Critically Important Antimicrobials for Human Medicine

5th Revision 2016

Ranking of antimicrobial agents 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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CONTENTS

1. Preamble 1

2. History of the current document 4

3. Purpose 6

4. Use of the document 6

5. The criteria 8

6. Interpretation of categorization 9

7. Prioritization within the Critically Important category .. 12

8. Highest Priority Critically Important Antimicrobials 20

Annex 1. Complete list of antimicrobials for human and veterinary use, categorized as Critically Important, Highly Important and Important 21

Annex 2. Antimicrobial classes currently not used in humans 37

Annex 3. Glossary of terms 38

1. Preamble

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 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 concluded 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, it concluded that 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 in humans. 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 made the recommendation 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

(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) in risk assessment
- 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 needs, human health needs, and public health considerations.

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.

Reference:

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 10 April 2017).

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 10 April 2017).

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. (ftp://ftp.fao.org/docrep/fao/010/i0204e/i0204e00.pdf, accessed 10 April 2017).

2. History of the current document

The WHO CIA List was first developed in 2005. It was updated in 2007, 2009, 2011, 2013 and 2016.

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 and categorized antimicrobials into three groups: *critically important, highly important,* and *important*, based on two criteria developed at the meeting[1].

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 are needed most urgently[2]. The classes of drugs that met all prioritization criteria were called Highest Priority Critically Important Antimicrobials. The 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. 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, additional information was added and the CIA list updated. 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 human medicines and

[1] See sections 5 and 6 below for definition of Criterions and categorization of antimicrobials.

[2] This was done by defining two prioritization criteria from Criterion 1 and one from Criterion 2. See section 7 for further details.

thus had greater potential to impact on the resistance to the critically important antimicrobials for human medicine.

A further revision of the list took place at the fifth AGISAR meeting held in Bogota, Colombia, in 2013. The list was then updated following the seventh AGISAR meeting in Raleigh, USA in 2016.

In summary, since its inception several changes have been made to the list. The updated list of Critically Important, Highly Important and Important antimicrobials is shown in the tables which have all antimicrobials plus the criteria used to classify each individual antimicrobial class. Additions to the Critically Important category (see Table 1 and the Annex 1) include phosphonic acid derivatives, monobactams and polymyxins, reflecting the greater importance of these classes for treatment of multi-resistant Gram negative infections. Streptogramins, initially classified as Critically Important are classified as Highly Important since 2011, because more effective antimicrobials with less side effects became available to treat Gram positive infections. However, glycopeptides are still one of the few available therapies for serious enterococcal infections. Considering the relatively high number of enterococcal infections, documented transmission of vancomycin-resistant enterococci (VRE) to people from food animals and the serious consequences of treatment failure, glycopeptides have been classified to the highest priority category. Previously, tetracyclines were placed in the Critically Important category, in part because they are the main treatment for *Brucella* infections transmitted from animals, but these infections have become less important with eradication of the animal reservoir in many countries. All aminoglycosides are now classified as Critically Important (previously kanamycin and neomycin were considered Highly Important) to address cross-resistance concerns. Lincosamides (e.g. clindamycin and lincomycin) were moved to Highly Important from Important because of their greater importance for treating *Staphylococcus aureus* (including methicillin-resistant *Staphylococcus aureus* from animals).

Changes made at the 5th revision (2016)

- Slight changes to the prioritization criteria 1 and 2 (P1 and P2) were made to better describe usage of antimicrobials that are used in seriously ill patients in healthcare facilities when there are few or no alternatives available for therapy.

- As a result, changes were made to the prioritization classification of antimicrobial classes on the CIA list for the polymyxins. 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 the *mcr1* and *mcr2* genes that confer transmissible resistance to colistin and the spread of colistin-resistant bacteria via the food chain (See sections 7 and 8 for more detailed information).

- Pleuromutilins have only been used as topical therapy in people and there has been no transmission of resistance in *S. aureus*, including MRSA, from non-human sources. So, this group was moved to "important".

3. Purpose

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 list of Critically Important Antimicrobials should be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance mainly due to non-human antimicrobial use.

The list supports strategies to mitigate the human health risks associated with antimicrobial use in food 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 to inform how this use might be better managed to minimize the risk of transmission of resistance to the human population. The use of this 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 animal sector, and in agriculture, through a coordinated One Health approach.

Some examples of use of the document include:

- Prioritizing the development of risk management strategies for those antimicrobials characterized as *critically important* in order to preserve their effectiveness in human medicine.
- Ensuring that critically important antimicrobials are included in antimicrobial susceptibility 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 potential future CIAs.
- Communicating risks to the public.

Reference:

1. OIE list of antimicrobial agents of veterinary importance. Paris. World Organisation for Animal Health. 2015. (http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf, accessed 10 April 2017).

2. WHO Model Lists of Essential Medicines [website]. Geneva. World Health Organization. (http://www.who.int/medicines/publications/essentialmedicines/en/ , accessed 10 April 2017).

5. The criteria

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 human medicine. Serious infections are likely to result in significant morbidity or mortality if left untreated. Seriousness of disease may relate to the site of infection (e.g. pneumonia, meningitis) or the host (e.g. infant, immunosuppression). Even though multidrug resistance alone may or may not always influence patient outcomes, in general it is associated with poorer outcomes.

It is of prime importance, then, 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 antimicrobial use. 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 the potential to cause human disease is greatest for certain bacteria (e.g. non-typhoidal *Salmonella*, *Campylobacter spp.*, *Escherichia*

coli, *Enterococcus spp.*, and *Staphylococcus aureus*). Commensal organisms from non-human sources (animals, water, food, or the environment) may also transmit resistance determinants to human pathogens; the commensals themselves may also be pathogenic in immunosuppressed hosts. It is important to note that the transmission of such organisms or their genes need not be demonstrated; rather, it is considered sufficient that the potential for such transmission exists.

6. Interpretation of categorization

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 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.

Table 1. List and classification of antimicrobials important for human medicine

Antimicrobial class	Example of drug(s)
CRITICALLY IMPORTANT ANTIMICROBIALS	
Aminoglycosides	gentamicin
Ansamycins	rifampicin
Carbapenems and other penems	meropenem
Cephalosporins (3^{rd},4^{th} and 5^{th} generation)	ceftriaxone, cefepime, ceftaroline
Glycopeptides	vancomycin
Glycylcyclines	tigecycline
Lipopeptides	daptomycin
Macrolides and ketolides	erythromycin, telithromycin
Monobactams	aztreonam
Oxazolidinones	linezolid
Penicillins (natural, aminopenicillins, and antipseudomonal)	ampicillin
Phosphonic acid derivatives	fosfomycin
Polymyxins	colistin
Quinolones	ciprofloxacin
Drugs used solely to treat tuberculosis or other mycobacterial diseases	isoniazid
HIGHLY IMPORTANT ANTIMICROBIALS	
Amidinopenicillins	mecillinam
Amphenicols	chloramphenicol
Cephalosporins (1^{st} and 2^{nd} generation) and cephamycins	cefazolin
Lincosamides	clindamycin
Penicillins (anti-staphylococcal)	oxacillin
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
Nitrofurantoins	nitrofurantoin
Nitroimidazoles	metronidazole
Pleuromutilins	retapamulin

See Annex 1 for the full list of antimicrobials used in human medicine and in animals. Some antimicrobials are used only in people, some in both people and animals (e.g. erythromycin, ampicillin, colistin) and some other antimicrobials are used only in animals (veterinary use only drugs; these are listed for each class). This list also gives a rationale for the classification of each individual drug class. In addition, there is also a list of all antimicrobial classes currently not use 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 criteria are used for prioritization:

Prioritization criterion 1 (P1): *High absolute number of people, or high proportion of use in patients with serious infections in health care settings affected by bacterial diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans.*

Prioritization criterion 2 (P2): *High frequency of use of the antimicrobial class for any indication in human medicine, or else high proportion of use in patients with serious infections in health care settings, since use may favour selection of resistance in both settings.*

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

Explanation: The first two prioritization criteria relate to the volume of antimicrobial use in humans. Increased volume of use directly relates to the development of resistance and, therefore, poses a greater threat to their use as sole therapies. Furthermore, humans receiving antimicrobials for any indication have a greater susceptibility to acquiring infection by a foodborne pathogen resistant to those antimicrobial agents.

The third prioritization criterion relates to transmission. Risk-management strategies are most urgently needed in situations where evidence suggests that the transmission of resistant bacteria or resistance genes from non-human sources is already occurring, or has occurred previously.

Antimicrobial classes that meet all three prioritization criteria (P1, P2, and P3) are considered the *highest priority critically important antimicrobials*.

Changes in prioritization criteria 2 (P2) were made for aminoglycosides, phosphonic acid derivatives, and polymyxins.

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 with serious infections in health care settings and where 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 all diseases for which the antimicrobial is the sole/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 all 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,* from non-human sources; spread of carbapenem-resistant *Salmonella* is increasing however. Detection of 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 all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of Enterobacteriaceae, including *E. coli* and *Salmonella*, 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 all diseases for which the antimicrobial is the sole/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 all diseases for which the antimicrobial is the sole/one of few therapies available.
Lipopeptides	Yes	No	No	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Macrolides and ketolides	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of *Campylobacter* spp. from non-human sources.
Monobactams	Yes	No	No	P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/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 all diseases for which the antimicrobial is the sole/one of few therapies available.
Penicillins (natural, aminopenicillins and antipseudomonal)	No	Yes	Yes	(P1) In certain geographic settings, this criterion may be met: there may be a high absolute number of people affected by all disease for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of *Enterococcus* spp. and *Enterobacteriaceae* (including *Salmonella* and *E. coli*)
Phosphonic acid derivatives	Yes	Yes	No*	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/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.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIMICROBIALS				
Antimicrobial class	**P1**	**P2**	**P3**	**Comments**
Polymyxins	Yes	Yes	Yes	(P1) High numbers of people affected by all diseases who are seriously ill in healthcare facilities in many countries for which the antimicrobial is the sole/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.
Quinolones	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine (P3) Transmission of *Campylobacter* spp. and *Enterobacteriaceae,* including *E. coli* and *Salmonella,* 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 all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine.

Table 3. Summary of classification and prioritization

Antimicrobial class	**Criterion**				
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 (natural, aminopenicillins, and antipseudomonal)	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**			
Amidinopenicillins	No	Yes	NA		
Amphenicols	No	Yes			
Cephalosporins (1st and 2nd generation) and cephamycins	No	Yes			
Lincosamides	No	Yes			
Penicillins (anti-staphylococcal)	No	Yes			
Pseudomonic acids	No	Yes			
Riminofenazines	Yes	No			
Steroid antibacterials	No	Yes			
Streptogramins	No	Yes			

Antimicrobial class	Criterion		
Sulfonamides, dihydrofolate reductase inhibitors and combinations	No	Yes	
Sulfones	Yes	No	
Tetracyclines	Yes	No	
IMPORTANT ANTIMICROBIALS	**C1**	**C2**	
Aminocyclitols	No	No	NA
Cyclic polypeptides	No	No	
Nitrofurantoins	No	No	
Nitroimidazoles	No	No	
Pleuromutilins	No	No	

8. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (P1, P2, and P3): quinolones, third- and fourth- and fifth-generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

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

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

Complete list of antimicrobials for human and veterinary use, categorized as Critically Important, Highly Important and Important

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
CRITICALLY IMPORTANT ANTIMICROBIALS				
Aminoglycosides	amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin framycetin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin streptomycin tobramycin *Veterinary only:* apramycin	Yes	Yes	(C1) Sole or limited therapy as part of treatment of enterococcal endocarditis and multidrug resistant (MDR) tuberculosis. (C2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *E. coli*), and *Mycobacterium* spp. from non-human sources.
Ansamycins	rifabutin rifampicin rifaximin rifapentine rifamycin	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	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Carbapenems and other penems	biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Yes	Yes	(C1) Limited therapy for infections due to MDR *Enterobacteriaceae*. (C2) May result from transmission of *Enterobacteriaceae,* including *E. coli* and *Salmonella*, from non-human sources.
Cephalosporins (3rd, 4th and 5th generation)	cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoperazone-sulbactam cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin ceftaroline fosamil ceftazidime ceftazidime-avibactam ceftibuten ceftizoxime ceftobiprole ceftolozane ceftriaxone ceftriaxone-sulbactam latamoxef tazobactam *Veterinary only:* ceftiofur cefovecin cefquinome	Yes	Yes	(C1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* 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*, from non-human sources.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Glycopeptides and lipoglycopeptides	dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary only:* avoparcin	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 MDR MRSA. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Macrolides and ketolides	azithromycin cethromycin clarithromycin dirithromycin erythromycin fidaxomicin flurithromycin josamycin midecamycin miocamycin oleandomycin ramoplanin rokitamycin roxithromycin spiramycin telithromycin troleandomycin solithromycin *Veterinary only:* gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin	Yes	Yes	(C1) Limited therapy for *Legionella*, *Campylobacter,* and MDR *Salmonella* and *Shigella* infections. (C2) May result from transmission of *Campylobacter* spp. and *Salmonella* 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	Example of drug products used in both human and veterinary medicine	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.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Penicillins (natural, aminopenicillins, and antipseudomonal)	amoxicillin amoxicillin-clavulanic -acid ampicillin ampicillin-sulbactam azidocillin azlocillin bacampicillin carbenicillin carindacillin clometocillin epicillin hetacillin metampicillin meticillin mezlocillin penamecillin penicillin G (=benzylpenicillin) penicillin V (=phenoxymethyl-penicillin) pheneticillin piperacillin piperacillin-tazobactam pivampicillin propicillin sulbenicillin sultamicillin talampicillin temocillin ticarcillin ticarcillin-clavulanic-acid *Veterinary only:* penethamate hydriodide	Yes	Yes	(C1) Limited therapy for syphilis (natural penicillins), *Listeria, Enterococcus* spp. (aminopenicillins), and MDR *Pseudomonas* spp. (antipseudomonal). (C2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae,* including *E. coli,* as well as *Pseudomonas aeruginosa* from non-human sources.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	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 includes colistin sulfate and colistin methanesulfonate. It also includes polymyxin E.

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

Antimicrobial class	Example of drug products used in both human and veterinary medicine	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				
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.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Amphenicols	chloramphenicol thiamphenicol *Veterinary only:* florfenicol	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,* from non-human sources.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Cephalosporins (1st and 2nd generation) and cephamycins	cefaclor cefacetrile cefadroxil cefaloridine cefalexin cefalotin cefamandole cefapirin cefatrizine cefazedone cefazolin cefbuperazone cefmetazole cefminox cefonicid ceforanide cefotetan cefotiam cefoxitin cefprozil cefradine cefroxadine ceftezole cefuroxime flomoxef loracarbef *Veterinary only:* cefalonium	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children. (C2) May result from transmission of *Enterobacteriaceae,* including *E. coli,* from non-human sources.
Lincosamides	clindamycin lincomycin *Veterinary only:* pirlimycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus,* including MRSA, from non-human sources.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Penicillins (anti-staphylococcal)	cloxacillin dicloxacillin flucloxacillin 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.
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.
Steroid antibacterials	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.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Streptogramins	quinupristin-dalfopristin pristinamycin *Veterinary only:* virginiamycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources
Sulfonamides, dihydrofolate reductase inhibitors and combinations	brodimoprim iclaprim 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 *Veterinary only:* formosulfathiazole phthalylsulfathiazole	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* infections, and other infections. (C2) May result from transmission of *Enterobacteriaceae,* including *E. coli,* from non-human sources.
Sulfones	aldesulfone dapsone	Yes	No	(C1) Limited therapy for leprosy.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Tetracyclines	chlortetracycline clomocycline demeclocycline doxycycline lymecycline metacycline minocycline omadacycline oxytetracycline penimepicycline rolitetracycline tetracycline	Yes	No*	(C1) Limited therapy for infections due to *Brucella* spp., *Chlamydia* spp., and *Rickettsia* spp. (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	Example of drug products used in both human and veterinary medicine	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.*
Cyclic polypeptides	bacitracin	No	No	
Nitrofurantoins	furazolidone nifurtoinol nitrofural nitrofurantoin *Veterinary only:* furaltadone	No	No	
Nitroimidazoles	metronidazole ornidazole 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*.

Antimicrobial class	Example of drug products used in both human and veterinary medicine	C1	C2	Comments
Pleuromutilins[2]	retapamulin *Veterinary only:* 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.

[2] Pleuromutilins were discovered as natural-product antibiotics in the 1950's. Tiamulin was the first pleuromutilin compound and was approved for veterinary use in 1979, followed by valnemulin in 1999. In 2007, retapamulin became the first pleuromutilin approved for use in humans; however it was limited to topical application. Some new pleuromutilins have now entered clinical trials as systemic therapy for people.

Annex 2

Antimicrobial classes currently not used in humans[1]

Antimicrobial Class	Example of drug products used in food animals
Aminocoumarins	novobiocin
Orthosomycins	avilamycin[2]
Phosphoglycolipids	bambermycin (=flavomycin)
Polyethers/Ionophores	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 categorized in the WHO "Critically Important" antimicrobials for human use 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: A drug that kills or inhibits bacteria.

Antibiotic: An agent or substance that is produced from microorganisms that can act against another living microorganism. Antimicrobial substances that are synthetic, semisynthetic, or those derived from plants or animals, are therefore, by strict definition, not considered antibiotics. 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 antibiotics are antimicrobials, but not all antimicrobials are antibiotics. 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 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. To date, two genes have been identified; *mcr*-1 and *mcr*-2.

Prioritization criterion 1 (P1): High absolute number of people, or high proportion of use in patients with serious infections in health care settings affected by bacterial diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans

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

Prioritization criterion 3 (P3): The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria or resistance genes from non-human sources.

http://who.int/foodsafety/publications/antimicrobials-fifth/en/