A
Lincosamides	No	N/A	N/A
Streptogramins	No	N/A	N/A
Aminoglycosides	Yes	Yes	No
Plazomicin	Yes	Yes	Yes
Aminocyclitols	No	N/A	N/A
Tetracyclines	No	N/A	N/A
Glycylcyclines	Yes	Yes	Yes
Minocycline	No	N/A	N/A
Eravacycline (fluorocycline)	Yes	Yes	Yes
Omadacycline	Yes	Yes	Yes
Amphenicols	No	N/A	N/A
Sulfonamides	No	N/A	N/A
Trimethoprim and derivates	No	N/A	N/A
Sulfonamides-trimethoprim derivates	Yes	Yes	No
Quinolones (non-fluorinated)	No	N/A	N/A
Fluoroquinolones	Yes	Yes	No
Nitrofurans derivates	No	N/A	N/A
Nitroimidazoles	Yes	Yes	No
Rifamycins	Yes	Yes	No
Substances used solely to treat tuberculosis or other mycobacterial diseases	Yes	No	N/A

Antimicrobial substance/(sub)class	Criterion A	Criterion B	Criterion C
Riminoferazines	Yes	No	N/A
Sulfones	Yes	No	N/A
Pseudomonic acids	Yes	Yes	No
Steroid antibacterials	No	N/A	N/A
Bicyclomycin (Bicozamycin)	No	N/A	N/A
Orthosomycins/Oligosaccharides	No	N/A	N/A
Quinoxalines	No	N/A	N/A
Thiopeptides	No	N/A	N/A
Phosphoglycolipids/Moenomycins	No	N/A	N/A
Elfamycins	No	N/A	N/A
Aminocoumarins	No	N/A	N/A

Yes – Criterion met

No – Criterion not met

N/A – Criterion not assessed

The highlighted antibiotic classes/substances are recommended to be designated for human use. The evaluations for each class/substance against the criteria are presented in Section 3.1. , including the supporting references.

2.6. Methodology used to evaluate antivirals

2.6.1. Introduction

In order to establish the recommendations for antivirals to be reserved for human use only, a specific approach has been taken to assess the risk of transfer of resistance to antivirals due to the particularities of viruses and antiviral substances when compared to bacteria and antibiotics (viral zoonoses and mechanisms of action of the antivirals).

The three criteria for designation of antimicrobials to be reserved for humans have been applied and, in this context, the following considerations have been taken into account:

Criterion A: High importance for human health

Antivirals are particularly important for human health as they are the only available antimicrobial class to treat viral diseases.

Criterion B: Risk of transmission of antiviral resistance

Exchange of genetic material between viruses is possible only when two different viruses simultaneously infect the same cells. In most cases however, viruses belonging to different families (or even different orders) compete against each other in using the cell machinery to replicate, each virus dedicating this to its own replication and survival. Therefore, contrary to the situation in bacteria, the transmission of resistance genes from one virus to another (horizontal transmission) is a rare phenomenon.

Selection of resistance in viruses occurs primarily following an antiviral treatment. Indeed, spontaneous mutations in viruses occur at a very high frequency (and much more often in RNA viruses than in DNA viruses). Therefore, viruses are constantly changing and can sometimes change in ways that might make antivirals work less well or not work at all: the use of an antiviral will block the replication of the antiviral-sensitive viruses without having any effect those that are resistant. In this way, antiviral-resistant viruses are selected because they can still replicate.

Criterion C: Non-essential need for animal health

The importance of antivirals in the veterinary sector is not quantifiable so far as:

- No antiviral is at present authorised in the EU in veterinary medicine.
- Antiviral use in animals has been sporadically reported at global level.
- Use of human antivirals, outside the terms of the marketing authorisation, in the veterinary sector has been reported to treat e.g. Herpes viruses in companion animals, zoo/exotic species and horses.
- Development of antivirals for use in veterinary medicine seems to be underway or imminent.

The potential risk resulting from the use of the antiviral in animals leading to the selection and dissemination of resistant viruses that could infect humans was used as a screening criterion (see Section Annex 2.)

2.6.2. High-level screening of antiviral classes

2.6.2.1. Principles

The recommendation for an antiviral/antiviral class to be reserved for human use should be based on an assessment of the potential risk of the use of the antiviral in animals leading to the selection and dissemination of a resistant virus that could infect humans.

In other terms, the use of antivirals in animals may present a risk for humans only if it leads to the selection of resistant viruses able to infect humans. This implies that the following steps should be considered:

- to consider only zoonotic viruses,
- to consider if the animal potentially infected by the zoonotic virus is liable to be treated with an antiviral,
- to consider the frequency of occurrence of the zoonotic disease in humans,
- to check which antivirals, primarily intended for human therapy, are used or could be used effectively, given their mechanism(s) of action, to treat these zoonotic viral diseases in the relevant animals.

2.6.2.2. Implementation

- Only zoonotic viruses present in the EU have been considered
- Only animal species that are candidates for antiviral treatment are considered, namely companion animals (including non-conventional pets) and food producing animals. Wild animals, hunted animals and zoo animals have not been included as the use of antivirals is improbable or may be so anecdotal that the risk for human health is negligible. Table 5 summarizes the outcome of this exercise.

Table 5. Zoonotic viruses, their animal hosts (companion and food producing animals), and the frequency of occurrence of the disease in humans within the EU

Disease	Aetiology (Genus & family of virus)	Animals affected	Frequency of the disease in humans
Bovine vesicular stomatitis	<i>Parapoxvirus</i> , <i>Poxviridae</i>	Cattle	Rare
Cowpox	<i>Orthopoxvirus</i> ,	Cattle, rodents, cats	Rare

Disease	Aetiology (Genus & family of virus)	Animals affected	Frequency of the disease in humans
	<i>Poxviridae</i>		
Crimean-Congo hemorrhagic fever	<i>Nairovirus</i> , <i>Bunyaviridae</i>	Cattle, sheep, goats, horses, pigs, hares	Sporadic
Eastern equine encephalomyelitis	<i>Alphavirus</i> , <i>Togaviridae</i>	Horses	Rare
Encephalomyocarditis	<i>Cardiovirus</i> , <i>Picornaviridae</i>	Rodents, horses, cattle, pigs, birds	Rare
Foot-and-mouth disease	<i>Aphthovirus</i> , <i>Picornaviridae</i>	Cattle, pigs, sheep, goats	Very rare
Hemorrhagic fever with renal syndrome	<i>Hantavirus</i> , <i>Bunyaviridae</i>	Rodents	Regular
Hepatitis E (HEV)	<i>Orthohepevirus A</i> , <i>Hepeviridae</i>	Pigs, rabbits, rats	Frequent
Influenza A	<i>Alphainfluenzavirus A</i> , <i>Orthomyxoviridae</i>	Pigs, horses, birds	Frequent
Lymphocytic choriomeningitis	<i>Arenavirus</i>	Mice, guinea pigs, rats, chinchillas, rabbits, dogs, pigs	Rare and sporadic
Louping-ill	<i>Flavivirus</i> , <i>Togaviridae</i>	Sheep, cattle, horse, rodents	Rare
Monkeypox	<i>Orthopoxvirus</i> , <i>Poxviridae</i>	Rabbits, rats, mice, squirrels	Sporadic
<i>Orthoavulavirus 1</i> (Newcastle disease)	<i>Orthoavulavirus</i> , <i>Paramyxoviridae</i>	Birds	Rare
Orf	<i>Parapoxvirus</i> , <i>Poxvirus</i>	Sheep, goats, dogs, cats	Rare
Pseudocowpox	<i>Parapoxvirus</i> , <i>Poxviridae</i>	Cattle	Sporadic
Rabies	<i>Lyssavirus</i> , <i>Rhabdoviridae</i>	All warm-blooded species	Rare and sporadic
Rotavirus gastroenteritis	<i>Rotavirus</i> , <i>Reoviridae</i>	Foals, calves, piglets, dogs, cats, rabbits, mice, birds	Frequent
Russian and Central-european Spring-Summer encephalitis	<i>Flavivirus</i> , <i>Togaviridae</i>	Rodents, goats, sheep	Sporadic
Sindbis fever	<i>Alphavirus</i> , <i>Togaviridae</i>	Birds, cattle, horses	Rare
Swine vesicular disease	<i>Enterovirus</i> , <i>Picornaviridae</i>	Pigs	Rare
Usutu virus disease	<i>Flavivirus</i> , <i>Flaviviridae</i>	Birds	Rare
West Nile fever	<i>Flavivirus</i> , <i>Flaviviridae</i>	Horses, dogs, cats, birds	Endemic

Note that infections with highly pathogenic strains of avian influenza (HPAI) virus are category A diseases in Aves under the Animal Health Law, Regulation (EU) 2016/429. According to Delegated Regulation (EU) 2020/687, animals of listed species (Aves) kept on any establishment where an outbreak of HPAI is confirmed should be killed as soon as possible, while in certain cases, emergency vaccination is offered as a possibility. The Commission is preparing a draft delegated act on the use of certain veterinary medicinal products for the purpose of disease prevention and control of certain listed diseases. The proposed approach in the draft is to prohibit the use of antivirals for all category A diseases, including HPAI. Therefore, it is highly unlikely that birds affected by HPAI would receive antiviral treatment in the EU. Low pathogenicity avian influenza (LPAI) is in categories D and E, with no EU harmonised prohibitions planned on the use of antivirals under the Animal Health Law, and therefore antiviral resistance theoretically might be passed on if LPAI converts to HPAI through antigenic drift.

Note that this table should be subject to regular re-evaluation considering that the epidemiology of zoonotic viral diseases in the EU is subject to change and new diseases or strains may emerge.

Table 6 lists the zoonoses that are frequent or endemic in humans that were retained for further assessment.

Table 6. Zoonoses from Table 5 that are frequent or endemic in humans in the EU

Zoonotic viruses, frequent or endemic in humans in the EU, retained for assessment for the recommendations on the antimicrobials to be reserved for human use
Hemorrhagic fever with renal syndrome virus (Hantavirus)
Hepatitis E virus (Orthohepevirus A)
Influenza A virus (Alphainfluenzavirus A)
Rotavirus gastroenteritis (Rotavirus)
West Nile fever virus (Flavivirus)

2.6.3. Evaluation of antiviral substance groups

The main considerations that were retained for classification of the antivirals are as follows (some additional factors were taken into account on a case-by-case basis):

- The human diseases/viruses against which each antiviral is claimed to be effective.
- The veterinary diseases/viruses against which each antiviral is claimed to be effective, or showed activity.
- The mechanism(s) of action, which allows specification as to whether the antiviral is virus-specific or whether it has a broader spectrum of activity.

Antivirals based on interferons were excluded from this analysis: interferons belong to several related families of cytokines (α , β and γ), naturally produced by the body (human and animals). They are highly potent antivirals *per se*, but by and large their major function is to regulate cellular proteins. As this is a natural immune process, it would not make sense to consider a ban on their use in animals.

Antivirals based on humanised monoclonal antibodies are also excluded from this analysis: monoclonal antibodies are dedicated to specific epitopes of a given virus. Although engineered, they behave like naturally produced antibodies: they bind to the epitope(s) of the targeted pathogens, to neutralize them and/or to prepare them for uptake and destruction by phagocytes. As this is a natural immune process, it would not make sense to consider their ban.

The report on antivirals is divided into sections: the first sections, each relating to a specific disease indication, address the antivirals which have received a Marketing Authorisation for human therapy within the EU and for which reliable data are available (through the SPCs); these are followed by a section that considers antivirals identified so far through textbooks and bibliographic data, taken on board by default, but for which the available information should be considered with prudence.

It cannot be excluded that some antivirals are missing. This is because no international comprehensive list of antivirals is currently available; furthermore, this category of medicines is quite novel, even on the human side, and is developing fast.

2.7. Methodology used to evaluate antifungals

The fungal diseases of greatest importance to human health have been summarised in Table 64, together with a consideration of their epidemiology and occurrence in animals, and the possibility for transmission of the infection (and potentially resistance to antifungals) between animals and humans. Based on this assessment, monographs have been prepared for the major classes of antifungal agents identified as used in human medicine to treat important fungal disease, addressing in more detail the three criteria evaluated for designation of antimicrobials to be reserved for humans. Antifungals are not in scope of the WHO's CIA List, OIE List or the AMEG's categorisation.

The criteria in the delegated regulation were addressed as follows:

Criterion A: High importance to human health

The estimated global and EU burden of the important human fungal diseases (where available) is provided in Table 64. In humans, most opportunistic fungal infections occur in critically ill or immunocompromised patients. The availability of antifungal agents is very limited, and hence there is heavy reliance on a few classes, in particular the azoles, to treat a range of different infections. For preparation of the monographs for each antifungal class, published treatment guidelines for the different diseases, amongst other sources, were reviewed. Recommendations for use are frequently dependent not only on the fungal organism involved, but also on the specific clinical circumstances, including the underlying primary disease and the severity and stage of the fungal infection. Different antifungal substances may be used in combination or sequentially according to individual patient needs. Hence, almost all antifungal classes are considered of high importance to human health.

There is no published information that indicates that any antifungal medicines have been formally categorised by Committee for Medicinal Products for Human Use (CHMP) as addressing 'unmet medical need' (see Annex 1.).

Criterion B: Risk of transmission of resistance

Table 64 also considers the transmissibility from animals to humans of fungi that may cause important human diseases. Only a small fraction of fungal species are adapted to animal hosts and able to act as zoonotic pathogens that are transmitted directly between animals and humans (e.g. *Microsporium canis*). Most fungi primarily occupy an environmental niche, but under certain conditions some can survive in animal host tissue causing opportunistic infections (e.g. *Aspergillus*). Fungal association with animals or their faeces may augment the infectious load in the environment, although there may be no direct transmission of infection between animal and human. See Seyedmousavi, Bosco [12], for further discussion.

The evidence for the occurrence of resistance to individual antifungal classes is addressed in the monographs. In human medicine, development of resistance to antifungal agents is of rising concern, particularly considering their increasing need for treatment of immunocompromised patients. However,

in veterinary medicine susceptibility testing is rarely undertaken, therefore the prevalence of resistance in animal fungal isolates is mostly unknown. It should also be considered that use of azole fungicides in agriculture contributes to the pool of resistance in environmental fungi such as *Aspergillus* spp., and to human exposure. The opportunity for transmission of drug-resistant fungi from animals to humans is limited within the context of the epidemiology outlined above.

Criterion C: Non-essential need for animal health

The need for the different antifungal classes in veterinary medicine has been reviewed in the monographs, taking into account existing marketing authorisations, treatment guidelines (where available), literature review and responses to the open call for data. The availability of different antifungal classes is even more restricted in veterinary medicine than in human medicine, with azoles being the mainstay of therapy in the EU. Use of antifungals outside the terms of a marketing authorisation (under Articles 112, 113 and 114 of the Regulation) is important to address therapeutic gaps. Consumption of veterinary antifungals is not recorded at EU level and antifungal agents are not addressed in the OIE's List of Antimicrobials of veterinary importance.

2.8. Methodology used to evaluate antiprotozoals

Antiprotozoals include a diverse range of substances and the mode of action against specific protozoa is often poorly understood. Although some substances are effective against a range of protozoa and bacteria, individual agents within a class may be specific to the protozoal species they treat, hence antiprotozoals are difficult to classify and are usually considered in the context of the disease they treat rather than in pharmacological groups.

For this reason, although based on the three criteria of the Commission Delegated Regulation, a different format was chosen to present the evaluations of antiprotozoal substances compared with that used for antibiotics. The individual substances are considered in reference to the important human protozoal disease for which they are a recognised treatment, rather than in pharmacological classes. The assessment is included in Table 65, with the criteria in the delegated regulation addressed as follows:

Criterion A: High importance to human health

Information in the column 'Important human protozoal diseases' outlines serious and life-threatening human infections that are potentially associated with significant morbidity and mortality. As protozoal diseases may be limited in their geographic distribution, further information is given in the second column so that the European and global perspectives can be understood. The column headed 'Recognised and commonly used medicines...' indicates if substances are included in the WHO's Essential Medicines List and recommended according to published treatment guidelines (where available), textbooks, literature and official reports. Available alternative treatments for each disease are listed. Antiprotozoals *per se* are not in scope of the WHO's CIA List or the AMEG's categorisation. There is no published information that indicates that any antiprotozoal medicines have been formally categorised by CHMP as addressing 'unmet medical need'.

Criterion B: Risk of transmission of resistance

The final column in Table 65 considers knowledge of the occurrence of resistance to the listed substances in the organism causing the disease under consideration. For the purpose of this exercise, the possibility of transfer of relevant resistance from animals to humans implies that animals will be treated with the given antiprotozoal and that there is potential for transmission of resistant protozoa from animals to humans who may subsequently require treatment with that same antiprotozoal

substance/class. This is addressed in the column 'Animal disease and zoonotic potential'. A detailed description of the resistance mechanism/resistance genes in protozoa is only provided where this is known and there is potential for transfer from animals to humans. Actual evidence for transfer of resistant protozoa from animals to humans is very limited. Note that for those diseases where vectors are involved in transmission, the geographical distribution of these vectors may evolve with changing climatic conditions in future.

Criterion C: Non-essential need for animal health

The relevance of the disease in animals, availability of alternative treatments (both EU-authorized and use outside the terms of a marketing authorisation) and potential impacts on animal health and welfare if infections could not be treated, are addressed in the third and fourth columns of the table.

Cocciostats and histomonostats that are regulated as feed additives in the EU under Regulation (EC) 1831/2013 are not addressed in this advice. Those anticoccidials that are regulated as veterinary medicinal products have been addressed in this section of the advice.

3. Tables providing the results of the evaluations

The results of the evaluations made for groups of antibiotics, antivirals, antifungals and antiprotozoals against the criteria for the designation of antimicrobials to be reserved for human use under Article 37(5) are presented below.

A compiled recommendation for the groups of antimicrobials to be reserved for treatment of humans is presented in the Summary to the report (**Table 1**).

Please refer to Section 2. of this report, Methodology, for an explanation as to how the criteria A, B and C, and sub-criteria, were applied for the evaluation. The criteria are laid out in full in Section 2.2. and in the Delegated Regulation (EU) 2021/1760 [2].

3.1. Antibiotics

For **antibiotics**, please refer to the discussion of the methodology in Section 2.5. of the report regarding the grouping of classes, subclasses and individual substances and the stepwise assessment process. Note that for the listed (sub)classes, the evaluations apply to all substances in the (sub)class, although some individual substances are discussed as typical examples of the (sub)class.

Tables of the outcome of the evaluation of antibiotics and antibiotic classes against the criteria for designation of antimicrobials to be reserved for humans

Table 7. Evaluation of natural, narrow spectrum penicillins (beta-lactamase-sensitive penicillins)

Natural, narrow spectrum penicillins (beta-lactamase-sensitive penicillins) See Table 76 for ATC(vet) codes	
Criterion A met: No	<p>Penicillins belong to a large group of beta-lactam antibiotics, which share a common structural feature – the beta-lactam ring. Penicillins are further classified based on their spectrum of activity to penicillins, aminopenicillins (evaluated separately), antistaphylococcal penicillins (evaluated separately). Penicillins (benzathine benzylpenicillin-penicillin G, penicillin V, pheneticillin, procaine penicillin) are evaluated here.</p> <p>Penicillins are active against Gram-positive cocci, such as <i>Streptococcus pyogenes</i> and other beta-haemolytic streptococci, <i>S. pneumoniae</i>, <i>S. Viridans</i>, and non-beta-lactamase-producing <i>Staphylococcus aureus</i>. Some Gram-negative bacteria such as <i>Neisseria meningitidis</i> and penicillin-sensitive <i>N. gonorrhoeae</i> are susceptible. Non-beta-lactamase-producing <i>Haemophilus influenzae</i> is moderately resistant, and all other aerobic Gram-negative bacilli are highly resistant. Many organisms that were originally highly susceptible have now developed resistance, which limits the usefulness of these antibiotics in clinical settings [13].</p> <p>Penicillin G remains a very effective treatment for infections caused <i>S. pyogenes</i>, such as pharyngitis, scarlet fever, cellulitis, necrotizing fasciitis, septic arthritis, uterine infection, and septicemia [13].</p> <p>There are several alternative treatment options for each indication.</p> <p>The recent data from the EARS-Net showed that in EU/EEA (population-weighted mean) in 2019, 12.1% of <i>S. pneumoniae</i> isolates were resistant to penicillin and 15.5% of <i>S. aureus</i> isolates were MRSA [14].</p> <p>Penicillins are nationally approved in the EU member states for indications that include the treatment of wound infections, pyogenic infections of the skin, soft tissue infections and infections of the nose, throat, nasal sinuses, respiratory tract and middle ear; they are also indicated for the following infections caused by penicillin-sensitive microorganisms: generalised infections, septicemia and pyaemia from susceptible bacteria; acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms; suspected meningococcal disease; gas gangrene, tetanus, actinomycosis, anthrax, leptospirosis, rat-bite fever, listeriosis, severe Lyme disease, and prevention of neonatal group B streptococcal infections; complications secondary to gonorrhoea and syphilis (e.g. gonococcal arthritis or endocarditis, congenital syphilis and neurosyphilis); diphtheria, brain abscesses and pasteurellosis.</p> <p>Penicillins do not fulfil criterion A, as other alternative options exist for the treatment of the above-mentioned infections.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 8. Evaluation of antistaphylococcal penicillins (beta-lactamase-resistant penicillins)

Antistaphylococcal penicillins (beta-lactamase-resistant penicillins) See Table 77 for ATC(vet) codes	
Criterion A met: Yes	<p>Antistaphylococcal penicillins (cloxacillin, dicloxacillin, nafcillin, oxacillin, flucloxacillin) inhibit penicillinase-producing staphylococci [15]. The spectrum of activity is similar to that of narrow-spectrum penicillins except that they are resistant to staphylococcal beta-lactamases.</p> <p>They are active against Gram-positive cocci (e.g., <i>Staphylococcus aureus</i>, <i>S. epidermidis</i>, <i>Streptococcus pyogenes</i>, <i>S. pneumoniae</i>). Antistaphylococcal penicillins have less intrinsic activity than penicillin G, and are ineffective for <i>enterococci</i>, <i>Listeria</i>, and <i>Neisseria</i> spp. They have no activity against Gram-negative bacteria [15].</p> <p>Antistaphylococcal penicillins are considered the agents of choice for the treatment of MSSA bacteraemia associated with a qualified infection [16]. They are used for treatment of penicillin-resistant methicillin susceptible staphylococcal infections such as skin and soft tissue infections (SSTIs), bone and joint infections, endocarditis, severe pneumonia and meningitis.</p> <p>Alternative treatment for invasive staphylococcal infections (i.e., bacteraemia and endocarditis) include 1st-generation cephalosporins but the antistaphylococcal penicillins are the preferred option. Vancomycin can be used for patients with allergy to penicillin but is less efficient [17, 18].</p> <p>The recent data from EARS-Net on bloodstream infections caused by MSSA and MRSA in EU/EEA showed that between 2005 and 2018, a total of 573,951 <i>S. aureus</i> bloodstream infection cases (96,918 MRSA and 477,033 MSSA) reported in EU/EEA countries. The EU/EEA population-weighted MRSA percentage decreased significantly from 30.2% in 2005 to 16.3% in 2018 ($p < 0.001$). At the same time, the total number of bloodstream infections caused by <i>S. aureus</i> increased by 57%, MSSA bloodstream infections increased by 84% and MRSA bloodstream infections decreased by 31%. This data points towards significantly increasing health burden of MSSA infections in EU/EEA [19].</p> <p>Antistaphylococcal penicillins are nationally approved in the EU, both alone and in combinations. Approved indications for use include the treatment of the following infections in adults and children: osteomyelitis, endocarditis and the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Flucloxacillin may also be used in the peri-operative prophylaxis for surgical procedures when appropriate, for example cardiothoracic or orthopaedic surgery.</p> <p>Antistaphylococcal penicillins fulfil criterion 1.A.(b). being an essential component of treatment for serious, life-threatening infections.</p>
Criterion B met: Yes	<p>Antistaphylococcal penicillins are stable to staphylococcal penicillinase, including <i>S. aureus</i> penicillinase. The most common mechanism of acquired resistance to these antibiotics in staphylococci is through acquisition of a <i>mec</i> gene that encodes a penicillin-binding protein (PBP) with lower affinity for several beta-lactams (e.g. PBP2a in MRSA, encoded by the <i>mecA</i> or <i>mecC</i> gene located on the mobile genetic element, SCC <i>mec</i>) [20-22]. The SCC <i>mec</i>, might carry resistance to other antimicrobials (e.g. aminoglycosides and macrolides) or virulence, and spread between different staphylococci species that are part of normal microbiota or potential pathogens [23].</p> <p>Cross-resistance between antistaphylococcal penicillins and other beta-lactams, with exception of ceftobiprole and ceftaroline, is commonly observed in staphylococci carrying <i>mec</i> genes. The animal origin of isolates carrying different <i>mec</i> genes has been suggested [20, 24, 25].</p> <p>There is no statutory monitoring of resistance to antistaphylococcal penicillins in animal isolates in the EU. Monitoring of MRSA under EFSA/ECDC surveillance in food-producing species is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence ranges from 0% to 100% depending on animal production type and country [26]. There is little reporting on prevalence of MRSA/P in companion animals, which appears to vary across the EU based on studies available [27-29].</p> <p>Transmission</p> <p>Food is generally not considered to be a significant source of MRSA in humans [30, 31]. MRSA is mainly transmitted by direct contact from food-producing animals [32]. In geographical areas with high density of farms, livestock associated MRSA (LA-MRSA) could contribute significantly to the burden of MRSA disease in humans [29, 33, 34]. There is evidence for rare zoonotic transmission of MRSA/P from companion animals to persons in contact [29, 33, 34].</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to antistaphylococcal penicillins from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met</p>
Criterion C met: No	<p>Antistaphylococcal penicillins are authorised in VMPs in the EU for use in cows, goats and sheep for local treatment of intramammary infections (IMI) due to <i>Staphylococcus aureus</i>, <i>Streptococcus</i> spp. and <i>Trueperella pyogenes</i> and for treatment of eye infections due to <i>Staphylococcus</i> spp., <i>Bacillus</i> spp. and <i>Moraxella bovis</i> in food-producing and companion animals. They are included in the Table 1 of the MRL Regulation (EU) 37/2010 and can be used in all food-producing species (except those producing eggs for human consumption).</p> <p>Food-producing species</p> <p>Mastitis due to IMI is one of the most common diseases in dairy cows, having well recognised effects on health and welfare and frequently requiring antimicrobial treatment [35-37]. Mastitis in sheep and goats is also recognised as</p>

	<p>a significant welfare issue [38]. Severe IMI due to <i>S. aureus</i> or <i>T. pyogenes</i> can result in potentially fatal sepsis. In addition, IMI due to <i>S. aureus</i> are contagious and if not treated promptly may become chronic, transmit within the herd and result in loss of yield and culling of animals [39, 40]. Antistaphylococcal penicillins are used for the treatment of penicillinase-producing strains of <i>S. aureus</i>, which are common in certain EU regions [41] (See annotation 1 under Table 61). Antistaphylococcal penicillins are a narrow-spectrum treatment option. Alternatives for intramammary treatment are TMPs and novobiocin [42], although only available in combination with other antibiotics, or substances from a higher AMEG category (e.g. lincosamides, amoxicillin-clavulanate, aminoglycosides, cephalosporins). Cloxacillin is one of few, if not the only, antibiotic authorised as a VMP for intramammary use in sheep in the EU.</p> <p>In conclusion, antistaphylococcal penicillins are primarily used to treat penicillin-resistant staphylococcal IMI which if inappropriately treated can lead to significant morbidity and mortality. For these infections, there are limited alternatives, other than from a higher AMEG category. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 9. Evaluation of aminopenicillins, without beta-lactamase inhibitors

Aminopenicillins, without beta-lactamase inhibitors See Table 78 for ATC(vet) codes	
Criterion A met: No	<p>Aminopenicillins are bactericidal beta-lactam antibiotics, which act by inhibiting bacterial cell wall synthesis. They are chemically similar to penicillin but have a broader spectrum of activity (expressed by a slightly higher activity against enterococci). They are susceptible to both acquired beta-lactamases (i.e., by <i>Staphylococcus</i> spp., <i>Haemophilus influenzae</i>, <i>Moraxella cattharalis</i>) and intrinsically produced beta-lactamases, such as <i>Enterobacter</i> spp., <i>Serratia</i> spp., <i>Acinetobacter</i> spp., <i>Pseudomonas</i> spp., indole-positive <i>Proteus</i>. Ampicillin and amoxicillin are two main compounds that belong to aminopenicillins [43].</p> <p>Aminopenicillins are active against many Gram-positive bacteria (e.g., <i>Streptococcus pyogenes</i>, <i>S. pneumoniae</i>, <i>S. Viridans</i>, <i>Enterococcus</i> spp., <i>Corynebacterium diphtheriae</i>, <i>Bacillus anthracis</i>, <i>Clostridium tetani</i>, <i>C. perfringens</i>, <i>C. botulinum</i>, and other <i>Clostridium</i> spp., <i>Listeria monocytogenes</i>). Many Gram-negative strains previously susceptible (e.g., <i>E. coli</i>, <i>Salmonella</i>) are nowadays frequently resistant to ampicillin and amoxicillin, but some remain susceptible (or infrequently resistant) (e.g., <i>Brucella</i> spp. and <i>Bordetella pertussis</i>, <i>Helicobacter pylori</i>). Some differences exist between the antibacterial actions of ampicillin and amoxicillin. Amoxicillin is about twice as active as ampicillin against <i>Enterococcus faecalis</i> and <i>Salmonella</i> spp., but twice less active against <i>Shigella</i> spp. <i>H. influenzae</i> also appears to be slightly less sensitive to amoxicillin than to ampicillin and the same applies for Gram-positive and Gram-negative anaerobic bacteria [43].</p> <p>Aminopenicillins are recommended for a wide range of infections which make ampicillin one of the most prescribed antibiotics. However, an increasing prevalence of beta-lactamase producing organisms has resulted in reduced use of aminopenicillins as monotherapy. Also, in many countries, ampicillin has been replaced by amoxicillin especially in oral therapy. Ampicillin can be used for upper and lower respiratory tract infections (RTIs) caused by <i>S. pneumoniae</i>, beta-haemolytic streptococci, and non-beta-lactamase-producing strains of <i>H. influenzae</i>. It is also used in the treatment of meningitis caused by group B streptococci, <i>L. monocytogenes</i>, <i>Neisseria meningitidis</i>, and penicillin-susceptible strains of <i>S. pneumoniae</i>. Amoxicillin is used to treat group A streptococcal pharyngitis, otitis media and acute sinusitis, urinary tract infections (UTIs), typhoid fever, gonorrhoea, uncomplicated mild community-acquired pneumonia (CAP) and for more severe cases can be used in combination with macrolides or doxycycline. Amoxicillin is one of the treatments of choice for erythema migrans as part of Lyme disease. Amoxicillin is now recommended to treat <i>E. faecalis</i> endocarditis (combination of intravenous ampicillin-amoxicillin plus either low-dose gentamicin or ceftriaxone). Amoxicillin or ampicillin can be used for neonatal septicaemia (usually combined with either gentamicin or amikacin, to provide treatment for aminopenicillin-resistant Gram-negative bacilli, such as <i>E. coli</i>, <i>Klebsiella</i> spp., and <i>P. aeruginosa</i>) [43].</p> <p>For the above-mentioned indications there are generally other effective alternatives available such as 3rd- and 4th-generation cephalosporins, fluoroquinolones, aminoglycosides.</p> <p>In 2019, 163 005 isolates of <i>E. coli</i> were reported in EU/EEA to EARS-Net. More than half (57%) were resistant to at least one of the antimicrobial groups under surveillance (i.e., aminopenicillins, fluoroquinolones, 3rd-generation cephalosporins, aminoglycosides and carbapenems). The highest EU/EEA population-weighted mean resistance percentage was reported for aminopenicillins (57%), followed by fluoroquinolones (24%), 3rd-generation cephalosporins (15%) and aminoglycosides (11%) [14].</p> <p>Ampicillin and amoxicillin are nationally approved in the EU Member States for the treatment of ear, nose and throat infections, bronchitis, pneumonia, urinary tract infections, gonorrhoea, gynaecological infections, septicaemia, peritonitis, endocarditis, meningitis, enteric fever, gastro-intestinal infections etc. They are also indicated for the prophylaxis of endocarditis.</p> <p>Aminopenicillins do not fulfil criterion A, as alternatives are available for the treatment of all infections for which they are approved.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 10. Evaluation of aminopenicillins in combination with beta-lactamase inhibitors

Aminopenicillins in combination with beta-lactamase inhibitors (BLI) See Table 79 for ATC(vet) codes	
Criterion A met: Yes	<p>Aminopenicillins (evaluated separately) in clinical practice are combined with beta-lactamase inhibitors (BLIs) such as clavulanic acid and sulbactam to broaden their spectrum of activity. Aminopenicillin-BLIs are well established in therapy of a wide range of infections. BLIs were developed to overcome increasing resistance of bacteria to aminopenicillins and work against MDR organisms [44, 45].</p> <p>Use of beta-lactamase inhibitors restores the activity of aminopenicillins on beta-lactamase-producing strains and allows for successful inhibition of beta-lactamases produced by Gram-positive (e.g., <i>Staphylococcus aureus</i>, excluding MRSA) and Gram-negative bacteria (<i>H. influenzae</i>, <i>Neisseria gonorrhoeae</i>, <i>Moraxella catarrhalis</i>, <i>Bacteroides fragilis</i> and most Enterobacterales) [44, 45].</p> <p>Aminopenicillin-BLIs are extensively used for a wide range of indications such as RTIs including otitis media, pharyngitis, sinusitis, UTIs and surgical prophylaxis including mainly abdominal and gynaecological surgeries. Amoxicillin-clavulanic acid (with or without macrolide) is recommended as one of several first-line treatment options for mild to moderate CAP. Moreover, they are used for treatment of mixed aerobic and anaerobic infections such as pelvic inflammatory disease or intraabdominal infections [44, 45].</p> <p>Sulbactam is the main treatment for MDR <i>Acinetobacter baumannii</i>, due to its intrinsic activity against <i>A. baumannii</i>, not due to inhibition of beta-lactamases, but it is not commercialised alone, only as ampicillin-sulbactam [46].</p> <p>Alternative treatment options include carbapenems to treat Enterobacterales and <i>P. aeruginosa</i>, ceftobiprole and ceftaroline to treat some Gram-positive infections (MRSA), 3rd-generation cephalosporines to treat <i>H. influenzae</i>, <i>M. catarrhalis</i>, <i>N. gonorrhoeae</i>, and cefiderocol and colistin to treat MDR <i>A. baumannii</i> [47-49].</p> <p>In 2019, in total 6113 isolates of <i>Acinetobacter</i> spp. were reported from EU/EEA to EARS-Net. More than half (53%) were resistant to at least one of the antimicrobial groups under surveillance (i.e., fluoroquinolones, aminoglycosides and carbapenems). The highest EU/EEA population-weighted mean resistance percentage was reported for fluoroquinolones (37%), followed by aminoglycosides (33%) and carbapenems (33%) [14].</p> <p>Medicines that contain aminopenicillin and BLI are nationally approved in the EU. The approved indications include the treatment of the following infections in adults and children: acute bacterial sinusitis, acute otitis media, acute exacerbations of chronic bronchitis, CAP, cystitis, pyelonephritis, SSTIs in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis, bone and joint infections, in particular osteomyelitis, intraabdominal infections, bacteraemia.</p> <p>Aminopenicillins in combination with BLIs fulfil criteria A.1.(b). They are essential components of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>The most important mechanisms of resistance to the beta-lactam antimicrobials are the beta-lactamase enzymes that catalyse the hydrolysis of the beta-lactam ring. There is a very wide variety of different beta-lactamases with varying substrate specificity [50]. Aminopenicillins are prone to hydrolysis by all clinically relevant beta-lactamases. Clavulanic acid and sulbactam are beta-lactam compounds that are hydrolysed by the serine beta-lactamases but remain bound to it, thereby inactivating the enzyme [51]. Additionally, sulbactam has inherent antibacterial activity against a few bacterial species, e.g. in <i>A. baumannii</i>, through PBP-binding [52]. These BLIs inhibit most class A beta-lactamases (e.g. TEM-1, SHV-1, SHV-5, CTX-M, but not KPC-2 or TEM-30), although not inhibiting class B (e.g. NDM), C (e.g. AmpC, CMY-2) and D (e.g. OXA-48 and OXA-23) [52, 53]. Moreover, when class A beta-lactamases are hyperproduced (e.g. isolate producing SHV-1 and CTX-M) the aminopenicillin-BLI combinations are inactive.</p> <p>In Gram-positive bacteria, PBP mutation or acquisition of PBPs with lower affinity for beta-lactams is an important resistance mechanism. This type of mechanism is common in staphylococci and is mediated by <i>mec</i> genes (e.g. <i>mecA</i> or <i>mecC</i> in MRSA) [20, 21, 54]. Modification of PBPs is also a cause of beta-lactam resistance in <i>Streptococcus</i> spp., <i>Enterococcus</i> spp., <i>Neisseria</i> spp. and <i>Haemophilus</i> spp., although the genes conferring resistance are dependent on the bacterial species in question [55].</p> <p>Beta-lactamases are encoded by genes located on plasmids, transposons and in the bacterial chromosome [54].</p> <p>Aminopenicillins-BLIs could select for resistance to other beta-lactam antibiotics such as penicillins, aminopenicillins and cephalosporins, including to extended-spectrum cephalosporins [54] and carbapenems.</p> <p>There is no monitoring of resistance specifically to aminopenicillin-BLI under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> shows that the prevalence of extended-spectrum beta-lactamases (ESBL) and AmpC producers is low in the EU overall, but varies greatly between animal production type and country [26].</p> <p>Monitoring of MRSA under EFSA/ECDC surveillance in food-producing species is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence ranges from 0% to 100% depending on animal production type and country [26]. There is no recent mandatory EU monitoring for enterococci.</p> <p>In food-producing animals, statistically significant positive associations between consumption of aminopenicillins and ampicillin resistance were found for the years 2016 and 2018 in indicator <i>E. coli</i> and for 2016 in <i>Salmonella</i> spp. from poultry [56]. Amoxicillin-clavulanate has a wider spectrum of activity and thus it is likely that it has higher chance to select multidrug resistant organisms, several ESBLs and all AmpC-producers compared to aminopenicillins alone [54].</p>

	<p>Enterobacterales producing ESBLs and AmpC and MRSA/P have also been isolated from companion animals [27, 28, 57-60].</p> <p>Transmission</p> <p>Enterobacterales are mainly transferred from food-producing animals to humans via the foodborne route [61, 62]. Transfer of resistant zoonotic pathogens is demonstrated for <i>Salmonella</i> spp. with mounting evidence for uropathogenic <i>E. coli</i> strains [63-66]. Moreover, the same or similar beta-lactam resistance genes (including ESBLs) have been isolated in bacteria of human and animal origin, and molecular studies support the potential for transfer of mobile genetic elements (MGEs) from animal to human enteric commensals, contributing to the spread and persistence of antibiotic resistance genes and resistant bacteria in the human intestinal tract [54, 67, 68]. Companion animals may also be a reservoir for beta-lactamase resistance that can be transferred between animals and humans via Enterobacterales that are zoonotic pathogens or commensal bacteria, and by direct and indirect transmission, although there are few studies investigating these pathways [69-71].</p> <p>Food is generally not considered to be a significant source of MRSA in humans [30, 72]. MRSA is mainly transmitted by direct contact from food-producing animals [32]. In geographical areas with high density of farms, livestock associated MRSA (LA-MRSA) contribution to the burden of MRSA disease could be significant [73, 74]. There is evidence for rare zoonotic transmission of MRSA/P from companion animals to persons in contact [29, 33, 34, 69]].</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to aminopenicillin-BLI combinations from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>Amoxicillin in combination with clavulanic acid (amoxiclav) is the only aminopenicillin-beta-lactamase inhibitor combination authorised in VMPs in the EU, included in VMPs for systemic and intramammary treatment. Amoxicillin is included in Table 1 of Regulation (EU) 37/2010 with MRLs for all food-producing species, whereas clavulanic acid has MRLs for bovine and porcine spp. only.</p> <p>Many veterinary pathogenic <i>Staphylococci</i> spp. and Enterobacterales such as <i>E. coli</i> are resistant to un-potentiated aminopenicillins through production of beta-lactamases [54] and amoxiclav is used for a wide range of indications for which alternatives may otherwise be in a higher AMEG category.</p> <p>Companion animals</p> <p>In dogs and cats, guidelines advise that amoxiclav is important as first tier for the treatment of SSTI caused by beta-lactamase-producing staphylococci. Skin infections are one of the most common reasons for antibiotic prescribing in dogs and cats in the EU and are serious when recurrent or progressing to cellulitis. The first-tier alternatives include 1st- generation cephalosporins, clindamycin or TMPS; however, variably high levels of resistance to the latter two classes are noted in <i>Staphylococcus pseudintermedius</i>. Otherwise, 3rd-generation cephalosporins or fluoroquinolones (AMEG Category B) might be used as second-line [35, 75-79] (See annotation 1 under Table 61).</p> <p>Amoxiclav is also recommended in ISCAID guidelines for dogs and cats as empiric treatment for bacterial cystitis due to staphylococci, <i>E. coli</i> and <i>Klebsiella</i> spp. where regional antimicrobial susceptibility testing (AST) data suggest resistance to amoxicillin alone. In dogs, TMPS is an alternative first-line [80]. Guidelines also recommend amoxiclav as a first tier alternative to doxycycline (if not tolerated) or amoxicillin for acute and chronic upper respiratory tract infections in cats and bacterial canine infectious respiratory disease complex (infectious tracheobronchitis) and for treatment of bacterial pneumonia associated with e.g. <i>E. coli</i>, <i>Klebsiella</i> spp., MSSA or <i>Bordetella bronchiseptica</i>. These diseases can have high morbidity and result in mortalities, particularly in vulnerable animals in rescue shelters [81-83]. Amoxiclav may also be used for treatment of sepsis in cats and dogs [84].</p> <p>Food-producing species</p> <p>Although aminopenicillins are one of the most important antibiotic classes used in food-producing species, aminopenicillin-BLI combinations make up only 2% of their total use [54, 85]. In ruminants and pigs, prevalence of resistance to first-line antimicrobials in respiratory pathogens is generally low (other than to tetracyclines) but amoxiclav is important for treatment of resistant infections e.g. <i>Mannheimia</i>, <i>Pasteurella</i>, and in particular <i>Actinobacillus</i> spp., the latter causing severe bronchopneumonia with high morbidity and mortality in young pigs [41, 84, 86, 87]) (See annotation 1 under Table 61). Levels of resistance to first-line antimicrobials (e.g. un-potentiated aminopenicillins, sulfonamides, tetracyclines) and amoxiclav suggest limited efficacy of these classes to treat diarrhoea due to <i>E. coli</i> in young ruminants and piglets; however, where susceptibility testing supports use, amoxiclav is an alternative to AMEG Category B substances [41, 84, 86, 88] (See annotation 1 under Table 61).</p> <p>All species</p> <p>Amoxiclav is also one of few options for treatment of anaerobic infections, including <i>Bacteroides</i> and <i>Prevotella</i> spp., producing beta-lactamases. Anaerobes may be a component of serious mixed infections e.g. cholecystitis, peritonitis following surgery and soft tissue infections. There are few alternatives, e.g. metronidazole or clindamycin for companion animals only, or for food-producing species, either 3rd-generation cephalosporins (AMEG category B) or potentially certain macrolides depending on the disease/target pathogen [84].</p> <p>In conclusion, aminopenicillin-BLI combinations are used predominantly in companion animal species, but also in food-producing species, mainly to treat diseases with high morbidity that are resistant to first-line antibiotics and that may become life-threatening. Alternatives are often from a higher AMEG category. Criterion C is not met.</p>
<p>Recommended to be designated as an antimicrobial class to be reserved for humans: No</p>	

Table 11. Evaluation of amdinopenicillins

Amdinopenicillins See Table 80 for ATC(vet) codes	
Criterion A met: No	<p>Amdinopenicillinic acids bind specifically to penicillin-binding protein 2 (PBP-2), thereby inhibiting cell wall synthesis [89]. Presently, there are two substances in the subclass - mecillinam and pivmecillinam.</p> <p>Amdinopenicillinic are mostly active against Enterobacterales. Activity against other Gram-negative organisms and also Gram-positive bacteria is relatively low: <i>Pseudomonas</i> spp., <i>Enterococcus faecalis</i> and <i>Staphylococcus aureus</i> are resistant to mecillinam. Pivmecillinam shows activity against <i>Salmonella</i> spp. and preliminary studies in a limited number of patients suggest that it may be a useful alternative antibiotic in the treatment of acute typhoid fever and in some carriers of <i>Salmonella</i> spp. [90].</p> <p>Mecillinam and pivmecillinam are mainly used for treatment of uncomplicated UTIs due to Enterobacterales, but mecillinam achieves sufficient concentrations in urine to treat UTIs due to <i>Staphylococcus saprophyticus</i> [91, 92]. These infections are not considered life-threatening. Due to its relative stability to extended-spectrum beta-lactamases (ESBLs), mecillinam may be an alternative treatment in certain systemic infections due to Enterobacterales, often in combination with other beta-lactam antibiotics or aminoglycosides.</p> <p>Sufficient alternatives are available for treatment of uncomplicated UTIs, including those caused by ESBL-producing Enterobacterales [93, 94].</p> <p>Data from a multi-country European study including France, Germany, Spain, Sweden, and the UK, showed that <i>E. coli</i> isolates from women with acute uncomplicated UTIs have increasing antimicrobial resistance. It was presented that since 2000, compared to 2014, only Spain showed a significant increase in resistance to mecillinam (1.0% to 6.5%) [95].</p> <p>Mecillinam (injection) is authorised for treatment of severe UTI. Pivmecillinam (oral) is authorised for treatment of uncomplicated UTI in adults [96, 97].</p> <p>Amdinopenicillins do not fulfil criterion A, as sufficient effective alternative options exist for the treatment of the presented serious infections.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 12. Evaluation of carboxypenicillins and ureidopenicillins, including their combinations with beta-lactamase inhibitors

Carboxypenicillins and ureidopenicillins, including their combinations with beta-lactamase inhibitors See Table 81 for ATC(vet) codes	
Criterion A met: Yes	<p>Carboxypenicillins, ureidopenicillins as well as their combinations with beta-lactamase inhibitors are summarised and categorised in one class of 'antipseudomonal penicillins' [11]. The scope of the assessment is at class level and is made together for carboxypenicillins and ureidopenicillins with and without beta-lactamase inhibitor (BLI) combinations, although the combinations compared to the respective monosubstances have a wider spectrum of activity.</p> <p>Carboxypenicillins are active against Gram-positive and Gram-negative bacteria (<i>Pseudomonas aeruginosa</i>, <i>Proteus</i> spp.) The ureidopenicillins are also active against Gram-positive and Gram-negative bacteria (<i>P. aeruginosa</i>, <i>Proteus</i> spp.). Mezlocillin has greater intrinsic activity against <i>Enterococcus faecalis</i>. Piperacillin is similar in activity to ampicillin against Gram-positive species and is active against many Gram-negative species including Enterobacterales and <i>P. aeruginosa</i>. Combination of ticarcillin-clavulanate: increases activity against beta-lactamase-producing staphylococci, <i>Escherichia coli</i>, <i>H. influenzae</i>, <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Pseudomonas</i> spp., <i>Providencia</i> spp., <i>Neisseria gonorrhoeae</i>, <i>Moraxella catarrhalis</i>, and <i>Bacteroides</i> spp. In addition, ticarcillin-clavulanate exhibits activity against the MDR <i>Stenotrophomonas maltophilia</i>, and the use of this combination in addition to other antimicrobials (e.g., aztreonam or trimethoprim-sulfamethoxazole) leads to synergistic killing [98, 99]. The activity of piperacillin against <i>P. aeruginosa</i>, pneumococci, streptococci, anaerobes, and <i>E. faecalis</i>, can be retained in combination with tazobactam.</p> <p>Carboxypenicillins and ureidopenicillins in combination with beta-lactamase inhibitors (especially piperacillin-tazobactam) are among the most important antibiotics for the treatment of a variety of serious, systemic healthcare-associated infections, including pneumonia, cUTI, surgical site infections, and complicated intra-abdominal infection (cIAIs) caused by Enterobacterales and <i>P. aeruginosa</i> that can lead to significant mortality or debilitating morbidity. They are also active against Gram-positive cocci (excluding MRSA and ampicillin-resistant <i>Enterococcus faecium</i>). These substances are furthermore an important part of antibiotic stewardship programmes to reduce the usage of carbapenems.</p> <p>New antibiotics and combinations with beta-lactamase inhibitors such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam and cefiderocol are alternatives but are, in many hospitals, restricted for the treatment of infections with additional resistance to carbapenems [100].</p> <p>In 2018, the highest EU/EEA population-weighted mean resistance percentage in <i>P. aeruginosa</i> was reported for fluoroquinolones (19.7%), followed by piperacillin-tazobactam (18.3%), carbapenems (17.2%), ceftazidime</p>

	<p>(14.1%) and aminoglycosides (11.8%). Highest resistance levels were found in east European countries. There were significantly decreasing trends in the EU/EEA population-weighted mean percentages of piperacillin-tazobactam resistance between 2015 and 2018 [101].</p> <p>Mezlocillin is nationally approved in some EU member states for the treatment of acute and chronic infections of the lower respiratory tract, gastrointestinal tract (including salmonellosis), biliary tract, renal and urogenital tract (including gonorrhoea), obstetric, bone and/or soft tissue infections, infected burns and lesions, as well as in immunocompromised patients, for the treatment of septicaemia, endocarditis, meningitis, peritonitis (when necessary in combination), and perioperative prophylaxis. Other substances e.g., piperacillin sodium and ticarcillin are nationally approved in some EU countries.</p> <p>Ticarcillin-clavulanate is authorised for the treatment of infections of the respiratory tract, otorhinolaryngological infections, gastrointestinal tract, intra-abdominal infections, peritonitis, septicaemia, skin and soft tissue infections, joint infections, urinary tract infections and polymicrobial aerobic/anaerobic infections except for meningitis.</p> <p>Piperacillin-tazobactam is authorised for the treatment of severe pneumonia including hospital-acquired and ventilator-associated pneumonia (VAP), complicated UTIs including pyelonephritis, complicated intra-abdominal infections, complicated SSTIs, including diabetic foot infections. In addition, it is authorised for the treatment of patients with bacteraemia that occurs in association with, or is suspected with, any of the infections listed above. It may also be used in the management of neutropenic patients with fever suspected to be due to a bacterial infection [102].</p> <p>Carboxypenicillins and ureidopenicillins, including their combinations with beta-lactamase inhibitors fulfil criterion A.1.(b). based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>Resistance to carboxy- and ureidopenicillins is usually due to beta-lactamases and may be chromosomal or plasmid encoded. Temocillin has greater stability including to AmpC beta-lactamases and Class A ESBLs. The BLI, tazobactam, used in combination with piperacillin confers stability to Class A ESBLs, but not AmpC, OXA- type or carbapenemases produced by Enterobacterales and <i>Pseudomonas</i> spp. In <i>Pseudomonas</i> spp., resistance to piperacillin also occurs due to changes in penicillin-binding proteins (PBPs) and over-expression of efflux pumps [103].</p> <p>There is cross-resistance between carbenicillin and ticarcillin [104].</p> <p>There is no monitoring of resistance specifically to carboxy-/ureido-penicillins under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> shows that the prevalence of ESBL-and AmpC producers is low in the EU overall, but varies greatly between animal production type and country [26]. Enterobacterales producing ESBLs and AmpC have also been isolated from companion animals [57-60].</p> <p>Transmission</p> <p>There is evidence to support the potential transmission of resistance to carboxy-ureidopenicillins from food-producing and companion animals to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>Therefore, although carboxy/ureidopenicillins/BLI combinations are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance from animals to humans if use became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Carboxypenicillins and ureidopenicillins, including combinations with beta-lactamase inhibitors have not been authorised for use in VMPs in the EU. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Ticarcillin was previously authorised for intrauterine use in mares in the US [105].</p> <p>Companion animals</p> <p>Use of ticarcillin with and without BLIs has been reported for treatment of serious infections including septicaemia in foals, pneumonia and metritis (e.g. <i>Klebsiella</i> spp.) in mares [106-108]. Adequate alternatives are available including aminoglycosides, 3rd- and 4th-generation cephalosporins, enrofloxacin, trimethoprim/sulfonamides for indications in horses [109]. In dogs, ticarcillin has been used for complicated otitis due to <i>Pseudomonas</i> spp. [110] and piperacillin with tazobactam has been used to treat various serious infections due to Enterobacterales and <i>Pseudomonas</i> spp. [111]. Alternatives for dogs include fluoroquinolones, aminoglycosides and polymyxin B [112, 113]; cases where there are no suitable alternatives are expected to be very rare.</p> <p>In conclusion, based on the literature available, loss of availability of carboxypenicillins and ureidopenicillins including BLI combinations in veterinary medicine would result in only limited morbidity or mortality in animals. Also considering the public health interest identified from criteria A and B, criterion C.1(c) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 13. Evaluation of 1st- and 2nd-generation cephalosporins, and cephamycins

1st- and 2nd-generation cephalosporins, and cephamycins See Table 82 for ATC(vet) codes	
Criterion A met: Yes	<p>In clinical practice, cephalosporins are grouped into "generations" based upon their spectrum of activity against aerobic and facultative Gram-negative bacilli and Gram-positive bacteria [114]. Cephalosporins interfere with bacterial cell wall synthesis by binding to penicillin-binding proteins (PBP), eventually leading to cell lysis and death.</p> <p>In general, the 1st- and 2nd-generation cephalosporins are active against a range of Gram-positive (e.g., <i>Staphylococcus</i> spp. except MRSA, <i>Streptococcus</i> spp.) and Gram-negative bacteria (e.g., <i>Escherichia coli</i>, <i>Klebsiella</i> spp., <i>Haemophilus influenzae</i>). 1st-generation cephalosporines (cefacetrile, cefaloridine, cefalotin, cefapirin, cefazolin, cefonicid, ceforanide, cefaclor, cefadroxil, cefalexin, cefatrizine, cefprozil, cefradine, cefroxadine, loracarbef) generally have a narrow spectrum, and are active on Gram-positive cocci, including MSSA (no coverage on <i>Enterococcus</i>) and some Gram-negative rods. 2nd-generation cephalosporins (cefamandole, cefbuperazone, cefmetazole, cefminox, cefotetan, cefotiam, ceftioxin, cefuroxime) have an intermediate spectrum and are active against the same pathogens as the 1st-generation, plus: beta-lactamase producing <i>H. influenzae</i>, <i>Moraxella catarrhalis</i>, <i>Neisseria meningitidis</i>, <i>E. coli</i>, <i>Klebsiella pneumoniae</i>, <i>Proteus</i> and oral anaerobes (cefoxitin and cefotetan cover <i>B. fragilis</i>) [115-119].</p> <p>1st-generation cephalosporins, specifically cefazolin, are considered antibiotics of choice for perioperative surgical prophylaxis in a wide variety of situations e.g. caesarean section, breast surgery, vaginal and abdominal hysterectomies [115]. 1st-generation cephalosporins are also used as chemoprophylaxis in preventing group B streptococcal disease in the new-born and may still be recommended for women with a history of penicillin allergy [115].</p> <p>Cefazolin is, in addition, suggested treatment option for MSSA bacteraemia and MSSA endocarditis [17, 18].</p> <p>2nd-generation cephalosporins are used to treat mild cases of pharyngitis, tonsillitis, sinusitis and bacterial bronchitis [118, 119]. 2nd-generation cephalosporines are also first empirical choice for UTI treatment in children [120, 121].</p> <p>For surgical prophylaxis, alternatives exist (but overall, in particular cefazolin is considered an antibiotic of choice and is therefore critical for surgical prophylaxis [122, 123]. For other indications, there are alternatives but some of them belong to classes that are classified by WHO as Critically Important Antimicrobials [11].</p> <p>The recent data from EARS-Net on bloodstream infections caused by MSSA and MRSA in EU/EEA showed that between 2005 and 2018, a total of 573,951 <i>Staphylococcus aureus</i> bloodstream infection cases (96,918 MRSA and 477,033 MSSA) reported in EU/EEA countries. The EU/EEA population-weighted MRSA percentage decreased significantly from 30.2% in 2005 to 16.3% in 2018 ($p < 0.001$). At the same time, the total number of bloodstream infections caused by <i>S. aureus</i> increased by 57%, MSSA bloodstream infections increased by 84% and MRSA bloodstream infections decreased by 31%. This data points towards significantly increasing health burden of MSSA infections in EU/EEA [19].</p> <p>1st- and 2nd-generation cephalosporins are nationally approved in the EU. The approved indications for 1st-generation cephalosporins include Streptococcal pharyngitis and tonsillitis, otitis media, bronchopneumonia, bacterial pneumonia, UTIs (pyelonephritis, cystitis), SSTIs (abscesses, furunculosis, impetigo, erysipelas, pyoderma, lymphadenitis), bone and joint infections. The approved indications for 2nd-generation cephalosporins include SSTIs as well as bone and joint infections caused by susceptible organisms, perioperative prophylaxis (for surgical operations with increased risk of infections with anaerobic pathogens, e.g. colorectal surgery, a combination with an appropriate substance with activity against anaerobes is recommended). Cefoxitin and cefotetan (both cephamycins) also have anti-anaerobic activity, but increasing resistance of anaerobic Gram-negative bacilli (e.g. <i>Bacteroides</i>) has been reported [124].</p> <p>1st- and 2nd-generation cephalosporines fulfil criterion A.1.(b), in particular because of their essential role in perioperative prophylaxis indication.</p>
Criterion B met: Yes	<p>Resistance to 1st- and 2nd-generation cephalosporins in Gram-negative rods is mainly due to production of beta-lactamases (of most beta-lactamase classes) (Bush et al., 2010). Beta-lactamases are encoded by genes located on plasmids, transposons and in the bacterial chromosome [54].</p> <p>In staphylococci, acquisition of <i>mec</i> genes is the main mechanism of acquired resistance (e.g. MRSA/MRSP).</p> <p>Cross-resistance between aminopenicillins, carboxypenicillins and 1st- and 2nd-generation cephalosporins is common. Cefuroxime and cefoxitin (2nd-generation cephalosporins) may retain activity against certain isolates resistant to 1st-generation cephalosporins (e.g. <i>E. coli</i> producing large spectrum beta-lactamases, such as TEM-1).</p> <p>Isolates resistant to 3rd-, 4th- or 5th-generation cephalosporins are also usually resistant to 1st- and 2nd-generation cephalosporins. Staphylococci carrying <i>mec</i> genes commonly show cross-resistance to all beta-lactams, with the exception of ceftobiprole and ceftaroline.</p> <p>There is no monitoring of resistance specifically to 1st- and 2nd-generation cephalosporins under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, resistance to aminopenicillins in Enterobacteriales from all food-producing species is generally high [26] and these isolates would mostly also be resistant to 1st- and 2nd-generation cephalosporins owing to cross-resistance. Monitoring of MRSA under EFSA/ECDC surveillance in food-producing species is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence ranges from 0% to 100% depending on animal production type and country [26].</p> <p>Resistance to aminopenicillins is reported in Enterobacteriales and staphylococci isolates from companion animals [54, 75] (See annotation 1 under Table 61). There is little reporting on prevalence of MRSA/P in companion animals, which appears to vary across the EU [27, 28].</p>

	<p>Transmission</p> <p>There is evidence for the transmission of resistance to 1st- and 2nd-generation cephalosporins from food-producing and companion to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>Methicillin-resistant staphylococci may also be transmitted from food-producing and companion animals to humans (See annotation 3 under Table 61).</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to 1st- and 2nd-generation cephalosporins from animals to humans via zoonotic pathogens or commensals bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
Criterion C met: No	<p>1st-generation cephalosporins are authorised in VMPs in the EU for use in cats, dogs and cattle to treat SSTI, respiratory and urogenital infections caused by a range of Gram-positive and Gram-negative bacteria. 1st-generation cephalosporins are also authorised in intramammary preparations for treatment of IMI in ruminants and in an intrauterine formulation for endometritis in cattle. 1st-generation cephalosporins are included in Table 1 of Regulation (EU) 37/2010 with MRLs for use in bovines; cefazolin has MRLs for bovines, ovines and caprine, for intramammary use only. There are no authorised VMPs containing 2nd-generation cephalosporins in the EU and no MRLs established for 2nd-generation cephalosporins, therefore they cannot be used in food-producing animals, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>There are few alternatives for treatment of staphylococcal skin infections in dogs. 1st-generation cephalosporins are notable for high activity against Gram-positive bacteria, including penicillinase-producing <i>Staphylococcus pseudintermedius</i> (not MRS), and their good oral bioavailability in monogastrics and tolerability for infections requiring extended treatment duration e.g. for deep pyoderma in dogs. They are recommended as a first-line/empirical treatment option for SSTI in dogs and cats. Skin infections are one of the most common reasons for antibiotic prescribing in dogs and cats in the EU and become serious if recurrent or progressing to cellulitis. Alternatives include amoxiclav, clindamycin or TMPS; however, variably high levels of resistance are noted to the latter two classes in <i>S. pseudintermedius</i>. Otherwise, 3rd-generation cephalosporins or fluoroquinolones (AMEG category B) might be used as second-line [35, 75-79] (See annotation 1 under Table 61).</p> <p>Food-producing species</p> <p>In cattle, 1st-generation cephalosporins are authorised for local treatment of IMI due to <i>Staphylococcus</i>, <i>Streptococcus</i>, <i>Trueperella</i> spp. and <i>E. coli</i>. 1st-generation cephalosporins are alternatives to lincosamides, penicillin-novobiocin and antistaphylococcal penicillins for local treatment of IMI due to Gram-positive cocci [84].</p> <p>In conclusion, 1st-generation cephalosporins are primarily important for their use in companion animals, as a first-line antibiotic for treatment of infections caused by Gram-positive beta-lactamase producing bacteria, especially SSTI which are important due to their frequency of occurrence and hence potential impact on animal welfare. Alternatives may be limited by resistance development or are from a higher AMEG category. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 14. Evaluation of 3rd- and 4th-generation cephalosporins, except combinations with beta-lactamase inhibitors

<p>3rd- and 4th-generation cephalosporins, except combinations with beta-lactamase inhibitors See Table 83 for ATC(vet) codes</p>	
Criterion A met: Yes	<p>3rd- and 4th-generation cephalosporins have enhanced activity against both Gram-positive and Gram-negative bacteria compared to the 1st- and 2nd-generation and are very important alternatives for empiric treatment of serious infections in humans.</p> <p>3rd-generation cephalosporins are active against <i>Haemophilus influenzae</i> and Enterobacterales (<i>E. coli</i>, <i>Proteus mirabilis</i>, <i>Klebsiella</i> spp.), including some ESBL-producing isolates. Most 3rd-generation cephalosporins, including ceftriaxone and cefotaxime, are also active against some Gram-positive species, especially streptococci [125, 126]. Cefazidime is active against <i>Pseudomonas aeruginosa</i> but has no appreciable Gram-positive activity [127]. 4th-generation cephalosporins have activity against Gram-positive cocci and enhanced activity against Gram-negative bacilli, including <i>P. aeruginosa</i> and some AmpC producing Enterobacterales (e.g. Enterobacter species) [128].</p> <p>3rd- and 4th-generation cephalosporins are used for the treatment of severe infections including meningitis, CAP and hospital-acquired pneumoniae, bacteraemia, gonorrhoea, endocarditis. 3rd-generation cephalosporins, including cefotaxime and ceftriaxone, are also alternative agents for quinolone-resistant typhoid fever [125, 126]. 4th-generation cephalosporins are used in combination with aminoglycosides to treat <i>Pseudomonas</i> spp. infections in neutropenic patients [129].</p> <p>Alternatives to treat infections with 3rd-generation cephalosporin-resistant Enterobacterales such as <i>E. coli</i> and <i>Klebsiella pneumoniae</i> are limited and include 'last resort' antibiotics such as combinations of 3rd-generation cephalosporins with BLI inhibitor (e.g. ceftazidime-avibactam), carbapenems and colistin, as well as monobactams, according to the specific mechanism of resistance and susceptibility to other classes.</p>

	<p>3rd- and 4th-generation cephalosporins are the treatment of choice for a very high number of patients with severe infections. Using 3rd- and 4th-generation cephalosporins in these patients prevents the use of other antibiotics with an even larger spectrum of activity and with a higher ecological impact. The recent data from the EARS-Net showed that in EU/EEA (population-weighted mean) in 2019, 84.9% of <i>E. coli</i> and 68.7% of <i>K. pneumoniae</i> isolates were susceptible to 3rd-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), and 85% of <i>P. aeruginosa</i> isolates were susceptible to cefazidime [14].</p> <p>Most 3rd- and 4th-generation cephalosporins are nationally approved in the EU. The approved indications may include the treatment of bacterial meningitis, CAP, hospital acquired pneumonia, acute otitis media, intra-abdominal infections, complicated UTIs (including pyelonephritis), infections of bones and joints, acute bacterial skin and skin structure infections, gonorrhoea, syphilis and bacterial endocarditis etc. The product information of medicines containing ceftriaxone has been harmonised and modernised by the EMA in 2014.</p> <p>3rd- and 4th-generation cephalosporins fulfil the criterion A.1.(b) as they are an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
<p>Criterion B met: Yes</p>	<p>Resistance to 3rd- and 4th-generation cephalosporins in <i>E. coli</i>, <i>Salmonella</i> spp. and <i>Klebsiella</i> spp. is mainly due to plasmid borne ESBLs or AmpC (pAmpC) encoding genes. Hyperexpression of chromosomal AmpC beta-lactamases can also lead to resistance to 3rd- and 4th-generation cephalosporins in Gram-negative bacilli [130, 131].</p> <p>Acquired resistance in Gram-positive bacteria may be due to the presence of PBPs which have reduced affinity for beta-lactams e.g. acquired PBP2a in MRSA, encoded by the <i>mecA</i> gene located on the mobile genetic element, SCC <i>mec</i> [132].</p> <p>Cross-resistance between 3rd- and 4th-generation cephalosporins is common, although due to the higher permeability across porins, 4th-generation cephalosporins could have higher activity than the 3rd-generation.</p> <p>Monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> under EFSA/ECDC mandatory EU surveillance in food-producing animals shows that the prevalence of ESBL- and AmpC-producers is low in the EU overall but varies greatly between animal production type and country [26]. There is evidence for the selection and spread of resistance to 3rd- and 4th-generation cephalosporins due to the use of these antimicrobials in food-producing animals [133, 134].</p> <p>Monitoring of MRSA under EFSA/ECDC surveillance is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence ranges from 0% to 100% depending on animal production type and country [26].</p> <p>Enterobacterales producing ESBLs and AmpC and MRSA/P have also been isolated from companion animals [27, 28, 57-60].</p> <p>Transmission</p> <p>There is evidence for the transmission of resistance to 3rd- and 4th-generation cephalosporins from food-producing and companion to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>Methicillin-resistant staphylococci may also be transmitted from food-producing and companion animals to humans (See annotation 3 under Table 61).</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to 3rd- and 4th-generation cephalosporins from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>3rd- and 4th-generation cephalosporins are included in Table 1 of the MRL Regulation (EU) 37/2010 and can be used in mammalian food-producing animals in the EU. They are authorised in VMPs in the EU for use in cattle, pigs, horses, dogs and cats, for local and systemic administration, for various indications including those highlighted below. 3rd- and 4th-generation cephalosporins are contra-indicated from use in poultry in the EU for public health reasons relating to AMR [135, 136]).</p> <p>Food-producing species</p> <p>Serious <i>E. coli</i> infections (e.g. leading to sepsis, meningitis and severe enteritis) are a major cause of morbidity and mortality in livestock, particularly juveniles and neonates [39, 137-141]. EFSA noted high levels of resistance to first line antimicrobials (e.g. aminopenicillins, potentiated sulfonamides, tetracyclines) in pathogenic <i>E. coli</i> from swine, horses, sheep, goats and calves, suggesting their limited efficacy against these infections in many EU countries [41, 86, 88, 142] (See annotation 1 under Table 61). Potential alternatives to 3rd- and 4th-generation cephalosporins for resistant <i>E. coli</i> infections are limited to AMEG Category B substances: colistin (not foals) or fluoroquinolones or, depending on patient/disease suitability, aminoglycosides (Category C). 3rd- and 4th-generation cephalosporins may also be used e.g. for treatment of respiratory tract infections in horses, cattle (e.g. <i>Mannheimia haemolytica</i>) and pigs (e.g. <i>Actinobacillus pleuropneumoniae</i>), metritis in cattle and pigs (due to e.g. <i>E. coli</i>) and interdigital necrobacillosis in cattle (e.g. <i>Fusobacterium</i> spp.). For these diseases, resistance to all first-line antimicrobials is uncommon in the EU [41, 86, 142] (See annotation 1 under Table 61); however, in line with VMP authorisations, use of 3rd- and 4th-generation cephalosporins is restricted to infections in individual animals that have responded poorly or are unlikely to respond to first-line antimicrobials e.g. based on susceptibility testing [135]. These diseases are associated with high impact on animal welfare and may lead to mortality or cull if untreated.</p> <p>Companion animals</p>

	<p>In dogs and cats, 3rd-generation cephalosporins are authorised for treatment of UTI, SSTI and severe periodontal infections with SPC restrictions as mentioned above. Pathogens causing UTI (e.g. Enterobacterales) and SSTI (e.g. <i>S. pseudintermedius</i>) in dogs and cats are increasingly resistant to first-line antibiotics. 3rd-generation cephalosporins are one of limited options for pyelonephritis which requires rapid empirical treatment; fluoroquinolones are the alternative [75, 80, 143, 144] (See annotation 1 under Table 61). SSTI become serious if recurrent or progressing to cellulitis; 3rd-generation cephalosporins may be used as second-line. Alternatives are fluoroquinolones or substances in AMEG Category A [77, 78, 145]. 3rd-generation cephalosporins are one of few antibiotics available for treatment of anaerobic infections in companion animals (other options are clindamycin and metronidazole) [84].</p> <p>In conclusion, 3rd- and 4th-generation cephalosporins are used in food-producing and companion animal species to treat serious life-threatening infections with significant morbidity or mortality, in particular when there are no alternatives from a lower AMEG category. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 15. Evaluation of ceftobiprole, ceftaroline

Ceftobiprole, ceftaroline See Table 84 for ATC(vet) codes	
Criterion A met: Yes	<p>Ceftaroline and ceftobiprole medocaril are sometimes referred to as 5th-generation cephalosporins.</p> <p>Ceftobiprole and ceftaroline have distinct activity compared with other cephalosporins. In addition to their activity against Gram-positive and Gram-negative microorganisms, including Enterobacterales, and organisms causing CAP (i.e., <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>) they have excellent activity against MRSA and against ampicillin-susceptible strains of <i>Enterococcus faecalis</i> [146, 147].</p> <p>These cephalosporins with activity against MRSA are important for the treatment of serious, life-threatening complicated SSTIs and pneumonia in humans where current alternatives cannot be used due to resistance or toxicity. In addition, they are the first choice in cases of severe polymicrobial infections in which MRSA is involved and can also be used as last resort in association with other antibiotics for the treatment of endocarditis and bacteraemia [148-152].</p> <p>Alternatives for the treatment of MRSA infections include oxazolidinones and glycopeptides. There are few alternative broad-spectrum antibiotics for the treatment of polymicrobial infections involving resistant bacteria, e.g., glycyclines, but these are not adequate for the treatment of pneumonia. Empiric therapy for CAP frequently consists of beta-lactam monotherapy or beta-lactam/macrolide combination therapy. However, such agents do not reflect the emergence and increasing prevalence of MRSA in the community setting. As ineffective empiric therapy is associated with adverse outcomes, including mortality and increased costs, ceftaroline, with its extended spectrum of activity, is an alternative to standard antibiotic CAP regimens [150].</p> <p>MRSA remains an important human health burden in the EU/EEA, estimated as causing approx. 150,000 infections and accounting for approximately 7,000 deaths per annum [153]. MRSA substantially increases the risk of mortality in hospitalised patients compared with MSSA.</p> <p>Ceftobiprole is currently authorised in 13 European countries for the treatment of hospital-acquired pneumonia (excluding ventilator-associated pneumonia) and CAP and is available for intravenous treatment only [154]. Ceftaroline is centrally authorised in the EU for the treatment of CAP and complicated SSTIs and is available for intravenous treatment only.</p> <p>Ceftobiprole and ceftaroline fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>In Enterobacterales, resistance to higher generation cephalosporins is most importantly mediated through ESBLs, AmpC and carbapenemases. Resistance may be chromosomal, but is mainly plasmid borne [155].</p> <p>Ceftobiprole and ceftaroline have high affinity for PBP2a and reduced susceptibility in MRSA is very uncommon but may be due to certain mobile <i>mec</i> genes or due to mutations in PBP4 [156]. Resistance to all classes of beta-lactam antibiotics, including anti-MRSA cephalosporins, was associated with <i>mecD</i> presence in <i>Macrococcus caseolyticus</i> strains from bovine and canine sources [24].</p> <p>There is no monitoring of resistance specifically to ceftobiprole or ceftaroline under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> shows that the prevalence of ESBL- and AmpC-producers is low in the EU overall, but varies greatly between animal production type and country [26]. Enterobacterales producing ESBLs and AmpC have also been isolated from companion animals [57-60].</p> <p>No evidence was found for specific reporting of resistance to ceftobiprole and ceftaroline in isolates from animals, including MRSA/P.</p> <p>Transmission</p> <p>There is evidence to support the potential selection and transmission of resistance to ceftobiprole and ceftaroline from food-producing and companion animals to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61). MRSA/P carrying <i>mec</i> genes may also be transmitted from animals to humans (See annotation 3 under Table 61).</p>

	<p>In conclusion, although they are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance to ceftobiprole and ceftaroline from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>There is no knowledge that ceftobiprole or ceftaroline have been authorised as VMPs in the EU or globally. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>No evidence could be found for the use of, or need for, ceftobiprole or ceftaroline to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as antimicrobials to be reserved for humans: Yes	

Table 16. Evaluation of combinations of cephalosporins and beta-lactamase inhibitors

Combinations of cephalosporins and beta-lactamase inhibitors See Table 85 for ATC(vet) codes	
Criterion A met: Yes	<p>Cephalosporins have a wide range of antibacterial activity but show considerable diversity in their antibacterial properties. Clavulanic acid, sulbactam, tazobactam, brobactam, avibactam, relebactam, and vaborbactam are beta-lactamase inhibitors that themselves have limited intrinsic antibacterial activity, but inhibit the activity of a number of beta-lactamases. Avibactam, sulbactam and tazobactam have been used in combination with cephalosporins.</p> <p>Against Enterobacterales, ceftazidime-avibactam has shown activity against ESBL producers and carbapenemase-producing Enterobacterales, except metallo-beta-lactamase (MBL) producers. Clinical trials published to date on ceftazidime-avibactam have shown its excellent safety and tolerability. It was advised that this new combination agent should be limited to patients without other treatment options in the empiric and documented treatment of multidrug-resistant Gram-negative organisms [157].</p> <p>Ceftolozane-tazobactam has demonstrated efficacy and safety in patients who are infected with ESBL-producing Enterobacterales and <i>Pseudomonas aeruginosa</i>. However, it has shown limited activity against ESBL-producing <i>Klebsiella pneumoniae</i> and no activity against carbapenemase-producing Enterobacterales; although isolates producing the carbapenemase OXA-48 that are susceptible to ceftazidime, are also susceptible to ceftolozane/tazobactam [158]. High rates of clinical cure by ceftolozane/tazobactam suggest that this antimicrobial will be valuable for treating infections caused by MDR Gram-negative bacteria.</p> <p>Cefoperazone-sulbactam: Cefoperazone is a 3rd-generation cephalosporin and has potency against most wild-type Enterobacterales and moderate to good activity against <i>P. aeruginosa</i>. The addition to cefoperazone of the beta-lactamase inhibitor, sulbactam, expands the spectrum to include <i>Acinetobacter baumannii</i> and some Gram-negative organisms with broader spectrum beta-lactamases. The combination is more resistant to attack by class A beta-lactamases but remains vulnerable to isolates producing class C beta-lactamases [159].</p> <p>Ceftazidime-avibactam is used as targeted therapy in severe infections caused by Gram-negative bacteria producing ESBLs, AmpCs or class A and D carbapenemases (KPC, GES, OXA-48) as a last-resort treatment option when other alternatives are not available. It is also used as empirical therapy in severe infections (including pneumonia and bacteraemia) in patients colonised by carbapenemase-producing Enterobacterales or MDR-<i>P. aeruginosa</i>.</p> <p>Ceftolozane-tazobactam is used in humans, either empirically or as targeted treatment for severe infections (urinary sepsis, peritonitis, pneumonia or bacteraemia) when there is a high probability of MDR Gram-negative bacteria, and when infection due to <i>P. aeruginosa</i> is known or suspected in patients with serious comorbidities (including patients admitted to ICUs, immunocompromised patients, or patients with neutropenia). Ceftolozane-tazobactam is used to spare carbapenem use for the treatment of infections with <i>P. aeruginosa</i> [160, 161].</p> <p>Cefoperazone-sulbactam has been used in many geographic regions to treat various serious Gram-negative infections, including multiply resistant <i>A. baumannii</i> such as nosocomial pneumonia, intra-abdominal infections, gynaecological infections, sepsis, and infections in febrile neutropenic patients [162].</p> <p>Infections with carbapenem-resistant Gram-negative bacteria are associated with high levels of mortality (see entry for carbapenems). Few alternative treatment options are available in case of carbapenem resistance, but include colistin combinations, novel tetracyclines or cefiderocol. So far, there are few clinical studies on alternative therapies for infections caused ceftazidime-avibactam resistant strains, but case reports indicate cefiderocol, tigecycline, imipenem-relebactam, meropenem-vaborbactam and aztreonam as potential alternatives [163].</p> <p>In 2018, the highest EU/EEA population-weighted mean resistance percentage in <i>Pseudomonas aeruginosa</i> was reported for fluoroquinolones (19.7%), followed by piperacillin-tazobactam (18.3%), carbapenems (17.2%), ceftazidime (14.1%) and aminoglycosides (11.8%). Highest resistance levels were found in east European countries. There were significantly decreasing trends in the EU/EEA population-weighted mean percentages of piperacillin-tazobactam resistance between 2015 and 2018 [101].</p> <p>Ceftazidime-avibactam is administered parenterally. It was authorised centrally in the EU in 2016 and is indicated for the treatment of the following infections in adults: cIAI, complicated UTI, including pyelonephritis, hospital-acquired pneumonia (HAP), including VAP. It is also indicated for the treatment of infections due to aerobic Gram-</p>

	<p>negative organisms in adult patients with limited treatment options. Ceftolozane-tazobactam was also centrally approved in 2015 and the indication is very similar but not exactly the same.</p> <p>Combinations of cephalosporins and beta-lactamase inhibitors fulfil criterion A.1(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans due to MDR Gram-negative infections, especially <i>P. aeruginosa</i> and carbapenem-resistant Enterobacterales, and in the patient groups noted.</p> <p>Ceftazidime-avibactam is classified by CHMP as fulfilling an 'unmet medical need' and therefore also fulfils criterion A.1(c).</p>
Criterion B met: Yes	<p>Resistance to the cephalosporin-BLI combinations is mainly due to beta-lactamase enzymes able to hydrolyse the specific generation of cephalosporins and not inhibited by the BLI. Resistance is mostly plasmid borne [164, 165]. Tazobactam, clavulanate and sulbactam confer stability to Class A ESBLs; whereas avibactam additionally provides stability to AmpC and certain carbapenemases (excluding MBLs) produced by Enterobacterales, and <i>Pseudomonas</i> spp. [159].</p> <p>There is no monitoring of resistance specifically to cephalosporin-BLI combinations under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> shows that the prevalence of ESBL-and AmpC-producers is low in the EU overall, but varies greatly between animal production type and country [26]. Enterobacterales producing ESBLs and AmpC have also been isolated from companion animals [57-60].</p> <p>Transmission</p> <p>There is evidence to support the potential transmission of resistance to cephalosporin-BLI from food-producing and companion animals to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>In conclusion, although they are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance to cephalosporin-BLI combinations from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Combinations of cephalosporins with beta-lactamase inhibitors have not been authorised for use in VMPs in the EU and there is no knowledge of their veterinary authorisation globally. Ceftazidime, ceftolozane, sulbactam, avibactam and tazobactam are not included in the Annex to the MRL Regulation (EU) 37/2010 and so cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6. MRLs have been established for other cephalosporins and clavulanic acid; therefore, although not in authorised VMPs, combinations could theoretically be used in food-producing animals under the Articles 113 & 114.</p> <p>No evidence could be found for the use of, or need for, cephalosporins in combination with BLIs to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 17. Evaluation of siderophore cephalosporins

<p>Siderophore cephalosporins See Table 86 for ATC(vet) codes</p>	
Criterion A met: Yes	<p>Cefiderocol is a novel siderophore cephalosporin with activity against a broad range of carbapenem resistant Gram-negative bacteria [166].</p> <p>Cefiderocol is active against Enterobacterales and other Gram-negative bacteria producing AmpC and the majority of Ambler class A, B, C and D ESBLs, including many MBLs and other carbapenemases. Cefiderocol also has very good activity against <i>Acinetobacter baumannii</i>, including carbapenem-resistant isolates and against other MDR carbapenem-resistant Gram-negative bacteria. A distinguishing feature of cefiderocol is its activity against MDR <i>Pseudomonas aeruginosa</i>, <i>A. baumannii</i>, <i>Stenotrophomonas maltophilia</i> and <i>Burkholderia cepacia</i> [167].</p> <p>Cefiderocol is one of the few treatment options for serious, life-threatening infections in humans caused by MDR, carbapenem-resistant Gram-negative bacteria [168, 169].</p> <p>Cefiderocol is exceptional in that it shows activity against Gram-negative bacteria producing all currently known beta-lactamases, including MBLs; there are very few alternatives e.g., eravacycline, but this is not adequate for the treatment of pneumonia or bacteraemia.</p> <p>Infections with carbapenem-resistant Gram-negative bacteria are associated with high levels of mortality, estimated as causing >8,700 deaths in the EU/EEA in 2015 (see carbapenems entry). <i>P. aeruginosa</i> is one of the major causes of healthcare-associated infections in the EU/EEA, commonly associated with surgical site infections, UTIs and ICU-acquired pneumonia. It is often MDR and challenging to control in hospitals. In 2015, MDR <i>P. aeruginosa</i> caused >8,700 infections and >550 deaths in the EU/EEA [153].</p>

	<p>Cefiderocol is centrally approved in the EU for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.</p> <p>Siderophores fulfil criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p> <p>Cefiderocol is classified by CHMP as fulfilling an 'unmet medical need' and therefore also fulfils criterion A.1(c).</p>
Criterion B met: Yes	<p>Cefiderocol is unique in that it enters the bacterial periplasmic space as a result of its siderophore-like property and is therefore less affected by resistance due to porin loss, efflux pumps and beta-lactamases. Although cefiderocol has enhanced stability to beta-lactamases, in vitro investigations have suggested incomplete stability to some carbapenemases (particularly NDM-1 and PER). Loss of iron uptake systems could also be a risk for resistance. Resistance development is probably multifactorial [159].</p> <p>Cefiderocol is a novel antibiotic, and prevalence of resistance in human isolates is very low at present. No evidence was found for specific reporting of resistance to siderophores in isolates from animals.</p> <p>Transmission</p> <p>There is evidence to support the potential transmission of resistance to siderophores from food-producing and companion animals to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>In conclusion, although they are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance to siderophores from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Cefiderocol has not been authorised for use in VMPs in the EU and there is no knowledge of its veterinary authorisation in VMPs globally. It is not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>No evidence could be found for the use of, or need for, siderophore cephalosporins to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1.(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 18. Evaluation of carbapenems, including carbapenems with beta-lactamase inhibitors

<p>Carbapenems, including carbapenems with beta-lactamase inhibitors See Table 87 for ATC(vet) codes</p>	
Criterion A met: Yes	<p>Carbapenems are beta-lactam antibiotics which have bactericidal effect, binding to penicillin-binding proteins and thereby inhibiting bacterial cell wall synthesis.</p> <p>They have a broad spectrum of activity against Gram-negative bacteria and activity against Gram-positive bacteria; although meropenem and imipenem do not have activity against MRSA or <i>Enterococcus faecium</i>. In general, they have good activity against anaerobes. Carbapenems are of importance as they are stable to several beta-lactamases, including AmpC and ESBLs, which confer resistance to 3rd-generation cephalosporins. Recently, resistance in Enterobacterales and other Gram-negative bacilli caused by production of carbapenemase enzymes has emerged and disseminated globally. This has led to development of carbapenem combinations with beta-lactamase inhibitor compounds e.g. meropenem-vaborbactam and imipenem-relebactam. Vaborbactam and relebactam inhibit Ambler class A and C beta-lactamases, including <i>Klebsiella pneumoniae</i> carbapenemases (KPCs) [170].</p> <p>Carbapenems are mainly used in hospitals to treat nosocomial infections involving MDR Gram-negative bacteria (especially ESBL and AmpC-producing Enterobacterales, MDR <i>Acinetobacter</i> spp. and <i>Pseudomonas aeruginosa</i>). Ertapenem has a more limited spectrum of activity compared to meropenem and imipenem as it is not active against <i>P. aeruginosa</i> [171].</p> <p>Human medicinal products containing meropenem and imipenem (IV) have broad indications in the EU including: pneumonia (including community-acquired and nosocomial (HAP, VAP)); bronchopulmonary infections in cystic fibrosis patients; cUTI including pyelonephritis; cIAI; intra- and post-partum infections; complicated SSSI; acute bacterial meningitis and management of neutropenic patients with fever suspected to be due to bacterial infection. Ertapenem is not indicated for meningitis but is additionally indicated for diabetic foot infections and prophylaxis of the surgical site for elective colorectal surgery.</p> <p>Meropenem-vaborbactam is indicated for the following infections: cUTI including pyelonephritis, cIAI, HAP and VAP.</p> <p>Imipenem-relebactam (+cilastatin) is indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options [172].</p>

	<p>Few alternative treatment options are available in case of carbapenem resistance but include colistin (see polymyxins below) as well as new antibiotics and combinations with beta-lactamase inhibitors such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam and cefiderocol [173-175].</p> <p>Infections with carbapenem-resistant bacteria are associated with high levels of mortality and were estimated as causing >8,700 deaths in the EU/EEA in 2015. For example, <i>K. pneumoniae</i> is a common cause of urinary, respiratory and bloodstream infections and a frequent cause of hospital outbreaks. Over recent years, there has been a rapid increase in carbapenem-resistant <i>K. pneumoniae</i> infections in the EU/EEA, and these were estimated to account for approx. 16,000 infections and 2,000 deaths in 2015. Infections with carbapenem-resistant <i>Acinetobacter baumannii</i> occur mainly in seriously ill patients in ICUs and have become endemic in healthcare settings in some EU/EEA countries. In 2015, there were an estimated 27,000 infections with carbapenem-resistant <i>Acinetobacter</i> spp. and >2000 deaths. Carbapenem-resistant <i>P. aeruginosa</i> was estimated to be responsible for >60,000 infections and 4,000 deaths in the EU/EEA in 2015 [153].</p> <p>These combinations are both centrally and nationally approved in the EU Member States.</p> <p>Meropenem-vaborbactam combination is centrally approved and is indicated for the treatment of the following infections in adults: complicated UTIs, including pyelonephritis, cIAI, HAP, including VAP. It is also indicated for the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Meropenem-vaborbactam is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.</p> <p>Another centrally approved combination is imipenem-relebactam (+cilastin). It is approved for the treatment of HAP, including VAP, in adults; treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adults; and for the treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options.</p> <p>Other members of the class are nationally approved for indications that include severe pneumonia, including hospital and ventilator-associated pneumonia, bronchopulmonary infections in cystic fibrosis, complicated UTIs, complicated intra-abdominal infections, intra- and post-partum infections, complicated SSTIs, acute bacterial meningitis; treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above; the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.</p> <p>Carbapenems (alone, i.e., not in combination with beta-lactamase inhibitors (BLI)) fulfil criterion A.1.(b), based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans due to MDR Gram-negative bacteria including Enterobacterales, <i>A. baumannii</i> and <i>P. aeruginosa</i>.</p> <p>Carbapenem-BLI combinations fulfil criterion A.1.(a), based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans due to MDR Gram-negative bacteria including Enterobacterales, <i>A. baumannii</i> and <i>P. aeruginosa</i>.</p> <p>Meropenem-vaborbactam and imipenem-relebactam are classified by CHMP as addressing an 'unmet medical need' and therefore also fulfil criterion A.1(c). They are last-resort treatment options for carbapenem-resistant Gram-negative infections (excluding MBL-producers).</p>
<p>Criterion B met: Yes</p>	<p>In Enterobacterales and <i>Acinetobacter</i> spp., enzyme-mediated resistance is the most important mechanism. Carbapenemase genes are mainly located on highly transmissible plasmids, but there are also chromosomally encoded mechanisms. In <i>Pseudomonas aeruginosa</i>, the most common mechanisms of resistance are efflux pumps and alteration of porins [176-178].</p> <p>Carbapenemases have been detected in <i>E. coli</i> and <i>Salmonella</i> spp. from food-producing animals (particularly pigs and poultry) on EFSA surveillance, but remaining at very low/sporadic prevalence [26].</p> <p>Carbapenemases have also been detected sporadically in Enterobacterales, <i>P. aeruginosa</i> and <i>A. baumannii</i> isolates from companion animals; prevalence unknown [179-183]. Zoonoanthroponotic transmission has been suspected [184, 185]).</p> <p>Transmission</p> <p>There is evidence to support the potential transmission of resistance to carbapenems(+BLI) from food-producing and companion animals to humans via Enterobacterales and other zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>In conclusion, although they are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance to carbapenems(+BLI) from animals to humans through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
<p>Criterion C met: Yes</p>	<p>There is no knowledge that carbapenems have been authorised as VMPs in the EU or globally. No carbapenems or the BLIs with which they are used, vaborbactam and relebactam, are included in the Annex to the MRL Regulation (EU) 37/2010 and therefore they cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>Little published evidence could be found for the use of carbapenems in domestic animals and hence it is likely to be rare. Based on published treatment guidelines, carbapenems may be used to treat cats and dogs suffering MDR skin, respiratory or urinary tract infections due to ESBL-producing Enterobacterales and <i>P. aeruginosa</i>, as a last resort to treat infections that are life-threatening. However, there are strong recommendations in some EU and</p>

	<p>international guidelines against the use of carbapenems in animals due to public health concerns, and some Member states have national legislation preventing their use [1, 77, 80, 83, 186, 187].</p> <p>Alternative antimicrobial treatments would be dependent on results of susceptibility testing and the underlying condition and may not be available in all cases.</p> <p>Although the extent of use of carbapenems in companion animals in the EU is unknown, based on the low number of reports it appears that impacts of inappropriate treatment on morbidity and mortality would be very limited.</p> <p>Other (non-food) species</p> <p>Some reports of carbapenem use in zoo animals were made to the open call for data.</p> <p>In conclusion, considering the public health interest identified from criteria A and B, criterion C.1(c) is met for carbapenems.</p> <p>No evidence was found for use of, or need for, carbapenems in combinations with beta-lactamase inhibitors to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1(a) is met for carbapenems in combination with BLIs.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 19. Evaluation of penems

Penems See Table 88 for ATC(vet) codes	
Criterion A met: Yes	<p>Penems are beta-lactam antibiotics related to carbapenems.</p> <p>Faropenem is an orally active penem that demonstrates broad-spectrum in vitro antimicrobial activity against many Gram-positive and Gram-negative aerobes and anaerobes and is resistant to hydrolysis by nearly all beta-lactamases, including ESBL and AmpC beta-lactamases. However, faropenem is not active against methicillin-resistant <i>Staphylococcus aureus</i>, VR <i>Enterococcus faecium</i>, <i>Pseudomonas aeruginosa</i> or <i>Stenotrophomonas maltophilia</i> [188].</p> <p>The importance of faropenem in human medicine is due to its potential for the oral treatment of severe, community-acquired or healthcare-associated life-threatening infections caused by many Gram-positive bacteria (<i>S. aureus</i> – excluding MRSA, <i>Enterococcus faecalis</i> – excluding VRE) and Gram-negative bacteria (e.g. Enterobacterales), since it is stable to many beta-lactamases, including some ESBLs and basal chromosomal AmpC (not isolates with derepressed AmpC), but excluding MBLs and other carbapenemases [189, 190].</p> <p>Although faropenem is not authorised for use in the EU, there are few oral treatment options globally in case of infections caused by ESBL-producing bacteria</p> <p>Faropenem is currently not authorised in the EU.</p> <p>If authorised for the use in the EU, faropenem would fulfil criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans due to Gram-positive and ESBL-producing Gram-negative bacteria, particularly in patient groups requiring oral administrations.</p>
Criterion B met: Yes	<p>Faropenem is hydrolysed by carbapenemases and there is potential for cross-resistance with carbapenems [191-193].</p> <p>Little surveillance data is available on the prevalence of resistance to faropenem.</p> <p>Reference is made to the carbapenem section (Table 18).</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Faropenem has not been authorised for use in VMPs in the EU and there is no knowledge of veterinary authorisation of penems globally. No penems are included in the Annex to the MRL Regulation (EU) 37/2010 and therefore they cannot be used to treat food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>No evidence could be found for the use of, or need for, penems to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 20. Evaluation of monobactams

Monobactams See Table 89 for ATC(vet) codes	
Criterion A met: Yes	<p>Monobactams are monocyclic beta-lactam antibiotics (no adjacent rings to the core beta-lactam ring) that inhibit bacterial cell wall synthesis. Aztreonam is the only monobactam antibiotic currently in clinical use in humans. Other monobactams not used in humans are tigemonam, carumonam and nocardicin A.</p> <p>The spectrum of activity of aztreonam is limited entirely to aerobic Gram-negative bacteria (e.g., <i>Escherichia coli</i>, <i>Proteus mirabilis</i>, other <i>Proteus</i> spp., <i>Klebsiella</i>, <i>Enterobacter</i>, <i>Serratia</i>, <i>Providencia</i>, <i>Citrobacter</i>, <i>Salmonella</i>, <i>Shigella</i> spp., and <i>Morganella morganii</i>, <i>Pseudomonas aeruginosa</i>) [194].</p> <p>Aztreonam (in combination with ceftazidime-avibactam) is one of few options for the treatment of various life-threatening infections caused by metallo-beta-lactamase (MBL)-producing <i>P. aeruginosa</i> and MBL-producing Enterobacterales [195, 196]. Aztreonam is also an important alternative for the treatment of infections in cystic fibrosis patients (either intravenously or by inhalation) [197, 198] and for the treatment of infections in patients with allergy to other beta-lactams [199].</p> <p>MBL-producing Gram-negative bacteria are not inhibited by the new beta-lactamase inhibitors (e.g., avibactam) and there are very limited alternative treatments, e.g., colistin combinations, cefiderocol. Some of these organisms can also be susceptible to aminoglycosides and fluoroquinolones [48].</p> <p>MBL-producing Gram-negative bacteria, e.g., NDM-producing <i>Klebsiella pneumoniae</i>, are increasingly reported as causing hospital outbreaks in the EU/EEA.</p> <p>Aztreonam is centrally approved for the suppressive therapy of chronic pulmonary infections due to <i>P. aeruginosa</i> in patients with cystic fibrosis (CF) aged 6 years and older. Aztreonam is nationally approved for the treatment of different infection types (UTIs, gonorrhoea, lower RTIs, septicæmia, meningitides, bone and joint infections, intra-abdominal infections and gynaecological infections) caused by aerobic Gram-negative microorganisms and for lung infections caused by <i>P. aeruginosa</i> in cystic fibrosis patients [200].</p> <p>Monobactams fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>Despite their stability to MBLs, common resistance mechanisms to aztreonam in Enterobacterales are AmpC, ESBLs and non-class B carbapenemases, chromosomally or plasmid encoded. Resistance in <i>Pseudomonas</i> spp. may evolve during treatment due to chromosomal mutations [194].</p> <p>There is no monitoring of resistance specifically to monobactams under EFSA/ECDC mandatory EU surveillance in food-producing animals; however, monitoring of <i>Salmonella</i> spp. and <i>E. coli</i> shows that the prevalence of ESBL- and AmpC-producers is low in the EU overall, but varies greatly between animal production type and country [26]. Enterobacterales producing ESBLs and AmpC have also been isolated from companion animals [57-60].</p> <p>Transmission</p> <p>There is evidence to support the potential transmission of resistance to monobactams from food-producing and companion animals to humans via Enterobacterales that are zoonotic pathogens or commensal bacteria (See annotation 2 under Table 61).</p> <p>In conclusion, although they are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance to monobactams from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Monobactams have not been authorised for use in VMPs in the EU and there is no knowledge of their veterinary authorisation globally. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>There are few reports of use of monobactams in companion animals to treat various serious Gram-negative infections, e.g. septicæmia [201, 202]. Alternative veterinary-authorized antimicrobials are available (e.g. 3rd- and 4th-generation cephalosporins, aminoglycosides).</p> <p>In conclusion, based on the low number of reports of use of monobactams in animals, it appears that impacts of inappropriate treatment on morbidity and mortality would be very limited. Considering the public health interest identified from criteria A and B, criterion C.1(c) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 21. Evaluation of polymyxins

Polymyxins See Table 90 for ATC(vet) codes	
Criterion A met: Yes	<p>Colistin (polymyxin E) and polymyxin B are rapidly bactericidal polypeptide antibiotics belonging to the polymyxin class. Polymyxins disrupt the outer bacterial cell membrane of certain Gram-negative bacteria [203].</p> <p>Polymyxins are active particularly against Gram-negative bacteria such as most Enterobacterales (e.g. <i>E. coli</i>, <i>Klebsiella</i> spp., <i>Salmonella</i> spp.), <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i>, including those displaying carbapenem resistance. Some Gram-negative bacteria are inherently resistant to polymyxins, such as <i>Serratia</i>, <i>Stenotrophomonas</i> and <i>Proteus</i> spp. [203].</p> <p>Intravenous polymyxins (colistin) are one of few available therapies for serious systemic healthcare-associated infections due to MDR Enterobacterales, <i>A. baumannii</i> and <i>P. aeruginosa</i>, especially in seriously ill patients in ICUs. Colistin should be used with care due to nephrotoxicity and is used as last resort in combination with meropenem, aminoglycosides or tigecycline for the treatment of infections caused by carbapenemase-producing Gram-negative bacteria, especially those producing KPC, MBL and OXA enzymes alone or in association with ESBLs or AmpC. It is also administered by inhalation for the treatment of infections in cystic fibrosis patients and in patients with ventilator-associated pneumonia [11, 203].</p> <p>Alternatives include new antibiotics and combinations with beta-lactamase inhibitors such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam and cefiderocol, as well as novel tetracyclines or fosfomycin, but these may also have limitations to their use. In the case of MDR-<i>A. baumannii</i>, the only alternative is cefiderocol and the novel tetracyclines [47, 49, 160].</p> <p>Infections caused by MDR Gram-negative bacteria are an increasing threat to healthcare delivery globally and colistin has increasingly been used in hospitals in the EU/EEA for the treatment of infections caused by carbapenem-resistant Enterobacterales, MDR-<i>Acinetobacter</i> spp. and MDR-<i>Pseudomonas</i> spp. Infections caused by carbapenem-resistant Gram-negative bacteria are associated with high levels of mortality (see Table 18, Carbapenems) and there were also an estimated 2,500 deaths due to colistin-resistant Gram-negative bacteria in the EU/EEA in 2015 [153].</p> <p>Colistin and Polymyxin B are nationally authorised in EU. A referral was conducted by the EMA in 2014 and recommendations were issued for safe use in patients with serious infections resistant to standard antibiotics.</p> <p>Polymyxins fulfil criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>Acquired resistance to polymyxins can be both chromosomal and plasmid-borne [204, 205]. The <i>mcr-1</i> gene encodes an enzyme (MCR-1) that modifies the lipopolysaccharide of the bacterial membrane, leading to resistance to polymyxins. Multiple <i>mcr</i> genes have now been described [206]. Resistance due to plasmid-mediated <i>mcr</i> genes has been detected in Enterobacterales, <i>Acinetobacter</i> and <i>Pseudomonas</i> spp. and is reported globally from animals, food produce and in human clinical and non-clinical (screening) specimens [204, 205, 207-213].</p> <p><i>mcr</i> and ESBL genes have been identified on the same plasmid in salmonellae from food-producing animals, indicating the possibility for co-selection of resistance. [204, 213, 214]. Co-existence of <i>mcr</i>-genes and genes encoding for carbapenem resistance (NDM) have been found in <i>E. coli</i> isolates (on different plasmids) from food-producing animals and meat in China [215-217].</p> <p>Although information about colistin resistance in bacteria derived from animals and food animal produce is still limited, a widespread dispersion of <i>mcr</i> genes in livestock animals has been described [218]. Recent mandatory EU surveillance reported a generally (very) low but variable prevalence of colistin resistance in <i>Salmonella</i> spp. and <i>E. coli</i> from different food producing animal species and countries [26].</p> <p>The <i>mcr-1</i> gene has incidentally been detected in <i>E. coli</i> from dogs in the EU, and globally [212, 219-221].</p> <p>Transmission</p> <p>Epidemiology suggests that the <i>mcr</i> resistance genes can be transferred from animals to humans via resistant bacteria or plasmids [204, 213]. <i>mcr</i> genes have been found in similar plasmids in the same bacterial species from food-producing animals and humans [204, 213, 222]. The more frequent isolation of <i>mcr</i> genes among animal isolates compared with human isolates, together with the higher use of colistin in livestock compared with human medicine in certain countries has been suggestive of transmission from animals to humans. The ban of the use of colistin in China as a growth promoter in agriculture has led to a decrease in colistin resistance in animals as well as humans [223].</p> <p>In conclusion, although not quantifiable at present, there is evidence for the selection and significant transmission of resistance to polymyxins from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: No	<p>Polymyxins are authorised in the EU and third countries in VMPs for systemic and local treatments. Colistin is included in Table 1 of the MRL Regulation (EU) 37/2010 and can be used in all food-producing species in the EU.</p> <p>Food-producing species</p> <p>Colistin is authorised in (group and individual) oral VMPs in the EU. In 2014 the CVMP recommended to restrict the indications for all VMPs containing colistin to be administered orally (in feed or water; calves, sheep, goats, pigs,</p>

	<p>poultry, rabbits) to 'Treatment and metaphylaxis of enteric infections caused by susceptible non-invasive <i>E. coli</i>.' only. Any indications for prophylaxis, general indications or indication for any other pathogen were removed (Commission Decision (2015)1916 of 16 March 2015). According to the SPC, use should be based on susceptibility testing [224, 225]. Colistin is also authorised for parenteral and intramammary use. Colibacillosis (diseases due to <i>E. coli</i>) is a major cause of morbidity and mortality in neonatal and juvenile livestock of various species, especially swine [137, 138, 140]. EFSA noted high levels of resistance to first line antimicrobials (e.g. aminopenicillins, potentiated sulfonamides, tetracyclines) in pathogenic <i>E. coli</i> from swine, horses, sheep, goats and calves, suggesting their limited efficacy against these infections in many EU countries [41, 86, 88, 142] (See annotation 1 under Table 61). Alternatives to colistin for resistant <i>E. coli</i> are limited to other AMEG Category B substances i.e. fluoroquinolones (not poultry laying eggs for human consumption), 3rd- and 4th-generation cephalosporins (not poultry), or, depending on resistance profile and disease/patient characteristics, aminoglycosides or aminopenicillin-BLI [139, 204].</p> <p>In 2016, EMA provided a risk-profiling on the use of colistin VMPs in animals and noted that, in addition to animal health and welfare impacts, removal of colistin from the market could increase the selection pressure for resistance to other human HPCIAAs e.g. fluoroquinolones, through their increased use [204]. Restrictions implemented in member states have led to a reduction in colistin use of 76.5% from 2011 to 2020 [85], currently without increased use of other HPCIAAs but the impact of a complete ban on use cannot yet be foreseen.</p> <p>Companion animals</p> <p>In dogs, polymyxin B is among few alternatives for topical treatment of serious otitis due to Gram-negative infections and is included for this indication in the WSAVA list of essential medicines for cats and dogs[226].</p> <p>In conclusion, polymyxins are used to treat serious, life-threatening infections in animals due to MDR Gram-negative bacteria, which inappropriately treated would result in significant morbidity and mortality and impacts on animal welfare. There are few alternatives and in most cases these are similarly AMEG Category B classes.</p> <p>Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 22. Evaluation of cyclic polypeptides

<p>Cyclic polypeptides See Table 91 for ATC(vet) codes</p>	
<p>Criterion A met: No</p>	<p>Bacitracin interferes with bacterial cell wall formation by inhibiting peptidoglycan synthesis, the major cell wall component in Gram-positive bacteria. Additionally, bacitracin has an ability to degrade nucleic acid and is particularly active against RNA [227].</p> <p>Bacitracin is active against most Gram-positive bacteria, particularly <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>, <i>Corynebacterium diphtheriae</i> and <i>Clostridioides difficile</i>, but susceptibility of Enterococcus species is variable. Among Gram-negative bacteria, bacitracin shows activity against <i>Neisseria</i> (meningococci and gonococci) and <i>Treponema pallidum</i>. <i>Haemophilus influenzae</i> is also susceptible [227].</p> <p>Bacitracin is mainly used topically and can be found as a compound in many over-the-counter products indicated for wound care. Bacitracin is frequently used in combination with neomycin and polymyxin B or with corticosteroids, by topical application [227].</p> <p>There are many alternative options for treatment of all infections for which it is approved/used.</p> <p>Bacitracin is nationally approved in some EU Member States, often as a combination for topical use. Approved indications include primary infected dermatoses, such as impetigo, bacterial otitis externa, ecthyma, folliculitis and paronychia; in secondarily infected dermatoses, such as infected eczema, secondarily infected lesions of infestations (e.g., scabies) and secondary bacterial infection accompanying viral infections.</p> <p>Cyclic polypeptide antibiotics do not fulfil criterion A, due to the limited use in human medicine and other treatment alternatives.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 23. Evaluation of phosphonic acid derivatives

<p>Phosphonic acid derivatives See Table 92 for ATC(vet) codes</p>	
<p>Criterion A met: Yes</p>	<p>Fosfomycin belongs to the phosphonic acid derivatives but it is the only substance from this class available for human use.</p> <p>Fosfomycin has broad-spectrum bactericidal activity against <i>Staphylococcus</i> spp. (including MRSA), <i>Enterococcus</i> spp. (including VR), <i>Haemophilus</i> spp., and most enteric Gram-negative bacteria. It also has excellent activity against most <i>E. coli</i>, including 95.5% of extended-spectrum beta-lactamase (ESBL)-producing <i>E. coli</i> [228, 229].</p>

	<p>Fosfomycin has activity against only 57.6% of ESBL-producing <i>Klebsiella</i> spp. [230]. <i>Pseudomonas aeruginosa</i> is variably susceptible to Fosfomycin. <i>Acinetobacter baumannii</i> is usually resistant. Fosfomycin retains excellent in vitro activity against both <i>Enterococcus faecalis</i> and <i>Enterococcus faecium</i> [231].</p> <p>Fosfomycin is used as a parenteral antibiotic for systemic infections and also as an oral formulation that is used nearly exclusively for the treatment of uncomplicated cystitis and prostatitis [229, 232, 233]. Fosfomycin has been used since its discovery mainly for the treatment of uncomplicated lower UTIs in (premenopausal) women. Nowadays, intravenous fosfomycin has gained increasing interest in its effectiveness against MDR or extensively drug-resistant (XDR) nosocomial infections, when limited treatment options are available. There is also interest in its potential synergistic activity with glycopeptides, rifampicin, or daptomycin against MRSA infections. In an era of antibiotic resistance and limited new treatment options, interest in fosfomycin is expected to culminate in the next decade [234].</p> <p>Although there are alternatives for the treatment of MDR Gram-positive (MRSA, VRE) and MDR Gram-negative bacteria (ESBL- and carbapenemase-producing Enterobacterales and <i>P. aeruginosa</i>), fosfomycin is important due to its synergistic or additive effects when used in combination with most antibiotics to treat infections caused by MDR bacteria. Fosfomycin is active against bacteria that produce all classes of carbapenemases, including metallo-beta-lactamase-producing Enterobacterales and <i>P. aeruginosa</i>, for which there are very few alternative treatments. The few alternatives for the treatment of MBL-producing Gram-negative bacteria include cefiderocol, eravacycline, aztreonam, colistin [100, 169, 203].</p> <p>Data on fosfomycin resistance in human isolates are not included in the annual EARS-Net report. The health burden relating to the various resistant phenotypes for which fosfomycin is a possible treatment option are indicated under various classes.</p> <p>Oral fosfomycin is authorised in the EU for the treatment of lower UTIs, particularly those caused by <i>E. coli</i> and <i>Enterococcus faecalis</i>.</p> <p>Intravenous fosfomycin is authorised in the EU for complicated or severe UTIs (pyelonephritis, hydronephrosis, renal abscess and prostatitis), dermatological, gynecological, respiratory (bronchopaties, acute or chronic lung abscess), digestive tract (cholecystitis, appendiceal abscess, peritonitis, etc.) joint and bone infections (acute or chronic arthritis, acute or chronic osteomyelitis), postsurgical, sepsis, endocarditis and meningitis caused by susceptible pathogens [235].</p> <p>Fosfomycin is nationally authorised in the EU member states. On 9 June 2020, EMA recommended that fosfomycin medicines given by infusion (drip) into a vein should only be used to treat serious infections when other antibiotic treatments are not suitable. Fosfomycin medicines given by mouth can continue to be used to treat uncomplicated bladder infections in women and adolescent girls. They can also be used to prevent infection in men who undergo a procedure whereby a tissue sample is taken from their prostate (biopsy).</p> <p>EMA further recommended that fosfomycin medicines given by mouth to children (under 12 years of age) and intramuscular formulations (fosfomycin medicines for injection into a muscle) should no longer be used as there are insufficient data available to confirm their benefits to patients. These recommendations follow a review by EMA's human medicines committee (CHMP) of the safety and effectiveness of these antibiotics [235].</p> <p>Phosphonic acid derivatives fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
<p>Criterion B met: Yes</p>	<p>Fosfomycin is important due to its activity against bacteria producing carbapenemases, including MBLs. Resistance to fosfomycin may be mutational or plasmid-borne (<i>fosA</i> genes) being observed already in isolates carrying multiple resistant determinants to CIAs (e.g. ESBL genes such as <i>bla_{CTX-M}</i>) [236, 237]. The spread of <i>fosA3</i> borne on multi-resistance plasmids in animals has most probably occurred through co-selection [238].</p> <p>In most European countries fosfomycin resistance in isolates of human origin is rare, but it is considerably higher in countries with higher usage such as China [239-241].</p> <p>Fosfomycin resistance in isolates of animal origin is rarely reported in Europe, while data from the Asian region indicate low to moderate resistance rates in <i>E. coli</i> isolated from companion and food-producing animals [238, 242-248].</p> <p>Transmission</p> <p>Transmission of resistance to fosfomycin from animals to humans is not likely to be significant at present in the EU; however, there is a potential pathway for transmission of mobile fosfomycin resistance genes through commensal <i>E. coli</i>.</p> <p>In conclusion, there is evidence for the potential for selection and likely significant transmission of resistance to phosphonic acids from animals to humans through commensal bacteria capable of transferring resistance to human pathogens, if use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
<p>Criterion C met: Yes</p>	<p>One suspended marketing authorisation for a VMP containing fosfomycin in the EU was identified [249]. Fosfomycin is not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Fosfomycin is authorised in Central and South America for the treatment of various infectious diseases (including <i>E. coli</i>) in broiler chickens and piglets [250]. It is also used to treat <i>E. coli</i>-related diarrhoea and salmonellosis in cattle [251]. Fosfomycin has been approved to combat bacterial infections in fish farming in Mexico as well as in Japan for the treatment of pseudotuberculosis (<i>Photobacterium damsellae</i>) in marine fish [252, 253]. It is noted that infections with <i>Photobacterium</i> spp. are often multi-resistant [254]; vaccines are also available for this disease in some countries.</p>

	<p>Companion animals</p> <p>Use of fosfomycin in the EU under Article 112 seems to be negligible in companion animals.</p> <p>In conclusion, no evidence was found for use of, or need for, phosphonic acid derivatives to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 24. Evaluation of glycopeptides

Glycopeptides See Table 93 for ATC(vet) codes	
Criterion A met: Yes	<p>The glycopeptide antibiotic class are actinomycete-derived antibiotics with unique tricyclic or tetracyclic heptapeptide cores. The common mode of action of members of this antibiotic class is inhibition of cell wall synthesis by inhibiting peptidoglycan synthesis [255, 256].</p> <p>Glycopeptide antibiotics exhibit a narrow spectrum of activity, being effective against Gram-positive bacteria (e.g., enterococci, staphylococci, streptococci, and anaerobic bacteria such as <i>Clostridioides difficile</i>, <i>C. perfringens</i>, <i>Peptostreptococcus</i> spp., and <i>Propionibacterium acnes</i>). Oritavancin is effective against vancomycin-resistant <i>Enterococcus</i> spp. and vancomycin-resistant <i>Staphylococcus aureus</i> (VRSA). Dalbavancin, teicoplanin and telavancin are effective against VRE that carry certain van genes (not vanA) [257-260].</p> <p>Glycopeptides are one of limited treatment options for life-threatening infections, including complicated skin and skin structure infections and bacteraemia caused by resistant Gram-positive human pathogens such as MRSA, ampicillin-resistant <i>Enterococcus</i> spp. and colitis due to <i>Clostridioides difficile</i> [257-260].</p> <p>Few alternative last-resort antimicrobials are available, e.g., oxazolidinones, glycyclines, daptomycin.</p> <p>MRSA remains an important human health burden in the EU/EEA, accounting for 7,000 deaths per annum. The incidence of healthcare-associated vancomycin-resistant <i>Enterococcus faecium</i> infections has increased in the EU/EEA in the last decade. VRE was estimated to cause >16,000 infections and to be associated with >1,000 deaths in the EU/EEA in 2015 [153].</p> <p>Vancomycin and teicoplanin are nationally authorised for serious infections including complicated skin and skin structure infections, hospital-acquired and ventilator-associated pneumonias, infective endocarditis and bacteraemia. Dalbavancin is authorised for acute bacterial skin and skin structure infections. These are serious infections, which when caused by resistant bacteria, e.g., MRSA, VRE, have limited treatment options e.g., oxazolidinones, glycyclines, daptomycin.</p> <p>Glycopeptides meet criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>Glycopeptide (vancomycin) resistance is most frequently seen in enterococci (VRE), to a lesser extent in <i>Staphylococcus aureus</i> (<i>vanA</i>), and uncommonly in <i>Streptococcus</i> spp. (<i>vanA</i> or <i>vanB</i>) except <i>S. pneumoniae</i> [261, 262]. Several glycopeptide resistance genes have been described in enterococci with <i>vanA</i> and <i>vanB</i> being predominant in resistant clinical isolates. VanA and VanB resistance is horizontally transmissible. VanB strains remain susceptible to teicoplanin, however, treatment with teicoplanin can induce emergence of resistance in these isolates.</p> <p>Rare, high level resistance in <i>S. aureus</i> (VRSA) is thought to result from <i>vanA</i> transferred from enterococci. The mechanism in vancomycin intermediate-resistant <i>S. aureus</i> (VISA) is independent of the acquisition of <i>van</i> genes [262].</p> <p>The latest EFSA surveillance reports found no VISAs in MRSA isolates from food animals [26]. EFSA does not monitor for VREs in food-producing animals; although other studies show that VREs persisted at low levels since the ban of avoparcin as growth promoter (AGP) – possibly due to co-selection by macrolides [263-268].</p> <p>VRSA has been detected in LA-MRSA from pigs and in bovine/caprine milk (from outside the EU) [269, 270].</p> <p>Companion animals (e.g. dogs) can also harbour VRE, with canine isolates mostly carrying <i>vanA</i> and being MDR [271].</p> <p>Transmission</p> <p>Pathogenic vancomycin-resistant <i>Enterococcus faecalis</i> can be transmitted from animals to humans, but glycopeptide resistance is far more commonly transferred from animal commensal <i>E. faecium</i> to human enterococci causing infections via MGEs. VRE carriage in humans in the EU was previously attributed to use of avoparcin as an AGP in livestock [272, 273]. VRE isolates from dogs demonstrate similar genetic lineages to hospital-acquired infections in humans [274-276] supporting transmission between pets and owners. There is also a potential pathway for transmission of VRSA between food-producing animals and humans.</p> <p>In conclusion, experience suggests that reintroduction of use of glycopeptides in animals could result in increased selection and prevalence of vancomycin resistance and likely significant transmission from animals to humans,</p>

	<p>mainly via commensal enterococci capable of transferring resistance to human pathogens, if use of glycopeptides in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Glycopeptides are not authorised for use in VMPs in the EU. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Glycopeptides may be used for treatment or prevention of necrotic enteritis in poultry in certain third countries [8]. Alternative antimicrobials are available for this indication (e.g. penicillins, tylosin).</p> <p>Companion animals</p> <p>Potentially serious life-threatening infections for which use of glycopeptides outside the terms of the marketing authorisation has been described in companion animals in the EU include septicaemia, clostridial infections, methicillin-resistant <i>Staphylococcus</i> and (uncommonly) macrolide-resistant <i>Rhodococcus equi</i> (<i>Rhodococcus hoagii</i>) in foals [277-280].</p> <p>Alternative antibiotics are currently available for these serious infections, as reflected in modern antimicrobial stewardship guidelines that also strongly discourage the use of glycopeptides in animals due to public health concerns [78, 281, 282]. Some EU member states have experience of prohibiting the use of glycopeptides in animals without documented negative consequences on animal health and welfare.</p> <p>Although the extent of use of glycopeptides in companion animals in the EU is unknown, based on the low number of reports it appears that impacts of inappropriate treatment on morbidity and mortality would be very limited.</p> <p>In conclusion, considering the public health interest identified from criteria A and B, criterion C.1(c) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 25. Evaluation of lipopeptides

Lipopeptides See Table 94 for ATC(vet) codes	
Criterion A met: Yes	<p>Daptomycin, produced by <i>Streptomyces roseosporus</i>, is the only available antibacterial cyclic lipopeptide. The primary mode of action of daptomycin is thought to lie in disruption of the bacterial cell membrane. Daptomycin inserts into the bacterial cell membrane in a Ca²⁺-dependent manner, leading to depolarisation and rapid bacterial cell death [283].</p> <p>Daptomycin has activity against a wide spectrum of aerobic and anaerobic Gram-positive organisms only, including VRE, vancomycin-intermediate <i>S. aureus</i> (VISA), MRSA and penicillin-resistant streptococci, for which there are very few therapeutic alternatives.</p> <p>Daptomycin is one of limited treatment options for life-threatening infections (e.g. cSSSIs, bacteraemia) caused by resistant Gram-positive pathogens, such as MRSA, VISA and ampicillin- and/or vancomycin-resistant <i>Enterococcus</i> spp. in adults and in the paediatric population [283].</p> <p>Few alternatives are available for the treatment of MRSA infections, e.g., glycopeptides, glycylicyclines, eravacycline, oxazolidinones, ceftobiprole and ceftaroline. Few alternatives are available for the treatment of VRE infections, e.g., oxazolidinones, oritavancin, fosfomycin and glycylicyclines.</p> <p>MRSA remains an important human health burden in the EU, accounting for 7,000 deaths per annum, and the incidence of healthcare-associated vancomycin-resistant <i>Enterococcus faecium</i> infections has increased in the last decade [153]</p> <p>In the EU, daptomycin is centrally authorised for the treatment of complicated SSTIs caused by susceptible strains of Gram-positive pathogens, and for the treatment of <i>Staphylococcus aureus</i> bloodstream infections when associated with cSSTI or right-sided infective endocarditis.</p> <p>Daptomycin fulfils criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>Resistance in human isolates is currently rare but there are increasing reports of decreased susceptibility to daptomycin in <i>S. aureus</i> and <i>Enterococcus</i> spp. Such resistance occurs through multiple stepwise chromosomal mutations resulting in changes in the cell membrane. Resistance occurs mostly in the context of prolonged treatment courses [284-286]. No horizontally transferable mechanisms of resistance transfer to daptomycin are reported.</p> <p>Surveillance studies have shown very low levels of daptomycin-resistance in enterococci from livestock in Europe [287, 288].</p> <p>Transmission</p> <p>There is potential for transmission of resistance via enterococci and (LA)MRSA from animals to humans [29, 30, 272, 273] (See annotation 3 under Table 61).</p>

	<p>In conclusion, there is evidence for the potential for selection and likely significant transmission of resistance to lipopeptides through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if use in animals became established.</p> <p>Criterion B.1(b) is met.</p>
Criterion C met: Yes	<p>Lipopeptides have not been authorised for use in VMPs in the EU and there is no knowledge of their veterinary authorisation globally. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and therefore cannot be used to treat food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>No evidence was found for use of, or need for, lipopeptides to treat serious infections in animals in the EU or globally at the present time.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 26. Evaluation of oxazolidinones

Oxazolidinones See Table 95 for ATC(vet) codes	
Criterion A met: Yes	<p>Oxazolidinone antibiotics are a class of synthetic antibacterial agents that act as protein synthesis inhibitors. Presently there are two oxazolidinones authorised for human use, linezolid and tedizolid.</p> <p>Oxazolidinones are active against a large spectrum of Gram-positive bacteria, including methicillin- and vancomycin-resistant staphylococci, vancomycin-resistant enterococci (VRE), penicillin-resistant pneumococci and anaerobes. Oxazolidinones have activity against <i>Mycobacterium tuberculosis</i> and a variety of nontuberculous mycobacteria. Tedizolid also displays in vitro activity against <i>Clostridioides difficile</i> and <i>Bacteroides fragilis</i> [289, 290].</p> <p>Oxazolidinones are one of limited options for treatment of VRSA, MRSA and VRE. Oxazolidinones are alternatives for treatment of MRSA SSTIs. Compared with vancomycin, oxazolidinones are more effective and safer for treating hospital patients with complicated SSTI caused by MRSA [291]. Updated guidance on MDR-TB treatment, released by WHO in 2018, now classifies linezolid as a Group A drug, meaning that it is a priority to include in individually constructed MDR-TB regimens for adults and children [292].</p> <p>Although alternative last-resort antimicrobials may be available for treatment of MRSA, VRSA and VRE infections, e.g., lipoglycopeptides, glycolcyclines, daptomycin, resistance has already developed to these options, and for some infections, oxazolidinones may be the only suitable treatment according to the specific clinical circumstances (good tissue penetration) [291]. They can also be administered orally in long term TB treatment. Alternatives for treatment of MDR-TB are addressed below.</p> <p>MRSA remains an important human health burden in the EU, accounting for 7,000 deaths per year, and the incidence of healthcare associated vancomycin-resistant <i>Enterococcus faecium</i> infections has increased in the last decade [153].</p> <p>Linezolid is nationally authorised in the EU for nosocomial and CAP and complicated SSTI, caused by Gram-positive bacteria. Tedizolid is centrally authorised for the treatment of acute bacterial skin and skin structure infections. They are one of the limited treatment options for SSTIs caused by VRSA, MRSA and VRE.</p> <p>Oxazolidinones fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>The most common mechanism of resistance to oxazolidinones in staphylococci and enterococci is mutations affecting the ribosomal binding site. In both staphylococci and enterococci there are also transferable resistance mechanisms emerging, conveying multidrug resistant profiles e.g. <i>optrA</i> gene (oxazolidinones, phenicols), <i>cf</i> conferring the PhLOPSA pattern (phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A) and the <i>poxtA</i> gene (oxazolidinones, phenicols and tetracyclines) [286, 293, 294]. Hence there is potential for co-selection by or for other antimicrobial classes.</p> <p>Although surveillance is limited, linezolid resistance in isolates from food-producing animals in the EU appears to be at very low levels presently, with the <i>cf</i> gene being detected sporadically in (LA)MRSA from pigs [26, 295].</p> <p>Transmission</p> <p>The same oxazolidinone-resistance mechanisms have been found in zoonotic pathogens and commensal bacteria from humans and animals [243, 296-300].</p> <p>Linezolid-resistant (LA)MRSA has potential to transfer from animals to humans in contact [301, 302] (See annotation 3 under Table 61) and commensal enterococci from animals may transfer resistance genes to human pathogenic <i>E. faecium</i> [272]. There is also the possibility of exchange of linezolid-resistant bacteria and transferrable resistance genes between companion animals and their owners [29].</p> <p>In conclusion, there is evidence for the potential for selection and likely significant transmission of resistance to oxazolidinones from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if use in animals became established.</p>

	Criterion B.1.(b) is met.
Criterion C met: Yes	<p>Oxazolidinones have not been authorised for use in VMPs in the EU and there is no knowledge of their veterinary authorisation globally. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>Evidence supports limited need for oxazolidinones in veterinary medicine to treat potentially serious MRSP infections in companion animals. MRSP is most commonly implicated in canine recurrent pyoderma, but may also be involved with surgical wounds, urinary and respiratory tract infections. [281, 303-305]. For multidrug resistant isolates, topical treatments may be effective or where systemic treatment is needed, rifampicin or amikacin could be alternatives for infections not susceptible to other veterinary-authorised antimicrobials. There are strong recommendations in some EU and international guidelines against the use of oxazolidinones in animals due to over-riding public health concerns [78, 281].</p> <p>Although the extent of use of oxazolidinones in companion animals in the EU is unknown, based on the low number of reports it appears that impacts of inappropriate treatment on morbidity and mortality would be very limited.</p> <p>In conclusion, considering the public health interest identified from criteria A and B, criterion C.1(c) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 27. Evaluation of pleuromutilins

<p>Pleuromutilins See Table 96 for ATC(vet) codes</p>	
Criterion A met: No	<p>Pleuromutilins are an antibiotic class commonly used in veterinary medicine. Pleuromutilins inhibit bacterial protein synthesis by binding to 50S ribosomal subunit. In human medicine, lefamulin is the first systematically administered pleuromutilin [306].</p> <p>Pleuromutilins are active against Gram-positive (<i>Staphylococcus</i> spp. – including MRSA and VRSA-), <i>Streptococcus</i> spp.- including MDR strains) and fastidious Gram-negative bacteria (e.g., <i>Haemophilus</i> spp., <i>Moraxella catarrhalis</i>, <i>Neisseria</i> spp., <i>Legionella pneumophila</i>) as well as against <i>Mycoplasma</i> and <i>Chlamydia</i> spp. [306, 307].</p> <p>Lefamulin is a relatively recently approved pleuromutilin for the treatment of CAP. Retapamulin is a topical antibiotic used to treat impetigo and infected small lacerations, abrasion or sutured wounds caused by <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>. The marketing authorisation in the EU has been withdrawn.</p> <p>Pleuromutilins are generally unaffected by resistance to other major antibiotic classes, such as macrolides, fluoroquinolones, tetracyclines, beta-lactam antibiotics, and others. The incidence of pleuromutilin-resistant bacterial isolates is low despite the use of tiamulin and valnemulin in veterinary medicine for more than 30 years [307].</p> <p>There are numbers of alternative treatment options recommended for treatment of CAP such as beta-lactams, macrolides, fluoroquinolones [308].</p> <p>Pneumonia, especially pneumococcal CAP is associated with significantly increased morbidity and healthcare costs. CAP remains one of the leading causes of death due to infectious diseases globally. Available data covering 16 European countries showed a significant burden of pneumococcal CAP, especially in the elderly. The overall incidence rate for CAP was 68–7000 per 100,000 and the incidence in hospitalised CAP cases of all causes was 16–3581 per 100,000 and the incidence increase consistently with age [309].</p> <p>Lefamulin is centrally approved in the EU and is indicated for the treatment of CAP in adults when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP or when these have failed [310]. Retapamulin was approved by EMA in 2007 as a topical agent to treat impetigo and infected small lacerations, abrasion or sutured wounds caused by <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i> and then withdrawn in 2019 [311].</p> <p>Pleuromutilins do not fulfil criterion A, due to other treatment alternatives to manage CAP.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 28. Evaluation of macrolides

<p>Macrolides See Table 97 for ATC(vet) codes</p>	
Criterion A met: Yes	<p>Macrolides is a class of antibiotics that includes among others erythromycin, roxithromycin, azithromycin, and clarithromycin [312-316]. Macrolides are bacteriostatic antibiotics, characterized by moderately broad spectra of</p>

	<p>activity. Macrolides bind to the 50S subunit of bacterial ribosomes, leading to inhibition of transpeptidation, translocation, chain elongation, and, ultimately, bacterial protein synthesis [317].</p> <p>Macrolides are active against most Gram-positive (e.g., <i>Staphylococcus</i> spp., including beta-lactamase-producing strains, <i>Streptococcus</i> spp., <i>Enterococcus</i> spp., <i>Clostridium</i> spp.) but only selected Gram-negative organisms (e.g. <i>Neisseria gonorrhoeae</i>, <i>Helicobacter pylori</i> and <i>Campylobacter</i> spp., <i>Shigella</i> and <i>Salmonella</i> spp.) as well as several species responsible for intracellular infections, such as <i>Mycobacterium</i> spp., <i>Chlamydia</i> spp., <i>Mycoplasma pneumoniae</i>, and <i>Legionella</i> spp. [312-316].</p> <p>Macrolides are among the most used classes of antibiotics. They are used in the management of RTIs, acute bacterial sinusitis, acute bacterial otitis media, pharyngitis, tonsillitis, mild to moderately severe CAP, uncomplicated chlamydia infections, urethritis, cervicitis, acute exacerbation of chronic bronchitis (adequately diagnosed), SSTIs, campylobacteriosis and <i>H. pylori</i> infections. Macrolides are an important treatment alternative for patients allergic to penicillin and cephalosporins.</p> <p>Fluoroquinolones are an alternative treatment option for RTIs (e.g. moxifloxacin for the treatment of moderately severe CAP) [318, 319]. Fluoroquinolones and tetracyclines are an alternative for treatment of campylobacteriosis.</p> <p>Although there is a comparatively high prevalence of food-borne zoonotic <i>Campylobacter</i> spp. infections in humans, only serious cases need treatment and the proportion of fatalities is low: ECDC reports 220,000 cases, 47 deaths (not necessarily due to resistant infections) in 2019 [320]. Antimicrobial resistance of <i>Campylobacter</i> bacteria in humans to ciprofloxacin and tetracyclines is reported to be very high [321]. The increasing incidence of fluoroquinolone resistance in <i>Campylobacter</i> spp. has rendered macrolides such as erythromycin and azithromycin the antibiotics of choice for human campylobacteriosis and <i>H.pylori</i> infections. Resistance to macrolides in human <i>Campylobacter</i> spp. infections remains low in the EU, and they are first choice for oral treatment of 'at-risk' patients, e.g. children. For severe cases or invasive infections, parenteral treatment is more likely: fluoroquinolones (if susceptible), aminoglycosides, carbapenems or TMPS [322, 323]. MDR infections are rare.</p> <p>Macrolides are nationally approved in the EU for the treatment of the following infections: acute bacterial sinusitis, acute bacterial otitis media, pharyngitis, tonsillitis, acute exacerbation of chronic bronchitis (adequately diagnosed), mild to moderately severe CAP, SSTIs uncomplicated <i>Chlamydia trachomatis</i> urethritis and cervicitis, <i>H. pylori</i> infections.</p> <p>Macrolides fulfil criterion 1.A.(b) based on being an essential component of limited treatment alternatives for the infections described above.</p>
<p>Criterion B met: Yes</p>	<p>Mechanisms of resistance to macrolides include modification of the target, drug inactivation and drug efflux. Resistance is conferred by chromosomal mutations as well as horizontal transfer of resistance genes. The most common mechanism is target site modification mediated by different rRNA methylases (<i>erm</i> genes), which confers resistance to macrolides, lincosamides and streptogramin B. <i>erm</i> genes have been identified on plasmids and transposons and are widely distributed in Gram-positive, Gram-negative and anaerobic bacteria from human and animal sources. Many efflux genes have been identified in Gram-positive and Gram-negative bacteria (e.g. <i>mefA</i>, <i>mefE</i>, <i>msr</i>), but not all confer resistance to 16-member ring macrolides. Enzymatic inactivation is a less common resistance mechanism (<i>mph</i>, <i>ere</i> genes) [294, 324, 325].</p> <p>Monitoring under mandatory EFSA/ECDC surveillance shows that resistance to macrolides in <i>C. jejuni</i> from food-producing animals and humans remains low in Europe overall; but it is at moderate levels in <i>C. coli</i> and is higher in certain EU countries. In <i>Salmonella</i> spp. and <i>E. coli</i> resistance to azithromycin is generally low [26]. Monitoring of MRSA is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence ranges from 0% to 100% depending on animal production type and country. High levels of macrolide resistance have been reported in MRSA from pigs in Belgium, Portugal and calves from Belgium and Switzerland [26].</p> <p>In the EU, <i>erm</i>(B) has been reported on plasmids and multidrug resistant islands in <i>C. coli</i> from poultry [326-328].</p> <p>There is evidence for selection and spread of resistance to macrolides due to the use of these antimicrobials in food-producing animals. Long term, in particular low-dose use of macrolides selects for emergence of erythromycin resistant campylobacter in animal reservoirs [324, 329].</p> <p>Transmission</p> <p>Resistance to macrolides can be transferred from food-producing and companion animals to humans via zoonotic pathogens (<i>Campylobacter</i>, <i>Salmonella</i> spp., LA-MRSA (See annotation 3 under Table 61), <i>Rhodococcus equi</i> and commensals [327, 330-333]. Most concern relates to poultry, which are the primary source of <i>C. jejuni</i> and campylobacter infection in humans [334]. A significant association has been shown between macrolide-resistance in <i>C. jejuni</i> isolates from poultry and from humans [56].</p> <p>There is evidence for the selection and significant transmission of resistance to macrolides from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>Macrolides are authorised in VMPs in the EU, predominantly for use in food-producing animals for gastrointestinal and respiratory infections. Several macrolides are included in Table 1 of the MRL Regulation (EU) 37/2010 and the class may be used in all food-producing species.</p> <p>Food-producing species</p> <p>Mycoplasmas primarily cause respiratory and synovial infections with high morbidity leading to important impacts on health and welfare in ruminants, pigs and occurring sporadically in poultry in the EU [335-337]. Alternative first-line antibiotics for mycoplasmas include tetracyclines; however, despite increasing resistance to both classes [338], macrolides remain important for bovine respiratory disease and enzootic pneumonia in calves due to <i>Mycoplasma</i></p>

	<p><i>bovis</i> and complicated by secondary pathogens as amphenicols or fluoroquinolones may be the only alternatives [41, 339] (See annotation 1 under Table 61).</p> <p>Disease due to <i>Lawsonia intracellularis</i> is of major importance in the swine industry and may manifest as proliferative haemorrhagic enteropathy with high mortality in acute outbreaks. Alternatives to macrolides under these circumstances include tetracyclines and pleuromutilins but are limited [84, 340, 341].</p> <p>Companion animals</p> <p>Macrolides (e.g. erythromycin, clarithromycin, azithromycin) are used in combination with rifampicin to treat cases of pneumonia in foals due to <i>Rhodococcus equi</i> when this is severe life-threatening. Alternatives such as doxycycline have only been investigated for treatment of less severe cases [331, 342-344]. Based on either clinical trial results or published AST, alternative antibiotics for <i>Rhodococcus equi</i> include doxycycline, fluoroquinolones, and aminoglycosides.</p> <p>Macrolides are also part of recommended treatment (in combination with e.g. rifampicin and a fluoroquinolone) in cats and dogs for rare but serious life-threatening infections due to <i>Mycobacteria</i> spp. Euthanasia may be considered as an alternative due to the guarded prognosis or zoonotic potential (e.g. <i>Mycobacterium bovis</i>) [345, 346].</p> <p>In conclusion, macrolides are used in food-producing and companion animal species to treat serious life-threatening infections with significant morbidity or mortality for which there are no or limited alternatives, in particular from a lower AMEG category. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 29. Evaluation of macrocycles

Macrocycles See Table 98 for ATC(vet) codes	
Criterion A met: Yes	<p>Fidaxomicin is a narrow spectrum, bactericidal agent that acts by inhibiting RNA polymerase at the bacterial transcription initiation pathway [347].</p> <p>Fidaxomicin is selectively active against Gram-positive anaerobic bacteria (e.g., <i>Clostridioides difficile</i> and <i>Clostridium perfringens</i>) and is poorly active against anaerobic Gram-negative bacteria [347].</p> <p>Fidaxomicin is a first line treatment option for <i>C. difficile</i> infections [348].</p> <p>The alternatives or traditional treatment options for <i>C. difficile</i> infections are metronidazole and vancomycin [348]. A recent network meta-analysis suggests that fidaxomicin and vancomycin are effective first-line treatments for mild or moderate <i>C. difficile</i> infections, however fidaxomicin may be more effective at preventing <i>C. difficile</i> infection recurrence than vancomycin [349].</p> <p>The estimated annual burden of healthcare associated <i>C. difficile</i> infections in EU/EEA, 2011–2012 was 152,905 cases and accounted for 8,382 deaths/year [350].</p> <p>Fidaxomicin is centrally approved in the EU for the treatment of <i>C. difficile</i> infections, also known as <i>C. difficile</i>-associated diarrhoea in adult and paediatric patients with a body weight of at least 12.5 kg.</p> <p>Fidaxomicin fulfils criterion A.1.(b), based on being an essential component of treatment for serious, life-threatening infections.</p>
Criterion B met: Yes	<p><i>C. difficile</i> resistant to fidaxomicin have been demonstrated under selective pressure in in vitro studies. Resistance is due to mutation in the <i>rpoB/C</i> genes, affecting the fidaxomicin binding site in the target enzyme, RNA polymerase. No cross-resistance has been observed with rifamycins or other antibiotics tested [159, 351, 352].</p> <p>There are no recommended breakpoints and reports of clinically relevant resistance in <i>C. difficile</i> isolates from humans are sparse and unclear [353, 354].</p> <p>No reports were found relating to resistance to fidaxomicin in (non-experimental) animal isolates.</p> <p>Transmission</p> <p><i>C. difficile</i> clones commonly associated with human diseases, such as ribotype 078, are found in companion and food-producing animals. There are differences between animal species in strain distribution, but in many studies, <i>C. difficile</i> has been found with high prevalence and shedding, especially in neonates. Hence <i>C. difficile</i> is a potentially important zoonotic pathogen for which animals are a reservoir, although further studies are needed to establish direct evidence for animal to human transmission [355-360].</p> <p>In conclusion, there is evidence for the potential for emergence of resistance to fidoxamicin, although its clinical relevance is very limited at this time. If use of fidaxomicin in animals became established, owing to the high prevalence of potentially zoonotic <i>C. difficile</i> in animal populations, there would be an important pathway for transmission of resistance from animals to humans which would likely be significant.</p> <p>Criterion B.1.(b) is met.</p>

Criterion C met: Yes	<p>Macrocycles have not been authorised for use in VMPs in the EU and there is no knowledge of veterinary authorisation globally. No macrocycles are included in the Annex to the MRL Regulation (EU) 37/2010 and they cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p><i>C. difficile</i> may cause peracute, potentially fatal, intestinal disease in foals and piglets. The role of <i>C. difficile</i> in enteric disease in cats and dogs is unclear at this time. In pigs, potential treatments include tetracyclines, macrolides and pleuromutilins, and in companion animals, metronidazole may be used [361] although disease due to <i>C. difficile</i> has often been associated with antibiotic treatment in horses [362].</p> <p>No evidence was found for use of fidaxomicin outside the terms of the marketing authorisation in companion animals.</p> <p>No evidence was found for the need for fidaxomicin to treat serious infections in animals in the EU at the present time.</p> <p>Criterion C.1.(a) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 30. Evaluation of ketolides

<p>Ketolides See Table 99 for ATC(vet) codes</p>	
Criterion A met: No	<p>The mode of action of ketolide molecules involves inhibition of protein synthesis by binding to the 50S subunit of the bacterial ribosome and by blocking the translation of messenger RNA [315].</p> <p>Ketolides have been developed for the treatment of RTIs due to Gram-positive and Gram-negative bacteria causing CAP (<i>Streptococcus pneumoniae</i>, <i>Haemophilus</i> spp., <i>Moraxella</i> spp.), particularly those resistant to beta-lactams and macrolide antimicrobials. Telithromycin is active against atypical organisms such as <i>Chlamydia</i> spp., <i>Mycoplasma</i> spp. and <i>Legionella</i> spp. Ketolides are not active against Enterobacterales and <i>Pseudomonas aeruginosa</i> [315].</p> <p>Safety and efficacy of telithromycin has been extensively studied in numerous trials involving several RTIs, including CAP, pharyngitis, sinusitis, acute exacerbations of chronic bronchitis and asthma [315]. Despite initial clinical promise, no ketolides are currently on the EU market due to the identified safety concerns.</p> <p>Alternatives have not been considered due to the current lack of marketing authorisation for ketolides in the EU.</p> <p>Telithromycin has been authorised for use in the EU but was withdrawn by the marketing authorisation holder in 2018 due to safety concerns.</p> <p>If authorised for use in the EU, ketolides would not fulfil criterion A, due to limited usefulness in the EU/EEA and due to other existing treatment alternatives.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 31. Evaluation of lincosamides

<p>Lincosamides See Table 100 for ATC(vet) codes</p>	
Criterion A met: No	<p>Lincosamides are mostly represented by two substances: clindamycin and lincomycin. Due to superior microbiological activity and bioavailability of clindamycin, lincomycin is infrequently used clinically today. Therefore, the evaluation focuses primarily on clindamycin. Clindamycin disrupts protein synthesis by binding to the 50s ribosomal subunit of bacteria, thereby inhibiting early chain elongation. The antibacterial spectrum of activity of clindamycin is similar to that of the macrolides, streptogramins, and chloramphenicol [363].</p> <p>Clindamycin is active against Gram-positive bacteria e.g. <i>Staphylococci</i> (including many beta-lactamase-producing strains), <i>Streptococci</i>, including penicillin-resistant <i>Streptococcus pneumoniae</i>, but it is not typically active against <i>Enterococcus</i> spp. or Gram-negative bacteria [364]. It also demonstrates a potent activity against anaerobic bacteria such as <i>Bacteroides fragilis</i>, <i>Clostridium perfringens</i>, <i>Fusobacterium</i> spp., <i>Prevotella melaninogenica</i> and <i>Peptostreptococcus</i> spp. [363].</p> <p>Lincosamides also have activity against some protozoa (for more information please see Table 65).</p> <p>Clindamycin is used in combination for the treatment of inhalational anthrax, however the burden of this disease is low [365]. Currently, clindamycin is regarded as the first-choice medicine for bacterial vaginosis. Other important indications are for the treatment of staphylococcal anaerobic infections, including mixed infections (for which they must be combined with an antibiotic with activity against aerobic Gram-negative bacilli) [124].</p> <p>The high prevalence of clindamycin-resistant staphylococci, streptococci, and anaerobes in some geographic locations limits the clinical usefulness of this agent. Also, as a bacteriostatic antibiotic, clindamycin is not</p>

	<p>considered to be suitable to treat severe infections as monotherapy, especially in immunocompromised hosts [364].</p> <p>To treat above-mentioned infections including staphylococcal infections, alternative antibiotic agents (e.g. penicillin-beta-lactamase inhibitor combinations tetracycline, cephalosporins and metronidazole,) are available [364]. For anthrax, there are alternatives to clindamycin, e.g. vancomycin or linezolid, that can be included as part of combination therapy [366].</p> <p>The incidence of anthrax has declined over the last decades and remains at a very low level. In 2020, there were only 3 confirmed cases reported in the EU/EEA area [365].</p> <p>Clindamycin is nationally approved in the EU and is indicated for the treatment of serious infections caused by anaerobic bacteria, including intra-abdominal infections, SSTIs; tonsillitis and dental infection. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against Gram-negative aerobic bacteria.</p> <p>Lincosamides (clindamycin) do not fulfil criterion A, as there are other treatment options available on the market.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 32. Evaluation of streptogramins

Streptogramins See Table 101 for ATC(vet) codes	
Criterion A met: No	<p>Streptogramins are a group of natural (virginiamycin, pristinamycin) or semisynthetic (quinupristin-dalfopristin) cyclic peptides belong to the macrolide-lincosamide-streptogramin group of antibiotics. Streptogramins act at the level of inhibition of translation through binding to the 50S subunit of the bacterial ribosome [367, 368].</p> <p>The combination of quinupristin and dalfopristin has a broad spectrum of activity against Gram-positive bacteria, including <i>Streptococcus pyogenes</i> and MDR staphylococcal strains, in particular MRSA. Most <i>Enterococcus faecium</i> are susceptible, including vancomycin-resistant strains, whereas <i>E. faecalis</i> is protected by an efflux pump. Quinupristin-dalfopristin is also active against respiratory tract pathogens (e.g., <i>Haemophilus influenzae</i>, <i>Mycoplasma</i> spp., <i>Legionella</i> spp., <i>Chlamydophila pneumoniae</i>). Virginiamycin is mainly active against Gram-positive aerobic cocci and anaerobic bacteria (such as <i>Clostridium perfringens</i>). Pristinamycin was developed as an oral agent to treat staphylococcal infections and streptococcal infections [367, 368].</p> <p>Quinupristin-dalfopristin was previously regarded as one of few available treatments for VR and MDR <i>E. faecium</i> and MDR <i>Staphylococcus aureus</i> infections in humans [369].</p> <p>There are more effective alternatives with better safety. Streptogramins have now been replaced in human medicine and have limited availability in the EU/EEA.</p> <p>MRSA is regarded as an important public health burden in the EU, accounting for c. 150,000 infections in the EU/EEA per annum, and 7,000 deaths [153]. Prevention and control of MRSA in the EU is a public health priority.</p> <p>Pristinamycin is nationally authorised in some EU member states for oral administration to treat acute maxillary sinusitis, acute exacerbations of chronic bronchitis, mild to moderate CAP and SSTIs.</p> <p>Quinupristin-dalfopristin no longer appears to be marketed in the EU and is not used to treat either MRSA or VRE as there are alternatives with better activity that are also less toxic.</p> <p>Streptogramins do not fulfil criterion A, due to limited use in the EU/EEA and due to other existing treatment alternatives.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 33. Evaluation of aminoglycosides

Aminoglycosides (excluding aminocyclitols and plazomicin) See Table 102 for ATC(vet) codes	
Criterion A met: Yes	<p>Aminoglycosides are broad-spectrum bactericidal antibiotics and include gentamicin, amikacin, tobramycin, neomycin, kanamycin, netilmicin, sisomicin, isepamicin. Aminoglycosides interrupt protein synthesis by binding irreversibly to the 16S ribosomal RNA receptor on the 30S subunit of the bacterial ribosome.</p> <p>Aminoglycosides are particularly active against Gram-negative, aerobic bacteria (e.g., <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Pseudomonas aeruginosa</i>, <i>Acinetobacter baumannii</i>) and Gram-positive bacteria (including MRSA and VR-<i>Staphylococcus aureus</i> and VR-<i>Enterococci</i>) as well as <i>Mycobacterium</i> spp. [370-372].</p>

	<p>Aminoglycosides have similar spectra of activity with some exceptions. Tobramycin has a slightly higher activity against wild-type <i>P. aeruginosa</i>. Amikacin is more active against ESBL-producing and quinolone-resistant <i>E. coli</i> than other aminoglycosides. Also, amikacin has good activity against <i>Mycobacterium tuberculosis</i> [373].</p> <p>Aminoglycosides have been used in clinical practice since 1940. Aminoglycosides are primarily used in combination with other antibiotics. They are used to treat severe infections such as septicæmia, endocarditis, complicated UTIs, severe pelvic inflammatory disease, peritonitis and other severe intra-abdominal infections [374]. In paediatrics, gentamicin is used for septicæmia, meningitis, biliary tract infections, acute pyelonephritis and endocarditis [375]. Aminoglycosides are used to treat serious infections caused by MDR Gram-negative bacteria when other alternatives are lacking, and endocarditis caused by difficult-to-treat pathogens when monotherapy with beta-lactam antibiotics is not sufficient. Beta-lactam antibiotics are often combined with an aminoglycoside for severe sepsis/septic shock to broaden the antibacterial spectrum and achieve rapid bactericidal, and possibly synergistic effects [373].</p> <p>Alternatives to treat severe MDR infections are limited and include beta-lactam antibiotics, fluoroquinolones.</p> <p>Infective endocarditis is associated with high morbidity, mortality and healthcare expenditure. A recent data from Finland showed that the standardised incidence rate of deaths associated with infective endocarditis was 1.42 (95% CI: 1.32-1.52) per 100,000 person-years. The incidence rate increased progressively with aging from 50 years of age [376].</p> <p>Aminoglycosides are nationally approved in the EU for indications that include the treatment of bacteraemia, UTIs, chest infections, severe neonatal infections and other serious systemic infections due to susceptible organisms, in adults and children including neonates.</p> <p>Aminoglycosides fulfil criterion 1.A.(b). They are essential components of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
<p>Criterion B met: Yes</p>	<p>The three main mechanisms of bacterial resistance to aminoglycosides are the reduction of the intracellular concentration of the antimicrobial, the enzymatic modification of the antibiotic and the modification of the molecular target. Resistance mechanisms are complex and differ between the aminoglycoside molecules and between bacterial species, and generally there is less cross-resistance when compared with other classes of antimicrobials. Enzymatic inactivation of aminoglycosides is the most common resistance mechanism [377-380]. Aminoglycosides are differently affected by these enzymes. Among those enzymes, AAC(6')-Ib-cr confers resistance to gentamicin and fluoroquinolones such as ciprofloxacin [378].</p> <p>Except in mycobacteria, resistance genes are often located on mobile genetic elements, facilitating their spread between different bacterial species and between animals and humans [377, 381-384].</p> <p>In <i>M. tuberculosis</i>, mutations in the genes <i>rpsL</i> and <i>rrs</i> encoding the ribosomal protein S12 and the 16S rRNA, respectively, are responsible for most of the high-level streptomycin resistance [385].</p> <p>EFSA/ECDC mandatory surveillance shows that the EU prevalence of resistance to gentamicin in <i>Campylobacter</i> spp. is low in food-producing animals except in Italy for <i>C. coli</i> (18.8%). Resistance to streptomycin was observed at low levels in <i>C. jejuni</i> isolates from carcasses and fresh meat, and at a moderate level in meat preparations. The median levels of resistance to gentamicin in indicator <i>E. coli</i> from all animal species was low [26].</p> <p>Resistance to aminoglycosides has been detected in isolates from companion animals including <i>Pseudomonas</i> spp., staphylococci including MRSP and Enterobacterales also producing ESBLs [377].</p> <p>There is evidence that the usage of aminoglycosides in veterinary medicine is associated with the increased prevalence of resistance to aminoglycosides and other antimicrobial classes in bacteria in animals [377, 386, 387].</p> <p>Transmission</p> <p>Aminoglycoside-resistance has been found in many different bacterial species, including those with zoonotic potential such as <i>Salmonella</i> spp., <i>Campylobacter</i> spp. and (LA)MRSA. The same resistance genes have been found in isolates from humans and animals [388-391].</p> <p>Evaluation of risk factors indicates that the probability of transmission of aminoglycoside-resistance from animals to humans through transfer of zoonotic pathogens or commensal foodborne bacteria and/or their mobile genetic elements can be regarded as high. The highest risk is anticipated from transfer of resistant enterococci or coliforms (<i>E. coli</i>) since infections with these pathogens in humans would potentially be treated with aminoglycosides [377, 378]. Aminoglycosides are not part of the recommended treatment regimen for mycobacterial infections in companion animals. See Table 49 (Rifamycins) for further information. In conclusion, there is evidence for the selection and significant transmission of resistance to aminoglycosides from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>Aminoglycosides are authorised in VMPs in the EU, for use in companion and food-producing animals (cattle, pigs, poultry, sheep, goats, horses, dogs and cats) for treatment of septicaemias, gastrointestinal, urinary and respiratory tract infections. Several aminoglycosides (e.g. streptomycin, neomycin, apramycin) are included in Table 1 of the MRL Regulation (EU) 37/2010 and certain substances in the class may be used in all food-producing species.</p> <p>Food-producing species</p> <p>Aminoglycosides are among few alternatives for treatment of weaning diarrhoea in piglets and other infections due to MDR Enterobacterales in various animal species. <i>E. coli</i> infections (e.g. septicaemia, meningitis, severe enteritis) are a major cause of morbidity and mortality in neonatal livestock and horses [137-140]. Recent EFSA opinions noted high levels of resistance to first line antimicrobials (e.g. aminopenicillins, potentiated sulfonamides, tetracyclines), often involving multidrug resistance, in pathogenic <i>E. coli</i> from swine, poultry, calves, lambs and</p>

	<p>horses. This suggests the limited efficacy of first-line antibiotics against these infections in many EU countries [41, 86, 88, 142, 392] (See annotation 1 under Table 61). Aminoglycosides are a treatment option where Enterobacterales spp. remain susceptible [378]. Alternatives for resistant <i>E. coli</i> are limited to AMEG Category B substances i.e. colistin (not foals), 3rd- and 4th-generation cephalosporins (not poultry) or fluoroquinolones.</p> <p>Companion animals</p> <p>Aminoglycosides (in particular gentamicin and amikacin) are also one of few treatment options in companion animals for treatment of MDR Gram-negative bacteria and <i>Pseudomonas</i> spp. causing a variety of serious, potentially life-threatening, infections (septicaemia, urinary and respiratory tract infections, otitis). They are used with caution due to potential nephrotoxicity and ototoxicity [80, 83, 226, 378, 393]. Fluoroquinolones (AMEG Category B) are the only veterinary-authorised alternative for systemic treatment of pseudomonas infections, although susceptibility is variable [183], whilst polymyxins might be used for localised infections amenable to topical treatment. In cases where topical treatment is unsuitable, amikacin (along with rifampicin) is often one of few systemic antimicrobials to which MRSP isolates remain susceptible. Prevalence of MRSP in companion animals varies across the EU. It is most commonly implicated in canine recurrent pyoderma, and may be involved in life-threatening surgical wound, urinary and respiratory tract infections. Use of other alternatives for MDR Gram-negative bacteria and MRS that are last resort classes in human medicine, such as carbapenems, oxazolidinones and glycopeptides, is avoided in animals [27, 28, 281, 303, 305].</p> <p>In conclusion, aminoglycosides are used in food-producing and companion animal species to treat serious life-threatening infections with significant morbidity or mortality. Due to resistance development, there are limited alternatives, and these are from a higher AMEG category. Criterion C is not met.</p>
	Recommended to be designated as an antimicrobial class to be reserved for humans: No

Table 34. Evaluation of plazomicin

<p>Plazomicin See Table 102 for ATC(vet) codes</p>	
<p>Criterion A met: Yes</p>	<p>Plazomicin is a novel aminoglycoside antibiotic that displays a broad spectrum of activity and was developed to overcome inactivation by aminoglycoside modifying enzymes (AMEs) e.g. acetyltransferases, phosphotransferases, nucleotidyltransferases. Plazomicin binds to the bacterial 30S ribosomal subunit inhibiting protein synthesis [394].</p> <p>Plazomicin is active against aerobic Gram-negative bacteria including many strains of extended-spectrum beta lactamase-producing Enterobacterales, carbapenem-resistant Enterobacterales, <i>Pseudomonas aeruginosa</i> (unless they produce RNA methyltransferases). Plazomicin also displays activity against <i>Staphylococcus</i> spp. including MRSA and organisms producing AMEs. As with other aminoglycosides, plazomicin exhibits poor activity against Gram-negative and Gram-positive anaerobes. Plazomicin also has reduced or no activity against <i>Enterococcus</i> spp., <i>Streptococcus</i> spp., <i>Acinetobacter</i> spp., and <i>Stenotrophomonas</i> spp. [394].</p> <p>In the future, plazomicin may be useful to treat cUTIs caused by MDR Gram-negative bacteria, or infections caused by carbapenem-resistant Enterobacterales (including MBLs, except for NDM).</p> <p>No alternatives considered due to lack of market authorisation.</p> <p>Data on plazomicin resistance in human isolates are not included in the Annual EARS-Net report.</p> <p>Plazomicin is not currently authorised for use in the EU; however, future development for the EU market cannot be excluded and the spectrum of activity includes several MDR pathogens with high health burden and for which there are few alternatives available.</p> <p>Plazomicin has been under investigation for treatment of complicated UTIs (marketing authorisation application withdrawn in the EU in 2020).</p> <p>If authorised in future for the use in the EU, plazomicin would fulfil criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
<p>Criterion B met: Yes</p>	<p>Resistance to plazomicin is most commonly due to ribosomal RNA methyltransferases, found in Enterobacterales, <i>Pseudomonas</i> and <i>Acinetobacter</i> spp. In addition, plazomicin may have reduced activity against Enterobacterales that overexpress certain efflux pumps (e.g. <i>acrAB-toiC</i>) or show lower expression of porins [395, 396].</p> <p>The genes encoding methyltransferases are usually located on plasmids encoding resistance to other antimicrobial classes, such as quinolones, beta-lactams including to carbapenems (e.g. NDM-1) [378]. Plasmids co-producing 16S rRNA methylases and carbapenemases such as NDM-1 have been observed in Enterobacterales, including <i>Salmonella</i> spp. [377]. 16S rRNA methylases are mainly reported from human clinical isolates; however, similar resistance genes have been identified in isolates of animal origin at low prevalence [378].</p> <p>The emergence of 16S rRNA methylases in bacteria of animal origin has been described in <i>E. coli</i> isolates from pigs, chickens, and cows [382, 384, 397-399].</p> <p>Transmission</p> <p>Similar resistance genes were identified in isolates from human and animal origins. [388, 390, 400]. Although 16S rRNA methylases are mainly reported from human clinical isolates, <i>arma</i>, <i>rmtB</i> and <i>rmtC</i> have also been found in isolates from pets and farm animals at low prevalence [397, 401-403]. There are potential pathways for</p>

	<p>transmission of resistance to plazomicin from animals to humans e.g. via transfer of MGE between commensal Enterobacterales.</p> <p>In conclusion, there is evidence for the potential for selection and likely significant transmission of resistance to plazomicin from animals to humans, through zoonotic pathogens or commensals capable of transferring resistance to human pathogens, if use in animals became established [378].</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Plazomicin has not been authorised for use in VMPs in the EU and there is no knowledge of its veterinary authorisation globally. Plazomicin is not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>No evidence was found for use in companion animals outside the terms of the marketing authorisation, or specific need for plazomicin, to treat serious infections in animals in the EU at the present time. Where aminoglycosides are specifically indicated in veterinary medicine, e.g. for certain Gram-negative infections including <i>Pseudomonas</i> spp., earlier generation substances are generally adequate.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial to be reserved for humans: Yes	

Table 35. Evaluation of aminocyclitols

<p>Aminocyclitols See Table 102 for ATC(vet) codes</p>	
Criterion A met: No	<p>Spectinomycin has structural similarity to streptomycin but it is not an aminoglycoside. The mechanism of action is based on inhibiting protein synthesis by binding to 30S ribosomal subunit [404].</p> <p>Spectinomycin shows some activity against Gram-positive bacteria (e.g., <i>Streptococcus pyogenes</i>, <i>Streptococcus pneumoniae</i>, and <i>Staphylococcus epidermidis</i>) and a wider range of activity against Gram-negative bacteria (e.g. Enterobacterales and <i>Neisseria gonorrhoeae</i>) [404].</p> <p>Uncomplicated gonorrhoea is the only relevant indication for spectinomycin (administered as a single injection) and is recommended for use among patients allergic to penicillin G or in patients with infections produced by penicillin G-resistant gonococcal strains [404].</p> <p>Ceftriaxone in combination with azithromycin or ceftriaxone alone are considered as treatment of choice for treatment of uncomplicated gonorrhoea in Europe [405].</p> <p>In 2019 there were 117881 cases of gonorrhoea reported in the EU/EEA. The proportion of resistant isolates was: 57.3% to ciprofloxacin, 0.9% cefixime and 0.1% to ceftriaxone.</p> <p>Spectinomycin is nationally approved in very few EU Member States for the treatment of uncomplicated gonorrhoea (urethritis, cervicitis).</p> <p>Aminocyclitols do not fulfil criterion A, due to limited use in the EU/EEA and due to other existing treatment alternatives for the treatment of uncomplicated gonorrhoea.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 36. Evaluation of tetracyclines

<p>Tetracyclines (excluding minocycline, eravacycline and omadacycline) See Table 103 for ATC(vet) codes</p>	
Criterion A met: No	<p>The tetracyclines are broad-spectrum bacteriostatic antibiotics that represent a large and diverse group of compounds. The class includes among others chlortetracycline, doxycycline, oxytetracycline, tetracycline, and (evaluated separately) tigecycline and minocycline. The use of tetracyclines has declined in recent decades due to emerge of resistance. Tetracycline resistance now occurs in an increasing number of pathogenic, opportunistic, and commensal bacteria.</p> <p>Tetracyclines are used to treat infections caused by many aerobic Gram-positive (e.g., <i>Streptococcus</i> spp., <i>Staphylococcus</i> spp.), and Gram-negative bacteria (e.g., Enterobacterales, <i>Brucella</i> spp.) as well as atypical pathogens, such as <i>Rickettsia</i> spp., <i>Chlamydia</i> spp., and <i>Mycoplasma pneumoniae</i> [406]. Tigecycline has a broader spectrum of activity when compared with other tetracyclines. Tigecycline (evaluated as a glycylycylone) has activity against Gram-positive pathogens including: <i>Enterococcus</i> spp., VR-enterococci, <i>Listeria</i>, <i>Streptococcus</i> spp., both MSSA and MRSA, and <i>Staphylococcus epidermidis</i>. Its Gram-negative activity includes <i>Acinetobacter baumannii</i>, <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Escherichia coli</i>, <i>Klebsiella</i> spp., <i>Pasteurella multocida</i>, <i>Serratia marcescens</i>, and <i>Stenotrophomonas maltophilia</i> [407].</p> <p>Tetracycline remains an important agent in the therapy of severe diarrhoea due to <i>Vibrio cholerae</i> and in salvage eradication regimens for <i>Helicobacter pylori</i>. [408]. Topical tetracycline is used for <i>Chlamydia trachomatis</i> infection</p>

	<p>causing trachoma [407]. Doxycycline is more widely used in clinical practice and it is effective for patients with nongonococcal urethritis caused by <i>C. trachomatis</i>; however, recurrent urethritis in patients previously treated with doxycycline may be the result of tetracycline resistant <i>Ureaplasma urealyticum</i>. Doxycycline is an alternative agent in the treatment of genital chlamydial infections. Tetracycline (doxycycline in combination with aminoglycosides) remains an effective treatment option for brucellosis. Tetracycline is an alternative antibiotic in the treatment of leptospirosis, gas-gangrene and tetanus [407, 409].</p> <p>For most of the approved indications, treatment alternatives are available: penicillins, cephalosporins, respiratory fluoroquinolones for pneumonia; beta-lactam-BLI, macrolides and cephalosporins for acute exacerbations of chronic obstructive pulmonary disease; fosfomycin trometamol, pivmecillinam, cephalosporins and TMP-SMX for uncomplicated UTI and a number of classes (fluoroquinolones, cefepime, ceftazidime, piperacillin-tazobactam, carbapenems) for complicated UTI - here combinations with other antibacterials are usually needed; azithromycin for Chlamydia, Mycoplasma and Ureaplasma STIs; macrolides in acne.</p> <p>There were 157.04 confirmed cases per 100,000 population of Chlamydia infection in EU/EEA in 2019.</p> <p>Tetracyclines are nationally approved in the EU Member States. Approved indications include: RTIs (pneumonia and other lower RTIs due to susceptible strains of <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Klebsiella pneumoniae</i> and other organisms); <i>Mycoplasma pneumoniae</i> pneumonia; treatment of chronic bronchitis (including the prophylaxis of acute exacerbations) and whooping cough; treatment of UTIs caused by susceptible strains of <i>Klebsiella</i> spp., <i>Enterobacter</i> spp., <i>Escherichia coli</i>, <i>Streptococcus faecalis</i> and other organisms; sexually transmitted diseases (infections due to <i>C. trachomatis</i> including uncomplicated urethral, endocervical or rectal infections; non-gonococcal urethritis caused by <i>U. urealyticum</i>; chancroid, granuloma inguinale and lymphogranuloma venereum). Tetracycline is an alternative antibiotic in the treatment of penicillin resistant gonorrhoea and syphilis; Skin Infections: Acne vulgaris when antibiotic therapy is considered necessary and severe rosacea; Ophthalmic infections: Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral tetracycline alone or in combination with topical agents; Rickettsial infections: Rocky Mountain spotted fever, typhus group, Q fever and Coxiella endocarditis and tick fevers; Other infections: Stagnant loop syndrome, psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia, glanders, melioidosis.</p> <p>Tetracyclines are generally safe, but some adverse effects may occur. Most tetracyclines are contraindicated in pregnancy due to the risk of hepatotoxicity in the mother and adverse effects on foetal bone and teeth [406].</p> <p>Tetracyclines do not fulfil criterion A, as there are newer treatment alternatives.</p>
	Recommended to be designated as an antimicrobial class to be reserved for humans: No

Table 37. Evaluation of glycylicyclines

Glycylicyclines See Table 104 for ATC(vet) codes	
Criterion A met: Yes	<p>The glycylicyclines are semi-synthetic or synthetic tetracyclines specifically developed to overcome common mechanisms of resistance to older tetracyclines (ribosomal protection and efflux). Tigecycline binds to the A site of the 30S subunit and also interacts with residues of H34 ribosomal subunit [410] in a stronger way than minocycline and tetracycline [411]. Tigecycline is the first glycylicycline that became available for clinical use.</p> <p>Tigecycline has a broad antimicrobial spectrum. As for tetracyclines, it is active against Gram-positive and Gram-negative microorganisms, including most Enterobacterales (some species of the Morganellaceae family are intrinsically resistant) and <i>Acinetobacter</i> spp., anaerobic bacteria, as well as most atypical microorganisms, including many rapidly growing non-tuberculous mycobacteria. However, it is not active against certain Gram-negative non-fermenters, including <i>Pseudomonas aeruginosa</i> [412].</p> <p>Tigecycline is used (often in combination) for treatment of certain serious infections, including cSSSIs and cIAIs, where it is last resort option to treat infections caused by carbapenem-resistant Enterobacterales, MDR <i>Acinetobacter baumannii</i>, MRSA and VRE. It may be used to treat polymicrobial infections and can also be used in patients with renal dysfunction or allergic to penicillins and/or cephalosporins [412].</p> <p>Few alternatives are available for the treatment of MRSA infections, but may include e.g. glycopeptides, oxazolidinones, daptomycin, ceftobiprole and ceftaroline. Few alternatives are available for the treatment of VRE infections, e.g. oxazolidinones, fosfomycin and daptomycin. Alternatives for the treatment of infections caused by carbapenem-resistant bacteria include new antibiotics and combinations with beta-lactamase inhibitors such as ceftazidime-avibactam, ceftolozane-tazobactam (<i>P. aeruginosa</i>), imipenem-relebactam, meropenem-vaborbactam and cefiderocol, as well as colistin and fosfomycin (in combination) [49, 157, 160, 167].</p> <p>MRSA infections and infections caused by carbapenem-resistant Gram-negative bacteria are an important health burden to the EU/EEA (see above). VRE was estimated to cause >16,000 infections and to be associated with >1,000 deaths in the EU/EEA in 2015 [153].</p> <p>In the EU, tigecycline is centrally approved for clinical use for the treatment of complicated SSTIs and complicated IAI.</p> <p>Glycylicyclines fulfil criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	Although glycylicyclines evade many resistance mechanisms encoded by plasmid-borne <i>tet</i> genes, in Gram-negative bacteria, clinical resistance is still mostly associated with overexpression of chromosomally-encoded RND multidrug

	<p>efflux pumps [413]. In addition, acquired resistance determinants include mutants of <i>Tet(A)</i>, or increased expression of <i>Tet(L)</i> and <i>Tet(M)</i>. <i>tet(X)</i> which encodes a tigeicycline-modifying enzyme, have recently been identified in Enterobacterales and <i>Acinetobacter</i> from food, animals and humans [413-415]. Over-expression of efflux pumps may also decrease activity against <i>Staphylococcus aureus</i> [416].</p> <p>The prevalence of resistance to tigeicycline in human isolates remains very low, although higher levels were reported in European carbapenem-resistant Enterobacterales [417] or in cephalosporin-resistant Enterobacterales in France [418].</p> <p>Very low levels of tigeicycline resistance have been reported in EFSA/ECDC EU surveillance of <i>Salmonella</i> spp. From food-producing animals [26, 295] and there are sporadic reports of resistance in Enterobacterales isolates from companion animals, in particular associated with clones of <i>Klebsiella pneumoniae</i> of concern to public health [419, 420].</p> <p>Transmission</p> <p>In conclusion, although glycylyclines are not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if their use in animals became established [413].</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>There is no knowledge of the authorisation of glycylyclines in VMPs in the EU or globally. They are not included in the Annex to the MRL Regulation (EU) 37/2010 and therefore cannot be used to treat food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>There is very limited evidence for use or need for tigeicycline in cats and dogs to treat MDR infections e.g. MRSA/P [413]; hence such use is expected to be very rare. In the absence of more specific evidence, alternatives cannot be proposed.</p> <p>Based on the low number of reports it appears that impacts of inappropriate treatment on morbidity and mortality would be very limited.</p> <p>In conclusion, considering the public health interest identified from criteria A and B, criterion C.1.(c) is met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: Yes	

Table 38. Evaluation of minocycline

<p>Minocycline See Table 103 for ATC(vet) codes</p>	
Criterion A met: No	<p>Minocycline is considered as a second-generation tetracycline (as doxycycline). This generation is characterised by longer serum half-life, high lipid solubility and enhanced activity against some pathogens [421]. Minocycline has a bacteriostatic effect based on inhibition of protein synthesis.</p> <p>Minocycline has a spectrum of activity that is largely similar to that of the tetracyclines. It is reported to be effective in vitro against some tetracycline-resistant <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., and certain strains of tetracycline-resistant <i>E. coli</i> and <i>Haemophilus influenzae</i>. It is active against a variety of intracellular microorganisms, including <i>Mycoplasma pneumoniae</i>, <i>Ureaplasma urealyticum</i>, <i>Chlamydia trachomatis</i>, <i>Chlamydophila psittaci</i>, and <i>Chlamydophila pneumoniae</i> [422].</p> <p>Minocycline is indicated for the treatment of the following infections: gonorrhoea, non-gonococcal urethritis, prostatitis, moderate to severe acne (use in moderate acne only if topical treatment is ineffective, if acne is extensive or hard to reach and if there is a high risk of scarring), acute and chronic bronchitis, bronchiectasis, lung abscess, pneumonia, ear, nose and throat infections, UTIs, pelvic inflammatory disease (e.g., salpingitis, oophoritis), SSTIs caused by minocycline sensitive organisms, ophthalmic infections, nocardiosis, prophylactic treatment of asymptomatic meningococcal carriers, pre- and post-operative prophylaxis of infection. It is a potential option for the treatment of infections caused by certain strains of MRSA and MDR <i>Acinetobacter baumannii</i>, although notably used in combination with other classes of antimicrobials (e.g., carbapenems) [422].</p> <p>Alternative and safer options are available.</p> <p>Data on minocycline resistance in human isolates are not included in the Annual EARS-Net report.</p> <p>Minocycline is nationally authorised in some of the EU member states for indications that include ear, nose and throat infections, RTIs such as pneumonia, bronchiectasis, lung abscess, acute and chronic bronchitis, prostatitis, venereal diseases (gonorrhoea), UTIs, pelvic inflammatory disease (salpingitis, oophoritis), SSTIs, ophthalmological infections, nocardiosis, prophylactic treatment of asymptomatic meningococcal carriers, preventative treatment before and after surgery, actinomycosis, anthrax patients, with a penicillin allergy.</p>

	Minocycline does not fulfil criterion A as sufficient effective or safer alternative options exist for the treatment of the presented serious infections.
Recommended to be designated as an antimicrobial to be reserved for humans: No	

Table 39. Evaluation of eravacycline (fluorocycline)

Eravacycline (fluorocycline) See Table 103 for ATC(vet) codes	
Criterion A met: Yes	<p>Eravacycline is a fully synthetic fluorocycline and newly approved tetracycline derivative. The mechanism of action of eravacycline involves the disruption of bacterial protein synthesis by binding to the 30S ribosomal subunit, thus preventing the incorporation of amino acid residues into elongating peptide chains [423].</p> <p>Eravacycline exhibits good activity against anaerobes, Gram-positive bacteria (including MRSA and VRE), Gram-negative bacteria (e.g., Enterobacterales and <i>Acinetobacter baumannii</i>), and those producing ESBLs, carbapenemases or carrying the <i>mcr-1</i> gene. It has limited activity against <i>Pseudomonas aeruginosa</i> [423].</p> <p>In the context of the growing health burden of infections caused by MDR bacteria, eravacycline fills a therapeutic gap, being one of few broad-spectrum antibiotics available to treat polymicrobial infections, e.g., cIAIs, complicated UTIs, and overcoming resistance to several antibiotic classes [423].</p> <p>Alternative broad-spectrum antibiotics used to treat infections with MDR bacteria include ceftobiprole and ceftaroline (for MRSA), oxazolidinones and daptomycin (for VRE) and new antibiotics and combinations with beta-lactamase inhibitors such as ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam and cefiderocol, as well as colistin and fosfomycin (in combination) for MDR Gram-negatives [49, 157, 160, 167].</p> <p>MRSA infections and infections caused by carbapenem-resistant Gram-negative bacteria are an important health burden to the EU/EEA (see above). VRE was estimated to cause >16,000 infections and to be associated with >1,000 deaths in the EU/EEA in 2015 [153].</p> <p>Eravacycline is centrally authorised in the EU/EEA for the treatment of cIAIs in adults.</p> <p>Eravacycline fulfils criterion A.1.(a) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>As for tigecycline, eravacycline remains vulnerable to upregulated non-specific intrinsic multidrug efflux pumps found in Gram-negative bacteria and monooxygenase enzymes mediated by <i>tet(X)</i> genes that confer resistance to all tetracyclines and tigecycline. As noted for glycylicyclines, <i>tet(X)</i> have been identified on a highly transferable plasmid in Enterobacterales and <i>Acinetobacter</i> spp. from food, animals and humans, hence there are concerns that there could be rapid dissemination of resistance [413, 414, 424].</p> <p>In addition, resistance to eravacycline has been observed in human isolates of <i>Enterococcus</i> spp. due to mutations in the ribosomal binding site [425].</p> <p>There is no EU-coordinated specific surveillance for eravacycline susceptibility in animal isolates.</p> <p>Transmission</p> <p>There are potential pathways for transmission of resistance to eravacycline from food-producing and companion animals to humans (see Table 37, Glycylicyclines).</p> <p>Although eravacycline is not authorised in VMPs, there is evidence for the potential for selection and likely significant transmission of resistance from animals to humans, through zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens, if use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Eravacycline has not been authorised for use in VMPs in the EU and there is no knowledge of its veterinary authorisation globally. Eravacycline is not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>No evidence was found for use in companion animals outside the terms of the marketing authorisation, or specific need for eravacycline, to treat serious infections in animals in the EU at the present time. Where tetracyclines are specifically indicated in veterinary medicine (e.g. vector-borne diseases), earlier generation substances are currently judged to be adequate.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial to be reserved for humans: Yes	

Table 40. Evaluation of omadacycline

Omadacycline See Table 103 for ATC(vet) codes	
Criterion A met: Yes	<p>Omadacycline is a semisynthetic tetracycline derivative and displays the same mechanism of action as the tetracycline class, inhibiting bacterial protein synthesis by binding to the primary tetracycline binding site on the 30S subunit of the bacterial ribosome [426].</p> <p>It is active against several types of resistant Gram-positive pathogens, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA); penicillin-resistant and multidrug-resistant <i>Streptococcus pneumoniae</i>, <i>Streptococcus pyogenes</i>, and <i>Streptococcus agalactiae</i>; and vancomycin-resistant <i>Enterococcus</i> (VRE) spp. It is also active against pathogens that are important in community-acquired respiratory tract infections, including <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>, and species of <i>Legionella</i>, <i>Chlamydia</i> and <i>Mycoplasma</i> spp. [426].</p> <p>Omadacycline is developed as a once-daily, intravenous and oral treatment for acute bacterial skin and skin structure infection and CAP. Omadacycline is currently approved by the FDA for use in treatment of acute bacterial skin and skin structure infection and community-acquired bacterial pneumonia [427-429].</p> <p>No alternatives considered due to lack of marketing authorisation.</p> <p>In October 2019, an application was withdrawn for a marketing authorisation in the EU for omadacycline for treatment of community-acquired bacterial pneumonia and bacterial infections of the skin and skin structures. The EMA/CHMP considered that the single clinical study in patients with CAP did not provide sufficient evidence of effectiveness.</p> <p>If authorised in future for the use in the EU, omadacycline would fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: Yes	<p>As for tigecycline, omadacycline remains vulnerable to upregulated non-specific intrinsic multidrug efflux pumps found in Gram-negative bacteria and monoxygenase enzymes mediated by <i>tet(X)</i> genes that confer resistance to all tetracyclines and tigecycline. As noted above, <i>tet(X)</i> have been identified on a highly transferable plasmid in Enterobacteriales and <i>Acinetobacter</i> spp. From food, animals and humans, hence there are concerns that there could be rapid dissemination of resistance. Resistance [413, 414, 424].</p> <p>There is no EU-coordinated specific surveillance for omadacycline susceptibility in animal isolates.</p> <p>Transmission</p> <p>There are potential pathways for transmission of resistance to omadacycline from food-producing and companion animals to humans (see Table 37, Glycylcyclines).</p> <p>Although omadacycline is not authorised in VMPs, there is evidence for the potential for selection and likely significant transfer of resistance from animals to humans, through zoonotic pathogens or commensals capable of transferring resistance to human pathogens, if use in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: Yes	<p>Omadacycline has not been authorised for use in VMPs in the EU and there is no knowledge of its veterinary authorisation globally. Omadacycline is not included in the Annex to the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>No evidence was found for use in companion animals outside the terms of the marketing authorisation, or specific need for omadacycline, to treat serious infections in animals in the EU at the present time. Where tetracyclines are specifically indicated in veterinary medicine (e.g. vector-borne diseases), earlier generation substances are currently judged to be adequate.</p> <p>Criterion C.1(a) is met.</p>
Recommended to be designated as an antimicrobial to be reserved for humans: Yes	

Table 41. Evaluation of amphenicols

Amphenicols See Table 105 for ATC(vet) codes	
Criterion A met: No	<p>Amphenicols are a class of broad-spectrum antibiotics that include thiamphenicol and chloramphenicol. Thiamphenicol is a chloramphenicol analogue and has limited use in human medicine. Therefore, the information provided in this section concerns primarily chloramphenicol. Chloramphenicol inhibits protein synthesis by reversibly binding to the peptidyl transferase cavity of the 50S subunit of the bacterial 70S ribosome. This prevents the aminoacyl-tRNA from binding to the ribosome, thus terminating polypeptide chain synthesis.</p> <p>Chloramphenicol is effective against a wide range of aerobic and anaerobic bacteria, including Gram-positive (e.g., <i>Staphylococcus aureus</i>, <i>Staphylococcus epidermidis</i>, <i>Streptococcus pyogenes</i>, <i>S. pneumoniae</i>, alpha-haemolytic</p>

	<p><i>streptococci</i>, <i>Enterococcus faecalis</i>) and Gram-negative bacteria (<i>Bacteroides fragilis</i>, <i>Neisseria</i>-meningococci and gonococci, <i>Haemophilus</i> spp., <i>Salmonella typhi</i>) [430].</p> <p>Chloramphenicol was the first broad-spectrum antibiotic and has been in clinical use since 1949 [430]. Currently it is no longer the antibiotic of choice for any specific infection and is not frequently used due to serious adverse effects (e.g., bone marrow toxicity). Chloramphenicol can be used for bacterial conjunctivitis (topical formulation), typhoid fever, meningitis (specifically in countries where access to recommended 3rd-generation cephalosporines is limited) or <i>S. aureus</i> infections (including VRSA) [430].</p> <p>It is recommended by the WHO as an option for the treatment of meningitis, meningococcal sepsis, osteoarthritis, and pyomyositis in children in low-income countries, and is included on their model list of essential medicines [431].</p> <p>There are alternative treatment options considered first choice such as fluoroquinolones to treat typhoid fever and conjunctivitis or 3rd-generation cephalosporines to treat meningitis and penicillinase-resistant penicillins and glycopeptides for <i>S. aureus</i> infections [430].</p> <p>Chloramphenicol is nationally approved in some of the EU Member States for the treatment of typhoid, meningitis caused by <i>H. influenzae</i> and of other serious infections; eyedrops are approved for the treatment of acute bacterial conjunctivitis.</p> <p>Amphenicols (chloramphenicol) do not fulfil criterion A, due to limited use in human medicine in the EU and due to the existence of other, safer treatment alternatives to manage above-mentioned infections.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 42. Evaluation of sulfonamides

<p>Sulfonamides See Table 106 for ATC(vet) codes</p>	
Criterion A met: No	<p>Sulfonamides (sulfamethoxazole, sulfamethizole, sulfadiazine) are synthetic antibacterials that contain the sulfonamide chemical group. They are bacteriostatic and work by interfering with the synthesis of folic acid (an essential component for DNA and RNA formation). Combinations with trimethoprim are bactericidal. Originally, sulfonamides had a broad spectrum of activity, but due to increasing resistance their use is limited [432]. The therapeutic role of sulfonamides is diminishing, however several agents from this class are used in combination with other agents (e.g., with trimethoprim).</p> <p>Sulfonamides show activity against Gram-positive (e.g., <i>Staphylococcus aureus</i>, <i>S. saprophyticus</i>, <i>Streptococcus pyogenes</i>, <i>S. pneumoniae</i>, <i>Bacillus anthracis</i>, <i>Clostridium tetani</i>, <i>C. perfringens</i>) and Gram-negative (Enterobacteriales, <i>Neisseria</i>, <i>Brucella</i>), <i>Actinomyces</i>, <i>Nocardia</i>, <i>Chlamydia</i>, <i>Plasmodium</i> and <i>Toxoplasma</i> spp. [432].</p> <p>Sulfonamides alone have been used to treat uncomplicated UTIs. Nowadays, their clinical use is diminishing due to emerging spread of resistance. Their importance is when used in combination with trimethoprim (evaluated separately). Topical argentic sulfadiazine is used for wound infections [432].</p> <p>There are several alternative options to treat UTIs.</p> <p>Data from a multi-country European study including France, Germany, Spain, Sweden, and the United Kingdom, showed that <i>E. coli</i> isolates from women with acute uncomplicated UTIs have increasing antimicrobial resistance. It was shown that since 2000, compared with 2014, there has been a significant increase in resistance to trimethoprim in Germany (23% to 37%), Spain (25% to 37%), Sweden (9% to 17%), and the UK (13% to 46%) [95].</p> <p>Sulfonamides are approved nationally in the EU. Since they were first approved a long time ago, some of them have authorised indications that need to be modernized, but in general they are approved in adults and children over 2 months of age, in the prevention and treatment of infections as part of the management of burns from the 2nd degree.</p> <p>Sulfonamides do not fulfil criterion A, as there are treatment alternatives.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 43. Evaluation of trimethoprim and derivates

<p>Trimethoprim and derivates See Table 106 for ATC(vet) codes</p>	
Criterion A met: No	<p>Trimethoprim (TMP) inhibits the action of dihydrofolate reductase (DHFR), an enzyme that catalyses the last step of folic acid synthesis, and ultimately, DNA synthesis. TMP has a broad-spectrum bacteriostatic activity [433].</p>

	<p>TMP is active against a range of bacterial species including Gram-positive (<i>Streptococcus</i>, <i>Staphylococcus</i>, <i>Corynebacterium</i>, <i>Listeria monocytogenes</i>) and Gram-negative bacteria (<i>E. coli</i>, <i>Enterobacter</i>, <i>Klebsiella</i>, <i>Proteus</i>, <i>Salmonella</i>, <i>Shigella</i>, <i>Providencia</i>, <i>Citrobacter</i>, <i>Hafnia</i>, <i>Edwardsiella</i>, <i>Serratia</i>, <i>Haemophilus influenzae</i>) [433].</p> <p>TMP has been widely used to treat UTIs. Nowadays, due to emerging spread of TMP-resistant organisms, the importance of this antibiotic is diminishing. It is used in combination with sulfamethoxazole (see Table 44).</p> <p>There are several alternative options to treat UTIs.</p> <p>Data from a multi-country European study including France, Germany, Spain, Sweden, and the UK, showed that <i>E. coli</i> isolates from women with acute uncomplicated UTIs have increasing antimicrobial resistance. It was shown that since 2000, compared to 2014, there has been a significant increase in resistance to trimethoprim in Germany (23% to 37%), Spain (25% to 37%), Sweden (9% to 17%), and the UK (13% to 46%) [95].</p> <p>TMP is nationally approved in the EU Member States. Approved indications include treatment of infections caused by trimethoprim-sensitive organisms including urinary and respiratory tract infections. TMP is also approved for the prophylaxis of recurrent UTIs.</p> <p>TMP does not fulfil criterion A, as there are other treatment alternatives.</p>
Recommended to be designated as an antimicrobial to be reserved for humans: No	

Table 44. Evaluation of sulfonamide-trimethoprim derivative combinations

Sulfonamide-trimethoprim derivative combinations See Table 106 for ATC(vet) codes	
Criterion A met: Yes	<p>Trimethoprim-sulfamethoxazole also known as co-trimoxazole, is a combination of two antimicrobial agents (sulfamethoxazole-SMX and trimethoprim-TMP) that act synergistically against a wide variety of bacteria. While TMP and SMX are weak bactericidal agents when given alone, the combination is highly bactericidal against many bacteria. Although other combinations of sulfonamides are available with trimethoprim, co-trimoxazole is by far the most widely used [434].</p> <p>Co-trimoxazole is effective against a wide variety of aerobic Gram-positive (<i>Staphylococcus</i> spp., including MRSA) and Gram-negative (e.g., Enterobacterales) bacteria. It is also active against certain nosocomial acquired and/or infections seen in immunocompromised patients (e.g., <i>Burkholderia cepacia</i> (formerly <i>Pseudomonas cepacia</i>), <i>Stenotrophomonas maltophilia</i> (formerly <i>Xanthomonas maltophilia</i>), <i>Serratia marcescens</i>, and <i>Nocardia</i> spp.) Co-trimoxazole also has an activity against fungi e.g., <i>Pneumocystis jirovecii</i> (Table 64).</p> <p>Co-trimoxazole is a treatment of choice for <i>P. jirovecii</i> pneumonia (PjP) which is a potentially life-threatening infection that occurs in immunocompromised individuals [434]. Co-trimoxazole is further among first choice agents for the treatment of MRSA infections, particularly those community acquired. Most importantly co-trimoxazole is a recommended treatment for nocardiosis [435]. Co-trimoxazole is the only available alternative against MDR <i>S. maltophilia</i> and <i>B. cepacia</i>.</p> <p>Alternative treatment options include (1) PjP: for patients with moderate-to-severe disease: pentamidine/ primaquine plus clindamycin; for patients with mild-to-moderate disease dapsone plus trimethoprim, primaquine plus clindamycin or atovaquone; (2) MRSA acute bacterial skin and skin structure infections: clindamycin, doxycycline, minocycline, linezolid, for complicated cases vancomycin, linezolid, daptomycin, telavancin; (3) Nocardiosis: imipenem or meropenem, ceftriaxone, cefotaxime, amikacin, linezolid [434, 435].</p> <p>PjP is a well-known opportunistic infection affecting immunocompromised patients. The European data about the epidemiology of pneumocystis pneumonia (PCP) are scarce, although a recent study from Spain showed 4,554 cases of PCP were reported, 1,204 (26.4%) in HIV-negative patients. During the study period (2008-2012), mean annual incidence (cases per million) was 19.4, remaining globally stable, increasing from 4.4 to 6.3 in HIV-negative patients and decreasing from 15.5 to 13.4 among HIV-infected patients [436].</p> <p>Co-trimoxazole is nationally approved in the EU member states. Among the approved indications are the following: treatment and prevention of PjP, treatment and prophylaxis of toxoplasmosis, treatment of nocardiosis. The following infections may be treated with co-trimoxazole where there is bacterial evidence of sensitivity to co-trimoxazole and good reason to prefer the combination of antibiotics in co-trimoxazole to a single antibiotic: acute uncomplicated UTIs, acute otitis media, acute exacerbation of chronic bronchitis.</p> <p>Co-trimoxazole fulfils the criterion A.1(b) by being essential component of limited treatment alternatives, specifically for life-threatening PjP in immunocompromised patients and nocardiosis in immunosuppressed patients.</p>
Criterion B met: Yes	<p>Both sulfonamides (S) and trimethoprim (TMP) affect bacterial folic acid synthesis. Sulfonamides inhibit dihydropteroate synthetase (DHPS), which catalyses the formation of dihydrofolate from para-aminobenzoic acid. In the subsequent step of the pathway, TMP inhibits dihydrofolate reductase (DHFR), which catalyses the formation of tetrahydrofolate from dihydrofolate. Bacterial resistance to TMP and to sulfonamides is mediated by the following 5 main mechanisms: (1) changes to the permeability barrier and/or efflux pumps, (2) naturally insensitive target enzymes, (3) regulational changes in the target enzymes, (4) mutational or recombinational changes in the target enzymes, and (5) acquired resistance by drug-resistant target enzymes [437].</p> <p>Resistance to TMPS can be chromosomal or the resistance genes can be located on MGE e.g. plasmids or transposons. Resistance in Gram-negative bacteria is mainly conferred by acquisition of <i>sul</i> genes and/or <i>dfr</i> genes [433]. Resistance in staphylococci to TMP is based on several <i>dfr</i> genes [243].</p>

	<p>The resistance mechanisms in <i>P. jirovecii</i> have not been fully elucidated, but genetic mutations within DHFR probably play a role [438]. The majority of patients with PCP and DHPS mutations who are treated with trimethoprim-sulfamethoxazole respond to this treatment, however, patients with DHPS mutations who are treated with trimethoprim-sulfamethoxazole tend to have worse outcomes compared with those with wild-type DHPS [438].</p> <p>The mechanisms of resistance in <i>Nocardia</i> spp. are not fully understood, but <i>sul</i> and <i>dfrA</i> genes play a role [433].</p> <p><i>Sul1</i> genes and <i>dfrA</i> genes are part of class1 integrons. MDR in Enterobacterales, particularly among isolates with ESBLs, is likely to be a result of the coexisting nature of <i>sul1</i> and <i>sul2</i>, <i>dfr</i> genes encoded within ESBL and carbapenemase-encoding plasmids (Grayson et al., 2018). Class 1 and 3 integrons carrying <i>sul</i> genes have been found in <i>Nocardia</i> spp. [439].</p> <p><i>Sul</i> and <i>dfr</i> genes have been detected in Enterobacterales from humans, food-producing and companion animals [243, 440]. The <i>dfrK</i> gene (linked to <i>tetL</i>) is widely disseminated on plasmids in LA-MRSA from food-producing species and has also been identified on a transposon in MSSA and <i>E. faecium</i> [23].</p> <p>In <i>Salmonella</i> spp. and indicator <i>E. coli</i> isolates recovered from animals and food during the 2018–2019 routine EU monitoring, resistance to sulfonamides was generally high to very high. Resistance to TMP is at a lower level [26]. In LA-MRSA, extremely high levels of TMP resistance were detected in isolates from pigs [26], although the number of isolates tested is small.</p> <p><i>Pneumocystis</i> spp. cannot be cultured. No EU monitoring of resistance in animals exists.</p> <p>Transmission</p> <p>Similar <i>sul</i> and <i>dfr</i> genes have been detected in Enterobacterales from food-producing and companion animals and humans [243, 440, 441]. <i>Sul</i> and <i>dfr</i> resistance genes are located on MGEs that have the potential to be transferred from animal commensal bacteria to pathogenic bacteria in humans (See annotation 2 under Table 61). There is also the possibility for transmission of TMPS-resistance from animals to humans via zoonotic pathogens, e.g. LA-MRSA (See annotation 3 under Table 61).</p> <p>The genus <i>Pneumocystis</i> is host-species specific and there is no evidence to support potential transfer of TMPS-resistance from animals to humans [438]. See also Table 63. <i>Nocardia</i> spp. are ubiquitous environmental saprophytes and are transmitted by inhalation, ingestion or inoculation through the skin [442]. Integrons carrying resistance genes could potentially be transmitted between different bacterial species. Although several references report <i>Nocardia</i> spp. as a potential zoonosis, there is no clear evidence supporting direct transmission from animals to humans [443].</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to sulfonamides and trimethoprim from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>Sulfonamide-trimethoprim combinations (TMPS) are authorised in VMPs in the EU for a wide range of infections in food-producing and companion animals and are one of few classes authorised for use in minor species including turkeys, goats, rabbits, fish and children’s pets.</p> <p>All substances belonging to the sulfonamide group and trimethoprim are included in Table 1 of the MRL Regulation (EU) 37/2010 and they may be used in all food-producing species (except those producing eggs for human consumption).</p> <p>All species</p> <p>The importance of TMPS combinations lies in their use as a first-line antibiotics for numerous potentially serious Gram-positive and Gram-negative infections of respiratory, gastrointestinal and urogenital tracts and SSTI including bovine interdigital necrobacillosis [84, 226, 444, 445]. They have an advantage compared with other first-line antibiotics used in horses because of the good safety profile and possibility for oral administration [84]. TMPS is the only authorised antibiotic for oral administration for horses in the EU. TMPS are one of few antibiotic classes authorised in the EU for use in fish, being important for treatment of e.g. <i>Aeromonas</i> spp., <i>Vibrio</i> spp., <i>Yersinia ruckerii</i>, <i>Streptococcus</i> [446]. However, use of TMPS is limited by high levels of resistance to common pathogens, particularly <i>E. coli</i> [41, 75, 86, 88, 142, 392] (See annotation 1 under Table 61) and the sulfonamide component has the potential to cause adverse effects if long treatment courses are required [445]. Depending on the animal species and susceptibility of the target pathogen under treatment, alternatives are often from a higher AMEG category.</p> <p>TMPS are also important as one of limited options for treatment of less common infections e.g. <i>Nocardia</i> spp. and certain protozoal infections e.g. toxoplasmosis, Equine Protozoal Myeloencephalitis (imported cases), Neospora [345] (Antiprotozoals are primarily addressed in Table 65). In addition, MRSA isolated from companion animals may remain susceptible to TMPS [281].</p> <p>In conclusion, sulfonamide-trimethoprim combinations are widely used as first-line antimicrobials to treat serious life-threatening infections with significant morbidity or mortality in food-producing and companion animal species. Alternatives are commonly in a higher AMEG category.</p> <p>Criterion C is not met.</p>
<p>Recommended to be designated as an antimicrobial class to be reserved for humans: No</p>	

Table 45. Evaluation of quinolones (non-fluorinated)

Quinolones (non-fluorinated) See Table 107 for ATC(vet) codes	
Criterion A met: No	<p>Non-fluorinated quinolones act by inhibiting the activity of two essential bacterial enzymes that modulate the chromosomal supercoiling required for critical nucleic acid processes (DNA gyrase and topoisomerase IV) therefore inhibiting bacterial DNA synthesis.</p> <p>Non-fluorinated quinolones (e.g., nalidixic acid) have activity against aerobic, Gram-negative bacteria. However, they are not very active against aerobic, Gram-positive bacteria or anaerobic bacteria [447].</p> <p>Non-fluorinated quinolones have been used historically to treat uncomplicated UTIs and are not recommended for use in patients with poor renal function because of significantly decreased urine concentrations [448]. They have had limited use due to short serum and tissue half-lives as result of rapid renal elimination.</p> <p>Newer quinolones (fluoroquinolones) can be an alternative treatment option.</p> <p>Data from a multi-country European study including France, Germany, Spain, Sweden, and the UK, showed that <i>E. coli</i> isolates from women with acute uncomplicated UTIs have increasing antimicrobial resistance. It was shown that since 2000, compared to 2014, there has been a significant increase in resistance to ciprofloxacin in Germany (2% to 21%), Spain (15% to 31%), Sweden (0% to 7%), and the UK (1% to 15) [95].</p> <p>EMA's Committee for Medicinal Products for Human Use (CHMP) endorsed the recommendations of EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and concluded that the marketing authorisations of medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended [449].</p> <p>Quinolones do not fulfil criterion A, as alternative treatment options are available.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 46. Evaluation of fluoroquinolones

Fluoroquinolones See Table 108 for ATC(vet) codes	
Criterion A met: Yes	<p>Fluoroquinolones are broad-spectrum antibiotics that directly inhibit bacterial DNA synthesis. With their widespread use, the antimicrobial resistance to fluoroquinolones has grown [450].</p> <p>Fluoroquinolones (norfloxacin, ciprofloxacin, levofloxacin, sparfloxacin, moxifloxacin) overall have activity against aerobic, enteric Gram-negative bacilli (e.g. Enterobacterales, including MDR <i>E. coli</i>, <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Salmonella</i> spp., <i>Shigella</i> spp. and <i>Campylobacter</i> spp.), many common respiratory pathogens (e.g., <i>Streptococcus pneumoniae</i> (including MDR strains), <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>). In addition, some fluoroquinolones are active against <i>Pseudomonas</i> species, some Gram-positive organisms (including MRSA), anaerobes, and have excellent activity in vitro against <i>Mycobacterium tuberculosis</i> [450]. The older fluoroquinolones (e.g., norfloxacin, ciprofloxacin) have high activity against Gram-negative bacteria and no activity against Gram-positives. Newer fluoroquinolones (e.g., levofloxacin, sparfloxacin, moxifloxacin) have enhanced activity against Gram-positive bacteria (<i>Streptococcus pneumoniae</i>, <i>Staphylococcus aureus</i> and <i>Enterococcus</i> species), as well as good activity against <i>Mycoplasma</i> and <i>Chlamydia</i>. The newest fluoroquinolones (e.g., moxifloxacin) have the most potent activity against anaerobic bacteria [451].</p> <p>The spectrum of activity and potency of fluoroquinolones has led to a wide range of clinical indications, including treatment of UTIs, RTIs, SSTIs, infectious diarrhoea, bone and joint infections and infections of the ear and eyes.</p> <p>Fluoroquinolones are used as second-line agents to treat TB in the context of resistance and/or intolerance to first-line agents, and similarly campylobacteriosis in HIV infection. Very relevant indications for which fluoroquinolones are first line are the post-exposure prophylaxis and the treatment of inhalational anthrax [366].</p> <p>For the above-mentioned life-threatening indications there are virtually no alternatives treatments. For other clinical indications there are alternatives as long as the pathogen is susceptible.</p> <p>In 2019, 29 countries in the European Union/European Economic Area (EU/EEA) reported a total of 49,752 TB cases (9.6 per 100,000 population). The overall TB notification rate in the EU/EEA continued to decline, as did most country-specific TB notification rates. However, the EU/EEA is not on track to reach the goal of ending the TB epidemic by 2030. MDR-TB was reported for 3.4% of TB cases with susceptibility testing results reported. XDR-TB was reported for 22.4% of MDR TB cases that underwent second-line substance susceptibility testing [452]. In 2019 795 cases of MDR-TB were reported in EU/EEA area [365].</p> <p>Most fluoroquinolones are nationally approved in the EU, except for delafloxacin, which is centrally approved. They are approved for a broad range of indications. EMA confirmed that the use of fluoroquinolones should be restricted to cases when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of the infections for which they are indicated (in particular in view of the risk of disabling sequelae) risk of serious adverse effects involving the musculoskeletal and nervous system).</p>

	<p>Fluoroquinolones fulfil criterion A1(b). They are essential components of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
<p>Criterion B met: Yes</p>	<p>In Enterobacterales, reduced susceptibility most commonly arises through stepwise chromosomal mutations in DNA gyrase and topoisomerase IV, with multiple mutations resulting in clinical resistance. Nevertheless, plasmid-mediated quinolone resistance genes (PMQR) (<i>qnr oqxAB</i>, <i>aac(6′)-Ib-cr</i>, <i>qep</i> and <i>crpP</i> genes) are increasing, with several reports of the isolation of quinolone-resistant microorganisms in the absence of target mutations, including in a <i>Salmonella</i> Rissen isolate [453]. The PMQR <i>aac(6′)-Ib-cr</i> gene also confer decrease susceptibility to aminoglycosides (kanamycin, tobramycin, and amikacin) [454] and <i>oqxAB</i> to antimicrobials, disinfectants and detergents [455].</p> <p>PMQR genes (mainly <i>qnr</i> genes) have been identified in isolates from food-producing and companion animals in the EU [61, 456, 457]. However, studies in companion animals have shown resistance in Enterobacterales isolates mostly associated with chromosomal mutations in quinolone resistance-determining region (<i>gyrA</i>, <i>parC</i>, <i>parE</i>) [456, 458].</p> <p>Co-selection of resistance to other antimicrobials might occur due to the frequent location of PMQR on plasmids carrying resistance genes to other antimicrobials.</p> <p>In <i>Campylobacter</i> spp., a single mutation in <i>gyrA</i> imparts high-level resistance to fluoroquinolones. The CmeABC efflux pump also contributes significantly to fluoroquinolone resistance in <i>Campylobacter jejuni</i>. Fluoroquinolone resistance develops rapidly in <i>Campylobacter</i> spp. in poultry following exposure [459].</p> <p>Resistance in <i>Pseudomonas</i> spp. is due to decreased permeability, over-expression of efflux pumps and mutations in topoisomerases which have been detected in isolates from dogs [460].</p> <p>Evidence for the selection and spread of resistance to fluoroquinolones due to the use of these antimicrobials in food-producing animals are available [133, 453].</p> <p>ECDC/EFSa mandatory surveillance shows very high levels of resistance to fluoroquinolones in <i>Salmonella</i> spp. from humans and poultry, <i>E. coli</i> from poultry and in <i>Campylobacter</i> from humans and food-producing animals [26].</p> <p>Transmission</p> <p>In the EU, non-typhoidal <i>Salmonella</i> and <i>Campylobacter</i> spp. infections in humans are predominantly foodborne. A significant association has been shown between fluoroquinolone-resistance in <i>C. jejuni</i> isolates from poultry and from humans [56].</p> <p>Epidemiological studies have shown similarity between fluoroquinolone-resistant <i>E. coli</i>, fluoroquinolone-resistant <i>Salmonella</i> and <i>Campylobacter</i> spp. isolates from humans and chickens [61, 62, 461, 462].</p> <p>There is also evidence for association between several PMQR carrying isolates and food-producing animals [453].</p> <p>Fluoroquinolone-resistant MDR <i>E. coli</i> of the ST131 clone of importance in human medicine has been isolated in dogs [463].</p> <p>In conclusion, there is evidence for the selection and significant transmission of resistance to fluoroquinolones from animals to humans via zoonotic pathogens or commensal bacteria capable of transferring resistance to human pathogens.</p> <p>Criterion B.1.(a) is met.</p>
<p>Criterion C met: No</p>	<p>Fluoroquinolones are authorised in VMPs in the EU for use in a wide range of food-producing and companion animal species, for local and systemic administration, for indications including gastrointestinal, respiratory and urogenital infections and septicaemia. SPC recommendations are for use to be restricted to infections that have, or are expected to, respond poorly to other antibiotic classes, and preferably based on susceptibility testing. Enrofloxacin is one of few antibiotics authorised for use in exotic species. Several fluoroquinolones are included in Table 1 of the MRL Regulation (EU) 37/2010 and they can be used in all food-producing animals in the EU, except poultry laying eggs for human consumption.</p> <p>Food-producing species</p> <p>Fluoroquinolones are among few alternatives for treatment of diarrhoeas in piglets (<i>E. coli</i>) and sepsis caused by Enterobacterales in various animal species, when these infections are resistant to antibiotics from lower AMEG categories. <i>E. coli</i> infections (e.g. septicaemia, meningitis, severe enteritis) are a major cause of morbidity and mortality in neonatal and juvenile livestock, and the most common cause of peracute mastitis leading to bacteraemia and fatality in adult cattle [39, 137-141]. Recent EFSA opinions noted high levels of resistance to first line antimicrobials (e.g. aminopenicillins, potentiated sulfonamides, tetracyclines), often involving multidrug resistance, in pathogenic <i>E. coli</i> from swine, poultry, calves, lambs and horses. This suggests the limited efficacy of first-line antibiotics against these infections in many EU countries [41, 86, 88, 142, 392] (See annotation 1 under Table 61). Levels of resistance to fluoroquinolones have remained lower. Alternatives for resistant <i>E. coli</i> are limited to AMEG Category B substances: colistin (not foals) or 3rd- and 4th-generation cephalosporins (not poultry) or, depending on patient/disease suitability, aminoglycosides (Category C).</p> <p>Fluoroquinolones are also important for treatment of <i>Mycoplasma bovis</i>, a cause of mastitis, arthritis and a frequent and challenging cause of enzootic pneumonia with potentially high morbidity/mortality in young calves. <i>M. bovis</i> is often resistant to tetracyclines and macrolides with alternatives otherwise being limited to florfenicol [41, 338, 339, 464] (See annotation 1 under Table 61).</p> <p>Companion animals</p>

	<p>In cats and dogs, fluoroquinolones are considered essential for treatment of life-threatening infections e.g. pyelonephritis, sepsis, acute pneumonia, and infections resistant to first-line agents [226]. They are recommended in international and EU treatment guidelines for respiratory infections due to <i>Pseudomonas aeruginosa</i> and empirical treatment of pneumonia accompanied by sepsis and pyothorax, whilst awaiting AST results [76, 83].</p> <p>UTI in dogs and cats are increasingly associated with pathogens resistant to first-line antibiotics [80, 143, 144, 465]. According to ISCAID guidelines, fluoroquinolones may be one of limited options for pyelonephritis, often due to Enterobacterales, a disease requiring prompt empirical treatment. 3rd-generation cephalosporins are the alternative [80]. In the case of severe sepsis, early treatment with a broad-spectrum bactericidal antimicrobial is critical for survival and fluoroquinolones are recommended alone or in combination. Alternatives include combinations of e.g. aminopenicillins, clindamycin, or for septicaemias caused by MDR Gram-negative bacteria, aminoglycosides, although the latter are limited by nephrotoxicity [84, 345, 466]. EFSA has noted high levels of resistance to aminopenicillins, 3rd-generation cephalosporins and fluoroquinolones in <i>E. coli</i> isolates from dogs and cats [75] (See annotation 1 under Table 61), supporting that a range of antibiotic classes should be available for their treatment.</p> <p>In conclusion, fluoroquinolones are used in food-producing and companion animal species to treat serious life-threatening infections with significant morbidity or mortality, in particular when there are no alternatives from a lower AMEG category. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 47. Evaluation of nitrofurans derivatives

<p>Nitrofurans derivatives See Table 109 for ATC(vet) codes</p>	
<p>Criterion A met: No</p>	<p>The most important members of the nitrofurans class with respect to the use in humans include nitrofurantoin, furazolidone and nitrofurazone. Therefore, the information provided below concerns primarily these three substances [467].</p> <p>Nitrofurantoin is active against most Gram-negative bacilli, which commonly cause UTIs. Most strains of <i>E. coli</i> remain susceptible, but <i>Enterobacter</i>, <i>Citrobacter</i>, and <i>Klebsiella</i> species are either less or variably susceptible. Nitrofurantoin is also active against Gram-positive cocci that sometimes cause UTIs, such as <i>Enterococcus</i> spp., (including VRE) and <i>Staphylococcus</i> spp. [467]. Furazolidone is a component of combination therapy for <i>Helicobacter pylori</i> infections [468].</p> <p>Nitrofurans also have an activity against protozoal infections - giardiasis (for more information please see Table 65).</p> <p>Nitrofurantoin is one of the first choices of antibiotics for treating uncomplicated UTI in women, including treatment of UTIs with ESBL-producing Enterobacterales. Nitrofurazone has been mainly used for topical chemotherapy of wounds, burns, and skin infections, and for infection in skin grafts [467].</p> <p>There are several alternatives for treatment of uncomplicated UTIs (fosfomycin trometamol, co-trimoxazole, trimethoprim and beta-lactam antibiotics) as well as for bacillary dysentery (ciprofloxacin, pivmecillinam, ceftriaxone, azithromycin). Nitrofurantoin is one of a few alternatives to treat UTI caused by vancomycin resistant <i>Enterococcus faecium</i> [469].</p> <p>Data from a multi-country European study including France, Germany, Spain, Sweden, and the UK, showed that <i>E. coli</i> isolates from women with acute uncomplicated UTIs have increasing antimicrobial resistance. However, it was presented that only in the UK, resistance to nitrofurantoin in 2014 was significantly greater than that recorded in 2008 (0% to 5.6%) [95].</p> <p>Nitrofurantoin is nationally approved in some of the EU Member States [470]. The main indication is for the treatment of and prophylaxis against acute or recurrent, uncomplicated UTIs or pyelonephritis, either spontaneous or following surgical procedures. It is indicated in adults and children over 3 months of age.</p> <p>Nitrofurans do not fulfil criterion A, as other treatment alternatives are available.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 48. Evaluation of the antibiotic substances in the class of nitroimidazoles

<p>Nitroimidazoles See Table 110 for ATC(vet) codes</p>	
<p>Criterion A met: Yes</p>	<p>Nitroimidazoles is a class of broad-spectrum antimicrobial agents. Metronidazole is commonly used in clinical practice. Metronidazole diffuses into the organism, inhibits protein synthesis by interacting with DNA and causing a loss of helical DNA structure and strand breakage leading to cell death in susceptible organisms [471].</p> <p>Nitroimidazoles (e.g. metronidazole) are active against a broad array of anaerobic Gram-negative (e.g., <i>Bacteroides</i> spp., <i>Prevotella</i> spp., <i>Porphyromonas</i> spp., <i>Fusobacterium</i> spp., <i>Bilophila wadsworthia</i>, and</p>

	<p><i>Capnocytophaga</i>) and Gram-positive bacteria (e.g., <i>Clostridium</i> spp.), and microaerophilic bacteria (<i>Helicobacter pylori</i>) [472].</p> <p>Nitroimidazoles also have an activity against protozoa and parasites (<i>Trichomonas vaginalis</i>, <i>Entamoeba histolytica</i>, trypanosomiasis, giardiasis, <i>Balantidium coli</i> and <i>Blastocystis hominis</i>) (for more information please Table 65).</p> <p>Nitroimidazoles (e.g. metronidazole) are effective in management of a wide range of anaerobic infections such as bacterial vaginosis, septicaemia, endocarditis, bone and joint infections, central nervous system infections, RTIs, skin and skin-structure infections [473]. Metronidazole has been the antibiotic of choice for the treatment of <i>Bacteroides</i> infection and remains reliable for this use [473]. Metronidazole is widely used to treat a broad range of infections and it is considered first line therapy in the paediatric population for <i>Clostridioides difficile</i>. Metronidazole is widely used as a therapeutic agent for <i>Helicobacter pylori</i> infection in the human gut and is one of the few antibiotics - primarily as part of a combined treatment regimen (e.g., in combination with omeprazole, clarithromycin, and amoxicillin) and for intra-abdominal infections (in combination with fluoroquinolones) [473].</p> <p>Vancomycin and fidaxomicin are alternative treatment options to treat <i>C. difficile</i> infections.</p> <p>The estimated annual burden of healthcare associated <i>C. difficile</i> infections in EU/EEA, 2011–2012 was 152,905 cases and accounted for 8,382 deaths/year [350].</p> <p>Metronidazole is nationally approved in the EU member states. Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause. Metronidazole is active against a wide range of pathogenic microorganisms notably species of <i>Bacteroides</i>, <i>Fusobacteria</i>, <i>Clostridia</i>, <i>Eubacteria</i>, anaerobic cocci and <i>Gardnerella vaginalis</i>.</p> <p>Indications approved for Metronidazole include: the prevention of post-operative infections due to anaerobic bacteria, particularly species of <i>Bacteroides</i> and anaerobic streptococci; the treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated; bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or <i>Gardnerella vaginitis</i>); acute ulcerative gingivitis; anaerobically-infected leg ulcers and pressure sores; acute dental infections (e.g., acute pericoronitis and acute apical infections). Tinidazole is nationally approved in the EU member states.</p> <p>Nitroimidazoles fulfil criterion A.1.(b), based on being an essential component of treatment for serious, life-threatening infections.</p>
<p>Criterion B met: Yes</p>	<p>The mechanisms of nitroimidazole resistance are complex and have not been extensively studied. Mechanisms described include reduced rate of uptake, by efflux or by reducing the rate of metronidazole reductive activation. Increased efficiency of DNA repair provides an additional mechanism [474]. Resistance to nitroimidazoles can be mediated by <i>nim</i> genes, which encode nitro-imidazole-reductases responsible for antibiotic inactivation. <i>nim</i> genes can be located on the chromosome or on a plasmid [475].</p> <p><i>nim</i> genes have been described in a variety of anaerobic genera encompassing the four main groups of Gram-negative and Gram-positive bacilli and cocci (e.g. <i>Bacteroides</i> spp.) [475, 476].</p> <p><i>C. difficile</i> can harbour a plasmid-borne resistance capable of horizontal transfer [477].</p> <p><i>C. difficile</i> clones commonly associated with human diseases, such as ribotype 078 are found in food-producing, companion animals and humans (see Table 29).</p> <p>Resistance to nitroimidazoles is reported from human and food-producing and companion animal isolates worldwide, but generally at low levels [353, 475, 478-481] [482]. There is no routine monitoring of nitroimidazole susceptibility in animal isolates at EU level.</p> <p>Transmission</p> <p>There is evidence for the selection of resistance to nitroimidazoles in companion animal isolates and there is a transmission pathway for this resistance from animals to humans via zoonotic pathogens or commensal bacteria (e.g. <i>C. difficile</i> isolates) [356, 358, 483].</p> <p>As nitroimidazoles are prohibited from use in food-producing animals, resistance in isolates from these species is unrelated to current nitroimidazole use in the EU.</p> <p>Criterion B.1.(a) is met (limited evidence)</p>
<p>Criterion C met: No</p>	<p>Metronidazole is authorised in VMPs intended for use in companion animals within the EU, for treatment of infections of gastrointestinal and urogenital tracts, mouth, pharynx and skin caused by obligate anaerobes (e.g. <i>Clostridium</i> spp. and <i>Clostridioides difficile</i> spp.) Metronidazole and dimetridazole are included in Table 2 of the MRL Regulation (EU) 37/2010 and thus are prohibited from use in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>Nitroimidazoles are among few alternatives for treatment of anaerobic infections in non-food-producing animals. Metronidazole has good tissue penetration and rapid bactericidal activity against <i>Clostridium</i> spp., <i>Clostridioides difficile</i>, <i>Prevotella</i>, <i>Bacteroides</i> and <i>Fusobacterium</i> spp. and in companion animals (including non-food horses) is important for treatment of life-threatening sepsis, peritonitis, intra-abdominal abscesses (horses), pleuropneumonia, osteomyelitis and central nervous system (CNS) infections, and for gastrointestinal and periodontal infections [484-490]. Alternatives include aminopenicillin-BLIs, clindamycin (not horses), 3rd-generation cephalosporins, carbapenems, ticarcillin/tazobactam; however, depending on the nature of the infection, alternatives may have less favourable pharmacokinetics, lower activity against the target pathogen(s) due to intrinsic or acquired resistance, or derive from a higher AMEG category [491-496].</p>

	<p>Metronidazole is also important for treatment of protozoal infections (see Table 65).</p> <p>In conclusion, nitroimidazoles are used in companion animal species to treat serious life-threatening anaerobic infections with significant morbidity and mortality and for which there are no or limited alternatives of lower importance to human health. Criterion C is not met.</p>
<p>Recommended to be designated as an antimicrobial class to be reserved for humans: No</p>	

Table 49. Evaluation of rifamycins

Rifamycins See Table 111 for ATC(vet) codes	
<p>Criterion A met: Yes</p>	<p>Rifamycins are part of the ansamycins class of antibiotics, which also includes streptovaricins and geldanamycin. Rifamycins enter bacteria and form stable complexes with the beta-subunit of bacterial DNA-dependent RNA polymerase, while not affecting mammalian polymerase at therapeutic doses. The degree of antibacterial activity of rifamycins is related to the binding affinity to the beta-subunit of prokaryotic DNA-dependent RNA polymerase. This binding results in inactivation of the enzymes and inhibition of RNA synthesis, by preventing chain initiation [497].</p> <p>Rifamycins are broad-spectrum, concentration or time-dependent, bactericidal and/or bacteriostatic antibiotics, with activity against mycobacteria, Gram-positive as well as facultative anaerobic organisms. For example, rifampicin demonstrates bactericidal concentration-dependent activity against <i>Mycobacterium tuberculosis</i> [498], whereas rifampicin demonstrates bacteriostatic time-dependent activity against <i>Rhodococcus equi</i> [343].</p> <p>Rifamycins are used for a variety of serious and life-threatening infections; notably rifampicin (in combination) is used as an essential component of first-line therapy for mycobacterial infections: <i>Mycobacterium tuberculosis</i> (tuberculosis, TB), <i>M. leprae</i> (leprosy) and <i>M. avium</i> complex. Rifampicin is also used for prophylaxis against meningitis (<i>Neisseria meningitidis</i>) or in combination with other antibiotics to treat MRSA and other serious staphylococcal infections, as well as brucellosis. Other clinical uses of rifamycins in human medicine include the treatment for traveller's diarrhoea, <i>Clostridioides difficile</i> associated-diarrhoea, and infections caused by <i>R. equi</i>. <i>R. equi</i> is an opportunistic pathogen, mostly reported in HIV-infected patients, where the most common manifestation of infection is pneumonia, often with cavitation and bacteraemia [499].</p> <p>For treatment of invasive infections with <i>Staphylococcus</i> spp., alternatives include e.g. lipoglycopeptides, oxazolidinones, daptomycin. For treatment of zoonotic infections alternatives include e.g. fluoroquinolones, doxycycline, aminoglycosides. Alternative treatment options for TB are mentioned below (see Substances used solely to treat tuberculosis or other mycobacterial diseases entry, Table 50).</p> <p>Globally, mycobacterial infection in humans, especially TB, remain one of the most common infectious diseases. In the EU in 2018, 53,000 cases of TB were reported to ECDC. Although cases have declined across the EU, MDR/XDR-TB remains a public health threat in some eastern and central European countries. In 2018, there were approximately 1,000 MDR-TB cases reported to ECDC, of which 20% were XDR. It is estimated that in 2019, there were approximately 280 deaths due to MDR-TB and 100 deaths due to XDR-TB in the EU [500]. Treatment is lengthy, expensive and associated with poor outcomes.</p> <p>Rifampicin and rifabutin are approved in the EU either as monoagents or part of combination human medicinal products. Indications for these rifamycins include the treatment of serious infections caused by mycobacteria, both <i>M. tuberculosis</i> and <i>M. avium-intracellulare</i> complex and other atypical mycobacteria, according to WHO guidelines. They are also approved for prophylaxis against <i>M. avium-intracellulare</i> colonization in patients with acquired immunodeficiency syndrome (AIDS). Rifaximin is approved in the EU for the treatment of adult patients with traveller's diarrhoea caused by non-invasive intestinal pathogens.</p> <p>Rifamycins fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans such as mycobacterial infections.</p>
<p>Criterion B met: Yes</p>	<p>In mycobacteria, <i>Rhodococcus</i> spp. and staphylococci, rifamycin resistance develops quickly, predominantly from single-point mutations of the chromosomal <i>rpoB</i> gene, which alters the binding site on RNA polymerase. Therefore, rifamycins are most often used in combination with other antimicrobials, with the exception of rifaximin which is used in human and veterinary medicine as monotherapy [294, 501, 502]. Rifampicin-resistance associated with the <i>rpo</i> gene has been reported in LA-MRSA from pigs, MRSP from dogs and <i>R. equi</i> from horses [14, 503, 504]. Rifampicin resistance has also been detected at low levels in <i>M. bovis</i> from cattle and humans [503-507].</p> <p>Monitoring of MRSA under EFSA/ECDC surveillance is voluntary and data are provided by few member states. Most isolates are LA-MRSA. The prevalence of (LA)MRSA ranges from 0% to 100% depending on animal production type and country and prevalence of rifampicin resistance in these isolates is low [26]. Rifampicin resistance is also at low level in human clinical <i>Staphylococcus aureus</i>, including MRSA, from EU-wide surveillance [14].</p> <p>There is no established mandatory European-wide surveillance of AMR in mycobacterial infections in either companion or food-producing animals.</p> <p>Transmission</p> <p>The major cause of tuberculosis in humans is <i>M. tuberculosis</i>, with human-to-human transmission accounting for the vast majority of cases.</p> <p>Food-producing animals are mostly affected by <i>Mycobacterium bovis</i> and transmission of infection to humans is rare in the EU due to the widespread pasteurisation of milk and the long-established eradication programmes whereby all animals testing positive are removed from the food chain [508, 509]. In 2020, there were 88 cases of</p>

	<p>tuberculosis due to <i>M.bovis/caprae</i> in humans (49 cases in individuals of EU origin) reported to EFSA surveillance of zoonoses. For the 68 tested cases, one case was rifampicin resistant [505]. However, recent evidence suggests that the prevalence could be higher than previously recognised in some food-producing animals e.g. goats [510]. Treatment of mycobacterial infections in food-producing animals is unlikely and illegal in most EU countries; therefore, the potential for emergence and transmission of resistance to rifamycins linked to their use in food-producing animals is low/negligible.</p> <p>Mycobacterial infections (<i>M. bovis</i>, <i>M. avium</i>, <i>M. tuberculosis</i>) historically have been reported rarely in companion animals in Europe [511, 512], however current prevalence data are not available. A risk assessment conducted in the UK following a cluster of nine <i>M. bovis</i> cases in cats in 2012-13 identified two cases of cat-to-human transmission and considered the risk as very low [513].</p> <p>Based on current evidence and frequency of use, although there is the potential for emergence of resistance to rifamycins in isolates from companion animals if their use became well established, transmission of resistant mycobacteria to humans is not likely to be significant at present. (Limited evidence).</p> <p>Food is generally not considered to be a significant source of MRSA in humans [30, 31]. MRSA is mainly transmitted by direct contact from food-producing animals [32]. In geographical areas with high density of farms, the livestock associated MRSA (LA-MRSA) contribution to the burden of MRSA disease could be significant [73, 74].</p> <p>There is the potential for transmission of rifampicin-resistant staphylococci including <i>S. aureus</i> and MRSA/P from companion animals to humans [69].</p> <p>Transmission of rifampicin resistant <i>R. equi</i> from foals to humans could occur. Nevertheless, human infection due to <i>R. equi</i> is a rare occurrence [514]</p> <p>In conclusion, there is evidence supporting the emergence of resistance to rifamycins in <i>S. aureus</i> (including MRSA) and MRSP in animals, and for the potential for significant transmission from animals to humans.</p> <p>Criterion B.1.(a/b) is met.</p>
Criterion C met: No	<p>Rifaximin is authorised in the EU in VMPS intended for cattle for intramammary use to treat IMI and intrauterine use to treat endometritis. Rifaximin is included in Table 1 of the MRL Regulation (EU) 37/2010 for intramammary use in bovines and topical use in all food-producing species. Other rifamycins are not included and therefore cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Companion animals</p> <p>Rifampicin is used off-label for the treatment of <i>R. equi</i> pneumonia in foals, in combination with a macrolide. Although severe pneumonia is uncommon in foals, <i>R. equi</i> is the most frequent cause and, if inappropriately treated, it can lead to mortality. Potential alternative antimicrobial options (macrolides, doxycycline, as monotherapy or combined) have been identified from scientific studies investigating sub-clinical to moderate <i>R. equi</i> pneumonia [344, 515-519]; however, efficacy for severe <i>R. equi</i> pneumonia has not been investigated and rifampicin in combination with a macrolide therefore remains the recommended treatment strategy [39, 342].</p> <p>Rifampicin is also used for rare serious infections in companion animals due to mycobacteria, and occasionally other resistant bacteria (e.g. MRSP). MRSP is most commonly implicated in canine recurrent pyoderma, but may also be involved with life-threatening surgical wounds, urinary and respiratory tract infections. Selection of appropriate antibiotic should be based on susceptibility testing as MRSP is often susceptible to only few antimicrobials e.g. rifampicin, amikacin. Alternatives of last resort in human medicine (e.g. oxazolidinones) are avoided due to the over-riding public health interest [281, 303, 305]. Tuberculosis complex and non-tuberculous mycobacterial infections are rare in cats and dogs but are usually serious/life-threatening [511]. Rifampicin is the recommended treatment, in combination with a macrolide and a fluoroquinolone [346]. Euthanasia may be considered as an alternative due to the guarded prognosis or zoonotic potential (<i>M. bovis</i>) [345, 346].</p> <p>In conclusion, rifampicin is used in companion animals to treat uncommon but serious infections which lead to significant mortality and for which no adequate alternative medicinal products are available.</p> <p>Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 50. Evaluation of substances used solely to treat tuberculosis or other mycobacterial diseases

Substances used solely to treat tuberculosis or other mycobacterial diseases See Table 112 for ATC(vet) codes	
Criterion A met: Yes	<p>The group of substances used solely to treat mycobacterial infections is a specialised group represented by several antimicrobial classes. The majority are for the treatment of tuberculosis (TB). This can include active and latent infections, as well as MDR-TB and XDR-TB. Many of these substances are active only against mycobacteria. They may be bacteriostatic or bactericidal and have different modes of action (RNA, mycolic acid suppression, ATP, etc).</p> <p>Tuberculosis is caused by one of several genetically related mycobacterial species that belong to the <i>Mycobacterium tuberculosis</i> complex. Best known TB pathogens include <i>M. tuberculosis</i>, <i>M. africanum</i>, and <i>M. bovis</i>. The other member of the complex, <i>M. microti</i>, is primarily a rodent pathogen. <i>M. tuberculosis</i> is the most important of the human pathogens</p>

	<p>Typical protocols for mycobacterial infections, as recommended by the WHO, involve combination therapy, over several months. Thus, these substances should be considered together because combination use is essential for successful treatment [520].</p> <p>Isoniazid (+rifampicin) is the mainstay first-line treatment combination for TB; however, resistance can develop rapidly, and they are often used in combination with other agents (e.g. pyrazinamide, ethambutol). For treatment of MDR-TB, regimens may include fluoroquinolones and other substances e.g. bedaquiline, delamanid; however, these regimens are often more toxic and involve prolonged treatment courses. There are few treatment options for XDR-TB (resistant to isoniazid, rifampicin, fluoroquinolones and at least one second-line substance) and in some cases it is incurable.</p> <p>There are essentially no alternative anti-mycobacterial agents beyond those listed in this group that can be used as treatment option.</p> <p>Globally, mycobacterial infection in people, especially TB, remains one of the most common infectious diseases. In the EU in 2018, 53,000 cases of TB were reported to ECDC. Although cases have declined across the EU in recent years, MDR/XDR-TB remains a public health threat in some eastern and central European countries. In 2018, there were approximately 1,000 MDR-TB cases reported to ECDC, of which 20% were XDR. It is estimated that in 2019, there were approximately 280 deaths due to MDR-TB and 100 deaths due to XDR-TB in the EU [500]. Treatment is lengthy, expensive and associated with poor outcomes.</p> <p>These medicines are approved in the EU either via centralised or national procedures.</p> <p>Medicines used solely to treat tuberculosis or other mycobacterial diseases fulfil criterion A.1.(b) based on being an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans such as serious mycobacterial infections.</p>
<p>Criterion B met: No</p>	<p>Most antimicrobial resistance mechanisms appear unique to the substances used solely for treatment of mycobacterial infections. They are chromosomally encoded, inactivating essential enzymatic house-keeping systems. Resistance to TB antibiotics can develop rapidly [521, 522].</p> <p>Cross-resistance between these antibiotics could be observed. Resistance to isoniazid from mutations of the <i>katG</i> gene and/or <i>inhA/nph</i> genes confers resistance to ethionamide. Furthermore, mutations of <i>ethA</i> gene can lead to multi-resistance to isoniazid, ethionamide (prothionamide), tiocarlide (Thiocarlide / Isoxyl) and thiacetazone. Mutations of the <i>thyA</i> gene can confer resistance to both para-Amino Salicylic Acid (as well as Calcium Aminosaliclylate and Sodium Aminosaliclylate) as well as cyclic peptides (Capreomycin, Viomycin). Mutations in the transcriptional regulator <i>Rv0678</i>, leading to upregulation of efflux pump <i>MmpL5</i>, can cause cross-resistance involving both clofazimine and bedaquiline [523, 524].</p> <p>Assessing the likely risk of transmission of resistance to TB antibiotics in mycobacteria is confounded by the knowledge that TB antibiotics are used as specialised combinations to delay the emergence of resistance and to enhance antimycobacterial efficacy, both in animals and humans. Thus, TB substances should be considered together because their combination use is essential for the successful treatment of mycobacterial infections.</p> <p>There is no established mandatory European-wide surveillance of AMR in mycobacterial infections in either companion or food-producing animals.</p> <p>There is a report of isolation from a pet dog in Portugal of pre-MDR <i>M. tuberculosis</i> that was resistant to isoniazid, ethambutol and streptomycin; however, the resistance was not linked to use of these antimicrobials in the dog. Such cases are usually suspected to be of human origin [525].</p> <p>Transmission</p> <p>The major cause of tuberculosis in humans is <i>M. tuberculosis</i>, with human-to-human transmission accounting for the vast majority of cases [510].</p> <p>Food-producing animals are mostly affected by <i>M. bovis</i> and transmission of infection to humans is rare in the EU due to the widespread pasteurisation of milk and the long-established eradication programmes whereby all animals testing positive are removed from the food chain [508, 509]. In 2020, there were 88 cases of tuberculosis due to <i>M. bovis/caprae</i> in humans (49 cases in individuals of EU origin) reported to EFSA surveillance of zoonoses. For the 68 tested cases, two cases were resistant to isoniazid [505]. However, recent evidence suggests that the prevalence could be higher than previously recognised in some food-producing animals e.g. goats [510]. Treatment of mycobacterial infections in food-producing animals is unlikely and illegal in most EU countries; therefore, the potential for emergence and transmission of resistance to TB antibiotics linked to their use in food-producing animals is low/negligible.</p> <p>Mycobacterial infections (<i>M. bovis</i>, <i>M. avium</i>, <i>M. tuberculosis</i>) historically have been reported rarely in companion animals in Europe [512, 526], however current prevalence data are not available. A risk assessment conducted in the UK following a cluster of nine <i>M. bovis</i> cases in cats in 2012-13 identified two cases of cat-to-human transmission and considered the risk as very low [513].</p> <p>In conclusion, based on current evidence and frequency of use, although there is the potential for emergence of resistance to TB antibiotics in isolates from companion animals if their use became established, transmission of resistant mycobacteria to humans is not likely to be significant at present. (Limited evidence).</p> <p>Criterion B is not met.</p>
<p>Recommended to be designated as an antimicrobial class to be reserved for humans: No</p>	

Table 51. Evaluation of riminofenazines

Riminofenazines See Table 113 for ATC(vet) codes	
Criterion A met: Yes	<p>Riminofenazines are currently represented by one antimicrobial - clofazimine. Clofazimine is a lipophilic compound (C₂₇H₂₂Cl₂N₄) that primarily acts on the bacterial outer membrane. It has broad-spectrum activity against bacteria, parasites and fungi. The WHO placed clofazimine in the group of five medicines for the management of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) [527].</p> <p>Clofazimine is active against Gram-positive organisms, while Gram-negative organisms are uniformly resistant. Clofazimine has demonstrated high activity against various mycobacterial species, and acts synergistically with other antimicrobial agents, such as amikacin and clarithromycin [528]. It is principally used as a treatment of leprosy (<i>Mycobacterium leprae</i> and <i>Mycobacterium lepromatosis</i>), a second-line treatment for rifampicin-resistant TB, as well as selected atypical mycobacterial infections (e.g., <i>Mycobacterium abscessus</i>).</p> <p>The approved indication of clofazimine is for treatment of lepromatous leprosy, including cases resistant to dapsone treatment and cases complicated by erythema nodosum. First line treatment of leprosy consists of multiple-drug therapy to prevent development of resistance and includes dapsone, rifampin and clofazimine. Therefore, clofazimine is deemed critical in leprosy treatment.</p> <p>While clofazimine is not approved in the EU for the treatment of drug-resistant tuberculosis (MDR-TB), it has been considered by WHO as a critical medicine in the treatment of drug-resistant TB for years and its importance has been growing. The WHO has recommended the use of clofazimine in the shorter regimen used to treat DR-TB since 2016. The current WHO guidance on treatment of drug-resistant TB has also prioritized clofazimine moving it into Group B for the longer DR-TB regimens [520].</p> <p>Alternative agents for treatment of leprosy include minocycline, ofloxacin, levofloxacin, clarithromycin, and moxifloxacin [529]. MDR tuberculosis can be treated with two regimens based on the length of the drug administration. The recommended treatment concerns 3 different groups of medicines (A, B and C) as well as other medicines. Medicines from group A are considered highly effective against MDR-TB (e.g., bedaquiline, levofloxacin, moxifloxacin, linezolid). Cycloserine or terizidone (group B) can be used as second line agents, but not in those patients who get only two medicines from the group A substances. When the medicines from group A and B cannot be used, then Group C is recommended (e.g., ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin, streptomycin, ethionamide or prothionamide, para-aminosalicylic acid). Clofazimine belongs to group B and is an integral part of the short-term regimen and some of these alternatives for the long-term regimen, are more toxic than clofazimine.</p> <p>There are recent reports of bedaquiline and clofazimine cross-resistance (e.g., in southern Africa this is emerging repeatedly, with evidence of onward transmission largely due to Rv0678 mutations in <i>M. tuberculosis</i> [530]).</p> <p>In 2019, there were 202,166 new cases of leprosy reported from 161 countries in six WHO Regions [531]. In 2019, 29 countries in the European Union/European Economic Area (EU/EEA) reported a total of 49 752 TB cases (9.6 per 100 000 population). The overall TB notification rate in the EU/EEA continued to decline, as did most country-specific TB notification rates. However, the EU/EEA is not on track to reach the goal of ending the TB epidemic by 2030. MDR-TB was reported for 3.4% of TB cases with susceptibility testing results reported. XDR-TB was reported for 22.4% of MDR TB cases that underwent second-line antibiotic susceptibility testing. area [452]. In 2019 795 cases of MDR-TB were reported in EU/EEA [365].</p> <p>Clofazimine is authorised for the treatment of leprosy in some EU countries (nationally approved product). Clofazimine has been granted orphan drug status in the EU for the treatment of non-tuberculous mycobacterial lung disease.</p> <p>Clofazimine fulfils criterion A.1.(b). It is an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: No	<p>Resistance to clofazimine has not yet been fully characterized; however, mutations in the chromosomal transcriptional regulator genes appear likely causes of resistance for <i>M. tuberculosis</i> and <i>M. leprae</i> [528, 532, 533].</p> <p>Cross resistance between clofazimine and bedaquiline (see 'other substances for treatment of tuberculosis') have been described in <i>M. tuberculosis</i> with mutations in the transcriptional regulator Rv0678 [530, 532].</p> <p>There is no established mandatory European-wide surveillance of AMR in mycobacterial infections in either companion or food-producing animals.</p> <p>No reports were found of resistance to clofazimine in mycobacteria isolates from animals.</p> <p>Transmission</p> <p>The major cause of tuberculosis in humans is <i>M. tuberculosis</i>, with human-to-human transmission accounting for the vast majority of cases.</p> <p>Food-producing animals are mostly affected by <i>M. bovis</i> and transmission of infection to humans is rare in the EU due to the widespread pasteurisation of milk and the long-established eradication programmes whereby all animals testing positive are removed from the food chain [508, 509]. In 2020, there were 88 cases of tuberculosis due to <i>M.bovis/caprae</i> in humans (49 cases in individuals of EU origin) reported to EFSA surveillance [505]. However, recent evidence suggests that the prevalence could be higher than previously recognised in some food-producing animals e.g. goats [510]. Treatment of mycobacterial infections in food-</p>

	<p>producing animals is unlikely and illegal in most EU countries; therefore, the potential for emergence and transmission of resistance to rimonofenazines linked to their use in food-producing animals is low/negligible.</p> <p>Mycobacterial infections (<i>M. bovis</i>, <i>M. avium</i>, <i>M. tuberculosis</i>) historically have been reported rarely in companion animals in Europe [511, 512], however current prevalence data are not available. A risk assessment conducted in the UK following a cluster of nine <i>M. bovis</i> cases in cats in 2012-13 identified two cases of cat-to-human transmission and considered the risk as very low [513].</p> <p>In cats, clofazimine is recommended for treatment of disseminated <i>Mycobacterium avium-intracellulare</i> complex infection, a serious disease with a poor prognosis, and for feline leprosy (e.g. <i>M. lepraemurium</i>) [346, 511, 534].</p> <p>Moreover, in companion animals leprosy has been associated with different mycobacterial species (e.g. <i>M. lepraemurium</i>) from that causing the disease in humans and there is no evidence that food-producing animals or companion animals could act as reservoirs of <i>M. leprae</i> or <i>M. lepromatosis</i> [535]. Clofazimine resistance has been only associated with chromosomal mutations, restricting any potential horizontal transmission of resistance between mycobacterial species.</p> <p>Therefore, transmission of clofazimine resistance from animal sources is not demonstrated to be relevant for treatment of <i>M. leprae</i> in humans.</p> <p>In conclusion, based on current evidences and frequency of use, although there is the potential for emergence of resistance to rimonofenazines in isolates from companion animals if their use became established, transmission of resistant mycobacteria to humans is not likely to be significant at present.</p> <p>Criterion B is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 52. Evaluation of sulfones

Sulfones See Table 114 for ATC(vet) codes	
Criterion A met: Yes	<p>Sulfones include two substances (dapson and sulfoxone) primarily used to treat leprosy. Dapsone (diaminodiphenyl sulfone-DDS) is the most effective sulfone derivative in the treatment of leprosy. It inhibits the synthesis of dihydrofolic acid through by competing with para-aminobenzoic acid for the active site of dihydropteroate synthetase.</p> <p>Sulfoxone (aldesulfone sodium) is another representative of sulfones which was, but is no longer, used to treat leprosy.</p> <p>Dapsone is active against many bacteria. Fully susceptible strains of <i>Mycobacterium leprae</i> are inhibited at very low minimum inhibitory concentrations (MICs). The antibiotic is primarily bacteriostatic. High-level resistance is acquired by several sequential mutations.</p> <p>Dapsone is also effective against some protozoa and fungi (e.g., malaria, <i>Pneumocystis jirovecii</i>).</p> <p>The relevant indication is for the treatment of leprosy. Since this requires combination treatment, and since dapsone and clofazimine are the mainstays of the therapy, use of dapsone in leprosy is deemed critical.</p> <p>Alternative agents for treatment of leprosy include minocycline, ofloxacin, levofloxacin, clarithromycin, and moxifloxacin [536].</p> <p>In 2019, there were 202,166 new cases of leprosy reported from 161 countries in six WHO Regions [531].</p> <p>Dapsone is approved in some EU member states for a number of indications: as part of a multi-drug regimen in the treatment of all forms of leprosy, for the treatment of dermatitis herpetiformis and other dermatoses, for the prophylaxis of malaria in combination with pyrimethamine and for the prophylaxis of <i>Pneumocystis carinii</i> (now <i>jirovecii</i>) pneumonia in immunodeficient subjects, especially AIDS patients [537]. It can also be used (off-label) for the prophylaxis of toxoplasmosis (in combination with pyrimethamine) [538] and for the treatment (in combination with trimethoprim) of <i>P. jirovecii</i> pneumonia [539].</p> <p>Dapsone fulfils criterion A.1.(b). It is an essential component of the limited treatment alternatives available for management of serious, life-threatening infections in humans.</p>
Criterion B met: No	<p>Resistance to dapsone has not yet been fully characterized; however mutations in the <i>folP1</i> gene-encoded dihydropteroate synthase (DHPS) and genomic reduction has been associated with decreased activity of dapsone in <i>M. leprae</i> [540].</p> <p>There is no established mandatory European-wide surveillance of AMR in mycobacterial infections in either companion or food-producing animals.</p> <p>No information could be found on the occurrence of resistance to sulfones in mycobacteria from animals.</p> <p>Transmission</p> <p>In companion animals, leprosy has been associated with different mycobacterial species (including <i>Mycobacterium lepraemurium</i>) from that causing the disease in humans. There is no evidence that food-producing animals or</p>

	<p>companion animals could act as reservoirs of <i>M. leprae</i> or <i>M. lepromatosis</i>. Potential wildlife reservoirs have been proposed (outside the EU), but the evidence for transmission from animals to humans is unclear [535].</p> <p>Sulfones are not authorised in VMPs in the EU and there is scant evidence for their use to treat feline leprosy [445, 541]. Potential selection of resistance in <i>Mycobacterium</i> spp. could occur if sulfones were authorised for the treatment of rare cases of lepromatosis/leprae infections in companion animals (other treatments are currently recommended, [346]).</p> <p>In conclusion, although there would be the potential for emergence of resistance to sulfones in isolates from companion animals if their use became established, the mycobacterial species causing leprosy in companion animals are not regarded as zoonotic and there is no likely significant pathway for transmission of resistance to relevant human pathogens.</p> <p>Criterion B is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 53. Evaluation of pseudomonic acids

Pseudomonic acids See Table 115 for ATC(vet) codes	
Criterion A met: Yes	<p>Mupirocin is also called pseudomonic acid because its major metabolite (pseudomonic acid A; responsible for most of the activity) is derived from submerged fermentation of <i>Pseudomonas fluorescens</i>. Three other minor metabolites (pseudomonic acids B, C and D) share a similar chemical structure and antimicrobial spectrum [542].</p> <p>Mupirocin shows a high level of activity against staphylococci and streptococci and against certain Gram-negative bacteria, including <i>Haemophilus influenzae</i> and <i>Neisseria gonorrhoeae</i>, but is much less active against most Gram-negative bacilli and anaerobes. Mupirocin inhibits bacterial RNA and protein synthesis by binding to bacterial isoleucyl tRNA synthetase, which catalyzes the formation of isoleucyl tRNA from isoleucine and tRNA. This prevents incorporation of isoleucine into protein chains, leading to arrest of protein synthesis [543-545].</p> <p>Mupirocin is the only antibiotic registered for the treatment of carriage (decolonisation therapy) of <i>Staphylococcus aureus</i>, including MRSA. Carriage of <i>S. aureus</i> is a well-defined risk factor for subsequent infection and screening for nasal carriage before a surgical intervention, followed by decolonisation therapy of positive patients to eliminate nasal carriage, is recommended to decrease the risk of subsequent <i>S. aureus</i> infection, including MRSA surgical site infection, particularly in patients undergoing cardiothoracic and orthopaedic surgery and those receiving implantable devices or undergoing organ or stem-cell transplants. Topical mupirocin is a cornerstone in decolonisation therapy for nasal carriage of <i>S. aureus</i>, especially MRSA, and thereby an essential component of the public health response against MRSA in many EU/EEA countries [546].</p> <p>Mupirocin is of essential importance for patient management in hospitals as the sole agent for eradication of MRSA carriage. For topical treatment of SSTIs fusidic acid is an alternative [547]. A further alternative is retapamulin ointment for topical treatment of cutaneous bacterial infections, particularly those caused by <i>S. aureus</i>; retapamulin is, however, not indicated for treatment of MRSA infections [548, 549].</p> <p>MRSA remains an important human health burden in the EU, accounting for 7,000 deaths per annum [153].</p> <p>Mupirocin is nationally authorised in the EU for topical use and is available as creams, ointments, nasal ointments. Mupirocin as nasal ointment is authorised for the elimination of nasal carriage of staphylococci, including MRSA. Decolonisation of MRSA is an essential part of infection control guidelines in several European countries e.g. The Netherlands and the Nordic countries. Mupirocin is also used preoperatively to reduce serious <i>S. aureus</i> infections associated with surgery as well as in patients receiving haemodialysis or continuous ambulatory peritoneal dialysis treatment. For these purposes, mupirocin is the sole antibiotic and is therefore essential for avoiding serious infections in a range of situations where patients are carrying <i>S. aureus</i>, especially MRSA, including surgery involving prosthetic implants.</p> <p>Creams containing mupirocin are authorised for the topical treatment of primary bacterial skin infections and secondarily infected traumatic lesions such as small lacerations, sutured wounds or abrasions, due to susceptible strains of <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i>. Mupirocin is not essential for treatment of these indications.</p> <p>Pseudomonic acids (mupirocin) fulfil criterion A.1.(b) due to its importance in the patient management approach for serious infections due to MRSA.</p>
Criterion B met: Yes	<p>Acquired resistance to mupirocin can be chromosomal and plasmid-mediated. In staphylococci, mupirocin resistance can be either low level (LL) or high level (HL). LL resistance is the result of point mutations in the chromosomally located <i>ileS</i> gene. High level resistance in staphylococci is mediated by the <i>mupA</i> gene which is located on a conjugative plasmid and can spread clonally and horizontally, even between different staphylococcal species and MRSA. The <i>mupB</i> gene is located on non-conjugative plasmids [294, 550, 551].</p> <p>There is no cross-resistance between mupirocin and other antimicrobial agents. Co-resistance of mupirocin with clindamycin, tetracycline, erythromycin and levofloxacin has been reported in MRSA isolates from humans in the USA [552]</p> <p>Mupirocin is not authorised for use in animals and presently mupirocin resistance in staphylococci of animal origin is not reported from food-producing animals and is rare in companion animals [281, 553-555].</p>

	<p><i>Staphylococcus</i> spp. (including MRSA/MRSP) may be transmitted from livestock and companion animals to humans [69, 132, 556] (See annotation 3 under Table 61).</p> <p>There is evidence for potential selection and likely significant transmission of resistance to pseudomonic acids from animals to humans through zoonotic bacteria if use of pseudomonic acids in animals became established.</p> <p>Criterion B.1.(b) is met.</p>
Criterion C met: No	<p>Pseudomonic acids have not been authorised for use in VMPs in the EU. They are not included in the MRL Regulation (EU) 37/2010 so cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6. In the USA, mupirocin is authorised for topical treatments in dogs, cats and equines.</p> <p>Companion animals</p> <p>Mupirocin is used outside the terms of the marketing authorisation in companion animals as topical treatment of serious skin infections caused by MRSP or MRSA that have been shown to be resistant to antimicrobials of lower importance [557-559]. Based on international guidelines, the frequency of such use is low and mupirocin is not used for decolonisation therapy in companion animals [281]. Whilst MRSA is more commonly associated with prosthetic implants or wounds, MRSP is most commonly implicated in canine skin infections, but may also be involved with surgical wounds, urinary and respiratory tract infections, which can be life-threatening. Where possible, early topical treatment is preferred and susceptibility testing may show that the only effective alternatives are systemically administered antibiotics of higher importance in human medicine (e.g. vancomycin, linezolid, rifamycin) [281, 303-305, 560-562].</p> <p>MRSA/P infections in companion animals are potentially zoonotic and considering the close and sustained contact between pet and owner, such infections should be treated effectively and efficiently [563].</p> <p>A distinction in terms of public health significance under this criterion is drawn between topical mupirocin, primarily used for MRSA decolonisation in humans, versus the need to ensure availability of systemically active antibiotics used in treatment of life-threatening MRSA infections in humans e.g. oxazolidinones.</p> <p>In conclusion, mupirocin is used in companion animals to treat uncommon but serious infections which may lead to mortality and are of zoonotic relevance. The only alternatives may be of higher importance in human medicine. Criterion C is not met.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 54. Evaluation of steroid antibacterials

<p>Steroid antibacterials See Table 116 for ATC(vet) codes</p>	
Criterion A met: No	<p>Fusidic acid has a narrow spectrum, bacteriostatic activity. It inhibits protein synthesis by interfering with ribosome translation.</p> <p>Fusidic acid has been shown to be active against Gram-positive cocci and bacilli such as <i>Staphylococcus aureus</i> (including MRSA), most coagulase-positive staphylococci, beta-haemolytic streptococci, <i>Corynebacterium</i> spp., and most <i>Clostridioides</i> spp. Fusidic acid has only limited activity against Gram-negative bacteria [564].</p> <p>Fusidic acid is mainly used for combination therapy in humans (systemic treatment) of staphylococcal infections or topically for treatment of skin or eye infections. Although effective, it is not recommended for initial monotherapy of severe staphylococcal infections owing to its bacteriostatic activity and the high risk of development of resistance.</p> <p>There are several alternative treatment options including penicillinase-resistant penicillins.</p> <p>Staphylococcal infections, especially by <i>S. aureus</i>, cause a wide range of diseases – from minor skin infections to life-threatening sepsis.</p> <p>Fusidic acid is approved nationally in several EU countries for systemic use. The approved indications are the treatment of primary and secondary skin infections caused by sensitive strains of <i>Staphylococcus aureus</i>, <i>Streptococcus</i> spp. and <i>Corynebacterium minutissimum</i>. Primary skin infections that may be expected to respond to treatment with fusidic acid applied topically include impetigo contagiosa, superficial folliculitis, sycosis barbae, paronychia and erythrasma; also such secondary skin infections as infected eczematoid dermatitis, infected contact dermatitis and infected cuts/abrasions.</p> <p>Fusidic acid does not fulfil criterion A, as other treatment alternatives exist to treat staphylococcal infections.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 55. Evaluation of bicyclomycin (bicozamycin)

Bicyclomycin (bicozamycin)	
Criterion A met: No	<p>Bicyclomycin is the only substance found in this class and its mechanism of action is based on inhibiting the rho transcription termination factor [565].</p> <p>Bicyclomycin is active against Gram-negative bacteria including <i>E. coli</i> and has little activity against Gram-positive bacteria (except <i>Micrococcus luteus</i>), anaerobes, <i>Proteus</i> or <i>Pseudomonas</i> [566]. In vitro studies have shown that bicyclomycin exhibits lethal synergy when combined with bacteriostatic concentrations of protein synthesis inhibitors (tetracyclines, chloramphenicol, rifampicin) [567].</p> <p>It has low oral bioavailability and has been used (historically) for treatment of acute and traveller's diarrhoea associated with enteric infections in humans and for enteric infections livestock [568, 569].</p> <p>Bicyclomycin is not approved in the EU, neither as a human nor as a veterinary medicine.</p> <p>Bicyclomycin, does not fulfil criterion A, as no currently available evidence supports its importance of use in human medicine.</p>
Recommended to be designated as an antimicrobial to be reserved for humans: No	

Table 56. Evaluation of orthosomycins/oligosaccharides

Orthosomycins/oligosaccharides	
Criterion A met: No	<p>Orthosomycins manifest their antimicrobial activity by binding to the 50S ribosomal subunit and inhibiting protein synthesis. The class contains several substances such as evernimicin, flambamycin and hygromycin.</p> <p>Orthosomycins are active against Gram-positive bacteria including enterococci, staphylococci, and streptococci.</p> <p>According to Arenz et al. [570] the binding site and mode of action of orthosomycins are distinct from other ribosome-targeting antibiotics and they do not display cross-resistance with other classes, suggesting possible scope for development of new agents. Evernimicin was investigated in human medicine as a treatment for Gram-positive infections including penicillin-resistant pneumococci but development was suspended due to poor efficacy [569]. In vitro, evernimicin has shown higher activity than vancomycin against Gram-positive cocci, including MRSA [571, 572].</p> <p>Orthosomycins are not approved in the EU as a human medicine.</p> <p>Orthosomycins, do not fulfil criterion A, as of now no evidence can be found to confirm their importance of use in human medicine.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 57. Evaluation of quinoxalines

Quinoxalines	
Criterion A met: No	<p>Quinoxalines class contains several substances such as carbadox, quinocetol, mequindox, quinocetone and cyadox. The mode of action of quinoxalines is not fully understood although they demonstrate bioreductive effects [573].</p> <p>Quinoxalines are active against Gram-positive, Gram-negative bacteria, including <i>E. coli</i> and <i>Salmonella</i> spp., and anaerobes [574].</p> <p>Quinoxaline derivatives have been investigated as antivirals [575]; they also have antimycobacterial, antifungal and antiprotozoal activity, suggesting development of less toxic derivatives is of interest [576]. No evidence could be found for current use of quinoxalines in human medicine.</p> <p>Quinoxalines are not approved in the EU as a human medicine</p> <p>Quinoxalines do not fulfil criterion A, as of now no evidence can be found to confirm their importance of use in human medicine.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 58. Evaluation of thiopeptides

Thiopeptides e.g. Nosiheptide	
Criterion A met: No	<p>The thiopeptides class contains several substances such as thiostrepton, cyclothiazomycin, nosiheptide, lactocillin. Thiopeptides inhibit bacterial protein synthesis by binding to the 23S rRNA and the N-terminal domain of ribosomal protein uL11.</p> <p>Thiostrepton is a cyclic peptide, produced by <i>Streptomyces aureus</i>, that is active predominantly against Gram-positive bacteria [577]. Thiopeptides have been investigated in in vitro studies for effectiveness against MRSA, methicillin resistant <i>Enterococcus faecium</i>, VRE, penicillin-resistant <i>Streptococcus pneumoniae</i> and mycobacteria, and in a human clinical study for treatment of <i>Clostridioides difficile</i>. Thiopeptides also have antimalarial, antifungal and anticancer properties [578-581].</p> <p>Thiopeptides are not approved in the EU as a human medicine.</p> <p>Thiopeptides, do not fulfil criterion A, as of now no evidence can be found to confirm their importance of use in human medicine.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 59. Evaluation of phosphoglycolipids/moenomycins

Phosphoglycolipids/moenomycins e.g. Bambermycin (ATCVet code QA07AA96)	
Criterion A met: No	<p>The moenomycins class contains substances such as bambermycin (syn. flavomycin, flavofosfolipol, menomycin) and moenomycin. Moenomycins are phosphoglycolipid antibiotics produced by <i>Streptomyces bambergiensis</i>. They have a distinct mode of action, competing as substrates for peptidoglycan glycosyltransferase enzymes involved with bacterial cell wall formation.</p> <p>They are mostly active against Gram-positive bacteria, including methicillin- and vancomycin-resistant cocci, and have activity against some Gram-negative bacteria.</p> <p>Moenomycins have not been used in human medicine due to poor pharmacokinetics – they are poorly absorbed from the gastrointestinal tract and have a very long half-life - although there is renewed interest in their development (Galley et al., 2014). Some strains of <i>Enterococcus faecium</i> are intrinsically resistant, otherwise there are almost no reports of naturally occurring resistance [582].</p> <p>Moenomycins are not approved in the EU as a human medicine.</p> <p>Moenomycins, do not fulfil criterion A, as of now no evidence can be found to confirm their importance of use in human medicine.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 60. Evaluation of elfamycins

Elfamycins e.g. Efrotomycin	
Criterion A met: No	<p>Substances in the elfamycin class include efrotomycin, kirromycin, enacycloxin, pulvomycin and aurodox. Efrotomycin is produced by <i>Nocardia lactamdurans</i>. Elfamycins act by interfering with bacterial protein synthesis, binding to the elongation factor EF-Tu.</p> <p>Efrotomycin is effective against a narrow spectrum of gram-positive bacteria, <i>Moraxella</i>, <i>Pasteurella</i>, <i>Yersinia</i>, <i>Haemophilus</i>, <i>Arcanobacterium</i> spp. and <i>Clostridioides difficile</i> [583, 584]. <i>Enterococcus faecium</i> and closely related spp. are susceptible, whereas other enterococcal spp. including <i>E. faecalis</i> are resistant [585].</p> <p>Elfamycins have been understudied due to poor pharmacokinetics, but there is renewed interest in their potential for clinical use [586]. No current therapeutic uses were found in human or veterinary medicine.</p> <p>Elfamycins are not approved in the EU as a human medicine.</p> <p>Elfamycins do not fulfil criterion A, as of now no evidence can be found to confirm their importance of use in human medicine. A potential for future development has been noted.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Table 61. Evaluation of aminocoumarins

Aminocoumarins e.g. Novobiocin	
Criterion A met: No	<p>Novobiocin is an aminocoumarin antibiotic which inhibits bacterial DNA synthesis by targeting at the bacteria DNA gyrase and the related enzyme DNA topoisomerase IV [587].</p> <p>Novobiocin is primarily active against Gram-positive microorganisms such as <i>Staphylococcus aureus</i> (including beta-lactamase-producing strains) and the pneumococci. <i>Enterococcus faecalis</i> is usually moderately resistant, but <i>Enterococcus faecium</i>, including MDR strains, is susceptible. It also has an activity against some Gram-negative bacteria (e.g., <i>Haemophilus influenzae</i>, pathogenic <i>Neisseria</i> spp.). Other Gram-negative bacilli, such as <i>Escherichia coli</i>, <i>Enterobacter</i>, <i>Klebsiella</i>, <i>Salmonella</i> and <i>Shigella</i> spp., and <i>Pseudomonas aeruginosa</i>, are novobiocin-resistant [587].</p> <p>Novobiocin formerly had a role in the treatment of staphylococcal infections [587].</p> <p>With the advent of the penicillinase-resistant penicillins and other antistaphylococcal agents, novobiocin is no longer used for this indication [587].</p> <p>Medicinal products containing novobiocin are not approved in the EU.</p> <p>Aminocoumarins do not fulfil criterion A, as there are newer and safer treatment alternatives.</p>
Recommended to be designated as an antimicrobial class to be reserved for humans: No	

Annotations to the antibiotics tables

Annotation 1: In the context of the Animal Health Law, Regulation (EU) 2016/429, EFSA has assessed AMR bacteria responsible for animal transmissible diseases, with a view to such pathogens being listed for EU action. For this assessment, EFSA conducted an extensive literature review to determine the global state of play of selected resistant bacteria that constitute a threat to animal health and this was used by experts to identify those bacteria most relevant to the EU. Scientific opinions were developed separately for dogs and cats, horses, pigs, poultry cattle, small ruminants, rabbits and aquatic species.

Annotation 2: Enterobacterales are mainly transferred from food-producing animals to humans via the foodborne route [61, 62]. Transfer of resistant zoonotic pathogens is demonstrated for *Salmonella* spp. with mounting evidence for uropathogenic *E. coli* strains [63-65, 588-590]. Moreover, the same or similar beta-lactam resistance genes (including ESBLs) have been isolated in bacteria of human and animal origin, and molecular studies support the potential for transfer of MGEs from animal to human enteric commensals, contributing to the spread and persistence of antibiotic resistance genes and resistant bacteria in the human intestinal tract [54, 67, 68]. Companion animals may also be a reservoir for beta-lactamase resistance that can be transferred between animals and humans via Enterobacterales that are zoonotic pathogens or commensal bacteria, and by direct and indirect transmission, although there are few studies investigating these pathways [69-71]

Annotation 3: Food is generally not considered to be a significant source of MRSA in humans [26, 72]. MRSA is mainly transmitted by direct contact from food-producing animals [32]. In geographical areas with high density of farms, livestock associated MRSA (LA-MRSA) contribution to the burden of MRSA disease could be significant [73, 74, 556]. There is evidence for rare zoonotic transmission of MRSA/P from companion animals to persons in contact [29, 33, 34, 69].

3.2. Antivirals - Confirmatory process

The antivirals in this table are those recommended to be reserved for human use according to the screening process outlined in the Methodology (Section 2.6. of this advice) and the evaluation shown in the Monograph on Antivirals (See Annex Section 2.). The table shows an analysis confirming their fulfilment of the relevant criteria. This table includes only those antivirals that fulfil all three criteria. Information on the ATC codes and EU authorisation status is presented in Annex 6.2.

Table 62. Summary table of antivirals that underwent detailed evaluation and fulfilled all three criteria for designation of antimicrobials to be reserved for humans

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
Amantadine, baloxavir marboxil, rimantadine, laninamivir, oseltamivir, peramivir, umifenovir and zanamivir	<p>These antivirals are acting against influenza viruses. Human influenza can cause severe illness and death, especially in high risk patients, and is associated with seasonal epidemics.</p> <p>Influenza spreads globally in yearly outbreaks, resulting in about three to five million cases of severe illness and about 290,000 to 650,000 deaths annually [591].</p> <p>Amantadine, rimantadine, laninamivir, oseltamivir, and zanamivir are authorised in the EU.</p> <p>Peramivir is authorised in Australia, Japan and South Korea. It is used, but unapproved, in the United States against the H1N1 influenza virus. Initially approved in the EU (Alpivab), it is no longer authorised.</p> <p>Baloxavir marboxil is approved in Japan and US.</p> <p>Umifenovir is approved in China and the Russian Federation.</p>	<p>Amantadine and Rimantadine (adamantanes) are M2 ion channel inhibitors, for human influenza A virus infection.</p> <p>Oseltamivir, zanamivir, laninamivir and peramivir are neuraminidase inhibitors, indicated for human influenza A and B virus infection.</p> <p>Baloxavir marboxil is a novel cap-dependent endonuclease inhibitor, for human influenza A and B virus infection.</p> <p>Resistance to all three classes is already recorded, including for peramivir [592] and baloxavir marboxil [593]. The levels of resistance to each antiviral fluctuate over time: therefore, M2 ion channel inhibitors are currently not used.</p> <p>Resistance to umifenovir is not recorded so far.</p> <p>Humans can be infected with influenza viruses that are usually circulating in animals, such as avian influenza virus subtypes A(H5N1) and</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>Outbreaks of HPAI are controlled by slaughter in the EU (DR (EU) 2020/687).</p> <p>Neuraminidase inhibitors (e.g. oseltamivir) and adamantane are prohibited by FDA from extra-label use in poultry in the US.</p> <p>Some evidence was found for use of antivirals against influenza in animals: - there are reports of adamantane use to treat avian and swine influenza outside the EU. - Oseltamivir is used to treat feline and canine parvovirus diseases. - amantadine is used to treat pain in companion animals, and oseltamivir may</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>Other non-authorized antivirals are active against influenza: favipiravir and triazavirin.</p> <p>Vaccines are currently available to prevent human influenza virus infections in the EU, but presently neuraminidase inhibitors and the endonuclease inhibitor are the only effective antivirals to treat infection – see column on the right.</p>	<p>A(H9N2) and swine influenza virus subtypes A(H1N1) and (H3N2).</p> <p>Other species including horses, cats and dogs also have their own varieties of influenza viruses. Although these viruses may be named as the same subtype as viruses found in humans, all of these animal viruses are distinct from human influenza viruses and do not easily transmit to and between humans. However, highly pathogenic (HP) Avian Influenza A virus can infect several animal species, notwithstanding birds and humans: HPAI infections were recorded in pigs, domestic cats and dogs [594]; because of the sometimes close proximity of these animals with owners, HPAI-infected animals can become a threat to humans. Moreover, because Influenza viruses can swap whole sections of their genome (shift), their antigenicity and/or pathogenicity can be radically altered through this mechanism, making Influenza viruses in their entirety a potential threat to humans</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>be used to treat canine influenza (although regularly discouraged on websites).</p> <p>Influenza mortality rates vary, depending on the virulence of the circulating strains. Typically, there are few deaths in pigs and horses, less than 10% in dogs, but around 50% in poultry, unless disease is exacerbated by secondary bacterial infection.</p> <p>Canine parvovirus disease has a mortality rate that can exceed 90% (especially in young puppies) [595]; feline panleukopenia virus has an approximate fatality rate of 50% [596].</p> <p>Availability of alternative treatments for infections in animals: none, except vaccines available in the EU for certain strains of avian, equine and swine influenza, and for canine and feline parvovirus.</p>	
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Favipiravir	<p>Currently approved to treat human influenza in Japan. It is however only indicated for novel influenza (causing more severe disease) rather than seasonal influenza [597].</p> <p>It is also under investigation for Yellow fever, Foot-and-mouth disease, flaviviruses (including West Nile virus), arenaviruses, bunyaviruses, alphaviruses (togaviridae) and SARS-CoV-2 coronavirus.</p> <p>Many of these viruses represent a major threat to humans. For instance: - Yellow fever (Flaviviridae) causes most commonly non-specific flu-like symptoms; but in 15% of people, abdominal pain occurs with liver and kidneys damage.</p>	<p>Resistance to this antiviral is already recorded [599].</p> <p>Influenza viruses, Picornaviridae, (eg Foot-and-mouth disease virus), flaviviruses (eg West Nile virus), arenaviruses (eg Akabane), alphaviruses (eg equine encephalitis virus) represent major threats to domestic animals. Amongst the quoted genera or families of viruses, the Influenza A virus, the hantavirus (Hemorrhagic fever with renal syndrome) and the West Nile virus (flavivirus) represent the only zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>Little evidence was found for use of favipiravir in animals: - Favipiravir (T-705) and its derivatives T-1105 and T-1106 are efficient inhibitors of foot-and-mouth disease virus replication in cell culture and in vivo [600]. - it was tested against canine distemper virus infection in vitro.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>- Several bunyaviruses can produce mild to severe diseases in humans: eg Hantaviruses (belonging to the Bunyaviridae family) can cause acute respiratory illness in humans.</p> <p>- Several alphaviruses can cause human disease (e.g. Chikungunya). Infectious arthritis, encephalitis, rashes and fever are the most commonly observed symptoms.</p> <p>- Refer also to the section about antivirals acting against influenza viruses above.</p> <p>Authorised in Japan against influenza viruses.</p> <p>Various antivirals are active against influenza: amantadine, rimantadine, laninamivir, oseltamivir, peramivir, zanamivir, baloxavir marboxil and umifenovir.</p> <p>Antiviral therapy for Bunyaviridae is currently limited: ribavirin can be used for Crimean-Congo hemorrhagic fever and hemorrhagic fever with renal syndrome, though efficacy is not clearly established [598].</p> <p>Remdesivir received a conditional authorisation in the EU to treat Covid-19.</p> <p>Specific antiviral treatment options, with proven efficacy, for Yellow fever and alphavirus infections are not available.</p> <p>Vaccines are currently available to prevent humans against Influenza, Yellow fever and Covid-19 infections.</p>		<p>The notion of 'availability of alternative treatments' does not apply here, as the use of faviripavir in veterinary field practice is anecdotal so far.</p>	
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Ribavirin	<p>Ribavirin is indicated against chronic hepatitis C virus (HCV), and could be relevant for chronic hepatitis E virus (HEV) infection.</p> <p>Both hepatitis viruses, HCV and HEV, can cause acute and chronic infections. Most people with chronic disease have no</p>	<p>Antiviral resistance to Ribavirin is already recorded [608].</p> <p>HCV is not involved so far in any zoonotic disease. Several animal species (rabbits, rats, pigs) are capable of hosting HEV, but the principal animal reservoir is <i>suidae</i> (swine) [609].</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under the Articles 113 & 114 of Regulation (EU) 2019/6.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>symptoms, but cirrhosis and liver cancer may sometimes occur; acute hepatitis can develop to fulminant liver failure.</p> <p>WHO estimates that about 71 million people are living with chronic hepatitis C [601] and more than 19 million with chronic hepatitis E [602]: representing 1% and 0.3% of the world's population, respectively. Worldwide, hepatitis C is the cause of about 25% of cirrhosis cases and about 25% of hepatocellular carcinoma [603, 604].</p> <p>Hepatitis C sometimes result in death (399,000 in 2016 for HCV) [602]. Up to 20–25% of pregnant women can die if they get hepatitis E in third trimester [605].</p> <p>Ribavirin is approved by FDA.</p> <p>Various antivirals, alone or associated, are active against HCV: sofosbuvir, glecaprevir, pibrentasvir, grazoprevir, elbasvir, ledipasvir, velpatasvir and voxilaprevir.</p> <p>In the treatment of hepatitis C, ribavirin works very successfully in combination with a variety of other treatments but has no impact on hepatitis C on its own [606]. Recent observations indicate that ribavirin will remain as a critical component of HCV therapy [607].</p> <p>No antiviral is officially recognised as active against HEV.</p> <p>There is no vaccine against hepatitis C. A recombinant subunit vaccine to prevent hepatitis E virus infection is registered in China.</p>	<p>HEV represents a zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>No evidence was found for use in companion animals, or specific need for these substances to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of Ribavirin in veterinary field practice is apparently non-existent.</p>	
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Celgosivir	Celgosivir is in development for the treatment of hepatitis C virus (HCV) infection [610].	Resistance to this antiviral is not recorded so far, probably because of its limited use (currently under development). There is however the potential for emergence,	No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU,	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>Various antivirals, alone or associated, are active against HCV: sofosbuvir, glecaprevir, pibrentasvir, grazoprevir, elbasvir, ledipasvir, velpatasvir and voxilaprevir.</p> <p>Ribavirin is commonly used (in combination with a variety of other treatments) at this time.</p> <p>There is no vaccine against hepatitis C.</p>	<p>dissemination and transmission of resistance to this antiviral, due to its mechanism of action.</p> <p>HCV is not involved so far in any zoonotic disease.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>No evidence was found for use in companion animals, or specific need for this antiviral to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of Celgosivir in veterinary field practice is apparently nonexistent.</p>	
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Galidesivir	<p>Currently tested against hepatitis C (HCV), Ebola virus disease, Marburg virus disease and SARS-CoV-2 coronavirus.</p> <p>It shows also a broad-spectrum antiviral effectiveness against RNA viruses (eg bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses, flaviviruses and phleboviruses).</p> <p>Many of these viruses represent a major threat to humans. For instance:</p> <ul style="list-style-type: none"> - Filoviruses (eg Ebola, Marburg disease) cause severe hemorrhagic fever, frequently lethal. The mortality rate of Ebola is about 50%. - Yellow fever (Flaviviridae) causes most commonly non-specific flu-like symptoms; but in 15% of people, abdominal pain occurs with liver and kidneys damage. - Several bunyaviruses can produce mild to severe diseases in humans, e.g. Hantaviruses (belonging to the Bunyaviridae family) can cause acute respiratory illness in humans. - chronic hepatitis C : Refer to section about antivirals against chronic viral hepatitis above. <p>Various antivirals, alone or associated, are active against HCV: sofosbuvir,</p>	<p>Resistance to this antiviral is not recorded so far, probably because of its limited use (currently not marketed).</p> <p>Arenaviruses (eg Akabane), paramyxoviruses (eg Newcastle disease), coronaviruses (eg feline infectious peritonitis), flaviviruses (eg West Nile virus) and phleboviruses (eg Rift Valley Fever) represent major threats to domestic animals.</p> <p>HCV and phleboviruses are not involved so far in any zoonotic disease.</p> <p>Amongst the quoted genera or families of viruses, the West Nile virus (flavivirus) represents the only zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>No evidence was found for use in companion animals, or specific need for this antiviral to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of galidesivir in veterinary field practice is apparently nonexistent so far.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>glecaprevir, pibrentasvir, grazoprevir, elbasvir, ledipasvir, velpatasvir and voxilaprevir.</p> <p>Ribavirin is commonly used (in combination with a variety of other treatments) at this time.</p> <p>Antiviral therapy for Bunyaviridae is currently limited: ribavirin can be used for Crimean-Congo hemorrhagic fever and hemorrhagic fever with renal syndrome, though efficacy is not clearly established [598].</p> <p>Remdesivir received a conditional authorisation in the EU to treat Covid-19</p> <p>Specific antiviral treatment options, with proven efficacy, for Ebola and Yellow fever are not available.</p> <p>Monoclonal antibodies were developed against flaviviruses and filoviruses.</p> <p>Vaccines against Ebola, Yellow fever and Covid-19 infections are currently available.</p>			
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Lactimidomycin	<p>Activity shown against a variety of RNA viruses, such as flaviviruses (dengue fever, Kunjin virus and Modoc virus), vesicular stomatitis virus and poliovirus.</p> <p>Dengue fever and the poliovirus (Picornaviridae) represent a major threat to humans. For instance:</p> <ul style="list-style-type: none"> - Recovery from dengue fever is the most general outcome, but in rare cases the disease may develop into severe dengue (hemorrhagic symptoms) or into dengue shock syndrome. The mortality rate with severe dengue is 0.8% to 2.5% (but less than 1% with adequate treatment), and up to 26% with the shock syndrome. - With regard to poliomyelitis, the infection is asymptomatic in 95% of cases. In about 5% of cases, viraemia leads to the development of minor symptoms but 	<p>Resistance to this antiviral is not recorded so far, probably because of its limited use (currently not marketed).</p> <p>Dengue fever virus and poliovirus are not associated with domestic animals so far. Other Picornaviridae (eg Foot-and-mouth disease virus) and flaviviruses (eg West Nile virus), represent major threats to domestic animals.</p> <p>Amongst the quoted genera or families of viruses, the West Nile virus (flavivirus) represents the only zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally. No evidence was found for use in companion animals, or specific need for this antiviral to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of lactimidomycin in veterinary field practice is apparently nonexistent.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>temporary or permanent paralysis can occur in less than 1% when the virus enters the central nervous system.</p> <p>Specific antiviral treatment options, with proven efficacy, for dengue fever, polio and vesicular stomatitis are not available. Vaccines against dengue fever and poliomyelitis are currently available.</p>			
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Methisazone/Metisazone	<p>This antiviral has been used in the past to treat human adenovirus and smallpox diseases.</p> <p>Adenoviruses most commonly cause respiratory illness; but they can cause other illnesses such as gastroenteritis or cystitis, sometimes neurological diseases. Orthopoxvirus infections cause a spectrum of illnesses in humans ranging from mild local infections to severe systemic disease.</p> <p>There are three primary antiviral therapies (Tecovirimat, Cidofovir and Brincidofovir) that have shown effectiveness against poxviruses including variola (the virus that causes smallpox) in animals and in vitro studies. However, there is no treatment for smallpox disease that has been tested in people who are sick with the disease and been proven effective in this population [611].</p> <p>Specific antiviral treatment options, with proven efficacy, for adenovirus diseases are not available.</p>	<p>Resistance to this antiviral is not recorded so far, probably because of its limited use (currently not marketed). There is however the potential for emergence, dissemination and transmission of resistance to this antiviral, due to its mechanism of action.</p> <p>Poxviruses and adenoviruses can infect domestic animals.</p> <p>Amongst the quoted genera or families of viruses, none represents a zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under the Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>No evidence was found for use in companion animals, or specific need for this antiviral to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of methisazone/metisazone in veterinary field practice is apparently nonexistent so far.</p>	Yes
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Molnupiravir (EIDD-2801)	<p>Active against major human viruses, such as norovirus, Chikungunya, Ebola, hepatitis C, Covid-19, human influenza A and B.</p> <p>These viruses represent major threats to humans. For instance:</p>	<p>There is no evidence of resistance to this AV so far.</p> <p>Given the mechanism of action of this AV, at least all single-stranded RNA viruses are targeted, whether human or veterinary. In particular, West Nile fever virus, Hepatitis E virus, Hemorrhagic fever with renal syndrome</p>	<p>No AVs are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>- Norovirus is the most common cause of acute gastroenteritis, annually causing an estimated 685 million cases. About 200 million cases are seen among children under 5 years old, leading to an estimated 50,000 child deaths every year [612].</p> <p>- Chikungunya is a worldwide disease, but Asia and the Americas are the most affected regions (for example 62 000 cases in India in 2017; 146 914 confirmed cases reported in 2016 to the PAHO regional office); in Europe, about 460 cases reported to ECDC in 2017 involving 10 countries, mainly Italy [613].</p> <p>- Ebola causes severe hemorrhagic fever, frequently lethal. The mortality rate of Ebola is about 50%.</p> <p>- WHO estimates that about 71 million people are living with chronic hepatitis C [601].</p> <p>- Covid-19 caused already more than 2.3 million deaths worldwide.</p> <p>- Influenza spreads around the world in yearly outbreaks, resulting in about three to five million cases of severe illness and about 290,000 to 650,000 deaths [591].</p> <p>Molnupiravir is approved in the UK (and already purchased in several other countries). It is under assessment for a marketing authorisation to treat Covid-19 in the EU.</p> <p>Several AVs are currently authorised to treat hepatitis C and human influenza virus infections. Remdesivir received a conditional marketing authorisation in the EU to treat COVID-19 in 2020; the FDA officially granted emergency use authorisation for remdesivir to treat COVID-19 in severe hospitalized patients in May 2020. However, WHO advised against its use.</p> <p>No specific antiviral available to treat Chikungunya, norovirus and Ebola.</p>	<p>virus and Influenza A virus, the latter one retained as major zoonotic viruses, are single-stranded RNA viruses.</p> <p>The likelihood of occurrence of resistance appears to be low [613, 614]</p>	<p>Not presently authorised as veterinary medicines in the EU or internationally. No evidence was found for its use in animals in veterinary practice. Given the mechanism of action of this AV, specific need for this antiviral to treat serious infections in animals in the EU would be likely.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of molnupiravir in veterinary field practice is non-existent so far.</p>	

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	<p>Vaccines are currently available to prevent humans against Ebola, influenza virus and Covid-19 infections; no vaccines available against Chikungunya, hepatitis C or norovirus infections.</p> <p>Criterion met: Yes</p>	<p>Criterion met: Yes</p>	<p>Criterion met: Yes</p>	
<p>Nitazoxanide/ Tizoxanide (Please also refer to use of nitazoxanide as an antiprotozoal substance)</p>	<p>Nitazoxanide showed activity in humans against influenza, chronic hepatitis B and C, rotavirus and norovirus gastroenteritis; and in vitro activity against the MERS-CoV and other coronaviruses.</p> <p>These viruses represent major threats to humans. For instance:</p> <ul style="list-style-type: none"> - Norovirus is the most common cause of acute gastroenteritis, annually causing an estimated 685 million cases. About 200 million cases are seen among children under 5 years old, leading to an estimated 50,000 child deaths every year [612]. - By the age of five, nearly every child in the world has been infected with rotavirus at least once. Nearly 500,000 of these children still die from rotavirus infection worldwide each year [615] and almost two million more become severely ill [616]. - Influenza and chronic viral hepatitis: refer to sections about antivirals acting against influenza viruses and chronic viral hepatitis above. <p>Antivirals other than nitazoxanide are currently authorised in the EU against influenza and chronic hepatitis B and C (see above).</p> <p>Specific antiviral treatment options, with proven efficacy, for rotavirus and norovirus diseases are not available. There is no specific antiviral treatment recommended for MERS-CoV infection [617].</p> <p>Vaccines against influenza, HBV and HEV are currently available.</p>	<p>Host-targeted nitazoxanide has a high barrier to antiviral resistance [618].</p> <p>Noroviruses can infect a broad range of hosts including livestock and pets. Rotaviruses have been recovered from diarrheal faeces of all domestic animals. Although still debated, rotaviruses are suspected to be zoonotic. Noroviruses are not classified as zoonotic so far, but they may not be host-restricted [619, 620]. Amongst the quoted genera or families of viruses, the Influenza A virus and the rotavirus represent the only zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally. Outbreaks of HPAI are controlled by slaughter (CD 92/40/EEC). No evidence was found for use in companion animals, or specific need for this antiviral to treat serious viral infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of nitazoxanide in veterinary field practice is apparently nonexistent.</p>	<p>Yes</p>

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	
Triazavirin	<p>Triazavirin showed activity against influenza viruses, tick-borne encephalitis virus (flavivirus) and perhaps against Lassa fever and Ebola virus. Its efficacy has been investigated in Russia with regard to Influenza [621] and in the US [622] and China with regard to Covid-19 [623].</p> <p>These viruses represent major threats to humans:</p> <ul style="list-style-type: none"> - Tick-borne encephalitis follows typically a biphasic pattern, first non-specific flu-like symptoms, followed by serious neurological symptoms. The mortality rate is of 1% to 2%; long-lasting or permanent neuropsychiatric consequences are observed in 10 to 20% of infected patients. - Lassa fever (not present in the EU) is often asymptomatic. When symptoms occur they are flu-like, with sometimes bleeding from the mouth or gastrointestinal tract. The mortality rate is of about 1%; of those who survive, about a quarter have hearing loss, which improves in about half of these cases [624]. In pregnant women, the mortality rate reaches 30%, and the foetus dies in 85% of cases [624]. - Ebola (not present in the EU) causes severe hemorrhagic fever, frequently lethal. The mortality rate is of about 50%. - Influenza: refer to section about antivirals acting against influenza viruses above. <p>Alternatives to triazavirin are available with regard to influenza (see above). Ribavirin, when used at an early stage of Lassa fever, is the only effective antiviral treatment against this disease.</p>	<p>Resistance to this antiviral is not recorded so far.</p> <p>Tick-borne encephalitis is known in dogs, in which peracute/lethal as well as subacute and chronic courses have been reported. Clinical signs (mainly serious neurological symptoms) are not systematic. Dogs and ruminants may be reservoirs for human infection [625]. Lassa fever virus and Ebola virus are not known to infect domestic animals. Amongst the quoted genera or families of viruses, the Influenza A virus and the West Nile virus (flavivirus) represent the only zoonotic threat to humans.</p> <p>No transfer of resistant viruses, from domestic animals to humans, was identified so far.</p>	<p>No antivirals are included in the Annex to the MRL Regulation (EU) 37/2010 and hence they cannot be used at present in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.</p> <p>Not presently authorised as veterinary medicines in the EU or internationally.</p> <p>No evidence was found for use in companion animals, or specific need for this antiviral to treat serious infections in animals in the EU at the present time.</p> <p>The notion of 'availability of alternative treatments' does not apply here, as the use of triazavirin in veterinary field practice is apparently nonexistent.</p>	Yes

Antivirals	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	Specific antiviral treatment options, with proven efficacy, for tick-borne disease and Ebola are not available. Vaccines against influenza, tick-borne encephalitis and Ebola are currently available.			
	Criterion met: Yes	Criterion met: Yes	Criterion met: Yes	

3.3. Antifungals

For antifungals, all groups that were identified as used for the treatment of important human fungal diseases (Table 64) are included in Table 63, below. Please refer to the discussion of the methodology in Section 2.7. of the report. More detailed monographs for antifungal classes and ATC(vet) codes are included in the Annex to the advice (See Annex 3. and 6.3. , respectively).

Table 63. Summary table of antifungal classes/substances that underwent detailed evaluation against the criteria for designation of antimicrobials to be reserved for humans

Antifungal agents	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
<p>Azoles e.g. miconazole, itraconazole, voriconazole</p>	<p>Important as first-line treatment for life-threatening invasive aspergillosis and chronic aspergillosis; and as a second-line and follow up treatment for invasive candidiasis. Azoles are also important for various other serious systemic mycoses (e.g. histoplasmosis, cryptococcal meningitis, <i>Scedosporium</i> and <i>Fusarium</i> spp.) that cause severe infections in immunocompromised patients.</p> <p>Azoles may be used prophylactically in high risk immunosuppressed patients. Additionally important due to the absence of alternative oral treatments for longer term follow up of fungal infections.</p> <p>The emergence of nosocomial infections in immunocompromised patients due to multidrug resistant <i>Candida</i> spp. (e.g. <i>C. auris</i>, <i>C. glabrata</i>) and azole-resistant <i>Aspergillus fumigatus</i> is a serious threat to human health.</p> <p>Azoles are also important for treatment of human dermatophytoses, which although common in healthy and immunocompromised people, rarely have serious human health consequences.</p> <p>See Table: <i>Important human fungal diseases</i> for further information on health burden and alternative treatments.</p>	<p><i>C. albicans</i> from humans largely remains susceptible, but azole resistance in other <i>Candida</i> spp. is increasing (see left). Azole-resistance in <i>A. fumigatus</i> has led to change in first-line therapy in some regions.</p> <p>Limited data are available on the occurrence of azole resistance in isolates from animals. Aspergillosis and candidiasis are not considered as direct zoonoses; therefore, the risk for direct transmission of azole-resistance in these pathogens from animals to humans is not likely to be significant. Animals could contribute to the pool of azole-resistance in environmental <i>Aspergillus</i> and <i>Candida</i> spp., but contribution is likely to be very low compared to that from other agricultural sources.</p> <p>Azole-resistant dermatophytes are a potential zoonotic hazard, but empirical evidence for this is weak and this disease rarely has serious human health consequences.</p>	<p>Enilconazole is included in Reg (EU)37/2010, for topical use only, and has been used to treat dermatophytosis in cattle and horses. Parconazole has 'no MRL required' status for guinea fowl. Ketoconazole is included on the list of substances essential for the treatment of equidae (Regulation (EU) 122/2013*) as a systemic treatment for fungal pneumonia and guttural pouch mycosis (although surgical intervention may now be a preferred option for the latter). Miconazole is included in the same list for topical treatment of fungal eye infections in horses.</p> <p>Azoles are the only antifungal agents authorised for systemic treatment of (companion) animals in the EU, other than griseofulvin (non-food horses, only). They are the only authorised antifungal for (zoonotic) dermatophytoses in cats and dogs, for which treatment is necessary on public health grounds, and for fungal respiratory infections in ornamental birds.</p> <p>Use of azoles outside of the terms of a marketing authorisation is important for treatment of a wide range of mostly sporadic but serious fungal diseases occurring in companion and zoo animals e.g. aspergillosis, histoplasmosis, zygomycosis, sporotrichosis and cryptococcosis. There are few or no alternatives to treat these diseases. Azoles are the preferred treatment owing to their safety profile. They are included in the <i>WSAVA List of Essential Medicines for Cats and Dogs</i> (2020) for topical and systemic treatment of superficial and deep fungal infections.</p>	<p>No</p>

Antifungal agents	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	The availability of alternative treatment options for fungal infections is generally limited.			
	Criterion met: Yes	Criterion met: No - Limited evidence	Criterion met: No	
Polyenes Nystatin, natamycin, amphotericin B (see also antiprotozoals)	Amphotericin B (AmB) is recommended as first-line treatment for mucormycosis, cryptococcal meningitis (combined with flucytosine) and some less common mycoses (blastomycosis, histoplasmosis, mucormycosis and sporotrichosis) when infections are severe and disseminated. AmB is a second-line (salvage) choice for treatment of severe invasive candidiasis or aspergillosis, or for strains resistant to first-line antifungals, such as azoles and echinocandins, hence its increasing importance. The availability of alternative treatment options for fungal infections is generally limited. See Table: <i>Important human fungal diseases</i> for information on health burden and alternative treatments.	Acquired resistance to polyenes remains very rare, but has been reported in human <i>Candida</i> spp. and <i>Aspergillus</i> spp. isolates. There is little convincing evidence of resistance in animal isolates. Other than <i>Sporothrix brasiliensis</i> (which does not occur naturally in EU) the fungal infections that are treated with polyenes in humans are not considered zoonotic. Transmission of polyene-resistant fungal infections from animals to humans is not likely to be significant in the EU.	Natamycin is included in Regulation (EU)37/2010 with 'no MRL required' status for topical use in bovines and <i>Equidae</i> , but no EU-authorisations were found. Nystatin is included in the list of essential substances for <i>Equidae</i> for yeast infections. Nystatin is authorised in topical ear products for pets in the EU, for which alternatives are available. Amphotericin B is not authorised as a VMP in the EU, and cannot be used in food-producing species as it is not included in the Annex to the MRL Regulation (EU) 37/2010. Amphotericin B is recommended in textbooks and guidelines for treatment of rare and serious fungal infections (e.g. <i>Candida</i> , <i>Blastomyces</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , <i>Cryptococcus</i> spp) in companion and zoo animals. Otherwise, it is usually used in cases of previous treatment failure or in combination with other antifungals for refractory cases. Amphotericin B is included in the <i>WSAVA List of Essential Medicines for Cats and Dogs (2020) (Complementary list)</i> for treatment of fungal infections.	No
	Criterion met: Yes	Criterion met: No	Criterion met: No	
Pyrimidine analogues - flucytosine	Flucytosine, in combination with amphotericin B, is important as first line treatment for cryptococcal meningitis, a serious disease in immunosuppressed humans, with few available alternatives. Flucytosine is also recommended in rare cases to be used in combination with other antifungals for the treatment of severe systemic candidiasis and azole-resistant <i>Aspergillus</i> spp. infections.	In humans, resistance to flucytosine develops rapidly during treatment, limiting its use as a single therapy. No reports were found that specifically identified resistance to flucytosine in fungal isolates from domestic animals; although it could be speculated that resistance would develop rapidly under treatment. Although bird droppings have been implicated as a source of <i>Cryptococcus</i> spp. for human infections, evidence of transmission from animals is weak.	Flucytosine is not included in Reg (EU)37/2010, therefore it cannot be used in food-producing animals in the EU. No EU-authorised VMPs containing flucytosine were found. Cryptococcosis occurs rarely or sporadically in domestic animals in Europe, but flucytosine is part of the first-line treatment for serious CNS or systemic disease in cats (European Advisory Board on Cat Diseases) and dogs. Azoles are an alternative for mild/moderate disease only.	No

Antifungal agents	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
	See Table: <i>Important human fungal diseases</i> for information on health burden and alternative treatments.	In addition, disease and therefore treatment is rare in animals suggesting that the risk of transfer of resistance in <i>Cryptococcus</i> spp. from animals to humans is very low.		
	Criterion met: Yes	Criterion met: No	Criterion met: No	
Griseofulvin	Griseofulvin is used for the topical or systemic treatment of dermatophyte infections, as a second-line alternative to modern antifungals with more favourable pharmacokinetic and safety profiles e.g. azoles and terbinafine. Although a common infection in immunocompromised people, dermatophytosis rarely has serious consequences. See Table: <i>Important human fungal diseases</i> for information on health burden and alternative treatments.	There are limited reliable reports of resistance in human isolates. There is a potential pathway for transmission of resistance from animals to humans, but no reports resistance in animal isolates were found.	Griseofulvin is not included in the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU. It is authorised as a VMP in the EU for oral administration to non-food horses*, for the treatment of dermatophytes. The potential alternative authorised treatment is enilconazole, for topical use. Griseofulvin (under Article 112 of Regulation (EU) 2019/6) is recommended in treatment guidelines for dermatophytosis in dogs and cats where systemic treatment is needed, but it is noted that it has more potential side effects compared with the alternatives, itraconazole and terbinafine. Dermatophytosis is not regarded as a life-threatening disease; however, it is a common zoonosis and animal treatment is necessary in the interests of animal and public health. Azoles are the authorised alternative.	No
	Criterion met: No	Criterion met: No - Limited evidence	Criterion met: No	
Allylamines e.g. terbinafine, naftifine	Terbinafine is important for the topical and systemic treatment of dermatophytosis. Although a common infection in healthy and immunocompromised people, dermatophytosis rarely has serious consequences. Azoles are an alternative treatment. See Table: <i>Important human fungal diseases</i> for information on health burden and alternative treatments.	Resistance to terbinafine in dermatophytes has historically been rare, but has increased in human isolates recently. There is a potential pathway for zoonotic transmission of terbinafine-resistant strains of dermatophytes but limited evidence of resistance in animal isolates.	Allylamines are not included in the MRL Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU. Terbinafine is authorised in topical ear products for pets in the EU, for which alternatives are available. Terbinafine may be used under Article 112 of Regulation (EU) 2019/6 as a systemic treatment for dermatophytosis and <i>Malassezia</i> spp. infections in cats and dogs. Neither disease is regarded as a life-threatening; however, dermatophytosis is a common zoonosis and animal treatment is necessary in the interests of animal and public health. Azoles are the authorised alternative.	No
	Criterion met: No	Criterion met: No - Limited evidence	Criterion met: Yes	

Antifungal agents	Criterion A - High importance to human health	Criterion B - Risk of transmission of resistance	Criterion C - Non-essential need for animal health	Recommended to be reserved for human use
Echinocandins Caspofungin, micafungin, anidulafungin	<p>Echinocandins are the first-line choice for treatment of invasive candidiasis, an important cause of mortality and morbidity in immunosuppressed patients. Azoles are an alternative, although resistance is an increasingly problematic and amphotericin B has a less favourable safety profile.</p> <p>Echinocandins may also be used to treat invasive aspergillosis in patients refractory to azoles, and as prophylaxis for <i>Candida</i> infection in immunosuppressed patients.</p> <p>The availability of alternative treatment options for fungal infections is generally limited.</p> <p>See Table: <i>Important human fungal diseases</i> for information on health burden and alternative treatments.</p>	<p>In human isolates, resistance has been reported for major <i>Candida</i> spp. but is rare except in <i>C. glabrata</i>. Resistance is also very rare in <i>Aspergillus</i> spp.</p> <p>No evidence found of resistance to echinocandins in fungal isolates from animals. Aspergillosis and candidiasis are not regarded a zoonoses and there is no direct pathway for transmission of echinocandin resistance from animals to humans.</p>	<p>Echinocandins have not been authorised for use in VMPPs in the EU. They are not included in Regulation (EU) 37/2010 and cannot be used in food-producing animals in the EU.</p> <p>Little evidence could be found for use in companion animals.</p>	No
	Criterion met: Yes	Criterion met: No	Criterion met: Yes C.1.(a)	

* Under Directive 2001/82/EC, substances included in the List of substances essential for the treatment of Equidae (Regulation (EU) 122/2013) were allowed for use in food-producing horses with a withdrawal period of 6 months applied.

Table 64. Important human fungal diseases

Human disease	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals
Conclusion			<i>For information on resistance, please refer to the individual monographs</i>
Candidiasis <i>Candida</i> is associated with a range of clinical manifestations from superficial mucosal infections to blood stream infections, intra-abdominal and deep-seated candidiasis. Invasive <i>Candida</i> (IC) infections are an important cause of morbidity and mortality, especially in critically ill patients, those undergoing abdominal surgery and the immunocompromised. <i>C. albicans</i> is the main hospital-acquired pathogen, but there has been a shift towards species that are	<p><i>Candida</i> are normal commensals of humans and therefore distribution is worldwide. Estimates indicate around 1million IC infections per year globally [630].</p> <p><i>C. auris</i> has emerged rapidly and is now in 30 countries across 6 continents. There are 4 distinct clades which all show intrinsic</p>	<p><i>Candida</i> can be found as part of the normal microbiota in healthy animals, especially birds [631, 632] which could therefore be a source of environmental contamination. However, human infections are usually caused by strains that commensally pre-colonize the host and then become opportunist pathogens, rather than by vertical or longitudinal transfer, and the</p>	<p>Humans Guidelines on the treatment of candidiasis are provided by ECIL [633], IDSA [634] and ESCMID [635, 636]. Recommendations vary somewhat according to specific clinical circumstances, but in general, echinocandins are recommended as the preferred treatment with lipid amphotericin B (L AmB) or certain azoles as the next option in case of intolerance or resistance. Fluconazole is recommended for prophylaxis of IC in patients at high risk and for step down (consolidation) therapy once</p>

Human disease <i>Conclusion</i>	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p>intrinsically resistant or less susceptible to commonly used antifungals. <i>C. glabrata</i>, <i>C. parapsilosis</i> and <i>C. tropicalis</i> increasingly account for invasive infections [626].</p> <p><i>C. auris</i>, first detected in 2009, has been identified as a major public health concern owing to its rapid global emergence, ability to cause nosocomial outbreaks and multidrug resistance [627].</p> <p>In an ECDC survey of healthcare-associated infections in EU acute care hospitals in 2011-12, <i>Candida</i> spp. was associated with 7.4% of bloodstream infections. A case-fatality rate of 30-40% is reported even in patients receiving treatment [628].</p> <p>The CDC has listed fluconazole-resistant <i>Candida</i> spp. amongst the pathogens posing a serious threat to human health [629].</p> <p>Conclusion <i>IC is a serious opportunistic infection in immunosuppressed humans with high prevalence and high mortality. Most infections derive from commensal organisms, but some strains are responsible for hospital outbreaks. In human medicine, resistance to both azoles and echinocandins is increasing (see related monographs). In veterinary medicine, azoles are occasionally used to treat clinical candidiasis in companion animals, which is rare, except in pet birds. The zoonotic potential of infections is very low and the risk of direct transfer of resistance in Candida spp. from animals to humans is considered very low.</i></p>	<p>resistance to fluconazole and variable susceptibility to other antifungals. Hospital outbreaks relate to the ability of <i>C. auris</i> to persist on environmental surfaces despite attempts to decontaminate, and patient-to-patient transmission is possible.</p>	<p>direct zoonotic potential can thus be considered to be low [12].</p> <p>Oral mucosal and gastrointestinal candidiasis occurs commonly in birds - 'sour crop'. In poultry, crop mycosis has low morbidity and mortality, occurring most commonly after prolonged antibiotic treatment. Cutaneous candidiasis may rarely be seen in dogs in association with atopy or immunosuppressive diseases. Systemic candidiasis occurs rarely in dogs and cats; often in association with trauma or foreign bodies. Environmental <i>Candida</i> spp. can cause mastitis in cattle and abortion in cattle and horses [12].</p>	<p>susceptibility is confirmed and the patient is stable. Azoles are currently the only option for oral treatment of fungal infections in humans.</p> <p>All the above classes are authorised in <u>HMPs</u> in the EU.</p> <p>For <i>C. auris</i>, echinocandins are recommended as first-line therapy due to more almost universal resistance to azoles and side-effects of AmB; however, there is a need for novel antifungal classes to treat candidiasis [637].</p> <p><u>EU VMPs</u> Parconazole has MRL status for guineafowl, relating to treatment of candidiasis. Itraconazole is authorised for respiratory candidiasis in ornamental birds.</p> <p>Azoles have been used (outside the terms of the marketing authorisation) to treat candida infections in cats and dogs [345].</p>
<p>Aspergillosis (e.g. <i>Aspergillus fumigatus</i>, <i>A. terreus</i>, <i>A. niger</i>). <i>A. fumigatus</i> is the cause of several pulmonary diseases in humans including allergic bronchopulmonary disease (Farmer's lung) and invasive pulmonary aspergillosis. It is also the most common species causing invasive aspergillosis (IA). Cerebral aspergillosis occurs in about 10-20% patients with IA. IA is mostly seen in immunosuppressed patients, in whom disease is severe. However, it has recently been recognised as an underdiagnosed infection in patients with severe influenza, increasing the mortality significantly [638]. This situation might also apply to Covid-19 patients. The overall mortality due to IA</p>	<p>Aspergillus is a globally distributed opportunist pathogen, found in a variety of ecological niches.</p> <p>ECDC estimated an incidence of 63,250 cases of invasive aspergillosis per year in the EU, and a prevalence of >2 million patients affected with allergic aspergillosis [640].</p> <p>It is estimated that globally, >350,000 patients develop IA each year [630]. GAFFI estimates that there are 1.2M chronic pulmonary</p>	<p><i>Aspergillus</i> is a saprophyte living in soil, decaying vegetation and grains. Following inhalation it is an opportunist pathogen of humans and animals, especially birds. There is no transmission between animal hosts.</p> <p>Lesions where conidial heads can be present (e.g. air sacs in birds or nasal cavities in dogs) may release conidia into the environment that could be inhaled by susceptible humans. However, in animal tissue, <i>Aspergillus</i> usually develop without producing conidial heads, and even if some conidia are finally released, their number is limited in comparison with the quantity of</p>	<p><u>Humans</u> Guidelines on the management and treatment of IA have been published by various organisations: ESCMID [643], IDSA [644], ECIL [633]. Recommendations vary somewhat according to specific clinical circumstances, but in general, itraconazole* is first line for chronic pulmonary aspergillosis whereas voriconazole* or isavuconazole* are recommended for first line treatment of invasive and pulmonary aspergillosis; with liposomal AmB* or echinocandins* as second-line or salvage therapy for example in the case of environmentally driven azole resistant invasive aspergillosis. Azoles are recommended for prophylaxis in patients at high risk of IA.</p>

Human disease <i>Conclusion</i>	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p>infections ranges from 30-90% in the EU [639]. Over the past decades, azole resistance has emerged worldwide even in azole naïve patients due to selection of resistant mutants of <i>A. fumigatus</i> in the environment. This resistance has been linked to use of azole fungicides in agriculture.</p> <p>Conclusion <i>IA is a serious opportunistic infection in immunosuppressed humans with high prevalence and high mortality. Azoles are used extensively for prophylaxis of aspergillosis in high risk patients and as first-line treatment, and resistance is increasing. Azoles are superior to other antifungal classes in susceptible infections and the only oral option. Azole pesticides used in agriculture have been linked to emerging resistance worldwide. A high concentration of Aspergillus conidia on poultry farms is a risk factor for colonisation of workers, but aspergillosis is generally not regarded as a direct zoonotic disease. In veterinary medicine, azoles are occasionally used to treat companion animals with aspergillosis, but they are not used as veterinary medicines to treat food-producing animals in the EU. The risk of transfer of antifungal-resistance in Aspergillus spp. from animals to humans in the EU is considered very low.</i></p>	<p>aspergillosis cases in association with TB.</p>	<p>conidia resulting from the development of <i>Aspergillus</i> species in the environment. As a consequence, animal aspergillosis should not be considered as a zoonotic disease [641]. A high density of environmental <i>Aspergillus</i> conidia could be a significant risk factor for developing invasive infection in haematological and immunocompromised patients. Cafarchia, Camarda [642] investigated the epidemiology of <i>Aspergillus</i> species in laying hen farms, their concentration in the environment and the occurrence of associated symptoms in birds and workers. Although high concentrations of airborne <i>Aspergillus</i> conidia did not cause disease in birds, a significant relationship was observed between occurrence of these fungi and human colonization, indicating a potential risk of infection for human health.</p> <p>In domestic animals, the most common manifestations are pulmonary infections in poultry, pneumonia and abortion in cattle, guttural pouch mycosis in horses and rhinosinusitis in dogs and cats; infections may also become systemic.</p>	<p>* Authorised in EU HMPs</p> <p><u>EU VMPs</u> Itraconazole is authorised to treat <i>Aspergillus</i> infections in captive pet birds.</p> <p>Infections in cattle are usually not treated as there are no EU- authorised systemic antifungals for major food-producing species. In poultry, environmental disinfection may be used to control infections. In cats and dogs, nasal aspergillosis is treated (outside the terms of the marketing authorisation) with azoles administered systemically and topically [345, 645-647].</p>
<p>Cryptococcosis Major pathogenic spp. are <i>Cryptococcus neoformans</i> (<i>Cn</i>) and <i>C. gattii</i>. <i>Cryptococcus</i> is an opportunistic pathogen in immunosuppressed (especially in HIV) patients, where <i>Cn</i> cause 98% of infections, but outbreaks have also been reported in immunocompetent humans and animals in which <i>C. gattii</i> is more common. The major sites for infection are CNS and lungs. Respiratory signs can include pneumonia and acute respiratory distress. Cryptococcal meningitis is a major cause of morbidity and mortality responsible for 15% of HIV deaths globally [648].</p> <p>Conclusion <i>Cryptococcal meningitis is a serious opportunistic infection in immunosuppressed humans with high prevalence in certain risk groups and high mortality.</i></p>	<p>Worldwide. The global burden is estimated at 1M cases/year [649].</p> <p>Incidence and mortality are high in regions where there is limited access to highly active antiretroviral therapy to control HIV disease. WHO estimates 181,000 deaths/year in HIV patients, most occurring in sub-Saharan Africa (WHO, 2018).</p> <p><i>C gattii</i> is more often seen in the (sub) tropics [345]. An outbreak of <i>C. gattii</i> in Vancouver and Northwestern regions of US affected humans, domestic animals and marine mammals.</p>	<p><i>Cryptococcus</i> spp. are mostly environmental saprophytes. <i>C. neoformans</i> is isolated mostly from soil and bird (especially pigeon) droppings; <i>C. gattii</i> from decaying plant material. Rodents may be considered as reservoirs, although <i>Crypto</i> have been recovered from various wild animals and birds. Transmission is by inhalation of spores or yeast.</p> <p><i>C. neoformans</i> most frequently infects cats producing respiratory infections, granulomas and disseminated infections. Dogs may be affected, also with CNS involvement. Occasionally <i>Cn</i> has been reported causing mastitis in cattle. <i>Cryptococcus</i> is an environmental opportunist sapronosis; there is no documented transmission between mammals. Likewise, although faeces of birds</p>	<p><u>Humans</u> For treatment of meningoencephalitis, the IDSA 2010 and WHO guidelines (2018) advise initial treatment with L AmB and flucytosine, followed by suppressive regimens using fluconazole [649].</p> <p>WHO guidelines recommend preventive treatment with fluconazole for advanced HIV patients who have positive cryptococcal antigen tests.</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p> <p>In dogs and cats, AmB, itraconazole and fluconazole have been used for treatment [645].</p>

Human disease <i>Conclusion</i>	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p>Although bird droppings have been implicated as a source of <i>Cryptococcus</i> for human infections, evidence is weak. In addition, disease and therefore treatment is rare in animals suggesting that the risk of transfer of resistance in <i>Cryptococcus</i> spp. from animals to humans is considered very low.</p>		<p>have been implicated as a source of <i>Cn</i> to humans in sporadic cases, there is no firm evidence for this [12, 650, 651].</p>	<p>The European Advisory Board on Cat Diseases recommends AmB as the most effective treatment, whereas itraconazole/fluconazole monotherapy is effective in cases without CNS involvement [652].</p>
<p>Mucormycosis (<i>Rhizopus</i>, <i>Mucor</i>, <i>Lichtheimia</i>, <i>Cunninghamella</i>, <i>Apophysomyces variabilis</i> etc). Mucormycosis (zygomycosis) is a rare aggressive fungal disease affecting specific patient groups including haematological and transplant patients, diabetics and individuals suffering a penetrating trauma. Signs are non-specific including rhinocerebral, pulmonary, cutaneous and disseminated infections. Mucormycosis associated with angio-invasion is related to high mortality.</p> <p>Conclusion <i>Invasive mucormycosis is a rare but serious opportunistic infection in immunosuppressed humans with high mortality. In veterinary medicine, mucormycosis is rare and there is no transmission from animals to humans, therefore the risk of transfer of resistance in Mucorales spp. from animals to humans is considered negligible.</i></p>	<p>Causative agents vary across geographic locations. The disease burden in Europe is increasing, with a reported incidence of up to 6.3 cases/100,000 hospital admissions in Switzerland. Nosocomial infections are also increasing [653]. No global estimate is available, but Gangneux, Bognoux [654] reported c. 79 cases of invasive infections/year in France.</p>	<p>Mucormycosis is a saprobic opportunistic infection caused by fungi in the order <i>Mucorales</i>. The natural habitat is soil, but they are also found in air, foodstuffs and dust. Humans acquire infection by inhalation, ingestion of contaminated food, or traumatic inoculation.</p> <p>Mucormycotic ruminitis is seen after intensive antibiotic treatment in cattle; intestinal lymphadenitis may occur after heavy exposure to <i>Mucorales</i> through contaminated feed. There is no transmission between animals and humans [12].</p>	<p>Humans Management requires a multidisciplinary approach, including surgery, therapy and controlling underlying conditions. Global guidelines recommend L AmB as first-line treatment, with isavuconazole or posaconazole as a salvage treatment [655].</p> <p>EU VMPs No VMPs could be found authorised for this indication in the EU. Little information was available on treatment in animals.</p>
<p>Dermatophytosis Dermatophytes cause superficial mycoses in humans affecting skin, scalp and nails. <i>Tinea capitis</i> occurs predominantly in children, <i>tinea pedis</i> in young adults and onychomycosis in older patients. Infections caused by anthropophilic species are transferred from human to human and include <i>Trichophyton rubrum</i>, <i>T. interdigitale</i> frequently causing nail and feet infections and <i>T. tonsurans</i> and <i>Microsporum audouinii</i> that have caused outbreaks of skin and scalp infections in humans.</p> <p>Infections caused by zoophilic dermatophytes are usually more inflammatory than those caused by anthropophilic dermatophytes and respond well to treatment. Common species involve <i>M. canis</i> and <i>T. verrucosum</i>.</p>	<p>Dermatophytes have worldwide distribution, although there is geographic variation in predominant spp. Fungal infections of skin, hair or nails are thought to affect c. 1 billion people worldwide [630].</p> <p>Anthropophilic spp. cause the majority of human infections. <i>T. rubrum</i> is the most frequent species in Europe (& worldwide) causing tinea pedis and unguium. Tinea capitis represents c. 1% of infections in Europe. Worldwide tinea capitis is mainly caused by zoophilic spp. [658].</p>	<p>A study in Germany showed a prevalence of <i>M. canis</i> of 1.5% and <i>T. benhamiae</i> of 2.9% in human skin samples [659]. <i>M. canis</i> is the main agent in tinea corporis and capitis in the Mediterranean; however recently anthropophilic spp. have resurged in Europe (Hayette 2015).</p> <p>The major zoonotic dermatophytes and host species are: <i>M. canis</i> (dogs, cats, rabbits, horses), <i>T. mentagrophytes</i> (rabbits rodents), <i>T. verrucosum</i> (cattle, ruminants), <i>T. erinacei</i> (hedgehogs), <i>T. benhamiae</i> (guinea pigs and other rodents) (Seyedmousavi 2018b). Direct transmission occurs from pets and domestic livestock to humans.</p>	<p>Humans Localised superficial infections are treated with topical antifungal creams (terbinafine clotrimazole, miconazole, etc).</p> <p>More extensive infections may be treated with oral systemic therapy where itraconazole is preferred for <i>Microsporum</i> and terbinafine for <i>Trichophyton</i> and <i>Epidermophyton</i> infections. Fluconazole is an alternative but less efficacious. Oral griseofulvin or terbinafine are used for tinea capitis depending on the involved species. Majocchi's granuloma has been treated with terbinafine, itraconazole or griseofulvin [661].</p> <p>There is no consensus for treatment of extensive or invasive dermatophytosis. Successful treatment has been reported with terbinafine or triazoles. Lifelong treatment may be needed [656].</p>

Human disease Conclusion	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p>Very rarely extensive or invasive forms (deep dermatophytosis, Majocchi granuloma) occur in immunocompromised individuals (especially those with CARD9 mutation). In this case, infection may spread e.g. to lymph nodes or CNS [656].</p> <p>Conclusion <i>Dermatophytosis is a common fungal infection in humans; systemic spread is very rare but tinea capitis may cause permanent alopecia and toe nail infections lead to secondary bacterial infections. The major zoonotic spp. are present in Europe. Terbinafine is used for treatment of infections in people and azoles are used for treatment of both humans and animals. It is important that animals are treated to prevent zoonotic transmission. Resistance to terbinafine and azoles has been reported in zoonotic dermatophyte spp. In India, a multidrug resistant T. mentagrophytes/T. interdigitale clade is potentially emerging epidemically and the distinction of anthropophilic and zoonotic species may be less well defined [657]. There is a risk of transfer of resistance from animals to humans in the EU, and oral alternative treatments are few in both cases. However, dermatophytosis is generally not regarded as a disease with serious human health consequences.</i></p>		<p><i>M. canis</i> may become enzootic in cat breeding establishments, where treatment may be absent or incomplete. The most common complication of <i>M. canis</i> in immunocompromised people is a prolonged treatment time. The true prevalence of dermatophytosis in cats and dogs and the rate of transmission from animals to people is unknown [660].</p>	<p>EU VMPs Vaccines are available in the EU for prevention of <i>T. verrucosum</i> in cattle, a disease of economic importance. Enilconazole is approved for topical treatment of dermatomycoses in cattle, horses, cats and dogs. Miconazole is approved for topical treatment of <i>M. canis</i> in cats. In regard to oral systemic treatment of dermatophytosis, itraconazole is authorised for cats, ketocaonazole for dogs, and griseofulvin for horses.</p> <p>The World Assoc for Veterinary Dermatology guidelines recommend <u>topical</u> treatment with (lime sulfur) enilconazole or miconazole/chlorhexidine shampoo for generalised dermatophytosis in dogs and cats. For <u>systemic</u> treatment, itraconazole and terbinafine are most safe and effective; griseofulvin has potential for more adverse effects [660].</p>
<p>Sporotrichosis <i>Sporothrix schenckii</i>, S. brasiliensis (Sb) Human infections usually involve localised cutaneous and sub-cutaneous granulomatous infections. In some cases infection spreads locally along lymphatics. Pulmonary infections are rare but may occur when <i>S. schenckii</i> conidia are inhaled. Disseminated disease including meningitis is opportunistic in immunosuppressed patients. Between 1998 to 2011, more than 4000 human cases of <i>Sb</i> associated with epizootics in cats were reported in Brazil [662].</p> <p>Conclusion</p>	<p><i>S schenckii</i> is found worldwide but is more common in the tropics. Brazil, S Africa and China are considered highly endemic areas. Most infections are isolated and outbreaks are uncommon. Disease is rarely/sporadically reported in Europe. <i>S brasiliensis</i> is an emerging spp. restricted to Brazil [663].</p>	<p><i>Sporotrix</i> is a dimorphic fungus. The main reservoir for <i>Ss</i> is soil and decaying vegetation, with transmission to humans by traumatic inoculation of contaminated soil or organic matter, and possibly inhalation. Disease has been reported in other domestic and wild animals. Classically, sporotrichosis is a sapronosis. Zoonotic transmission has been suspected in armadillo hunters [663]. Cats are the animal host most susceptible to infection with <i>Sb</i>. Occasionally epizootics have occurred with cat-cat transmission in domestic cats in S and SE Brazil, and zoonotic transmission to owners via bites or scratches. In these circumstances, Sb is considered to be a true zoonosis [12].</p>	<p>Humans For localised lymphocutaneous infections, Kauffman, Bustamante [664] advises oral itraconazole is the treatment of choice, with terbinafine as an option in patients who fail to respond. Rare life-threatening pulmonary, osteo-articular, meningeal or visceral infections should be treated with AmB, with step-down to itraconazole (Kauffman 2007).</p> <p>EU VMPs No VMPs could be found authorised for this indication in the EU.</p>

Human disease Conclusion	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p><i>Disseminated sporotrichosis is a serious disease in immunosuppressed patients, sporadically reported in Europe.</i></p> <p><i>S. braziliensis has been responsible for zoonotic outbreaks. Azoles are the treatment of choice and there is a theoretical risk for transfer of azole- or other antifungal-resistant Sb from cats to humans; however, Sb infection is so far restricted to Brazil.</i></p>		<p>In cats, signs range from isolated pyogranulomatous skin lesions to multiple lesions with extension into bone and respiratory signs.</p>	<p>In cats, itraconazole is the treatment of choice. Refractory cases may also be treated with intralesional or IV AmB [662, 665].</p>
<p>Histoplasmosis <i>Histoplasma capsulatum (Hc)</i> Initial disease can range from asymptomatic/ minor self-limiting infection to severe pneumonia. Complications of pulmonary histoplasmosis include lymphadenitis, pericarditis and arthritis. Disseminated disease may develop in immunocompromised patients, especially those with HIV in whom the mortality rate is >50% [630].</p> <p>Conclusion <i>Disseminated histoplasmosis is a serious disease in immunosuppressed patients, sporadically reported in Europe.</i> <i>Azoles are the treatment of choice in animals; although clinical disease is rare. Histoplasma is a sapronosis and transmission from companion animals to humans has not been reported. The risk of transfer of antifungal-resistance in Histoplasma spp. from animals to humans in the EU is therefore considered negligible.</i></p>	<p><i>H capsulatum var capsulatum</i> is found in many regions worldwide, being a problem especially in countries where access to antiretroviral therapy is limited.</p> <p><i>Hc var duboisii</i> is endemic in certain areas of Africa (incl. Nigeria, Senegal and Congo Uganda) and <i>Hc var farciminosum</i> is found in Africa, Asia and S America. It is estimated that globally there are about 100,000 AIDS-related cases of disseminated histoplasmosis annually [630].</p> <p>Europe is usually considered non-endemic/enzootic, although autochthonous cases occur sporadically in humans (Italy, Germany, Turkey) and animals [12, 666].</p>	<p><i>H capsulatum</i> is a dimorphic fungus which infects a diversity of mammalian hosts. The main reservoirs are soil and bats, and the mode of transmission to humans is by inhalation of fungal spores. Birds may also act as hosts, helping to disperse fungal spores in the environment. Histoplasma is an environmental opportunist, a sapronosis which is considered as non-transmissible.</p> <p>Transmission from companion animals to humans has not been reported; although there may be concurrent infections after exposure to the same environmental source [12].</p> <p><i>Hc capsulatum</i> has been reported in dogs, cats, cattle and horses. <i>Hc farciminosum</i> is endemic in horses in some parts of Africa and Asia (epizootic lymphangitis) and in cats and badgers in Europe (Seyedmousavi 2018b, OIE 2012).</p>	<p><u>Humans</u> Liposomal AmB followed by itraconazole is recommended in IDSA guidelines for treatment of acute and chronic pulmonary histoplasmosis, for moderate-severe disseminated histoplasmosis and for CNS infection. Itraconazole is used for follow up and prophylaxis in HIV patients [667].</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p> <p><u>In dogs and cats</u>, the preferred treatment is itraconazole [12]. Fluconazole or AmB may also be used for severe cases or CNS involvement (Lloret 2013). Without treatment, disseminated infections are usually fatal [345].</p> <p>The OIE lists AmB as the antifungal of choice to treat epizootic lymphangitis in horses [668, 669]</p>
<p>Blastomycosis <i>Blastomyces dermatitidis</i> Disease can range from subclinical infection to acute or chronic pneumonia. Acute pulmonary blastomycosis can lead to acute respiratory distress syndrome or disseminated infection, especially in immunocompromised patients. Disseminated disease is uncommon and may affect the osteoarticular or genitourinary systems.</p> <p>Conclusion <i>Acute/disseminated blastomycosis is a serious disease in immunosuppressed patients.</i> <i>Acquired resistance is not described.</i></p>	<p>Blastomycosis is endemic in N. America (Great Lakes) and parts of Africa, the Middle East and India.</p>	<p><i>Blastomyces</i> is a group of dimorphic fungi. A serious fungal disease in humans, dogs and occasionally cats and horses; also seen in livestock and wildlife. Affected dogs are usually immunocompetent. Disease affects the lungs and disseminates with ocular and cutaneous involvement is common. Transmission is by inhalation of conidia from soil contaminated with decaying organic matter and animal droppings. [12]. Outbreaks in both dogs and people can often be traced back to a common environmental source, but blastomycosis is not</p>	<p>IDSA [670] and ATS [671] guidelines in general recommend treatment L AmB if disease is severe or where there is CNS involvement and with itraconazole in mild moderate cases. Fluconazole and other azoles are second line options in patients intolerant to amphotericin B or itraconazole.</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p>

Human disease <i>Conclusion</i>	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<p><i>Azoles are the treatment of choice in animals; although clinical disease is rare in the EU. Blastomycosis is not transmitted from animals to humans. Therefore the risk of transfer of antifungal-resistance from animals to humans in the EU is considered negligible.</i></p>		<p>transmitted directly between animal hosts. Following entry via the respiratory tract in dogs, haematogenous and lymphatic dissemination results in systemic pyogranulomatous disease [345].</p>	<p>The European Advisory Board on Cat Diseases [652] recommends itraconazole in most cases, with AmB or fluconazole for severe cases or where there is CNS involvement. Similar treatments have been used in dogs, with fluconazole often used as an alternative to itraconazole [345, 645, 647].</p>
<p>Coccidioidomycosis Coccidioides infections (<i>C. immitis</i>, <i>C. posadasii</i>) range from mild or asymptomatic infection localised to the lungs to severe disseminated infections which can affect the CNS and may be fatal.</p> <p>Conclusion <i>Disseminated coccidioidomycosis is a serious disease in human patients. AmB and azoles are the treatment of choice people and in animals; although clinical disease is rare in the EU. Coccidioidomycosis is not directly transmitted from animals to humans; therefore the risk of transfer of antifungal-resistance from animals to humans in the EU is considered negligible.</i></p>	<p>Coccidioidomycosis has mostly been reported in animals in California (Valley fever) and S America (Mexico, and arid regions of Argentina, Brazil, Columbia, Guatemala, Honduras, Paraguay, and Venezuela). Fungal Infection Trust [630] gave an estimate of 150,000 cases in the US each year.</p>	<p><i>Coccidioides immitis</i> and <i>C. posadasii</i> are dimorphic soil-borne fungi. Infections in humans and animals are caused by inhalation of conidia and often relate to soil disruption following geo-climatic events [345]. Coccidioidomycosis is an endemic infection with indirect transmission to humans from the environment [12].</p> <p>Severe, disseminated pyogranulomatous disease is mostly reported in dogs; although infection may also be asymptomatic. There may also be skin, bone and CNS involvement. Infections have also been reported in cats, livestock and wildlife. Direct transmission from infected pets has not been reported (other than via bites), but dogs may act as sentinels [345, 651].</p>	<p>The recommended treatments in humans are L AmB or azoles (fluconazole, itraconazole); although infection may recur and treatment may need to be lifelong [672, 673].</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p> <p>Animals with pulmonary disease may respond to monotherapy with azoles, but combination with AmB is recommended for disseminated or refractory infections. Lifelong treatment is often required [345]. Ketoconazole or fluconazole are recommended for treatment of feline coccidioidomycosis (Lloret 2013).</p>
<p>Paracoccidioidomycosis <i>Paracoccidioides</i> spp.</p> <p>Most infections are mild or asymptomatic but acute (juvenile) paracoccidioidomycosis may develop with fever, lymphadenopathy, hepatosplenomegaly and anaemia. Chronic disease is seen in adults with a male to female ratio of 20:1, the lungs being the most common site of infection. The sequelae lead to fibrosis which impacts organ function and cannot be treated with antifungals.</p> <p>Conclusion <i>Paracoccidioidomycosis is a serious disease in humans in Central and South America. AmB, cotrimoxazole and azoles are the treatment of choice in humans. Clinical disease is v. rare in the EU. Paracoccidioidomycosis is not directly transmitted from animals to humans; and no reports were found relating to treatment of animals in the EU; therefore, the risk of</i></p>	<p>Paracoccidioidomycosis is the major systemic mycosis in Latin America. [12]. The prevalence of paracoccidioidomycosis vary between different endemic regions. However, skin testing has revealed up to 50-75% within an endemic region have been infected. The incidence of symptomatic infection ranges from 1-3/100,000 to 9-40 /100,000 in hyperendemic regions of Brazil. with mortality from 6.1 to 7.6% [674].</p> <p>Cases have been described in migrant populations in US, Italy and Spain [675].</p>	<p><i>Paracoccidioides</i> in a dimorphic fungus. Endemic/enzootic mycosis acquired by airborne inhalation of conidia of <i>Paracoccidioides</i> spp. present in the environment. Agricultural workers and those in occupations involving disturbance to soil are at greatest risk.</p> <p>Naturally acquired infection has been reported most commonly in dogs and armadillos, but infections also occur in other wild animals. A high proportion of infections may be asymptomatic; otherwise, the main sign is lymphadenopathy. The disease is classified as a saprozoonosis; indirect transmission to humans occurs from the environment [12].</p>	<p><u>Humans</u> Brazilian guidelines recommend (L) AmB or cotrimoxazole IV to treat severe infections, and itraconazole as first choice in milder disease [676].</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p> <p>Azoles (fluconazole) and AmB have been used to treat a cat [647].</p>

Human disease <i>Conclusion</i>	Global distribution of human disease	Occurrence in animals and zoonotic potential	Antifungal treatments in humans and animals <i>For information on resistance, please refer to the individual monographs</i>
<i>transfer of antifungal-resistance from animals to humans in the EU is considered negligible.</i>			
<p>Pneumocystis pneumonia (PCP) <i>Pneumocystis jirovecii</i> <i>Pj</i> is specific to humans and causes life-threatening pneumonia (PCP) in immunosuppressed patients, particularly those with HIV/AIDS. Frequency is increasing in organ transplant patients.</p> <p>Conclusion <i>Pneumocystis jirovecii</i> is a serious disease in immunosuppressed human patients, but there is no significant animal reservoir and therefore no risk for transfer of antifungal-resistance from animals to humans.</p>	<p>Ubiquitous. The estimate of global annual incidence is >400,000 cases per year. In the US and UK, PCP has a mortality of 10-30% [630].</p>	<p>In humans, <i>Pj</i> is acquired in early life, considered a commensal. Immunocompetent individuals are a reservoir; person-to-person transmission has been reported in PCP outbreaks [677]. <i>Pj</i> has been reported as a rare opportunist causing disease in immunodeficient foals but is not regarded as a zoonosis [39, 678].</p>	<p>The ECIL published guidelines for the treatment of <i>Pneumocystis</i> in various patient sub-groups [679, 680]. Trimethoprim/sulfamethoxazole is recommended as the first-line for prevention and treatment. Pentamidine, atovaquone and dapsone may be alternatives when TMPS is poorly tolerated or contraindicated [539, 681].</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU. In foals, TMPS is the treatment of choice [39].</p>
<p>Microsporidiosis <i>Encephalitozoon cuniculi, E hellem, E intestinalis, Enterocytozoon bieneusi</i> Exposure is thought to be common, with infections asymptomatic or self-limiting in immunocompetent hosts. In immunosuppressed patients, opportunistic infections have been associated with a variety of syndromes including diarrhoea, hepatitis, myositis, encephalitis, keratoconjunctivitis and disseminated disease.</p> <p>Conclusion <i>Clinical microsporidiosis is mostly identified in immunocompromised people. There may be a risk of zoonotic transmission, especially related to pet rabbits. As both humans and pets may be treated with benzimidazoles, there is a theoretical risk of transmission of resistant strains; however, knowledge on the epidemiology of microsporidiosis is currently limited and benzimidazoles are highly important as antiparasitic agents in livestock and companion animals.</i></p>	<p>Worldwide. Most human clinical cases are due to <i>Enterocytozoon bieneusi</i> and <i>Encephalitozoon intestinalis</i>. Prevalence is decreasing in HIV patients where antiretroviral therapy is available, but increasingly recognised in organ transplant patients, the elderly and causing corneal infections.</p>	<p>Key animal hosts include: <i>E. cuniculi</i> – rabbits and other mammals. <i>E. hellem</i> – Birds (<i>Psittacidae</i>) <i>E. intestinalis</i> – Ruminants, pigs <i>E. bieneusi</i> - Various mammals Transmission to humans is by inhalation of fungal spores shed in animal urine or faeces, or via contaminated food and water. Human-to-human transmission could also occur.</p> <p>Clinical disease has not been reported in cattle or pigs, although human pathogenic strains of <i>Eb</i>, <i>Ec</i> and <i>Ei</i> have been detected in their faeces. Publications on zoonotic transfer from major livestock spp. are rare (Stentiford 2016). <i>E. cuniculi</i> is an emerging disease in pet and livestock rabbits, where it is highly endemic. Infections with rabbit strains of <i>Ec</i> have been reported in humans. Genetic analysis supports the zoonotic potential for <i>Ec</i>, <i>Ei</i> and <i>Eh</i>, but epidemiological evidence is lacking due to the low number of reported human infections [12, 682, 683].</p>	<p>Fumagillin and albendazole (<i>Encephalitozoon</i> spp. only) have demonstrated most consistent efficacy in human infections [684, 685].</p> <p><u>EU VMPs</u> No VMPs could be found authorised for this indication in the EU.</p> <p>In pet rabbits, fenbendazole has been recommended to treat <i>Ec</i> [686, 687].</p>

3.4. Antiprotozoals

For antiprotozoals, the groups are presented according to the important human protozoal disease that they treat, rather than pharmacological class (Table 65). Please refer to the discussion of the methodology in Section 2.8. of the report. A conclusion is given in the first column of the table regarding compliance with the three criteria (Criterion A: High importance to human health; Criterion B: Risk of transmission of resistance; Criterion C: Non-essential need for animal health). There are no detailed monographs. The ATC and ATCvet codes for antiprotozoal substances are tabulated in Table 128 in the Annex.

Table 65. Antiprotozoals: Recommendations on their designation as antimicrobials to be reserved for the treatment of human infections only

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>Malaria Human malaria is caused by five <i>Plasmodium</i> spp. – <i>P falciparum</i>, <i>P vivax</i>, <i>P ovale</i>, <i>P malariae</i>, <i>P knowlesi</i>. Malaria is an acute febrile illness with signs including joint pain, jaundice, headache, abdominal pain and death. Parasites cause red blood cell lysis and hepatosplenomegaly. Associated organ failure may result in renal failure, circulatory collapse and seizures. There were more than 200M cases and >435,000 deaths due to malaria worldwide in 2017 [688].</p> <p>Conclusion <i>Malaria is mainly seen in travellers in the EU; but at global level there may be few treatments alternatives in some geographical regions due to resistance. The potential for zoonotic malaria infection in the EU is extremely low/negligible considering the minimal animal reservoir and vector epidemiology. Hence there is no significant route for transmission of resistant malaria parasites from animals to humans in the EU. There is no known need for use of specific antimalarial drugs in domestic animals in the EU. Although</i></p>	<p>Endemic in tropical and subtropical Africa, S America, Asia and Oceania.</p> <p><i>P falciparum</i> and <i>P vivax</i> account for most infections. <i>P knowlesi</i> is mostly reported from Borneo and Malaysia.</p> <p>Eradicated from Europe in the 1970s, now seen in travellers from endemic regions. Transmitted between humans by Anopheles mosquito. Autochthonous transmission has occurred in the EU since the 1990s, but due to various epidemiological factors is v rare. Climate change could favour mosquito proliferation in the EU in future [689, 690].</p>	<p><i>P knowlesi</i> recently identified in forest macaque monkeys, therefore this species should be considered potentially zoonotic [691]. Humans have been affected by ‘monkey malaria’ while staying in rainforest areas in SE Asia [692]. Otherwise there is no animal reservoir.</p> <p>Potential for zoonotic infection in the EU is extremely low/negligible considering the minimal animal reservoir and unfavourable vector epidemiology.</p>	<p>Treatment depends on <i>Plasmodium</i> spp, drug-resistance epidemiology and patient factors. Because of changing patterns of resistance worldwide, treatment options have to be carefully considered.</p> <p>Antimalarials include inhibitors of heme detoxification (quinolines); folate antagonists e.g. DHFR/TS inhibitors (pyrimethamine, proguanil), para-aminobenzoic acid antagonists (sulfonamides, sulfones); inhibitors of translation/protein synthesis (tetracyclines); inhibitors of the electron transport chain (primaquine, atovaquone) and artemesinins which act by production of free radicals.</p> <p>Treatment is now based on use of artemisinin combination therapies (ACTs) in most countries.</p> <p>WHO EML [3], lists the following medicines: For curative treatment - Amodiaquine*, artemether*(+lumefantrine*), artesunate* (+ amodiaquine*) (+mefloquine*) (+pyronaridine* tetraphosphate), chloroquine* (<i>P vivax</i> only), dihydroartemesine +</p>	<p>Extensive use of chloroquine in the 1980s led to resistant strains of <i>P falciparum</i> that have extended from SE Asia and have also been reported in Africa and Latin America.</p> <p>Resistance to artemisinin in <i>Plasmodium falciparum</i>, <i>P vivax</i> and <i>P malariae</i> is now especially problematic in SE Asia. WHO refers to multidrug resistance (MDR) as resistance to more than 2 antimalarials of different chemical classes. This usually refers to <i>P falciparum</i> resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound. [688, 693, 694].</p> <p>Emergence of MDR malaria parasites is a major public health concern.</p>

Important human protozoal disease Conclusion Recommendation	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p><i>non-malaria specific substances (doxycycline, sulfonamides) are used in animals, this would not lead to exposure of malaria parasites. Doxycycline and sulfonamides are veterinary critically important antimicrobials (VCIAs) according to OIE.</i></p> <p>Recommendation <i>Criterion B is not met and no anti-malarials have been recommended to be designated for use in humans only.</i></p>			<p>piperaquine* phosphate, doxycycline* (+ quinine*), mefloquine* (+ artesunate*), primaquine* (<i>P vivax</i> and <i>P ovale</i>), quinine* (+doxycycline, management of severe malaria), sulfadoxine* + pyrimethamine* (+artesunate) For chemoprevention - amodiaquine-sulfadoxine + pyrimethamine, chloroquine (<i>P vivax</i>, <i>C. America</i>), doxycycline, mefloquine, proguanil* (+ chloroquine), sulfadoxine + pyrimethamine.</p> <p><u>HMPs in the EU</u> *All these substances are authorised for use in HMPs in the EU (Article 57 database, EMA).</p> <p><u>VMPs</u> Of the substances categorised specifically as antimalarials according to human ATC codes, only pyrimethamine also has an ATCvet code. No veterinary authorisations of this substance were found in the EU. According to US Pharmacopeia 2007, pyrimethamine is used to treat equine protozoal encephalitis, <i>Neospora caninum</i> and Toxoplasmosis. Tetracyclines and sulfonamides are used extensively in veterinary medicine, but treatment of animals would not lead to exposure of human malarial parasites. There is no known need for specific antimalarials in veterinary medicine in the EU.</p>	
<p>Amoebiasis <i>Entamoeba histolytica</i> is the primary cause of amoebic colitis, liver and (rarely) brain abscesses. Amoebic colitis ranges in severity from</p>	<p>Higher transmission rates are usually related to poor health and sanitation. Although distribution is worldwide, infection is more common in LMICs, affecting children <5</p>	<p>Infection is from human to human, or via contaminated food or water. It has been suggested that dogs, pigs and monkeys may act as reservoir hosts, but this has not been proven [699] (original source not located).</p>	<p>Humans Non-invasive infections may be treated with luminal agents - paromomycin* or diloxanide [542].</p>	<p>Resistance to Metronidazole in <i>Eh</i> has been induced in vitro, associated with increased expression of iron-containing superoxide dismutase and peroxiredoxin and decreased</p>

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>diarrhoea to dysentery to necrotising colitis and intestinal perforation. Although most infections are asymptomatic, an estimated 40-50M people each year develop amoebic colitis or extraintestinal abscesses, leading to >100,000 deaths per year [695, 696]. <i>E. moshkovskii</i> causes non-invasive diarrhoea.</p> <p>Conclusion <i>Animals appear to be a minor reservoir for Entamoeba infections of human significance. There is limited evidence of clinically relevant resistance to standard therapy, at this time, although concerns have been raised about emergence of resistance to metronidazole. Nitroimidazoles are excluded from use in food-producing animals in the EU (Regulation (EU) 37/2010), due to their potential carcinogenicity. They have important therapeutic use in companion animals for treatment of anaerobic infections but use to treat amoebiasis is likely to be extremely rare based on frequency of the disease. Paromomycin is not used to treat Eh in livestock in the EU. The potential risk for transfer of resistant Entamoeba histolytica from animals to humans is extremely low. Paromomycin is VCIA according to OIE.</i></p> <p>Recommendation <i>Criterion B is not met; therefore no anti-amoebiasis substances have been recommended to be designated for use in humans only.</i></p>	<p>years old. Most cases in Europe are seen in immigrants, international travellers and MSM, and in association with immunosuppression [697]. A hypervirulent strain of <i>Eh</i> was responsible for an outbreak in Canada [698].</p>	<p>According to Ji, Cao [700], <i>E. histolytica</i> has not been detected in farmed pigs to date. Less pathogenic <i>E. polecki</i> has been found in many hosts including humans, non-human primates and pigs, with some overlap in sub-types between, suggesting the possibility for pigs to act as a reservoir for human infection.</p> <p>Overall, the possibility of animals to act as a reservoir for human highly pathogenic Entamoeba species appears to be low.</p> <p>Reports of clinical amoebiasis in dogs in the EU are scant.</p>	<p>Tinidazole* and metronidazole* (nitroimidazoles) are the main treatments for invasive amoebiasis, amoebic colitis and liver abscess. Metronidazole is activated in the presence of PFOR², a fermentation enzyme produced by protozoa. Metronidazole is considered the treatment of choice [701]. According to a Cochrane Review [696], tinidazole was more effective than metronidazole in treating clinical symptoms of amoebic colitis; however, better quality trials were recommended. Nitazoxanide is a new alternative treatment, structurally related to metronidazole. The mode of action is related to PFOR inhibition. Further studies are needed to determine its effectiveness [542, 702]. Emetine is associated with toxicity and safer options are now available [703].</p> <p>WHO <u>EML</u> includes diloxanide and metronidazole* as anti-amoebic medicines.</p> <p><u>HMPs in the EU</u> Tinidazole and metronidazole are specifically authorised for treatment of amoebiasis in EU (Article 57 database, EMA).</p> <p><u>VMPs</u> Veterinary need for specific treatments for amoebiasis is very low and no EU-authorised VMPs could be found with this indication. Recognised treatments in human medicine have alternative veterinary uses:</p>	<p>expression of ferredoxin 1 and flavin reductase, but high level clinical resistance is not reported [701].</p> <p>The mode of action for diloxanide is unknown. No clinically relevant resistance to diloxanide has been identified [704].</p> <p>No reports were found of clinically relevant resistance to paromomycin in <i>Eh</i>.</p> <p>There is limited evidence of clinically relevant resistance to standard therapies; however, new therapeutic strategies are under investigation due to concerns about possible emergence of metronidazole-resistance [705].</p>

² Pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism

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Nitazoxanide has also been recognised as having antiviral properties. Please refer to separate considerations for antivirals.			Metronidazole is authorised for use in dogs and cats in the EU for treatment of anaerobic bacterial infections. Paromomycin is authorised to treat enteric <i>E. coli</i> infections in livestock and <i>C. parvum</i> in small ruminants. No EU-authorised VMPs containing diloxanide or tinidazole could be found.	
<p>Giardiasis <i>Giardiasis in humans is caused by Giardia lamblia (syn. G duodenalis, G intestinalis). Severity of disease varies from asymptomatic to acute diarrhoea requiring hospitalisation, chronic diarrhoea with malabsorption, or irritable bowel syndrome (IBS). Giardiasis affects 280M people annually (Einarsson 2016). Public health significance relates to the high prevalence and potential for disease outbreaks.</i></p> <p>Conclusion <i>Giardiasis is an important human protozoal disease in the EU in terms of the potential for disease outbreaks although clinical disease is generally not severe. The significance of the animal reservoir with respect to human infections needs further investigation. Treatment failures in humans and resistance to nitroimidazoles is increasing in Giardia spp. Nitroimidazoles (NI) are excluded from use in food-producing animals in the EU (Regulation (EU) 37/2010), due to their potential carcinogenicity. Although there is no evidence, there is theoretically a low risk that NI-resistant infections could be transmitted from pets to people. NI also have important therapeutic use in companion animals for treatment</i></p>	<p>Giardia occurs worldwide. In low-income countries, nearly all children become infected. Prevalence is much lower in developed countries with infections related to travel and occasional outbreaks in residential facilities or connected to contamination of water supplies. In the EU, except in Nordic countries, most cases are domestically acquired. In 2017, 19,473 cases were reported to ECDC [706]. According to the EU One Health Zoonoses report, there were 18 food/water borne outbreaks and no deaths were reported in the EU in 2018.</p>	<p>Human infection occurs mostly through person-to-person transmission, or through ingestion of contaminated food or water (faulty purification systems). Specific human genotypes (assemblages A and B) are found in some animals, but genetic sub-typing indicates low zoonotic potential for most animal isolates. Although giardiasis has been established as a zoonotic disease, the burden of zoonotic disease needs further evaluation [707, 708].</p> <p>Assemblage A: humans, primates, dogs, cats, pigs, cattle, sheep, deer, horses, rodents Assemblage B: humans, primates, dogs, cattle, horses, beaver. Assemblages C to H are found in animal hosts.</p> <p>Giardia infections are common in the major mammalian livestock species in Europe and some studies have shown impacts on growth rates. In dogs, infection rates were c. 25% in one European study, and 20% in cats [707]; although clinical signs are generally seen only in puppies and kittens [709].</p>	<p>Treatment of choice in humans is tinidazole* or metronidazole* [542]. Tinidazole or metronidazole treatment has a reported efficacy of 90% but may be used in combination with alternative agents in refractory cases. A Cochrane review [710] found that albendazole* (benzimidazole) had similar efficacy to metronidazole in treatment of symptomatic giardiasis. Benzimidazoles act by binding to tubulin and blocking glucose uptake.</p> <p>WHO <u>EML</u> lists diloxanide and metronidazole* as treatments. Prevention of infection is through provision of clean water and adequate sewage systems.</p> <p><u>HMPs in the EU</u> *These substances are authorised for use in HMPs in the EU (Article 57 database, EMA) and are indicated for treatment of giardiasis.</p> <p><u>VMPs</u> In dogs and cats, pyrantel+febantel, fenbendazole and metronidazole are authorised for treatment of Giardia in the EU. Tinidazole may also be used (under Articles 112 of Regulation (EU) 2019/6), but no authorised products were found. For food-producing animals, no EU-authorised VMPs with indications for</p>	<p>Treatment failure is increasing in travellers contracting Giardia in Asia. Resistance to 5-nitroimidazoles has been detected both in vitro and in vivo. Mechanisms include down-regulation of PFOR and NR1 (nitroreductase) activity and up-regulation of NR2. Resistance has also been shown to albendazole, furazolidone, mepacrine and nitazoxanide. No resistance is known for chloroquine and paromomycin [711]. No clinically relevant resistance has been shown for diloxanide [704].</p>

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<p>of anaerobic infections. There is a need for Giardia treatments in livestock, but benzimidazoles are authorised as VMPs in the EU and hence more likely to be used for this indication. Benzimidazoles are also essential anthelmintics for livestock spp.</p> <p>Recommendation Criterion A is not met and no antiprotozoals for treatment of giardia have been recommended to be designated for use in humans only. Nitazoxanide has also been recognised as having antiviral properties. Please refer to separate considerations for antivirals.</p>			<p>giardiasis were found. Clinical giardiasis in calves and lambs may adversely affect production and may be treated with albendazole, fenbendazole or paromomycin [707]. There is a need for Giardia treatments for both livestock and companion animals in the EU.</p>	
<p>Coccidiosis/Cryptosporidiosis <i>Cryptosporidium hominis</i>, <i>C. parvum</i>, <i>Cystoisospora belli</i> and <i>Cyclospora cayentanensis</i></p> <p>Infection may be asymptomatic or cause watery diarrhoea which is usually self-limiting except in immunocompromised patients where it may be severe and life-threatening. Before the advent of combination antiretroviral therapy, cryptosporidiosis was a serious complication of AIDS. It is problematic in transplant patients on immunosuppressive therapy and may lead to IBS longer term.</p> <p>Conclusion <i>Cryptosporidiosis is an important human protozoal disease in the EU in terms of the potential for disease outbreaks, although clinical disease is generally not severe except in immunocompromised patients. There</i></p>	<p><i>Cryptosporidium</i> spp. are found worldwide. In 2016 the estimated global deaths in children under 5 years was >48,000 and [712] showed substantial longer term impacts on childhood growth, with disease burden focused in resource-poor regions in C and W sub-Saharan Africa.</p> <p>In immunocompetent individuals in high income countries outbreaks have been reported in hospitals and care homes, or due to contamination of drinking water supplies or open water (swimming) [542, 713]. According to ECDC [713], in 2017 11,418 confirmed cases of <i>Cryptosporidium</i> were reported in the EU, although reporting is likely to be incomplete. EFSA recorded that in 2018 there were 9 food or</p>	<p>Direct person-to-person and animal-to-person transmission can occur but transmission is mainly through contaminated water and food. In the EU, most human infections are caused by species that mainly infect humans (especially <i>C. hominis</i>), but several <i>Cryptosporidium</i> spp. are zoonotic, including <i>C. parvum</i>. <i>C. hominis</i> and <i>C. parvum</i> are together responsible for 90% of cases in humans [715].</p> <p>A review of studies in Eastern European countries showed that <i>Cryptosporidium</i> spp. are common parasites in domestic animals, including pets, with human pathogenic <i>C. parvum</i> strains being prevalent [716]. Ruminants, particularly calves, are the major animal reservoir for human infections with <i>C. parvum</i>. Clinical signs in calves include diarrhoea, anorexia and weight loss.</p>	<p>HMPs Most human patients and animals with an intact immune system recover without treatment.</p> <p>No specific treatments are listed in the EML [3]. No authorised treatment is available for human cryptosporidiosis in Europe and there is limited evidence for effectiveness of treatments [718, 719]. Nitazoxanide (a thiazolide, PFOR inhibitor) is approved by the FDA. Focus is on vaccine development and identification of new drug targets [718].</p> <p>VMPs authorised in the EU Halofuginone (a quinazolinone) is used for control of <i>Cryptosporidium</i> in calves. Paromomycin is authorised for control of <i>Cryptosporidium</i> disease in calves and goats.</p>	<p>Mechanisms of nitazoxanide resistance require further investigation [702].</p>

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>are no authorised HMPs in the EU. Domestic animals may act as a reservoir for human infections with <i>C. parvum</i>. Nitazoxanide is used to treat human infections in the US, and could potentially be used in pet animals in the EU (under Article 112 of Regulation (EU) 2019/6, if available). Resistance to nitazoxanide is not well evidenced. Calves are the major animal reservoir for potentially zoonotic <i>C. parvum</i> but the veterinary- authorised treatments (halofuginone, paromomycin) are not currently used to treat this disease in humans and animal treatment is essential for economic and welfare reasons. Paromomycin is VCIA according to OIE.</p> <p>Recommendation Criteria A and B are not met in the EU and substances used to treat coccidiosis in animals are not used to treat humans; therefore, no anti-coccidials have been recommended to be designated for use in humans only.</p> <p>Nitazoxanide has also been recognised as having antiviral properties. Please refer to separate considerations for antivirals.</p>	<p>waterborne outbreaks of cryptosporidiosis in the EU, with no associated deaths [714]. Due to under-reporting, the burden of disease in the EU is not clear.</p>	<p>The risk of human infection from pets is believed to be low [717].</p> <p>Humans are the only recognised host for <i>Cystisopora belli</i> and <i>Cyclospora cayetanensis</i>.</p> <p>Likewise, Cystisporosis of cats and dogs is host specific [542].</p>	<p>No EU-authorised VMPs were found for treatment of <i>Cryptosporidium</i> spp. in dogs and cats. Infections are mostly self-limiting but nitazoxanide, paromomycin and azithromycin may be used (under Article 112 of Regulation (EU) 2019/6) [345].</p> <p><u>Cocciostats</u> that are regulated as feed additives in the EU are not addressed in this advice.</p>	
<p>Toxoplasmosis <i>Toxoplasma gondii</i> Usually toxoplasmosis is asymptomatic, but it may cause signs (chorioretinitis, neurological signs) and mortality in immunosuppressed people. Congenital infection may result in abortion or in malformations of the eyes and brain.</p>	<p>Toxoplasmosis is distributed worldwide and across economic strata, with seropositivity in humans ranging from 10 to 90% (Torgerson and Mastroiacovo, 2013).</p> <p>In 2017, there were 194 confirmed cases of congenital toxoplasmosis in the EU/EEA [720]. EU surveillance in animals</p>	<p><i>T gondii</i> can infect any mammalian species. Cats are the definitive reservoir host, excreting cysts which infect humans and other animals through contact with faeces or ingestion of contaminated water, fruit/vegetables. Ruminants (esp sheep), dogs, rodents and pigs may also act as intermediate host reservoirs. Human infection can also</p>	<p>In immunocompromised human patients, treatment is pyrimethamine* (+ folinic acid) (DHFR/TS inhibitor), with sulfadiazine* for maintenance. Pyrimethamine + sulfadiazine act synergistically. Treatments have toxic effects and require long term administration, hence change in therapy is common. Clindamycin*,</p>	<p>Strains of <i>T. gondii</i> resistant to pyrimethamine have been demonstrated in vitro (point mutations) [726, 727]. Variability in susceptibility to sulfadiazine has been shown in strains of <i>T gondii</i> from human clinical cases and livestock in Brazil [728]. Dunay, Gajurel [729] reported that resistance to currently used substances had not been reported</p>

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<p>Conclusion Although the number of cases is low, congenital toxoplasmosis and infection in immunosuppressed patients are important in the EU due to the severity of the disease. Cats are the definitive reservoir host for <i>T gondii</i>, and lamb and pig meat are also sources of human infection. Use of sulfonamides/folate synthesis inhibitors and macrolides in both cats and livestock could potentially lead to a source of resistant organisms for humans; although resistance does not appear to be a significant problem at present and there are alternative treatments available in human medicine. Sulfonamides and macrolides are VCIAAs.</p> <p>Recommendation For those substances used both in humans and animals, Criterion C is not met; therefore, no substances for treating Toxoplasmosis have been recommended to be designated for use in humans only.</p>	<p>is based on testing of a limited number of clinical cases. In 2018, 18% of samples from sheep, 28% from cattle and 11% from pets were seropositive [714].</p> <p>In FR in 2007, the estimated prevalence of congenital toxoplasmosis was 3.3 per 10,000 live births. Congenital infection and HIV co-infection cause the most serious morbidity. In the US in 2008, 83% of adult toxoplasmosis cases were in HIV infected individuals [721]. The WHO estimated an incidence of congenital toxoplasmosis of 190,000 cases p.a. (1.2 M disability-adjusted life years). The highest burden is in S America where strains are more pathogenic [722].</p>	<p>be acquired from consumption of undercooked meat containing cysts, especially pork/lamb, and congenitally. Toxoplasmosis has been highlighted as one of the most important food borne pathogens in Europe and the US [723]; no foodborne outbreaks have been reported to EFSA since data collection started in 2004, but 40-60% of individual cases are estimated associated with foodborne transmission.</p>	<p>atovaquone*, dapsone* and TMPS* are alternatives [538, 542]. Spiramycin* may sometimes be used (preventively) in women in early pregnancy when antifolates should be avoided [542]. In France, affected newborns are treated with pyrimethamine* + sulfadiazine*/sulfadoxine* [724].</p> <p>The WHO <u>EML</u> includes pyrimethamine, sulfadiazine, sulfamethoxazole + trimethoprim as treatment options. Pentamidine is on the complementary list.</p> <p><u>HMPs in the EU</u> *These substances are authorised for use in HMPs in the EU (Article 57 database, EMA). Pyrimethamine products include a specific indication for toxoplasmosis.</p> <p><u>VMPs</u> In the EU there are authorised VMPs containing sulfadiazine, trimethoprim and clindamycin, but they do not have a specific indication for treatment of <i>T gondii</i>. No authorised VMPs were found containing pyrimethamine. Infected cats are mostly asymptomatic and are therefore not treated. Pyrimethamine/sulfonamide combination has been used to treat clinical toxoplasmosis in dogs and cats, but is associated with toxicity in cats particularly. Clindamycin is the preferred treatment for cats; TMPS and azithromycin have also been used [345, 445]. In sheep, toxoplasmosis is a leading cause of abortions, although control is usually via vaccination programmes ('Toxovax') as once an outbreak of abortions has started it is too late for</p>	<p>as a clinical problem; whereas Alday and Doggett [730] noted that resistance was suspected to contribute to treatment failure in 10-20% of patients. Alternative treatments are under investigation.</p> <p>Clinical resistance does not appear to be a significant problem at present, with toxicity being the main driver for development of new treatments.</p>

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			<p>treatment. Decoquinate premix is authorised in the EU for prevention of abortion in sheep and perinatal losses due to <i>Tg</i>. Antimicrobial treatments have been investigated experimentally in ruminants [725].</p> <p>Pyrimethamine is included in the list of substances essential for the treatment of Equidae (Regulation EU 122/2013) for treatment of equine protozoal myeloencephalitis and is also used for treatment of neosporosis in dogs [445].</p>	
<p>Trichomonas Four trichomonas spp. are recognised as human parasites. <i>T vaginalis</i> and <i>T tenax</i> are considered human-specific. <i>T vaginalis</i> is a common STD causing vaginitis and pre-term birth; it also can increase the risk for transmission of HIV. <i>Dientamoeba fragilis</i> and <i>Pentatrichomonas hominis</i> have also been isolated from domestic and farm animals. There is limited knowledge on their pathogenicity in humans [731].</p> <p>Conclusion <i>The major human pathogenic strain (T vaginalis) is not zoonotic. The potential for zoonotic transmission of animal strains needs evaluation. There is insufficient rationale to recommend anti-trichomonal substances to be designated for use in humans only</i></p> <p>Recommendation <i>Criterion B is not met; therefore, no substances for treating Trichomonas have been recommended to be designated for use in humans only.</i></p>	<p>According to Cooper [732], the global incidence of Trichomoniasis in 2017 was c. 245M cases.</p>	<p>Trichomonosis occurs in several animal species: Birds – <i>T gallinae</i>, <i>T stableri</i>, <i>Tetratrichomonas gallinarum</i> Cattle – <i>T foetus</i> is a sexually transmitted disease causing abortions. Cats – <i>Tritrichomonas foetus</i> Pigs – <i>Tritrichomonas suis</i></p> <p>There is a close genetic relationship between avian and human trichomonads and animal trichomonads have been reported in human clinical samples therefore the potential for emerging zoonoses should be investigated (Maritz 2014).</p> <p>No evidence for zoonotic transmission of the major human pathogenic strain, <i>T vaginalis</i>, was found.</p>	<p>In humans, treatment is with metronidazole* or tinidazole* [542, 733].</p> <p><u>HMPs in the EU</u> *These substances are authorised for use in HMPs in the EU (Article 57 database, EMA) and include indications for trichomoniasis. In the EU, fenticonazole (topical) is also authorised.</p> <p><u>VMPs</u> In cattle, control of <i>T foetus</i> is usually through identifying and culling infected bulls. Nitroimidazoles are excluded from use in food-producing animals in the EU (Regulation (EU) 37/2010). In cats, ronidazole (outside the terms of a marketing authorisation) is the only substance that has shown to be effective in eliminating <i>T foetus</i> [734]). No authorised VMPs in the EU containing ronidazole or indicated for treatment of trichomoniasis could be found.</p>	<p>Resistance to metronidazole is due to mutations; tinidazole is an alternative to treat resistant infections [735, 736].</p>

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>Trypanosomiasis American trypanosomiasis or 'Chagas disease' is caused by <i>Trypanosoma cruzi</i>. Acute disease is characterised by a red lesion at the site of inoculation, fever and lymphadenopathy. Chronic disease includes cardiomyopathy, megaesophagus, megacolon and CNS disease.</p> <p>Human African trypanosomiasis (HAT) 'sleeping sickness' is caused by <i>T. brucei</i> complex, transmitted by the tsetse fly. Pathology for <i>Tbr</i> includes vasculitis, pancarditis and CNS effects. Untreated, HAT results in death.</p> <p>Conclusion <i>Trypanosomiasis does not occur in animals in Europe, other than imported cases, and is rare in humans. Livestock and companion animals can act as a reservoir for human infections in countries where the diseases are endemic. Substances from the same classes may be used to treat animals and humans. Resistance to trypanocidals is common and there is frequently cross-resistance between classes. Resistant trypanosomes could pass from animals to humans. Treatment of AAT to reduce the animal reservoir is part of the One Health programmes aimed at eliminating HAT. There are animal health, public health and economic needs for control of trypanosomiasis.</i></p> <p>Recommendation <i>Criteria A and B are not met in the EU. At present, trypanosomiasis is not endemic and occurs rarely in</i></p>	<p>Chagas disease is widespread in Mexico, C and S America, and less common in N America. According to Cooper [732], the incidence of Chagas disease was 163,000 cases (prevalence 6 M cases). PAHO estimates that 12,000 people die from Chagas disease each year.</p> <p>Chagas disease has been reported in Europe in migrants from these countries and as a result of congenital infection and has been acknowledged as a public health challenge [737].</p> <p>HAT is endemic in sub-Saharan Africa. Disease incidence has been markedly reduced (95% from 2000 to 2018) by vector control programmes. The incidence of human African trypanosomiasis was 3,300 cases [732]; according to WHO [738] there were 997 new cases reported in 2018.</p>	<p><i>T. cruzi</i> is transmitted amongst mammalian hosts by triatome insect vectors (kissing bugs). It can also be transmitted from mother to foetus, by ingestion of contaminated food or by blood transfusion. Triatominae do not occur in Europe. Wild animals and dogs are the predominant reservoirs in the Americas [721].</p> <p><i>T. cruzi</i> appears to have low pathogenicity in livestock but is highly pathogenic in dogs.</p> <p><i>T. brucei</i> is transmitted by the tsetse fly. Among <i>T. brucei</i> complex, humans are the main reservoir host for <i>T.b. gambiense</i>, (West African trypanosomiasis).</p> <p><i>T.b. rhodesiensi</i> (East African trypanosomiasis) has its main reservoir host in antelope and cattle. <i>Tbr</i> accounts for only 2% of HAT cases (WHO 2020); it often co-exists with a number of other trypanosomes that cause African Animal Trypanosomiasis (AAT, 'nagana'): <i>T congolense</i> – in most domestic and many wild animals <i>T vivax</i> – domestic and wild ruminants, horses <i>T simiae</i> – domestic and wild pigs <i>T.b. brucei</i> – ungulates, dogs, cats, camels</p> <p><i>T evansi</i> (S America) is closely related to African trypanosomes. Vectors are tabanids and <i>Stomoxys</i> spp. It causes 'surra' in ruminants, camels and horses, and severe disease in dogs, often resulting in death. There have been imported outbreaks of surra in S. Europe</p>	<p>Humans American trypanosomiasis – is treated with benznidazole (nitroimidazole) and nifurtimox (nitrofurantoin) in the acute phase [3].</p> <p>HAT – According to Mandell, Dolin [542], suramin* is the treatment of choice for early stage <i>rhodesiense</i> infection. Once there is CNS involvement, melarsoprol* is used, although it has high toxicity.</p> <p>The EML includes for E and W African trypanosomiasis: fexinidazole, pentamidine*, suramin*, eflornithine*, melarsoprol*, nifurtimox.</p> <p>HMPs in the EU *These substances are authorised in HMPs in the EU (Article 57 database, EMA).</p> <p>VMPs None of the substances listed above or below could be identified as authorised in VMPs in the EU. For treatment of dogs with Chagas disease, benznidazole is recommended [741].</p> <p>AAT causes high morbidity and mortality in livestock; 35M doses of trypanocidals are administered per year to combat severe economic losses [742]. The main trypanocidals used are diminazene aceturate, quinapyramine methylsulfate, (curative/prophylactic) and isometamidium (prophylactic) [743, 744]. In addition, trypanocidal treatment of cattle has been shown to decrease human cases due to <i>T. rhodesiense</i> [745]. Control of AAT is part of the One Health approach</p>	<p>Treatment failure for <i>T. cruzi</i> has been reported for both benznidazole and nifurtimox, with in vitro resistance mechanisms identified [746, 747]. Giangaspero [748] suggested this might be linked to extensive use of imidazole derivatives in veterinary medicine.</p> <p><i>Tbr</i> is intrinsically resistant to eflornithine. Resistance to melarsoprol and safety issues lead to 30% failure rate in treatment of HAT [749]. Resistance has also now been reported to pentamidine, and cross-resistance shown between melarsoprol and pentamidine [750, 751]. Resistance to suramin is apparently rare, although recent reports are lacking.</p> <p>Resistance to veterinary trypanocidals is problematic as a result of widespread use. Diminazene belongs to the same class as pentamidine (diamidine). There is cross-resistance within the class and with melaninophenyl arsenicals (melarsoprol, melarsomine). Cross-resistance between isometamidium and diminazene is considered rare. Quinapyramine is cross-resistant with both diminazene and homidium. Resistance to suramin in <i>T evansi</i> is widespread. Research into novel trypanocidals is being taken forwards under various initiatives (e.g. Drugs for Neglected Diseases Initiative DNDi) [752].</p>

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>humans in Europe. The possibility for the diseases to establish will be influenced by distribution of vectors which may change over time. According to future changes in epidemiology, recommendations for these substances not to be designated for use in humans only may need to be re-considered.</p>		<p>[739]. TroCCAP [740] reports that it is rarely (5 reported cases) zoonotic.</p>	<p>to eliminate HAT, established under the FAO Programme Against African Trypanosomiasis. Other treatments are homidium bromide/chloride (highly toxic), suramin and melarsomine).</p> <p>In dogs, <i>T. evansi</i> is treated with diminazene aceturate or suramin (TroCCAP).</p>	
<p>Neobalantidiasis <i>Neobalantidium (=Balantioides) coli (Nc)</i> Most infections in humans are asymptomatic. Clinical signs are of acute colitis - diarrhoea, dysentery. Infections can be severe or even fatal in immunocompromised patients. Rarely infection may become systemic [753].</p> <p>Conclusion <i>Pigs are the primary reservoir for Nc infection. Nitroimidazoles are excluded from use in food-producing animals in the EU (Regulation (EU) 37/2010), due to their potential carcinogenicity. Owing to the high prevalence of Nc and common use of tetracyclines in pigs to treat other infections, it is likely that the organism would be collaterally exposed and a theoretical route for transmission of tetracycline-resistant Nc to humans exists. No information could be found regarding treatment failures or resistance in human infections to the treatments of choice. Tetracyclines are included in AMEG Category D and WHO's VCIA and are an important first-line antimicrobial treatment in pigs for various bacterial infections.</i></p>	<p><i>Nc</i> occurs worldwide but is more common where pigs are raised in unsanitary conditions and have close contact with humans. May present in travellers from SE Asia, Pacific Is., S America [754]. Also occurs in the Middle East [542].</p> <p>Surveys of pigs in DE and DK showed high prevalence of <i>Nc</i> in most age groups [755, 756].</p>	<p>The primary reservoir host is pigs. Humans and other primates and rodents can act also as reservoirs. Human hosts ingest cysts from contaminated food or water.</p>	<p>Tetracyclines (doxycycline*) and metronidazole* are treatments of choice. Iodoquinol (hydroxyquinolone) and nitazoxanide are alternatives [542, 754].</p> <p><u>HMPs in the EU</u> *These substances are authorised in HMPs in the EU (Article 57 database, EMA).</p> <p>No H/VMPs authorised in the EU with a specific indication for <i>Nc</i> could be found.</p> <p><u>VMPs</u> Disease is mostly asymptomatic in pigs, which are therefore rarely likely to be treated, although due to high prevalence the organism could be collaterally exposed to antibiotics (e.g. doxycycline) at the time of treatment of other diseases. A report was found indicating use of metronidazole+furazolidone or oxytetracycline to control <i>Nc</i> in pigs in India [757].</p>	<p>No information could be found in regard to development of resistance in <i>Nc</i>.</p>

Important human protozoal disease <i>Conclusion Recommendation</i>	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p>Recommendation Criterion C is not met; therefore, no substances for treatment of <i>Neobalantidium coli</i> have been recommended to be designated for use in humans only.</p> <p>Nitazoxanide has also been recognised as having antiviral properties. Please refer to separate considerations for antivirals.</p>				
<p>Leishmaniasis There are >20 species of leishmania parasite. Disease is associated with poverty, malnutrition, immunosuppression and environmental changes. There are 3 clinical forms of disease. Cutaneous leishmaniasis (CL) is most common, producing ulcers on exposed parts of the body. In mucocutaneous leishmaniasis there may be total or partial destruction of nose, mouth and throat. Visceral leishmaniasis (kala-azar, VL) is characterised by fever, weight loss, hepatosplenomegaly and anaemia. If untreated, fatality rate can be as high as 100%. According to the WHO most of the reported infections of VL in adults are associated with concomitant HIV infections. In these cases, the risk of treatment failure for VL is high leading to constant relapses. [758]. The burden of protozoan diseases is increasing globally due to increasing resistance to antiprotozoals and toxicity of the current agents [749].</p> <p>Conclusion <i>Leishmaniasis is an important protozoal disease in humans in the Mediterranean region of the EU;</i></p>	<p>Geographical regions have their own combinations of vectors, mammalian hosts and human hosts. There are only two transmission cycles endemic in Europe: 1. Visceral and cutaneous human leishmaniasis caused by <i>Leishmania infantum</i> throughout the Mediterranean region. Based on data from 2003 to 2008 from 9 EU countries, the WHO estimated about 410 – 620 cases of VL occurring in the Mediterranean region/year. CL is under-reported, and there are likely to be more cases. 2. Anthroponotic cutaneous human leishmaniasis caused by <i>Leishmania tropica</i>, which occurs sporadically in Greece and in neighbouring countries. Many human leishmaniasis cases in the EU are imported, after travel to tropical countries (ECDC). Although deaths due to VL are rare in the EU, they may be associated with co-morbidities or inappropriate use of anti-VL substances [760]. Outbreaks of VL were reported in Fuenlabrada (ES) 2010-12 and Bologna (IT) 2012-13 [761, 762].</p>	<p>Leishmania is transmitted between mammalian reservoir hosts and to humans by the phlebotomine sand fly. Reservoirs include humans, marsupials, monkeys, edentates, rodents and small carnivores (foxes, jackals) including dogs.</p> <p>In the EU, dogs are the main reservoir for <i>L. infantum</i> (cats are a less common reservoir). CanL infections range from sub-clinical or self-limiting to severe fatal disease. Cutaneous lesions are most frequent, but renal disease may also occur and is the main cause of mortality.</p> <p>Treatment of sick dogs in endemic areas has been shown to decrease their infectiveness [765], and is recommended in the WHO Manual 2017.</p>	<p><u>Humans</u> Treatment regimens vary according to region, parasite strain and severity of disease. According to Mandell, Dolin [542], the treatments of choice for treatment of <u>cutaneous</u> leishmaniasis are sodium stibogluconate* or meglumine antimonate* (pentavalent antimonials) or liposomal amphotericin B*. Antimonials are being replaced by less toxic substances. Miltefosine* is an alternative treatment for CL and VL. For <u>mucosal and visceral</u> leishmania, liposomal amphotericin B* is the treatment of choice [542, 766]. L-AmB is also recommended for treatment of VL in IDSA guidelines; although it is noted that choice of therapy should be individualised [767].</p> <p>WHO <u>EML</u> includes amphotericin B, miltefosine, paromomycin*, sodium stibogluconate* or meglumine antimonate*. Combination therapies are recommended to shorten treatment and prevent resistance emergence.</p> <p>No vaccines are available to prevent infection in humans, although clinical trials are underway [768].</p>	<p>Resistance has rendered sodium stibogluconate obsolete in the Indian sub-continent for treatment of VL (<i>L. donovani</i>). Although this is not yet the case for other antileishmanials, or in other geographical regions, the adaptive plasticity of the <i>Leishmania</i> genome suggests that resistance emergence and spread should be considered for every drug [772]. Treatment failures have been reported uncommonly with alternative anti-leishmanial drugs (particularly miltefosine); and drug resistance has been shown experimentally to AmB and miltefosine [688, 773, 774] and paromomycin[775]. Parasite and host immunological factors can also be reasons for treatment failures. Drug resistance could develop in Europe in the context of migration, immune status and treatment of canine VL with the same drugs as for humans [772]; although in the EU amphotericin B is the preferred treatment for VL in humans, whereas meglumine, miltefosine and allopurinol are used in dogs. Canine leishmania isolates from Portugal showed low susceptibility to the main drugs</p>

Important human protozoal disease Conclusion Recommendation	Geographical distribution – occurrence of human disease in Europe	Animal disease and Zoonotic potential	Recognised and commonly used medicines, human (HMP) and veterinary (VMP)	Occurrence of resistance to antimicrobials
<p><i>although the proportion of clinical cases is low and infection is rarely fatal. There is potential for the expansion of the geographical range with climate change.</i></p> <p><i>Dogs are the reservoir for L infantum. Resistance has been demonstrated to all three substances used to treat dogs (meglumine, miltefosine and allopurinol), hence resistant parasites could potentially pass from animals to humans. However, treatment of sick dogs reduces their infectiveness and euthanasia as a means to control the Leishmania reservoir is of questionable value [759]. In humans amphotericin B is a recommended first line treatment for VL, whereas its use in dogs has been discouraged to avoid the development of resistant strains and alternatives are usually employed.</i></p> <p><i>Amphotericin B is also used rarely in dogs to treat a variety of uncommon fungal diseases (e.g. cryptococcosis, histoplasmosis, candidiasis). It is used to treat sporotrichosis in cats and fungal infection in horses and zoo animals.</i></p> <p>Recommendation <i>Criterion C is not met; therefore, no substances for treatment of Leishmania spp. have been recommended to be designated for use in humans only.</i></p>	<p>Leishmaniasis is considered a neglected disease in the WHO European region.</p> <p><u>Worldwide</u>, the Global Burden of Disease Study 2017 [732] reported a global incidence of Leishmaniasis of 670,000 cases, of which 42,000 are the visceral form (VL). WHO reports up to 1 M new cases annually. VL is caused mainly by <i>L donovani</i> and <i>L infantum</i> and is endemic in the tropics and subtropics (esp. India, E Africa), predominantly in LMICs. The vector for <i>Ld</i> is absent from Europe. CL is endemic in scattered regions throughout the world (Mediterranean, central Asia, Americas, Middle East).</p> <p>The risk of introduction of exotic Leishmania spp. to the EU is considered low in the absence of proven vectors/reservoir hosts [763], but the increasing number of cases of leishmaniasis in N African countries around the Mediterranean coast is seen as a risk (ECDC CDTR, week 10, 2019). Leishmania is strongly affected by climate change [764].</p>		<p><u>HMPs in the EU</u> *These substances are authorised in the EU (Article 57 database, EMA). HMPs containing sod. stibogluconate, meglumine antimonate, amphotericin B and miltefosine have been authorised in the EU for leishmaniasis.</p> <p><u>VMPs authorised in the EU</u> Meglumine antimonate (ES, FR) and miltefosine (ES) are authorised in the EU for treatment of leishmaniasis in dogs. Allopurinol is used outside the terms of the marketing authorisation [769].</p> <p>Vaccines (Letifend, Canileish) are also available for dogs.</p> <p>Treatment protocols for dogs in Europe include meglumine antimonate or miltefosine combined with allopurinol long term to maintain clinical remission [765, 770]. Use of amphotericin B in dogs is discouraged to avoid the development of resistant strains [771]. Topical insect repellents and vaccines are used to prevent infection and reduce the disease transmission risk. They may work at individual level, but their effectiveness for control programmes at community level needs further investigation [765].</p>	<p>used in dogs [776]. Resistance has been demonstrated to allopurinol and antimonials in <i>Li</i> isolates from dogs [777, 778].</p>

4. Conclusions

A compiled recommendation for the groups of antimicrobials to be reserved for treatment of humans only (**Article 37(5)**) is presented in **Table 1** in the Summary. The Summary also includes further recommendations based on considerations of the Agency that developed from the scientific review process.

Annex

1. Antibiotics authorised in human medicine for unmet needs

The Delegated Regulation (EU) 2021/1760, establishing the criteria for antimicrobials to be designated for human use only, states that Criterion A (High Importance to Human Health) is met for antimicrobials that are 'recognised as addressing an unmet medical need related to antimicrobial resistance' (Part A.1.(c)).

Commission Regulation (EC) No. 507/2006 foresees that a conditional marketing authorisation can be granted for a medicinal product for human use in some cases including when there are unmet medical needs. Article 4 paragraph 2 defines "unmet medical needs":

'unmet medical needs' means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected'.

At the time of this report, the following substance and antimicrobial combinations have been designated by CHMP as complying with an unmet medical need for antibacterials to address carbapenem-resistant Gram-negative organisms, and have been authorised in products in Europe:

- cefiderocol
- ceftazidime-avibactam
- meropenem-vaborbactam
- Imipenem-cilastatin-relebactam

In line with the delegated regulation, it is proposed that these four substances/combinations are deemed to have met the criterion of high importance to human health.

2. Monograph on antivirals

The main considerations that were retained for classification of the antivirals are as follows (some additional factors were taken into account on a case-by-case basis):

- The human diseases/viruses against which each antiviral is claimed to be effective.
- The veterinary diseases/viruses against which each antiviral is claimed to be effective, or showed activity.
- The mechanism(s) of action, which allows specification as to whether the antiviral is virus-specific or whether it has a broader spectrum of activity.

Antivirals based on interferons were excluded from this analysis: interferons belong to several related families of cytokines (α , β and γ), naturally produced by the body (human and animals). They are highly potent antivirals per se, but by and large their major function is to regulate cellular proteins. As this is a natural immune process, it would not make sense to consider a ban on their use in animals.

Antivirals based on humanized monoclonal antibodies are also excluded from this analysis: monoclonal antibodies are dedicated to specific epitopes of a given virus. Although engineered, they behave like naturally-produced antibodies: they bind to the epitope(s) of the targeted pathogens, to neutralize

them and/or to prepare them for uptake and destruction by phagocytes. As this is a natural immune process, it would not make sense to consider their ban.

The following chapter is divided into two sections: the first is related to the antivirals which have received a Marketing Authorisation for human therapy within the EU and for which reliable data are available (through the SPCs); the second relates to a set of antivirals identified so far through textbooks and bibliographic data, taken on board by default, but for which the available information should be considered with prudence.

It cannot be excluded that some antivirals are missing. This is because no international comprehensive list of antivirals is currently available; furthermore, this category of medicines is quite novel, even on the human side, and is developing fast.

2.1. Antivirals against HIV (Retroviridae, Lentivirus)

Abacavir, bictegravir, cobicistat, dolutegravir, efavirenz, elvitegravir, emtricitabine, enfuvirtide, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, tenofovir alafenamide, tenofovir disoproxil, tipranavir and zidovudine are approved within the EU (Table 117).

To be noted that Cobicistat has no antiretroviral activity per se but increases the half-life of Elvitegravir.

Resistance to all current anti-HIV antivirals, including newer classes, is already recorded [779]. No transfer of resistant viruses, from domestic animals to humans, was identified so far.

Retroviruses do exist in the veterinary field, including within the Lentivirus family: few attempts to use the HIV antivirals against Feline infectious peritonitis were published. Zidovudine is included in the complementary part of the WSAVA List of Essential Medicines for Dogs and Cats as shown to improve the clinical status of feline immunodeficiency virus-infected cats, but evidence is limited.

To date none of the Retroviruses of domestic animals has been identified as causing a zoonotic disease; in particular, HIV is strictly restricted to humans and some non-human primates. Therefore, no specific restriction seems necessary with regard to this group of antivirals.

2.1.1. Conclusions

No reason could be identified for restricting veterinary use of abacavir, bictegravir, cobicistat, dolutegravir, efavirenz, elvitegravir, emtricitabine, enfuvirtide, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, tenofovir alafenamide, tenofovir disoproxil, tipranavir and zidovudine, as retroviruses are not involved in zoonotic diseases as listed in **Table 5**, and as the mechanism of action of these antivirals seems to be restricted to HIV.

2.2. Antivirals against influenza

Amantadine, baloxavir marboxil, oseltamivir, rimantadine and zanamivir are approved within the EU (Table 118).

Influenza viruses represent four of the seven genera of the *Orthomyxoviridae* family (Alphainfluenzavirus, Betainfluenzavirus, Deltainfluenzavirus and Gammmainfluenzavirus). Although influenza A and C viruses, such as avian influenza virus subtypes A(H5N1) and A(H9N2) and swine influenza virus subtypes A(H1N1) and A(H3N2), can become a significant threat to public health, the

highly pathogenic avian influenza (HPAI) viruses currently represent the highest risk. With rare exceptions, HPAI viruses found in nature have so far always contained the H5 or H7 hemagglutinin.

It is to be noted that, although animal viruses may be named as the same subtype as viruses found in humans, all of these animal viruses are distinct from human influenza viruses and do not easily transmit between humans.

Three classes of influenza antivirals are currently licensed, based on the mechanisms of action: M2 ion channel inhibitors (amantadine, rimantadine), neuraminidase inhibitors (oseltamivir, zanamivir) and cap-dependent endonuclease inhibitors (baloxavir marboxil). Resistance to all three classes is already recorded [593, 780]. The levels of resistance to each antiviral fluctuate over time: currently, the neuraminidase inhibitors and the endonuclease inhibitors are the sole remaining antiviral class available to prevent or treat human influenza A and B virus infection.

The antivirals amantadine and rimantadine inhibit the M2 protein (blocking the replication of the virus), that exists only on the type A influenza virus: they are therefore not active against type B influenza.

Zanamivir is used for the treatment and prophylaxis of influenza virus A and B. It is approved in the US.

Other pharmaceutical specialities contain amantadine as an active ingredient to control pain in humans, without claiming any action against influenza viruses. These products might also be used in small companion animals, primarily for the treatment of chronic severe e.g. neuropathic pain, often paired in veterinary practice with other pain medications such as NSAIDs, opioids, or gabapentin [781-787].

There is limited good quality evidence of efficacy of amantadine in animals for analgesia, although its mode of action (NMDA antagonist) is a rationale for its use in the treatment of chronic severe pain in veterinary medicine. However, this particular use of amantadine does not relate to treatment of infectious disease.

Amantadine is important for treatment of influenza A in humans. If use in animals is permitted in the EU and it is used for treatment of Influenza A virus infections in pet animals (e.g. cat, dog, non-food-producing horse), this would lead to the likely occurrence of amantadine-resistant Influenza A viruses in animals, which could become a threat to humans. On balance, given that some alternatives are available for analgesia in animals, there is an overriding public health interest not to use amantadine in animals.

The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) currently recommend oseltamivir and zanamivir for the treatment and prevention of avian influenza in humans.

Amantadine is used against avian flu in the veterinary field outside the EU [788]. Once the presence of HPAI is confirmed in a farm within the EU, the birds must be killed according to Council directive 92/40/EEC. Treatment as such is therefore not allowed within the EU.

In the US, medicines containing adamantane or neuraminidase inhibitors, approved for treating or preventing influenza A, are prohibited from extra-label uses in chickens, turkeys, and ducks [789].

Attempts to treat avian influenza in Northern China have been reported, and amantadine-resistance among H5N1 was detected: amantadine was used extensively in poultry farms in this area, which could explain the high amantadine-resistance incidence [790]. Attempts at similar treatment in other regions are likely [791].

Amantadine and derivatives could be used against swine influenza, paramyxoviruses (e.g. bovine parainfluenza type 3) and togaviruses (bovine diarrhea virus).

Zanamivir and oseltamivir could be used against HPAI in chickens [792].

Oseltamivir has gained popularity in the veterinary field for use in canine and feline parvovirus infections: it is thought to decrease the chance of the patient developing a bacterial superinfection [793]. Anecdotally, oseltamivir may be used to treat canine influenza (although regularly discouraged on websites).

Baloxavir marboxil showed activity against human influenza A and influenza B viruses. No publication was found on its use in the veterinary field. It is an enzyme inhibitor, targeting the influenza virus cap-dependent endonuclease activity, used in "cap snatching" by the virus polymerase complex [794]. It is approved by the Japan's Ministry of Health, Labour and Welfare and the FDA.

As influenza virus is quoted in **Table 6**, all the antivirals against influenza viruses may be considered for recommendation to be reserved for human use only.

2.2.1. Conclusions and recommendations

Amantadine, baloxavir marboxil, oseltamivir, rimantadine and zanamivir could generate viral resistance amongst influenza viruses, which could affect human health. **It is recommended that they should be designated to be reserved for human treatment only.**

2.3. Antivirals against chronic viral hepatitis

Adefovir dipivoxil, elbasvir, glecaprevir, grazoprevir, lamivudine, ledipasvir, pibrentasvir, ribavirin, sofosbuvir, tenofovir disoproxil, velpatasvir and voxilaprevir are approved within the EU (Table 119).

Alone or in association, these antivirals are specifically active against hepatitis B virus (HBV) or against hepatitis C virus (HCV). Indeed, according to bibliographical data and the SPCs of the corresponding human products:

- The metabolite of Adefovir dipivoxil (Adefovir-DP) is an analogue of deoxyadenosine-TP (dATP) which inhibits selectively the DNA-polymerase of HBV: it blocks the elongation of the viral DNA chain.
- Adefovir is also used for treatment of herpes simplex virus infection (*Alphaherpesvirinae* group). To be noted that two infectious outbreaks of herpesvirus simplex type 1 were recorded in non-human primates, one in the three-striped night monkey (*Aotus trivirgatus*), the other in the lar gibbon (*Hylobates lar*).
- The metabolite of Lamivudine (Lamivudine-TP) acts as a substrate for the DNA-polymerase of HBV: it blocks DNA expression and replication of HBV.
- Lamivudine is also used against both HIV-1 and HIV-2: it blocks the HIV reverse transcriptase.
- Telbivudine is the synthetic L-isomer of thymidine. The metabolite of Telbivudine (Telbivudine-TP) of thymidine-TP (dTTP) acts as a substrate for the DNA-polymerase of HBV: it blocks the elongation of the viral DNA chain.
- Tenofovir disoproxil is a nucleotidic analogue which acts as a substrate for the DNA-polymerase of HBV: it causes premature termination of DNA transcription, preventing viral replication. Tenofovir disoproxil is also used against HIV-1: it blocks the HIV reverse transcriptase.

- According to the SPC of Rebetol, the mechanism of action of Ribavirin is unknown. However according to publications, Ribavirin is a synthetic guanosine analogue, which acts against hepatitis C virus (HCV) through several mechanisms that include 1) immune modulation; 2) inhibition of inosine monophosphate dehydrogenase 3) inhibition of RNA-dependent RNA polymerase; 4) induction of HCV mutagenesis; and 5) modulation of interferon-stimulated gene expression.
- Ribavirin is effective against many DNA and RNA viruses: human respiratory syncytial virus, influenza B virus, measles (*Morbillivirus*, *Paramyxoviridae*), herpesvirus (HSV-1, HSV-2), Rift Valley Fever virus, Lassa fever (*Arenaviridae*), Crimean-Congo (*Nairovirus*, *Bunyaviridae*) and other hemorrhagic diseases (the efficacy of ribavirin is however questioned with regard to Crimean-Congo hemorrhagic fever virus). Ribavirin could also be relevant as an initial treatment of chronic HEV (hepatitis E virus) infection. Ribavirin, when used at an early stage of the disease, is the only effective antiviral treatment against Lassa fever so far [624].
- In the treatment of hepatitis C, it works very successfully in combination with a variety of other treatments but has no impact on hepatitis C on its own [606].
- Ribavirin seems active against a broad range of different viruses. Hence, this molecule could be effective against various other viruses, including the zoonotic ones listed in **Table 6**, and its use in veterinary medicine should be forbidden.
- Glecaprevir, Elbasvir and Voxilaprevir are inhibitors targeting protease NS3/4A of HCV (*Hepacivirus*, *Flaviviridae*).
- Pibrentasvir, Grazoprevir, Ledipasvir and Velpatasvir are inhibitors targeting protease NS5A of HCV.
- Sofosbuvir is an inhibitor targeting the fraction NS5B of the RNA-dependent RNA polymerase of HCV.

2.3.1. Conclusions and recommendations

- No reason could be identified for forbidding the veterinary use of adefovir dipivoxil, lamivudine, tenofovir disoproxil, glecaprevir, elbasvir, voxilaprevir, pibrentasvir, grazoprevir, ledipasvir, velpatasvir and sofosbuvir, as HBV/HCV are not listed in **Table 6** and as their mechanism of action seems to be specific to HBV/HCV.
- Ribavirin could generate viral resistance amongst viruses which could affect human health: its relevance for chronic HEV is already established, and it appears also that this molecule could be effective against various viruses including the zoonotic viruses listed in **Table 6**. **It is recommended that ribavirin should be designated to be reserved for human treatment only.**

2.4. Antivirals against herpes viruses

Aciclovir, famciclovir, foscarnet, ganciclovir, valaciclovir and valganciclovir are approved within the EU (Table 120).

Aciclovir is a nucleosidic analogue inhibiting the DNA polymerase of the herpesviruses (HSV). It blocks the synthesis of the viral DNA. This action is specific against human herpesviruses as the first step of the phosphorylation process is achieved by the virus-specific thymidine-kinase. It is currently authorised against varicella-zoster virus (human alphaherpesvirus type 3) and herpesvirus simplex types 1 and 2.

In the veterinary field, oral aciclovir appeared to significantly shorten clinical signs in primary herpesvirus infections in pinnipeds [795] (if efficacious, it would mean that it is not specific to human herpesviruses, contrary to the applicant's claim). It could be used more widely against other animal herpesviruses (its use against feline rhinotracheitis caused by feline herpesvirus type 1 is already quoted by stakeholders).

Valaciclovir is the L-valine ester of aciclovir with the same mechanism of action. This antiviral is said to be specific against human herpesviruses. It is currently authorised against herpesvirus simplex types 1 and 2, varicella-zoster virus (human alphaherpesvirus type 3), Epstein-Barr virus (human gammaherpesvirus type 4), cytomegalovirus (family *Herpesviridae*, sub-family *Betaherpesvirinae*) and human herpesvirus type 6.

It could be used in animal herpesviruses (its use in horses against infections caused by equine herpesvirus type 1 is already quoted by stakeholders).

Famciclovir is phosphorylated into penciclovir-triphosphate (a synthetic analogue of 2'-desoxyguanosine triphosphate), which blocks the elongation of the DNA strand. This action is specific against human herpesviruses as the first step of the phosphorylation process is achieved by the virus-specific thymidine-kinase. It is currently authorised against herpesvirus simplex types 1 and 2, varicella-zoster virus (human alphaherpesvirus type 3) Epstein-Barr virus (human gammaherpesvirus type 4) and cytomegalovirus (family *Herpesviridae*, subfamily *Betaherpesvirinae*).

It could be used in animal herpesviruses (as already quoted by stakeholders). Valganciclovir is a synthetic analogue of 2'-desoxyguanosine inhibiting viral replication. This action is specific against human herpesviruses as the first step of the phosphorylation process is achieved by the virus-specific protein-kinase pUL97. It is currently authorised against herpesvirus simplex types 1 and 2, varicella-zoster virus (human alphaherpesvirus type 3) Epstein-Barr virus (human gammaherpesvirus type 4), cytomegalovirus (family *Herpesviridae*, subfamily *Betaherpesvirinae*), human herpesvirus types 6, 7 and 8 and against hepatitis B virus (HBV).

Foscarnet (trisodium phosphonoformate hexahydrate) is a pyrophosphate analogue that interacts with the enzymatic action of polymerases and inhibits the cleavage of pyrophosphate from the nucleoside triphosphate. Because of this mechanism, its antiviral activity is broad. Foscarnet is a non-competitive inhibitor of herpesvirus DNA polymerase, hepatitis B virus DNA polymerase, and reverse transcriptases [796]. Foscarnet has in vitro activity against several herpesviruses (HSV, VZV, CMV, EBV and HHV-6) [797].

Foscarnet can be used to treat highly treatment-experienced patients with HIV as part of salvage therapy [798]. Although foscarnet is a non-competitive inhibitor of hepatitis B virus DNA polymerase [796], it seems to have only a modest antiviral activity in chronic HBV carriers [799].

Ganciclovir is a DNA polymerase inhibitor used to treat cytomegalovirus and herpetic keratitis of the eye. The primary mechanism of ganciclovir action against CMV is inhibition of the replication of viral DNA by ganciclovir-5'-triphosphate (ganciclovir-TP). This inhibition includes a selective and potent inhibition of the viral DNA polymerase [800].

Ganciclovir is used to treat viral infections caused by herpes viruses, especially for the treatment of ocular herpesvirus infections, in horses, cats [801] and possibly dogs [802].

No reason could be identified for restricting the veterinary use of ganciclovir, famciclovir, aciclovir/valaciclovir and valganciclovir, as no herpesvirus is listed in **Table 6** and as their mechanism of action seems to be restricted to herpesviruses.

No reason could be identified for restricting the veterinary use of foscarnet: this substance is active against CMV, HIV, and HSV infections (hence with a broader spectrum than the substances listed above), but there is no evidence so far that this molecule could be effective against the zoonotic viruses listed in **Table 6** (herpesviruses, hepatitis B virus and retroviruses (the last two using reverse transcriptases) are not included in **Table 6**).

2.5. Other quoted antivirals

See table Table 121.

According to various sources [803-805], the following antivirals were identified:

Brincidofovir/cidofovir is an experimental antiviral for the treatment of humans against cytomegalovirus, adenovirus and poxvirus infections [806]. Its activity against BK virus (polyomavirus) and Herpes simplex virus is also quoted.

Cidofovir diphosphate acts as inhibitor of the DNA polymerase, resulting in decreased DNA synthesis and chain termination [805]. Resistance to this antiviral already recorded [807].

In laboratory tests, cidofovir and brincidofovir have been shown to be effective against the variola virus (smallpox) [611]. Cidofovir was formerly approved in the EU for treatment of cytomegalovirus retinitis, but the authorisation is now withdrawn.

In the veterinary field, cidofovir was used to treat poxvirus disease in pinnipeds [808]. In laboratory tests, cidofovir and brincidofovir have been shown to be effective in treating animals that had diseases similar to smallpox [611].

It seems that brincidofovir/cidofovir is not specific of one DNA polymerase, as it is active against herpesviruses and adenoviruses (using the cellular DNA-dependent RNA polymerase) but also against poxviruses (using their own DNA-dependent RNA polymerase). However, as none of these viruses are retained in **Table 5**, the use of brincidofovir/cidofovir in the veterinary sector should not be restricted.

Camostat mesylate (FOY-305) is a serine protease inhibitor. Serine protease enzymes have a variety of functions in the body, and so camostat has a diverse range of uses. In the case of its antiviral activity against SARS-CoV-2, the only virus under consideration so far, camostat mesylate inhibits the action of the serine protease TMPRSS2, preventing the priming [809]³ of the viral spike protein for attachment to ACE2, and entry into the cell[810]⁴.

In-vitro studies suggest that camostat might constitute a treatment option against SARS-CoV infections [810-812], but these results were mitigated by clinical trials [813, 814]. It is currently in several Phase I/II clinical trials [815, 816].

Occurrence of viral resistance to camostat mesylate is not documented so far, but is suspected to be low. Indeed, a possible advantage of blocking TMPRSS2 using camostat mesylate, and not targeting the virus itself, is that it will be more resilient to the rapid development of viral resistance, since individual point mutations in viral components are unlikely to compensate for the loss of a critical host factor [817].

Camostat mesilate is approved in Japan with various indications, but not as an antiviral; Camostat is not approved for any use by EMA or FDA [818].

³ The spike proteins of SARS-CoV-1 and 2 are activated ("primed") upon proteolysis of two peptide bonds

⁴ Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. SARS-CoV-2 uses the receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming

Given the low level of knowledge about this molecule as an antiviral and as no coronavirus is listed in **Table 5**, no reason could be identified for restricting its veterinary use so far.

Celgosivir is an experimental antiviral for the treatment of human hepatitis C virus infection. No publication was found on its use in the veterinary field.

It inhibits alpha-glucosidase I, an enzyme that is necessary for the processing of the viral envelope glycoproteins [610]. Resistance to this antiviral is not recorded so far, but resistance would probably occur if this antiviral would be used under field conditions. Moreover, alpha-glucosidase I is a cell enzyme: hence, it is not virus-specific, and it cannot be excluded that it could become a treatment for viruses listed in **Table 5**. Therefore, it may be considered for a recommendation to be reserved for human use only.

Favipiravir showed activity against human influenza viruses, but it is also under consideration for the treatment of various other RNA viral infections [819], such as West Nile virus, Yellow fever, Foot-and-mouth disease, as well as other flaviviruses, arenaviruses, bunyaviruses and alphaviruses [820]. It is also under investigation against the SARS-CoV-2 coronavirus.

In the veterinary field, favipiravir was tested against canine distemper virus infection in vitro [821]. Favipiravir (T-705) and its derivatives T-1105 and T-1106 are efficient inhibitors of foot-and-mouth disease virus replication in cell culture and in vivo [600].

It is authorised in Japan against human influenza virus, but indicated only for novel influenza (causing more severe disease) rather than seasonal influenza [597].

The mechanism of action is still unclear: it is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase [822]. Other researchers suggest that it induces lethal RNA transversion mutations, producing a nonviable viral phenotype [823]. Resistance to this antiviral is already recorded [599].

Despite these uncertainties, it appears that its mechanism of action is not virus-specific, and it cannot be excluded that it could become a treatment for some viruses listed in **Table 5**. Moreover, this antiviral is active against influenza viruses, which are quoted in **Table 6**. Therefore, it may be considered for a recommendation to be reserved for human use only.

Galidesivir is an adenosine analog, showing activity against hepatitis C, but also against filovirus infections such as Ebola virus disease and Marburg virus disease [824].

It also shows broad-spectrum antiviral effectiveness against various other RNA viruses, such as bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses, flaviviruses and phleboviruses [825]. Galidesivir showed efficacy against Zika virus in a mouse model [826] and it is one of several antivirals being tested for coronavirus disease [827]. No publication was found on its use in the veterinary field.

Galidesivir blocks the viral RNA polymerase that plays a crucial role in the viral replication process, including transcription and replication of the virus genome, leading ultimately to chain termination.

Galidesivir is currently not marketed, but it could become an important antiviral with regard to human health; resistance to galidesivir is not recorded so far, probably because of its limited use (currently not marketed). Resistance could already be obtained under very special in-vitro conditions (human-induced mutation of the tick-borne encephalitis virus) [828].

Given that one flavivirus is retained in **Table 5**, and as it appears that its mechanism of action is not virus-specific, it could potentially be used against other viruses of **Table 5**. Therefore, it may be considered for recommendation to be reserved for human use.

Lactimidomycin showed activity against a variety of RNA viruses, such as flaviviruses (dengue fever, Kunjin virus and Modoc virus), as well as vesicular stomatitis virus and poliovirus [829]. No publication was found on its use in the veterinary field.

It acts as a direct inhibitor of protein translation in ribosomes.

Resistance to this antiviral is not recorded so far, probably because of its limited use (currently not marketed).

Given that one flavivirus is retained in **Table 5**, and as it appears that its mechanism of action is not virus-specific (it is said to be active against a variety of RNA viruses), lactimidomycin could potentially be used against other viruses of **Table 5**. Therefore, it may be considered for recommendation to be reserved for human use.

Laninamivir is a neuraminidase inhibitor for the treatment and prophylaxis of Influenzavirus A and B: neuraminidase cleaves the glycosidic linkages of neuraminic acids which are responsible for binding new viruses to infected cells, thereby allowing viruses to release and infect other cells. Laninamivir prevents the replication of all influenza viruses, as neuraminidase is essential in this process.

Laninamivir is approved in Japan.

As influenza virus is quoted in **Table 6**, it may be considered for a recommendation to be reserved for human use only.

Methisazone/metisazone has been used in the past to treat human adenovirus and smallpox diseases [830]. It inhibits mRNA and protein synthesis.

No publication was found on its use in the veterinary field.

Resistance to this antiviral is not recorded so far, probably because of its limited use (currently not marketed).

Adenoviruses and poxviruses are not retained in **Table 5**. However, its mechanism of action does not appear to be virus-specific, and it cannot be excluded that it could become a treatment for some viruses listed in **Table 5**. Therefore, it may be considered for a recommendation to be reserved for human use only.

Molnupiravir (EIDD-2801) [831] is an isopropylester prodrug of the nucleoside analog beta-D-N4-hydroxycytidine (also named NHC or EIDD-1931), which is the active form of molnupiravir. Available data suggest that molnupiravir acts as a lethal mutagenizing agent that impairs SARS-CoV-2 replication: schematically, in a first step, the viral RNA-dependent RNA polymerase (RdRp) readily incorporates NHC, instead of cytidine or uridine when it uses the positive-strand RNA of the virus as a template to synthesize the negative-strand RNA; in a second step, the resulting NHC-containing RNA will be used as a template for the synthesis of positive-strand RNAs, which do not support formation of intact new viruses. Moreover, molnupiravir escapes viral RNA proofreading because NHC incorporation and NHC-directed misincorporation are apparently not recognised by the viral exonuclease. This two-step mutagenesis mechanism probably applies to various viral polymerases and can explain the broad-spectrum antiviral activity of molnupiravir.

Indeed, molnupiravir is suspected to interfere with the replication of various viruses [831], already shown for pandemic and seasonal influenza A virus (*Alphainfluenzavirus A*, *Orthomyxoviridae*), Venezuelan equine encephalitis virus (*Alphavirus*, *Togaviridae*), human respiratory syncytial virus (*Orthopneumovirus*, *Pneumoviridae*), Chikungunya virus (*Alphavirus*, *Togaviridae*), Ebola virus (*Ebolavirus*, *Filoviridae*), norovirus (*Norovirus*, *Caliciviridae*), bovine viral diarrhea virus (*Pestivirus*, *Flaviviridae*) and hepatitis C virus (*Hepacivirus*, *Flaviviridae*).

The likelihood of occurrence of resistance appears to be low [614].

Molnupiravir is approved in the UK (and already purchased in several other countries). It is under assessment for a marketing authorisation in the EU for the treatment of patients with Covid-19.

Given that its mechanism of action is not virus-specific and that it is active against pandemic influenza A virus, listed in **Table 5**, therefore, it may be considered for recommendation to be reserved for human use.

Nitazoxanide/Tizoxanide is an antiparasitic showing activity in humans against influenza, chronic hepatitis B and C, rotavirus and norovirus gastroenteritis [832]. It showed in vitro activity against the MERS-CoV and other coronaviruses [833].

No publication was found on its use against viruses in the veterinary field.

Nitazoxanide is authorised in the United States against a variety of parasites including protozoa, giardia, nematodes, trematodes, and some bacteria.

In the viral domain, it blocks maturation of the viral hemagglutinin at the post-translational stage [834]. It also potentiates the production of type 1 interferons (alpha and beta) produced by the host's fibroblasts [835], which could explain its (indirect) activity on viruses other than Influenza.

To be noted that the epidemiology of the rotavirus disease is still not yet fully clarified. Some strains appear to be species-specific, but others are strongly suspected to be able to infect both animals and humans. Formal proof is however not yet available.

Host-targeted nitazoxanide has a high barrier to antiviral resistance [618]. However, given that rotavirus and influenza virus are quoted in **Table 5**, therefore, it may be considered for recommendation to be reserved for human use.

Peramivir was developed for the treatment of influenza. It has been effective in treating humans suffering from swine flu [836]. It is a neuraminidase inhibitor, acting as an analogue inhibitor of influenza neuraminidase and thereby preventing new viruses from emerging from infected cells. Peramivir is approved in Australia, Japan and South Korea. It is used, but unapproved, in the United States against the H1N1 influenza virus [837]. Initially approved in the EU (Alpivab), it is no longer authorised. As influenza virus is quoted in **Table 6**, therefore, it may be considered for recommendation to be reserved for human use.

Nirmatrelvir (PF-07321332) is one of the 2 components of Paxlovid™ (Pfizer), the other component being ritonavir, already approved as an antiviral against HIV. Ritonavir is added in small quantities to lower the metabolism or degradation of PF-07321332, increasing the efficacy of the medicinal product against the four main variants of SARS-CoV-2.

PF-07321332 acts as a 3C-like protease (3CL^{pro}) inhibitor. 3CL^{pro} is one of the two main proteases found in coronaviruses. It cleaves the coronavirus polyprotein 1ab, which is a multifunctional protein essential to transcription and replication of the coronavirus, at eleven conserved sites.

PF-07321332 is presented as specifically inhibiting SARS-CoV2 replicase polyprotein 1ab of coronaviruses. No data could be found about the potential activity of PF-07321332 against other single-stranded RNA viruses: indeed, 3C^{pro} and 3CL^{pro} are widely found in (+)ssRNA viruses, and some protease inhibitors, such as GC373, GC375 and GC376 with a similar (but not identical) structure

compared to PF-07321332, are active against picornaviridae and caliciviridae [838]⁵, but no evidence so far was found to support a similar activity for PF-07321332.

Occurrence of resistance to this substance is likely [839], although not formally demonstrated yet. However, it was already shown that a model coronavirus, the mouse hepatitis virus, became resistant to a broad-spectrum CoV 3CL^{pro} inhibitor, GRL-001⁶.

PF-07321332 has conditional approval in the US and in the UK [840, 841]. In combination with ritonavir, it has a conditional marketing authorisation in the EU for treatment of Covid-19 [842].

Given the specificity of the mechanism of action of PF-07321332 and as no coronavirus is listed in **Table 5**, no reason could be identified for restricting its veterinary use so far.

PF-07304814 [843] is a small molecule prodrug that targets the 3CL^{pro} proteases. After intravenous infusion, the compound is cleaved into PF-00835231, which is the active compound. PF-00835231 was shown to have potent and broad-spectrum inhibitory activity against numerous coronavirus 3CL proteases. No data could be found about the potential activity of PF-00835231 against other viruses.

Given the similarity of PF-07304814/ PF-00835231 with PF-07321332, occurrence of resistance can be expected, although not demonstrated yet.

PF-07304814 is currently being tested in conjunction with Remdesivir to treat Covid-19 infection, but the development is still in its early stages. There is no approval worldwide (it is currently investigational).

Given the specificity of the mechanism of action of PF-07304814/ PF-00835231, no reason could be identified for restricting its veterinary use, as no *Coronaviridae* is listed in **Table 5**.

Remdesivir showed activity against Ebola and Covid-19, with an antiviral activity in vitro against multiple filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses [844]. Remdesivir ('Veklury') has a conditional marketing authorisation in the EU for the treatment of Covid-19 in humans [845]. It appears also to be a good candidate for treating feline infectious peritonitis (FIP) caused by a coronavirus [846-851].

As an adenosine nucleoside triphosphate analogue, it causes a decrease in viral RNA production and induces an irreversible chain termination [852], as it interferes with the action of the viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease [852, 853].

Resistance to this antiviral is strongly suspected [854].

No filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses are retained in Table 5. However, as it appears that its mechanism of action is not virus-specific (it is said to interfere with the viral RNA-dependent RNA polymerase), it could potentially be used against other RNA viruses of Table 5.

However, FIP is a severe, life-threatening disease in cats for which no adequate and efficacious treatment has been established yet. As FIP is not a zoonotic virus, the public health risk for transmission of resistance to remdesivir due to its use in cats for treatment of this disease is not likely to be significant. Therefore criterion C is not met.

Rupintrivir (AG-7088, Rupinavir) is a peptidomimetic antiviral which acts as a 3C and 3CL protease inhibitor. It was developed for the treatment of rhinovirus infections, but as the 3C proteases of

⁵ Picornaviridae and caliciviridae, being grouped on the basis of phylogenetic analysis with coronaviruses into the picornavirus-like supercluster, have a picornavirus 3C^{pro} and a caliciviridae 3CL^{pro} respectively.

⁶ GRL-001 is a 5-chloropyridyl ester-derived compound which has been shown to inhibit 3CL^{pro} enzymatic activity of SARS-CoV and MERS-CoV.

various viral species are structurally very similar, it has subsequently been investigated for the treatment of other viral diseases, such as enteroviruses, noroviruses and SARS-CoV-2.

Rupintrivir may be a promising candidate for treating diseases due to enteroviruses [855] and noroviruses [856], but its activity against SARS-CoV-2 [857] seems weak. Moreover, in the Phase II clinical trials with regard to rhinovirus infections, rupintrivir demonstrated moderate antiviral and clinical efficacy, and further development was stopped [858].

The currently available studies suggest that there is a high genetic barrier to the development of resistance within the 3C protease for rupintrivir [859].

There is no approval worldwide (it is currently investigational).

Given the low level of knowledge about this molecule as an antiviral, and as no rhinoviruses, enteroviruses, noroviruses and coronaviruses are listed in **Table 5**, no reason could be identified for restricting its veterinary use so far.

Tecovirimat showed activity against orthopoxviruses such as smallpox and monkeypox. No publication was found on its use in the veterinary field.

It is approved in the United States for treatment of smallpox.

Tecovirimat inhibits the function of a major envelope protein required for the production of extracellular virus. Thus the virus is prevented from leaving an infected cell and therefore cannot spread within the body [860].

There are no known instances of naturally occurring tecovirimat resistant orthopoxviruses, although tecovirimat resistance may develop under drug selection [861]. No transfer of resistant viruses from domestic animals to humans was identified so far. Given that no poxvirus is retained in **Table 5**, its use in the veterinary sector should not be restricted.

Triazavirin showed activity against influenza viruses, in particular the H5N1 pandemic influenza strain [862], but also a number of other viruses such as Tick-borne encephalitis virus (family *Flaviviridae*); its activity against Lassa fever (*Arenaviridae*) and Ebola virus (*Filoviridae*) disease is currently investigated. No publication was found on its use in the veterinary field.

It appears that its mechanism of action (not very detailed) is not virus-specific: it inhibits the synthesis of viral RNA and DNA and replication of genomic fragments [863]. While resistance to this antiviral is not yet recorded, we should be preparing for the fact that over time there will be strains of viruses resistant to triazavirin. Therefore, given that influenza virus and flavivirus are quoted in **Table 5**, therefore, it may be considered for recommendation to be reserved for human use.

Umifenovir showed activity against human influenzaviruses. Umifenovir acts as a fusion inhibitor interfering with the binding, fusion and entry of a virus into a human cell. It is approved in Russia and China. No publication was found on its use in the veterinary field. Given that influenza virus is quoted in **Table 5**, and as it appears that the mechanism of action of umifenovir (not very detailed) is not virus-specific, therefore, it may be considered for recommendation to be reserved for human use.

The following antivirals may be recommended to be reserved for human use, as they could generate viral resistance amongst viruses which could affect human health: celgosivir, favipiravir, galidesivir, lactimidomycin, laninamivir, methisazone/metisazone, molnupiravir, nitazoxanide/tizoxanide, peramivir, triazavirin and umifenovir.

2.6. Conclusion

The following antivirals are recommended to be reserved for human use only: amantadine, baloxavir marboxil, celgosivir, favipiravir, galidesivir, lactimidomycin, laninamivir, methisazone/metisazone, molnupiravir, nitazoxanide/tizoxanide, oseltamivir, peramivir, ribavirin, rimantadine, triazavirin, umifenovir and zanamivir.

3. Monographs on antifungals

3.1. Azoles

3.1.1. Introduction

'Azoles' (Table 122) include a diverse range of therapeutic classes and have a wide range of pharmacological effects; therefore, the scope of this monograph has been restricted to azoles with antimycotic effect.

Imidazoles and triazoles exert their antifungal effect by inhibiting 14 α -sterol demethylase, an enzyme required for the synthesis of ergosterol, the principle sterol used to maintain the structural integrity of the fungal cell membrane. Azoles are generally fungistatic. Triazoles tend to have less effect on human sterol synthesis than imidazoles and can exert fungicidal effects against some moulds (e.g. voriconazole against *Aspergillus (A.) fumigatus*). Imidazoles (e.g. clotrimazole, miconazole), with the exception of ketoconazole, are limited to topical treatment of superficial fungal infections whereas triazoles (fluconazole, itraconazole, voriconazole) are also administered intravenously and orally for systemic mycoses. Mostly, the azole antifungals mostly have a good safety profile.

The spectrum of activity varies according to substance, but in general azoles have good activity against: *Blastomyces dermatidis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides* spp., *Paracoccidioides brasiliensis*, most *Candida* spp. *Aspergillus* spp. and dermatophytes.

They have intermediate activity against: *Fusarium*, and *Sporothrix schenckii*

3.1.2. Assessment against the criteria

3.1.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity?

According to [ESCMID guidelines](#) [643], isavuconazole and (for children) voriconazole are recommended as first-line treatments for invasive aspergillosis, including *A. fumigatus* if susceptibility has been shown [864]. Prophylactic use of fluconazole is recommended to manage *Candida* infections in patients with recent abdominal surgery or other high-risk conditions. Posaconazole, also, is used for antifungal prophylaxis in high-risk patients (e.g. hematopoietic stem-cell transplantation). Otherwise azoles are recommended as second line and de-escalation options for candidaemia once fluconazole susceptibility is confirmed. For cryptococcal meningitis, IDSA guidelines [649] suggest that fluconazole is used as a longer term suppressive follow up after the use of initial fungicidal regimens (e.g. polyenes + flucytosine). Treatment guidelines recommend azoles for a wide range of fungal infections, including sporotrichosis, histoplasmosis and blastomycosis.

Invasive aspergillosis (IA) and invasive candidiasis are a significant cause of morbidity and mortality and economic burden in Europe [865]. The incidence of nosocomial infections has increased in recent years in association with the increase in immunocompromised patients.

WHO EML (2021): Azoles are included on the EML for systemic treatment of acute invasive (voriconazole and chronic (voriconazole, itraconazole) pulmonary aspergillosis. Itraconazole is also included for histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by *Talaromyces marneffe* and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by *T. marneffe* in AIDS patients.

Fluconazole (oral), clotrimazole (gynaecological use) and miconazole (topical) are listed in the EML as antifungals without specific indications stated.

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR?

In the EU, voriconazole is authorised in HMPs for treatment of invasive aspergillosis, candidaemia (non-neutropenic patients), fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*) and serious infections due to *Scedosporium* and *Fusarium* spp.

Itraconazole is authorised for parenteral treatment of histoplasmosis, and as second-line treatment of aspergillosis, candidiasis and cryptococcosis. Fluconazole is authorised for parenteral treatment of cryptococcal meningitis, coccidioidomycosis and invasive and mucosal candidiasis. It is also used for prophylaxis of *Candida* infections in high risk patients.

The above are serious infections with limited treatment options.

By oral administration, azoles including clotrimazole, miconazole and enconazole are authorised for follow up of parenteral treatments and for oral and oesophageal candidiasis, for vulvovaginal candidiasis, pityriasis and dermatophytoses.

Topical and oral azoles can be bought over the counter in the EU for self-medication of common localised fungal infections.

No medicines containing azoles have been categorised by CHMP as addressing an unmet medical need.

Data on mechanisms and the prevalence of resistance in human isolates

In *Candida* spp., mechanisms of acquired resistance include alteration in the target enzyme, 14- α -demethylase (reduced drug-target affinity, upregulated production, or both), due to mutation in the *ERG11* gene and over-expression of the *CDR1*, *CDR2* and *MDR1* genes encoding efflux pumps (ABC and MFS transporters) [866]. Resistance may be associated with prolonged prophylactic use of azoles [867]. Although *C. albicans* largely remains susceptible, the SENTRY programme [868] reported levels of resistance to fluconazole in *C. glabrata* of 4.9% in European isolates from 2006-2016. There have been increasing reports of multidrug resistance to the azoles, echinocandins, and polyenes, most notably in *C. glabrata* and more recently *C. auris* [869]. *C. auris* also has high propensity for patient-to-patient transmission; hospital outbreaks have been reported in UK and Spain [628]. The CDC [629] listed fluconazole-resistant *Candida* spp. amongst the pathogens posing a serious threat to human health. CDC estimates that about 30% of patients with resistant blood stream infections die, and that each case leads to an additional 3-13 days hospitalisation. MDR *C. auris* is an emerging global health threat.

In *Aspergillus fumigatus*, the most common mechanism of azole resistance is due to mutations in the *CYP51A* gene encoding 14 α -sterol demethylase. Isolates with environmental exposure to azoles most often have alterations at codon TR₃₄/L98H or TR₄₆/Y121F/T289A of this gene and its promotor region. Emergence of these resistance mechanisms is thought to have been driven by use of azole fungicides on crops. Based on Eurostat data, at least 10,000 tonnes of imidazole/triazole based fungicides were used as plant protection products in the EU in 2018. TR₃₄/L98H isolates show a pan-azole-resistant phenotype - exhibiting resistance to itraconazole, voriconazole, and posaconazole and TR₄₆/Y121F/T289A isolates are highly resistant to voriconazole and isavuconazole and variably resistant to itraconazole and posaconazole. TR₃₄/L98H is now thought to be the predominant resistance mechanism in IA patients in the EU, although triazole resistance can also develop in individual patients during long term therapy for chronic aspergillosis. On surveillance of clinical *A. fumigatus* isolates from 18 EU and 4 non-EU sites, Van der Linden, Arendrup [870] detected a prevalence of azole resistance of 3.2% with the TR₃₄/L98H mechanism present in 48.9% of resistant isolates. The TR₃₄/L98H mutation has been shown to be associated with a significantly higher mortality rate of 88%, compared with 30%–50% for WT-aspergillosis. It has led to a change in first line therapy to voriconazole/echinocandin combination or liposomal amphotericin B in areas with high resistance rates [640, 871-873].

Treatment of dermatophytosis due to *Microsporum canis* with azoles in humans is associated with treatment failures but this may be related to pharmacokinetic and compliance issues in addition to AMR. Determination of antifungal susceptibility is not routinely performed and association with clinical response in dermatophytes is problematic. Azole resistance has been seldom reported in dermatophytes, except in *Trichophyton rubrum* where it has been associated with ABC transporter efflux pumps [874, 875]. A study investigating the susceptibility of *M. canis* from patients and animals with dermatophytosis in Iran, France and Turkey found that all of 208 isolates exhibited high susceptibility to the majority of novel triazoles and imidazoles tested [876].

Conclusions

Azoles are important in human medicine as first-line treatment for life-threatening invasive aspergillosis as well as chronic aspergillosis. They are also important as a second-line and follow up treatment for invasive candidiasis and for various other serious systemic mycoses, and may be used prophylactically in high risk immunosuppressed patients. They are particularly important due to the absence of alternative oral treatment options for these diseases.

The emergence of nosocomial infections in immunocompromised patients due to multidrug resistant *Candida* spp. (e.g. *C. auris*, *C. glabrata*) and azole-resistant *Aspergillus fumigatus* is a serious threat to human health. Increasing levels of resistance have necessitated review of treatment protocols and azoles may need to be used in combination with other antifungal classes to treat certain infections in specific settings; alternative treatments are limited.

Azoles are also important for treatment of human dermatophytoses, which although common, rarely have serious human health consequences.

Azoles are of high importance to human health for treatment of life-threatening invasive fungal infections in immunosuppressed patients (aspergillosis, candidiasis).

3.1.2.2. Risk of transmission of resistance

Risk for transmission of resistance from animals to humans

Although there are limited data on animal isolates, resistance to certain azoles is common in *Candida* spp. isolated from horses and birds [12]. A study investigating mechanisms of azole resistance in *C.*

albicans from animals identified overexpression of *CDR1*, *CDR2*, *MDR1* and mutations in *ERG11* [877], i.e. similar mechanisms as those seen in human isolates. Castelo-Branco, Paiva [878] reported a high prevalence of azole-resistance in *Candida* spp. (especially *C. albicans* and *C. tropicalis*) from different animal species (dogs, wild birds) in Brazil. Mechanisms seemed to be non-specific ABC and MFS efflux pumps, and it was suggested that selection pressure originates from environmental determinants (e.g. heavy metals, antimicrobials) or agricultural use of azoles. The need for a One Health approach to management of resistance was noted.

Reports of azole resistance in animal isolates of *A fumigatus* are sparse; Talbot, Kidd [879] examined 50 isolates from sino-nasal aspergillosis in dogs and cats collected from 1988 to 2014 and identified one isolate carrying a *cyp51A* mutation.

Aspergillus usually develops in animal tissues without producing conidial heads and aspergillosis is therefore not considered a direct zoonosis [12]; although potentially highly colonised environments such as bird farms may pose increased risk to workers for acquiring infections [642]. *Aspergillus* on poultry farms is usually controlled through environmental disinfection rather than medication of birds.

In most cases of invasive candidiasis in humans the infecting strain is part of the host's commensal flora, although nosocomial infections involving transmission between humans occur in healthcare settings (*C. auris*, *C. parapsilosis*).

The zoonotic potential for both *Aspergillus* and *Candida* spp. is very low.

In Europe, dermatophyte infections in companion animals (*Microsporum canis*, *Trichophyton* spp.) and cattle (*Trichophyton verrucosum*) are potentially zoonotic (especially transmission of *M. canis* from cats) and dermatophytes are found on animals in pet shops [880]. Azole resistance may be emerging but reports to date are sparse.

Is transmission of resistance significant?

Aspergillosis and candidiasis are not considered as a direct zoonoses; therefore the risk for direct transmission of azole-resistance in these pathogens is not likely to be significant. Animals could contribute to the pool of azole-resistance in environmental *Aspergillus* and *Candida* spp., but the contribution is likely to be very low compared to that from other agricultural sources.

There is a risk for transmission of azole-resistant dermatophytes from animals to humans.

Conclusions

There are limited data available on the occurrence of azole resistance in fungal isolates from animals. Despite this, the risk of zoonotic transmission of (azole-resistant) fungal organisms with potential to cause serious invasive fungal infections (e.g. *Candida* spp., *Aspergillus* spp.) in humans is currently regarded extremely low.

In humans, resistant nosocomial infections are likely to reflect selection pressure arising from hospital use, but environmental sources of resistance due to heavy use of azoles as plant protection products for crops are especially significant in *Aspergillus* spp. There is little evidence to support direct zoonotic transfer of potentially serious mycotic infections such as aspergillosis and candidiasis from domestic animals. Domestic animals could contribute to the environmental load of azole-resistant *Candida* and *Aspergillus* spp., although the contribution is likely to be very low.

Azole-resistant dermatophytes are a potential zoonotic hazard, but empirical evidence for this is weak, potentially in part because susceptibility testing of dermatophytes is not routinely performed. Dermatophytosis is not a disease with serious human health consequences.

3.1.2.3. Non-essential need for animal health

Consideration of authorised veterinary medicines

Food-producing animals

Enilconazole is the only antifungal included within the Annex to the MRL Regulation 37/2010 that can be used to treat dermatophytosis in cattle and horses (by topical application). Cattle may recover spontaneously from infection with *T. verrucosum*; alternatively, vaccination may be used to eliminate the infection from a herd and limit zoonotic infection.

Parconazole has been evaluated for MRLs as a treatment for candidiasis in guinea fowl and is included in the MRL Regulation for use in this species ('No MRL required'), although no current EU-authorised VMP was found. Morbidity and mortality of candidiasis in poultry is generally low. Minimising the use of antibiotics and improving hygiene can reduce the incidence of candidiasis.

Ketoconazole is included on the list of substances essential for the treatment of equidae (Regulation (EU) 122/2013) as a systemic treatment for fungal pneumonia and guttural pouch mycosis (although surgical intervention may now be a preferred option for the latter). Miconazole is included in the same list for topical treatment of fungal eye infections in horses.

Companion animals

In the EU, azoles (itraconazole, ketoconazole) are authorised in veterinary medicines for systemic treatment of dermatophytoses in cats and dogs. Griseofulvin has been used as an alternative for the treatment of dermatophytosis in animals, but may now only be available as an authorised VMP for treatment of non-food-producing horses. Otherwise, to our knowledge, azoles are the only antifungals authorised for the systemic treatment of animals in the EU.

Dermatophytosis is not regarded as a life-threatening disease; however, it is a common zoonosis and animal treatment is necessary in the interests of animal and public health.

Azoles (clotrimazole, miconazole, posaconazole) are included in topical ear preparations to treat otitis due to *Malassezia* infections, which occur commonly in cats and dogs. Limited alternatives include nystatin and terbinafine.

Itraconazole is authorised for the treatment of respiratory infections caused by *Aspergillus* and *Candida* spp. in ornamental birds. Candidiasis may be severe in juvenile birds, where it leads to anorexia, regurgitation and weight loss. Aspergillosis may develop into systemic infections affecting internal organs including bone, liver, kidneys and brain and associated with high mortality.

Antifungals are not addressed in the OIE list.

Azoles are included in the WSAVA List of Essential Medicines for Cats and Dogs (2020) as topical agents for treatment of superficial yeast, principally *Malassezia*, and dermatophyte infections (Core List), and as oral preparations for systemic activity against superficial and deep fungal infections (Complementary List).

Consideration of use outside the terms of the marketing authorisation

Azoles are used (outside the terms of the marketing authorisation) for uncommon but serious animal diseases e.g. aspergillosis, histoplasmosis, zygomycosis, sporotrichosis and cryptococcosis, in companion and zoo animals. Of these, sporotrichosis (*S. brasiliensis*) is the only infection with significant zoonotic risk and hence possibility for direct transfer of azole resistance from animals to

humans. Limited information is available on alternative treatments for these indications (e.g. amphotericin B, flucytosine) and azoles are preferred [84, 345, 647, 652].

Ketoconazole is included on the list of substances essential for the treatment of equidae (Regulation (EU) 122/2013) as a systemic treatment for fungal pneumonia and guttural pouch mycosis. Surgical intervention may now be a preferred option for the latter [881]. Miconazole is included in the same list for topical treatment of fungal eye infections in horses.

Table 66. Information on use of azoles outside the terms of the marketing authorisation from the open data call

Substance	Nature of use outside the terms of the marketing authorisation	Respondents
Clotrimazole	Human oral formulation for fungal skin infections in dogs	National Control Authority
	Horses – uterine yeast infection	Equine vet
'Conazole'	Dermatophytosis in rabbits	Poultry/rabbit vet
Fluconazole	Cetaceans, pinnipeds – fungal infections	Zoo vet
	Fungal eye infection in horses	National Control Authority
Itraconazole	Penguins, pelicans, anatids, waterbirds, cetaceans, elasmobranchs – fungal infections	Zoo vet
	Dermatophytosis in dogs	Veterinarian
Ketoconazole	Human oral preparation for chronic <i>Malassezia</i> skin infection in dogs	Veterinarian
Miconazole	Fungal eye infection in horses	National Control Authority
Posaconazole	Cetaceans – fungal infections Bottlenose dolphin - zygomycosis	Zoo vet
Ronidazole	<i>Tritrichomonas foetus</i> in cats	Veterinarians National Control Authority
Triazoles	Systemic fungal infections, not specified	National Control Authority
Voriconazole	Penguins, cetaceans, elasmobranchs – fungal infections	Zoo vet
	Bottlenose dolphin – Aspergillosis, Fusariosis	Zoo vet
	Fungal eye infection in horses	National Control Authority

Conclusions

Azoles are the only antifungal agents authorised for systemic treatment of animals in the EU, other than griseofulvin (non-food horses only). Although there are few antimycotic azoles authorised (other than in ear preparations for treatment of otitis in companion animals), they are important for treatment of a wide range of mostly sporadic but serious fungal diseases in companion and zoo animals. They are the preferred option owing to their proven safety profile and a lack of information on safety and efficacy of alternative antifungal agents. Azoles are the only authorised VMPs for zoonotic dermatophytoses in cats and dogs, for which treatment is necessary on public health grounds.

3.1.3. Recommendation

Azoles fulfil the criterion A of high importance to human health.

Azoles do not fulfil the criterion B of significant risk of transmission of resistance.

The criterion C of non-essential need for animal health is not considered to have been met.

It is recommended that Azoles should not be designated to be reserved for human treatment only.

3.2. Polyenes

3.2.1. Introduction

Polyenes (Table 123) are naturally occurring compounds that act by binding with ergosterol in the fungal cell membrane, increasing its permeability and causing leakage of ions and essential small organic molecules from the fungal cell. The oxidation of amphotericin also destabilizes the fungal membrane by generating toxic free radicals. In addition, amphotericin induces oxidative stress causing fungal cell death. Toxicity limits use of most polyenes to topical treatment only, except for amphotericin B (AmB) which is administered systemically with care. Lipid formulations of AmB are generally used to reduce nephrotoxicity and include a liposomal preparation (LAmB) and a lipid complex (ABLC). AmB has the advantage of being fungicidal, although its usefulness is limited by inability to distribute to certain body niches; penetration into cerebrospinal fluid is increased in the presence of meningitis and by the LAmB formulation.

Table 67. Information on the spectrum of activity of polyenes

Source: Grayson, Cosgrove [159]

Substance	Spectrum of activity
Nystatin	Yeast: <i>Candida</i> spp., <i>Malassezia</i> spp., <i>Cryptococcus neoformans</i> Molds, Filamentous fungi: <i>Aspergillus</i> spp., <i>Trichophyton</i> spp., <i>Epidermophyton</i> spp., and <i>Microsporum</i> spp. Dimorphic fungi: <i>Histoplasma capsulatum</i> , <i>Blastomyces dermatitidis</i> , <i>Coccidioides immitis</i> ,
Natamycin (pimaricin)	Yeast: <i>Candida</i> spp., <i>Malssezia</i> spp., <i>Cryptococcus neoformans</i> Molds, Filamentous fungi: <i>Aspergillus fumigatus</i> , <i>Fusarium</i> spp., <i>Alternaria alternata</i> Dimorphic fungi: <i>Histoplasma capsulatum</i> , <i>Blastomyces dermatitidis</i> , <i>Coccidioides immitis</i> , <i>Sporothrix schenckii</i>
Amphotericin B	Yeast: <i>Candida</i> spp., <i>Malssezia</i> spp., <i>Saccharomyces</i> spp., <i>Cryptococcus</i> spp. Molds, Filamentous fungi: <i>Aspergillus</i> spp. (excluding <i>A terreus</i> and <i>A flavus</i>), Mucorales Dimorphic fungi: <i>Histoplasma capsulatum</i> , <i>Blastomyces dermatitidis</i> , <i>Coccidioides immitis</i> , <i>Penicillium marneffeii</i> , <i>Sporothrix schenckii</i> Also active against <i>Prototheca</i> spp. and some protozoa, including <i>Leishmania</i> spp.

In the EU, amphotericin B, natamycin and nystatin are authorised in human medicines, and nystatin in veterinary medicines. Hachimycin (trichomycin) is no longer marketed [882].

3.2.2. Assessment against the criteria

3.2.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity?

Amphotericin B

Aspergillosis: Azoles (isavuconazole, voriconazole) are generally recommended as first-line treatment for IA, with AmB reserved for treatment of species intrinsically resistant to azoles, or strains that have acquired azole-resistance [643]. AmB is recommended as second-line alternative to triazoles for treatment of chronic pulmonary aspergillosis. It is the antifungal of choice for local instillation in aspergilloma cavities [883]. L AmB is also recommended as an alternative for prophylaxis and treatment of IA in neonates and children (Warris 2019).

Candidiasis: Echinocandins are recommended for the initial treatment of candidaemia, with liposomal AmB a second-line choice owing to concerns regarding renal and infusion-related toxicity. In neonates, AmB, fluconazole or micafungin are recommended for treatment of disseminated invasive candidiasis [884]. In adults with haematological malignancies and after hematopoietic stem-cell transplantation, liposomal AmB is recommended as first-choice for treatment of chronic disseminated candidiasis [885]. Ocular infections may be treated with intra-vitreal injections of AmB [636].

Blastomycosis: Lipid AmB is the recommended treatment for moderate to severe pulmonary blastomycosis and disseminated blastomycosis, with step-down to azoles for longer term treatment [670].

Coccidioidomycosis: AmB is generally recommended as a second-line treatment for patients that fail to respond to azoles, or for use in patients with severe rapidly progressing disease when intravenous treatment is required [672].

Cryptococcosis: AmB is recommended in combination with flucytosine as first-line treatment for Cryptococcal meningoencephalitis, and for children and pregnant women with disseminated disease. Azoles are recommended for treatment of pulmonary infections [649].

Histoplasmosis: Lipid AmB followed by itraconazole is the recommended treatment for acute and chronic pulmonary histoplasmosis, for moderate-severe disseminated histoplasmosis and for CoNS infection [667].

Mucormycosis: liposomal AmB is recommended as first-line treatment, together with surgical debridement [886]. Isavuconazole is also recommended.

Sporotrichosis: AmB is the preferred treatment for life-threatening pulmonary, meningeal or disseminated sporotrichosis, and infections in pregnant women and children [664].

Nystatin: In the EU, nystatin is authorised for oral administration for the prevention and treatment of candida infections of the oral cavity, oesophagus and intestinal tract. It is also authorised in cutaneous preparations for treatment of dermatoses, and as a vaginal tablet and cream.

Natamycin: In the EU, vaginal tablets are available for treatment of candida infections. Natamycin is also authorised in cutaneous preparations for treatment of dermatoses. According to textbooks, natamycin is used for fungal keratitis and vaginal trichomoniasis.

AmB (deoxycholate and liposomal) and nystatin are included on the EML [3], without specific indications. Natamycin is also included as anti-infective eye drops, without specific indication.

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR?

Amphotericin B (AmB): In the EU AmB is indicated for treatment of severe systemic and deep mycoses; presumed fungal infections in febrile neutropenic patients; disseminated candidiasis, aspergillosis, mucormycosis, chronic mycetoma, cryptococcal meningitis, blastomycosis, sporotrichosis (and visceral leishmaniasis). In some SPCs it is stated that it should primarily be used to treat patients with progressive potentially fatal fungal infections. It may be administered intravenously, by inhalation, intrathecally and by local instillation.

No medicines containing polyenes have been categorised by CHMP as addressing an unmet medical need.

Data on the mechanism and the prevalence of resistance in human isolates

Data on resistance to antifungals are not collected by EARS-Net.

Despite more than 50 years of use, resistance to polyenes remains very rare [887]. There are methodological difficulties associated with susceptibility testing [888]. In the FILPOP survey of Spanish clinical isolates collected in 2010-11, 14% of *Aspergillus flavus* were reported as resistant to polyenes [889]. Surveillance performed in Denmark from 2012-15 showed acquired resistance to AmB in 1.3% of overall fungaemia isolates and 1.0% (18/1851) *Candida* spp. isolates [890]. In cases of Candidaemia screened in Sweden in 2005-6, 3 of 403 isolates were resistant to AmB [891]; and in 2015/16 none of 488 isolates were resistant [892].

Intrinsic resistance to AmB is common for *Aspergillus terreus*, *A. flavus*, *Scedosporium* spp., and *Trichosporon* and is also seen in *C. auris* and *C. lusitaniae* [542]. The underlying mechanism is poorly understood [893]. *A. terreus* is responsible for 3-4% of *Aspergillus* spp. infections, but is an emerging opportunist pathogen, associated with disseminated infections and high mortality rates.

Acquired resistance is usually due to reduction of ergosterol content in the in the fungal cell membrane, resulting from mutations in ergosterol biosynthesis genes, or increased production of reactive-oxidant scavengers. Emergence of resistance during AmB therapy is uncommon [888]. Vincent, Lancaster [887] demonstrated that mutations that conferred in vitro resistance in *C. albicans* simultaneously created stresses that required high levels of the molecular chaperone (heat shock protein) Hsp90 to survive host immune defense, i.e. there was a fitness-cost that restricted evolution of resistance.

In *C. albicans*, mutations in *ERG2*, *ERG3* and *ERG11* genes which encode for enzymes involved in the ergosterol biosynthetic pathway cause a reduction in ergosterol in the fungal cell membrane and hence resistance to AmB. In other *Candida* spp., resistance results from alteration in *ERG2* and *ERG6* [894].

Resistance to AmB may also arise in *C. albicans* strains that produce increased amounts of catalase, which helps cope with oxidative cell damage [888].

Conclusions

AmB is recommended as a second-line choice for treatment of severe invasive candidiasis or aspergillosis, or for the treatment of strains resistant to first-line antifungals. It is recommended as first-line treatment for mucormycosis, cryptococcal meningitis (combined with flucytosine) and some less common mycoses (blastomycosis, histoplasmosis, mucormycosis and sporotrichosis) when infections are severe and disseminated. The availability of alternative treatment options for fungal infections is generally limited.

Resistance to polyenes remains very rare, but has been reported in *Candida* and *Aspergillus* spp.

3.2.2.2. Risk of transmission of resistance

Potential risk for transmission of resistance from animals to humans

Resistance in animal isolates

Few studies were available relating to the susceptibility of veterinary isolates to polyenes.

No resistance to amphotericin was found in 64 isolates of *C. tropicalis* from healthy domestic and wild animals from Brazil [895].

In a study including 14 strains of *A. fumigatus* from the lungs of diseased geese raised on farms in Poland, 100% were resistant to AmB; although it was noted that this was not consistent with data from other researchers [896].

Other than *Sporothrix brasiliensis*, which does not occur naturally in the EU, the fungal infections that are treated with polyenes in humans are not considered zoonotic. For those infections that are saproscous, there is no direct pathway for transmission of polyene resistant infections from animals to humans.

Is transmission of resistance likely to be significant?

Transmission of polyene-resistant fungal infections from animals to humans is not likely to be significant in the EU.

3.2.2.3. Non-essential need for animal health

Consideration of authorised veterinary medicines

There are no authorised veterinary medicines containing **AmB** in the EU. It cannot be used in food-producing species as it is not included in the Annex to the MRL Regulation (EU) 37/2010.

Nystatin is authorised in the EU in ear treatments for dogs and cats, for treatment of *Malassezia* otitis. Alternatives include azoles and terbinafine. Nystatin cannot be used in food-producing species (other than horses*) in the EU as it is not included in the Annex to the MRL Regulation (EU) 37/2010.

No EU-authorised VMPs could be found containing **natamycin**; however, natamycin has 'no MRL required' status for topical use in bovines and *Equidae*, for which it was intended as a ringworm treatment.

Consideration of use of human products

Textbooks suggest that **AmB** has been used to treat systemic fungal infections in companion animals (*Candida*, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus* spp). In cats, it has been used in combination with azoles to treat sporotrichosis. In horses it has been used to treat pulmonary cryptococcosis, by regional limb perfusion to treat pythiosis and by subconjunctival injection to treat ocular fungal disease [84, 445, 645].

AmB is included in the WSAVA List of Essential Medicines for Cats and Dogs (2020) for systemic activity against fungal infections (Complementary List).

In relation to the serious life-threatening diseases for which use of AmB is reported outside the terms of the marketing authorisation, it is probable that azoles would be the first-choice treatment, with AmB used in case of treatment failure or in combination.

The alternatives to use of AmB in veterinary medicine may be equally, if not more, important antifungals for human medicine.

***Nystatin** is included in the list of essential substances for equidae (Regulation (EU) 122/2013) for treatment of yeast infections of the eye and genital tract. According to texts, it has been used to treat mastitis caused by yeast in cattle and metritis due to *Candida* in horses. In exotic birds and pets it has been used to treat intestinal candidiasis and other mycoses.

According to texts, **natamycin** has been used to treat keratomycosis and nasal and guttural pouch mycosis in horses [445].

In the case of nystatin and natamycin, azoles or terbinafine may be alternatives for the given indications.

Table 68. Information on use of polyenes outside the terms of the marketing authorisation from the open data call

Substance	Nature of use outside the terms of the marketing authorisation	Respondents
Amphotericin	Cetaceans: susceptible fungal diseases	Zoo vet
	Horses: Systemic and local fungal infections, including eye infections	National Control Authority
Nystatin	Cetaceans: susceptible fungal diseases (digestive tract)	Zoo vet

3.2.3. Recommendation

Polyenes fulfil the criterion A of high importance to human health.

Polyenes do not fulfil the criterion B of significant risk of transmission of resistance.

The criterion C of non-essential need for animal health is not considered to have been met.

It is recommended that Polyenes should not be designated to be reserved for human treatment only.

Further consideration has been given to the use of AmB for treatment of Leishmaniasis (see under Antiprotozoals).

3.3. Pyrimidine analogues – Flucytosine

3.3.1. Introduction

Flucytosine is a pyrimidine analogue (Table 124). Aided by permease enzymes, it is selectively taken up by fungal cells. Flucytosine is then converted by cytosine deaminase to 5-fluorouracil and subsequently to further metabolites: 5-fluorodeoxyuridylic acid inhibits the enzyme thymidylate synthase, involved with fungal DNA synthesis and cell division; phosphorylated 5-fluorouridylic acid is incorporated into fungal RNA and disrupts protein synthesis.

The spectrum of activity of flucytosine is restricted to pathogenic yeast including *Candida* spp. (excluding *C. krusei*), *Cryptococcus neoformans* and *C. gattii*. It has limited activity against filamentous fungi when used alone but is often used in combination with other antifungals for synergistic effect, e.g. with amphotericin B to treat *Aspergillus* spp. infections. Resistance develops rapidly during use unless used as part of combination therapy [542, 897].

3.3.2. Assessment against the criteria

3.3.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity?

For treatment of cryptococcal meningoencephalitis, the IDSA [649] and WHO guidelines [648] advise initial treatment with LAmB and flucytosine as a fungicidal regimen, followed by suppressive regimens using fluconazole. Flucytosine is recommended in rare cases to be used in combination with other antifungals for the treatment of triazole-resistant *Aspergillus* spp. infections [643].

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR?

Flucytosine is authorised in HMPs in the EU for parenteral treatment of systemic yeast and fungal infections e.g. cryptococcosis, candidiasis and chromomycosis. For cryptococcal meningitis and severe systemic candidiasis, it should be administered in combination with amphotericin B or fluconazole.

It is also authorised as an oral treatment, including additionally for certain *Aspergillus* spp.

No medicines containing flucytosine have been categorised by CHMP as addressing an unmet medical need.

EML 2021: Flucytosine is included as an antifungal medicine for oral and parenteral administration.

Data on mechanism and the prevalence of resistance in human isolates

Resistance to flucytosine develops rapidly during treatment, limiting its use as a single therapy.

The incidence of intrinsic resistance is low and is due to decreased uptake of flucytosine by the enzyme cytosine permease (encoded by *FCY2*). Acquired resistance is due to mutations in *FCY2* and genes encoding the enzymes responsible for its metabolic activation, cytosine deaminase (*FCY1*) and UPRTase (*FUR1*).

Resistance in the majority of *Candida* spp. and *C. neoformans* is due to decreased activity of cytosine deaminase or UPRase due to gene mutations [897, 898]. Further mechanisms of resistance have been identified in *C. glabrata* [899].

Information on the prevalence of resistance was sparse.

Conclusions

Flucytosine, in combination with AmB, is important as first line for the treatment of cryptococcal meningitis, a serious disease in humans, with few available alternatives. Resistance to flucytosine develops rapidly during treatment, limiting its use as a single therapy.

3.3.2.2. Risk of transmission of resistance

Potential risk for transmission of resistance from animals to humans

No reports were found that specifically identified resistance to flucytosine in fungal isolates from domestic animals; although it could be speculated that resistance would develop rapidly under treatment.

Is transmission of resistance likely to be significant?

No.

Conclusions

Considering the minor use of flucytosine in animals and limited evidence for transmission of *Cryptococcus* from domestic animals to humans, the risk of transfer of resistant organisms is considered to be extremely low.

3.3.2.3. Non-essential need for animal health

No EU-authorized veterinary medicines could be found containing flucytosine. Flucytosine not included in the Annex to the MRL Regulation 37/2010 and cannot be used in food-producing animals in the EU.

Consideration of use of human products

It has been reported that flucytosine has been used to treat cryptococcosis in dogs and cats [345, 445, 900]. *Cryptococcus* causes ulcers and granulomatous lesions, affecting the upper respiratory tract, pharynx, skin, eyes and CNS. The European Advisory Board on Cat Diseases advises that for CNS or systemic cases, amphotericin alone or in combination with flucytosine may be the first choice treatment [901]. Azoles are an alternative treatment for mild to moderately severe disease, but not when there is CNS involvement.

No use of flucytosine was reported in the open data call on use outside the terms of the marketing authorisation.

Conclusions

Cryptococcosis occurs rarely or sporadically in domestic animals in Europe, but it is noted that flucytosine is part of the first-line treatment for serious CNS or systemic disease in cats and dogs.

3.3.3. Recommendations

Pyrimidine analogues fulfil the criterion A of high importance to human health.

Pyrimidine analogues do not fulfil the criterion B of significant risk of transmission of resistance.

The criterion C of non-essential need for animal health is not considered to have been met.

It is recommended that Pyrimidine analogues should not be designated to be reserved for human treatment only.

3.4. Griseofulvin

3.4.1. Introduction

Griseofulvin (Table 125) inhibits fungal mitosis by disrupting the assembly of the mitotic spindle. It is also reported to inhibit fungal RNA and DNA synthesis. Griseofulvin binds to keratin in keratin precursor cells and only reaches the site of action when old hair or skin is replaced. The spectrum of activity includes the dermatophytes *Trichophyton*, *Microsporum* and *Epidermophyton*. Griseofulvin is not effective against yeast and dimorphic fungi.

The arrival of antifungals with more favourable pharmacokinetic and safety profiles has rendered griseofulvin as a second-line treatment [882, 902].

3.4.2. Assessment against the criteria

3.4.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity?

Griseofulvin is used as an oral treatment for dermatophyte infections (e.g. tinea capitis), depending on the fungal species involved. Tinea infections are rarely regarded as having serious human health consequences (see Table 64 of fungal diseases).

A systematic review comparing efficacy and safety of systemic antifungals for Tinea capitis in children found that both griseofulvin and terbinafine were effective, but terbinafine was more effective against *T. tonsurans* and griseofulvin against *M. canis* [903].

Very rarely Majocchi's granuloma has been treated with terbinafine, itraconazole or griseofulvin [661].

Other than Majocchi's granuloma, griseofulvin is not used to treat diseases with serious human health consequences.

EML: Griseofulvin is included as an oral antifungal medicine [3].

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR?

Griseofulvin is authorised in HMPs in the EU for oral use for treatment of fungal infections of the skin, scalp, hair, or nails (tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, tinea unguium) where topical therapy is considered inappropriate.

Griseofulvin is authorised in topical formulations for treatment of mycotic infections due to superficial dermatophytes e.g. treatment of tinea pedis (athlete's foot).

These are not regarded as serious infections.

No medicines containing griseofulvin have been categorised by CHMP as addressing an unmet medical need.

Data on the mechanisms and prevalence of resistance in human isolates

Although treatment failures are reported, there are limited reliable reports on resistance in dermatophytes to griseofulvin. Breakpoints have not been established and mechanisms for elevated MICs are unknown [902].

Conclusions

Griseofulvin is used for the topical or systemic treatment of dermatophyte infections, as a second-line alternative to modern antifungals with more favourable pharmacokinetic and safety profiles - azoles and terbinafine - although griseofulvin has been shown to have better efficacy than terbinafine in the treatment of tinea capitis caused by *M. canis*. Other than Majocchi's granuloma, griseofulvin is not used to treat diseases with serious human health consequences.

Treatment failures are reported, but there are limited reliable reports on resistance in dermatophytes to griseofulvin.

3.4.2.2. Risk of transmission of resistance

Risk for transmission of resistance from animals to humans

See above.

Conclusions

There is a theoretical risk that griseofulvin-resistant strains of zoonotic dermatophytes could be transmitted from animals to humans, but no reliable published reports of resistance in animal isolates were found.

3.4.2.3. Non-essential need for animal health

Griseofulvin is not included in the Annex to the MRL Regulation 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.

Consideration of authorised veterinary medicines

Griseofulvin is authorised as a VMP in some EU member states for oral administration to horses, only, for the treatment of dermatophytes, *Trichophyton* and *Microsporum* spp. Griseofulvin is also included in the list of substances essential for the treatment of equidae (Regulation (EU) 122/2013) for the treatment of ringworm. The alternative authorised treatment for horses is enilconazole, for topical use.

Consideration of use outside the terms of the marketing authorisation

Griseofulvin could be used in accordance with Article 112 of Regulation (EU) 2019/6 for treatment of dermatophytosis in companion animals in the EU, including rabbits and rodents [445]. Griseofulvin is recommended in treatment guidelines for dermatophytosis in dogs and cats where systemic treatment is needed, but it is noted that it has more potential side effects compared with itraconazole and terbinafine [660]. Azoles are the only authorised alternative systemic treatment, authorised in the EU for dogs and cats only.

Dermatophytosis is not regarded as a life-threatening disease; however, it is a common zoonosis and animal treatment is necessary in the interests of animal and public health.

Table 69. Information on use of griseofulvin outside the terms of the marketing authorisation from the open data call

Substance	Nature of use outside the terms of the marketing authorisation	Respondents
Griseofulvin	Cats: fungal infections	National Control Authority

3.4.3. Recommendation

Griseofulvin does not fulfil the criterion A of high importance to human health.

Griseofulvin does not fulfil the criterion B of significant risk of transmission of resistance (limited evidence).

The criterion C of non-essential need for animal health is considered to have been met.

It is recommended that Griseofulvin should not be designated to be reserved for human treatment only.

3.5. Allylamines

3.5.1. Introduction

Allylamines (terbinafine, naftifine) (Table 126) act by inhibition of squalene epoxidase, leading to deficiency in ergosterol and accumulation of squalene in the fungal cell membrane. High levels of squalene cause release of lytic enzymes which are lethal to the fungal cell [159]. Terbinafine has a broad spectrum of activity. It is fungicidal against virtually all dermatophytes. Terbinafine is active against *Aspergillus* spp. in vitro but showed poor efficacy in the treatment of aspergillosis in an in vivo rat model [904]. It is also active against certain yeast in vitro, but has only fungistatic effect against *C. albicans* and no effect against *C. glabrata*, *C. tropicalis* and *C. krusei*. It is active against some dimorphic fungi (*Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Histoplasma capsulatum* and *Sporothrix schenckii*).

Terbinafine accumulates in keratin and hence persists in skin, hair and nails.

Butenafine is a benzylamine with mechanism of action and spectrum of activity similar to the allylamines.

3.5.2. Assessment against the criteria

3.5.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity? and

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR

Terbinafine is primarily used in human medicine for fungal infections of the skin, hair and nails. Dermatophytosis is a common disease in immunocompetent and immunocompromised people, causing skin lesions which are treatable and curable. Alternative treatments include azoles and griseofulvin. A systematic review comparing efficacy and safety of systemic antifungals for tinea capitis in children found that both griseofulvin and terbinafine were effective, but terbinafine was more effective against *T. tonsurans* and griseofulvin against *M. canis*. Azoles were alternatives, but not optimal choices, for Trichophyton infections [903].

Terbinafine may also be used for Majocchi's granuloma and invasive dermatophytosis [656, 661]. According to IDSA guidelines [664], terbinafine is an option for the treatment of localised lymphocutaneous sporotrichosis in patients who fail to respond to itraconazole.

Terbinafine is authorised in HMPs in the EU as topical preparations for the treatment of fungal skin infections caused by *Trichophyton* spp., *Microsporum canis* and *Epidermophyton floccosum*; and yeast infections caused by *Candida* spp. It is also authorised for topical treatment of Pityriasis versicolor due to *Pityrosporum orbiculare*.

Terbinafine is also authorised for oral administration for treatment of fungal infections such as tinea corporis, tinea cruris, tinea pedis and onychomycosis caused by dermatophytes.

Naftifine is authorised in topical products for the treatment of tinea infections.

EML: Terbinafine is included on the EML [3] as a topical antifungal for dermatological use.

No medicines containing allylamines have been categorised by CHMP as addressing an unmet medical need.

Data on the mechanisms and prevalence of resistance in human isolates

Susceptibility testing of dermatophytes is not routinely performed, not even in cases failing to respond to treatment. Hence, resistance is likely under-detected. Mechanisms of resistance to allylamines reported include efflux via ABC transporters, mutations in *ERG1P* gene encoding squalene epoxidase (SQLE), stress tolerance induction and detoxification [905, 906].

Resistance has been described in *T. rubrum* and *T. interdigitale* due to mutations in the SQLE gene that affect the allylamine binding site on the enzyme [907, 908]. Yamada, Maeda [909] found that about 1% of isolates collected at a Swiss hospital showed reduced susceptibility to terbinafine, and these were all found to harbour mutations in the SQLE gene. Terbinafine resistance was also identified in Danish patients with *T. rubrum* or *T. interdigitale* infections that were refractory to treatment [908]. Although previously rarely reported, terbinafine resistance in *Trichophyton* spp. has increased in recent years, especially in India [657, 910].

Terbinafine resistance in *M. canis* has been reported due to overexpression of the genes encoding ABC transporter proteins [911].

Production of melanins by *Sporothrix brasiliensis* and *S. schenkii* has also been shown in vitro to be protective against terbinafine [912].

Conclusions

Terbinafine is important in human medicine in the EU for the topical and systemic treatment of dermatophytosis, which although a common infection in immunocompromised people, is treatable and rarely has serious consequences. Resistance to terbinafine in dermatophytes has historically been rare, but has increased in recent years. Alternative treatments are griseofulvin and azoles; however, a move to increased use of azoles would increase the selective pressure on the *Candida* biome.

3.5.2.2. Risk of transmission of resistance

Potential risk for transmission of resistance from animals to humans

In an Austrian study of 37 cats and dogs with dermatophytosis due to *Microsporum* spp. or *Trichophyton* spp., oral therapy with terbinafine for up to 39 weeks caused no increase in MIC or minimum fungicidal concentration (MFC) and it was concluded that terbinafine has low potential to induce clinical resistance [913]. Resistance to terbinafine was reported in an *M. canis* isolate from a single cat in China that had been on treatment with terbinafine. It was speculated that this was due to over-expression of genes encoding for ABC transporters [914].

Is transmission of resistance likely to be significant?

There is a risk that terbinafine-resistant strains of zoonotic dermatophytes could be transmitted from animals to humans, but no reports were found. Allylamine resistance is largely an understudied topic and susceptibility testing is not routinely performed. A clade of terbinafine-resistant *T. mentagrophytes*/*T. interdigitale* has recently arisen and the borders between anthropophilic and zoophilic infections are becoming less clear.

Conclusion

There is a potential risk that terbinafine resistant strains of zoonotic dermatophytes could transfer from companion animals to humans; however, this area is under-investigated and no reports have been found.

There is a risk that increased terbinafine resistance in humans (subsequent to zoonotic terbinafine-resistant dermatophyte infection) could result in increased use of azoles and selection pressure on the commensal candida microbiota. However, the relative impact on azole-resistance is likely to be low considering the overall extent of human use of azoles and there may be impacts on public health if animals cannot be treated effectively for dermatophytosis.

3.5.2.3. Non-essential need for animal health

No allylamines are included in the Annex to the MRL Regulation 37/2010 and therefore they cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.

Consideration of authorised veterinary medicines

In the EU, combination antimicrobial ear preparations contain terbinafine for the treatment of otitis externa in dogs due to *Malassezia pachydermatitis*. Terbinafine is an alternative to azoles and nystatin, included as antifungals in other ear preparations. No EU-authorized veterinary medicines containing terbinafine for systemic treatment were identified.

Consideration of use of human products

Studies have investigated the use of oral terbinafine to treat dermatophytosis and *Malassezia* infections in dogs and cats [445] and it is recommended in treatment guidelines for dermatophytosis where systemic treatment is needed [660]. Azoles are the only authorised alternative systemic treatment.

Dermatophytosis is not regarded as a life-threatening disease; however, it is a common zoonosis and animal treatment is necessary in the interests of animal and public health.

Use outside the terms of the marketing authorisation as reported to the open data call

Table 70. Information on use of allylamines outside the terms of the marketing authorisation from the open data call

Substance	Nature of use outside the terms of the marketing authorisation	Respondents
terbinafine	To treat susceptible fungal diseases in Penguins, cetaceans, elasmobranchs (fusariosis)	Zoo veterinarian

Terbinafine is included in the WSAVA List of Essential Medicines for Cats and Dogs (2020) as a topical agent for treatment of superficial yeast, principally *Malassezia*, and dermatophyte infections (Core List), and as an oral preparation for systemic activity against superficial and deep fungal infections (Complementary List).

3.5.3. Recommendation

Allylamines do not fulfil the criterion A of high importance to human health.

Allylamines not fulfil the criterion B of significant risk of transmission of resistance (limited evidence).

The criterion C of non-essential need for animal health is considered to have been met.

It is recommended that Allylamines should not be designated to be reserved for human treatment only.

3.6. Echinocandins

3.6.1. Introduction

The echinocandins (Table 127) are lipopeptides that inhibit the enzyme 1,3-beta-D-glucan synthase and hence the production of glucan, an essential polysaccharide in the cell wall of many fungi. They are fungicidal against *Candida* spp., and fungistatic against *Aspergillus* spp. They also have activity against *Pneumocystis jirovecii* but are not active against *Cryptococcus* spp. Echinocandins have limited oral bioavailability and are mostly administered intravenously, after which they have good tissue distribution, except to the cerebrospinal fluid, eye, peritoneal cavity and the urine. They are generally well tolerated. Echinocandins have not been authorised in veterinary medicines in the EU.

3.6.2. Assessment against the criteria

3.6.2.1. High importance to human health

Is the antimicrobial a sole or last resort treatment, or one of limited or few alternatives, to treat a disease that leads to significant mortality or debilitating morbidity?

In European treatment guidelines, echinocandins are recommended as the preferred treatment for invasive candidiasis, particularly *C. auris* and *C. glabrata* for which resistance to azoles is more common [633, 635, 636].

Echinocandins are highly active against most *Candida* spp., but less active against *C. parapsilosis* which is responsible for at least 15% of infections in Europe [868]. However, *C. parapsilosis* is a low virulent species and outcome of fluconazole and echinocandin treatment has been found equal based on 30-day mortality [915].

In an ECDC survey of hospital-acquired infections in EU acute care hospitals in 2011-12, *Candida* spp. was associated with 7.4% of bloodstream infections. A case-fatality rate of 30-40% is reported even in patients receiving treatment [628]. See table of fungal diseases.

Echinocandins are recommended as second-line, or salvage therapy for treatment of invasive aspergillosis.

EML: Echinocandins are not included in the WHO's Model List of Essential Medicines [3].

Is the class/substance authorised in the European Union for treatment of serious infections in patients with limited treatment options, and is it recognised by CHMP as addressing an unmet medical need related to AMR?

Echinocandins are authorised in the EU in intravenous preparations for:

- Treatment of invasive candidiasis (C, M, A)
- Treatment of oesophageal candidiasis (M)
- Prophylaxis of *Candida* infection in patients undergoing hematopoietic stem-cell transplantation or with neutropenia (M)
- Treatment of invasive aspergillosis in patients refractory or intolerant to amphotericin B and/or itraconazole (C)
- Empirical treatment for presumed fungal infections in febrile neutropenic patients (C)

As noted above, invasive candidiasis and invasive aspergillosis are serious infections.

No medicines containing echinocandins have been categorised by CHMP as addressing an unmet medical need.

Data on mechanisms and the prevalence of resistance in human isolates

Acquired resistance has been reported for major *Candida* spp. but is rare (<1% in major species) except for *C. glabrata*, where resistance to caspofungin in isolates was 3.5% in global isolates from 2006-16 [868]. Resistance to echinocandins is conferred by amino acid substitutions in two hot spot regions of the Fks subunits of the target enzyme, glucan synthase, as a result of mutations in *FKS1* and (in *C. glabrata*) *FKS2* genes. The median treatment duration before resistance is detected is 30 days and thus much shorter than for azoles and amphotericin B. Fks target gene mutations were found in ~15% of *C. glabrata* in the oral cavity in patients after echinocandin therapy for candidaemia illustrating the potential for resistance development in this species [916]. Levels of resistance to echinocandins vary depending on the mutations and levels of expression of these genes, but Fks-related resistance is associated with poor clinical outcomes and confers resistance across the class. In *C. albicans*, alteration of Fks1 is often associated with fitness cost.

Some fungal strains have adaptive mechanisms in response to echinocandin exposure (heat shock protein 90, cell wall integrity pathway, high osmolarity glycerol pathway and chitin biosynthesis). In themselves they do not lead to clinical failure but may stabilise cells until *FKS* mutations arise. *FKS* resistance is associated with long term and/or repeated echinocandin exposure [917].

C. glabrata is increasingly resistant to both azoles and echinocandins [918, 919].

Acquired resistance of *Aspergillus* spp. to echinocandins has also been associated with *FKS1* mutations and is very rare [917, 920].

Conclusions

Echinocandins are the first-line choice for treatment of invasive candidiasis, an important cause of mortality and morbidity in immunosuppressed patients. Azoles are an alternative, although resistance is an increasing problem. The remaining alternative, amphotericin B, should be used with care due to potential nephrotoxicity. Levels of resistance to echinocandins in the EU are reported as very low at present, but likely higher in difficult to reach foci like intraabdominal infections and on mucosal surfaces.

3.6.2.2. Risk of transmission of resistance

Potential risk for transmission of resistance from animals to humans

No information could be found on resistance to echinocandins in fungal isolates from animals.

Conclusions

No evidence could be found of resistance to echinocandins in fungal isolates from animals. Aspergillosis and candidiasis are not regarded a zoonoses and there is no direct pathway for transmission of echinocandin resistance from animals to humans.

3.6.2.3. Non-essential need for animal health

Echinocandins have not been authorised for use in VMPs in the EU. They are not included in the Annex to the MRL Regulation 37/2010 and cannot be used in food-producing animals in the EU, including under Articles 113 & 114 of Regulation (EU) 2019/6.

Consideration of use of human products

Use outside the terms of the marketing authorisation relates to companion animals, only.

There is little information about the use of echinocandins in veterinary medicine in the EU. Pharmacological studies have been conducted and there are rare reports of the use of echinocandins to treat aspergillosis in cats and dogs [921]. Nasal aspergillosis in these species has been reported as treated (outside the terms of the marketing authorisation) with azoles administered systemically and topically [345, 645-647]

No use of echinocandins was reported in the open call for data on use outside the terms of the marketing authorisation.

Conclusions

There is little evidence for an important need for echinocandins in veterinary medicine.

3.6.3. Recommendation

Echinocandins fulfil the criterion A of high importance to human health.

Echinocandins do not fulfil the criterion B of significant risk of transmission of resistance (limited evidence).

The criterion C of non-essential need for animal health is considered to have been met.

It is recommended that Echinocandins should not be designated to be reserved for human treatment only.

4. Analysis of the answers from stakeholders on the open call for data on use of antimicrobials in animals

4.1. Introduction

On 9 December 2020, the EMA/CVMP launched an open call for data on the cascade⁷ use of antimicrobials in animals. The purpose was to gain information to support the EMA's scientific advice to the Commission in relation to Articles 37(5) and 107(6) of the Regulation (EU) 2019/6. Data were requested via the interactive 'EUSurvey' tool⁸ and the deadline for responses was 6 March 2020. Only the responses that are relevant to the Article 37(5) mandate have been summarised in the Results section, below.

4.2. Material and method

Questions sent to stakeholders:

In order to support the EMA in the preparation of its scientific advice, the CVMP invited all interested parties, such as pharmaceutical industry, veterinarians, professional groups, learned societies, governmental institutions as well as EU and EEA Member States, to submit information on cascade use of antimicrobials in animals and any scientific evidence of an impact on public and animal health that the CVMP should consider. A survey using the European Commission's EUSurvey tool was developed and adopted by CVMP. The following questions were included:

Question 1: Please advise which antimicrobials (label or 'cascade use') are used to treat serious life-threatening infections in animals for which no or only few authorised* alternative antimicrobial treatment options are available. For each antimicrobial use quoted, please detail the animal species, the indication, alternative treatment options (if available) and the consequences if the antimicrobial used would no longer be available. *'Authorised' means a veterinary medicinal product that has a marketing authorisation ('licence') in Europe to treat specified diseases and animal species.

Question 2: Please provide any scientific evidence (e.g. scientific publication) or experience from your personal practice (e.g. due to lack of availability of medicines) over the last five years of the use in animals of antimicrobials that have only been authorised in human medicine.

Question 3: Please provide any scientific evidence (e.g. scientific publication) or experience from your personal practice (e.g. due to lack of availability of medicines) over the last five years of the use of any veterinary antimicrobial substances or formulations in animal species for which they are not authorised.

Question 4: Please provide any scientific evidence (e.g. scientific publication) or experience from your personal practice (e.g. due to lack of availability of medicines) over the last five years of the use of any veterinary antimicrobial substances or formulations for indications for which they are not authorised.

4.3. Normalisation of the answers

As there was no standardisation in the answers provided by the stakeholders, a normalisation step has been performed in order to analyse the data. Normalisation of the answers to the four questions was done at the level of antimicrobial classes, antimicrobial substances, animal species and indications.

⁷ Directive 2001/82/EC (repealed) included provisions that, when no suitable authorised veterinary medicinal product (VMP) was available and under exceptional circumstances, allowed a veterinarian to use a VMP outside of its authorised conditions of use or to use an unauthorised medicine, according to given criteria – the 'cascade'.

⁸ <https://ec.europa.eu/eusurvey/home/welcome>

Concerning animal species, the answers were grouped into the following animal categories: Avian (food-producing avian); Bovine; Caprine; Companion animals (dogs and cats); Equine; Fish; Mink; Other Companion Animals (ornamental birds/fish, rodents, ferrets); Ovine; Rabbit; Swine; Zoo / Exotic animals and Not Determined (ND).

4.4. Data sources

The followings data sources were used to prepare this report:

- Primary data collected through questionnaire sent to stakeholders
- Information on antimicrobial substances/class and corresponding importance for veterinary medicine as described in the OIE List of antimicrobial agents of veterinary importance
- Information on antimicrobial substances/class used in animals and their impact on public health and animal health based on the EMA's scientific advice "Categorisation of antibiotics in the European Union" [922].

4.5. Limitations

Due to the timelines, it was not possible to perform a pilot survey to check if the questions could be understood and the required data would be collected. The questionnaire was available online in English only and publicised by e-mail to the CVMP's interested parties contact list. There was no control over who could respond to the survey and the respondents were self-selected. In addition, there was no verification of the respondent's professional status and their understanding of the cascade, or validation of the responses. The responses received were not always clear or appropriate to the question asked. It cannot be assumed that the findings are fully representative of antimicrobial use across all sectors of veterinary medicines use or across the EU. Therefore, the descriptive presentation of the findings from the survey should be interpreted in this context.

4.6. Results

The objective of the questionnaire was to gain information to support the EMA's scientific advice to the European Commission in relation to Articles 37(5), relating to antimicrobials to be reserved for human use, and 107(6) regarding restrictions on cascade use. From the questionnaire, different levels of information were extracted in order to answer the general questions related to i) the uses of antimicrobials that are important for animal health because no or only few authorised alternative antimicrobial treatment options are available, ii) the uses in veterinary practice of antibiotics that are only authorised for human medicine, and iii) the uses of other antimicrobials in veterinary medicine (antiprotozoal, antifungal and antiviral). From questions 3 and 4, information on cascade use per animal species was extracted and summarised. Even where few answers to a question were received, the information could be of interest in relation to a potential antimicrobial therapeutic gap for the animal species.

Responses were received from 127 interested parties via the interactive EUSurvey tool and from six parties in writing, across 17 European countries.

Table 71. Summary information of respondents to the questionnaire.

Type of respondents	Number of respondents
Small (pet) or companion animal practitioners	18
Researchers/University-based small animal practitioners, or self-identified referral vets or specialists	7
Equine practitioners	6
Livestock practitioners (general)	3
Pig specialists	8
Cattle specialists	12
Poultry (+ game) specialists	8
Rabbit (livestock) specialists	4
Fish/aquaculture specialists	6
Sheep/other ruminant specialists	2
Mink/fur specialists	9
Zoo/exotic/Laboratory/ornamental fish animal veterinarians	5
Specialist dermatologist, ophthalmologist, internal medicine	5
General/mixed practitioners	6
Government e.g. control authorities and other	2
Veterinarians, otherwise not categorised	19
Industry	8
Professional bodies – pigs, equine	7

It should be noted that there was a disparity in the number of answers to each question. A total of 610 answers were received for question 1, whereas 150, 250 and 86 answers were received for questions 2, 3 and 4, respectively. In addition, each answer was not considered as a single citation if several antimicrobial substances, indications and animal species were mentioned.

Concerning the most cited animal species, altogether the analysis of the questionnaire revealed that across all the animal species citations (n=1227), the answers to question 1 accounted for 55% (n=675), question 2 for 16% (n=193), question 3 for 22% (n=272) and question 4 for 7% (n=87).

Considering all questions combined, 'Companion animals' and 'Equine' were the most cited animal species, with 19.4% and 18.3% respectively. These were followed by 'Zoo/Exotic animals' with 9.9%, 'Bovine' with 9.5%, 'Other companion animals' with 8.3% and 'Mink' with 7% of the citations. The distribution of all citations by animal category is presented in Figure 1.

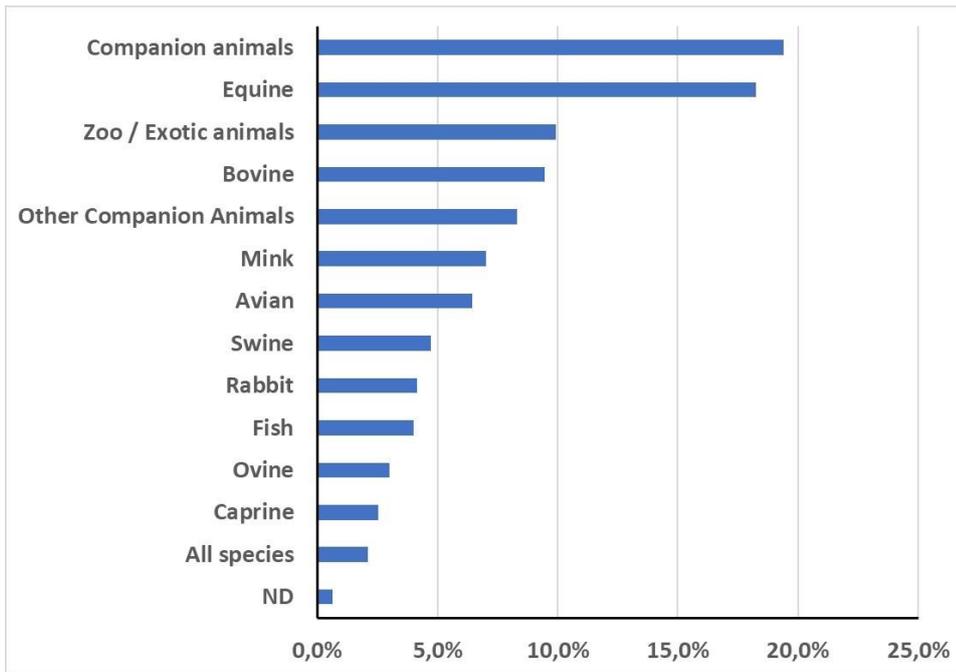


Figure 1. Distribution of the citations by animal category (n=1227)

Concerning the most cited indications of use, altogether the analysis of the questionnaire revealed that across all the indications cited in the answers (n=1391), the answers to question 1 accounted for 57% (n=787), question 2 for 12% (n=172), question 3 for 23% (n=324) and question 4 for 8% (n=108).

In a large proportion of the answers citing an indication, the level of information presented was not sufficient to normalise the answer and they were thus classified as "ND" (n=238; corresponding to 17.2%). Considering all questions combined, 'Enteric', 'Respiratory' and 'Septicaemic' infections were the most cited indications, with 15.4%, 12.4% and 10.4%, respectively. Other frequently cited indications included 'Protozoal' (6.4%), 'Cutaneous' (6.2%), 'Uro-genital' (5.1%) and 'Ocular' (5%) infections. The distribution of all citations by indication category is presented in Figure 2.

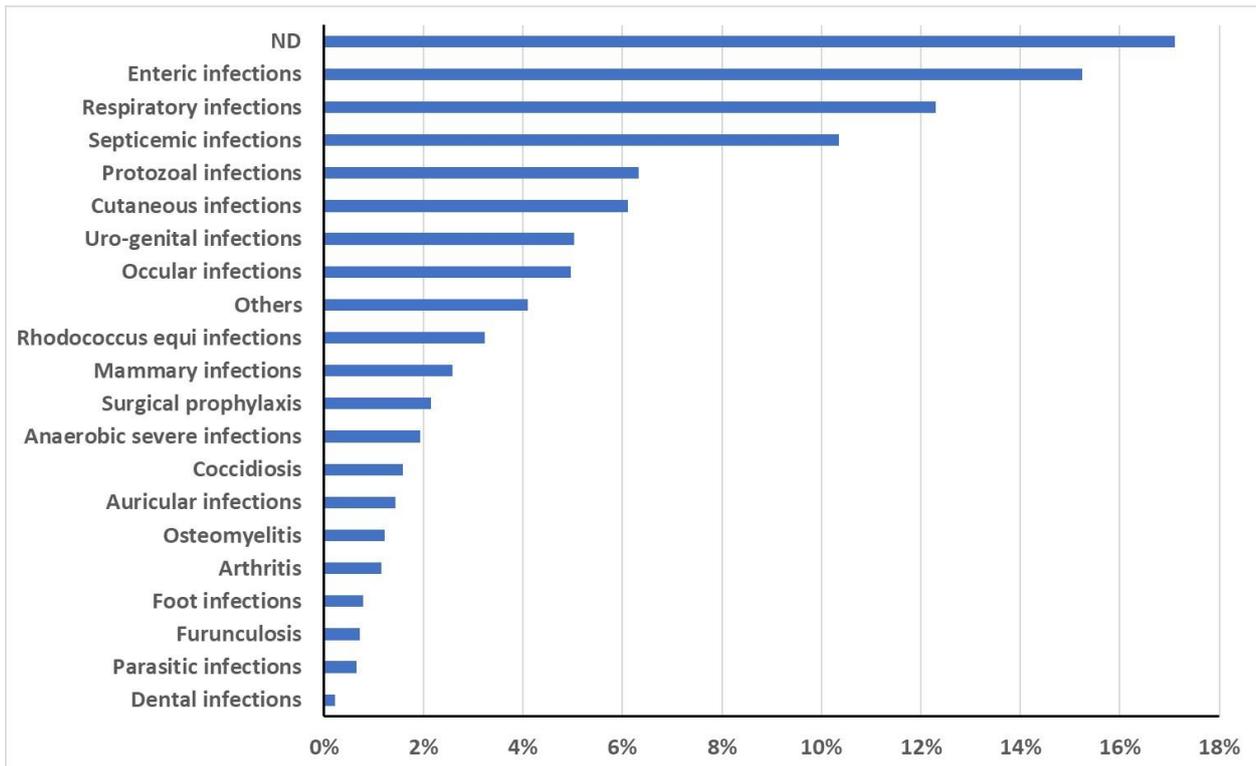


Figure 2. Distribution of the citations by indication category (n=1391)

It should also be highlighted that many answers did not provide a sufficient level of information to clearly determine for which infection/s the antimicrobial was being used. This means that in relation to question 1 for example, it was not always clear that the quoted infection would be regarded as life-threatening. In order to avoid misinterpretation of the answers it was decided to present a general high-level analysis.

4.6.1. Uses of antimicrobials that are important for animal health because no or only few authorised alternative antimicrobial treatment options are available

A classification of the antimicrobial substances/classes cited in the responses, according to their respective OIE categorisation, is presented in Figure 3.

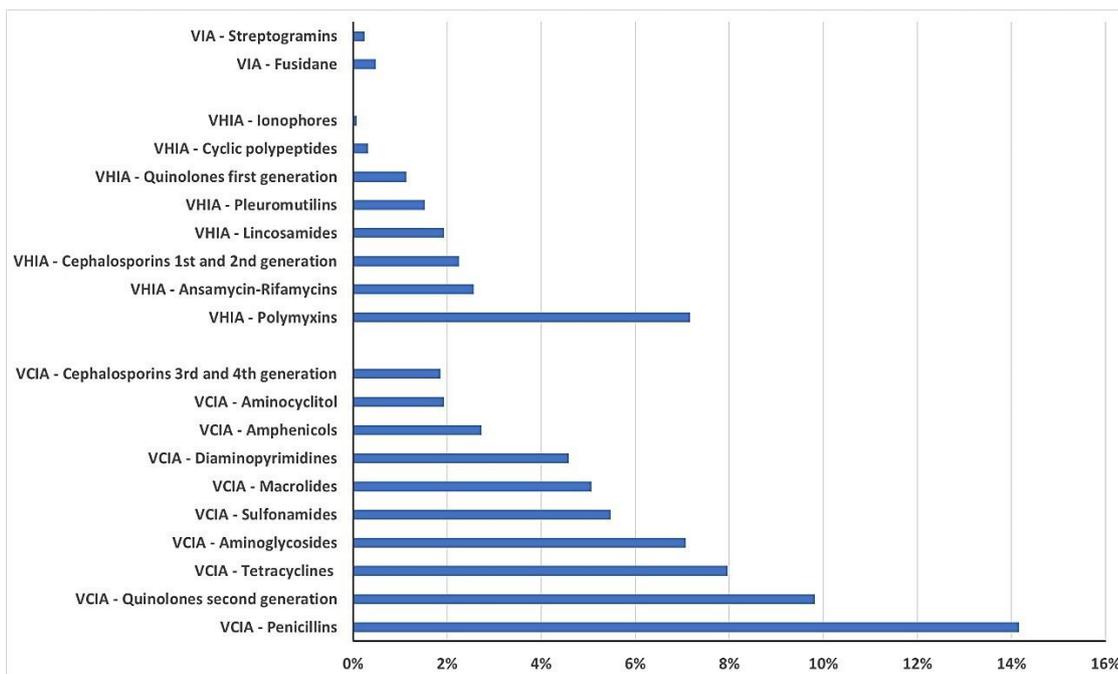


Figure 3. Percentage of the citations (considering all questions) for each antimicrobial class (n =1246 citations). Antimicrobial classes were grouped based on their corresponding OIE categorization (importance for animal health) as VCIA= Veterinary Critically Important Antimicrobial; VHIA= Veterinary Highly Important Antimicrobial; VIA= Veterinary Important Antimicrobial

Across all the answers, the most cited antimicrobial class was Penicillins, accounting for 14% of the citations (n=176). The Penicillins class included Aminopenicillins 6%, Natural penicillins 4%, Aminopenicillins + beta-lactamase inhibitor 3%, Antistaphylococcal penicillins 1%, Phenoxyphenicillins and Carboxypenicillins <1%. Second generation Quinolones were the second most cited antimicrobial class with 10% of the citations (n=122) followed by Tetracyclines with 8% (n=102), and Polymyxins (corresponding to colistin) and Aminoglycosides each accounting for 7% of citations (n=89 and 88 respectively).

The analysis of the most frequently cited antimicrobial substances and the corresponding OIE categorisations, which give information on the importance of the antimicrobials for veterinary medicine, revealed that 61% of the cited antimicrobials were classified as VCIA, 17% as VHIA, and 1% as VIA.

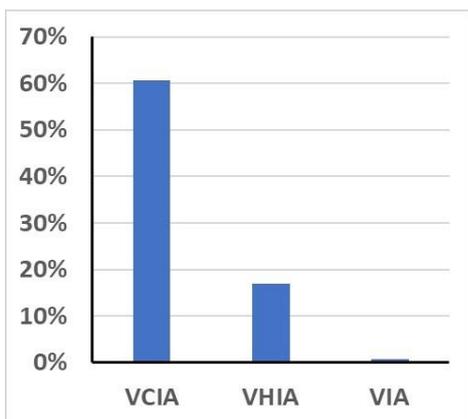


Figure 4. Distribution of the antibacterial citations by OIE category (n= 1246). Antimicrobial classes were grouped based on their corresponding OIE categorization (importance for animal health) as VCIA= Veterinary Critically Important Antimicrobial; VHIA= Veterinary Highly Important Antimicrobial; VIA= Veterinary Important Antimicrobial

The findings in this survey of veterinary antimicrobial use in the EU were consistent with the OIE's categorisation of the relative importance of different antimicrobial classes; although polymyxins appeared to be relatively more important in the EU setting.

An analysis was carried out to provide an overview of the use of antibacterials in particular. Across all responses, there were 1246 citations of antimicrobial substance uses. Of these, 1035 were antibacterial substances. The answers to Question 1, 2, 3 and 4 accounted respectively for 56.6% (n=705), 13.1% (n=163), 22.7% (n=283) and 7.6% (n=95). The most cited antibiotic substances are presented in Table 72 as examples.

Table 72. Summary information of the most cited antimicrobials substances

Substance	AMEG class	OIE category	AMEG category	Total answers	%
ND	ND	ND	ND	125	10.0%
Colistin	Polymyxins	VHIA	B	67	5.4%
Enrofloxacin	Fluoroquinolones and other quinolones	VCIA	B	57	4.6%
Trimethoprim	Sulfonamides, dihydrofolate reductase inhibitors and combinations	VCIA	D	57	4.6%
Amoxicillin	Aminopenicillins	VCIA	D	50	4.0%
Doxycycline	Tetracyclines	VCIA	D	45	3.6%
Amoxicillin-clavulanic acid	Aminopenicillins, in combination with beta-lactamase inhibitors	VCIA	C	42	3.4%
Metronidazole	Nitroimidazoles	ND*	D	40	3.2%
Gentamicin	Aminoglycosides (except spectinomycin)	VCIA	C	35	2.8%
Marbofloxacin	Fluoroquinolones and other quinolones	VCIA	B	35	2.8%
Rifampicin	Rifamycins	VHIA	A	32	2.6%

Substance	AMEG class	OIE category	AMEG category	Total answers	%
Florfenicol	Amphenicols	VCIA	C	31	2.5%
Oxytetracycline	Tetracyclines	VCIA	D	31	2.5%
Lincomycin	Lincosamides	VHIA	C	24	1.9%
Spectinomycin	Aminoglycosides: spectinomycin only	VCIA	D	24	1.9%
Azithromycin	Macrolides (not including ketolides)	VCIA	C	22	1.8%
Polymyxin B	Polymyxins	VHIA	B	22	1.8%
Sulfadiazine	Sulfonamides, dihydrofolate reductase inhibitors and combinations	VCIA	D	21	1.7%

*= metronidazole is not included in the OIE antimicrobial categorisation.

4.6.2. Information extracted from the questionnaire related to the uses in veterinary practices of antibiotics that are only authorised for human medicine

In relation to the uses in veterinary practices of antibiotics that are only authorised for human medicine, most of the citations came from answers to question 2. Only 114 (9.1%) out of 1246 citations for all question combined contained non veterinary-authorised antimicrobials. Although the frequency of reporting was low, these answers provide an interesting overview of the panel of non-authorized antibiotics used in veterinary medicine. The active substances cited in the answers are listed in the following table (Table 73). A summary of the main information on animal species and indications of use is also detailed.

Table 73. Summary information of the antibacterial substances cited as used in veterinary medicine while authorised only for human medicine

Substance	Class	Number of citations	%	Main information of use
Rifampicin	Rifamycins	32	2.6%	Equine; Companion animals – <i>Rhodococcus equi</i> infections; MDR infections
Azithromycin*	Macrolides (not including ketolides)	22	1.8%	Equine; Companion animals, Others companion animals – <i>Rhodococcus equi</i> infections; respiratory infections
Clarithromycin*		6	0.5%	
Ceftazidime*	Cephalosporins: 3rd- and 4th-generation, except combinations with beta-lactamase inhibitors	11	0.9%	Zoo/exotic animals; Companion animals, Others companion animals – Respiratory, cutaneous infections; MDR infections
Cefixime*		1	0.1%	
Ceftriaxone*		1	0.1%	
Ciprofloxacin*		9	0.7%	Companion animals; Zoo/exotic animals – Auricular infections; ND
Ofloxacin*		6	0.5%	

Substance	Class	Number of citations	%	Main information of use
Moxifloxacin*	Quinolones: fluoroquinolones and other quinolones	3	0.2%	
Levofloxacin*		2	0.1%	
Norfloxacin*		1	0.1%	
Mupirocin	Pseudomonic acids	5	0.4%	Equine; Companion animals – Furunculosis; Cutaneous infections
Vancomycin	Glycopeptides	5	0.4%	Equine; Zoo/Exotic animals - Surgical prophylaxis; ND
Isoniazid	Substances used solely to treat tuberculosis or other mycobacterial diseases	2	0.2%	Zoo/Exotic animals - ND
Ethambutol		1	0.1%	
Virginiamycin	Streptogramins	3	0.2%	Avian; Equine _ Enteric infections; Foot infections
Imipenem	Carbapenems	1	0.1%	Zoo/exotic animals; Companion animals, Others companion animals – Surgical prophylaxis
Meropenem		1	0.1%	
Piperacillin- Tazobactam	Carboxypenicillins/u reidopenicillins, including combinations	1	0.1%	ND
Teicoplanin	Glycopeptides	1	0.1%	Zoo/exotic animals; Companion animals, Others companion animals – Surgical prophylaxis

*Substances not authorised in veterinary medicine in the EU, but from classes authorised in veterinary medicine.

4.6.3. The use of other antimicrobials in veterinary medicine (antiprotozoal, antifungal and antiviral)

As well as antibiotic substances, other substances were cited that fall into the definition of an antimicrobial substance. There were 65 citations containing an antiprotozoal (n=33), antifungal (n=27) or antiviral (n=5) over the 1246 citations when all questions combined were considered. The active substances cited in the answers are listed in the following table (Table 74). A summary of the main information on animal species and indications of use is also detailed.

Table 74. Summary information of the other antimicrobial substances cited (antiprotozoal, antifungal and antiviral) as used in veterinary while authorised only for human medicine

Substance	Antimicrobial Class	Number of citations (n=1246)	%	Main information of use
Imidocarb	Antiprotozoal	13	1.3%	Companion animals; Bovine, Equine – Babesiosis; Piraplasmosis

Substance	Antimicrobial Class	Number of citations (n=1246)	%	Main information of use
Ronidazole	Antiprotozoal	5	0.4%	Zoo/Exotic animals – Protozoal infection, Enteric infections
Toltrazuril	Antiprotozoal	5	0.4%	Rabbits – Coccidiosis
Meglumine antimoniate	Antiprotozoal	2	0.2%	Companion animals – Leishmaniosis
Chloroquine*	Antiprotozoal	2	0.2%	Zoo/Exotic animals – Cryptocariosis
Diclazuril	Antiprotozoal	2	0.2%	Swine; Zoo/Exotic animals – Coccidiosis
Dimetridazole	Antiprotozoal	1	0.1%	Avian - Protozoal infection (trichomonosis)
Amprolium	Antiprotozoal	1	0.1%	Rabbits – Coccidiosis
Salinomycin	Antiprotozoal	1	0.1%	Rabbits – Coccidiosis
Miltefosine	Antiprotozoal	1	0.1%	Companion animals – Leishmaniosis
Fluconazole	Antifungal	4	0.4%	Equine; Zoo/Exotic animals – local (eye) and systemic fungal infections
Voriconazole	Antifungal	4	0.4%	Equine; Zoo/Exotic animals – local (eye) and systemic fungal infections
Clotrimazole	Antifungal	3	0.3%	Companion animals; Equine – Urogenital and skin fungal infections
Itraconazole	Antifungal	3	0.3%	Companion animals; Zoo/Exotic animals – Dermatophytosis
Terbinafine	Antifungal	3	0.2%	Zoo/Exotic animals _ Fungal infections
Amphotericin B*	Antifungal	2	0.2%	Equine; Zoo/Exotic animals – local (eye) and systemic fungal infections
Ketoconazole	Antifungal	2	0.2%	Companion animals – cutaneous infections
Posaconazole	Antifungal	2	0.2%	Zoo/Exotic animals _ Fungal infections
Conazole	Antifungal	1	0.1%	Rabbit – skin fungal infections
Griseofulvin	Antifungal	1	0.1%	Companion animals – fungal infections
Miconazole	Antifungal	1	0.1%	Equine – local (eye) fungal infections
Nystatin	Antifungal	1	0.1%	Zoo/Exotic animals – Digestive fungal infections
Famciclovir*	Antiviral	3	0.2%	Companion animals; Zoo/Exotic animals – herpesvirus
Valanycyclovir*	Antiviral	1	0.1%	Equine – herpesvirus
Acyclovir*	Antiviral	1	0.1%	Companion animals – herpesvirus

* Substances not authorised in EU for veterinary medicines

5. Categorisation of antibiotics and antibiotic classes

Table 75 summarises the categorisation of antibiotics and antibiotic classes by the World Health Organization (WHO), the European Medicines Agency with its Antimicrobial Ad Hoc Expert Group (AMEG) and the World Organisation for Animal Health (OIE).

The WHO list of critically important antimicrobials for human medicine can be used as a reference to help formulate and prioritize risk assessment and risk management strategies to mitigate the human health risks associated with antimicrobial use in food-producing animals [11].

The WHO also classifies antibiotic substances ('AWaRe'), to emphasize the importance of their optimal use and with the aim to reduce AMR [923]. Not all the antimicrobials included in the AwaRe list are authorised for use in the EU.

The EMA's AMEG categorisation [922] considers the risk to public health from AMR due to the use of antimicrobials in veterinary medicine.

The OIE List of Antimicrobial Agents Of Veterinary Importance [7] addresses antimicrobials authorised for use in food-producing animals and is intended to complement the human CIA List developed by WHO.

Table 75. Categorisation of antibiotics and antibiotic classes

Antibiotic/classes	Classifications
Natural, narrow spectrum penicillins (beta-lactamase-sensitive penicillins)	WHO: HIA WHO AwaRe: Access: Benzylpenicillin, Phenoxymethylpenicillin, Penamecillin, Clometocillin, Benzathine benzylpenicillin, Procaine benzylpenicillin; Watch: Pheneticillin AMEG: Category D OIE: VCIA
Antistaphylococcal penicillins (beta-lactamase-resistant penicillins)	WHO: HIA WHO AwaRe: Access: cloxacillin, dicloxacillin, nafcillin, oxacillin, flucloxacillin AMEG: Category D OIE: VCIA
Aminopenicillins, without beta-lactamase inhibitors	WHO: CIA WHO AwaRe: Access: e.g. Ampicillin, Amoxicillin, Hetacillin. AMEG: Category D OIE: VCIA
Aminopenicillins in combination with beta-lactamase inhibitors (BLI)	WHO: CIA WHO AwaRe: Access: e.g. Amoxicillin-Clavulanic acid, Ampicillin-Sulbactam AMEG: Category C OIE: VCIA
Amdinopenicillins	WHO: HIA WHO AwaRe: Access: mecillinam, pivmecillinam AMEG: Category A OIE: VCIA (mecillinam)
Carboxypenicillins and ureidopenicillins, including their	WHO: CIA WHO AwaRe: Watch: ticarcillin, carbenicillin, temocillin, azlocillin, mezlocillin, piperacillin and piperacillin-tazobactam

Antibiotic/classes	Classifications
combinations with beta-lactamase inhibitors	AMEG: Category A OIE: Carboxypenicillins are VCIA
1st- and 2nd-generation cephalosporins, and cephamycins	WHO: HIA WHO AWaRe: Access (First-generation cephalosporins): e.g. Cefacetrile, Cefadroxil, Cefalexin, Cefapirin, Cefatrizine, Cefazolin; Watch (Second-generation cephalosporins): e.g. Cefaclor, Cefonicid, Ceforanide, Cefotiam, Cefoxitin, Cefprozil, Cefuroxime, AMEG: Category C OIE: VCIA
3rd- and 4th-generation cephalosporins, except combinations with beta-lactamase inhibitors	WHO: HPCIA WHO AWaRe: Watch (third-generation cephalosporins): e.g. Cefixime, Cefmenoxime, Cefodizime, Cefoperazone, Cefotaxime, Cefpiramide, Cefpodoxime proxetil, Ceftazidime, Ceftizoxime, Ceftriaxone, Latamoxef; Watch (fourth-generation cephalosporins): e.g. Cefepime, Cefozopran, Cefpirome AMEG: Category B OIE: VCIA
Ceftobiprole, Ceftaroline	WHO: HPCIA (as 5th-generation cephalosporins) WHO AWaRe: Ceftaroline and ceftobiprole are in the Reserve group AMEG: Category A OIE: Not included
Combinations of cephalosporins and beta-lactamase inhibitors	WHO: HPCIA (as 3rd, 4th, 5th-generation cephalosporins) WHO AWaRe: Reserve: ceftolozane-tazobactam and ceftazidime-avibactam. 'Not recommended': Cefotaxime-sulbactam, cefoperazone-sulbactam, ceftriaxone-sulbactam, cefpodoxime proxetil-clavulanic acid and cefpodoxime proxetil-sulbactam AMEG: Category A OIE: Not included
Siderophore cephalosporins	WHO: Not included WHO AWaRe: Cefiderocol is in the Reserve group AMEG: Category A OIE: Not included
Carbapenems, including carbapenems with beta-lactamase inhibitors	WHO: CIA WHO AWaRe: Watch: e.g. imipenem, meropenem, ertapenem. Reserve: Meropenem-vaborbactam, Imipenem-relebactam AMEG: Category A OIE: Not included
Penems	WHO: CIA WHO AWaRe: Faropenem is included in the Reserve group AMEG: Category A OIE: Not included
Monobactams	WHO: CIA WHO AWaRe: Aztreonam and Carumonam are in the Reserve group AMEG: Category A OIE: Not included
Polymyxins	WHO: HPCIA

Antibiotic/classes	Classifications
	WHO AWaRe: Polymyxin B and colistin are in the Reserve group AMEG: Category B OIE: VHIA
Cyclic polypeptides	WHO: IA WHO AWaRe: - AMEG: Category D OIE: VHIA
Phosphonic acid derivates	WHO: CIA WHO AWaRe: Fosfomycin IV route is included in the Reserve group and fosfomycin oral route is included in the Watch group. AMEG: Category A OIE: Fosfomycin is VHIA
Glycopeptides	WHO: HPCIA WHO AWaRe: Watch: Vancomycin and teicoplanin. Reserve: telavancin, dalbavancin and oritavancin are included in the Reserve group. AMEG: Category A OIE: Not included
Lipopeptides	WHO: CIA WHO AWaRe: Daptomycin is in the Reserve group AMEG: Category A OIE: Not included
Oxazolidinones	WHO: CIA WHO AWaRe: Linezolid and tedizolid are in the Reserve group AMEG: Category A OIE: Not included
Pleuromutilins	WHO: IA WHO AWaRe: Lefamulin in the Reserve group AMEG: Category C (e.g. e.g. tiamulin, valnemulin) OIE: VHIA
Macrolides	WHO: HPCIA WHO AWaRe: Watch: e.g. Azithromycin, Clarithromycin, Erythromycin, Spiramycin AMEG: Category C e.g. tylosin, tulathromycin OIE: VCIA
Macrocycles	WHO: HPCIA (included in macrolides) WHO AWaRe: Fidaxomicin is in the Watch group AMEG: - OIE: -
Ketolides	WHO: HPCIA WHO AWaRe: Watch: Telithromycin, Solithromycin AMEG: Category A OIE: Not included
Lincosamides	WHO: HIA WHO AWaRe: Access: Clindamycin. Watch: Lincomycin AMEG: Category C OIE: VHIA

Antibiotic/classes	Classifications
Streptogramins	WHO: HIA WHO AWaRe: quinupristin-dalfopristin is included in the Reserve group; pristinamycin is in the Watch group AMEG: Category A OIE: Virginiamycin is VIA
Aminoglycosides	WHO: CIA WHO AWaRe: Reserve: Plazomicin; Watch: e.g. Kanamycin, Neomycin, Netilmicin, Sisomicin, Streptomycin, Tobramycin; Access: Amikacin, Gentamicin AMEG: Category C OIE: VCIA
Plazomicin	WHO: CIA WHO AWaRe: Reserve group AMEG: Aminoglycoside class in Category C OIE: Aminoglycoside class is VCIA
Aminocyclitols	WHO: IA WHO AWaRe: Access: Spectinomycin AMEG: Category D OIE: VCIA
Tetracyclines	WHO: HIA WHO AWaRe: Watch: e.g. chlortetracycline, metacycline , oxytetracycline; Access: doxycycline, tetracycline AMEG: Category D OIE: VCIA
Glycylcyclines	WHO: CIA WHO AWaRe: Tigecycline is in the Reserve group AMEG: Category A OIE: Not included
Minocycline	WHO: HIA (as tetracyclines) WHO AWaRe: IV route in Reserve group; Oral route in Watch group AMEG: Tetracycline class in Category D OIE: Tetracycline class in VCIA
Eravacycline (fluorocycline)	WHO: HIA (as tetracyclines) WHO AWaRe: Reserve group AMEG: Tetracycline class in Category D OIE: Tetracycline class in VCIA
Omadacycline	WHO: HIA (as tetracyclines) WHO AWaRe: Reserve group AMEG: Tetracycline class in Category D OIE: Tetracycline class in VCIA
Amphenicols	WHO: HIA WHO AWaRe: Access: Chloramphenicol, Thiamphenicol AMEG: Category C e.g. florfenicol OIE: VCIA
Sulfonamides	WHO: HIA WHO AWaRe: Access: e.g. sulfadiazine, sulfamethoxazole, sulfadimidine

Antibiotic/classes	Classifications
	AMEG: Category D OIE: VCIA
Trimethoprim and derivatives	WHO: HIA WHO AWaRe: Access: trimethoprim, brodimoprim AMEG: Category D OIE: VCIA
Sulfonamide-trimethoprim derivative combinations	WHO: HIA WHO AWaRe: Access: Sulfadiazine-trimethoprim, Sulfamethizole-trimethoprim, Sulfamethoxazole-trimethoprim, Sulfametrole-trimethoprim, Sulfamoxole-trimethoprim, AMEG: Category D OIE: VCIA
Quinolones (non-fluorinated)	WHO: HPCIA WHO AWaRe: Watch: e.g. flumequine, oxolinic acid, rosoxacin AMEG: Category B OIE: VCIA
Fluoroquinolones	WHO: HPCIA WHO AWaRe: Watch: Ciprofloxacin, Delafloxacin, Enoxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin, Sitafloxacin, Sparfloxacin, Tosufloxacin AMEG: Category B e.g. enrofloxacin OIE: VCIA
Nitrofurantoin derivatives	WHO: IA WHO AWaRe: Access: Nitrofurantoin, Nifurtinol, Furazidin AMEG: Category D OIE: Not included
Nitroimidazoles	WHO: IA WHO AWaRe: Access: Metronidazole (IV) and Metronidazole (oral); Watch: spiramycin-metronidazole combination AMEG: Category D OIE: Not included
Rifamycins	WHO: CIA (as ansamycins) WHO AWaRe: Watch: e.g. rifampicin, rifamycin, rifaximin AMEG: Rifamycins (except rifaximin): Category A; rifaximin: Category C OIE: VHIA (rifampicin and rifaximin)
Substances (drugs) used solely to treat tuberculosis or other mycobacterial diseases	WHO: CIA (bedaquiline, calcium aminosalicylate, capreomycin, cycloserine, delamanid, ethambutol, ethionamide, isoniazid, morinamide, para-aminosalicylic-acid, protionamide, pyrazinamide, terizidone, thioacetazone and tiocarlide) WHO AWaRe: Not in scope AMEG: Category A OIE: Not included
Riminofenazines	WHO: HIA WHO AWaRe: - AMEG: Category A (e.g. clofazimine) OIE: Not included

Antibiotic/classes	Classifications
Sulfones	WHO: HIA WHO AWaRe: - AMEG: Category A OIE: Not included
Pseudomonic acids	WHO: HIA WHO AWaRe: - AMEG: Category A OIE: Not included
Steroid antibacterials	WHO: HIA WHO AWaRe: Watch: Fusidic acid AMEG: Category D OIE: VIA
Bicyclomycin (Bicozamycin)	WHO: - WHO AWaRe: - AMEG: - OIE: VIA
Orthosomycins/ Oligosaccharides	WHO: - WHO AWaRe: - AMEG: - OIE: VIA e.g. avilamycin (ATCVet code: QA07AA95)
Quinoxalines	WHO: - WHO AWaRe: - AMEG: - OIE: VIA e.g. carbadox, olaquinox
Thiopeptides	WHO: - WHO AWaRe: - AMEG: - OIE: VIA e.g. Thiostrepton, (Nosiheptide)
Phosphoglycolipids/ Moenomycins	WHO: - WHO AWaRe: - AMEG: - OIE: -
Elfamycins	WHO: - WHO AWaRe: - AMEG: - OIE: -
Aminocoumarins	WHO: - WHO AWaRe: - AMEG: - OIE: -

6. ATC(vet) codes

Please refer to Section 2.3. of the report for an explanation of how the ATC(vet) codes can be used to identify which antimicrobials belong to which grouping.

It should be noted that not all antimicrobial substances have ATC(vet) codes assigned.

The tables may not be complete and in some cases it is not possible to verify the authorisation status due to the absence of a comprehensive international database.

6.1. Antibiotics

Table 76. ATC(vet) codes and EU-authorisation status for natural, narrow-spectrum penicillins (beta-lactamase-sensitive penicillins)

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Azidocillin	J01CE04	QJ01CE04	None found	None found
Benethamine penicillin	-	QJ01CE91	None found	Yes
Benzathine benzylpenicillin	J01CE08	QJ01CE08	Yes	Yes
Benzathine phenoxymethylpenicillin	J01CE10	QJ01CE10	Yes	Yes
Benzylpenicillin	J01CE01	QJ01CE01	Yes	Yes
Clometocillin	J01CE07	QJ01CE07	None found	None found
Penamecillin	J01CE06	QJ01CE06	None found	None found
Penethamate hydriodide	-	QJ01CE90	None found	Yes
Pheneticillin	J01CE05	QJ01CE05	Yes	Yes
Phenoxymethylpenicillin	J01CE02	QJ01CE02	Yes	Yes
Procaine benzylpenicillin	J01CE09	QJ01CE09	Yes	Yes
Propicillin	J01CE03	QJ01CE03	None found	None found
combinations with other antibacterial	J01CE30	QJ01CE30	Yes	Yes

Table 77. ATC(vet) codes and EU-authorisation status for antistaphylococcal penicillins (beta-lactamase-resistant penicillins)

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cloxacillin	J01CF02	QJ01CF02	Yes	Yes
Dicloxacillin	J01CF01	QJ01CF01	Yes	Yes
Flucloxacillin	J01CF05	QJ01CF05	Yes	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Methicillin	J01CF03	QJ01CF03	None found	None found
Nafcillin	J01CF06	QJ01CF06	None found	Yes
Oxacillin	J01CF04	QJ01CF04	Yes	Yes

Table 78. ATC(vet) codes and EU-authorisation status for aminopenicillins, without beta-lactamase inhibitors

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Amoxicillin	J01CA04	QJ01CA04	Yes	Yes
Ampicillin	J01CA01	QJ01CA01	Yes	Yes
Aspoxicillin	J01CA19	QJ01CA19	None found	None found
Azlocillin	J01CA09	QJ01CA09	None found	None found
Bacampicillin	J01CA06	QJ01CA06	Yes	None found
Carbenicillin	J01CA03	QJ01CA03	None found	None found
Carindacillin	J01CA05	QJ01CA05	None found	None found
Epicillin	J01CA07	QJ01CA07	None found	None found
Hetacillin	J01CA18	QJ01CA18	None found	None found
Mecillinam	J01CA11	QJ01CA11	Yes	None found
Metampicillin	J01CA14	QJ01CA14	None found	Yes
Mezlocillin	J01CA10	QJ01CA10	Yes	None found
Piperacillin	J01CA12	QJ01CA12	Yes	None found
Pivampicillin	J01CA02	QJ01CA02	Yes	None found
Pivmecillinam	J01CA08	QJ01CA08	Yes	None found
Sulbenicillin	J01CA16	QJ01CA16	None found	None found
Talampicillin	J01CA15	QJ01CA15	None found	None found
Temocillin	J01CA17	QJ01CA17	Yes	None found
Ticarcillin	J01CA13	QJ01CA13	Yes	None found
Ampicillin combinations with another antibacterial	J01CA51	QJ01CA51	Yes	Yes
Combinations of penicillins	J01CA20	QJ01CA20	Yes	Yes

Table 79. ATC(vet) codes and EU-authorisation status for aminopenicillins, in combination with beta-lactamase inhibitors

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Amoxicillin and beta-lactamase inhibitor	J01CR02	QJ01CR02	Yes	Yes
Ampicillin and beta-lactamase inhibitor	J01CR01	QJ01CR01	Yes	Yes
Piperacillin and beta-lactamase inhibitor	J01CR05	QJ01CR05	Yes	None found
Sultamicillin	J01CR04	QJ01CR04	Yes	None found
Ticarcillin and beta-lactamase inhibitor	J01CR03	QJ01CR03	None found	None found
Combinations of penicillins	J01CR50	QJ01CR50	Yes	Yes

Table 80. ATC(vet) codes and EU-authorisation status for amdinopenicillins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Mecillinam	J01CA11	QJ01CA11	Yes	None found
Pivmecillinam	J01CA08	QJ01CA08	Yes	None found

Table 81. ATC(vet) codes and EU-authorisation status for carboxypenicillins and ureidopenicillins and their combinations with beta-lactamase inhibitors

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
J01CA PENICILLINS WITH EXTENDED SPECTRUM: CARBOXYPENICILLINS				
Carbenicillin	J01CA03	QJ01CA03	None found	None found
Carindacillin	J01CA05	QJ01CA05	None found	None found
Temocillin	J01CA17	QJ01CA17	Yes	None found
Ticarcillin	J01CA13	QJ01CA13	None found	None found
J01CA PENICILLINS WITH EXTENDED SPECTRUM: UREIDOPENICILLINS				
Azlocillin	J01CA09	QJ01CA09	None found	None found
Mezlocillin	J01CA10	QJ01CA10	Yes	None found
Piperacillin	J01CA12	QJ01CA12	None found	None found
J01CR COMBINATIONS OF PENICILLINS, INCLUDING BETA-LACTAMASE INHIBITORS				

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Piperacillin and beta-lactamase inhibitor	J01CR05	QJ01CR05	Yes	None found
Ticarcillin and beta-lactamase inhibitor	J01CR03	QJ01CR03	Yes	None found

Table 82. ATC(vet) codes and EU-authorisation status for 1st- and 2nd-generation cephalosporins and cephamycins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cefacetrile	J01DB10	QJ01DB10, QJ51DB10	None found	Yes
Cefaclor	J01DC04	QJ01DC04	Yes	None found
Cefadroxil	J01DB05	QJ01DB05	Yes	Yes
Cefalexin	J01DB01	QJ01DB01, QJ51DB01	Yes	Yes
Cefalonium	-	QJ51DB90	None found	Yes
Cefaloridine	J01DB02	QJ01DB02	None found	None found
Cefalotin	J01DB03	QJ01DB03	Yes	None found
Cefamandole	J01DC03	QJ01DC03	Yes	None found
Cefapirin	J01DB08	QJ01DB08, QJ51DB08	None found	Yes
Cefatrizine	J01DB07	QJ01DB07	Yes	None found
Cefazedone	J01DB06	QJ01DB06	None found	None found
Cefazolin	J01DB04	QJ01DB04, QJ51DB04	Yes	Yes
Cefbuperazone	J01DC13	QJ01DC13	None found	None found
Cefmetazole	J01DC09	QJ01DC09	Yes	None found
Cefminox	J01DC12	QJ01DC12	Yes	None found
Cefonicid	J01DC06	QJ01DC06	Yes	None found
Ceforanide	J01DC11	QJ01DC11	Yes	None found
Cefotetan	J01DC05	QJ01DC05	None found	None found
Cefotiam	J01DC07	QJ01DC07	Yes	None found
Cefoxitin	J01DC01	QJ01DC01	Yes	None found
Cefprozil	J01DC10	QJ01DC10	Yes	None found
Cefradine	J01DB09	QJ01DB09	Yes	None found
Cefroxadine	J01DB11	QJ01DB11	None found	None found
Ceftezole	J01DB12	QJ01DB12	None found	None found
Cefuroxime	J01DC02	QJ01DC02, QJ51DC02	Yes	None found
Flomoxef	J01DC14	QJ01DC14	None found	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Loracarbef	J01DC08	QJ01DC08	None found	None found

Table 83. ATC(vet) codes and EU-authorisation status for 3rd- and 4th-generation cephalosporins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cefcapene	J01DD17	QJ01DD17	None found	None found
Cefdinir	J01DD15	QJ01DD15	None found	None found
Cefditoren	J01DD16	QJ01DD16	Yes	None found
Cefepime	J01DE01	QJ01DE01	Yes	None found
Cefetamet	J01DD10	QJ01DD10	None found	None found
Cefixime	J01DD08	QJ01DD08	Yes	None found
Cefmenoxime	J01DD05	QJ01DD05	None found	None found
Cefodizime	J01DD09	QJ01DD09	Yes	None found
Cefoperazone	J01DD12	QJ01DD12, QJ51DD12	Yes	Yes
Cefotaxime	J01DD01	QJ01DD01	Yes	None found
Cefovecin	-	QJ01DD91	None found	Yes
Cefozopran	J01DE03	QJ01DE03	None found	None found
Cefpiramide	J01DD11	QJ01DD11	None found	None found
Cefpirome	J01DE02	QJ01DE02	Yes	None found
Cefpodoxime	J01DD13	QJ01DD13	Yes	None found
Cefquinome	-	QJ01DE90, QJ51DE90	None found	Yes
Cefsulodin	J01DD03	QJ01DD03	None found	None found
Ceftazidime	J01DD02	QJ01DD02	Yes	None found
Cefteram	J01DD18	QJ01DD18	None found	None found
Ceftibuten	J01DD14	QJ01DD14	Yes	None found
Ceftiofur	-	QJ01DD90, QJ51DD90	None found	Yes
Ceftizoxime	J01DD07	QJ01DD07	Yes	None found
Ceftriaxone	J01DD04	QJ01DD04	Yes	None found
Latamoxef	J01DD06	QJ01DD06	None found	None found
Ceftiofur combinations	-	QJ01DD99	None found	Yes

Table 84. ATC(vet) codes and EU-authorisation status for ceftobiprole and ceftaroline

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ceftaroline fosamil	J01DI02	QJ01DI02	Yes	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ceftobiprole medocartil	J01DI01	QJ01DI01	Yes	None found

Table 85. ATC(vet) codes and EU-authorisation status for combinations of cephalosporins and beta-lactamase inhibitors

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cefoperazone and beta-lactamase inhibitor	J01DD62	QJ01DD62	Yes	None found
Cefotaxime and beta-lactamase inhibitor	J01DD51	QJ01DD51	None found	None found
Cefpodoxime and beta-lactamase inhibitor	J01DD64	QJ01DD64	None found	None found
Ceftazidime and beta-lactamase inhibitor	J01DD52	QJ01DD52	Yes	None found
Ceftolozane and beta-lactamase inhibitor	J01DI54	QJ01DI54	Yes	None found
Ceftriaxone and beta-lactamase inhibitor	J01DD63	QJ01DD63	None found	None found

Table 86. ATC(vet) codes and EU-authorisation status for siderophore cephalosporins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cefiderocol	J01DI04	QJ01DI04	Yes	None found

Table 87. ATC(vet) codes and EU-authorisation status for carbapenems and their combinations with beta-lactamase inhibitors

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Biapenem	J01DH05	QJ01DH05	None found	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Doripenem	J01DH04	QJ01DH04	None found	None found
Ertapenem	J01DH03	QJ01DH03	Yes	None found
Imipenem and cilastatin†	J01DH51	QJ01DH51	Yes	None found
Meropenem	J01DH02	QJ01DH02	Yes	None found
Meropenem and vaborbactam	J01DH52	QJ01DH52	Yes	None found
Panipenem and betamipron‡	J01DH55	QJ01DH55	None found	None found
Tebipenem pivoxil	J01DH06	QJ01DH06	None found	None found

†Inhibits degradation of imipenem in kidneys

‡Prevents nephrotoxicity

Table 88. ATC(vet) codes and EU-authorisation status for penems

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Faropenem	J01DI03	QJ01DI03	None found	None found

Table 89. ATC(vet) codes and EU-authorisation status for monobactams

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Aztreonam	J01DF01	QJ01DF01	Yes	None found
Carumonam	J01DF02	QJ01DF02	None found	None found
Nocardicin A	-	-	None found	None found
Tigemonam	-	-	None found	None found

Table 90. ATC(vet) codes and EU-authorisation status for polymyxins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Colistin	J01XB01, A07AA10	QJ01XB01, QA07AA10, QJ51XB01, QJ51XB02	Yes	Yes
Polymyxin B	J01XB02, A07AA05, S01AA18, S02AA11, S03AA03	QJ01XB02, QA07AA05, QS01AA18, QS02AA11, QS03AA03	Yes	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ampicillin and colistin	J01CA51	QG51AG07	None found	None found
Colistin combinations with other antibacterials	-	QA07AA98	None found	None found
Polymyxins combinations with other antibacterials	-	QJ01RA95	None found	None found

Table 91. ATC(vet) codes and EU-authorisation status for cyclic polypeptides

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Bacitracin	D06AX05, J01XX10, R02AB04,	QD06AX05, QJ01XX10, QR02AB04, QA07AA93	Yes	Yes

Table 92. ATC(vet) codes and EU-authorisation status for fosfomycin

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Fosfomycin	J01XX01	QJ01XX01	Yes	None found

Table 93. ATC(vet) codes and EU-authorisation status for glycopeptides

Substance	ATC code(s)	ATCvet code (s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Avoparcin	-	-	None found	None found
Dalbavancin	J01XA04	QJ01XA04	Yes	None found
Oritavancin	J01XA05	QJ01XA05	Yes	None found
Ramoplanin	J01XA0		None found	None found
Teicoplanin	J01XA02	QJ01XA02	Yes	None found
Telavancin	J01XA03	QJ01XA03	None found	None found
Vancomycin	J01XA01, A07AA09, S01AA28	QJ01XA01, QA07AA09, QS01AA28	Yes	None found

Table 94. ATC(vet) codes and EU-authorisation status for lipopeptides

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Daptomycin	J01XX09	QJ01XX09	Yes	None found

Table 95. ATC(vet) codes and EU-authorisation status for oxazolidinones

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Contezolid	-	-	None found	None found
Eperezolid	-	-	None found	None found
Linezolid	J01XX08	QJ01XX08	Yes	None found
Posizolid	-	-	None found	None found
Radezolid	-	-	None found	None found
Ranbezolid	-	-	None found	None found
Sutezolid	-	-	None found	None found
Tedizolid	J01XX11	QJ01XX11	Yes	None found

Table 96. ATC(vet) codes and EU-authorisation status for pleuromutilins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Retapamulin	D06AX13	QD06AX13	Yes	None found
Tiamulin	-	QJ01XQ01	None found	Yes
Valnemulin	-	QJ01XQ02	None found	Yes

Table 97. ATC(vet) codes and EU-authorisation status for macrolides

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Azithromycin	J01FA10, S01AA26	QJ01FA10, QS01AA26	Yes	None found
Clarithromycin	J01FA09	QJ01FA09	Yes	None found
Dirithromycin	J01FA13	QJ01FA13	None found	None found
Erythromycin	J01FA01	QJ01FA01	Yes	Yes
Flurithromycin	J01FA14	QJ01FA14	None found	None found
Gamithromycin	-	QJ01FA95	None found	Yes
Josamycin	J01FA07	QJ01FA07	Yes	None found
Kitasamycin	-	QJ01FA93	None found	None found
Midecamycin	J01FA03	QJ01FA03	Yes	None found
Miocamycin	J01FA11	QJ01FA11	None found	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Oleandomycin	J01FA05	QJ01FA05	Yes	None found
Rokitamycin	J01FA12	QJ01FA12	None found	None found
Roxithromycin	J01FA06	QJ01FA06	Yes	None found
Spiramycin	J01FA02	QJ01FA02	Yes	Yes
Tildipirosin	-	QJ01FA96	None found	Yes
Tilmicosin	-	QJ01FA91	None found	Yes
Troleandomycin	J01FA08	QJ01FA08	None found	None found
Tulathromycin	-	QJ01FA94	None found	Yes
Tylosin	-	QJ01FA90	None found	Yes
Tylvalosin	-	QJ01FA92	None found	Yes
Azithromycin, fluconazole and secnidazole	J01RA07	QJ01RA07	None found	None found
Macrolides combinations with other substances	-	QJ01FA99	None found	Yes

Table 98. ATC(vet) codes and EU-authorisation status for macrocycles

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Fidaxomicin	A07AA12	QA07AA12	Yes	None found

Table 99. ATC(vet) codes and EU-authorisation status for ketolides

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Telithromycin	J01FA15	QJ01FA15	None found	None found
Solithromycin	J01FA16	QJ01FA16	None found	None found

Table 100. ATC(vet) codes and EU-authorisation status for lincosamides

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Clindamycin	D10AF01, G01AA10, J01FF01	QD10AF01, QG01AA10, QJ01FF01	Yes	Yes
Lincomycin	J01FF02	QJ01FF02, QJ51FF02	Yes	Yes
Pirlimycin	-	QJ51FF90	None found	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Clindamycin combinations with other antibacterial	D10AF51	QD10AF51	Yes	None found
Lincomycin combinations with other antibacterial	-	QJ01FF52, QJ51RF03	None found	Yes

Table 101. ATC(vet) codes and EU-authorisation status for streptogramins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Pristinamycin	J01FG01	QJ01FG01	Yes	None found
Quinupristin/ Dalfopristin	J01FG02	QJ01FG02	None found	None found
Virginiamycin	D06AX10	QD06AX01, QJ01FG90	None found	None found

Table 102. ATC(vet) codes and EU-authorisation status for aminoglycosides and aminocyclitols

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Amikacin	D06AX12, J01GB06, S01AA21	QD06AX12, QJ01GB06, QS01AA21	Yes	Yes
Apramycin	-	QJ01GB90, QA07AA92, QJ51GB90	None found	Yes
Arbekacin	J01GB12	QJ01GB12	None found	None found
Bekanamycin	J01GB13	QJ01GB13	Yes	None found
Capreomycin	J04AB30	QJ04AB30	Yes	None found
Dibekacin	J01GB09	QJ01GB09	None found	None found
Dihydrostreptomycin	S01AA15	QJ01GA90, QS01AA15, QA07AA90, QJ51GA90	Yes	Yes
Enviomycin	J04AB06	QJ04AB06	None found	None found
Framycetin	S01AA07	QJ01GB91, QS01AA07	Yes	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Gentamicin	D06AX07, J01GB03, S01AA11	QD06AX07, QJ01GB03, QS01AA11, QA07AA91, QJ51GB03	Yes	Yes
Isepamicin	J01GB11	QJ01GB11	None found	None found
Kanamycin	J01GB04, S01AA24, A07AA08	QJ01GB04, QS01AA24, QA07AA08	Yes	Yes
Micronomicin	S01AA22	QS01AA22	None found	None found
Neomycin	D06AX04, J01GB05, S01AA03, A07AA01	QD06AX04, QJ01GB05, QS01AA03, QA07AA01	Yes	Yes
Netilmicin	J01GB07, S01AA23	QJ01GB07, QS01AA23	Yes	None found
Paromomycin	A07AA06	QJ01GB92, QA07AA06	Yes	Yes
Plazomicin	J01GB14	QJ01GB14	Yes. Evaluated separately to Aminoglycosides class	None found
Ribostamycin	J01GB10	QJ01GB10	None found	None found
Sisomicin	J01GB08	QJ01GB08	None found	None found
Spectinomycin	J01XX04	QJ01XX04	Yes	Yes
Streptoduocin	J01GA02	QJ01GA02	None found	None found
Streptomycin	J01GA01, A07AA04	QJ01GA01, QA07AA04	Yes	Yes
Tobramycin	J01GB01, S01AA12	QJ01GB01, QS01AA12	Yes	Yes
Aminoglycosides combinations with other antibacterials	-	QJ01RA97	Yes	Yes
Neomycin combinations with other antibacterials	A07AA51	QA07AA51, QJ51RG01	Yes	Yes
Streptomycin combinations with other antibacterials	A07AA54	QA07AA54, QJ01GA99	None found	Yes

Table 103. ATC(vet) codes and EU-authorisation status for tetracyclines

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Chlortetracycline	J01AA03	QJ01AA03	None found	Yes
Clomocycline	J01AA11	QJ01AA11	None found	None found
Demeclocycline	J01AA01	QJ01AA01	Yes	None found
Doxycycline	J01AA02	QJ01AA02	Yes	Yes
Eravacycline	J01AA13	QJ01AA13	Yes. Evaluated separately to Tetracyclines class	None found
Lymecycline	J01AA04	QJ01AA04	Yes	None found
Metacycline	J01AA05	QJ01AA05	Yes	None found
Minocycline	J01AA08	QJ01AA08	Yes. Evaluated separately to Tetracyclines class	None found
Omadacycline	J01AA15	QJ01AA15	None found. Evaluated separately to Tetracyclines class	None found
Oxytetracycline	J01AA06	QJ01AA06	Yes	Yes
Penimepicycline	J01AA10	QJ01AA10	None found	None found
Rolitetracycline	J01AA09	QJ01AA09	None found	None found
Sarecycline	J01AA14	QJ01AA14	None found	None found
Tetracycline	J01AA07	QJ01AA07	Yes	Yes
Tigecycline	J01AA12	QJ01AA12	Yes	None found
Combinations of tetracyclines	J01AA20	QJ01AA20	Yes	Yes
Chlortetracycline combinations with other antibacterial	-	QJ01AA53	None found	Yes
Oxytetracycline combinations with other antibacterial	J01AA56	QJ01AA56	Yes	Yes

Table 104. ATC(vet) codes and EU-authorisation status for glycylyclines

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Tigecycline	J01AA12	QJ01AA12	Yes	None found

Table 105. ATC(vet) codes and EU-authorisation status for amphenicols

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Azidamfenicol	S01AA25	QS01AA25	Yes	None found
chloramphenicol	J01BA01, S01AA01	QJ01BA01, QS01AA01	Yes	Yes
Florfenicol	-	QJ01BA90	None found	Yes
Thiamphenicol	J01BA02	QJ01BA02	Yes	Yes
Amphenicols combinations with other antibacterial	-	QJ01BA99	None found	None found
Thiamphenicol combinations with other antibacterial	J01BA52	QJ01BA52	None found	None found

Table 106. ATC(vet) codes and EU-authorisation status for sulfonamides, dihydrofolate reductase inhibitors and combinations

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Brodimoprim	J01EA02	QJ01EA02	None found	None found
Formosulfathiazole	-	QA07AB90	None found	Yes
Iclaprim	J01EA03	QJ01EA03	None found	None found
Phthalylsulfathiazole	A07AB02	QA07AB02	None found	Yes
Succinylsulfathiazole	A07AB04	QA07AB04	None found	None found
Sulfacetamide	-	QJ01EQ21	None found	Yes
Sulfachlorpyridazine	-	QJ01EQ12	None found	Yes
Sulfaclozine	-	QP51AG04	None found	Yes
Sulfadiazine	J01EC02	QJ01EQ10	Yes	Yes
Sulfadimethoxine	J01ED01	QJ01EQ09, QP51AG02	None found	Yes
Sulfadimidine	J01EB03	QJ01EQ03 QP51AG01	None found	Yes
Sulfadoxine	-	QJ01EQ13	None found	Yes
Sulfafurazole	J01EB05	QJ01EQ05	Yes	Yes
Sulfaguanidine	A07AB03	QA07AB03	None found	Yes
Sulfaisodimidine	J01EB01	-	None found	None found
Sulfalene	J01ED02	QJ01EQ19	None found	Yes
Sulfamazone	J01ED09	-	None found	None found
Sulfamerazine	J01ED07	QJ01EQ17	None found	Yes
Sulfamethizole	J01EB02	QJ01EQ02	Yes	None found
Sulfamethoxazole	J01EC01	QJ01EQ11	None found	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Sulfamethoxyipyridazine	J01ED05	QJ01EQ15	None found	Yes
Sulfametomidine	J01ED03	-	None found	None found
Sulfametoxydiazine	J01ED04	-	None found	None found
Sulfamonomethoxine	-	QJ01EQ18	None found	Yes
Sulfamoxole	J01EC03	-	None found	None found
Sulphanilamide	J01EB06	QJ01EQ06	None found	Yes
Sulfaperin	J01ED06	-	None found	None found
Sulfaphenazole	J01ED08	QJ01EQ08	None found	None found
Sulfapyrazole	-	QJ01EQ01	-	None found
Sulfapyridine	J01EB04	QJ01EQ04	None found	Yes
Sulfaquinoxaline	-	QJ01EQ16, QP51AG03	None found	Yes
Sulfathiazole	J01EB07	QJ01EQ07	None found	Yes
Sulfathiourea	J01EB08	-	None found	None found
Sulfatroxazol	-	QJ01EQ14	None found	None found
Trimethoprim	J01EA01	QJ01EA01, QJ51EA01	Yes	Yes
Combinations of sulfonamides and trimethoprim	-	QJ01EW30	Yes	Yes
Sulfachlorpyridazine and trimethoprim	-	QJ01EW12	None found	Yes
Sulfadiazine and tetroxoprim	J01EE06	-	None found	None found
Sulfadiazine and trimethoprim	J01EE02	QJ01EW10, QJ51RE01	Yes	Yes
Sulfadimethoxine and ormetoprim	-	QJ01EW19	None found	None found
Sulfadimethoxine and trimethoprim	-	QJ01EW09	None found	Yes
Sulfadimidine and trimethoprim	J01EE05	QJ01EW03	None found	Yes
Sulfadoxine and trimethoprim	-	QJ01EW13	None found	Yes
Sulfamerazine and trimethoprim	J01EE07	QJ01EW18	None found	Yes
Sulfamethoxazole and trimethoprim	J01EE01	QJ01EW11	Yes	Yes
Sulfamethoxyipyridazine and trimethoprim	-	QJ01EW15	None found	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Sulfametrole and trimethoprim	J01EE03	-	Yes	None found
Sulfamonomethoxine and trimethoprim	-	QJ01EW17	None found	None found
Sulfamoxole and trimethoprim	J01EE04	-	None found	None found
Sulfaquinoxaline and trimethoprim	-	QJ01EW16	None found	None found
Sulfatroxazol and trimethoprim	-	QJ01EW14	None found	None found
Combinations of sulfonamides	J01EB20, J01EC20, J01ED20	QA07AB20, QA07AB99, QJ01EQ30, QP51AG30	Yes	Yes
Phthalylsulfathiazole combinations with other antibacterial	-	QA07AB92	None found	None found
Sulfadimethoxine combinations with other antibacterial	-	QJ01EQ59	None found	Yes
Sulfadimidine combinations with other antibacterial	-	QP51AG51	None found	Yes
Sulfaquinoxaline combinations with other antibacterial	-	QP51AG53	None found	Yes

Table 107. ATC(vet) codes and EU-authorisation status for quinolones (non-fluorinated)

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Cinoxacin	J01MB06	QJ01MB06	Yes	None found
Flumequine	J01MB07	QJ01MB07	None found	Yes
Nalidixic acid	J01MB02	QJ01MB02	None found	None found
Nemonoxacin	J01MB08	QJ01MB08	None found	None found
Oxolinic acid	J01MB05	QJ01MB05	None found	Yes
Pipemidic acid	J01MB04	QJ01MB04	Yes	None found
Piromidic acid	J01MB03	QJ01MB03	None found	None found
Rosoxacin	J01MB01	QJ01MB01	None found	None found

Table 108. ATC(vet) codes and EU-authorisation status for fluoroquinolones

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ciprofloxacin	J01MA02	QJ01MA02	Yes	None found
Danofloxacin	-	QJ01MA92	None found	Yes
Delafloxacin	J01MA23	QJ01MA23	Yes	None found
Difloxacin	-	QJ01MA94	None found	Yes
Enoxacin	J01MA04	QJ01MA04	None found	None found
Enrofloxacin	-	QJ01MA90	None found	Yes
Fleroxacin	J01MA08	QJ01MA08	None found	None found
Garenoxacin	J01MA19	QJ01MA19	None found	None found
Gatifloxacin	J01MA16	QJ01MA16	None found	None found
Gemifloxacin	J01MA15	QJ01MA15	None found	None found
Grepafloxacin	J01MA11	QJ01MA11	None found	None found
Ibafloxacin	-	QJ01MA96	None found	None found
Lascufloxacin	J01MA25	QJ01MA25	None found	None found
Levofloxacin	J01MA12	QJ01MA12	Yes	None found
Levonadifloxacin	J01MA24	QJ01MA24	None found	None found
Lomefloxacin	J01MA07	QJ01MA07	Yes	None found
Marbofloxacin	-	QJ01MA93	None found	Yes
Moxifloxacin	J01MA14	QJ01MA14	Yes	None found
Nadifloxacin	D10AF05	QD10AF05	Yes	None found
Norfloxacin	J01MA06	QJ01MA06	Yes	Yes
Ofloxacin	J01MA01	QJ01MA01	Yes	None found
Orbifloxacin	-	QJ01MA95	None found	Yes
Ozenoxacin	D06AX14	QD06AX14	Yes	None found
Pazufloxacin	J01MA18	QJ01MA18	None found	None found
Pefloxacin	J01MA03	QJ01MA03	Yes	None found
Pradofloxacin	-	QJ01MA97	None found	Yes
Prulifloxacin	J01MA17	QJ01MA17	Yes	None found
Rufloxacin	J01MA10	QJ01MA10	Yes	None found
Sarafloxacin	-	QJ01MA98	None found	None found
Sitafoxacin	J01MA21	QJ01MA21	None found	None found
Sparfloxacin	J01MA09	QJ01MA09	None found	None found
Temafloxacin	J01MA05	QJ01MA05	None found	None found
Tosufloxacin	J01MA22	QJ01MA22	None found	None found
Trovafoxacin	J01MA13	QJ01MA13	None found	None found

Table 109. ATC(vet) codes and EU-authorisation status for nitrofurans

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Furazidin	J01XE03	QJ01XE03	Yes	None found
Furazolidone	G01AX06	QG01AX06	Yes	Yes

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Furazolidone	-	QJ01XE90	None found	Yes
Nifuratel	G01AX05	QG01AX05	Yes	None found
Nifuroxazide	A07AX03	QA07AX03	Yes	None found
Nifurpirinol	-	QJ01XE91	None found	Yes
Nifurtimox	P01CC01	QP51AC01	None found	None found
Nifurtoinol	J01XE02	QJ01XE02	None found	None found
Nifurzide	A07AX04	QA07AX04	None found	None found
Nitrofurural	P01CC02, S01AX04, S02AA02, B05CA03, D08AF01, D09AA03	QB05CA03, QD08AF01, QD09AA03, QP51AC02, QG01AX90, QS01AX04, QS02AA02	Yes	Yes
Nitrofurantoin	J01XE01	QJ01XE01	Yes	None found
Nitrofurantoin combinations	J01XE51	QJ01XE51	Yes	None found

Table 110. ATC(vet) codes and EU-authorisation status for antibiotic substances included in the class of Nitroimidazoles

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Metronidazole	A01AB17, D06BX01, G01AF01, J01XD01	QA01AB17, QD06BX01, QG01AF01, QJ01XD01	Yes	Yes
Bismuth subcitrate, tetracycline and metronidazole	A02BD08	-	None found	None found
Cefuroxime and metronidazole	J01RA03	QJ01RA03	None found	None found
Ciprofloxacin and metronidazole	J01RA10	QJ01RA10	None found	None found
Lansoprazole, amoxicillin and metronidazole	A02BD03	-	None found	None found
Lansoprazole, tetracycline and metronidazole	A02BD02	-	None found	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Omeprazole, amoxicillin and metronidazole	A02BD01	QA02BD01	None found	None found
Pantoprazole, amoxicillin, clarithromycin and metronidazole	A02BD11	QA02BD11	None found	None found
Rabeprazole, amoxicillin and metronidazole	A02BD13	QA02BD13	None found	None found
Spiramycin and metronidazole	J01RA04	QJ01RA04	Yes	Yes
Vonoprazan, amoxicillin and metronidazole	A02BD15	QA02BD15	None found	None found

Nitroimidazole derivatives as antiprotozoals are also listed in Table 128.

Table 111. ATC(vet) codes and EU-authorisation status for rifamycins

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Rifabutin	J04AB04	QJ04AB04	Yes	None found
Rifampicin	J04AB02	QJ04AB02	Yes	None found
Rifamycin	A07AA13 J04AB03 D06AX15	QA07AA13 QJ04AB03 QD06AX15	Yes	None found
Rifapentine	J04AB05	QJ04AB05	No	None found
Rifaximin	A07AA11	QA07AA11 QG51AA06	Yes	Yes

Table 112. ATC(vet) codes and EU-authorisation status for anti-tuberculosis substances considered in this class

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Bedaquiline	J04AK05	QJ04AK05	Yes	None found
Calcium aminosalicilate	J04AA03	QJ04AA03		None found
Capreomycin	J04AB30	QJ04AB30	Yes	None found
Cycloserine	J04AB01	QJ04AB01	Yes	None found
Delamanid	J04AK06	QJ04AK06	Yes	None found
Ethambutol	J04AK02	QJ04AK02	Yes	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ethionamide	J04AD03	QJ04AD03	Yes	None found
Isoniazid	J04AC01	QJ04AC01	Yes	None found
Morinamide	J04AK04	QJ04AK04	Yes	None found
Para-aminosalicylic-acid	J04AA01	QJ04AA01	None found	None found
Protionamide	J04AD01	QJ04AD01	Yes	None found
Pyrazinamide	J04AK01	QJ04AK01	Yes	None found
Sodium aminosalicylate	J04AA02	QJ04AA02	Yes	None found
Terizidone	J04AK03	QJ04AK03	Yes	None found
Thioacetazone	J04AK07	QJ04AK07	None found	None found
Tiocardide	J04AD02	QJ04AD02	None found	None found
Viomycin	-	-	None found	None found

Table 113. ATC(vet) codes and EU-authorisation status for riminofenazines

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Clofazimine	J04BA01	QJ04BA01	Yes	None found

Table 114. ATC(vet) codes and EU-authorisation status for sulfones

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Aldesulfone sodium	J04BA03	QJ04BA03	None found	None found
Dapsone	J04BA02	QJ04BA02	Yes	None found
Dapsone	D10AX05	QD10AX05	None found	None found

Table 115. ATC(vet) codes and EU-authorisation status for mupirocin

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Mupirocin	D06AX09, R01AX06	QD06AX09	Yes	None found

Table 116. ATC(vet) codes and EU-authorisation status for steroid antibacterials

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Fusidic acid	J01XC01	QJ01XC01	Yes	Yes

6.2. Antivirals

Table 117. ATC codes and EU-authorisation status for antivirals against HIV

Antiviral substance	ATC code	Authorised as human medicine in EU
Abacavir	J05AF06	Yes
Bictegravir	J05AR20 emtricitabine, tenofovir alafenamide and bictegravir	Yes
Cobicistat	V03AX03	Yes
Dolutegravir	J05AX12	Yes
Efavirenz	J05AG03	Yes
Elvitegravir	J05AX11	Yes
Emtricitabine	J05AF09	Yes
Enfuvirtide	J05AX07	Yes
Fosamprenavir	J05AE07	Yes
Indinavir	J05AE02	None found
Lamivudine	J05AF05	Yes
Lopinavir	J05AR10 lopinavir and ritonavir	Yes
Maraviroc	J05AX09	Yes
Nevirapine	J05AG01	Yes
Raltegravir	J05AX08	Yes
Rilpivirine	J05AG05	Yes
Ritonavir	J05AE03	Yes
Tenofovir alafenamide	J05AF13	Yes
Tenofovir disoproxil	J05AF07	Yes
Tipranavir	J05AE09	Yes
Zidovudine	J05AF01	Yes

Table 118. ATC codes and EU-authorisation status for antivirals against Influenza

Antiviral substance	ATC code	Authorised as human medicine in EU
Amantadine	N04BB01	Yes
Baloxavir marboxil	J05AX25	Yes
Oseltamivir	J05AH02	Yes
Rimantadine	J05AC02	Yes
Zanamivir	J05AH01	Yes

Table 119. ATC codes and EU-authorisation status for antiviral substances against Chronic Viral Hepatitis

Antiviral substance	ATC code	Authorised as human medicine in EU
Adefovir dipivoxil	J05AF08	Yes
Elbasvir	J05AP10	Yes
Glecaprevir	J05AP57 glecaprevir and pibrentasvir	Yes
Grazoprevir	J05AP11	Yes
Lamivudine	J05AF05	Yes
Ledipasvir	J05AP51 sofosbuvir and ledipasvir	Yes
Pibrentasvir	J05AP57 glecaprevir and pibrentasvir	Yes
Ribavirin	J05AP01	Yes
Sofosbuvir	J05AP56 sofosbuvir, velpatasvir and voxilaprevir	Yes
Tenofovir disoproxil	J05AF07	Yes
Velpatasvir	J05AP56 sofosbuvir, velpatasvir and voxilaprevir	Yes
Voxilaprevir	J05AP56 sofosbuvir, velpatasvir and voxilaprevir	Yes

Table 120. ATC codes and EU-authorisation status for antivirals against Herpes viruses

Antiviral substance	ATC code	Authorised as human medicine in EU
Aciclovir	D06BB03, J05AB01, J05AB01, S01AD03, D06BB53	Yes
Famciclovir	J05AB09, S01AD07	Yes
Foscarnet	J05AD01	Yes
Ganciclovir	QJ05AB06	Yes
Valaciclovir	J05AB11	Yes
Valganciclovir	J05AB14	Yes

Table 121. ATC codes and EU-authorisation status for other quoted antivirals

Antiviral substance	ATC code	Authorised as human medicine in EU
Brincidofovir/cidofovir	QJ05AB12 (cidofovir)	Yes
Camostat mesylate	B02AB04	None found
Celgosivir	-	None found
Favipiravir	J05AX27	Yes
Galidesivir	-	None found
Lactimidomycin	-	None found

Antiviral substance	ATC code	Authorised as human medicine in EU
Laninamivir	J05AH04	None found
Methisazone/Metisazone	J05AA01	None found
Molnupiravir	Not yet assigned.	None found
Nitazoxanide/Tizoxanide	P01AX11	None found
Peramivir	J05AH03	None found
PF-07304814 / PF-00835231	-	None found
PF-07321332	-	None found
Remdesivir	-	Yes
Rupintrivir	-	None found
Triazavirin	-	None found
Umifenovir	J05AX13	None found

6.3. Antifungals

Table 122. ATC(vet) codes and EU-authorisation status for azoles

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Miconazole	A01AB09, A07AC01, D01AC02, G01AF04, J02AA13, S02AA13	QA01AB09, QA07AC01, QD01AC02, QG01AF04, QJ02AB01, QS02AA13	Yes	Yes
Clotrimzole	A01AB18, D01AC01, G01AF02	QA01AB18, QD01AC01, QG01AF0	Yes	Yes
Econazole	D01AC03, G01AF05	QD01AC03, QG01AF05	Yes	None found
Chlormidazole	D01AC04	-	Yes	None found
Isoconazole	G01AF07	QG01AF07	Yes	None found
Tioconazole	D01AC07	QD01AC07	Yes	None found
Ketoconazole	D01AC08, G01AF11, J02AB02	QD01AC08, QG01AF11, QJ02AB02	Yes	Yes
Sulconazole	D01AC09, D01AC09	QD01AC09, QD01AC09	Yes	None found
Bifonazole	D01AC10	QD01AC10	Yes	None found
Oxiconazole	D01AC11, G01AF17	QD01AC11, QG01AF17	Yes	None found
Fenticonazole	D01AC12	QD01AC12	Yes	None found
Omoconazole	D01AC13, G01AF16	QD01AC13, QG01AF16	Yes	None found

Substance	ATC code(s)	ATCvet code(s)	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Fluconazole	D01AC15, J02AC01	QD01AC15, QJ02AC01	Yes	None found
Flutrimazole	D01AC16	QD01AC16	Yes	None found
Sertaconazole	D01AC14, G01AF19	QD01AC14, QG01AF19	Yes	None found
Eberconazole	D01AC17	QD01AC17	Yes	None found
Luliconazole	D01AC18	QD01AC18	None found	None found
Efinaconazole	D01AC19	QD01AC19	None found	None found
Enilconazole	-	QD01AC90	None found	Yes
Ornidazole	G01AF06	QG01AF06	Yes	None found
Isoconazole	D01AC05, G01AF07	-	Yes	None found
Tioconazole	G01AF08	QG01AF08	Yes	None found
Fenticonazole	G01AF12	QG01AF12	Yes	None found
Butoconazole	G01AF15	QG01AF15	Yes	None found
Omoconazole	D01AC13, G01AF16	-	Yes	None found
Flutrimazole	G01AF18	QG01AF18	Yes	None found
Terconazole	G01AG02	QG01AG02	None found	None found
Itraconazole	J02AC02	QJ02AC02	Yes	Yes
Voriconazole	J02AC03	QJ02AC03	Yes	None found
Posaconazole	J02AC04	QJ02AC04	Yes	Yes
Isavuconazole	J02AC05	QJ02AC05	None found	None found

Table 123. ATC(vet) codes and EU-authorisation status for polyenes

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
	A01AB antiinfectives and antiseptics, oral treatment	QA01AB antiinfectives and antiseptics, oral treatment		
Amphotericin B	A01AB04	QA01AB04	Yes	None found
Natamycin	A01AB10	QA01AB10	Yes	None found
	D01AA Antibiotics	QD01AA Antibiotics		
Nystatin	D01AA01	QD01AA01	Yes	Yes, ear drops
Natamycin	D01AA02	QD01AA02	Yes	None found
Hachimycin	D01AA03	QD01AA03	None found	None found
	G01AA Antibiotics	QG01AA Antibiotics		
Nystatin	G01AA01	QG01AA01	Yes	None found

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Natamycin	G01AA02	QG01AA02	Yes	None found
Amphotericin B	G01AA03	QG01AA03	Yes	None found
Candididin	G01AA04	QG01AA04	None found	None found
Hachimycin	G01AA06	QG01AA06	None found	None found
	J02AA Antibiotics	QJ02AA Antibiotics		
Amphotericin B	J02AA01	QJ02AA01	Yes	None found
Hachimycin	J02AA02	QJ02AA02	None found	None found

Table 124. ATC(vet) codes and EU-authorisation status for pyrimidine analogues

Substance	ATC code(s)	ATCvet code(s)	Human authorised in the EU	Veterinary Authorised in the EU
	D01AE Other antifungals for topical use	QD01AE Other antifungals for topical use		
Flucytosine	D01AE21	QD01AE21	None found	None found
	J02AX Other antimycotics, systemic use	QJ02AX Other antimycotics, systemic use		
Flucytosine	J02AX01	QJ02AX01	Yes	None found

Table 125. ATC(vet) codes and EU-authorisation status for griseofulvin

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Griseofulvin (topical)	D01AA07	QD01AA07	Yes	None found
Griseofulvin (systemic)	D01BA01	QD01BA01	Yes	Yes

Table 126. ATC(vet) codes and EU-authorisation status for allylamines

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
	D01AE Other antifungals for topical use	QD01AE Other antifungals for topical use		
Terbinafine	D01AE15	QD01AE15	Yes	Yes
Naftifine	D01AE22	QD01AE22	Yes	None found

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Butenafine	D01AE23	D01AE23	Not found	None found
	D01BA Systemic use	QD01BA Systemic use		
Terbinafine	D01BA02	QD01BA02	Yes	None found

Table 127. ATC(vet) codes and EU-authorisation status for echinocandins

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Caspofungin (C)	J02AX04	QJ02AX04	Yes	None found
Micafungin (M)	J02AX05	QJ02AX05	Yes	None found
Anidulafungin (A)	J02AX06	QJ02AX06	Yes	None found

6.4. Antiprotozoals

Table 128. ATC(vet) codes and EU-authorisation status for antiprotozoals

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
P01 ANTIPROTOZOALS				
P01A AGENTS AGAINST AMOEBIASIS AND OTHER PROTOZOAL DISEASES				
QP51 ANTIPROTOZOALS				
P01AA Hydroxyquinoline derivatives				
Broxyquinoline	P01AA01	-	None found	None found
Clioquinol	P01AA02	-	Yes	None found
Chlorquinaldol	P01AA04	-	Yes	None found
Tilbroquinol	P01AA05	-	Yes	None found
Clioquinol, combinations	P01AA52	-	Yes	None found
P01AB Nitroimidazole derivatives		QP51AA Nitroimidazole derivatives		
Metronidazole	P01AB01	QP51AA01	Yes	Yes
Tinidazole	P01AB02	QP51AA02	Yes	None found
Ornidazole	P01AB03	QP51AA03	Yes	None found
Azanidazole	P01AB04	QP51AA04	None found	None found
Propenidazole	P01AB05	QP51AA05	None found	None found
Nimorazole	P01AB06	QP51AA06	None found	None found
Secnidazole	P01AB07	-	Yes	None found

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Metronidazole, combinations	P01AB51	-	Yes	Yes
Dimetridazole	-	QP51AA07	None found	Yes
Ronidazole	-	QP51AA08	None found	Yes
Carnidazole	-	QP51AA09	None found	Yes
Ipronidazole	-	QP51AA10	None found	None found
P01AC Dichloroacetamide derivatives				
Diloxanide	P01AC01	-	None found	None found
Clefamide	P01AC02	-	None found	None found
Etofamide	P01AC03	-	None found	None found
Teclozan	P01AC04	-	None found	None found
P01AR Arsenic compounds				
Arsthinol	P01AR01	QP51AD01	None found	None found
Difetarsone	P01AR02	QP51AD02	None found	None found
Glycobiarsol	P01AR03	QP51AD03	None found	None found
Glycobiarsol, combinations	P01AR53	QP51AD53	None found	None found
P01AX Other agents against amoebiasis and other protozoal diseases		QP51AX Other antiprotozoal agents		
Chiniofon	P01AX01	QP51AX01	None found	None found
Emetine	P01AX02	QP51AX02	None found	None found
Phanquinone	P01AX04	QP51AX03	None found	None found
Mepacrine	P01AX05	QP51AX04	None found	None found
Atovaquone	P01AX06	-	Yes	None found
Trimetrexate	P01AX07	-	None found	None found
Tenonitrozole	P01AX08	-	Yes	None found
Dehydroemetine	P01AX09	-	None found	None found
Fumagillin	P01AX10	QP51AX23	Yes	None found
Nitazoxanide	P01AX11	-	None found	None found
Emetine, combinations	P01AX52	-	None found	None found
Nifursol	-	QP51AX05	None found	None found
Homidium	-	QP51AX06	None found	None found
Diminazen	-	QP51AX07	None found	None found
Halofuginone	-	QP51AX08	None found	Yes
Amprolium	-	QP51AX09	None found	Yes
Maduramicin	-	QP51AX10	None found	None found
Arprinocid	-	QP51AX11	None found	None found
Dinitolmide	-	QP51AX12	None found	None found
Robenidine	-	QP51AX13	None found	None found
Decoquinat	-	QP51AX14	None found	Yes
Aminonitrothiazol	-	QP51AX16	None found	None found

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Ethonabate	-	QP51AX17	None found	None found
Diaverdine	-	QP51AX18	None found	Yes
Isometamidium	-	QP51AX19	None found	None found
Quinapyramine	-	QP51AX20	None found	None found
Parvaquone	-	QP51AX21	None found	None found
Buparvaquone	-	QP51AX22	None found	None found
Domperidone	-	QP51AX24	None found	Yes
P01B ANTIMALARIALS				
P01BA Aminoquinolines				
Chloroquine	P01BA01	-	Yes	None found
Hydroxychloroquine	P01BA02	-	Yes	None found
Primaquine	P01BA03	-	Yes	None found
Amodiaquine	P01BA06	-	Yes	None found
P01BB Biguanides				
Proguanil	P01BB01	-	Yes	None found
Cycloguanil embonate	P01BB02	-	None found	None found
Proguanil, combinations	P01BB51	-	Yes	None found
P01BC Methanolquinolines				
Quinine	P01BC01	-	Yes	None found
Mefloquine	P01BC02	-	Yes	None found
P01BD Diaminopyrimidines		Other antiprotozoals		
Pyrimethamine	P01BD01	QP51AX51	Yes	Yes
P01BE Artemisinin and derivatives				
Artemisinin	P01BE01	-	None found	None found
Artemether	P01BE02	-	Yes	None found
Artesunate	P01BE03	-	Yes	None found
Artemotil	P01BE04	-	None found	None found
Artenimol	P01BE05	-	Yes	None found
P01BF Artemisinin and derivatives, combinations				
Artemether and lumefantrine	P01BF01	-	Yes	None found
Artesunate and mefloquine	P01BF02	-	Yes	None found
Artesunate and amodiaquine	P01BF03	-	None found	None found
Artesunate, sulphamethopyrazine and pyrimethamine	P01BF04	-	None found	None found
Artenimol and piperazine	P01BF05	-	Yes	None found

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Artesunate and pyronaridine	P01BF06	-	Yes	None found
P01BX Other antimalarials				
Halofantrine	P01BX01	-	None found	None found
Arterolane and piperazine	P01BX02	-	None found	None found
P01C AGENTS AGAINST LEISHMANIASIS AND TRYPANOSOMIASIS				
P01CA Nitroimidazole derivatives				
Benznidazole	P01CA02	-	None found	None found
Fexinidazole	P01CA03	-	None found	None found
P01CB Antimony compounds		QP51AB Antimony compounds		
Meglumine antimonate	P01CB01	QP51AB01	Yes	Yes
Sodium stibogluconate	P01CB02	QP51AB02	None found	None found
P01CC Nitrofurans derivatives		QP51AC Nitrofurans derivatives		
Nifurtimox	P01CC01	QP51AC01	None found	None found
Nitrofurantoin	P01CC02	QP51AC02	None found	None found
P01CD Arsenic compounds		QP51AD Arsenic compounds		
Arsthinol	-	QP51AD01	None found	None found
Difetarsone	-	QP51AD02	None found	None found
Glycobiarsol	-	QP51AD03	None found	None found
Melarsoprol	P01CD01	QP51AD04	Yes	None found
Acetarsol	P01CD02	QP51AD05	None found	None found
Melarsamin	-	QP51AD06	None found	None found
Glycobiarsol, combinations	-	QP51AD53	None found	None found
P01CX Other agents against leishmaniasis and trypanosomiasis		QP51AE Carbanilides QP51AF Aromatic diamidines		
Imidocarb	-	QP51AE01	None found	Yes
Diminazen	-	QP51AF01	None found	None found
Pentamidine isethionate	P01CX01	QP51AF02	Yes	None found
Suramin sodium	P01CX02	QP51AE02	Yes	None found
Eflornithine	P01CX03	-	Yes	None found
Miltefosine	P01CX04	-	Yes	Yes

Substance	ATC code	ATCvet code	Authorised as human medicine in EU	Authorised as veterinary medicine in the EU
Nicarbazine	-	QP51AE03	None found	Yes
Phenamidine	-	QP51AF03	None found	None found
		QP51AG Sulfonamides		
Sulfadimidine	-	QP51AG01	Yes	Yes
Sulfadimethoxine	-	QP51AG02	None found	Yes
Sulfaquinoxaline	-	QP51AG03	None found	Yes
Sulfaclozine	-	QP51AG04	None found	None found
		QP51AJ Triazines		
Toltrazuril	-	QP51AJ01	None found	Yes
Clazuril	-	QP51AJ02	None found	None found
Diclazuril	-	QP51AJ03	None found	Yes
Ponazuril	-	QP51AJ04	None found	None found
P02 ANTHELMINTICS				
P02CA Antinematodal agents, Benzimidazole derivatives		QP52 Anthelmintics QP52AC Benzimidazoles		
Albendazole	P02CA03	QP52AC11	Yes	Yes
J02 ANTIMYCOTICS FOR SYSTEMIC USE (Q)J02AA Antibiotics				
Amphotericin B	J02AA01	QJ02AA01	Yes	None found

Nitroimidazoles as antibiotics are also listed in Table 110.

7. Abbreviations

AAT	African Animal Trypanosomiasis
AGP	antibiotic growth promoter
AIDS	Acquired immunodeficiency syndrome
AMEG	Antimicrobial Advice ad hoc Expert Group (EMA)
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
ATC	anatomical therapeutic chemical classification system
ATS	American Thoracic Society
BLI	beta-lactamase inhibitor
CAP	community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use (EMA)
CIA	Critically Important Antimicrobials for Human Medicine (WHO)
cIAI	complicated intra-abdominal infection

AAT	African Animal Trypanosomiasis
CL	cutaneous leishmaniasis
CNS	central nervous system
CoV	coronavirus
CVMP	Committee for Veterinary Medicinal Products (EMA)
DHFR	dihydrofolate reductase
DHPS	dihydropteroate synthase
EARS-Net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
ECIL	European Conference on Infections in Leukemia
EEA	European Economic Area
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EML	Essential Medicines List (WHO)
ESBL	extended-spectrum beta-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	The United States Food and Drug Administration
FVE	Federation of Veterinarians of Europe
GAFFI	Global Action Fund for Fungal Infections
GBD	Global Burden of Disease
HAP	hospital-acquired pneumonia
HAT	Human African trypanosomiasis
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HIA	Highly Important Antimicrobials for Human Medicine (WHO)
HIV	human immunodeficiency virus
HMP	human medicinal product
HPAI	Highly Pathogenic Avian Influenza
HPCIA	Highest Priority Critically Important Antibiotics for Human Medicine (WHO)
IA	invasive aspergillosis
IBS	irritable bowel syndrome
IC	invasive Candida
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IMI	intramammary infection
ISCAID	International Society for Companion Animal Infectious Diseases
IV	intravenous
KPC	<i>Klebsiella pneumoniae</i> carbapenemase
LA(MRSA)	livestock-associated MRSA
LMIC	Low and middle income countries
MBL	metallo-beta-lactamase
MDR	multidrug resistant
MERS	Middle East Respiratory Syndrome

AAT	African Animal Trypanosomiasis
MGE	mobile genetic element
MIC	minimum inhibitory concentration
MRL	maximum residue limit
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRSP	methicillin-resistant <i>Staphylococcus pseudintermedius</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
NI	nitroimidazoles
OIE	World Organization for Animal Health
PAHO	Pan American Health Organization
PBP	penicillin-binding protein
PCP	pneumocystis pneumonia
PFORM	pyruvate:ferredoxin oxidoreductase
PMQR	plasmid-mediated quinolone resistance
QRDR	quinolone resistance-determining regions
RTI	respiratory tract infection
SARS	Severe acute respiratory syndrome
SCC	Staphylococcal cassette chromosome
SMX	sulfamethoxazole
SPC	Summary of Product Characteristics
spp.	species (plural)
SSSI	skin and skin structure infection
SSTI	skin and soft tissue infection
STD	sexually transmitted disease
TB	tuberculosis
TMP	trimethoprim
TMPS	Trimethoprim/Sulfamethoxazole
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
VCIA	Veterinary Critically Important Antimicrobial Agent (OIE)
VHIA	Veterinary Highly important Antimicrobial Agent (OIE)
VIA	Veterinary Important Antimicrobial Agent (OIE)
VISA	vancomycin-intermediate <i>Staphylococcus aureus</i>
VL	Visceral leishmaniasis
VMP	veterinary medicinal product
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant <i>Staphylococcus aureus</i>
WHO	World Health Organization
WSAVA	World Small Animal Veterinary Association
XDR	extensively drug-resistant

Please refer to [ISO 3166 international standard](#) for representation codes of names of countries and their subdivisions.

8. References

1. EMA/CVMP, *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 human (EMA/CVMP/158366/2019)*. 2019: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/advice-implementing-measures-under-article-374-regulation-eu-2019/6-veterinary-medicinal-products-criteria-designation-antimicrobials-be-reserved-treatment-certain_en.pdf.
2. Official Journal of the European Union, *Commission Delegated Regulation (EU) 2021/1760 of 26 May 2021 supplementing Regulation (EU) 2019/6 of the European Parliament and of the Council by establishing the criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans*. 2021: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32021R1760>.
3. WHO, *WHO Model List of Essential Medicines, 22nd List*. 2021: <https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02>.
4. Official Journal of the European Union, *Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC*. 2019: <https://eur-lex.europa.eu/eli/reg/2019/6/oj>.
5. WHO, *Guidelines for ATC classification and DDD assignment 2020*. 2019: https://www.whocc.no/filearchive/publications/2020_guidelines_web.pdf.
6. EMA/CVMP/AWP, *Reflection paper on off-label use of antimicrobials in veterinary medicine in the European Union (EMA/CVMP/AWP/237294/2017)*. 2018: <https://www.ema.europa.eu/en/off-label-use-antimicrobials-veterinary-medicine-european-union>.
7. OIE, *OIE List of antimicrobial agents of veterinary importance*. 2021: <https://www.oie.int/app/uploads/2021/06/a-oie-list-antimicrobials-june2021.pdf>.
8. OIE, *Fifth OIE Annual Report on Antimicrobial Agents Intended for Use in Animals*. 2021: <https://www.oie.int/en/document/fifth-oie-annual-report-on-antimicrobial-agents-intended-for-use-in-animals/>.
9. FDA, *2018 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*. 2019: <https://www.fda.gov/media/133411/download>.
10. New Zealand Food Safety, *Antibiotic Sales Analysis 2017*. 2019: <https://www.mpi.govt.nz/dmsdocument/37886-antibiotic-sales-analysis-2017>.
11. 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*. 2019: <https://www.who.int/publications-detail-redirect/9789241515528>.
12. Seyedmousavi, S., et al., *Fungal infections in animals: a patchwork of different situations*. *Medical mycology*, 2018. **56**(suppl_1): p. S165-S187.
13. Geddes, A.M., et al., *Benzylpenicillin (Penicillin G)*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
14. ECDC, *Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report for 2019*. 2020: <https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019>.
15. Letourneau, A.R., *Penicillin, antistaphylococcal penicillins, and broad-spectrum penicillins*. In: *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
16. Shi, C., et al., *Efficacy and safety of cefazolin versus antistaphylococcal penicillins for the treatment of methicillin-susceptible Staphylococcus aureus bacteremia: a systematic review and meta-analysis*. *BMC Infect Dis*, 2018. **18**(1): p. 508.
17. Lefevre, B., et al., *Antistaphylococcal penicillins vs. cefazolin in the treatment of methicillin-susceptible Staphylococcus aureus infective endocarditis: a quasi-experimental monocentre study*. *Eur J Clin Microbiol Infect Dis*, 2021. **40**(12): p. 2605-2616.
18. Luque Paz, D., I. Lakbar, and P. Tattevin, *A review of current treatment strategies for infective endocarditis*. *Expert Rev Anti Infect Ther*, 2021. **19**(3): p. 297-307.
19. Gagliotti, C., et al., *Staphylococcus aureus bloodstream infections: diverging trends of methicillin-resistant and methicillin-susceptible isolates, EU/EEA, 2005 to 2018*. *Euro Surveill*, 2021. **26**(46).
20. Garcia-Álvarez, L., et al., *Methicillin-resistant Staphylococcus aureus with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study*. *The Lancet infectious diseases*, 2011. **11**(8): p. 595-603.
21. Feng, Y., et al., *Evolution and pathogenesis of Staphylococcus aureus: lessons learned from genotyping and comparative genomics*. *FEMS microbiology reviews*, 2008. **32**(1): p. 23-37.

22. Fisher, J.F. and S. Mobashery, *β -Lactam resistance mechanisms: Gram-positive bacteria and Mycobacterium tuberculosis*. Cold Spring Harbor perspectives in medicine, 2016. **6**(5): p. a025221.
23. Argudín, M.A., et al., *Bacteria from Animals as a Pool of Antimicrobial Resistance Genes*. Antibiotics, 2017. **6**(2): p. 12.
24. Schwendener, S., K. Cotting, and V. Perreten, *Novel methicillin resistance gene mecD in clinical Macrococcus caseolyticus strains from bovine and canine sources*. Scientific Reports, 2017. **7**(1): p. 1-11.
25. Tsubakishita, S., et al., *Origin and molecular evolution of the determinant of methicillin resistance in staphylococci*. Antimicrobial agents and chemotherapy, 2010. **54**(10): p. 4352-4359.
26. EFSA/ECDC, *The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2018/2019*. EFSA Journal, 2021. **19**(4): p. e06490.
27. Beever, L., et al., *Increasing antimicrobial resistance in clinical isolates of Staphylococcus intermedius group bacteria and emergence of MRSP in the UK*. Veterinary Record, 2014.
28. Pires dos Santos, T., et al., *Systematic review on global epidemiology of methicillin-resistant Staphylococcus pseudintermedius: inference of population structure from multilocus sequence typing data*. Frontiers in microbiology, 2016. **7**: p. 1599.
29. Pomba, C., et al., *Public health risk of antimicrobial resistance transfer from companion animals*. J Antimicrob Chemother, 2017. **72**(4): p. 957-968.
30. ECDC/EFSA/EMA, *Joint scientific report of ECDC, EFSA and EMA on methicillin resistant Staphylococcus aureus (MRSA) in livestock, companion animals and food. Summary of the scientific Opinion of the Panel on Biological Hazards (EFSA/BIOHAZ) on "Assessment of the Public Health significance of methicillin resistant Staphylococcus aureus (MRSA) in animals and foods" and the Reflection paper of the Committee for Medicinal Products for Veterinary Use (EMA/CVMP) on "MRSA in food producing and companion animals and in the European Union: Epidemiology and control options for human and animal health"*. 2009: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004306.
31. Stone, K., *Risk Assessment on Methicillin-Resistant Staphylococcus aureus (MRSA), with a focus on Livestock-Associated MRSA, in the UK Food Chain*. Food Standards Agency, 2017.
32. Lakhundi, S. and K. Zhang, *Methicillin-resistant Staphylococcus aureus: molecular characterization, evolution, and epidemiology*. Clinical microbiology reviews, 2018. **31**(4): p. e00020-18.
33. Ferreira, J.P., et al., *Transmission of MRSA between companion animals and infected human patients presenting to outpatient medical care facilities*. PLoS One, 2011. **6**(11): p. e26978.
34. Drougka, E., et al., *Interspecies spread of Staphylococcus aureus clones among companion animals and human close contacts in a veterinary teaching hospital. A cross-sectional study in Greece*. Preventive veterinary medicine, 2016. **126**: p. 190-198.
35. De Briyne, N., et al., *Antibiotics used most commonly to treat animals in Europe*. The Veterinary record, 2014. **175**(13): p. 325.
36. Ruegg, P.L., *A 100-Year Review: Mastitis detection, management, and prevention*. Journal of dairy science, 2017. **100**(12): p. 10381-10397.
37. Dalanezi, F., et al., *Influence of pathogens causing clinical mastitis on reproductive variables of dairy cows*. Journal of dairy science, 2020. **103**(4): p. 3648-3655.
38. EFSA, *Scientific opinion on the welfare risks related to the farming of sheep for wool, meat and milk production*, in EFSA Journal. 2014: <https://www.efsa.europa.eu/en/efsajournal/pub/3933>. p. 3933.
39. Smith, B.P., *Large animal internal medicine. 6th Edition*. 2020: Elsevier Health Sciences.
40. Heikkilä, A.-M., et al., *Pathogen-specific production losses in bovine mastitis*. Journal of dairy science, 2018. **101**(10): p. 9493-9504.
41. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: cattle*, in EFSA Journal. 2021: <https://www.efsa.europa.eu/en/efsajournal/pub/9978>. p. e06955.
42. PubChem, *Novobiocin*. last accessed: 2022: <https://pubchem.ncbi.nlm.nih.gov/compound/Novobiocin>.
43. Geddes, A.M., et al., *Ampicillin and Amoxicillin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
44. Gordon, D., *Amoxicillin-Clavulanic Acid*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
45. Rafailidis, P.I. and M.E. Falagas, *Ampicillin-Sulbactam*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.

46. Zeina A Kanafani, S.S.K., *Acinetobacter infection: Treatment and prevention*. In UpToDate. UpToDate. 2021, Waltham, MA: Post TW (Ed).
47. Carcione, D., et al., *In Vitro Antimicrobial Activity of the Siderophore Cephalosporin Cefiderocol against Acinetobacter baumannii Strains Recovered from Clinical Samples*. *Antibiotics (Basel)*, 2021. **10**(11).
48. Karlowsky, J.A., et al., *In Vitro Susceptibility of Gram-negative Pathogens to Cefiderocol in Five Consecutive Annual Multinational SIDERO-WT Surveillance Studies (2014-2019)*. *Antimicrob Agents Chemother*, 2021: p. AAC0199021.
49. Pascale, R., et al., *Cefiderocol treatment for carbapenem-resistant Acinetobacter baumannii infection in the ICU during the COVID-19 pandemic: a multicentre cohort study*. *JAC Antimicrob Resist*, 2021. **3**(4): p. dlab174.
50. Bush, K., *Proliferation and significance of clinically relevant β -lactamases*. *Annals of the New York Academy of Sciences*, 2013. **1277**(1): p. 84-90.
51. Mojica, M.F., et al., *The urgent need for metallo- β -lactamase inhibitors: an unattended global threat*. *Lancet Infect Dis*, 2022. **22**(1): p. e28-e34.
52. Penwell, W.F., et al., *Molecular mechanisms of sulbactam antibacterial activity and resistance determinants in Acinetobacter baumannii*. *Antimicrobial agents and chemotherapy*, 2015. **59**(3): p. 1680-1689.
53. Papp-Wallace, K.M., et al., *Variants of β -Lactamase KPC-2 That Are Resistant to Inhibition by Avibactam*. *Antimicrobial Agents and Chemotherapy*, 2015. **59**(7): p. 3710-3717.
54. EMA/CVMP/AWP, *Reflection paper on the use of aminopenicillins and their beta-lactamase inhibitor combinations in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/842786/2015)*. 2021: <https://www.ema.europa.eu/aminopenicillins-their-beta-lactamase-inhibitor-combinations-animals-european-union-development>.
55. Zapun, A., P. Macheboeuf, and T. Vernet, *Penicillin-binding proteins and β -lactam resistance, in Antimicrobial Drug Resistance*. 2017, Springer. p. 177-211.
56. ECDC/EFSA/EMA, *Third joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA (JIACRA III)*. 2021: https://www.ema.europa.eu/en/documents/report/ema/ecdc/efsa-third-joint-report-integrated-analysis-consumption-antimicrobial-agents-occurrence_en.pdf.
57. Bortolami, A., et al., *Diversity, virulence, and clinical significance of extended-spectrum β -lactamase-and pAmpC-producing Escherichia coli from companion animals*. *Frontiers in microbiology*, 2019. **10**: p. 1260.
58. Gijsbers, E., et al., *The prevalence of ESBL-producing E. coli carriage in personnel and horses of an equine clinic in the Netherlands (P1739)*, in *28th ECCMID*. 2018: Madrid, Spain.
59. Hordijk, J., et al., *High prevalence of fecal carriage of extended spectrum beta-lactamase/AmpC-producing Enterobacteriaceae in cats and dogs*. *Front Microbiol*, 2013. **4**: p. 242.
60. Zogg, A.L., et al., *High prevalence of extended-spectrum β -lactamase producing Enterobacteriaceae among clinical isolates from cats and dogs admitted to a veterinary hospital in Switzerland*. *Frontiers in veterinary science*, 2018. **5**: p. 62.
61. Antunes, P., et al., *Salmonellosis: the role of poultry meat*. *Clinical Microbiology and Infection*, 2016. **22**(2): p. 110-121.
62. Campos, J., et al., *Non-typhoidal Salmonella in the pig production chain: a comprehensive analysis of its impact on human health*. *Pathogens*, 2019. **8**(1): p. 19.
63. Kathayat, D., et al., *Avian pathogenic Escherichia coli (APEC): an overview of virulence and pathogenesis factors, zoonotic potential, and control strategies*. *Pathogens*, 2021. **10**(4): p. 467.
64. Jørgensen, S.L., et al., *Diversity and population overlap between avian and human Escherichia coli belonging to sequence type 95*. *MSphere*, 2019. **4**(1): p. e00333-18.
65. Mughini-Gras, L., et al., *Attributable sources of community-acquired carriage of Escherichia coli containing β -lactam antibiotic resistance genes: a population-based modelling study*. *The Lancet Planetary Health*, 2019. **3**(8): p. e357-e369.
66. Díaz-Jiménez, D., et al., *Microbiological risk assessment of Turkey and chicken meat for consumer: Significant differences regarding multidrug resistance, mcr or presence of hybrid aEPEC/ExPEC pathotypes of E. coli*. *Food Control*, 2021. **123**: p. 107713.
67. Carattoli, A., et al., *Contemporary IncI1 plasmids involved in the transmission and spread of antimicrobial resistance in Enterobacteriaceae*. *Plasmid*, 2021. **118**: p. 102392.

68. Lazarus, B., et al., *Do Human Extraintestinal Escherichia coli Infections Resistant to Expanded-Spectrum Cephalosporins Originate From Food-Producing Animals? A Systematic Review*. Clin Infect Dis, 2014.
69. EMA/CVMP/AWP, *Reflection paper on the risk of antimicrobial resistance transfer from companion animals (EMA/CVMP/AWP/401740/2013)*. 2015: <https://www.ema.europa.eu/en/risk-antimicrobial-resistance-transfer-companion-animals>.
70. Fong, I., *Animals and Mechanisms of Disease Transmission*. Emerging Zoonoses, 2017: p. 15-38.
71. Marques, C., et al., *Evidence of sharing of Klebsiella pneumoniae strains between healthy companion animals and cohabiting humans*. Journal of clinical microbiology, 2019. **57**(6): p. e01537-18.
72. FSA, *Risk Assessment on Meticillin - Resistant Staphylococcus aureus (MRSA), with a focus on Livestock - associated MRSA in the UK Food Chain*. 2017: <https://www.ruma.org.uk/wp-content/uploads/2020/09/Risk-Assessment-on-Meticillin-Resistant-Staphylococcus-aureus-FSA.pdf>
73. Cuny, C., L.H. Wieler, and W. Witte, *Livestock-associated MRSA: the impact on humans*. Antibiotics, 2015. **4**(4): p. 521-543.
74. Kinross, P., et al., *Livestock-associated meticillin-resistant Staphylococcus aureus (MRSA) among human MRSA isolates, European Union/European Economic Area countries, 2013*. Eurosurveillance, 2017. **22**(44).
75. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: Dogs and cats*, in *EFSA Journal*. 2021: <https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2021.6680>. p. e06680.
76. FECAVA, *Recommendations for appropriate antimicrobial therapy*. 2018: <https://www.fecava.org/wp-content/uploads/2020/01/FECAVA-Recommendations-for-Appropriate-Antimicrobial-ENGLISH-1.pdf>.
77. Beco, L., et al., *Suggested guidelines for using systemic antimicrobials in bacterial skin infections: part 2—antimicrobial choice, treatment regimens and compliance*. Veterinary Record, 2013. **172**(6): p. 156-160.
78. Hillier, A., et al., *Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases)*. Veterinary dermatology, 2014. **25**(3): p. 163-e43.
79. De Jong, A., et al., *Antimicrobial susceptibility monitoring of canine and feline skin and ear pathogens isolated from European veterinary clinics: Results of the ComPath Surveillance programme*. Veterinary Dermatology, 2020. **31**(6): p. 431-e114.
80. Weese, J.S., et al., *International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats*. The Veterinary Journal, 2019. **247**: p. 8-25.
81. Day, M., et al., *Aetiology of canine infectious respiratory disease complex and prevalence of its pathogens in Europe*. Journal of comparative pathology, 2020. **176**: p. 86-108.
82. Dear, J.D., *Bacterial pneumonia in dogs and cats: an update*. Veterinary Clinics: Small Animal Practice, 2020. **50**(2): p. 447-465.
83. Lappin, M., et al., *Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: antimicrobial guidelines working group of the International Society for Companion Animal Infectious Diseases*. Journal of veterinary internal medicine, 2017. **31**(2): p. 279-294.
84. Giguère, S., J.F. Prescott, and P.M. Dowling, *Antimicrobial Therapy in Veterinary Medicine, 5th edition*. 2013.
85. EMA/ESVAC, *European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. Sales of veterinary antimicrobial agents in 31 European countries in 2019 and 2020. Trends from 2010 to 2020. Eleventh ESVAC report*. 2021: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2019-2020-trends-2010-2020-eleventh_en.pdf.
86. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: Swine*, in *EFSA Journal*. 2021: <https://www.efsa.europa.eu/en/efsajournal/pub/9983>.
87. Vanni, M., et al., *Antimicrobial resistance of Actinobacillus pleuropneumoniae isolated from swine*. Veterinary microbiology, 2012. **156**(1): p. 172-177.
88. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: sheep and goats*, in *EFSA Journal*. 2021: <https://www.efsa.europa.eu/en/efsajournal/pub/9977>.
89. Lund, F. and L. Tybring, *6-aminopenicillanic acids--a new group of antibiotics*. Nat New Biol, 1972. **236**(66): p. 135-7.

90. Dewar, S., L.C. Reed, and R.J. Koerner, *Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria*. J Antimicrob Chemother, 2014. **69**(2): p. 303-8.
91. Tybring, L., *Mecillinam (FL 1060), a 6 β -amidinopenicillanic acid derivative: In vitro evaluation*. Antimicrobial agents and chemotherapy, 1975. **8**(3): p. 266-270.
92. Hovelius, B. and P.A. Mardh, *Staphylococcus saprophyticus as a common cause of urinary tract infections*. Rev Infect Dis, 1984. **6**(3): p. 328-37.
93. Pedersen, G., H.C. Schonheyder, and H.T. Sorensen, *Antibiotic therapy and outcome of monomicrobial gram-negative bacteraemia: a 3-year population-based study*. Scand J Infect Dis, 1997. **29**(6): p. 601-6.
94. King, J.W., et al., *Systemic infections treated with amdinocillin in combination with other beta-lactam antibiotics*. Am J Med, 1983. **75**(2A): p. 90-5.
95. Kahlmeter, G., J. Ahman, and E. Matuschek, *Antimicrobial Resistance of Escherichia coli Causing Uncomplicated Urinary Tract Infections: A European Update for 2014 and Comparison with 2000 and 2008*. Infect Dis Ther, 2015. **4**(4): p. 417-23.
96. Wagenlehner, F., et al., *A global perspective on improving patient care in uncomplicated urinary tract infection: expert consensus and practical guidance*. J Glob Antimicrob Resist, 2021. **28**: p. 18-29.
97. Boel, J.B., et al., *Intravenous mecillinam compared with other beta-lactams as targeted treatment for Escherichia coli or Klebsiella spp. bacteraemia with urinary tract focus*. J Antimicrob Chemother, 2021. **76**(1): p. 206-211.
98. Fuchs, P.C., et al., *In vitro activity of ticarcillin plus clavulanic acid against 632 clinical isolates*. Antimicrob Agents Chemother, 1984. **25**(3): p. 392-4.
99. Paisley, J.W. and J.A. Washington, 2nd, *Combined activity of clavulanic acid and ticarcillin against ticarcillin-resistant, gram-negative bacilli*. Antimicrob Agents Chemother, 1978. **14**(2): p. 224-7.
100. Chatterjee, S., et al., *Cefiderocol- A New Antimicrobial for Complicated Urinary Tract Infection (CUTI) Caused by Carbapenem Resistant Enterobacteriaceae (CRE)*. Curr Drug Res Rev, 2021.
101. ECDC, *Surveillance of antimicrobial resistance in Europe 2018*. 2019: <https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018>.
102. Gutierrez-Gutierrez, B., et al., *A Multinational, Preregistered Cohort Study of beta-Lactam/beta-Lactamase Inhibitor Combinations for Treatment of Bloodstream Infections Due to Extended-Spectrum-beta-Lactamase-Producing Enterobacteriaceae*. Antimicrob Agents Chemother, 2016. **60**(7): p. 4159-69.
103. Tramontana, A. and K. Thursky, *Mezlocillin, Azlocillin, Apalcillin, and Piperacillin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
104. Dzintars, K., *Carbenicillin, Carindacillin, Carfecillin, and Ticarcillin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
105. LeBlanc, M., *The current status of antibiotic use in equine reproduction*. Equine Veterinary Education, 2009. **21**(3): p. 156-167.
106. Sweeney, R.W., J. Beech, and R.D. Simmons, *Pharmacokinetics of intravenously and intramuscularly administered ticarcillin and clavulanic acid in foals*. Am J Vet Res, 1988. **49**(1): p. 23-6.
107. Wilson, W.D., et al., *Pharmacokinetics and bioavailability of ticarcillin and clavulanate in foals after intravenous and intramuscular administration*. J Vet Pharmacol Ther, 1991. **14**(1): p. 78-89.
108. Prescott, J.F., *Beta-lactam Antibiotics: Penam Penicillins*. Antimicrobial Therapy in Veterinary Medicine, 5th edition, 2013.
109. Wilson, W.D. *Rational selection of antimicrobials for use in horses*. in *Proc AAEP*. 2001.
110. Nuttall, T., *Use of ticarcillin in the management of canine otitis externa complicated by Pseudomonas aeruginosa*. Journal of small animal practice, 1998. **39**(4): p. 165-168.
111. Papich, M., *Handbook of Veterinary Drugs. 4th edition*. 2016, Saunders.
112. Barnard, N. and A. Foster, *Pseudomonas otitis in dogs: a general practitioner's guide to treatment*. In *Practice*, 2017. **39**(9): p. 386-398.
113. Pye, C., *Pseudomonas otitis externa in dogs*. The Canadian Veterinary Journal, 2018. **59**(11): p. 1231.
114. Alyssa R Letourneau, M., *Cephalosporines*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).

115. Denny, K.J., J. Lipman, and J.A. Roberts, *Cephalothin and Cefazolin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
116. Rafiei, N., *Cephalexin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
117. Paterson, D.L., *Cefadroxil, Cephaloridine, Cephacetrile, Cephapirin, Cephadrine, and Other Rarely Used First-Generation Cephalosporins*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
118. Paterson, D.L. and Y. Doi, *Cefaclor, Cefprozil, and Loracarbef*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
119. Baba, H. and D.L. Paterson, *Cefotiam, Cefuzonam, Cefamandole, Cefonicid, and Ceforanide*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
120. Robinson, J.L., et al., *Urinary tract infections in infants and children: Diagnosis and management*. *Paediatr Child Health*, 2014. **19**(6): p. 315-25.
121. Chua, M., et al., *A critical review of recent clinical practice guidelines for pediatric urinary tract infection*. *Can Urol Assoc J*, 2018. **12**(4): p. 112-118.
122. Bardia, A., et al., *Adherence to Guidelines for the Administration of Intraoperative Antibiotics in a Nationwide US Sample*. *JAMA Netw Open*, 2021. **4**(12): p. e2137296.
123. Kheir, M.M., et al., *Vancomycin Prophylaxis for Total Joint Arthroplasty: Incorrectly Dosed and Has a Higher Rate of Periprosthetic Infection Than Cefazolin*. *Clin Orthop Relat Res*, 2017. **475**(7): p. 1767-1774.
124. Roger G. Finch, D.G., Richard J. Whitley, S. Ragnar Norrby, *Antibiotic and chemotherapy: anti-infective agents and their use in therapy*. 9th Edition ed. 2010: Saunders.
125. Kim, B.-N. and D.L. Paterson, *Cefotaxime*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
126. Kim, B.-N., A.M. Peri, and D.L. Paterson, *Ceftriaxone*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
127. Wright, H. and A. Endimiani, *Ceftazidime and Ceftazidime-Avibactam*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
128. Endimiani, A. and P. Sendi, *Cefepime, Cefpirome, and Cefepime-Tazobactam*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
129. Freifeld, A.G., et al., *Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america*. *Clin Infect Dis*, 2011. **52**(4): p. e56-93.
130. Bush, K. and J.F. Fisher, *Epidemiological expansion, structural studies, and clinical challenges of new β -lactamases from gram-negative bacteria*. *Annual review of microbiology*, 2011. **65**: p. 455-478.
131. Pfeifer, Y., A. Cullik, and W. Witte, *Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens*. *International journal of medical microbiology*, 2010. **300**(6): p. 371-379.
132. EMEA/CVMP/SAGAM, *Reflection paper on MRSA in food producing and companion animals in the European Union: epidemiology and control options for human and animal health (EMEA/CVMP/SAGAM/68290/2009)*. 2009: <https://www.ema.europa.eu/en/meticillin-resistant-staphylococcus-aureus-food-producing-companion-animals-european-union>.
133. Dutil, L., et al., *Ceftiofur resistance in Salmonella enterica serovar Heidelberg from chicken meat and humans, Canada*. *Emerg Infect Dis*, 2010. **16**(1): p. 48-54.
134. Dohmen, W., et al., *Risk factors for ESBL-producing Escherichia coli on pig farms: A longitudinal study in the context of reduced use of antimicrobials*. *PLoS One*, 2017. **12**(3): p. e0174094.
135. Official Journal of the European Union, *Summary of European Union decisions on marketing authorisations in respect of medicinal products from 1 January 2012 to 31 January 2012 (2012/C 78/02)*. *Cephalosporins*. 2012: <https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1420644411495&uri=CELEX:52012XC0316%2804%29>.
136. EMA/CVMP. *Opinion following an Article 35 referral for all veterinary medicinal products containing systemically administered (parenteral and oral) 3rd and 4th generation cephalosporins intended for use in food producing species*. 2012 10 March 2014].
137. Kolenda, R., M. Burdukiewicz, and P. Schierack, *A systematic review and meta-analysis of the epidemiology of pathogenic Escherichia coli of calves and the role of calves as reservoirs for human pathogenic E. coli*. *Frontiers in cellular and infection microbiology*, 2015. **5**: p. 23.

138. Luppi, A., *Swine enteric colibacillosis: diagnosis, therapy and antimicrobial resistance*. Porcine health management, 2017. **3**(1): p. 1-18.
139. Lhermie, G., et al., *Indications for the use of highest priority critically important antimicrobials in the veterinary sector*. Journal of Antimicrobial Chemotherapy, 2020.
140. VanderWaal, K. and J. Deen, *Global trends in infectious diseases of swine*. Proceedings of the National Academy of Sciences, 2018. **115**(45): p. 11495-11500.
141. Suojala, L., L. Kaartinen, and S. Pyörälä, *Treatment for bovine E scherichia coli mastitis - an evidence -based approach*. Journal of veterinary pharmacology and therapeutics, 2013. **36**(6): p. 521-531.
142. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: Horses*, in *EFSA Journal*. 2021: <https://www.efsa.europa.eu/en/efsajournal/pub/9986>.
143. DANMAP, *DANMAP 2020 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. 2021: <https://www.danmap.org/reports>.
144. NORM/NORM-VET, *Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway 2020*. 2021: <https://www.vetinst.no/en/surveillance-programmes/norm-norm-vet-report>.
145. Beco, L., et al., *Suggested guidelines for using systemic antimicrobials in bacterial skin infections: part 1—diagnosis based on clinical presentation, cytology and culture*. Veterinary Record, 2013. **172**(3): p. 72-72.
146. Jones, R.N., et al., *In vitro evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci*. J Antimicrob Chemother, 2002. **50**(6): p. 915-32.
147. Brown, S.D. and M.M. Traczewski, *In vitro antimicrobial activity of a new cephalosporin, ceftaroline, and determination of quality control ranges for MIC testing*. Antimicrob Agents Chemother, 2009. **53**(3): p. 1271-4.
148. Giacobbe, D.R., et al., *Ceftobiprole: drug evaluation and place in therapy*. Expert Rev Anti Infect Ther, 2019. **17**(9): p. 689-698.
149. Mpenge, M.A. and A.P. MacGowan, *Ceftaroline in the management of complicated skin and soft tissue infections and community acquired pneumonia*. Ther Clin Risk Manag, 2015. **11**: p. 565-79.
150. Welte, T., et al., *Ceftaroline fosamil as a potential treatment option for Staphylococcus aureus community-acquired pneumonia in adults*. Int J Antimicrob Agents, 2019. **54**(4): p. 410-422.
151. White, B.P., K.E. Barber, and K.R. Stover, *Ceftaroline for the treatment of methicillin-resistant Staphylococcus aureus bacteremia*. Am J Health Syst Pharm, 2017. **74**(4): p. 201-208.
152. Sakoulas, G., et al., *Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline*. Clin Ther, 2014. **36**(10): p. 1317-33.
153. Cassini, A., et al., *Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis*. Lancet Infect Dis, 2019. **19**(1): p. 56-66.
154. Aktie., B.P. *Basilea to launch Zevtera®/Mabelio®(ceftobiprole medocaril) in Europe through a commercial services provider*. 2014; Available from: <https://www.finanzen.at/nachrichten/aktien/basilea-to-launch-zevtera-mabelio-ceftobiprole-medocaril-in-europe-through-a-commercial-services-provider-1000213450>.
155. EFSA, *Scientific Opinion on the public health risks of bacterial strains producing extended-spectrum β -lactamases and/or AmpC β -lactamases in food and food-producing animals*. EFSA Journal, 2011. **9**(8):2322.
156. Morosini, M.-I., M. Díez-Aguilar, and R. Cantón, *Mechanisms of action and antimicrobial activity of ceftobiprole*. Revista Española de Quimioterapia, 2019. **32**(Suppl 3): p. 3.
157. Sharma, R., T.E. Park, and S. Moy, *Ceftazidime-Avibactam: A Novel Cephalosporin/beta-Lactamase Inhibitor Combination for the Treatment of Resistant Gram-negative Organisms*. Clin Ther, 2016. **38**(3): p. 431-44.
158. Viala, B., et al., *Assessment of the In Vitro Activities of Ceftolozane/Tazobactam and Ceftazidime/Avibactam in a Collection of Beta-Lactam-Resistant Enterobacteriaceae and Pseudomonas aeruginosa Clinical Isolates at Montpellier University Hospital, France*. Microb Drug Resist, 2019. **25**(9): p. 1325-1329.
159. Grayson, M.L., et al., *Kucers' the use of antibiotics: A clinical review of antibacterial, antifungal, antiparasitic, and antiviral drugs, seventh edition*. 2018: CRC Press.
160. Sader, H.S., et al., *Antimicrobial activities of ceftazidime/avibactam, ceftolozane/tazobactam, imipenem/relebactam, meropenem/vaborbactam, and comparators against Pseudomonas aeruginosa from patients with skin and soft tissue infections*. Int J Infect Dis, 2021. **113**: p. 279-281.

161. Sader, H.S., et al., *Comparative activity of newer beta-lactam/beta-lactamase inhibitor combinations against Pseudomonas aeruginosa from patients hospitalized with pneumonia in European medical centers in 2020*. Eur J Clin Microbiol Infect Dis, 2021.
162. Sader, H.S., et al., *Antimicrobial activity of cefoperazone-sulbactam tested against Gram-Negative organisms from Europe, Asia-Pacific, and Latin America*. Int J Infect Dis, 2020. **91**: p. 32-37.
163. Wang, Y., et al., *Resistance to ceftazidime-avibactam and underlying mechanisms*. Journal of global antimicrobial resistance, 2020. **22**: p. 18-27.
164. Barriere, S.L. and J.F. Flaherty, *Third-generation cephalosporins: a critical evaluation*. Clinical pharmacy, 1984. **3**(4): p. 351-373.
165. Garau, J., et al., *Fourth - generation cephalosporins: a review of in vitro activity, pharmacokinetics, pharmacodynamics and clinical utility*. Clinical Microbiology and Infection, 1997. **3**: p. s87-s101.
166. Paterson, D.L., *Cefiderocol (S-649266)*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
167. Zhanel, G.G., et al., *Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli*. Drugs, 2019. **79**(3): p. 271-289.
168. Candel, F.J., et al., *In vitro activity of the novel siderophore cephalosporin, cefiderocol, in Gram-negative pathogens in Europe by site of infection*. Clin Microbiol Infect, 2021.
169. Simner, P.J., et al., *Cefiderocol Activity Against Clinical Pseudomonas aeruginosa Isolates Exhibiting Ceftolozane-Tazobactam Resistance*. Open Forum Infect Dis, 2021. **8**(7): p. ofab311.
170. Wong, D. and D. van Duin, *Novel Beta-Lactamase Inhibitors: Unlocking Their Potential in Therapy*. Drugs, 2017. **77**(6): p. 615-628.
171. Zhanel, G.G., et al., *Comparative review of the carbapenems*. Drugs, 2007. **67**(7): p. 1027-1052.
172. Bassetti, M., et al., *Role of new antibiotics in extended-spectrum beta-lactamase-, AmpC-infections*. Curr Opin Infect Dis, 2021. **34**(6): p. 748-755.
173. Daikos, G.L., et al., *Review of Ceftazidime-Avibactam for the Treatment of Infections Caused by Pseudomonas aeruginosa*. Antibiotics (Basel), 2021. **10**(9).
174. Sader, H.S., et al., *Antimicrobial activity of ceftazidime/avibactam, ceftolozane/tazobactam and comparator agents against Pseudomonas aeruginosa from cystic fibrosis patients*. JAC Antimicrob Resist, 2021. **3**(3): p. dlab126.
175. Puzniak, L., et al., *Systematic Literature Review of Real-world Evidence of Ceftolozane/Tazobactam for the Treatment of Respiratory Infections*. Infect Dis Ther, 2021. **10**(3): p. 1227-1252.
176. Botelho, J., F. Grosso, and L. Peixe, *Antibiotic resistance in Pseudomonas aeruginosa- Mechanisms, epidemiology and evolution*. Drug Resistance Updates, 2019. **44**: p. 100640.
177. Francis, C. and D. Eric, *Carbapenem resistance: A review*. Medical Sciences, 2017. **6**(1): p. 1.
178. Meletis, G., *Carbapenem resistance: overview of the problem and future perspectives*. Therapeutic advances in infectious disease, 2016. **3**(1): p. 15-21.
179. Köck, R., et al., *Carbapenem-resistant Enterobacteriaceae in wildlife, food-producing, and companion animals: a systematic review*. Clinical Microbiology and Infection, 2018. **24**(12): p. 1241-1250.
180. González-Torralba, A., et al., *Survey of carbapenemase-producing Enterobacteriaceae in companion dogs in Madrid, Spain*. Antimicrobial agents and chemotherapy, 2016. **60**(4): p. 2499-2501.
181. Melo, L.C., et al., *OXA-48-producing ST372 Escherichia coli in a French dog*. Journal of Antimicrobial Chemotherapy, 2017. **72**(4): p. 1256-1258.
182. Stolle, I., et al., *Emergence of OXA-48 carbapenemase-producing Escherichia coli and Klebsiella pneumoniae in dogs*. Journal of Antimicrobial Chemotherapy, 2013.
183. Lupo, A., M. Haenni, and J.-Y. Madec, *Antimicrobial resistance in Acinetobacter spp. and Pseudomonas spp*. Microbiology spectrum, 2018. **6**(3): p. 6.3. 01.
184. Grönthal, T., et al., *Sharing more than friendship- transmission of NDM-5 ST167 and CTX-M-9 ST69 Escherichia coli between dogs and humans in a family, Finland, 2015*. Eurosurveillance, 2018. **23**(27): p. 1700497.
185. Fernandes, M.R., et al., *Zoonothroponotic transmission of drug-resistant Pseudomonas aeruginosa, Brazil*. Emerging infectious diseases, 2018. **24**(6): p. 1160.
186. Jessen, L., et al., *Antibiotic Use Guidelines for Companion Animal Practice (2nd edition)*. 2018: https://www.ddd.dk/media/2175/assembled_final.pdf.
187. BSAVA. *Are you PROTECTing your antibacterials*. 2012.

188. Gettig, J.P., C.W. Crank, and A.H. Philbrick, *Faropenem medoxomil*. *Ann Pharmacother*, 2008. **42**(1): p. 80-90.
189. Schurek, K.N., et al., *Faropenem: review of a new oral penem*. *Expert review of anti-infective therapy*, 2007. **5**(2): p. 185-198.
190. Gandra, S., et al., *Faropenem consumption is increasing in India*. *Clinical Infectious Diseases*, 2016. **62**(8): p. 1050-1052.
191. Dalhoff, A., T. Nasu, and K. Okamoto, *Beta-lactamase stability of faropenem*. *Chemotherapy*, 2003. **49**(5): p. 229-236.
192. Mushtaq, S., et al., *Activity of faropenem against cephalosporin-resistant Enterobacteriaceae*. *Journal of antimicrobial chemotherapy*, 2007. **59**(5): p. 1025-1030.
193. Woodcock, J., et al., *The in-vitro activity of faropenem, a novel oral penem*. *The Journal of antimicrobial chemotherapy*, 1997. **39**(1): p. 35-43.
194. Baba, H., *Aztreonam and Aztreonam-Avibactam*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
195. Khan, A., et al., *Evaluation of Susceptibility Testing Methods for Aztreonam and Ceftazidime-Avibactam Combination Therapy on Extensively Drug-Resistant Gram-Negative Organisms*. *Antimicrob Agents Chemother*, 2021. **65**(11): p. e0084621.
196. Mauri, C., et al., *The Revival of Aztreonam in Combination with Avibactam against Metallo-beta-Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases*. *Antibiotics (Basel)*, 2021. **10**(8).
197. Elson, E.C., et al., *Aztreonam Lysine Inhalation Solution in Cystic Fibrosis*. *Clin Med Insights Circ Respir Pulm Med*, 2019. **13**: p. 1179548419842822.
198. EUCAST. *Expert Rules Version 3.1. Intrinsic Resistance and Exceptional Phenotypes Tables*. . 2016; Available from: https://eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Expert_Rules/Expert_rules_intrinsic_exceptional_V3.1.pdf.
199. Ortega-Cisneros, M., et al., [*Penicillin allergy*]. *Rev Alerg Mex*, 2022. **69 Suppl 1**: p. s81-s93.
200. Taccetti, G., et al., *Cystic Fibrosis: Recent Insights into Inhaled Antibiotic Treatment and Future Perspectives*. *Antibiotics (Basel)*, 2021. **10**(3).
201. Paxson, J. and M. Paradis, *Pharmacokinetics of aztreonam after intravenous administration in foals*. *Journal of veterinary pharmacology and therapeutics*, 2011. **34**(1): p. 92-94.
202. Lewbart, G., *Antimicrobial and antifungal agents used in fish*. *Exotic Animal Formulary*. 3rd Edition, 2005: p. 5-12.
203. Nation, R.L., *Polymyxins*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
204. EMA/CVMP/CHMP, *Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health (EMA/CVMP/CHMP/231573/2016)*. 2016: https://www.ema.europa.eu/documents/scientific-guideline/updated-advice-use-colistin-products-animals-within-european-union-development-resistance-possible_en-0.pdf.
205. Poirel, L., et al., *Plasmid-mediated carbapenem and colistin resistance in a clinical isolate of Escherichia coli*. *The Lancet Infectious Diseases*, 2016. **16**(3): p. 281.
206. Ling, Z., et al., *Epidemiology of mobile colistin resistance genes mcr-1 to mcr-9*. *Journal of Antimicrobial Chemotherapy*, 2020. **75**(11): p. 3087-3095.
207. Liu, Y.-Y., et al., *Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study*. *The Lancet Infectious Diseases*, 2015. **16**(2): p. 161-168.
208. Wang, C., et al., *Identification of novel mobile colistin resistance gene mcr-10*. *Emerging microbes & infections*, 2020. **9**(1): p. 508-516.
209. Martins-Sorenson, N., et al., *A novel plasmid-encoded mcr-4.3 gene in a colistin-resistant Acinetobacter baumannii clinical strain*. *Journal of Antimicrobial Chemotherapy*, 2020. **75**(1): p. 60-64.
210. Kuo, S.-C., et al. *Colistin resistance gene mcr-1 in Escherichia coli isolates from humans and retail meats, Taiwan*. *Journal of Antimicrobial Chemotherapy*, 2016.
211. Bitar, I., et al., *Complete nucleotide sequences of mcr-4.3-carrying plasmids in Acinetobacter baumannii sequence type 345 of human and food origin from the Czech Republic, the first case in Europe*. *Antimicrobial agents and chemotherapy*, 2019. **63**(10): p. e01166-19.
212. Guenther, S., et al., *Environmental emission of multiresistant Escherichia coli carrying the colistin resistance gene mcr-1 from German swine farms*. *Journal of Antimicrobial Chemotherapy*, 2017. **72**(5): p. 1289-1292.

213. Catry, B., et al., *Use of colistin-containing products within the European Union and European Economic Area (EU/EEA): development of resistance in animals and possible impact on human and animal health*. Int J Antimicrob Agents, 2015. **46**(3): p. 297-306.
214. Yang, Y.-Q., et al., *Co-occurrence of mcr-1 and ESBL on a single plasmid in Salmonella enterica*. Journal of Antimicrobial Chemotherapy, 2016. **71**(8): p. 2336-2338.
215. Wang, R., et al., *The prevalence of colistin resistance in Escherichia coli and Klebsiella pneumoniae isolated from food animals in China: coexistence of mcr-1 and blaNDM with low fitness cost*. International journal of antimicrobial agents, 2018. **51**(5): p. 739-744.
216. Yang, R.-S., et al., *Emergence of NDM-5-and MCR-1-producing Escherichia coli clones ST648 and ST156 from a single muscovy duck (Cairina moschata)*. Antimicrobial agents and chemotherapy, 2016. **60**(11): p. 6899-6902.
217. Yao, X., et al., *Carbapenem-resistant and colistin-resistant Escherichia coli co-producing NDM-9 and MCR-1*. The Lancet Infectious Diseases, 2016. **16**(3): p. 288-289.
218. Valiakos, G. and I. Kapna, *Colistin Resistant mcr Genes Prevalence in Livestock Animals (Swine, Bovine, Poultry) from a Multinational Perspective. A Systematic Review*. Veterinary Sciences, 2021. **8**(11): p. 265.
219. Ortega-Paredes, D., et al., *Multidrug-resistant Escherichia coli isolated from canine faeces in a public park in Quito, Ecuador*. Journal of global antimicrobial resistance, 2019. **18**: p. 263-268.
220. Rumi, M.V., et al., *Co-occurrence of clinically relevant β -lactamases and MCR-1 encoding genes in Escherichia coli from companion animals in Argentina*. Veterinary microbiology, 2019. **230**: p. 228-234.
221. Lei, L., et al., *mcr-1 in Enterobacteriaceae from companion animals, Beijing, China, 2012–2016*. Emerging infectious diseases, 2017. **23**(4): p. 710.
222. Lima, T., S. Domingues, and G.J. Da Silva, *Plasmid-mediated colistin resistance in Salmonella enterica: a review*. Microorganisms, 2019. **7**(2): p. 55.
223. Wang, Y., et al., *Changes in colistin resistance and mcr-1 abundance in Escherichia coli of animal and human origins following the ban of colistin-positive additives in China: an epidemiological comparative study*. The Lancet Infectious Diseases, 2020. **20**(10): p. 1161-1171.
224. EMA, *Questions and answers on veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally. Outcome of a referral procedure under Article 35 of Directive 2001/82/EC (EMEA/V/A/111)*. 2016: https://www.ema.europa.eu/en/documents/referral/questions-answers-veterinary-medicinal-products-containing-colistin-combination-other-antimicrobial_en.pdf.
225. European Commission, *Union Register of medicinal products. Procedures for nationally authorised veterinary medicinal products. Veterinary medicinal products containing colistin to be administered orally*. 2015: <https://ec.europa.eu/health/documents/community-register/html/vo25478.htm>.
226. WSAVA, *List of Essential Medicines for Cats and Dogs*. 2020: <https://wsava.org/wp-content/uploads/2020/03/WSAVA List of Essential Medicines for Cats and Dogs final.pdf>.
227. Murk, J.-L., *Bacitracin and Gramicidin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
228. Diez-Aguilar, M. and R. Canton, *New microbiological aspects of fosfomycin*. Rev Esp Quimioter, 2019. **32 Suppl 1**: p. 8-18.
229. Raz, R., *Fosfomycin: an old--new antibiotic*. Clin Microbiol Infect, 2012. **18**(1): p. 4-7.
230. Liu, H.Y., et al., *Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan*. J Microbiol Immunol Infect, 2011. **44**(5): p. 364-8.
231. Butcu, M., et al., *In vitro susceptibility of enterococci strains isolated from urine samples to fosfomycin and other antibiotics*. J Infect Chemother, 2011. **17**(4): p. 575-8.
232. Kwan, A.C.F. and N.P. Beahm, *Fosfomycin for bacterial prostatitis: a review*. Int J Antimicrob Agents, 2020. **56**(4): p. 106106.
233. Karaiskos, I., et al., *Oral fosfomycin for the treatment of chronic bacterial prostatitis*. J Antimicrob Chemother, 2019. **74**(5): p. 1430-1437.
234. Falagas, M.E., et al., *Fosfomycin*. Clin Microbiol Rev, 2016. **29**(2): p. 321-47.
235. EMA, *Fosfomycin-containing medicinal products*. 2020: <https://www.ema.europa.eu/en/medicines/human/referrals/fosfomycin-containing-medicinal-products>.
236. Shrestha, N.K. and J.W. Tomford, *Fosfomycin: a review*. Infectious Diseases in Clinical Practice, 2001. **10**(5): p. 255-260.

237. Rigsby, R.E., et al., *Fosfomycin resistance proteins: a nexus of glutathione transferases and epoxide hydrolases in a metalloenzyme superfamily*. *Methods in enzymology*, 2005. **401**: p. 367-379.
238. Lupo, A., et al., *Emergence of bla CTX-M-55 associated with fosA, rmtB and mcr gene variants in Escherichia coli from various animal species in France*. *Journal of Antimicrobial Chemotherapy*, 2018. **73**(4): p. 867-872.
239. Huang, L., Y.Y. Hu, and R. Zhang, *Prevalence of fosfomycin resistance and plasmid-mediated fosfomycin-modifying enzymes among carbapenem-resistant Enterobacteriaceae in Zhejiang, China*. *Journal of medical microbiology*, 2017. **66**(9): p. 1332-1334.
240. Cao, X.-L., et al., *High prevalence of fosfomycin resistance gene fosA3 in bla CTX-M-harboursing Escherichia coli from urine in a Chinese tertiary hospital during 2010–2014*. *Epidemiology & Infection*, 2017. **145**(4): p. 818-824.
241. Wu, D., et al., *Prevalence of fosfomycin resistance in methicillin-resistant Staphylococcus aureus isolated from patients in a university hospital in China, 2013-2015*. *Japanese Journal of Infectious Diseases*, 2018: p. JJID. 2018.013.
242. Ho, P., et al., *Dissemination of plasmid - mediated fosfomycin resistance fosA3 among multidrug - resistant E scherichia coli from livestock and other animals*. *Journal of applied microbiology*, 2013. **114**(3): p. 695-702.
243. Schwarz, S., L.M. Cavaco, and J. Shen, *Antimicrobial Resistance in Bacteria from Livestock and Companion Animals*. 2018: John Wiley & Sons.
244. Jiang, W., et al., *Prevalence of plasmid-mediated fosfomycin resistance gene fosA3 among CTX-M-producing Escherichia coli isolates from chickens in China*. *Foodborne Pathogens and Disease*, 2017. **14**(4): p. 210-218.
245. Xie, M., et al., *Molecular characterization of Escherichia coli strains isolated from retail meat that harbor blaCTX-M and fosA3 genes*. *Antimicrobial agents and chemotherapy*, 2016. **60**(4): p. 2450-2455.
246. Tseng, S.-P., et al., *Characterization of fosfomycin resistant extended-spectrum β -lactamase-producing Escherichia coli isolates from human and pig in Taiwan*. *PLoS One*, 2015. **10**(8): p. e0135864.
247. Yao, H., et al., *The detection of fosfomycin resistance genes in Enterobacteriaceae from pets and their owners*. *Veterinary microbiology*, 2016. **193**: p. 67-71.
248. DiCicco, M., et al., *Fosfomycin susceptibility of canine methicillin-resistant Staphylococcus pseudintermedius isolates*. *Research in veterinary science*, 2014. **96**(2): p. 251-253.
249. ICBMV, *Fosbac Plus T*. last accessed: 2022: <http://www.icbmv.ro/en/veterinary-products-catalog?view=details&id=18138>.
250. Pérez, D.S., M.O. Tapia, and A.L. Soraci, *Fosfomycin: Uses and potentialities in veterinary medicine*. *Open veterinary journal*, 2014. **4**(1): p. 26-43.
251. FAO/WHO, *Evaluation of certain veterinary drug residues in food: eighty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives*. 2020: <https://apps.who.int/iris/handle/10665/330821>.
252. Aoki, T., *Fish Diseases*. 2016: Eolss Publishers Co. Ltd. UK.
253. Ocampo, L. and H. Sumano, *Pharmacokinetics of disodium fosfomycin in the shrimp Litopenaeus vannamei*. *Israel Journal of Veterinary Medicine*, 2010. **65**(1): p. 19.
254. Chiu, T.H., L.Y. Kao, and M.L. Chen, *Antibiotic resistance and molecular typing of P hotobacterium damsela subsp. damsela, isolated from seafood*. *Journal of applied microbiology*, 2013. **114**(4): p. 1184-1192.
255. Kahne, D., et al., *Glycopeptide and lipoglycopeptide antibiotics*. *Chemical reviews*, 2005. **105**(2): p. 425-448.
256. Zuegg, J., et al., *Carbohydrate scaffolds as glycosyltransferase inhibitors with in vivo antibacterial activity*. *Nature communications*, 2015. **6**(1): p. 1-11.
257. Gyssens, I.C. and N.E. Holmes, *Vancomycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
258. Muller, A.E. and I.C. Gyssens, *Teicoplanin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
259. Ghazi, I.M., J.L. Kuti, and D.P. Nicolau, *Telavancin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
260. Monogue, M.L. and D.P. Nicolau, *Dalbavancin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
261. Ahmed, M.O. and K.E. Baptiste, *Vancomycin-resistant enterococci: a review of antimicrobial resistance mechanisms and perspectives of human and animal health*. *Microbial Drug Resistance*, 2018. **24**(5): p. 590-606.

262. Pootoolal, J., J. Neu, and G.D. Wright, *Glycopeptide antibiotic resistance*. Annual review of pharmacology and toxicology, 2002. **42**(1): p. 381-408.
263. Ramos, S., et al., *Genetic characterisation of antibiotic resistance and virulence factors in vanA-containing enterococci from cattle, sheep and pigs subsequent to the discontinuation of the use of avoparcin*. The Veterinary Journal, 2012. **193**(1): p. 301-303.
264. Klare, I., et al., *Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry*. Microbial drug resistance, 1999. **5**(1): p. 45-52.
265. Del Grosso, M., et al., *Detection and characterization of vancomycin-resistant enterococci in farm animals and raw meat products in Italy*. Microbial Drug Resistance, 2000. **6**(4): p. 313-318.
266. Kruse, H., et al., *The use of avoparcin as a growth promoter and the occurrence of vancomycin-resistant Enterococcus species in Norwegian poultry and swine production*. Microbial Drug Resistance, 1999. **5**(2): p. 135-139.
267. Bortolaia, V., et al., *Persistence of vancomycin resistance in multiple clones of Enterococcus faecium isolated from Danish broilers 15 years after the ban of avoparcin*. Antimicrobial agents and chemotherapy, 2015. **59**(5): p. 2926-2929.
268. Wist, V., et al., *Phenotypic and genotypic traits of vancomycin-resistant enterococci from healthy food-producing animals*. Microorganisms, 2020. **8**(2): p. 261.
269. Kwok, G.M.L., et al., *Reduced vancomycin susceptibility in porcine ST9 MRSA isolates*. Frontiers in microbiology, 2013. **4**: p. 316.
270. Bhattacharyya, D., et al., *First report on vancomycin-resistant Staphylococcus aureus in bovine and caprine milk*. Microbial Drug Resistance, 2016. **22**(8): p. 675-681.
271. Guardabassi, L., S. Schwarz, and D.H. Lloyd, *Pet animals as reservoirs of antimicrobial-resistant bacteria*. Journal of antimicrobial chemotherapy, 2004. **54**(2): p. 321-332.
272. Hammerum, A., *Enterococci of animal origin and their significance for public health*. Clinical Microbiology and Infection, 2012. **18**(7): p. 619-625.
273. Torres, C., et al., *Antimicrobial Resistance in Enterococcus spp. of animal origin*. Antimicrobial Resistance in Bacteria from Livestock and Companion Animals, 2018: p. 185-227.
274. Simjee, S., et al., *Characterization of Tn1546 in Vancomycin-Resistant Enterococcus faecium Isolated from Canine Urinary Tract Infections: Evidence of Gene Exchange between Human and Animal Enterococci*. J Clin Microbiol, 2002. **40**(12): p. 4659-4665.
275. Herrero, I.A., et al., *Dogs should be included in surveillance programs for vancomycin-resistant enterococci*. J Clin Microbiol, 2004. **42**(3): p. 1384-5.
276. Manson, J.M., et al., *Characterization of a Vancomycin-Resistant Enterococcus faecalis (VREF) Isolate from a Dog with Mastitis: Further Evidence of a Clonal Lineage of VREF in New Zealand*. J Clin Microbiol, 2003. **41**(7): p. 3331-3333.
277. Orsini, J.A., et al., *Vancomycin for the treatment of methicillin-resistant staphylococcal and enterococcal infections in 15 horses*. Can J Vet Res, 2005. **69**(4): p. 278-86.
278. Nath, S.R., et al., *Rhodococcus equi granulomatous mastitis in an immunocompetent patient*. Journal of medical microbiology, 2013. **62**(8): p. 1253-1255.
279. Giguère, S., et al., *Prevalence of Rhodococcus equi isolates resistant to macrolides or rifampin and outcome of infected foals*. Journal of Veterinary Internal Medicine, 2008. **22**(3): p. 737-737.
280. Fish, R., et al., *Intraperitoneal vancomycin concentrations during peritoneal dialysis-associated peritonitis: correlation with serum levels*. Peritoneal dialysis international, 2012. **32**(3): p. 332-338.
281. Morris, D.O., et al., *Recommendations for approaches to methicillin-resistant staphylococcal infections of small animals: diagnosis, therapeutic considerations and preventative measures. Clinical Consensus Guidelines of the World Association for Veterinary Dermatology*. Veterinary dermatology, 2017. **28**(3): p. 304-e69.
282. BSAVA, *Position statement: Responsible use of antibacterials*. Last accessed: 2022: <https://www.bsava.com/Resources/Veterinary-resources/Position-statements/Responsible-use-of-antibacterials>.
283. Muller, A.E. and I.C. Gyssens, *Daptomycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
284. Bayer, A.S., T. Schneider, and H.G. Sahl, *Mechanisms of daptomycin resistance in Staphylococcus aureus: role of the cell membrane and cell wall*. Annals of the New York Academy of Sciences, 2013. **1277**(1): p. 139-158.
285. Gómez Casanova, N., M. Siller Ruiz, and J.L. Muñoz Bellido, *Mechanisms of resistance to daptomycin in Staphylococcus aureus*. Rev Esp Quimioter, 2017. **30**(6): p. 391-396.

286. Bender, J.K., et al., *Update on prevalence and mechanisms of resistance to linezolid, tigecycline and daptomycin in enterococci in Europe: Towards a common nomenclature*. Drug Resistance Updates, 2018. **40**: p. 25-39.
287. DANMAP, *DANMAP 2019 - Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. 2020: <https://www.danmap.org/reports>.
288. De Jong, A., et al., *Antimicrobial resistance monitoring in commensal enterococci from healthy cattle, pigs and chickens across Europe during 2004–14 (EASSA Study)*. Journal of Antimicrobial Chemotherapy, 2019. **74**(4): p. 921-930.
289. Goldstein, E.J., et al., *The underappreciated in vitro activity of tedizolid against Bacteroides fragilis species, including strains resistant to metronidazole and carbapenems*. Anaerobe, 2017. **43**: p. 1-3.
290. Binyamin, D., et al., *In Vitro Activity of Tedizolid, Dalbavancin, and Ceftobiprole Against Clostridium difficile*. Front Microbiol, 2018. **9**: p. 1256.
291. McCool, R., et al., *Systematic review and network meta-analysis of tedizolid for the treatment of acute bacterial skin and skin structure infections caused by MRSA*. BMC Infect Dis, 2017. **17**(1): p. 39.
292. WHO, *Global tuberculosis report 2018*. . 2018: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports>.
293. Mendes, R.E., L.M. Deshpande, and R.N. Jones, *Linezolid update: stable in vitro activity following more than a decade of clinical use and summary of associated resistance mechanisms*. Drug Resistance Updates, 2014. **17**(1-2): p. 1-12.
294. Van Duijkeren, E., et al., *Mechanisms of Bacterial Resistance to Antimicrobial Agents*. Microbiol Spectr, 2018. **6**(1).
295. EFSA/ECDC, *The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2017/2018*. EFSA Journal, 2020. **18**(3):6007.
296. Freitas, A.R., et al., *Linezolid-resistant (Tn 6246:: fexB-poxA) Enterococcus faecium strains colonizing humans and bovines on different continents: similarity without epidemiological link*. Journal of Antimicrobial Chemotherapy, 2020. **75**(9): p. 2416-2423.
297. Wang, J., et al., *Distribution of the multidrug resistance gene cfr in Staphylococcus isolates from pigs, workers, and the environment of a hog market and a slaughterhouse in Guangzhou, China*. Foodborne pathogens and disease, 2015. **12**(7): p. 598-605.
298. Tyson, G.H., et al., *Novel linezolid resistance plasmids in Enterococcus from food animals in the USA*. Journal of Antimicrobial Chemotherapy, 2018. **73**(12): p. 3254-3258.
299. Elghaieb, H., et al., *Dispersal of linezolid-resistant enterococci carrying poxA or optrA in retail meat and food-producing animals from Tunisia*. Journal of Antimicrobial Chemotherapy, 2019. **74**(10): p. 2865-2869.
300. Shen, J., Y. Wang, and S. Schwarz, *Presence and dissemination of the multiresistance gene cfr in Gram-positive and Gram-negative bacteria*. The Journal of Antimicrobial Chemotherapy, 2013. **68**(8): p. 1697-706.
301. Ruiz-Ripa, L., et al., *Detection of a cfr-positive MRSA CC398 strain in a pig farmer in Spain*. Enfermedades infecciosas y microbiologia clinica (English ed.), 2021. **39**(3): p. 139-141.
302. Paridaens, H., et al., *Clinical case of cfr-positive MRSA CC398 in Belgium*. European Journal of Clinical Microbiology & Infectious Diseases, 2017. **36**(8): p. 1527-1529.
303. Papich, M.G., *Antibiotic treatment of resistant infections in small animals*. Veterinary Clinics: Small Animal Practice, 2013. **43**(5): p. 1091-1107.
304. Lynch, S.A. and K.J. Helbig, *The Complex Diseases of Staphylococcus pseudintermedius in Canines: Where to Next?* Veterinary Sciences, 2021. **8**(1): p. 11.
305. Frank, L.A. and A. Loeffler, *Meticillin - resistant Staphylococcus pseudintermedius: clinical challenge and treatment options*. Veterinary dermatology, 2012. **23**(4): p. 283-e56.
306. Chen, C.M., *Lefamulin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
307. Paukner, S. and R. Riedl, *Pleuromutilins: Potent Drugs for Resistant Bugs-Mode of Action and Resistance*. Cold Spring Harb Perspect Med, 2017. **7**(1).
308. File, T.M., *Treatment of community-acquired pneumonia in adults in the outpatient setting*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
309. Torres, A., et al., *Burden of pneumococcal community-acquired pneumonia in adults across Europe: A literature review*. Respir Med, 2018. **137**: p. 6-13.
310. EMA, *Xenleta (lefamulin). An overview of Xenleta and why it is authorised in the EU (EMA/297995/2020)*. 2020: https://www.ema.europa.eu/en/documents/overview/xenleta-epar-medicine-overview_en.pdf.

311. EMA, *Altargo. Withdrawal of the marketing authorisation in the European Union (EMA/76365/2019)*. 2019: https://www.ema.europa.eu/en/documents/public-statement/public-statement-altargo-withdrawal-marketing-authorisation-european-union_en.pdf.
312. Van Bambeke, F., *Erythromycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
313. Van Bambeke, F., *Roxithromycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
314. Gordon, C.L., *Azithromycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
315. Wenzler, E. and K.A. Rodvold, *Telithromycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
316. Van Ingen, J., *Clarithromycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
317. Graziani, A.L., *Azithromycin and clarithromycin*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
318. Portier, H., et al., *Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for nonsevere community-acquired pneumonia in adults with risk factors*. *Eur J Clin Microbiol Infect Dis*, 2005. **24**(6): p. 367-76.
319. Ortqvist, A., et al., *Oral empiric treatment of community-acquired pneumonia. A multicenter, double-blind, randomized study comparing sparfloxacin with roxithromycin*. *The Scandinavian Sparfloxacin Study Group*. *Chest*, 1996. **110**(6): p. 1499-506.
320. EFSA/ECDC, *The European Union One Health 2019 Zoonoses Report*. *EFSA J*, 2021. **19**(2): p. e06406.
321. ECDC, *Campylobacteriosis. Annual epidemiological report for 2017*. 2019: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-campylobacteriosis.pdf.
322. Dai, L., et al., *New and alternative strategies for the prevention, control, and treatment of antibiotic-resistant Campylobacter*. *Transl Res*, 2020. **223**: p. 76-88.
323. Trott, D.J., et al., *Comparative macrolide use in humans and animals: should macrolides be moved off the World Health Organisation's critically important antimicrobial list?* *J Antimicrob Chemother*, 2021. **76**(8): p. 1955-1961.
324. Pyorala, S., et al., *Macrolides and lincosamides in cattle and pigs: use and development of antimicrobial resistance*. *Vet J*, 2014. **200**(2): p. 230-9.
325. Shen, Z., et al., *Antimicrobial resistance in Campylobacter spp.* *Microbiology spectrum*, 2018. **6**(2): p. 6.2. 11.
326. Florez-Cuadrado, D., et al., *Genome comparison of erythromycin resistant Campylobacter from turkeys identifies hosts and pathways for horizontal spread of erm (B) genes*. *Frontiers in microbiology*, 2017. **8**: p. 2240.
327. Elhadidy, M., et al., *Molecular epidemiology and antimicrobial resistance mechanisms of Campylobacter coli from diarrhoeal patients and broiler carcasses in Belgium*. *Transboundary and emerging diseases*, 2019. **66**(1): p. 463-475.
328. Bolinger, H. and S. Kathariou, *The current state of macrolide resistance in Campylobacter spp.: trends and impacts of resistance mechanisms*. *Applied and environmental microbiology*, 2017. **83**(12): p. e00416-17.
329. EMA/CVMP/SAGAM, *Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMEA/CVMP/SAGAM/741087/2009)*. 2011: <https://www.ema.europa.eu/en/use-macrolides-lincosamides-streptogramins-food-producing-animals-european-union-development>.
330. De Leener, E., et al., *Molecular analysis of human, porcine, and poultry Enterococcus faecium isolates and their erm (B) genes*. *Applied and environmental microbiology*, 2005. **71**(5): p. 2766-2770.
331. Álvarez-Narváez, S., et al., *Epidemiology and Molecular Basis of Multidrug Resistance in Rhodococcus equi*. *Microbiology and Molecular Biology Reviews*, 2021. **85**(2): p. e00011-21.
332. Iannino, F., et al., *Campylobacter and antimicrobial resistance in dogs and humans: "One health" in practice*. *Veterinaria italiana*, 2019. **55**(3): p. 203-220.
333. Whitehouse, C.A., S. Zhao, and H. Tate, *Chapter One - Antimicrobial Resistance in Campylobacter Species: Mechanisms and Genomic Epidemiology*, in *Advances in Applied Microbiology*, S. Sariaslani and G.M. Gadd, Editors. 2018, Academic Press. p. 1-47.
334. EFSA, *Scientific opinion on quantification of the risk posed by broiler meat to human campylobacteriosis in the EU*. *EFSA Journal*, 2010. **8**(1): p. 1437.

335. EFSA, *Assessment of listing and categorisation of animal diseases within the framework of the Animal Health Law (Regulation (EU) No 2016/429): avian mycoplasmosis (Mycoplasma gallisepticum, M. meleagridis)*, in *EFSA Journal*. 2017: <https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4953>.
336. Pieters, M.G. and D. Maes, *Mycoplasmosis. Diseases of swine*, 2019: p. 863-883.
337. Dudek, K., et al., *Mycoplasma bovis infections—Occurrence, diagnosis and control*. *Pathogens*, 2020. **9**(8): p. 640.
338. Gautier-Bouchardon, A.V., *Antimicrobial resistance in Mycoplasma spp.* *Microbiology spectrum*, 2018. **6**(4): p. 6.4. 07.
339. Lysnyansky, I. and R.D. Ayling, *Mycoplasma bovis: mechanisms of resistance and trends in antimicrobial susceptibility*. *Frontiers in microbiology*, 2016. **7**: p. 595.
340. Karuppanan, A.K. and T. Opriessnig, *Lawsonia intracellularis: revisiting the disease ecology and control of this fastidious pathogen in pigs*. *Frontiers in veterinary science*, 2018. **5**: p. 181.
341. Arnold, M., et al., *Prevalence of Lawsonia intracellularis in pig herds in different European countries*. *Porcine health management*, 2019. **5**(1): p. 1-11.
342. Giguère, S., et al., *Diagnosis, treatment, control, and prevention of infections caused by Rhodococcus equi in foals*. *Journal of Veterinary Internal Medicine*, 2011. **25**(6): p. 1209-20.
343. Giguère, S., et al., *In vitro synergy, pharmacodynamics, and postantibiotic effect of 11 antimicrobial agents against Rhodococcus equi*. *Vet Microbiol*, 2012. **160**(1-2): p. 207-13.
344. Venner, M., et al., *Efficacy of mass antimicrobial treatment of foals with subclinical pulmonary abscesses associated with Rhodococcus equi*. *J Vet Intern Med*, 2013. **27**(1): p. 171-6.
345. Ettinger, S., *Textbook of veterinary internal medicine : diseases of the dog and the cat, 8th edition*. 2018: Elsevier, Philadelphia.
346. Möstl, K., et al., *Something old, something new: update of the 2009 and 2013 ABCD guidelines on prevention and management of feline infectious diseases*. *Journal of feline medicine and surgery*, 2015. **17**(7): p. 570-582.
347. Kuijper, E.J., *Fidaxomicin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
348. van Prehn, J., et al., *European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults*. *Clin Microbiol Infect*, 2021. **27 Suppl 2**: p. S1-S21.
349. Okumura, H., et al., *Fidaxomicin compared with vancomycin and metronidazole for the treatment of Clostridioides (Clostridium) difficile infection: A network meta-analysis*. *J Infect Chemother*, 2020. **26**(1): p. 43-50.
350. Cassini, A., et al., *Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study*. *PLoS Med*, 2016. **13**(10): p. e1002150.
351. EMA, *Dificlir - Assessment report (EMA/857570/2011)*. 2011: https://www.ema.europa.eu/en/documents/assessment-report/dificlir-epar-public-assessment-report_en.pdf.
352. Leeds, J.A., et al., *In vitro selection, via serial passage, of Clostridium difficile mutants with reduced susceptibility to fidaxomicin or vancomycin*. *Journal of Antimicrobial Chemotherapy*, 2014. **69**(1): p. 41-44.
353. Sholeh, M., et al., *Antimicrobial resistance in Clostridioides (Clostridium) difficile derived from humans: a systematic review and meta-analysis*. *Antimicrobial Resistance & Infection Control*, 2020. **9**(1): p. 1-11.
354. Goldstein, E.J., F. Babakhani, and D.M. Citron, *Antimicrobial activities of fidaxomicin*. *Clinical infectious diseases*, 2012. **55**(suppl_2): p. S143-S148.
355. Rodriguez, C., et al., *Clostridium difficile in Food and Animals: A Comprehensive Review*, in *Advances in Microbiology, Infectious Diseases and Public Health: Volume 4*, G. Donelli, Editor. 2016, Springer International Publishing: Cham. p. 65-92.
356. Weese, J.S., *Clostridium (Clostridioides) difficile in animals*. *Journal of veterinary diagnostic investigation*, 2020. **32**(2): p. 213-221.
357. Hernandez, B.G., et al., *Prevalence, Colonization, Epidemiology, and Public Health Significance of Clostridioides difficile in Companion Animals*. *Frontiers in Veterinary Science*, 2020. **7**: p. 663.
358. Rabold, D., et al., *The zoonotic potential of Clostridium difficile from small companion animals and their owners*. *PLoS one*, 2018. **13**(2): p. e0193411.
359. Pirš, T., et al., *Antimicrobial susceptibility of animal and human isolates of Clostridium difficile by broth microdilution*. *Journal of medical microbiology*, 2013. **62**(9): p. 1478-1485.
360. Spigaglia, P., et al., *Antibiotic resistance patterns and PCR-ribotyping of Clostridium difficile strains isolated from swine and dogs in Italy*. *Anaerobe*, 2015. **31**: p. 42-46.

361. Kachrimanidou, M., E. Tzika, and G. Filioussis, *Clostridioides (Clostridium) difficile in food-producing animals, horses and household pets: a comprehensive review*. Microorganisms, 2019. **7**(12): p. 667.
362. Diab, S.S., G. Songer, and F.A. Uzal, *Clostridium difficile infection in horses: a review*. Veterinary microbiology, 2013. **167**(1-2): p. 42-49.
363. Johnson, M., *Clindamycin: An overview*. In UpToDate. UpToDate. 2021, Waltham, MA: Post TW (Ed).
364. Danziger, L., *Clindamycin and Lincomycin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
365. ECDC, *Surveillance Atlas of Infectious Disease*. Last accessed: 2022: <https://atlas.ecdc.europa.eu/public/index.aspx>.
366. Wilson, K.H., *Treatment of anthrax*. In UpToDate. UpToDate. 2021, Waltham, MA: Post TW (Ed).
367. Frasca, D., *Quinupristin-Dalfopristin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
368. Frasca, D., *Pristinamycin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
369. WHO, *Critically important antimicrobials for human medicine : categorization for the development of risk management strategies to contain antimicrobial resistance due to non-human antimicrobial use : report of the second WHO Expert Meeting, Copenhagen, 29-31 May 2007*. 2007: <https://apps.who.int/iris/handle/10665/43765>.
370. Sojo-Dorado, J. and J. Rodríguez-Baño, *Gentamicin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
371. Nesbitt, W.J. and D. Aronoff, *Amikacin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
372. Gálvez-Acebal, J. and J. Rodríguez-Baño, *Tobramycin*, in Kucers' *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
373. Hanberger, H., et al., *Rational use of aminoglycosides--review and recommendations by the Swedish Reference Group for Antibiotics (SRGA)*. Scand J Infect Dis, 2013. **45**(3): p. 161-75.
374. Gonzalez, L.S., 3rd and J.P. Spencer, *Aminoglycosides: a practical review*. Am Fam Physician, 1998. **58**(8): p. 1811-20.
375. Germovsek, E., C.I. Barker, and M. Sharland, *What do I need to know about aminoglycoside antibiotics?* Arch Dis Child Educ Pract Ed, 2017. **102**(2): p. 89-93.
376. Ahtela, E., et al., *Occurrence of fatal infective endocarditis: a population-based study in Finland*. BMC Infect Dis, 2019. **19**(1): p. 987.
377. Van Duijkeren, E., et al., *The use of aminoglycosides in animals within the EU: development of resistance in animals and possible impact on human and animal health: a review*. Journal of Antimicrobial Chemotherapy, 2019. **74**(9): p. 2480-2496.
378. EMA/CVMP/AWP, *Reflection paper on use of aminoglycosides in animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/AWP/721118/2014)*. 2018: <https://www.ema.europa.eu/en/use-aminoglycosides-animals-european-union-development-resistance-impact-human-animal-health>.
379. Ramirez, M.S. and M.E. Tolmasky, *Aminoglycoside modifying enzymes*. Drug Resistance Updates, 2010. **13**(6): p. 151-171.
380. Roberts, M.C., S. Schwarz, and H.J. Aarts, *Erratum: Acquired antibiotic resistance genes: an overview*. Frontiers in microbiology, 2012. **3**: p. 384.
381. Ramirez, M.S., N. Nikolaidis, and M.E. Tolmasky, *Rise and dissemination of aminoglycoside resistance: the aac (6')-Ib paradigm*. Frontiers in microbiology, 2013. **4**.
382. Du, X.D., et al., *Plasmid-mediated ArmA and RmtB 16S rRNA methylases in Escherichia coli isolated from chickens*. J Antimicrob Chemother, 2009. **64**(6): p. 1328-30.
383. Davis, M.A., et al., *Discovery of a gene conferring multiple-aminoglycoside resistance in Escherichia coli*. Antimicrobial agents and chemotherapy, 2010. **54**(6): p. 2666-2669.
384. Chen, L., et al., *Emergence of RmtB methylase-producing Escherichia coli and Enterobacter cloacae isolates from pigs in China*. J Antimicrob Chemother, 2007. **59**(5): p. 880-5.
385. Cohen, K., W. Bishai, and A. Pym, *Molecular Basis of Drug Resistance in Mycobacterium tuberculosis*. Microbiology spectrum, 2014. **2**(3).
386. Jensen, V.F., et al., *Correlation between apramycin and gentamicin use in pigs and an increasing reservoir of gentamicin-resistant Escherichia coli*. Journal of Antimicrobial Chemotherapy, 2006. **58**(1): p. 101-107.
387. Herrero-Fresno, A., et al., *Apramycin treatment affects selection and spread of a multidrug-resistant Escherichia coli strain able to colonize the human gut in the intestinal microbiota of pigs*. Veterinary research, 2016. **47**(1): p. 1-10.

388. Wendlandt, S., et al., *Transmission of methicillin-resistant Staphylococcus aureus isolates on broiler farms*. Vet Microbiol, 2013.
389. Hall, R.M., *Salmonella genomic islands and antibiotic resistance in Salmonella enterica*. Future microbiology, 2010. **5**(10): p. 1525-1538.
390. García, P., et al., *Diversity of plasmids encoding virulence and resistance functions in Salmonella enterica subsp. enterica serovar Typhimurium monophasic variant 4,[5], 12: i:- strains circulating in Europe*. PLoS one, 2014. **9**(2): p. e89635.
391. Meistere, I., et al., *Campylobacter species prevalence, characterisation of antimicrobial resistance and analysis of whole-genome sequence of isolates from livestock and humans, Latvia, 2008 to 2016*. Eurosurveillance, 2019. **24**(31): p. 1800357.
392. EFSA, *Assessment of animal diseases caused by bacteria resistant to antimicrobials: Poultry*, in *EFSA Journal*. 2021: <https://www.efsa.europa.eu/en/efsajournal/pub/9981>.
393. Dowling, P.M., *Aminoglycosides and Aminocyclitols. Principles of Antimicrobial Drug Selection and Use*. In: *Antimicrobial Therapy in Veterinary Medicine*. Eds. Giguère, S., J.F. Prescott, and P.M. Dowling. 5th edition. 2013, Wiley Blackwell, Ames, Iowa, USA, Oxford. p. 233-255.
394. Bush, K., *Plazomicin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
395. Clark, J.A. and D.S. Burgess, *Plazomicin: a new aminoglycoside in the fight against antimicrobial resistance*. Therapeutic Advances in Infectious Disease, 2020. **7**: p. 2049936120952604.
396. Shaeer, K.M., et al., *Plazomicin: A Next - Generation Aminoglycoside*. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2019. **39**(1): p. 77-93.
397. Deng, Y., et al., *F33:A-B- and F2:A-B- plasmids mediate dissemination of rmtB-blaCTX-M-9 group genes and rmtB-qepA in Enterobacteriaceae isolates from pets in China*. Antimicrob Agents Chemother, 2011. **55**(10): p. 4926-9.
398. Hopkins, K.L., et al., *16S rRNA methyltransferase RmtC in Salmonella enterica serovar Virchow*. Emerg Infect Dis, 2010. **16**(4): p. 712-5.
399. Liu, J.-H., et al., *Coprevalence of plasmid-mediated quinolone resistance determinants QepA, Qnr, and AAC (6')-Ib-cr among 16S rRNA methylase RmtB-producing Escherichia coli isolates from pigs*. Antimicrobial agents and chemotherapy, 2008. **52**(8): p. 2992-2993.
400. Wendlandt, S., et al., *The diversity of antimicrobial resistance genes among staphylococci of animal origin*. Int J Med Microbiol, 2013. **303**(6-7): p. 338-49.
401. Wachino, J.-i. and Y. Arakawa, *Exogenously acquired 16S rRNA methyltransferases found in aminoglycoside-resistant pathogenic Gram-negative bacteria: an update*. Drug Resistance Updates, 2012. **15**(3): p. 133-148.
402. Liu, B.-T., et al., *Prevalence of β -lactamase and 16S rRNA methylase genes among clinical Escherichia coli isolates carrying plasmid-mediated quinolone resistance genes from animals*. Microbial Drug Resistance, 2013. **19**(3): p. 237-245.
403. Xia, J., et al., *Persistent spread of the rmtB 16S rRNA methyltransferase gene among Escherichia coli isolates from diseased food-producing animals in China*. Veterinary Microbiology, 2016. **188**: p. 41-46.
404. Mouton, J.W., *Spectinomycin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
405. Unemo, M., et al., *2020 European guideline for the diagnosis and treatment of gonorrhoea in adults*. Int J STD AIDS, 2020: p. 956462420949126.
406. May, D.B., *Tetracyclines*. In: *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
407. Grayson, M.L., *Tetracyclines and Related Drugs*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
408. Randel, A., *H. pylori Infection: ACG Updates Treatment Recommendations*. Am Fam Physician, 2018. **97**(2): p. 135-137.
409. Internet Medicin. *Brucellosis*. Last accessed: 2022.
410. Olson, M.W., et al., *Functional, biophysical, and structural bases for antibacterial activity of tigecycline*. Antimicrobial agents and chemotherapy, 2006. **50**(6): p. 2156-2166.
411. Doan, T.-L., et al., *Tigecycline: a glycylicycline antimicrobial agent*. Clinical therapeutics, 2006. **28**(8): p. 1079-1106.
412. Nabuurs-Franssen, M.H., *Tigecycline*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
413. EMA, *Use of glycylicyclines in animals in the European Union: development of resistance and possible impact on human and animal health (EMA/291760/2013)*. 2013: https://www.ema.europa.eu/en/documents/report/use-glycylicyclines-animals-european-union-development-resistance-possible-impact-human-animal-health_en.pdf.

414. He, T., et al., *Emergence of plasmid-mediated high-level tigecycline resistance genes in animals and humans*. *Nature microbiology*, 2019. **4**(9): p. 1450-1456.
415. Bai, L., et al., *Detection of plasmid-mediated tigecycline-resistant gene tet (X4) in Escherichia coli from pork, Sichuan and Shandong Provinces, China, February 2019*. *Eurosurveillance*, 2019. **24**(25): p. 1900340.
416. McAleese, F., et al., *A novel MATE family efflux pump contributes to the reduced susceptibility of laboratory-derived Staphylococcus aureus mutants to tigecycline*. *Antimicrob Agents Chemother*, 2005. **49**(5): p. 1865-71.
417. Sader, H.S., et al., *Tigecycline activity tested against carbapenem-resistant Enterobacteriaceae from 18 European nations: results from the SENTRY surveillance program (2010–2013)*. *Diagnostic microbiology and infectious disease*, 2015. **83**(2): p. 183-186.
418. Jean-Pierre, H., et al., *Tigecycline: CMI 50/90 towards 1766 Gram-negative bacilli (3rd generation cephalosporins resistant Enterobacteriaceae), Acinetobacter baumannii and Bacteroides fragilis group, University Hospital-Montpellier, 2008-2011*. *Pathologie-biologie*, 2013. **61**(6): p. 282-285.
419. Ovejero, C.M., et al., *Highly tigecycline-resistant Klebsiella pneumoniae sequence type 11 (ST11) and ST147 isolates from companion animals*. *Antimicrobial agents and chemotherapy*, 2017. **61**(6).
420. Sato, T., et al., *Tigecycline susceptibility of Klebsiella pneumoniae complex and Escherichia coli isolates from companion animals: the prevalence of tigecycline-nonsusceptible K. pneumoniae complex, including internationally expanding human pathogenic lineages*. *Microbial Drug Resistance*, 2018. **24**(6): p. 860-867.
421. Cunha, B.A., J. Baron, and C.B. Cunha, *Similarities and differences between doxycycline and minocycline: clinical and antimicrobial stewardship considerations*. *Eur J Clin Microbiol Infect Dis*, 2018. **37**(1): p. 15-20.
422. Grayson, M.L., *Minocycline*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
423. Rodvold, K.A., *Eravacycline*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
424. Wang, L., et al., *Novel Plasmid-Mediated tet (X5) Gene Conferring Resistance to Tigecycline, Eravacycline, and Omadacycline in a Clinical Acinetobacter baumannii Isolate*. *Antimicrobial agents and chemotherapy*, 2019. **64**(1).
425. Boukthir, S., et al., *In vitro activity of eravacycline and mechanisms of resistance in enterococci*. *International Journal of Antimicrobial Agents*, 2020. **56**(6): p. 106215.
426. Mouton, J.W., *Omadacycline*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
427. Stets, R., et al., *Omadacycline for Community-Acquired Bacterial Pneumonia*. *N Engl J Med*, 2019. **380**(6): p. 517-527.
428. O'Riordan, W., et al., *Omadacycline for Acute Bacterial Skin and Skin-Structure Infections*. *N Engl J Med*, 2019. **380**(6): p. 528-538.
429. Dougherty, J.A., et al., *Omadacycline: A New Tetracycline Antibiotic*. *Ann Pharmacother*, 2019. **53**(5): p. 486-500.
430. MacLaren, G., *Chloramphenicol and Thiamphenicol*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
431. WHO, *Integrated Management of Childhood Illness: Chart Booklet*. 2014: <https://www.who.int/docs/default-source/mca-documents/imci-chart-booklet.pdf>.
432. Holmes, N.E. and M.L. Grayson, *Sulfonamides*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
433. Trubiano, J.A. and M.L. Grayson, *Trimethoprim and Trimethoprim-Sulfamethoxazole (Cotrimoxazole)*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
434. May, D.B., *Trimethoprim-sulfamethoxazole: An overview*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
435. Spelman, D., *Treatment of nocardiosis*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
436. Pereira-Diaz, E., et al., *Changing Trends in the Epidemiology and Risk Factors of Pneumocystis Pneumonia in Spain*. *Front Public Health*, 2019. **7**: p. 275.
437. Eliopoulos, G.M. and P. Huovinen, *Resistance to Trimethoprim-Sulfamethoxazole*. *Clinical Infectious Diseases*, 2001. **32**(11): p. 1608-1614.
438. Huang, L., et al., *HIV-associated Pneumocystis pneumonia*. *Proceedings of the American Thoracic Society*, 2011. **8**(3): p. 294-300.

439. Valdezate, S., et al., *Resistance gene pool to co-trimoxazole in non-susceptible Nocardia strains*. *Frontiers in Microbiology*, 2015. **6**: p. 376.
440. Sköld, O., *Resistance to trimethoprim and sulfonamides*. *Veterinary research*, 2001. **32**(3-4): p. 261-273.
441. Hammerum, A.M., et al., *Detection of sul1, sul2 and sul3 in sulphonamide resistant Escherichia coli isolates obtained from healthy humans, pork and pigs in Denmark*. *International journal of food microbiology*, 2006. **106**(2): p. 235-237.
442. Condas, L.A., et al., *Molecular identification and antimicrobial susceptibility of Nocardia spp. isolated from bovine mastitis in Brazil*. *Veterinary microbiology*, 2013. **167**(3-4): p. 708-712.
443. Brown-Elliott, B.A., et al., *Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy*. *Clinical microbiology reviews*, 2006. **19**(2): p. 259-282.
444. Papich, M.G., *Papich Handbook of Veterinary Drugs. 5th edition*. 2020: Elsevier Health Sciences.
445. Riviere, J.E. and M.G. Papich, *Veterinary pharmacology and therapeutics. 10th edition*. 2018: John Wiley & Sons.
446. FVE, *Antimicrobial use in food-producing animals (Annex A of the RONAFSA opinion)*. 2017: https://www.ema.europa.eu/documents/report/annex-replies-efsa/ema-questions-use-antimicrobials-food-producing-animals-eu-possible-measures-reduce-antimicrobial_en.pdf.
447. McCormack, J., *Nalidixic Acid and Other Quinolones*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
448. King, D.E., R. Malone, and S.H. Lilley, *New classification and update on the quinolone antibiotics*. *Am Fam Physician*, 2000. **61**(9): p. 2741-8.
449. EMA, *Quinolone- and fluoroquinolone-containing medicinal products*. 2018: <https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products>.
450. Hooper, D.C., *Fluoroquinolones*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
451. Goldstein, E.J., et al., *In vitro activity of moxifloxacin against 923 anaerobes isolated from human intra-abdominal infections*. *Antimicrob Agents Chemother*, 2006. **50**(1): p. 148-55.
452. ECDC, *Tuberculosis. Annual epidemiological report for 2019*. 2021: <https://www.ecdc.europa.eu/sites/default/files/documents/AER-TB-2019.pdf>.
453. Ruiz, J., *Transferable mechanisms of quinolone resistance from 1998 onward*. *Clinical microbiology reviews*, 2019. **32**(4): p. e00007-19.
454. Robicsek, A., G.A. Jacoby, and D.C. Hooper, *The worldwide emergence of plasmid-mediated quinolone resistance*. *The Lancet Infectious Diseases*, 2006. **6**(10): p. 629-640.
455. Hansen, L.H., et al., *Substrate specificity of the OqxAB multidrug resistance pump in Escherichia coli and selected enteric bacteria*. *Journal of Antimicrobial Chemotherapy*, 2007. **60**(1): p. 145-147.
456. De Jong, A., et al., *Characterization of quinolone resistance mechanisms in Enterobacteriaceae isolated from companion animals in Europe (ComPath II study)*. *Veterinary microbiology*, 2018. **216**: p. 159-167.
457. Veldman, K., et al., *International collaborative study on the occurrence of plasmid-mediated quinolone resistance in Salmonella enterica and Escherichia coli isolated from animals, humans, food and the environment in 13 European countries*. *J Antimicrob Chemother*, 2011. **66**(6): p. 1278-86.
458. Singleton, D.A., et al., *Temporal, Spatial, and Genomic Analyses of Enterobacteriaceae Clinical Antimicrobial Resistance in Companion Animals Reveals Phenotypes and Genotypes of One Health Concern*. *Frontiers in Microbiology*, 2021. **12**.
459. Luo, N., et al., *In vivo selection of Campylobacter isolates with high levels of fluoroquinolone resistance associated with gyrA mutations and the function of the CmeABC efflux pump*. *Antimicrobial agents and chemotherapy*, 2003. **47**(1): p. 390-394.
460. Lin, D., et al., *Characterization of antimicrobial resistance of Pseudomonas aeruginosa isolated from canine infections*. *Journal of applied microbiology*, 2012. **113**(1): p. 16-23.
461. Wu, T., et al., *Molecular epidemiology of nalidixic acid-resistant campylobacter isolates from humans and poultry by pulsed-field gel electrophoresis and flagellin gene analysis*. *Epidemiology & Infection*, 2002. **129**(1): p. 227-231.
462. Johnson, J.R., et al., *Similarity between human and chicken Escherichia coli isolates in relation to ciprofloxacin resistance status*. *The Journal of infectious diseases*, 2006. **194**(1): p. 71-78.
463. Platell, J.L., et al., *Commonality among fluoroquinolone-resistant sequence type ST131 extraintestinal Escherichia coli isolates from humans and companion animals in Australia*. *Antimicrobial agents and chemotherapy*, 2011. **55**(8): p. 3782-3787.
464. Klein, U., et al., *New antimicrobial susceptibility data from monitoring of Mycoplasma bovis isolated in Europe*. *Veterinary microbiology*, 2019. **238**: p. 108432.

465. Marques, C., et al., *European multicenter study on antimicrobial resistance in bacteria isolated from companion animal urinary tract infections*. BMC veterinary research, 2016. **12**(1): p. 213.
466. Robbins, S.N., et al., *Antimicrobial prescribing practices in small animal emergency and critical care*. Frontiers in veterinary science, 2020. **7**: p. 110.
467. Huttner, A. and A. Stewardson, *Nitrofurans: Nitrofurazone, Furazidine, and Nitrofurantoin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
468. Zhuge, L., et al., *Furazolidone treatment for Helicobacter Pylori infection: A systematic review and meta-analysis*. Helicobacter, 2018. **23**(2): p. e12468.
469. Murray, B.E., *The life and times of the Enterococcus*. Clin Microbiol Rev, 1990. **3**(1): p. 46-65.
470. EMA, *List of nationally authorised medicinal products. Active substance: nitrofurantoin / nifurtoinol (EMA/230060/2016)*. 2015: https://www.ema.europa.eu/en/documents/psusa/nitrofurantoin/nifurtoinol-list-nationally-authorized-medicinal-products-psusa/00002174/201502_en.pdf.
471. Chua, K.Y.L., *Metronidazole*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
472. Johnson, M., *Metronidazole: An overview*. In: *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
473. Lofmark, S., C. Edlund, and C.E. Nord, *Metronidazole is still the drug of choice for treatment of anaerobic infections*. Clin Infect Dis, 2010. **50 Suppl 1**: p. S16-23.
474. Dingsdag, S.A. and N. Hunter, *Metronidazole: an update on metabolism, structure–cytotoxicity and resistance mechanisms*. Journal of Antimicrobial Chemotherapy, 2017.
475. Alauzet, C., A. Lozniewski, and H. Marchandin, *Metronidazole resistance and nim genes in anaerobes: A review*. Anaerobe, 2019. **55**: p. 40-53.
476. Alauzet, C., et al., *Metronidazole resistance in Prevotella spp. and description of a new nim gene in Prevotella baroniae*. Antimicrobial agents and chemotherapy, 2010. **54**(1): p. 60-64.
477. Boekhoud, I.M., et al., *Plasmid-mediated metronidazole resistance in Clostridioides difficile*. Nature communications, 2020. **11**(1): p. 1-12.
478. Orden, C., et al., *Isolation of Clostridium difficile from dogs with digestive disorders, including stable metronidazole-resistant strains*. Anaerobe, 2017. **43**: p. 78-81.
479. Lawhon, S., A. Taylor, and V. Fajt, *Frequency of resistance in obligate anaerobic bacteria isolated from dogs, cats, and horses to antimicrobial agents*. Journal of Clinical Microbiology, 2013. **51**(11): p. 3804-3810.
480. Andersen, S.R., et al., *Metronidazole resistance in Campylobacter jejuni from poultry meat*. Journal of food protection, 2006. **69**(4): p. 932-934.
481. Andrés-Lasheras, S., et al., *Preliminary studies on isolates of Clostridium difficile from dogs and exotic pets*. BMC veterinary research, 2018. **14**(1): p. 1-8.
482. Thitaram, S., et al., *Antimicrobial susceptibility of Clostridium difficile isolated from food animals on farms*. International journal of food microbiology, 2016. **227**: p. 1-5.
483. Knight, D.R. and T.V. Riley, *Genomic delineation of zoonotic origins of Clostridium difficile*. Frontiers in public health, 2019. **7**: p. 164.
484. Bush, M., et al., *The effect of time until surgical intervention on survival in dogs with secondary septic peritonitis*. The Canadian Veterinary Journal, 2016. **57**(12): p. 1267.
485. Abelson, A.L., G.J. Buckley, and E.A. Rozanski, *Positive impact of an emergency department protocol on time to antimicrobial administration in dogs with septic peritonitis*. Journal of Veterinary Emergency and Critical Care, 2013. **23**(5): p. 551-556.
486. Ganz, H., D. Kingsbury, and E. Barber, *Rethinking the role of metronidazole in veterinary medicine*, in *Innovative Veterinary Care*. 2021: <https://ivcjournal.com/metronidazole-veterinary-medicine/>.
487. Tsuyuki, Y., et al., *Antimicrobial susceptibility patterns of anaerobic bacteria identified from clinical specimens of diseased dogs and cats*. Journal of Veterinary Medical Science, 2020: p. 20-0294.
488. Brook, I., H.M. Wexler, and E.J. Goldstein, *Antianaerobic antimicrobials: spectrum and susceptibility testing*. Clinical Microbiology Reviews, 2013. **26**(3): p. 526-546.
489. Davis, J.L., *Treatment of peritonitis*. Veterinary Clinics: Equine Practice, 2003. **19**(3): p. 765-778.
490. Berlin, D., et al., *Successful medical management of intra-abdominal abscesses in 4 adult horses*. The Canadian Veterinary Journal, 2013. **54**(2): p. 157.
491. Fish, D.N., *Meropenem in the treatment of complicated skin and soft tissue infections*. Therapeutics and clinical risk management, 2006. **2**(4): p. 401.
492. Di Bella, S., et al., *Antimicrobial stewardship: from bedside to theory. thirteen examples of old and more recent strategies from everyday clinical practice*. Antibiotics, 2020. **9**(7): p. 398.

493. Mankin, J.M., *Top 5 Antibiotics for Neurologic Infections in Dogs*. Clinicians brief, 2017. **23**(1): p. 83-86.
494. Elce, Y.A., *Infections in the equine abdomen and pelvis: perirectal abscesses, umbilical infections, and peritonitis*. Veterinary Clinics: Equine Practice, 2006. **22**(2): p. 419-436.
495. Kuroda, T., et al., *Single-dose pharmacokinetics of orally administered metronidazole and intravenously administered imipenem in healthy horses and computer-based simulation of pleural fluid concentrations with multiple dosing*. American Journal of Veterinary Research, 2020. **81**(10): p. 783-789.
496. Kinoshita, Y., et al., *Dominant obligate anaerobes revealed in lower respiratory tract infection in horses by 16S rRNA gene sequencing*. Journal of Veterinary Medical Science, 2014. **76**(4): p. 587-591.
497. Adams, R.A., et al., *Rifamycin antibiotics and the mechanisms of their failure*. The Journal of Antibiotics, 2021. **74**(11): p. 786-798.
498. Yamori, S., et al., *Bacteriostatic and bactericidal activity of antituberculosis drugs against Mycobacterium tuberculosis, Mycobacterium avium-Mycobacterium intracellulare complex and Mycobacterium kansasii in different growth phases*. Microbiol Immunol, 1992. **36**(4): p. 361-8.
499. Torres-Tortosa, M., et al., *Prognosis and clinical evaluation of infection caused by Rhodococcus equi in HIV-infected patients: a multicenter study of 67 cases*. Chest, 2003. **123**(6): p. 1970-6.
500. GHDE. *Global Health Data Exchange. GBD Results Tool*. 2019; Available from: <http://ghdx.healthdata.org/gbd-results-tool>.
501. Thornsberry, C., et al., *Rifampin: spectrum of antibacterial activity*. Reviews of infectious diseases, 1983. **5**(Supplement_3): p. S412-S417.
502. Goldstein, B.P., *Resistance to rifampicin: a review*. The Journal of antibiotics, 2014. **67**(9): p. 625-630.
503. Kadlec, K., et al., *Molecular basis of rifampicin resistance in methicillin-resistant Staphylococcus pseudintermedius isolates from dogs*. Journal of antimicrobial chemotherapy, 2011. **66**(6): p. 1236-1242.
504. Riesenber, A., et al., *MICs of 32 antimicrobial agents for Rhodococcus equi isolates of animal origin*. Journal of Antimicrobial Chemotherapy, 2014. **69**(4): p. 1045-1049.
505. EFSA/ECDC, *The European Union One Health 2020 Zoonoses Report*. EFSA Journal, 2021. **19**(12): p. e06971.
506. Franco, M.M.J., et al., *Genotyping and rifampicin and isoniazid resistance in Mycobacterium bovis strains isolated from the lymph nodes of slaughtered cattle*. Tuberculosis, 2017. **104**: p. 30-37.
507. Li, J., et al., *Molecular basis of rifampicin resistance in multiresistant porcine livestock-associated MRSA*. Journal of Antimicrobial Chemotherapy, 2016. **71**(11): p. 3313-3315.
508. Esteban, J. and M.-C. Muñoz-Egea, *Mycobacterium bovis and other uncommon members of the Mycobacterium tuberculosis complex*. Tuberculosis and Nontuberculous Mycobacterial Infections, 2017: p. 753-765.
509. Olea-Popelka, F., et al., *Zoonotic tuberculosis in human beings caused by Mycobacterium bovis—a call for action*. The Lancet Infectious Diseases, 2017. **17**(1): p. e21-e25.
510. Ramos, B., et al., *Estimates of the global and continental burden of animal tuberculosis in key livestock species worldwide: A meta-analysis study*. One Health, 2020. **10**: p. 100169.
511. Lloret, A., et al., *ABCD guidelines on prevention and management*. Journal of Feline Medicine and Surgery, 2013. **15**: p. 624-627.
512. Mitchell, J.L. and D.A. Gunn-Moore, *Mycobacterial infections in cats and dogs*. Veterinary Nursing Journal, 2019. **34**(4): p. 102-107.
513. HAIRS, *Human Animal Infections and Risk Surveillance (HAIRS) group. Qualitative assessment of the risk that cats infected with Mycobacterium bovis present to human health*. 2014: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/457151/M_bovis_cats_Risk_Assessment_Web_FINAL.pdf.
514. Stewart, A., et al., *Rhodococcus equi infection: A diverse spectrum of disease*. IDCases, 2019. **15**: p. e00487.
515. Venner, M., et al., *Failure of antimicrobial therapy to accelerate spontaneous healing of subclinical pulmonary abscesses on a farm with endemic infections caused by Rhodococcus equi*. Vet J, 2012. **192**(3): p. 293-8.
516. Venner, M., et al., *Comparison of tulathromycin, azithromycin and azithromycin-rifampin for the treatment of mild pneumonia associated with Rhodococcus equi*. Vet Rec, 2013. **173**(16): p. 397.

517. Hildebrand, F., M. Venner, and S. Giguère, *Efficacy of gamithromycin for the treatment of foals with mild to moderate bronchopneumonia*. Journal of veterinary internal medicine, 2015. **29**(1): p. 333-338.
518. Rutenberg, D., M. Venner, and S. Giguère, *Efficacy of tulathromycin for the treatment of foals with mild to moderate bronchopneumonia*. Journal of veterinary internal medicine, 2017. **31**(3): p. 901-906.
519. Wetzig, M., M. Venner, and S. Giguère, *Efficacy of the combination of doxycycline and azithromycin for the treatment of foals with mild to moderate bronchopneumonia*. Equine veterinary journal, 2020. **52**(4): p. 613-619.
520. WHO, *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment*. 2020: <https://www.who.int/publications/i/item/9789240007048>.
521. Zhang, Y. and W. Yew, *Mechanisms of drug resistance in Mycobacterium tuberculosis [State of the art series. Drug-resistant tuberculosis. Edited by CY. Chiang. Number 1 in the series]*. The International Journal of Tuberculosis and Lung Disease, 2009. **13**(11): p. 1320-1330.
522. Nguyen, T.V.A., et al., *Bedaquiline resistance: its emergence, mechanism, and prevention*. Clinical Infectious Diseases, 2018. **66**(10): p. 1625-1630.
523. Palomino, J.C. and A. Martin, *Drug resistance mechanisms in Mycobacterium tuberculosis*. Antibiotics, 2014. **3**(3): p. 317-340.
524. Zhang, Y. and W. Yew, *Mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015*. The International Journal of Tuberculosis and Lung Disease, 2015. **19**(11): p. 1276-1289.
525. Botelho, A., et al., *Pre-multidrug-resistant Mycobacterium tuberculosis Beijing strain associated with disseminated tuberculosis in a pet dog*. Journal of clinical microbiology, 2014. **52**(1): p. 354-356.
526. Lloret, A., et al., *Mycobacterioses in cats: ABCD guidelines on prevention and management*. Journal of feline medicine and surgery, 2013. **15**(7): p. 591-597.
527. Falzon, D., et al., *World Health Organization treatment guidelines for drug-resistant tuberculosis, 2016 update*. Eur Respir J, 2017. **49**(3).
528. Cholo, M.C., et al., *Mechanisms of action and therapeutic efficacies of the lipophilic antimycobacterial agents clofazimine and bedaquiline*. J Antimicrob Chemother, 2017. **72**(2): p. 338-353.
529. Scollard, D., B. Stryjewska, and M. Dacso, *Leprosy: Treatment and prevention*. 2021: UpToDate.
530. Nimmo, C., et al., *Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa: a phenotypic and phylogenetic analysis*. Lancet Microbe, 2020. **1**(4): p. e165-e174.
531. WHO, *Leprosy (Hansen's disease)*. 2021: <https://www.who.int/news-room/fact-sheets/detail/leprosy>.
532. Hartkoorn, R.C., S. Uplekar, and S.T. Cole, *Cross-resistance between clofazimine and bedaquiline through upregulation of MmpL5 in Mycobacterium tuberculosis*. Antimicrob Agents Chemother, 2014. **58**(5): p. 2979-81.
533. Yew, W.W., et al., *Molecular mechanisms of clofazimine resistance in Mycobacterium tuberculosis*. Journal of Antimicrobial Chemotherapy, 2017. **72**(10): p. 2943-2944.
534. Malik, R., et al., *Ulcerated and nonulcerated nontuberculous cutaneous mycobacterial granulomas in cats and dogs*. Veterinary dermatology, 2013. **24**(1): p. 146-e33.
535. Ploemacher, T., et al., *Reservoirs and transmission routes of leprosy; A systematic review*. PLoS neglected tropical diseases, 2020. **14**(4): p. e0008276.
536. David Scollard, B.S., Mara Dacso, *Leprosy: Treatment and prevention*. In *UpToDate*. UpToDate. 2021, Waltham, MA: Post TW (Ed).
537. Helweg-Larsen, J., et al., *Clinical efficacy of first- and second-line treatments for HIV-associated Pneumocystis jirovecii pneumonia: a tri-centre cohort study*. J Antimicrob Chemother, 2009. **64**(6): p. 1282-90.
538. Basavaraju, A., *Toxoplasmosis in HIV infection: An overview*. Trop Parasitol, 2016. **6**(2): p. 129-135.
539. Evans, R.A., et al., *Efficacy of once-weekly dapsons dosing for Pneumocystis jirovecii pneumonia prophylaxis post transplantation*. Transpl Infect Dis, 2015. **17**(6): p. 816-21.
540. Reja, A.H.H., et al., *Genomic Reduction at TTC Repeats in the Bacterial Genome of Treated Cases of Hansen's Disease: A Possible Survival Mechanism of Mycobacterium leprae*. Indian J Dermatol, 2018. **63**(6): p. 449-454.
541. Clark-Price, S.C., et al., *Use of dapsons in the treatment of Pneumocystis carinii pneumonia in a foal*. Journal of the American Veterinary Medical Association, 2004. **224**(3): p. 407-410.

542. Mandell, G., R. Dolin, and J. Bennett, *Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 9th edition.* 2019: Elsevier.
543. Cohen J, P.W., Opal S., *Infectious Diseases, 4th edition.* 2017.
544. Hughes, J. and G. Mellows, *On the mode of action of pseudomonic acid: inhibition of protein synthesis in Staphylococcus aureus.* J Antibiot (Tokyo), 1978. **31**(4): p. 330-5.
545. Sutherland, R., et al., *Antibacterial activity of mupirocin (pseudomonic acid), a new antibiotic for topical use.* Antimicrob Agents Chemother, 1985. **27**(4): p. 495-8.
546. Verkaik, N.J., *Mupirocin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
547. Long, B.H., *Fusidic acid in skin and soft-tissue infections.* Acta Dermato-Venereologica, 2008.
548. Bohaty, B.R., et al., *Clinical and bacteriological efficacy of twice daily topical retapamulin ointment 1% in the management of impetigo and other uncomplicated superficial skin infections.* International Journal of Women's Dermatology, 2015. **1**(1): p. 13-20.
549. Danish Health Authority, *Guidance on Preventing the Spread of MRSA. 3rd edition.* 2016: <https://www.sst.dk/-/media/Udgivelser/2017/MRSA-EN/Guidance-on-preventing-the-spread-of-MRSA-3rd-edition-2016.ashx>.
550. Dadashi, M., et al., *Mupirocin resistance in Staphylococcus aureus: A systematic review and meta-analysis.* Journal of global antimicrobial resistance, 2020. **20**: p. 238-247.
551. Khoshnood, S., et al., *A review on mechanism of action, resistance, synergism, and clinical implications of mupirocin against Staphylococcus aureus.* Biomedicine & Pharmacotherapy, 2019. **109**: p. 1809-1818.
552. Han, L.L., et al., *High frequencies of clindamycin and tetracycline resistance in methicillin-resistant Staphylococcus aureus pulsed-field type USA300 isolates collected at a Boston ambulatory health center.* Journal of Clinical Microbiology, 2007. **45**(4): p. 1350-1352.
553. Kizerwetter-Świda, M., D. Chrobak-Chmiel, and M. Rzewuska, *High-level mupirocin resistance in methicillin-resistant staphylococci isolated from dogs and cats.* BMC veterinary research, 2019. **15**(1): p. 238.
554. Rossi, C., et al., *Identification of Staphylococcus epidermidis with transferrable mupirocin resistance from canine skin.* The Veterinary Journal, 2018. **235**: p. 70-72.
555. Perreten, V., et al., *Clonal spread of methicillin-resistant Staphylococcus pseudintermedius in Europe and North America: an international multicentre study.* J Antimicrob Chemother, 2010.
556. Filippitzi, M.-E., et al., *Microbiological zoonotic emerging risks, transmitted between livestock animals and humans (2007–2015).* Transboundary and emerging diseases, 2017. **64**(4): p. 1059-1070.
557. Mueller, R.S., et al., *A review of topical therapy for skin infections with bacteria and yeast.* Veterinary Dermatology, 2012. **23**(4): p. 330-e62.
558. Godbeer, S.M., R.M. Gold, and S.D. Lawhon, *Prevalence of mupirocin resistance in Staphylococcus pseudintermedius.* Journal of clinical microbiology, 2014. **52**(4): p. 1250-1252.
559. Park, J.H., et al., *Low prevalence of mupirocin resistance in Staphylococcus pseudintermedius isolates from canine pyoderma in Korea.* Veterinary dermatology, 2018. **29**(2): p. 95-e37.
560. De Lucia, M., et al., *Rifampicin treatment of canine pyoderma due to multidrug - resistant methicillin - resistant staphylococci: a retrospective study of 32 cases.* Veterinary dermatology, 2017. **28**(2): p. 171-e36.
561. DeStefano, I.M., et al., *Parenterally administered vancomycin in 29 dogs and 7 cats (2003 - 2017).* Journal of veterinary internal medicine, 2019. **33**(1): p. 200-207.
562. Foster, J.D., L.A. Trepanier, and J.A. Ginn, *Use of linezolid to treat MRSP bacteremia and discospondylitis in a dog.* Journal of the American Animal Hospital Association, 2014. **50**(1): p. 53-58.
563. Hartantyo, S.H.P., et al., *Sick pets as potential reservoirs of antibiotic-resistant bacteria in Singapore.* Antimicrobial Resistance & Infection Control, 2018. **7**(1): p. 1-3.
564. Collignon, P. and J. Turnidge, *Fusidic acid in vitro activity.* Int J Antimicrob Agents, 1999. **12 Suppl 2**: p. S45-58.
565. Kohn, H. and W. Widger, *The molecular basis for the mode of action of bicyclomycin.* Curr Drug Targets Infect Disord, 2005. **5**(3): p. 273-95.
566. Yanofsky, C. and V. Horn, *Bicyclomycin sensitivity and resistance affect Rho factor-mediated transcription termination in the tna operon of Escherichia coli.* J Bacteriol, 1995. **177**(15): p. 4451-6.
567. Malik, M., et al., *Lethal synergy involving bicyclomycin: an approach for reviving old antibiotics.* J Antimicrob Chemother, 2014. **69**(12): p. 3227-35.
568. Harford, P.S., et al., *Bacteriological studies of the enteric flora of patients treated with bicozamycin (CGP 3543/E) for acute nonparasitic diarrhea.* Antimicrob Agents Chemother, 1983. **23**(4): p. 630-3.

569. Sweetman, S.C., *Martindale: the complete drug reference*. 2009.
570. Arenz, S., et al., *Structures of the orthosomycin antibiotics avilamycin and evernimicin in complex with the bacterial 70S ribosome*. Proc Natl Acad Sci U S A, 2016. **113**(27): p. 7527-32.
571. Terakubo, S., et al., *Antimicrobial activity of evernimicin against clinical isolates of Enterococcus spp., Staphylococcus spp., and Streptococcus spp. tested by Etest*. J Infect Chemother, 2001. **7**(4): p. 263-6.
572. Jones, R.N., et al., *In vitro Gram-positive antimicrobial activity of evernimicin (SCH 27899), a novel oligosaccharide, compared with other antimicrobials: a multicentre international trial*. J Antimicrob Chemother, 2001. **47**(1): p. 15-25.
573. Xu, F., et al., *Mechanisms of Antibacterial Action of Quinoxaline 1,4-di-N-oxides against Clostridium perfringens and Brachyspira hyodysenteriae*. Front Microbiol, 2016. **7**: p. 1948.
574. Hansen, L.H., et al., *Plasmid-encoded multidrug efflux pump conferring resistance to olaquinox in Escherichia coli*. Antimicrob Agents Chemother, 2004. **48**(9): p. 3332-7.
575. Montana, M., et al., *Quinoxaline Derivatives as Antiviral Agents: A Systematic Review*. Molecules, 2020. **25**(12).
576. Cheng, G., et al., *Quinoxaline 1,4-di-N-Oxides: Biological Activities and Mechanisms of Actions*. Front Pharmacol, 2016. **7**: p. 64.
577. Jim E. Riviere, M.G.P., *Veterinary Pharmacology and Therapeutics, 10th Edition*. 2017.
578. Haste, N.M., et al., *Activity of the thiopeptide antibiotic nosiheptide against contemporary strains of methicillin-resistant Staphylococcus aureus*. The Journal of antibiotics, 2012. **65**(12): p. 593-598.
579. Just-Baringo, X., F. Albericio, and M. Álvarez, *Thiopeptide antibiotics: retrospective and recent advances*. Marine drugs, 2014. **12**(1): p. 317-351.
580. Mullane, K., et al., *Multicenter, randomized clinical trial to compare the safety and efficacy of LFF571 and vancomycin for Clostridium difficile infections*. Antimicrobial agents and chemotherapy, 2015. **59**(3): p. 1435-1440.
581. Kim, T.H., et al., *Thiostrepton: a novel therapeutic drug candidate for Mycobacterium abscessus infection*. Molecules, 2019. **24**(24): p. 4511.
582. Ostash, B. and S. Walker, *Moenomycin family antibiotics: chemical synthesis, biosynthesis, and biological activity*. Nat Prod Rep, 2010. **27**(11): p. 1594-617.
583. Clabots, C.R., et al., *In vitro activity of efrotomycin, ciprofloxacin, and six other antimicrobials against Clostridium difficile*. Diagn Microbiol Infect Dis, 1987. **6**(1): p. 49-52.
584. Frost, B.M., et al., *Antibacterial activity of efrotomycin*. J Antibiot (Tokyo), 1976. **29**(10): p. 1083-91.
585. Miele, A., et al., *Differential susceptibilities of enterococcal species to elfamycin antibiotics*. J Clin Microbiol, 1994. **32**(8): p. 2016-8.
586. Prezioso, S.M., N.E. Brown, and J.B. Goldberg, *Elfamycins: inhibitors of elongation factor-Tu*. Mol Microbiol, 2017. **106**(1): p. 22-34.
587. Mouton, J.W., *Novobiocin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
588. Stromberg, Z.R., et al., *Evaluation of Escherichia coli isolates from healthy chickens to determine their potential risk to poultry and human health*. PloS one, 2017. **12**(7): p. e0180599.
589. Díaz-Jiménez, D., et al., *Chicken and turkey meat: Consumer exposure to multidrug-resistant Enterobacteriaceae including mcr-carriers, uropathogenic E. coli and high-risk lineages such as ST131*. International Journal of Food Microbiology, 2020. **331**: p. 108750.
590. Meena, P.R., et al., *Poultry - origin extraintestinal Escherichia coli strains carrying the traits associated with urinary tract infection, sepsis, meningitis and avian colibacillosis in India*. Journal of Applied Microbiology, 2021. **130**(6): p. 2087-2101.
591. WHO, *Up to 650 000 people die of respiratory diseases linked to seasonal flu each year*. 2017: <https://www.who.int/news/item/13-12-2017-up-to-650-000-people-die-of-respiratory-diseases-linked-to-seasonal-flu-each-year>.
592. Alame, M.M., E. Massaad, and H. Zaraket, *Peramivir: a novel intravenous neuraminidase inhibitor for treatment of acute influenza infections*. Frontiers in microbiology, 2016. **7**: p. 450.
593. Lampejo, T., *Influenza and antiviral resistance: an overview*. European Journal of Clinical Microbiology & Infectious Diseases, 2020. **39**(7): p. 1201-1208.
594. CDC, *Highly Pathogenic Avian Influenza A(H5N1) in Birds and Other Animals*. 2015: <https://www.cdc.gov/flu/avianflu/h5n1-animals.htm>.
595. University of Glasgow, *Canine Parvovirus. Advice For Owners*. Last accessed: 2022: https://www.gla.ac.uk/media/Media_425194_smx.pdf.

596. DVM360, *Factors Influencing Outcome in Shelter Cats with Panleukopenia*. 2018: <https://www.dvm360.com/view/factors-influencing-outcome-in-shelter-cats-with-panleukopenia>.
597. Shiraki, K. and T. Daikoku, *Favipiravir, an anti-influenza drug against life-threatening RNA virus infections*. *Pharmacology & therapeutics*, 2020. **209**: p. 107512.
598. Rusnak, J.M., *Experience with ribavirin for treatment and postexposure prophylaxis of hemorrhagic fever viruses: Crimean Congo hemorrhagic fever, Lassa fever, and hantaviruses*. *Applied Biosafety*, 2011. **16**(2): p. 67-87.
599. Goldhill, D.H., et al., *The mechanism of resistance to favipiravir in influenza*. *Proceedings of the National Academy of Sciences*, 2018. **115**(45): p. 11613-11618.
600. De Avila, A.I., et al., *Favipiravir can evoke lethal mutagenesis and extinction of foot-and-mouth disease virus*. *Virus research*, 2017. **233**: p. 105-112.
601. WHO, *Global hepatitis report*. 2017: <https://www.who.int/publications/i/item/global-hepatitis-report-2017>.
602. James, S.L., et al., *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017*. *The Lancet*, 2018. **392**(10159): p. 1789-1858.
603. Alter, M.J., *Epidemiology of hepatitis C virus infection*. *World journal of gastroenterology: WJG*, 2007. **13**(17): p. 2436.
604. WHO, *Fact sheets. Hepatitis B*. Last accessed: 2022: <https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b>.
605. WHO, *Fact sheets. Hepatitis E*. Last accessed: 2022: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-e>.
606. The Hepatitis C Trust, *Ribavirin*. Last accessed: 2022: <http://www.hepctrust.org.uk/information/treatment/current-treatments/ribavirin>.
607. Bunchorntavakul, C. and K.R. Reddy, *Ribavirin: how does it work and is it still needed?* *Current Hepatitis Reports*, 2011. **10**(3): p. 168-178.
608. Feigelstock, D.A., K.B. Mihalik, and S.M. Feinstone, *Selection of hepatitis C virus resistant to ribavirin*. *Virology journal*, 2011. **8**(1): p. 1-8.
609. García, N., et al., *Occurrence of hepatitis E virus in pigs and pork cuts and organs at the time of slaughter, Spain, 2017*. *Frontiers in microbiology*, 2020. **10**: p. 2990.
610. Durantel, D., *Celgosivir, an α -glucosidase I inhibitor for the potential treatment of hepatitis C virus infection*. *Curr. Opin. Invest. Drugs*, 2009. **10**: p. 860-870.
611. CDC, *Smallpox. Treatment*. Last accessed: 2022: <https://www.cdc.gov/smallpox/clinicians/treatment.html>.
612. CDC, *Norovirus Worldwide*. Last accessed: 2022: <https://www.cdc.gov/norovirus/trends-outbreaks/worldwide.html>.
613. WHO, *Fact sheets. Chikungunya*. Last accessed: 2022: <https://www.who.int/news-room/fact-sheets/detail/chikungunya>.
614. Agostini, M.L., et al., *Small-molecule antiviral β -d-N 4-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance*. *Journal of virology*, 2019. **93**(24): p. e01348-19.
615. Tate, J.E., et al., *2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis*. *The Lancet infectious diseases*, 2012. **12**(2): p. 136-141.
616. Simpson, E., et al., *Use of formative research in developing a knowledge translation approach to rotavirus vaccine introduction in developing countries*. *BMC public health*, 2007. **7**(1): p. 1-11.
617. CDC, *Middle East Respiratory Syndrome (MERS)*. Last accessed: 2022: <https://www.cdc.gov/coronavirus/mers/about/prevention.html>.
618. Tilmanis, D., et al., *Host-targeted nitazoxanide has a high barrier to resistance but does not reduce the emergence or proliferation of oseltamivir-resistant influenza viruses in vitro or in vivo when used in combination with oseltamivir*. *Antiviral Research*, 2020. **180**: p. 104851.
619. Villabruna, N., M.P. Koopmans, and M. de Graaf, *Animals as reservoir for human norovirus*. *Viruses*, 2019. **11**(5): p. 478.
620. Cook, N., et al., *The zoonotic potential of rotavirus*. *Journal of Infection*, 2004. **48**(4): p. 289-302.
621. Kiselev, O., et al., *A new antiviral drug Triazavirin: results of phase II clinical trial*. *Voprosy virusologii*, 2012. **57**(6): p. 9-12.

622. ClinicalTrials.gov, *PHRU CoV01 A Trial of Triazavirin (TZV) for the Treatment of Mild-moderate COVID-19 (PHRUCov01)*. last accessed: 2022: <https://clinicaltrials.gov/ct2/show/NCT04581915>.
623. Wu, X., et al., *The efficacy and safety of Triazavirin for COVID-19: a trial protocol*. Engineering, 2020. **6**(10): p. 1199-1204.
624. WHO, *Fact sheets. Lassa Fever*. Last accessed: 2022: <https://www.who.int/en/news-room/fact-sheets/detail/lassa-fever>.
625. Mansfield, K., et al., *Tick-borne encephalitis virus—a review of an emerging zoonosis*. Journal of General Virology, 2009. **90**(8): p. 1781-1794.
626. Kullberg, B.J. and M.C. Arendrup, *Invasive candidiasis*. New England Journal of Medicine, 2015. **373**(15): p. 1445-1456.
627. Rhodes, J. and M.C. Fisher, *Global epidemiology of emerging Candida auris*. Current opinion in microbiology, 2019. **52**: p. 84-89.
628. ECDC, *Candida auris in healthcare settings – Europe – first update, 23 April 2018*. 2018: <https://www.ecdc.europa.eu/sites/portal/files/documents/RRA-Candida-auris-European-Union-countries.pdf>.
629. CDC, *Antibiotic resistance threats in the United States, 2013*. 2013: <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>.
630. Fungal Infection Trust, *How Common are Fungal Diseases?* 2019: <https://life-slides-and-videos.s3.eu-west-2.amazonaws.com/LIFE+website/How+Common+are+Fungal+Diseases+v13.pdf>.
631. Medina, I.R., et al., *Pigeons and their droppings as reservoirs of Candida and other zoonotic yeasts*. Revista iberoamericana de micología, 2017. **34**(4): p. 211-214.
632. Brillhante, R.S.N., et al., *Characterization of the gastrointestinal yeast microbiota of cockatiels (Nymphicus hollandicus): a potential hazard to human health*. Journal of medical microbiology, 2010. **59**(6): p. 718-723.
633. Tissot, F., et al., *ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients*. haematologica, 2017. **102**(3): p. 433-444.
634. Pappas, P.G., et al., *Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America*. Clinical Infectious Diseases, 2016. **62**(4): p. e1-e50.
635. Ullmann, A., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)*. Clinical Microbiology and Infection, 2012. **18**: p. 53-67.
636. Cornely, O., et al., *ESCMID guideline for the diagnosis and management of Candida diseases 2012: non - neutropenic adult patients*. Clinical Microbiology and Infection, 2012. **18**: p. 19-37.
637. Cortegiani, A., et al., *Epidemiology, clinical characteristics, resistance, and treatment of infections by Candida auris*. Journal of intensive care, 2018. **6**(1): p. 69.
638. Schauwvlieghe, A.F., et al., *Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study*. The Lancet Respiratory Medicine, 2018. **6**(10): p. 782-792.
639. Drgona, L., et al., *Clinical and economic burden of invasive fungal diseases in Europe: focus on pre-emptive and empirical treatment of Aspergillus and Candida species*. European Journal of Clinical Microbiology & Infectious Diseases, 2014. **33**(1): p. 7-21.
640. ECDC, *Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in Aspergillus species*. 2013: <https://www.ecdc.europa.eu/en/publications-data/risk-assessment-impact-environmental-usage-triazoles-development-and-spread>.
641. Seyedmousavi, S., et al., *Aspergillus and aspergilloses in wild and domestic animals: a global health concern with parallels to human disease*. Medical Mycology, 2015. **53**(8): p. 765-797.
642. Cafarchia, C., et al., *Environmental contamination by Aspergillus spp. in laying hen farms and associated health risks for farm workers*. Journal of medical microbiology, 2014. **63**(3): p. 464-470.
643. Ullmann, A.J., et al., *Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline*. Clinical Microbiology and Infection, 2018. **24**: p. e1-e38.
644. Patterson, T.F., et al., *Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America*. Clinical Infectious Diseases, 2016. **63**(4): p. e1-e60.
645. Seyedmousavi, S., et al., *Emerging and Epizootic Fungal Infections in Animals*. 2018: Springer.

646. Tell, L.A., *Aspergillosis in mammals and birds: impact on veterinary medicine*. Medical Mycology, 2005. **43**(Supplement_1): p. S71-S73.
647. Elad, D., *Therapy of non-dermatophytic mycoses in animals*. Journal of Fungi, 2018. **4**(4): p. 120.
648. WHO, *Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. Supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. 2018: <https://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/>.
649. Perfect, J.R., et al., *Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America*. Clinical infectious diseases, 2010. **50**(3): p. 291-322.
650. Fessel, W.J., *Cryptococcal meningitis after unusual exposures to birds*. New England Journal of Medicine, 1993. **328**(18): p. 1354-1355.
651. Weese, J.S. and M. Fulford, *Companion animal zoonoses*. 2011: John Wiley & Sons.
652. Lloret, A., et al., *Rare systemic mycoses in cats: blastomycosis, histoplasmosis and coccidioidomycosis: ABCD guidelines on prevention and management*. Journal of feline medicine and surgery, 2013. **15**(7): p. 624-627.
653. Prakash, H. and A. Chakrabarti, *Global epidemiology of mucormycosis*. Journal of Fungi, 2019. **5**(1): p. 26.
654. Gangneux, J.-P., et al., *An estimation of burden of serious fungal infections in France*. Journal de mycologie medicale, 2016. **26**(4): p. 385-390.
655. Cornely, O.A., et al., *Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium*. The Lancet infectious diseases, 2019. **19**(12): p. e405-e421.
656. Rouzaud, C., et al., *Severe dermatophytosis and acquired or innate immunodeficiency: a review*. Journal of Fungi, 2016. **2**(1): p. 4.
657. Singh, A., et al., *A unique multidrug-resistant clonal Trichophyton population distinct from Trichophyton mentagrophytes/Trichophyton interdigitale complex causing an ongoing alarming dermatophytosis outbreak in India: genomic insights and resistance profile*. Fungal Genetics and Biology, 2019. **133**: p. 103266.
658. Hayette, M.-P. and R. Sacheli, *Dermatophytosis, trends in epidemiology and diagnostic approach*. Current Fungal Infection Reports, 2015. **9**(3): p. 164-179.
659. Uhrlaß, S., C. Krüger, and P. Nenoff, *Microsporum canis: Aktuelle Daten zur Prävalenz des zoophilen Dermatophyten im mitteldeutschen Raum. [Microsporum canis: Current data on the prevalence of the zoophilic dermatophyte in central Germany]*. Der Hautarzt, 2015. **66**(11): p. 855-862.
660. Moriello, K.A., et al., *Diagnosis and treatment of dermatophytosis in dogs and cats. Clinical Consensus Guidelines of the World Association for Veterinary Dermatology*. Veterinary dermatology, 2017. **28**(3): p. 266-e68.
661. Baumgardner, D.J., *Fungal infections from human and animal contact*. Journal of Patient-Centered Research and Reviews, 2017. **4**(2): p. 78.
662. Gremião, I.D., et al., *Feline sporotrichosis: epidemiological and clinical aspects*. Medical mycology, 2015. **53**(1): p. 15-21.
663. Chakrabarti, A., et al., *Global epidemiology of sporotrichosis*. Medical mycology, 2015. **53**(1): p. 3-14.
664. Kauffman, C.A., et al., *Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America*. Clinical Infectious Diseases, 2007. **45**(10): p. 1255-1265.
665. Pereira, S., et al., *Response to azolic antifungal agents for treating feline sporotrichosis*. Veterinary Record, 2010. **166**(10): p. 290-294.
666. Ashbee, H., et al., *Histoplasmosis in Europe: report on an epidemiological survey from the European Confederation of Medical Mycology Working Group*. Medical mycology, 2008. **46**(1): p. 57-65.
667. Wheat, L., et al., *Infectious diseases Society of a: clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America*. Clin Infect Dis, 2007. **45**(7): p. 807-25.
668. Scantlebury, C. and K. Reed, *Epizootic lymphangitis*. Infectious diseases of the horse. EVJ Ltd, Fordham, Cambridgeshire, United Kingdom, 2009.
669. OIE, *Epizootic lymphangitis*, in *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Chapter 2.5.13*. 2004.

670. Chapman, S.W., et al., *Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America*. Clinical Infectious Diseases, 2008. **46**(12): p. 1801-1812.
671. Limper, A.H., et al., *An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients*. American journal of respiratory and critical care medicine, 2011. **183**(1): p. 96-128.
672. Galgiani, J.N., et al., *2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis*. Clinical Infectious Diseases, 2016. **63**(6): p. e112-e146.
673. Catanzaro, A., J. Fierer, and P.J. Friedman, *Fluconazole in the treatment of persistent coccidioidomycosis*. Chest, 1990. **97**(3): p. 666-669.
674. Griffiths, J., A.L. Colombo, and D.W. Denning, *The case for paracoccidioidomycosis to be accepted as a neglected tropical (fungal) disease*. PLoS neglected tropical diseases, 2019. **13**(5).
675. GAFFI, *Paracoccidioidomycosis (Fact sheet)*. 2018: <https://www.gaffi.org/wp-content/uploads/Paracoccidioidomycosis-Briefing-Note.pdf>.
676. Shikanai-Yasuda, M.A., et al., *Brazilian guidelines for the clinical management of paracoccidioidomycosis*. Revista da Sociedade Brasileira de Medicina Tropical, 2017. **50**(5): p. 715-740.
677. GAFFI, *Pneumocystis pneumonia (Fact sheet)*. 2017: <https://www.gaffi.org/wp-content/uploads/Briefing-note-PCP-GAFFI-December-2017-V4.pdf>.
678. Gigliotti, F. and T.W. Wright, *Pneumocystis: where does it live?* PLoS pathogens, 2012. **8**(11): p. e1003025.
679. Maertens, J., et al., *ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients*. Journal of Antimicrobial Chemotherapy, 2016. **71**(9): p. 2397-2404.
680. Maschmeyer, G., et al., *ECIL guidelines for treatment of Pneumocystis jirovecii pneumonia in non-HIV-infected haematology patients*. Journal of Antimicrobial Chemotherapy, 2016. **71**(9): p. 2405-2413.
681. Huang, Y.-S., et al., *Treatment of Pneumocystis jirovecii pneumonia in HIV-infected patients: a review*. Expert review of anti-infective therapy, 2017. **15**(9): p. 873-892.
682. Stentiford, G., et al., *Microsporidia—emergent pathogens in the global food chain*. Trends in parasitology, 2016. **32**(4): p. 336-348.
683. Mathis, A., R. Weber, and P. Deplazes, *Zoonotic potential of the microsporidia*. Clinical microbiology reviews, 2005. **18**(3): p. 423-445.
684. Didier, E.S., *Microsporidiosis: an emerging and opportunistic infection in humans and animals*. Acta tropica, 2005. **94**(1): p. 61-76.
685. Han, B. and L.M. Weiss, *Therapeutic targets for the treatment of microsporidiosis in humans*. Expert opinion on therapeutic targets, 2018. **22**(11): p. 903-915.
686. Latney, L., C.W. Bradley, and N.R. Wyre, *Encephalitozoon cuniculi in pet rabbits: diagnosis and optimal management*. Veterinary Medicine: Research and Reports, 2014. **5**: p. 169-180.
687. Vergneau-Grosset, C. and S. Larrat, *Microsporidiosis in vertebrate companion exotic animals*. Journal of Fungi, 2016. **2**(1): p. 3.
688. Capela, R., R. Moreira, and F. Lopes, *An Overview of Drug Resistance in Protozoal Diseases*. International journal of molecular sciences, 2019. **20**(22): p. 5748.
689. Piperaki, E. and G. Daikos, *Malaria in Europe: emerging threat or minor nuisance?* Clinical Microbiology and Infection, 2016. **22**(6): p. 487-493.
690. Hertig, E., *Distribution of Anopheles vectors and potential malaria transmission stability in Europe and the Mediterranean area under future climate change*. Parasites & vectors, 2019. **12**(1): p. 18.
691. Ramasamy, R., *Zoonotic malaria—global overview and research and policy needs*. Frontiers in public health, 2014. **2**: p. 123.
692. WHO, *Malaria*. Last accessed: 2022: <https://www.who.int/ith/diseases/malaria/en/>.
693. Rosenthal, P.J., *The interplay between drug resistance and fitness in malaria parasites*. Molecular microbiology, 2013. **89**(6): p. 1025-1038.
694. WHO, *Antimalarial drug efficacy and drug resistance*. 2018: https://www.who.int/malaria/areas/treatment/drug_efficacy/en/.
695. Bercu, T.E., W.A. Petri, and B.W. Behm, *Amebic colitis: new insights into pathogenesis and treatment*. Current gastroenterology reports, 2007. **9**(5): p. 429-433.
696. Gonzales, M.L.M., L.F. Dans, and J. Sio - Aguilar, *Antiamoebic drugs for treating amoebic colitis*. Cochrane Database of Systematic Reviews, 2019(1).

697. Roure, S., et al., *Approach to amoebic colitis: Epidemiological, clinical and diagnostic considerations in a non-endemic context (Barcelona, 2007-2017)*. PLoS one, 2019. **14**(2).
698. Salit, I.E., et al., *A possible cluster of sexually transmitted Entamoeba histolytica: genetic analysis of a highly virulent strain*. Clinical infectious diseases, 2009. **49**(3): p. 346-353.
699. Dans, L.F. and E.G. Martínez, *Amoebic dysentery*. BMJ clinical evidence, 2007. **2007**.
700. Ji, T., et al., *Prevalence and Genetic Identification of Three Entamoeba Species in Pigs in Southeastern China*. BioMed research international, 2019. **2019**.
701. Penuliar, G.M., K. Nakada-Tsukui, and T. Nozaki, *Phenotypic and transcriptional profiling in Entamoeba histolytica reveal costs to fitness and adaptive responses associated with metronidazole resistance*. Frontiers in microbiology, 2015. **6**: p. 354.
702. Reynoso, D. and C. White, *Nitazoxanide*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
703. Upcroft, P. and J.A. Upcroft, *Drug targets and mechanisms of resistance in the anaerobic protozoa*. Clinical microbiology reviews, 2001. **14**(1): p. 150-164.
704. Eisemann, J.E. and G.P. M., *Diloxanide Furoate*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
705. Nagaraja, S. and S. Ankri, *Target identification and intervention strategies against amebiasis*. Drug Resistance Updates, 2019. **44**: p. 1-14.
706. ECDC, *Giardiasis (lambliaosis) - Annual Epidemiological Report for 2017*. 2019: <https://www.ecdc.europa.eu/en/publications-data/giardiasis-lambliaosis-annual-epidemiological-report-2017>.
707. Feng, Y. and L. Xiao, *Zoonotic potential and molecular epidemiology of Giardia species and giardiasis*. Clinical microbiology reviews, 2011. **24**(1): p. 110-140.
708. Sprong, H., S.M. Cacciò, and J.W. van der Giessen, *Identification of zoonotic genotypes of Giardia duodenalis*. PLoS neglected tropical diseases, 2009. **3**(12).
709. Baneth, G., et al., *Major parasitic zoonoses associated with dogs and cats in Europe*. Journal of comparative pathology, 2016. **155**(1): p. S54-S74.
710. Granados, C.E., et al., *Drugs for treating giardiasis*. Cochrane database of systematic reviews, 2012(12).
711. Carter, E., et al., *Nitroimidazole-refractory giardiasis: a growing problem requiring rational solutions*. Clinical Microbiology and Infection, 2018. **24**(1): p. 37-42.
712. Khalil, I.A., et al., *Morbidity, mortality, and long-term consequences associated with diarrhoea from Cryptosporidium infection in children younger than 5 years: a meta-analysis study*. The Lancet Global health, 2018. **6**(7): p. e758-e768.
713. ECDC, *Cryptosporidiosis - Annual Epidemiological Report for 2017*. 2019: <https://www.ecdc.europa.eu/en/publications-data/cryptosporidiosis-annual-epidemiological-report-2017>.
714. EFSA/ECDC, *The European Union One Health 2018 Zoonoses Report*. EFSA Journal, 2019. **17**(12):5926: p. 276.
715. Xiao, L. and U.M. Ryan, *Cryptosporidiosis: an update in molecular epidemiology*. Current opinion in infectious diseases, 2004. **17**(5): p. 483-490.
716. Plutzer, J., et al., *Review of Cryptosporidium and Giardia in the eastern part of Europe, 2016*. Eurosurveillance, 2018. **23**(4).
717. Rabinowitz, P.M. and L.A. Conti, *Human-Animal Medicine-E-Book: Clinical Approaches to Zoonoses, Toxicants and Other Shared Health Risks*. 2009: Elsevier Health Sciences.
718. Cacci, S. and R. Chalmers, *Human cryptosporidiosis in Europe*. Clinical Microbiology and Infection, 2016. **22**(6): p. 471-480.
719. Abubakar, I.I., et al., *Prevention and treatment of cryptosporidiosis in immunocompromised patients*. Cochrane Database of Systematic Reviews, 2007(1).
720. ECDC, *Congenital toxoplasmosis - Annual Epidemiological Report for 2017*. 2019: <https://www.ecdc.europa.eu/en/publications-data/congenital-toxoplasmosis-annual-epidemiological-report-2017>.
721. Esch, K.J. and C.A. Petersen, *Transmission and epidemiology of zoonotic protozoal diseases of companion animals*. Clinical microbiology reviews, 2013. **26**(1): p. 58-85.
722. Torgerson, P.R. and P. Mastroiacovo, *The global burden of congenital toxoplasmosis: a systematic review*. Bulletin of the World Health Organization, 2013. **91**: p. 501-508.
723. Havelaar, A.H., et al., *World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010*. PLoS medicine, 2015. **12**(12): p. e1001923.
724. El Bissati, K., et al., *Global initiative for congenital toxoplasmosis: an observational and international comparative clinical analysis*. Emerging microbes & infections, 2018. **7**(1): p. 1-14.

725. Sánchez-Sánchez, R., et al., *Treatment of toxoplasmosis and neosporosis in farm ruminants: state of knowledge and future trends*. Current topics in medicinal chemistry, 2018. **18**(15): p. 1304-1323.
726. Graves, B., D. Looke, and M.L. Grayson, *Pyrimethamine*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
727. Montazeri, M., et al., *Drug resistance in Toxoplasma gondii*. Frontiers in microbiology, 2018. **9**: p. 2587.
728. Oliveira, C., et al., *Pathogenicity and phenotypic sulfadiazine resistance of Toxoplasma gondii isolates obtained from livestock in northeastern Brazil*. Memórias do Instituto Oswaldo Cruz, 2016. **111**(6): p. 391-398.
729. Dunay, I.R., et al., *Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice*. Clinical microbiology reviews, 2018. **31**(4): p. e00057-17.
730. Alday, P.H. and J.S. Doggett, *Drugs in development for toxoplasmosis: advances, challenges, and current status*. Drug design, development and therapy, 2017. **11**: p. 273.
731. Maritz, J.M., et al., *What is the importance of zoonotic trichomonads for human health?* Trends in parasitology, 2014. **30**(7): p. 333-341.
732. Cooper, C., *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017*. The Lancet, 2018. **392**(10159): p. 1789-1858.
733. WHO, *Guidelines for the management of sexually transmitted infections*. 2001: https://www.who.int/hiv/topics/vct/sw_toolkit/guidelines_management_sti.pdf.
734. Gookin, J.L., K. Hanrahan, and M.G. Levy, *The condundrum of feline trichomonosis—the more we learn the 'trickier' it gets*. Journal of feline medicine and surgery, 2017. **19**(3): p. 261-274.
735. Schwebke, J.R. and D. Burgess, *Trichomoniasis*. Clinical microbiology reviews, 2004. **17**(4): p. 794-803.
736. Bouchemal, K., C. Bories, and P.M. Loiseau, *Strategies for prevention and treatment of Trichomonas vaginalis infections*. Clinical microbiology reviews, 2017. **30**(3): p. 811-825.
737. Albajar-Vinas, P. and J. Jannin, *The hidden Chagas disease burden in Europe*. Eurosurveillance, 2011. **16**(38): p. 19975.
738. WHO, *Trypanosomiasis, human African (sleeping sickness)*. 2020: [https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-\(sleeping-sickness\)#.XpxXR0sTgQQ.link](https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)#.XpxXR0sTgQQ.link).
739. Gutiérrez Cabrera, C.J., et al., *Descripción de un caso de Tripanosomosis en el dromedario por T. evansi en Canarias*. Medicina Veterinaria, 1998.
740. TroCCAP, *Guidelines for the diagnosis, treatment and control of canine endoparasites in the tropics*. 2018: <http://www.troccap.com/2017press/wp-content/uploads/2018/04/TroCCAP-Canine-Endo-Guidelines-English.pdf>.
741. CAPC, *Trypanosomiasis*. 2013: <https://capcvet.org/guidelines/trypanosomiasis/>.
742. FAO, *Controlling tsetse and trypanosomosis to protect African livestock keepers, public health and farmers' livelihoods*. 2019: <http://www.fao.org/3/ca3887en/CA3887EN.pdf>.
743. FAO, *Intervening against bovine trypanosomosis in eastern Africa: mapping the costs and benefits*. 2017: <http://www.fao.org/3/a-i7342e.pdf>.
744. OIE, *Technical disease cards. Trypanosomosis (tsetse-transmitted)*. 2013: https://www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/TRYPANO_TSETSE.pdf.
745. Hamill, L., et al., *Evaluating the impact of targeting livestock for the prevention of human and animal trypanosomiasis, at village level, in districts newly affected with T. b. rhodesiense in Uganda*. Infectious diseases of poverty, 2017. **6**(1): p. 16.
746. Junckerstorff, R.K. and R.J. Murray, *Benznidazole*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
747. Murray, R.J., *Nifurtimox*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
748. Giangaspero, M., *Trypanosoma Cruzi and Domestic Animals*. Clin Microbiol, 2017. **6**(3).
749. Lee, S.-M., et al., *Recent Advances in the Discovery of Novel Antiprotozoal Agents*. Molecules, 2019. **24**(21): p. 3886.
750. Darby, J., *Melarsoprol*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
751. Darby, J., *Pentamidine*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
752. Giordani, F., et al., *The animal trypanosomiasis and their chemotherapy: a review*. Parasitology, 2016. **143**(14): p. 1862-1889.

753. CDC, *DPDx - Laboratory Identification of Parasites of Public Health Concern. Balantidiasis*. 2019: <https://www.cdc.gov/dpdx/balantidiasis/index.html>.
754. Schuster, F.L. and L. Ramirez-Avila, *Current world status of Balantidium coli*. Clinical microbiology reviews, 2008. **21**(4): p. 626-638.
755. Damriyasa, I. and C. Bauer, *Prevalence and age-dependent occurrence of intestinal protozoan infections in suckling piglets*. Berliner und Munchener tierarztliche Wochenschrift, 2006. **119**(7-8): p. 287-290.
756. Hindsbo, O., et al., *Age-dependent occurrence of the intestinal ciliate Balantidium coli in pigs at a Danish research farm*. Acta Veterinaria Scandinavica, 2000. **41**(1): p. 79-83.
757. Bauri, R., et al., *Prevalence and sustainable control of Balantidium coli infection in pigs of Ranchi, Jharkhand, India*. Veterinary World, 2012. **5**(2): p. 94.
758. Alvar, J., et al., *The relationship between leishmaniasis and AIDS: the second 10 years*. Clinical microbiology reviews, 2008. **21**(2): p. 334-359.
759. Dantas-Torres, F., et al., *Canine leishmaniasis control in the context of One Health*. Emerging infectious diseases, 2019. **25**(12): p. 1.
760. Gradoni, L., *Epidemiological surveillance of leishmaniasis in the European Union: operational and research challenges*. Eurosurveillance, 2013. **18**(30): p. 20539.
761. Aguado, M., et al., *Outbreak of cutaneous leishmaniasis in Fuenlabrada, Madrid*. Actas Dermo-Sifiliográficas (English Edition), 2013. **104**(4): p. 334-342.
762. Varani, S., et al., *Ongoing outbreak of visceral leishmaniasis in Bologna Province, Italy, November 2012 to May 2013*. Eurosurveillance, 2013. **18**(29): p. 20530.
763. ECDC, *Leishmaniasis emergence in Europe*. 2011: <https://www.ecdc.europa.eu/en/news-events/leishmaniasis-emergence-europe>.
764. WHO, *Leishmaniasis. Fact sheet No. 375*. 2014: <http://www.who.int/mediacentre/factsheets/fs375/en/>.
765. Travi, B.L., et al., *Canine visceral leishmaniasis: diagnosis and management of the reservoir living among us*. PLoS neglected tropical diseases, 2018. **12**(1).
766. WHO, *Manual on case management and surveillance of the leishmaniases in the WHO European Region*. 2017: <http://www.euro.who.int/en/publications/abstracts/manual-on-case-management-and-surveillance-of-the-leishmaniases-in-the-who-european-region-2017>.
767. Aronson, N., et al., *Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH)*. Clinical infectious diseases, 2016. **63**(12): p. e202-e264.
768. Moafi, M., et al., *Leishmania vaccines entered in clinical trials: A review of literature*. International journal of preventive medicine, 2019. **10**.
769. Leal, R., *Medical Management of Canine Leishmaniasis: The European Perspective*, in ACVIM FORUM. 2019: Phoenix, Arizona.
770. Solano-Gallego, L., et al., *LeishVet guidelines for the practical management of canine leishmaniasis*. Parasites & vectors, 2011. **4**(1): p. 86.
771. Oliva, G., et al., *Guidelines for treatment of leishmaniasis in dogs*. Journal of the American Veterinary Medical Association, 2010. **236**(11): p. 1192-1198.
772. Hefnawy, A., et al., *Exploiting knowledge on Leishmania drug resistance to support the quest for new drugs*. Trends in parasitology, 2017. **33**(3): p. 162-174.
773. Mwenechanya, R., et al., *Sterol 14 α -demethylase mutation leads to amphotericin B resistance in Leishmania mexicana*. PLoS neglected tropical diseases, 2017. **11**(6): p. e0005649.
774. Ponte-Sucre, A., et al., *Drug resistance and treatment failure in leishmaniasis: A 21st century challenge*. PLoS neglected tropical diseases, 2017. **11**(12).
775. Bhandari, V., et al., *Elucidation of cellular mechanisms involved in experimental paromomycin resistance in Leishmania donovani*. Antimicrobial agents and chemotherapy, 2014. **58**(5): p. 2580-2585.
776. Maia, C., et al., *In vitro drug susceptibility of Leishmania infantum isolated from humans and dogs*. Experimental Parasitology, 2013. **135**(1): p. 36-41.
777. Yasur-Landau, D., et al., *Resistance of Leishmania infantum to allopurinol is associated with chromosome and gene copy number variations including decrease in the S-adenosylmethionine synthetase (METK) gene copy number*. International Journal for Parasitology: Drugs and Drug Resistance, 2018. **8**(3): p. 403-410.
778. Pérez, V.G., et al., *Decreased antimony uptake and overexpression of genes of thiol metabolism are associated with drug resistance in a canine isolate of Leishmania infantum*. International Journal for Parasitology: Drugs and Drug Resistance, 2016. **6**(2): p. 133-139.
779. WHO, *HIV drug resistance report*. 2019: <https://www.who.int/publications/i/item/WHO-CDS-HIV-19.21>.

780. Bright, R.A., et al., *Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern*. The Lancet, 2005. **366**(9492): p. 1175-1181.
781. VCA, *Amantadine*. Last accessed: 2022: <https://vcahospitals.com/know-your-pet/amantadine>.
782. ScienceDirect, *Amantadine*. last accessed: 2022: <https://www.sciencedirect.com/topics/veterinary-science-and-veterinary-medicine/amantadine>.
783. Lascelles, B., et al., *Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs*. Journal of Veterinary Internal Medicine, 2008. **22**(1): p. 53-59.
784. Shipley, H., et al., *Owner evaluation of quality of life and mobility in osteoarthritic cats treated with amantadine or placebo*. Journal of Feline Medicine and Surgery, 2021. **23**(6): p. 568-574.
785. Moore, S.A., *Managing neuropathic pain in dogs*. Frontiers in veterinary science, 2016. **3**: p. 12.
786. Epstein, M., et al., *2015 AAHA/AAFP pain management guidelines for dogs and cats*. Journal of the American Animal Hospital Association, 2015. **51**(2): p. 67-84.
787. WSAVA, *Global Pain Council. Pain Management Protocol: Neuropathic pain 2014*: <https://wsava.org/wp-content/uploads/2020/01/Neuropathic-pain.pdf>.
788. Parry, J., *Use of antiviral drug in poultry is blamed for drug resistant strains of avian flu*. Bmj, 2005. **331**(7507): p. 10.
789. FDA, *The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians*. 2020: <https://www.fda.gov/animal-veterinary/resources-you/ins-and-outs-extra-label-drug-use-animals-resource-veterinarians#prohibited>.
790. He, G., et al., *Amantadine-resistance among H5N1 avian influenza viruses isolated in Northern China*. Antiviral research, 2008. **77**(1): p. 72-76.
791. Nguyen, H.T., et al., *Antiviral susceptibility of highly pathogenic avian influenza A (H5N1) viruses isolated from poultry, Vietnam, 2009–2011*. Emerging infectious diseases, 2013. **19**(12): p. 1963.
792. Meijer, A., et al., *Oseltamivir reduces transmission, morbidity, and mortality of highly pathogenic avian influenza in chickens*. in *International Congress Series*. 2004. Elsevier.
793. Hilling, K. and R. Hanel, *Canine influenza*. Compend Contin Educ Vet, 2010. **32**(6): p. E1-9.
794. Noshi, T., et al., *In vitro characterization of baloxavir acid, a first-in-class cap-dependent endonuclease inhibitor of the influenza virus polymerase PA subunit*. Antiviral research, 2018. **160**: p. 109-117.
795. Stoskopf, M., *Viral diseases of marine mammals*, in *MSD Manual Veterinary Manual*. 2015: <https://www.msdveterinary.com/exotic-and-laboratory-animals/marine-mammals/viral-diseases-of-marine-mammals>.
796. Aronson, J.K., *Meyler's side effects of drugs: the international encyclopedia of adverse drug reactions and interactions*. 2015: Elsevier.
797. Salvaggio, M.R. and J.W. Gnann Jr, *Drugs for herpesvirus infections*, in *Infectious Diseases*. 2017, Elsevier. p. 1309-1317. e1.
798. Canestri, A., et al., *Foscarnet salvage therapy for patients with late-stage HIV disease and multiple drug resistance*. Antiviral therapy, 2006. **11**(5): p. 561.
799. Bain, V., et al., *Foscarnet therapy in chronic hepatitis B virus e antigen carriers*. Journal of Medical virology, 1989. **29**(2): p. 152-155.
800. Matthews, T. and R. Boehme, *Antiviral activity and mechanism of action of ganciclovir*. Reviews of infectious diseases, 1988. **10**(Supplement_3): p. S490-S494.
801. Plumb's Veterinary Medication Guides, *Ganciclovir, Ophthalmic*. Last accessed: 2022: <https://cdn.brief.vet/web-files/PVD/drupal-uploads/files/VMG-Ganciclovir-Ophthalmic-2019-01-28-1022.pdf>.
802. Ledbetter, E.C., et al., *Evaluation of topical ophthalmic ganciclovir gel for the treatment of dogs with experimentally induced ocular canine herpesvirus-1 infection*. American journal of veterinary research, 2018. **79**(7): p. 762-769.
803. Dal Pozzo, F. and E. Thiry, *Antiviral chemotherapy in veterinary medicine: current applications and perspectives*. Rev Sci Tech, 2014. **33**(3): p. 25812204.
804. Rollinson, E., *Prospects for antiviral chemotherapy in veterinary medicine: 2. Avian, piscine, canine, porcine, bovine and equine virus diseases*. Antiviral Chemistry and Chemotherapy, 1992. **3**(6): p. 311-326.
805. Gupta, S.P., *Viral Polymerases: Structures, Functions and Roles as Antiviral Drug Targets*. 2018: Academic Press.
806. Lanier, R., et al., *Development of CMX001 for the treatment of poxvirus infections*. Viruses, 2010. **2**(12): p. 2740-2762.

807. Erice, A., *Resistance of human cytomegalovirus to antiviral drugs*. Clinical Microbiology Reviews, 1999. **12**(2): p. 286-297.
808. Nollens, H.H., *Poxvirus infections in North American pinnipeds*. 2005, University of Florida.
809. Fuentes-Prior, P., *Priming of SARS-CoV-2 S protein by several membrane-bound serine proteinases could explain enhanced viral infectivity and systemic COVID-19 infection*. Journal of Biological Chemistry, 2021. **296**.
810. Hoffmann, M., et al., *SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor*. cell, 2020. **181**(2): p. 271-280. e8.
811. Kawase, M., et al., *Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry*. Journal of virology, 2012. **86**(12): p. 6537-6545.
812. Hofmann-Winkler, H., et al., *Camostat mesylate may reduce severity of coronavirus disease 2019 sepsis: a first observation*. Critical care explorations, 2020. **2**(11).
813. Aarhus Universitet, *Middel mod halsbrand bremsede ikke Covid-19*. Last accessed: 2022: <https://newsroom.au.dk/nyheder/vis/artikel/middel-mod-halsbrand-bremsede-ikke-covid-19/>.
814. EurekaAlert!, *ACTG announces Camostat will not advance to phase 3 in outpatient treatment study for COVID-19*. Last accessed: 2022: <https://www.eurekaalert.org/news-releases/723362>.
815. ClinicalTrials.gov, *Novel Agents for Treatment of High-risk COVID-19 Positive Patients*. Last accessed: 2022: <https://clinicaltrials.gov/ct2/show/NCT04374019>.
816. ClinicalTrials.gov, *The Impact of Camostat Mesilate on COVID-19 Infection (CamoCO-19)*. Last accessed: 2022: <https://clinicaltrials.gov/ct2/show/NCT04321096>.
817. Breining, P., et al., *Camostat mesylate against SARS - CoV - 2 and COVID - 19—Rationale, dosing and safety*. Basic & Clinical Pharmacology & Toxicology, 2021. **128**(2): p. 204-212.
818. EUNETHTA, *"Rolling Collaborative Review" of Covid-19 treatments. Camostat for the treatment of COVID-19 2021*: <https://www.eunethta.eu/wp-content/uploads/2021/07/EUnetHTA-COVID-19-RollingCR04-v10.0.pdf>.
819. Du, Y.X. and X.P. Chen, *Favipiravir: pharmacokinetics and concerns about clinical trials for 2019 - nCoV infection*. Clinical Pharmacology & Therapeutics, 2020.
820. Furuta, Y., et al., *T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections*. Antiviral research, 2009. **82**(3): p. 95-102.
821. Xue, X., et al., *Antiviral efficacy of favipiravir against canine distemper virus infection in vitro*. BMC veterinary research, 2019. **15**(1): p. 316.
822. Jin, Z., et al., *The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5' -triphosphate towards influenza A virus polymerase*. PloS one, 2013. **8**(7): p. e68347.
823. Baranovich, T., et al., *T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro*. Journal of virology, 2013. **87**(7): p. 3741-3751.
824. Warren, T.K., et al., *Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430*. Nature, 2014. **508**(7496): p. 402-405.
825. Westover, J.B., et al., *Galidesivir limits Rift Valley fever virus infection and disease in Syrian golden hamsters*. Antiviral research, 2018. **156**: p. 38-45.
826. Julander, J.G., et al., *Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model*. Antiviral research, 2017. **137**: p. 14-22.
827. Duddu, P., *Coronavirus outbreak: Vaccines/drugs in the pipeline for Covid-19*. Clinicaltrialsarena. com, 2020. **19**.
828. Eyer, L., et al., *An E460D substitution in the NS5 protein of tick-borne encephalitis virus confers resistance to the inhibitor Galidesivir (BCX4430) and also attenuates the virus for mice*. Journal of virology, 2019. **93**(16): p. e00367-19.
829. Carocci, M. and P.L. Yang, *Lactimidomycin is a broad-spectrum inhibitor of dengue and other RNA viruses*. Antiviral research, 2016. **128**: p. 57-62.
830. Meyers, F.H., E. Jawetz, and A. Goldfien, *Lehrbuch der Pharmakologie: für Studenten der Medizin aller Studienabschnitte und für Ärzte*. 2013: Springer-Verlag.
831. Kabinger, F., et al., *Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis*. Nature structural & molecular biology, 2021. **28**(9): p. 740-746.
832. Rossignol, J.-F., *Nitazoxanide: a first-in-class broad-spectrum antiviral agent*. Antiviral research, 2014. **110**: p. 94-103.
833. Rossignol, J.-F., *Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus*. Journal of infection and public health, 2016. **9**(3): p. 227-230.
834. Rossignol, J.F., et al., *Thiazolidines, a new class of anti-influenza molecules targeting viral hemagglutinin at the post-translational level*. Journal of Biological Chemistry, 2009. **284**(43): p. 29798-29808.

835. Clerici, M., et al., *The anti-infective Nitazoxanide shows strong immunomodulating effects (155.21)*. 2011, Am Assoc Immunol.
836. CBS News, *Life-Saving H1N1 Drug Unavailable to Most*. 2009: <https://www.cbsnews.com/news/life-saving-h1n1-drug-unavailable-to-most/>.
837. FDA, *Peramivir Fact Sheet For Health Care Providers*. 2009: <https://www.fda.gov/media/77787/download#:~:text=Peramivir%2C%20a%20neuraminidase%20inhibitor%2C%20is,or%20suspected%202009%20H1N1%20influenza.>
838. Kim, Y., et al., *Broad-spectrum antivirals against 3C or 3C-like proteases of picornaviruses, noroviruses, and coronaviruses*. Journal of virology, 2012. **86**(21): p. 11754-11762.
839. Deng, X., et al., *Coronaviruses resistant to a 3C-like protease inhibitor are attenuated for replication and pathogenesis, revealing a low genetic barrier but high fitness cost of resistance*. Journal of virology, 2014. **88**(20): p. 11886-11898.
840. FDA, *Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19*. 2021: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19>.
841. MHRA, *Oral COVID-19 antiviral, Paxlovid, approved by UK regulator*. 2021: <https://www.gov.uk/government/news/oral-covid-19-antiviral-paxlovid-approved-by-uk-regulator>.
842. EMA, *Paxlovid*. 2022: <https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid>.
843. DrugBank, *PF-07304814*. last accessed: 2022: <https://go.drugbank.com/drugs/DB16514>.
844. Lo, M., et al., *GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses*. Sci Rep 7: 43395. 2017.
845. EMA, *Veklury*. 2022: <https://www.ema.europa.eu/en/medicines/human/EPAR/veklury>.
846. Pedersen, N.C., et al., *Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis*. Journal of feline medicine and surgery, 2019. **21**(4): p. 271-281.
847. Dickinson, P.J., et al., *Antiviral treatment using the adenosine nucleoside analogue GS - 441524 in cats with clinically diagnosed neurological feline infectious peritonitis*. Journal of veterinary internal medicine, 2020. **34**(4): p. 1587-1593.
848. Yin, Y., et al., *A retrospective study of clinical and laboratory features and treatment on cats highly suspected of feline infectious peritonitis in Wuhan, China*. Scientific reports, 2021. **11**(1): p. 1-9.
849. Murphy, B.G., et al., *The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies*. Veterinary microbiology, 2018. **219**: p. 226-233.
850. Krentz, D., et al., *Curing cats with feline infectious peritonitis with an oral multi-component drug containing GS-441524*. Viruses, 2021. **13**(11): p. 2228.
851. Hughes, D., G. Howards, and R. Malik, *Treatment of FIP in cats with Remdesivir*. Veterinarian, 2021. **5-6**.
852. Scavone, C., et al., *Current pharmacological treatments for COVID - 19: What's next?* British Journal of Pharmacology, 2020.
853. Ferner, R.E. and J.K. Aronson, *Remdesivir in covid-19*. 2020, British Medical Journal Publishing Group.
854. Agostini, M.L., et al., *Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease*. MBio, 2018. **9**(2): p. e00221-18.
855. Zhang, X., et al., *Rupintrivir is a promising candidate for treating severe cases of enterovirus-71 infection: evaluation of antiviral efficacy in a murine infection model*. Antiviral research, 2013. **97**(3): p. 264-269.
856. Rocha-Pereira, J., et al., *The enterovirus protease inhibitor rupintrivir exerts cross-genotypic anti-norovirus activity and clears cells from the norovirus replicon*. Antimicrobial agents and chemotherapy, 2014. **58**(8): p. 4675-4681.
857. Lockbaum, G.J., et al., *Pan-3C Protease Inhibitor Rupintrivir Binds SARS-CoV-2 Main Protease in a Unique Binding Mode*. Biochemistry, 2021. **60**(39): p. 2925-2931.
858. Clinical Trials Arena, *Rupintrivir (AG7088)*. Last accessed: 2022: <https://www.clinicaltrialsarena.com/projects/ag7088/>.
859. Binford, S., et al., *In vitro resistance study of rupintrivir, a novel inhibitor of human rhinovirus 3C protease*. Antimicrobial agents and chemotherapy, 2007. **51**(12): p. 4366-4373.
860. Yang, G., et al., *An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge*. Journal of virology, 2005. **79**(20): p. 13139-13149.

861. FDA, *TPOXX. Highlights of prescribing information*. website, last accessed in 2021: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf.
862. Sia, L., et al., *Investigation of triazavirin antiviral activity against influenza A virus (H5N1) in cell culture*. *Antibiotiki i Khimioterapiia= Antibiotics and Chemotherapy [sic]*, 2007. **52**(11-12): p. 18-20.
863. MedChemExpress, *Triazavirin* Last accessed: 2022: <https://www.medchemexpress.com/triazavirin.html>.
864. Warris, A., et al., *ESCMID-ECMM guideline: diagnosis and management of invasive aspergillosis in neonates and children*. *Clinical Microbiology and Infection*, 2019. **25**(9): p. 1096-1113.
865. Hamdy, R.F., T.E. Zaoutis, and S.K. Seo, *Antifungal stewardship considerations for adults and pediatrics*. *Virulence*, 2017. **8**(6): p. 658-672.
866. Beardsley, J., et al., *Responding to the emergence of antifungal drug resistance: perspectives from the bench and the bedside*. *Future microbiology*, 2018. **13**(10): p. 1175-1191.
867. Bassetti, M., et al., *What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead*. *Journal of Antimicrobial Chemotherapy*, 2018. **73**(suppl_1): p. i14-i25.
868. Pfaller, M.A., et al. *Twenty years of the SENTRY antifungal surveillance program: results for Candida species from 1997–2016*. in *Open forum infectious diseases*. 2019. Oxford University Press US.
869. Arendrup, M.C. and T.F. Patterson, *Multidrug-resistant Candida: epidemiology, molecular mechanisms, and treatment*. *The Journal of infectious diseases*, 2017. **216**(suppl_3): p. S445-S451.
870. Van der Linden, J.W., et al., *Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus*. *Emerg Infect Dis*, 2015. **21**(6): p. 1041-4.
871. Chowdhary, A., C. Sharma, and J.F. Meis, *Azole-resistant aspergillosis: epidemiology, molecular mechanisms, and treatment*. *The Journal of infectious diseases*, 2017. **216**(suppl_3): p. S436-S444.
872. Lestrade, P., et al., *Triazole resistance in Aspergillus fumigatus: recent insights and challenges for patient management*. *Clinical Microbiology and Infection*, 2019. **25**(7): p. 799-806.
873. Lelièvre, L., et al., *Azole resistant Aspergillus fumigatus: an emerging problem*. *Medecine et maladies infectieuses*, 2013. **43**(4): p. 139-145.
874. Monod, M., et al., *Trichophyton rubrum azole resistance mediated by a new ABC transporter, TruMDR3*. *Antimicrobial agents and chemotherapy*, 2019. **63**(11): p. e00863-19.
875. Aneke, C.I., D. Otranto, and C. Cafarchia, *Therapy and antifungal susceptibility profile of Microsporum canis*. *Journal of Fungi*, 2018. **4**(3): p. 107.
876. Abastabar, M., et al., *In vitro activities of 15 antifungal drugs against a large collection of clinical isolates of Microsporum canis*. *Mycoses*, 2019. **62**(11): p. 1069-1078.
877. Rocha, M.F.G., et al., *Azole resistance in Candida albicans from animals: highlights on efflux pump activity and gene overexpression*. *Mycoses*, 2017. **60**(7): p. 462-468.
878. Castelo-Branco, D.d.S.C., et al., *Azole resistance in Candida from animals calls for the One Health approach to tackle the emergence of antimicrobial resistance*. *Medical Mycology*, 2020.
879. Talbot, J.J., et al., *Azole resistance in canine and feline isolates of Aspergillus fumigatus*. *Comparative immunology, microbiology and infectious diseases*, 2015. **42**: p. 37-41.
880. Tekin, H.G., et al., *Would you like to purchase a rodent with dermatophytes?* *Mycoses*, 2019. **62**(7): p. 584-587.
881. Freeman, D.E., *Update on disorders and treatment of the guttural pouch*. *Veterinary Clinics: Equine Practice*, 2015. **31**(1): p. 63-89.
882. Buckingham, R., *Martindale: The Complete Drug Reference*. Last accessed: 2022: <http://www.medicinescomplete.com>.
883. Denning, D.W., et al., *Chronic pulmonary aspergillosis: rationale and clinical guidelines for diagnosis and management*. *European Respiratory Journal*, 2016. **47**(1): p. 45-68.
884. Hope, W., et al., *ESCMID* guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp*. *Clinical Microbiology and Infection*, 2012. **18**: p. 38-52.
885. Ullmann, A., et al., *ESCMID** This guideline was presented in part at ECCMID 2011. European Society for Clinical Microbiology and Infectious Diseases. guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT)*. *Clinical Microbiology and Infection*, 2012(18): p. 53-67.
886. Cornely, O., et al., *ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013*. *Clinical Microbiology and Infection*, 2014. **20**: p. 5-26.

887. Vincent, B.M., et al., *Fitness trade-offs restrict the evolution of resistance to amphotericin B*. PLoS biology, 2013. **11**(10).
888. O'Shaughnessy, E.M., C.A. Lyman, and T.J. Walsh, *Amphotericin B: Polyene resistance mechanisms*, in *Antimicrobial drug resistance*. 2009, Springer. p. 295-305.
889. Alastruey-Izquierdo, A., et al., *Population-based survey of filamentous fungi and antifungal resistance in Spain (FILPOP Study)*. Antimicrobial agents and chemotherapy, 2013. **57**(7): p. 3380-3387.
890. Astvad, K., et al., *Update from a 12-year nationwide fungemia surveillance: increasing intrinsic and acquired resistance causes concern*. Journal of clinical microbiology, 2018. **56**(4): p. e01564-17.
891. Ericsson, J., et al., *Candidaemia in Sweden: a nationwide prospective observational survey*. Clinical Microbiology and Infection, 2013. **19**(4): p. E218-E221.
892. Klingspor, L., et al., *Epidemiology of fungaemia in Sweden: A nationwide retrospective observational survey*. Mycoses, 2018. **61**(10): p. 777-785.
893. Posch, W., et al., *Aspergillus terreus: Novel lessons learned on amphotericin B resistance*. Medical mycology, 2018. **56**(suppl_1): p. S73-S82.
894. Jensen, R.H., et al., *Stepwise emergence of azole, echinocandin and amphotericin B multidrug resistance in vivo in Candida albicans orchestrated by multiple genetic alterations*. Journal of Antimicrobial Chemotherapy, 2015. **70**(9): p. 2551-2555.
895. Cordeiro, R.d.A., et al., *Candida tropicalis isolates obtained from veterinary sources show resistance to azoles and produce virulence factors*. Sabouraudia, 2014. **53**(2): p. 145-152.
896. Ziółkowska, G., S. Tokarzewski, and A. Nowakiewicz, *Drug resistance of Aspergillus fumigatus strains isolated from flocks of domestic geese in Poland*. Poultry science, 2014. **93**(5): p. 1106-1112.
897. Ghannoum, M.A. and L.B. Rice, *Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance*. Clinical microbiology reviews, 1999. **12**(4): p. 501-517.
898. Vu, K., et al., *Flucytosine resistance in Cryptococcus gattii is indirectly mediated by the FCY2-FCY1-FUR1 pathway*. Medical mycology, 2018. **56**(7): p. 857-867.
899. Costa, C., et al., *New mechanisms of flucytosine resistance in C. glabrata unveiled by a chemogenomics analysis in S. cerevisiae*. PloS one, 2015. **10**(8).
900. Trivedi, S.R., et al., *Feline cryptococcosis: impact of current research on clinical management*. Journal of feline medicine and surgery, 2011. **13**(3): p. 163-172.
901. Pennisi, M.G., et al., *Cryptococcosis in cats: ABCD guidelines on prevention and management*. Journal of Feline Medicine and Surgery, 2013. **15**(7): p. 611-618.
902. Turtle, L. and W. Hope, *Griseofulvin*, in *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs (7th ed.)*. 2018.
903. Chen, X., et al., *Systemic antifungal therapy for tinea capitis in children: An abridged Cochrane Review*. Journal of the American Academy of Dermatology, 2017. **76**(2): p. 368-374.
904. Schmitt, H., et al., *Inactivity of terbinafine in a rat model of pulmonary aspergillosis*. European Journal of Clinical Microbiology and Infectious Diseases, 1990. **9**(11): p. 832-835.
905. Cannon, R.D., et al., *Efflux-mediated antifungal drug resistance*. Clinical microbiology reviews, 2009. **22**(2): p. 291-321.
906. Martinez-Rossi, N.M., et al., *Dermatophyte resistance to antifungal drugs: mechanisms and prospectus*. Frontiers in microbiology, 2018. **9**: p. 1108.
907. Osborne, C.S., et al., *Amino acid substitution in Trichophyton rubrum squalene epoxidase associated with resistance to terbinafine*. Antimicrobial agents and chemotherapy, 2005. **49**(7): p. 2840-2844.
908. Saunte, D.M., et al., *Emerging Terbinafine Resistance in Trichophyton: Clinical Characteristics, Squalene Epoxidase Gene Mutations, and a Reliable EUCAST Method for Detection*. Antimicrobial agents and chemotherapy, 2019. **63**(10): p. e01126-19.
909. Yamada, T., et al., *Terbinafine resistance of Trichophyton clinical isolates caused by specific point mutations in the squalene epoxidase gene*. Antimicrobial agents and chemotherapy, 2017. **61**(7): p. e00115-17.
910. Rudramurthy, S.M., et al., *Mutation in the squalene epoxidase gene of Trichophyton interdigitale and Trichophyton rubrum associated with allylamine resistance*. Antimicrobial agents and chemotherapy, 2018. **62**(5): p. e02522-17.
911. Kano, R., et al., *Resistance mechanism in a terbinafine-resistant strain of Microsporum canis*. Mycopathologia, 2018. **183**(3): p. 623-627.
912. Almeida-Paes, R., et al., *Melanins protect Sporothrix brasiliensis and Sporothrix schenckii from the antifungal effects of terbinafine*. PLoS One, 2016. **11**(3).

913. Hofbauer, B., I. Leitner, and N. Ryder, *In vitro* susceptibility of *Microsporum canis* and other dermatophyte isolates from veterinary infections during therapy with terbinafine or griseofulvin. *Medical mycology*, 2002. **40**(2): p. 179-183.
914. Hsiao, Y.-H., et al., *The first report of terbinafine resistance Microsporum canis from a cat*. *Journal of Veterinary Medical Science*, 2018: p. 17-0680.
915. Chiotos, K., et al., *Comparative effectiveness of echinocandins versus fluconazole therapy for the treatment of adult candidaemia due to Candida parapsilosis: a retrospective observational cohort study of the Mycoses Study Group (MSG-12)*. *Journal of Antimicrobial Chemotherapy*, 2016. **71**(12): p. 3536-3539.
916. Jensen, R., et al., *Posttreatment antifungal resistance among colonizing Candida isolates in candidemia patients: results from a systematic multicenter study*. *Antimicrobial agents and chemotherapy*, 2016. **60**(3): p. 1500-1508.
917. Perlin, D.S., R. Rautemaa-Richardson, and A. Alastruey-Izquierdo, *The global problem of antifungal resistance: prevalence, mechanisms, and management*. *The Lancet infectious diseases*, 2017. **17**(12): p. e383-e392.
918. Healey, K.R., et al., *Prevalent mutator genotype identified in fungal pathogen Candida glabrata promotes multi-drug resistance*. *Nature communications*, 2016. **7**(1): p. 1-10.
919. Dellière, S., et al., *Fluconazole and echinocandin resistance of Candida glabrata correlates better with antifungal drug exposure rather than with MSH2 mutator genotype in a French cohort of patients harboring low rates of resistance*. *Frontiers in microbiology*, 2016. **7**: p. 2038.
920. Arendrup, M., *Update on antifungal resistance in Aspergillus and Candida*. *Clinical microbiology and infection*, 2014. **20**: p. 42-48.
921. Leshinsky, J., et al., *Pharmacokinetics of caspofungin acetate to guide optimal dosing in cats*. *PLoS one*, 2017. **12**(6).
922. EMA/CVMP/CHMP, *Categorisation of antibiotics in the European Union (EMA/CVMP/CHMP/682198/2017)*. 2019: https://www.ema.europa.eu/en/documents/report/categorisation-antibiotics-european-union-answer-request-european-commission-updating-scientific_en.pdf.
923. WHO, *AWaRe classification*. 2021: <https://www.who.int/publications/i/item/2021-aware-classification>.