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

World Health Organization

WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

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1. Background

The WHO List of Critically Important Antimicrobials for Human Medicine (*WHO CIA List*) was originally developed following recommendations from two consecutive expert meetings organized by the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO). The first workshop was convened in Geneva, December 2003 (*1*) and the second workshop in Oslo, March 2004 (*2*) to address the public health consequences associated with the use of antimicrobial agents in food-producing animals.

The first expert workshop recognized that antimicrobial resistance was a global public and animal health concern that has been impacted by the use of antimicrobial agents in all sectors, and highlighted that the types of antimicrobials used in animals for growth promotion, prophylactic or therapeutic purposes were frequently the same, or closely related to those used in human medicine.

The first expert workshop concluded that, firstly, there was clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials: increased frequency of infections, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented by fluoroquinolone-resistant human *Salmonella* infections. Secondly, the amount and pattern of non-human usage of antimicrobials affected the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria. Thirdly, the consequences of antimicrobial resistance were particularly severe when pathogens were resistant to antimicrobials critically important for human health. The workshop therefore recommended that an expert clinical medical group, appointed by WHO, define and provide a list of antimicrobials that were considered critically important in humans.

The second expert workshop recommended that the concept of "critically important" classes of antimicrobials for people should be developed by WHO: "WHO should convene an international expert group (including a broad range of clinical experts in infectious diseases and microbiology), to develop first criteria for defining critically important antimicrobials for human by class and/or subgroup, and then to propose a list of those antimicrobials. This list needs to take into account relevant bacteria-both pathogens and commensals (or their genes) that are likely to transfer to people from animals, food products or the environment".

The experts recognized that the implementation of the concept at national levels required that national considerations would be taken into account, and consequently lists may vary from country to country, and that the lists should be made publicly available and could be used for the following purposes:

- to give guidance on resource allocation and prioritization of risk assessment and management processes for both new and existing drug applications
- to estimate consequences (for harm to people) by non-human antimicrobial use within risk assessments
- to develop risk management options that involve restriction of use in a country

The same FAO/OIE/WHO expert workshop recommended that the OIE identify and list antimicrobial agents that are critically important for veterinary medicine. The overlap of the two lists should be considered for risk management options, allowing an appropriate balance between animal health and welfare, and public health.

A third FAO/OIE/WHO expert meeting met in Rome in 2007 (*3*) to consider the WHO and OIE lists of critically important antimicrobials and begin to address the overlap of the two lists, for example, the potential hazards to public health resulting from this overlap and the combinations

of pathogen, antimicrobial and animal species of most concern. The meeting concluded that the lists of critically important antimicrobials should be revised on a regular basis in a collaborative and coordinated approach by FAO, OIE and WHO.

References:

1. Joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: scientific assessment. Food and Agriculture Organization of the United Nations / World Organisation for Animal Health / World Health Organization. 2003. (http://apps.who.int/iris/bitstream/10665/68883/1/WHO_CDS_CPE_ZFK_2004.7.pdf?ua=1 , accessed 4 March 2019).

2. Second joint FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance: management options. Food and Agriculture Organization of the United Nations / World Organisation for Animal Health / World Health Organization. 2004. (http://apps.who.int/iris/bitstream/10665/68701/1/WHO_CDS_CPE_ZFK_2004.8.pdf?ua=1, accessed 4 March 2019).

3. Joint FAO/WHO/OIE expert meeting on critically important antimicrobials. Report of the FAO/WHO/OIE Expert meeting. Food and Agriculture Organization of the United Nations / World Organisation for Animal Health / World Health Organization. 2007. (http://www.fao.org/3/a-i0204e.pdf, accessed 4 March 2019).

2. History of the document

The WHO CIA List was first developed in 2005. It was updated in 2007, 2009, 2011, 2013, 2016 and most recently in 2018 (the current version). Since its inception, several changes have been made to the list. Specific details are available in previous versions of the *WHO CIA List*.[1]

The first WHO Expert Meeting on Critically Important Antimicrobials (CIA) for Human Health was held in Canberra, Australia in 2005. During that meeting, participants considered the list of all antimicrobial classes used in human medicine (i.e. medically important antimicrobials) and categorized antimicrobials into three groups: critically important, highly important, and important, based on two criteria developed at the meeting.[2]

The second WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark in 2007. During the second meeting, participants reviewed the two criteria and re-examined the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. Participants were also requested to prioritize agents within the critically important category in order to allow allocation of resources towards the agents for which management of the risks from antimicrobial resistance were needed most urgently.[3] The classes of drugs that met all prioritization criteria were called Highest Priority Critically Important Antimicrobials.

Subsequently, a WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was formed in 2009, following a worldwide solicitation of experts from a variety of relevant fields, including human health and veterinary medicine, to serve as members.

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[1] Available at: https://www.who.int/foodsafety/areas_work/antimicrobial-resistance/cia/en/

[2] See Sections 5 and 6 below for definition of criteria and "categorization of antimicrobials".

[3] This was done by defining two prioritization criteria (now called factors) from Criterion 1 and one from Criterion 2. See Section 7 for further details.

Reviewing and updating the *WHO CIA List* became a part of AGISAR's Terms of Reference.

At the third AGISAR meeting held in Oslo, Norway in 2011, the *WHO CIA List* was updated with additional information. Veterinary drugs falling in the same classes of antimicrobials as those in the human medicine list were also listed in the tables. This was done to help risk managers more readily identify those drugs and classes that were analogous to those used in human medicine and thus had greater potential to impact antimicrobial resistance to the critically important antimicrobials for human medicine.

A further revision of the *WHO CIA List* took place at the fifth AGISAR meeting held in Bogota, Colombia in 2013. The *WHO CIA List* was again updated following the seventh AGISAR meeting in Raleigh, United States of America in 2016. At this meeting, slight changes to the prioritization criteria 1 and 2 (P1 and P2) were made to better describe antimicrobial use in seriously ill patients in healthcare facilities when there are few or no alternatives available for therapy. As a consequence, polymyxins were moved to the "Highest Priority Critically Important Antimicrobials" classification because of the increasing usage of colistin to treat serious infections in humans in many parts of the world, the discovery of *mcr* genes that confer transmissible resistance to colistin, and the spread of colistin-resistant bacteria via the food chain. Since pleuromutilins have only been used as topical therapy in people to date, and there has been no transmission of resistance in *S. aureus*, including MRSA, from non-human sources, this group was moved to "Important".

Changes made in the 6th revision (2018):

- It was decided, on the basis of resistance mechanisms and availability of alternative therapies, to split penicillins into six groups for classification: antipseudomonal penicillins (e.g. piperacillin), aminopenicillins (e.g. ampicillin), aminopenicillin with beta-lactamase inhibitors (e.g. amoxicillin-clavulanic acid), amidinopenicillins (e.g. mecillinam), anti-staphylococcal

penicillins (e.g. flucloxacillin), and narrow spectrum penicillins (e.g. benzylpenicillin).

- In the case of simple penicillins, since there are now alternative therapies available for syphilis and enterococcal infections, this group was moved to "Highly Important" from "Critically Important".
- Minor editorial changes were made to the criteria used for prioritization within the "Critically Important" category. The term "criteria" was changed to "factors" to lessen confusion with Criterion 1 and 2 (C1 and C2). In the interests of clarity, minor changes to the wording of three prioritization factors (P1, P2, and P3) were also made.
- Separate listing in Annex 1 of antimicrobials used in human and veterinary medicine was removed; they are now listed together. To accurately distinguish those products used only in humans from those also used in one or more types of animals (e.g. food-producing, companion) or plants requires a level of complexity and information on possible off-label use (particularly in companion animals) not needed for the *WHO CIA List*.

Besides, it was emphasized that the *WHO CIA List* continues to base decisions on whether classes should be split for categorizations primarily on resistance mechanisms and not on the chemical structure. The categorization by resistance mechanism explains why some classes (e.g. macrolides) are not split into sub-groups in the *WHO CIA List* while they are in some national or regional lists.

3. Purpose of the document

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders involved in managing antimicrobial resistance to ensure that all

antimicrobials, especially critically important antimicrobials, are used prudently both in human and veterinary medicine.

4. Use of the document

The *WHO CIA List* should be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance.

The *WHO CIA List* supports strategies to mitigate the human health risks associated with antimicrobial use in food-producing animals and has been used by both public and private sector organizations. The list helps regulators and stakeholders know which types of antimicrobials used in animals present potentially higher risks to human populations and how use of antimicrobials might be managed to minimize antimicrobial resistance of medical importance. The use of the *WHO CIA List*, in conjunction with the OIE list of antimicrobials of veterinary importance (*1*) and the WHO Model Lists of Essential Medicines (*2*), will allow for prioritization of risk management strategies in the human sector, the food animal sector, in agriculture (crops) and horticulture, through a coordinated multisectoral One Health approach.

Some examples of use of the document include:

- Prioritizing the development of risk management strategies for those antimicrobials categorized as critically important in order to preserve their effectiveness in human medicine;
- Ensuring that critically important antimicrobials are included in antimicrobial resistance monitoring programmes;
- Refining and prioritizing risk profile and hazard analysis activities for interventions by species or by region;
- Developing risk management options such as restricted use, labelling, limiting or prohibiting extra-label use, and making antimicrobial agents available by prescription only;

- Developing prudent use and treatment guidelines in humans and animals;
- Directing special research projects to address data gaps on existing or future critically important antimicrobials; and
- Communicating risks to the public.

References:

1. OIE list of antimicrobial agents of veterinary importance. Paris. World Organisation for Animal Health. 2018. (http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/A_OIE_List_antimicrobials_May2018.pdf, accessed 4 March 2019).

2. WHO Model Lists of Essential Medicines [website]. Geneva. World Health Organization. (http://www.who.int/medicines/publications/essentialmedicines/en/ , accessed 4 March 2019).

5. Criteria for categorization

Two criteria are used to categorize antimicrobial classes used in human medicine as Critically Important, Highly Important or Important. Those classes categorized as Critically Important are further prioritized on the basis of three additional factors as depicted in Figure 1.

Since the *WHO CIA List* is intended to be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance, antimicrobial classes are sub-divided into sub-classes for categorization only if justified on the basis of mechanisms of resistance. For example, there are sufficient differences in mechanisms of resistance to various cephalosporins to separate the 1st and 2nd generation from the 3rd to 5th generation cephalosporins for the purposes of categorization. However, there is no such basis for dividing members of the macrolide class.

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

Explanation: It is evident that antimicrobials that are the sole or one of few alternatives for the treatment of serious bacterial infections in humans occupy an important place in medicine. While severity of illness may relate to the site of infection (e.g. pneumonia, meningitis) or the host (e.g. infant, immunosuppressed), serious infections are overall more likely to result in increased morbidity or mortality if left untreated because no effective antibacterial agents are available.

It is of prime importance that the use of such antibacterial agents be preserved, as loss of efficacy in these drugs due to the emergence of resistance would have a significant impact on human health, especially for people with life-threatening infections. This criterion does not consider the likelihood that these pathogens may be transmitted, or have been transmitted, from non-human sources to humans.

Criterion 2 (C2): The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from non-human sources, or (2) bacteria that may acquire resistance genes from non-human sources.

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

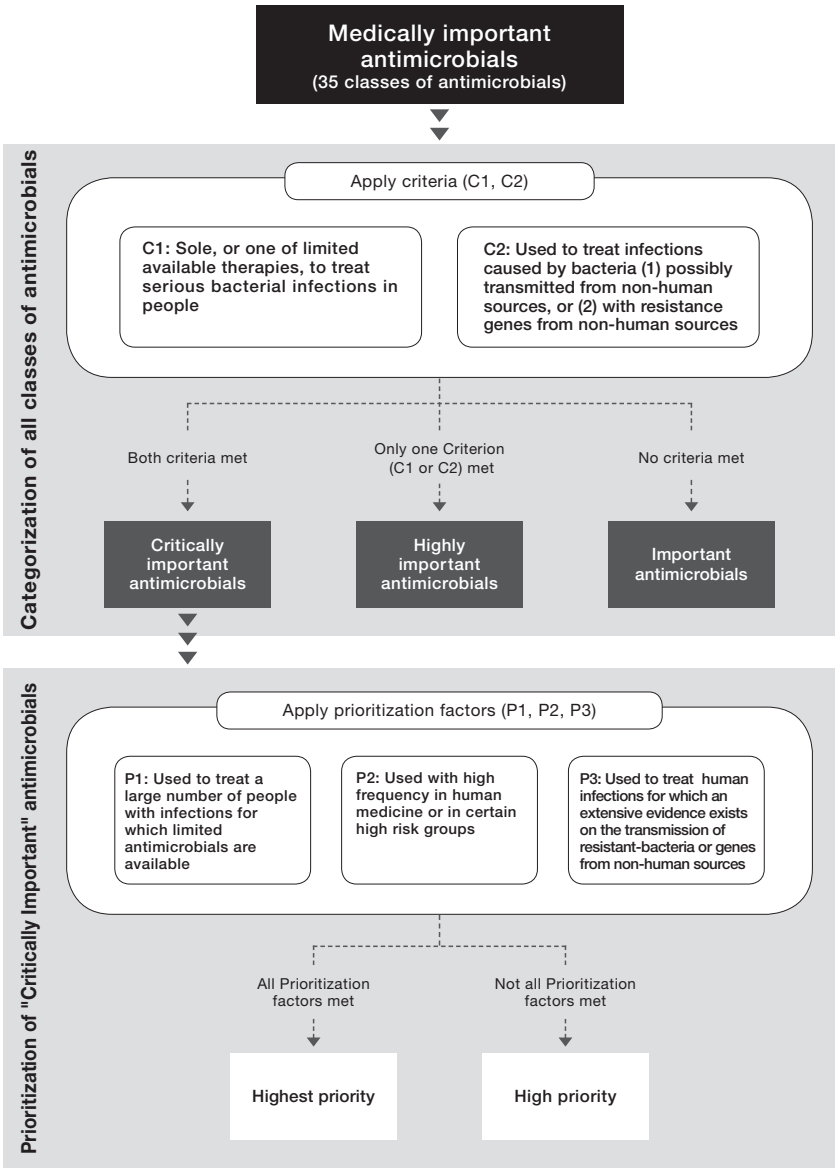

Figure 1. Flow chart of application of criteria and prioritization factors to medically important antimicrobials

6. Interpretation of categorization

All antimicrobials used in human medicine (i.e. medically important antimicrobials) are categorized according to specified criteria as either "Critically important", "Highly important", or "Important" for human medicine.

Critically important: Antimicrobial classes which meet both C1 and C2 are termed critically important for human medicine.

Highly important: Antimicrobial classes which meet either C1 or C2 are termed highly important for human medicine.

Important: Antimicrobial classes used in humans which meet neither C1 nor C2 are termed important for human medicine.

The list below (Table 1) shows the overall results of categorization. It is meant to show examples of members of each class of drugs and is not meant to be inclusive of all drugs. Not all drugs listed in a given class have necessarily been proven safe and effective for the diseases listed in Table 2 and Annex 1. The specific result of C1 and C2 application are shown in Table 3 and Annex 1.

Table 1. Listing of antimicrobial classes and example antimicrobial agents used in human medicine (i.e. medically important antimicrobials)

Antimicrobial class	Example of antimicrobials(s)
CRITICALLY IMPORTANT ANTIMICROBIALS	
Aminoglycosides	gentamicin
Ansamycins	rifampicin
Carbapenems and other penems	meropenem
Cephalosporins (3rd,4th and 5th generation)	ceftriaxone, cefepime, ceftaroline, ceftobiprole
Glycopeptides	vancomycin
Glycylcyclines	tigecycline
Lipopeptides	daptomycin
Macrolides and ketolides	azithromycin, erythromycin, telithromycin
Monobactams	aztreonam
Oxazolidinones	linezolid
Penicillins (antipseudomonal)	piperacillin
Penicillins (aminopenicillins)	ampicillin
Penicillins (aminopenicillin with beta-lactamase inhibitors)	amoxicillin-clavulanic-acid
Phosphonic acid derivatives	fosfomycin
Polymyxins	colistin
Quinolones	ciprofloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid
HIGHLY IMPORTANT ANTIMICROBIALS	
Amphenicols	chloramphenicol, thiamphenicol
Cephalosporins (1st and 2nd generation) and cephamycins	cefazolin
Lincosamides	clindamycin
Penicillins (amidinopenicillins)	mecillinam
Penicillins (anti-staphylococcal)	flucloxacillin
Penicillins (narrow spectrum)	benzathine-benzylpenicillin, phenoxymethylpenicillin
Pseudomonic acids	mupirocin
Riminofenazines	clofazimine
Steroid antibacterials	fusidic acid
Streptogramins	quinupristin/dalfopristin

Sulfonamides, dihydrofolate reductase inhibitors and combinations	sulfamethoxazole, trimethoprim
Sulfones	dapsone
Tetracyclines	chlortetracycline
IMPORTANT ANTIMICROBIALS	
Aminocyclitols	spectinomycin
Cyclic polypeptides	bacitracin
Nitrofuran derivatives	nitrofurantoin
Nitroimidazoles	metronidazole
Pleuromutilins	retapamulin

See Annex 1 for the full list of medically important antimicrobials. Some of the antimicrobial agents listed are used only in people, some in both people and animals (e.g. erythromycin, ampicillin, colistin) and some are used only in animals (e.g. ceftiofur, florfenicol, virginiamycin, tiamulin). This list also gives a rationale for the categorization of each individual drug class. In addition, there is also a list of all antimicrobial classes currently not used in humans (Annex 2).

7. Prioritization within the "Critically Important" category

Antimicrobials within the critically important category are prioritized to assist in allocating resources towards agents for which risk management strategies are needed most urgently (see Section 8 for more details). The following three factors are used for prioritization:

Explanation: The first two prioritization factors relate to the first Criterion (C1) used to categorize antimicrobials. The first prioritization factor (P1) relates to the number of people that might need therapy and the second prioritization factor (P2) relates to the frequency of and the intensity of antimicrobial use in humans. The third prioritization factor (P3) relates to the second Criterion (C2) which is used to classify antimicrobials and relates to the amount of evidence already available that shows transmission of resistant bacteria or their genetic elements, is already occurring relatively frequently.

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

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

Prioritization factor 3 (P3): The antimicrobial class is used to treat infections in people for which there is already extensive evidence of transmission of resistant bacteria (e.g., non-typhoidal *Salmonella* spp. and *Campylobacter* spp.) or resistance genes (high for *E. coli* and *Enterococcus* spp.) from non-human sources.

Table 2. Prioritization of antimicrobials categorized as "Critically Important" in human medicine.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Aminoglycosides	No*	Yes	Yes	(P1*) In some countries there is a high proportion of use in patients in health care settings with serious infections for which, because of resistance, it is one of few alternatives. (P2) High frequency of use in human medicine. (P3) Transmission of *Enterococcus* spp., Enterobacteriaceae (including *E. coli*), and *Mycobacterium* spp. from non-human sources.
Ansamycins	Yes	Yes	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Carbapenems and other penems	Yes	Yes	No*	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3*) Still limited transmission of carbapenem-resistant Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources; spread of carbapenem-resistant *Salmonella* spp. is increasing however. Detection of Carbapenem-resistant Enterobacteriaceae (CRE) in the food chain has been reported from both developed and developing countries.
Cephalosporins (3rd, 4th and 5th generation)	Yes	Yes	Yes	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of extended spectrum beta-lactamase producing (ESBL) Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Glycopeptides	Yes	Yes	Yes	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of vancomycin-resistant enterococci (VRE) has occurred in past when avoparcin was used in food animals.
Glycylcyclines	Yes	No	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available.
Lipopeptides	Yes	No	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available.
Macrolides and ketolides	Yes	Yes	Yes	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of resistant *Campylobacter* spp. from non-human sources.
Monobactams	Yes	No	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Oxazolidinones	Yes	No	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available.
Penicillins (antipseudomonal)	No*	Yes	No	(P1*) In certain geographic settings, this factor may be met: there may be a high absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine.
Penicillins (aminopenicillins)	No*	Yes	Yes	(P1*) In certain geographic settings, this factor may be met: there may be a high absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of resistant *Enterococcus* spp. and Enterobacteriaceae (including *Salmonella* spp. and *E. coli*).
Penicillins (aminopenicillin with beta-lactamase inhibitors)	No*	Yes	Yes	(P1*) In certain geographic settings, this factor may be met: there may be a high absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
				(P3) Transmission of resistant *Enterococcus* spp. and Enterobacteriaceae (including *Salmonella* spp. and *E. coli*).
Phosphonic acid derivatives	Yes	Yes	No*	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine. (P3*) There are concerns that in some countries high volumes of fosfomycin are used in food animals.
Polymyxins	Yes	Yes	Yes	(P1) High numbers of people affected by diseases who are seriously ill in healthcare facilities in many countries for which the antimicrobial is the sole or one of few therapies available. (P2) In multiple countries there is high use in people in critical care settings or where multidrug resistant organisms are prevalent. (P3). Colistin resistant bacteria and the *mcr* family genes can be transmitted via the food chain.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Quinolones	Yes	Yes	Yes	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine (P3) Transmission of resistant *Campylobacter* spp. and Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Yes	Yes	No	(P1) High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few therapies available. (P2) High frequency of use in human medicine.

Table 3. Summary of categorization and prioritization[4]

Antimicrobial class	Criterion / Prioritization Factor				
CRITICALLY IMPORTANT ANTIMICROBIALS	**C1**	**C2**	**P1**	**P2**	**P3**
Highest Priority Critically Important Antimicrobials					
Cephalosporins (3rd, 4th and 5th generation)	Yes	Yes	Yes	Yes	Yes
Glycopeptides	Yes	Yes	Yes	Yes	Yes
Macrolides and ketolides	Yes	Yes	Yes	Yes	Yes
Polymyxins	Yes	Yes	Yes	Yes	Yes
Quinolones	Yes	Yes	Yes	Yes	Yes
High Priority Critically Important Antimicrobials					
Aminoglycosides	Yes	Yes	No	Yes	Yes
Ansamycins	Yes	Yes	Yes	Yes	No
Carbapenems and other penems	Yes	Yes	Yes	Yes	No
Glycylcyclines	Yes	Yes	Yes	No	No
Lipopeptides	Yes	Yes	Yes	No	No
Monobactams	Yes	Yes	Yes	No	No
Oxazolidinones	Yes	Yes	Yes	No	No
Penicillins (antipseudomonal)	Yes	Yes	No	Yes	No
Penicillins (aminopenicillins)	Yes	Yes	No	Yes	Yes
Penicillins (aminopenicillins with beta-lactamase inhibitors)	Yes	Yes	No	Yes	Yes
Phosphonic acid derivatives	Yes	Yes	Yes	Yes	No
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Yes	Yes	Yes	Yes	No
HIGHLY IMPORTANT ANTIMICROBIALS	**C1**	**C2**			
Amphenicols	No	Yes	NA		
Cephalosporins (1st and 2nd generation) and cephamycins	No	Yes			

[4] See definitions of criteria and prioritization factors in Section 5 and 7, respectively.

Antimicrobial class	Criterion / Prioritization Factor		
Lincosamides	No	Yes	
Penicillins (amidinopenicillins)	No	Yes	
Penicillins (anti-staphylococcal)	No	Yes	
Penicillins (narrow spectrum)	No	Yes	
Pseudomonic acids	No	Yes	
Riminofenazines	Yes	No	
Steroid antibacterials	No	Yes	
Streptogramins	No	Yes	
Sulfonamides, dihydrofolate reductase inhibitors and combinations	No	Yes	
Sulfones	Yes	No	
Tetracyclines	Yes	No	
IMPORTANT ANTIMICROBIALS	**C1**	**C2**	
Aminocyclitols	No	No	
Cyclic polypeptides	No	No	
Nitrofuran derivatives	No	No	NA
Nitroimidazoles	No	No	
Pleuromutilins	No	No	

8. Highest Priority Critically Important Antimicrobials

The following classes of antimicrobial drugs met all three prioritization factors (P1, P2, and P3): quinolones, 3rd and higher generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

Quinolones are known to select for quinolone-resistant *Salmonella* spp. and *E. coli* in animals. At the same time, quinolones are one of few available therapies for serious *Salmonella* spp. and *E. coli* infections. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

Cephalosporins (3rd and higher generation) are known to select for cephalosporin-resistant *Salmonella* spp. and *E. coli* in animals. At the same time, 3rd and higher generation cephalosporins are one of few available therapies for serious *Salmonella* spp. and *E. coli* infections in humans, particularly in children. Given the high incidence of human disease due to *Salmonella* spp. and *E. coli*, the absolute number of serious cases is substantial.

Macrolides and Ketolides are known to select for macrolide-resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. At the same time, macrolides are one of few available therapies for serious *Campylobacter* infections, particularly in children, for whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., especially *Campylobacter jejuni,* the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptide-resistant *Enterococcus* spp. in food animals (e.g. when avoparcin was used as a growth promoter, vancomycin-resistant enterococci (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals, and the very serious consequences of treatment failures in such cases, glycopeptides are classified as being of the highest priority.

Polymyxins (e.g. colistin) are known to select for plasmid mediated polymyxin-resistant *E. coli* in food animals. At the same time, intravenous polymyxins are one of few available therapies for serious *Enterobactericeae* and *Pseudomonas aeruginosa* multi-resistant infections in people in healthcare settings in many countries, especially in seriously ill patients in critical care. Given the high incidence of human disease due to *Enterobactericiae*, the absolute number of serious cases where colistin is needed can be considered substantial.

Annex 1

List of Medically Important Antimicrobials, categorized as Critically Important, Highly Important and Important

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
CRITICALLY IMPORTANT ANTIMICROBIALS				
Aminoglycosides	amikacin apramycin arbekacin astromicin bekanamycin dibekacin dihydrostreptomycin framycetin gentamicin isepamicin kanamycin neomycin netilmicin paromomycin plazomicin ribostamycin streptomycin tobramycin	Yes	Yes	(C1) Sole or limited therapy as part of treatment of enterococcal endocarditis and multidrug-resistant (MDR) tuberculosis and MDR Enterobacteriaceae. (C2) May result from transmission of *Enterococcus* spp., Enterobacteriaceae (including *E. coli*), and *Mycobacterium* spp. from non-human sources.
Ansamycins	rifabutin rifampicin rifamycin rifapentine rifaximin	Yes	Yes	(C1) Limited therapy as part of treatment of mycobacterial diseases including tuberculosis; single drug therapy may select for resistance. (C2) May result from transmission of *Mycobacterium* spp. from non-human sources and MDR *Staphylococcus aureus* through the food chain.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Carbapenems and other penems	biapenem doripenem ertapenem faropenem imipenem meropenem meropenem/vaborbactam panipenem	Yes	Yes	(C1) Limited therapy for infections due to MDR Enterobacteriaceae. (C2) May result from transmission of Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.
Cephalosporins (3rd, 4th and 5th generation)	cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoperazone-sulbactam cefoselis cefotaxime cefovecin cefozopran cefpiramide cefpirome cefpodoxime cefquinome cefsulodin ceftaroline fosamil ceftazidime ceftazidime-avibactam ceftibuten ceftiofur ceftizoxime ceftobiprole ceftolozane ceftriaxone ceftriaxone-sulbactam latamoxef tazobactam	Yes	Yes	(C1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* spp. in children. Limited therapy for infections due to MDR Enterobacteriaceae, which are increasing in incidence worldwide. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (C2) May result from transmission of Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Glycopeptides and lipoglycopeptides	avoparcin dalbavancin oritavancin ramoplanin teicoplanin telavancin vancomycin	Yes	Yes	(C1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.
Glycylcyclines	tigecycline	Yes	Yes	(C1) Limited therapy for infections due to MDR Enterobacteriaceae. Limited therapy for infections due to MRSA. (C2) May result from transmission of MRSA and Enterobacteriaceae from non-human sources.
Lipopeptides	daptomycin	Yes	Yes	(C1) Limited therapy for infections due to *Enterococcus* spp. or MDR MRSA. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Macrolides and ketolides	azithromycin cethromycin clarithromycin dirithromycin erythromycin fidaxomicin flurithromycin gamithromycin josamycin kitasamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin tildipirosin tilmicosin troleandomycin solithromycin tulathromycin tylosin tylvalosin	Yes	Yes	(C1) Limited therapy for *Legionella*, *Campylobacter,* and MDR *Salmonella* spp. and *Shigella* infections. (C2) May result from transmission of *Campylobacter* spp. and *Salmonella* spp. from non-human sources.
Monobactams	aztreonam carumonam	Yes	Yes	(C1) Limited therapy for infections with MDR gram-negatives, especially with limited other options including for ESBLs. (C2) May result from transmission of Enterobacteriaceae, including *E. coli,* from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Oxazolidinones	cadazolid linezolid radezolid tedizolid	Yes	Yes	(C1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp.. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.
Penicillins (antipseudomonal)	azlocillin carbenicillin carindacillin mezlocillin piperacillin piperacillin-tazobactam sulbenicillin ticarcillin ticarcillin-clavulanic-acid	Yes	Yes	(C1) Limited therapy of *Pseudomonas aeruginosa*. (antipseudomonal). (C2) May result from transmission of Enterobacteriaceae, including *E. coli*, as well as *Pseudomonas aeruginosa* from non-human sources.
Penicillins (aminopenicillins)	amoxicillin ampicillin azidocillin bacampicillin epicillin hetacillin metampicillin pivampicillin sultamicillin talampicillin temocillin	Yes	Yes	(C1) Limited therapy for Listeria and *Enterococcus* spp. (aminopenicillins), (C2) May result from transmission of *Enterococcus* spp., Enterobacteriaceae, including *E. coli* from non-human sources
Penicillins (aminopenicillins with beta-lactamase inhibitors)	amoxicillin-clavulanic-acid ampicillin-sulbactam	Yes	Yes	(C1) Limited therapy for Listeria and *Enterococcus* spp. (aminopenicillins), (C2) May result from transmission of *Enterococcus* spp., Enterobacteriaceae, including *E. coli* from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Phosphonic acid derivatives	fosfomycin	Yes	Yes	(C1) Limited therapy for ESBL *E. coli* causing urinary tract infections. (C2) May result from transmission of Enterobacteriaceae, including *E. coli,* from non-human sources.
Polymyxins	colistin[1] polymyxin B	Yes	Yes	(C1) Limited therapy for infections with MDR Enterobacteriaceae (e.g. *Klebsiella* spp., *E. coli, Acinetobacter, Pseudomonas* spp.). (C2) May result from transmission of Enterobacteriaceae from non-human sources.

[1] Colistin also known as Polymixin E includes colistin sulfate and colistin methanesulfonate.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Quinolones and fluoroquinolones	besifloxacin cinoxacin ciprofloxacin danofloxacin delafloxacin difloxacin enoxacin enrofloxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin ibafloxacin levofloxacin lomefloxacin marbofloxacin moxifloxacin nadifloxacin nalidixic acid norfloxacin ofloxacin orbifloxacin ozenoxacin oxolinic acid pazufloxacin pefloxacin pipemidic acid piromidic acid pradofloxacin prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin	Yes	Yes	(C1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp., and MDR *Shigella* spp. infections. (C2) May result from transmission of *Campylobacter* spp. and Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Drugs used solely to treat tuberculosis or other mycobacterial diseases	bedaquiline calcium aminosalicylate capreomycin cycloserine delamanid ethambutol ethionamide isoniazid morinamide para-aminosalicylic-acid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	Yes	Yes	(C1) Limited therapy for tuberculosis and other *Mycobacterium* spp. disease; for many of these drugs, single drug therapy may select for resistance. (C2) May result from transmission of *Mycobacterium* spp. from non-human sources.
HIGHLY IMPORTANT ANTIMICROBIALS				
Amphenicols	chloramphenicol florfenicol thiamphenicol	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may represent one of the limited therapies for acute bacterial meningitis, typhoid and non-typhoid fever, and respiratory infections. (C2) May result from transmission of Enterobacteriaceae, including *E. coli* and *Salmonella* spp., from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Cephalosporins (1st and 2nd generation) and cephamycins	cefacetrile cefaclor cefadroxil cefalexin cefalonium cefaloridine cefalotin cefalotin cefamandole cefapirin cefatrizine cefazedone cefazolin cefbuperazone cefmetazole cefminox cefonicid ceforanide cefotetan cefotiam cefoxitin cefprozil cefradine cefroxadine ceftezole cefuroxime flomoxef loracarbef	No	Yes	(C2) May result from transmission of Enterobacteriaceae, including *E. coli,* from non-human sources.
Lincosamides	clindamycin lincomycin pirlimycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus,* including MRSA, from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Penicillins (amidinopenicillins)	mecillinam pivmecillinam	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for infections with MDR *Shigella* spp. (C2) May result from transmission of Enterobacteriaceae, including *E. coli*, from non-human sources.
Penicillins (anti-staphylococcal)	cloxacillin dicloxacillin flucloxacillin meticillin (=methicillin) oxacillin nafcillin	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for staphylococcal infections (*S. aureus*). (C2) May result from transmission of *S. aureus*, including MRSA, from non-human sources.
Penicillins (narrow spectrum)	benzathine-benzylpenicillin benethamine-benzylpenicillin benzylpenicillin (=penicillin G) clometocillin penamecillin penethamate hydriodide pheneticillin phenoxymethylpenicillin (=penicillin V) procaine benzylpenicillin propicillin	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for streptococcal infections, yaws and syphilis. (C2) May result from transmission of penicillin-resistant *Staphylococcus aureus*, from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Pseudomonic acids	mupirocin	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for topical *Staphylococcus aureus* infections. (C2) May result from transmission of MRSA from non-human sources.
Riminofenazines	clofazimine	Yes	No	(C1) Limited therapy for leprosy.
Fusidane	fusidic acid	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for infections with MRSA. (C2) May result from transmission of MRSA from non-human sources.
Streptogramins	pristinamycin quinupristin-dalfopristin virginiamycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
Sulfonamides, dihydrofolate reductase inhibitors and combinations	brodimoprim formosulfathiazole iclaprim phthalylsulfathiazole pyrimethamine sulfadiazine sulfadimethoxine sulfadimidine sulfafurazole (=sulfisoxazole) sulfaisodimidine sulfalene sulfamazone sulfamerazine sulfamethizole sulfamethoxazole sulfamethoxypyridazine sulfametomidine sulfametoxydiazine sulfametrole sulfamoxole sulfanilamide sulfaperin sulfaphenazole sulfapyridine sulfathiazole sulfathiourea tetroxoprim trimethoprim	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, systemic non-typhoidal *Salmonella* spp. infections, and other infections. (C2) May result from transmission of Enterobacteriaceae, including *E. coli,* from non-human sources.
Sulfones	aldesulfone sodium dapsone	Yes	No	(C1) Limited therapy for leprosy.

Tetracyclines	chlortetracycline clomocycline demeclocycline doxycycline eravacycline lymecycline metacycline minocycline omadacycline oxytetracycline penimepicycline rolitetracycline tetracycline	No*	Yes	(C1*) Countries where transmission of brucellosis from non-human sources to humans is common should consider making tetracycline a critical antibiotic, as there is considerable concern regarding the availability of effective products where *Brucella* spp. are endemic. (C2) Countries where transmission of brucellosis from non-human sources to humans is common should consider making tetracycline a critical antibiotic, as there is considerable concern regarding the availability of effective products where *brucella* spp. are endemic. †There are differences in activity and resistance mechanisms in tetracyclines (e.g. minocycline, doxycycline compared to chlortetracycline) against some bacteria such as *acinetobacter*. In future editions, the tetracycline class may need to be separated into different groups.

Antimicrobial class	Examples of antimicrobial agents	C1	C2	Comments
IMPORTANT ANTIMICROBIALS				
Aminocyclitols	spectinomycin	No*	No*	(C1*) In some areas spectinomycin may be one of limited antimicrobials still active against *Gonococcus.* (C2*) May result from transmission of Enterobacteriaceae, including *E. coli,* from non-human sources, but there is no demonstrated transmission from *E. coli* to *Gonococcus.*
Polypeptides	bacitracin	No	No	
Nitrofurans derivatives	furaltadone furazolidone furazidin nifurtoinol nitrofural nitrofurantoin	No	No	
Nitroimidazoles	metronidazole ornidazole secnidazole tinidazole	No*	No	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for anaerobic infections including *C. difficile*.
Pleuromutilins	retapamulin tiamulin valnemulin	No	No*	(C2*) To date pleuromutilins have only been used as topical therapy in people. There has to date been no transmission of resistance in *S. aureus,* including MRSA, from non-human sources.

Annex 2

Antimicrobial classes currently not used in humans[1]

Antimicrobial Class	Example of drug products used in food animals
Aminocoumarins	novobiocin
Arsenical	roxarsone, nitarsone
Bicyclomycin	bicozamycin
Orthosomycins	avilamycin[2]
Phosphoglycolipids	bambermycin (=flavomycin)
Ionophores (including polyesthers)	lasalocid, monensin, narasin, salinomycin
Quinoxalines	carbadox, olaquindox

[1] These drug classes are currently not approved for use in human medicine for systemic use and as such are not included in the *WHO CIA List*. Not all these drug products are used as antibacterial agents e.g. polyethers and ionophores, but they all have antibacterial activity.

[2] Some of these antibiotic classes have been used in people previously or have been considered for use in people. As examples, two structurally unique ribosomal antibiotics belonging to the orthosomycin family, avilamycin (growth promoter and therapeutic use in animals) and evernimicin (previously considered for use in human medicine), possess activity against enterococci, staphylococci, and streptococci, and other Gram-positive bacteria (*Clostridium difficile* and others). With increasing emergence of multi-drug resistance among Gram-positive organisms to multiple potent antimicrobials, the need for new antibiotics is more urgent than ever before.

Annex 3. Glossary of terms

Antibacterial: Refers to antibiotics including semi-synthetic or synthetic substances that kill or inhibit the growth of bacteria.

Antibiotic: An agent or substance that is produced from microorganisms that can act against another living microorganism. Although not completely technically correct, for purposes of this document the use of the term "antibiotic" should be interpreted as "antibacterial".

Antimicrobial: An agent or substance, derived from any source (microorganisms, plants, animals, synthetic or semisynthetic) that acts against any type of microorganism: bacteria (antibacterial), mycobacteria (antimycobacterial), fungi (antifungal), parasite (antiparasitic), and viruses (antiviral). All antibacterials are antimicrobials, but not all antimicrobials are antibacterials. The scope of this report is limited to the antibacterial antimicrobials.

Antimicrobial class: Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanisms of resistance. Variations in the properties of antimicrobial agents within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.

Antimicrobial resistance (AMR): Antimicrobial resistance happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others. Also, the ability of microorganism to multiply or persist in the presence of increased level

of an antimicrobial agent relative to the susceptible counterpart of the same species.

Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR): An advisory group established by the World Health Organization in December of 2008 to support WHO's efforts to minimize the public health impact of antimicrobial resistance associated with the use of antimicrobials in food animals.

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

Criterion 2 (C2): The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from non-human sources, or (2) bacteria that may acquire resistance genes from non-human sources.

Critically important antimicrobials (CIA): Antimicrobial classes used in humans which meet both C1 and C2 are termed critically important for human medicine.

Disease Treatment/Therapy/Therapeutic Use: Treatment/Therapeutic Use refers to use of an antimicrobial(s) for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness (Codex texts on foodborne antimicrobial resistance, 2015).

Disease Prevention/Prophylactic Use: Prevention/Prophylactic Use refers to use of an antimicrobial(s) in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This treatment includes:

- control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and
- prevention of an infectious disease that has not yet been clinically diagnosed.

  (Codex texts on foodborne antimicrobial resistance, 2015).

Growth Promotion/Growth Promoter: Growth Promotion refers to the use of antimicrobial substances to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means. The term does not apply to the use of antimicrobials for the specific purpose of treating, controlling, or preventing infectious diseases, even when an incidental growth response may be obtained. (Codex texts on foodborne antimicrobial resistance, 2015).

Highly important antimicrobials: Antimicrobial classes used in humans which meet either C1 or C2, but not both, are termed highly important for human medicine.

Highest priority critically important antimicrobials: Antimicrobial classes used in humans that meet all three prioritization criteria (P1, P2, and P3). Currently, these drugs include: quinolones, third- and fourth- and fifth-generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

Important antimicrobials: Antimicrobial classes used in humans which meet neither C1 or C2 are termed highly important for human medicine.

***mcr* genes:** there are colistin resistance genes that are on plasmids and thus mobile so can be readily transferred between bacteria. They confer resistance to colistin, which is a polymyxin.

Medically important antimicrobial: Antimicrobial used in human medicine, and therefore listed on the *WHO CIA list*. Medically important antimicrobials are categorized on the *WHO CIA list*, according to specific criteria, as either "Critically important", "Highly important", or "Important" for human medicine.

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

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

Prioritization factor 3 (P3): The antimicrobial class is used to treat infections in people for which there is already extensive evidence of transmission of resistant bacteria (e.g., non-typhoidal *Salmonella* spp. and *Campylobacter* spp.) or resistance genes (high for *E. coli* and *Enterococcus* spp.) from non-human sources.

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https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/