WHO List of Medically Important Antimicrobials

A risk management tool for mitigating antimicrobial resistance due to non-human use

Previously known as the WHO Critically Important Antimicrobial List for Human Medicine

World Health Organization

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Abbreviations and acronyms

AG CIA	Advisory Group on Critically Important Antimicrobials for Human Medicine
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	antimicrobial resistance
AMU	antimicrobial use and consumption
AWaRe	Access, Watch, Reserve
C1, C2	criterion 1, criterion 2
CIA	critically important antimicrobial
CRE	carbapenem-resistant Enterobacterales
EML	Essential Medicines List
FAO	Food and Agriculture Organization of the United Nations
GAP	Global Action Plan on AMR
IA	important antimicrobial
IV	intravenous
HIA	highly important antimicrobial
HPCIA	highest priority critically important antimicrobial

MDR	multidrug-resistant
MIA	medically important antimicrobial
MRSA	methicillin-resistant *Staphylococcus aureus*
NAP	national action plan on AMR
P	prioritization factor (WHO CIA List 6th revision)
PF	prioritization factor (WHO MIA List)
spp.	species
UNEP	United Nations Environment Programme
WG	working group
WHO	World Health Organization
WOAH	World Organisation for Animal Health (formerly OIE)

1. Background

There is a global need to preserve the efficacy of antimicrobial agents and minimize the risk of antimicrobial resistance (AMR). Because AMR develops and transfers within and among all sectors, minimizing the risk of emergence and transmission of AMR calls for a One Health approach *(1)*. To improve the responsible and prudent use of antimicrobial agents – and in particular medically important antimicrobial agents – it is thus essential to decrease their inappropriate use across sectors.[1]

To support this goal, in 2005 the World Health Organization (WHO) developed a list of critically important antimicrobials (CIA) *(2)*. The list categorizes antimicrobial classes authorized for both humans and animals based on the importance of these classes in human medicine and the contribution of non-human use to the risk of transmitting AMR to humans.

Through the Global Action Plan on AMR (GAP) adopted in 2015, the Quadripartite organizations (WHO, the Food and Agriculture Organization of the United Nations (FAO), the United Nations Environment Programme (UNEP) and the World Organisation for Animal Health (WOAH, formerly OIE)) collaborate to develop tools and guidance to support countries in implementing national action plans (NAPs) on AMR. It is thought that this work will lead to implementing actions for the responsible and prudent use of antimicrobials in different sectors.

The CIA list has been revised regularly. The last revision (6th Revision) was published in 2018 *(3)*.

In 2019 Member States made a request to the WHO director-general to maintain and systematically update the WHO CIA List *(4)*, renamed with this publication the WHO Medically Important Antimicrobials List (WHO MIA List).

As AMR is a multisectoral problem, many national and international guidelines aim at mitigating its risks to human and animal health. For example, the WHO AWaRe (Access, Watch, Reserve) classification *(5)* supports appropriate access to antimicrobials based on their availability. AWaRe also intends to help policymakers develop stewardship guidelines regarding the appropriate use of antimicrobials in human medicine. The Access, Watch and Reserve groupings consider the impact of different antimicrobials and antimicrobial classes on AMR, together with their importance, availability and affordability in treating human infections globally.

In addition, the *WHO AWaRe (Access, Watch, Reserve) antibiotic book (6)* provides guidance for countries in optimizing the use of antimicrobials in humans as well as recommendations on the choice of antimicrobial, dose, route of administration and duration of treatment for common infectious syndromes. The AWaRe classification is built into the WHO AWaRe (Access, Watch, Reserve) antibiotic book. The WHO MIA List is the only WHO document intended to provide guidance to countries for establishing principles and guidelines for the responsible and prudent use of antimicrobials in non-human sectors, to minimize the risk of development and transfer of resistant bacteria to humans. This document also supports implementation of NAPs by promoting optimal use of antimicrobials in both humans and animals (in keeping with the fourth strategic objective of the GAP). The WHO MIA List is based on specific criteria, categorizations and groupings of each class of antimicrobials, based on their medical importance for treating serious disease in humans and potential transmission of AMR from bacteria to humans due to use of these agents in non-human sectors.

1 In this document, the term “antimicrobial” refers to antibacterials. Lists focused on other antimicrobials, such as antifungals, will be developed in the future to complement this list.

1.1 Definition of non-human use

Antimicrobials are used in a diverse range of situations across the One Health spectrum. “Non-human use” refers to the use of antimicrobials in animals, plants, crops and the environment. However, based on current limitations of data regarding antimicrobial use in these sectors, and the potential impact of AMR on human health, in this document “non-human” considers only the use of antimicrobials in animals. Nevertheless, similar principles regarding antimicrobial use and consumption (AMU) and the development and spread of resistant microorganisms may apply to all situations where antimicrobials are used.

Use of antimicrobials in animals involves a broad range of species, sectors and applications, including terrestrial and aquatic, food-producing animals, companion animals (pets or small animals and exotic pets), fibre and fur-bearing animals, laboratory animals, conservation animals and working animals. While the focus historically has been on food-producing animals, which are probably the main source of AMR risk to humans. It is recognized that resistance poses increased risk with any AMU. Unless specifically noted, comments about non-human or animal use refer to this broad scope, but with greater concern regarding food-producing animals. However, specific considerations for food-producing animals are provided in some areas. It is also recognized that AMU in animals encompasses a diverse range of veterinary medical uses, including treatment, control (metaphylaxis), prevention (prophylaxis) and non-veterinary medical use, including growth promotion *(7)*. All of these uses are taken into account when evaluating AMU.

2. Purpose of the WHO MIA List

This list aims to:

- help competent authorities in the public health and animal health sectors, regulators, veterinarians, veterinary paraprofessionals, aquatic animal/plant/crop health professionals, practicing physicians and prescribers of antimicrobials, and stakeholders know which types of antimicrobials used in non-human sectors present potentially higher risk to human populations and how AMU might be managed to minimize medically important AMR;
- categorize antimicrobial classes authorized for use in humans, in both humans and animals, and those not authorized in humans, based on their medical importance in human medicine while considering the potential risk of the development and spread of AMR; and
- assist in risk management relating to AMU and AMR in non-human sectors.

3. Target audience

The target audience for this document includes but is not limited to:

- national regulators, competent authorities and policymakers in ministries of health and ministries of agriculture or equivalent authorities responsible for regulating, monitoring and assuring prudent use of antimicrobials;
- veterinarians, veterinary paraprofessionals, aquatic animal/plant/crop health professionals, practicing physicians and prescribers of antimicrobials;
- national AMR steering or coordinating committees responsible for developing, implementing and monitoring NAPs, policies and standards for mitigating AMR at the national level; and
- food-animal producers; institutional food purchasers; food companies, including restaurants and catering companies; grocery stores; and other purveyors of meat, poultry and dairy products.

4. Explanation of changes included in the WHO MIA List

4.1 Introduction of "authorized for use in humans only", "medically important' and "not medically important" groups

These groups are described in Table 1. They were created to provide a more comprehensive pathway for assessing all antimicrobial classes, those used in humans only (authorized for use in humans only), those used in animals only (not authorized in human medicine) and those used in both (authorized for use in both humans and animals). At the same time, it is recognised that antimicrobial classes used in both humans and animals are the focus of this document with regard to mitigating AMR risk to human health.

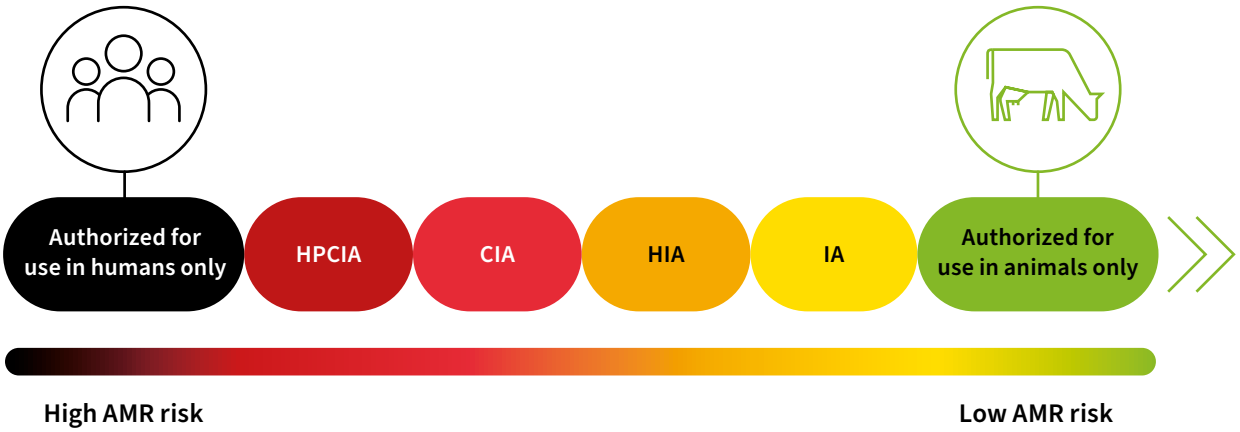
Antimicrobial classes authorized only for topical use were not considered unless they are frequently used to treat multidrug-resistant pathogens in humans. Accordingly, pseudomonic acids were evaluated because of the use of mupirocin for methicillin-resistant *Staphylococcus aureus* (MRSA) infection and colonization in humans.

4.1.1 Authorized for use in humans only

Drug classes in this category were not assessed as part of the CIA pathway, owing to the lack of data on transmission of resistance for most of the antimicrobial agents in these classes. Since most of these drug classes are not used in animals, there are no data to assess prioritization factor (PF) 2 (section 5.2.2).

It is important to note that placement of these classes in a separate category (human use only) does not reduce or minimize AMR concerns about the use of these products. Indeed, they should be considered by default to be the most critical and to have the highest AMR risk (at a minimum, similar to highest priority critically important antimicrobials (HPCIA)), as several of these drug products are considered a last resort or sole therapy for treating serious multidrug-resistant infections in humans (Fig. 1). This group also aligns with the WHO best practices statement (section 5.3.1) that antimicrobial classes not currently authorized in food-producing animals should not be used in such animals in the future. Moreover, it creates a pathway whereby any new antimicrobial classes authorized for use only in humans would automatically be added to this group pending risk assessment, without having to wait for review in a future edition of this list.

Fig. 1. Prioritization of antimicrobial classes in the WHO MIA List



AMR: antimicrobial resistance; CIA: critically important antimicrobial; HIA: highly important antimicrobial; HPCIA: highest priority critically important antimicrobial; IA: important antimicrobial; MIA: medical important antimicrobial; WHO: World Health Organization.

4.1.2 Not medically important for humans

This group was added to the main decision-making process, as opposed to placing a selection of these drugs in Annex 2 as in the previous edition, without evaluation. This group consists of antimicrobials that are only authorized for use in animals and for which there is no substantial evidence that use of these drug classes could result in resistance to MIA. This group was added to try to ensure that all antimicrobials used in animals come under scrutiny as part of the standard evaluation approach, so that they would not be placed in a low-priority category by default, without proper assessment of the potential risk of AMR in humans.

4.2 Changes to prioritization factors

In the previous edition, CIA were further assessed using three prioritization factors. The first was related to the number of people that might need to be treated and the second related to the frequency and intensity of AMU in humans. However, it was apparent that the previous prioritization factors 1 and 2 (P1 and P2) were somewhat confusing and potentially overlapping. Since those prioritization factors were designed to assess the importance of antimicrobials in humans, it was decided to use the WHO EML and the WHO AWaRe classification, established systems that indicate the importance of individual antimicrobials (EML) and that categorize antimicrobial drugs into Access, Watch and Reserve categories based on their importance and AMR concerns (AWaRe classification). Since this AWaRe classification is based on the individual drug level and not at the class level, it was necessary to determine how to address situations where drugs within a class were distributed to different AWaRe rankings. The lists were used together to assess two different aspects of importance. If an antimicrobial drug was both on the EML and categorized as Watch or Reserve on the AWaRe list, the corresponding class or subclass was deemed to have fulfilled the new PF1.

Any potential changes to the EML or the AWaRe list will be assessed to determine whether the lists remain appropriate for these categorization purposes.

The new PF2 represents a slight modification of the previous P3 *(1)*, and an added assessment of the degree of evidence of the impact of AMU in animals on the treatment of serious and life-threatening diseases in humans (e.g., the frequency of bloodstream infections).

4.3 Categorization of ketolides, fidaxomicin, fluorocyclines, aminomethylcyclines and plazomicin

Previously, ketolides were assessed alongside macrolides. However, based on differences in antimicrobial activity, resistance mechanisms and AWaRe categorization, it was decided to separate these two classes. Additionally, while fidaxomicin is a macrolide, it has a very different spectrum of activity, different resistance mechanisms and different indications for use compared with other macrolides; therefore, it was evaluated separately.

Fluorocyclines (eravacycline) and aminomethylcyclines (omadacycline) were removed from the broader tetracycline category based on differences in resistance mechanisms, consistent with the previous approach to glycylcyclines.

Plazomicin was also removed from the aminoglycoside class and evaluated individually, because resistance is nearly always only conferred by a specific resistance mechanism (16S methyltransferases) compared to other aminoglycosides. As the only aminoglycoside in the AWaRe Reserve category and only authorized for use in humans, plazomicin was classified as "aminoglycosides (Reserve)".

Based on this separation, all of these classes were placed in the authorized in humans only group.

4.4 Macrolides

Macrolides were reclassified from HPCIA to CIA after a thorough review. Macrolides were not deemed to have fulfilled the "frequent causes of invasive and life-threatening infections" component of PF2. While macrolides are important in treating campylobacteriosis, most cases are self-limiting, antibiotic therapy is not advised, and *Campylobacter* spp are infrequent causes of invasive and life-threatening diseases.

4.5 Aminopenicillins

Aminopenicillins were previously categorized as CIA, fulfilling both the C1 and C2 criteria. They were deemed to have fulfilled the C1 criterion in large part because of their importance in treating enterococcal infections and listeriosis. However, new antimicrobial options for enterococci are available in many regions. While aminopenicillins remain important in treating listeriosis, there are other treatment options. It was determined that C1 no longer applies. This decision resulted in recategorizing this drug class as highly important antimicrobials (HIA).

4.6 Phosphonic acid derivatives

Phosphonic acid derivatives were reclassified from CIA to HPCIA. They were previously deemed not to have fulfilled the criterion "used to treat infections in people for which there is already extensive evidence of transmission of resistant bacteria or resistance genes". However, with evidence of the emergence and dissemination of plasmid-mediated fosfomycin resistance genes in food-producing animals, and the limited therapeutic options for treating life-threatening carbapenem-resistant Enterobacterales (CRE) infections, they are now considered as fulfilling PF2.

4.7 Nitroimidazoles

Nitroimidazoles were previously categorized as important, as they were considered to fulfil C1 only in some geographical settings. However, since therapeutic options to treat anaerobic infections – including *Clostridium* (*Clostridioides*) *difficile* infection – are limited worldwide, nitroimidazoles have been reclassified as HIA.

5. Classes, groups and categorization of antimicrobials

5.1 Antimicrobial agents: classes and subclasses

All classes of antimicrobials used in both animals and humans were analysed and categorized according to two criteria (see section 5.2). Antimicrobial classes were divided into subclasses for categorization only if justified based on mechanisms of resistance. For example, mechanisms of resistance to the cephalosporin groups differ sufficiently to separate the first and second generations from the third through fifth generations for the purposes of categorization. Additionally, in some situations an antimicrobial agent was deemed sufficiently different from other members of a class or subclass based on factors such as resistance mechanisms or AWaRe list ranking.

Consequently, antimicrobials were assessed at the class level unless there were reasons for separating them based on one or more of the following:

- being a recognized subclass (e.g., 1st- and 2nd-generation cephalosporins);
- combination with an inhibitor (e.g., β-lactam, β-lactamase inhibitor);
- presence of different resistance mechanisms compared with other members within the class/subclass; or
- presence in the AWaRe classification as a reserve drug when other members of the drug class/subclass are categorized as Access or Watch (e.g., plazomicin).

For the purposes of this document, “class” is used to denote the antimicrobial drug class, subclass or other separation as described previously.

5.2 Criteria and prioritization for categorization

5.2.1 The criteria

Two criteria are used to categorize antimicrobial classes authorized for use in both humans and animals as CIA, HIA or IA (Fig. 1).

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 have an important place in medicine. While severity of illness may relate to the site of infection (e.g., bacteraemia, endocarditis, pneumonia, meningitis or bone and joint infections), the host (e.g., infant, elderly, immunosuppressed, immunocompromised) or the bacterial agent, serious infections are generally more likely to result in increased morbidity or mortality if left untreated because few or no effective antibacterial agents are available.

It is very important that the effectiveness of such antimicrobial agents be preserved, as loss of their efficacy due to the emergence of resistance would have a significant impact on human health, especially for people with life-threatening infections. This first 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 caused by bacteria *(1)* possibly transmitted from non-human sources or *(2)* with 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 for the purposes of this classification 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 *S. aureus*). Commensal organisms from non-human sources may also transmit resistance determinants to human pathogens. Commensals may also be pathogenic in immunosuppressed hosts. It is important to note that transmission of such organisms or their genes does not need to be demonstrated; rather, it is considered sufficient that substantive potential for such transmission is identified through risk assessment.

5.2.2 Prioritization

Antimicrobials within the CIA category by virtue of fulfilling both C1 and C2 were prioritized to assist in allocating resources towards agents for which risk management strategies are needed most urgently. The following two factors were used for prioritization:

Prioritization factor 1 (PF1): The class contains at least one antimicrobial that is BOTH on the WHO EML *(7)* and is classified as Watch or Reserve on the AWaRe classification list.

Prioritization factor 2 (PF2): 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.) or resistance genes (e.g., *E. coli*, *Klebsiella* spp., *S. aureus* and *Enterococcus* spp.) for the particular antimicrobial from non-human sources, and these infections are frequent causes of invasive and life-threatening infections.

Explanation: The first prioritization factor (PF1) has been linked with classes of antimicrobials included on the EML and considered Watch or Reserve on the AWaRe list. While the EML and the AWaRe list categorize drugs with different methods and for different purposes than this list does, they are important indicators of the importance of antimicrobial drugs in human medicine.

The second prioritization factor (PF2) relates to the second criterion (C2), with an emphasis on the amount of evidence already available on transmission of resistant bacteria or their genetic elements for that antimicrobial class from non-human sources (e.g., resistance developing against ceftriaxone in human pathogens such as *Salmonella* and *E. coli*, following the use of ceftiofur in animals), as C2 only evaluates whether there is any potential for this to occur. PF2 also assesses the frequency of life-threatening and invasive diseases, as those are most likely to result in severe outcomes and mortality. For example, resistance to macrolides in *Campylobacter* spp. can occur after macrolides are used in animals. However, life-threatening infection with *Campylobacter* spp., as defined by bloodstream or sterile site infections, is rare.

5.3 Authorization status

Antimicrobial groups were evaluated based on their current authorization status. Antimicrobial classes were considered authorized for human and/or non-human use if any member of the drug class was authorized for use in any country.

Antimicrobial classes that are only authorized for topical use were not considered unless they are frequently used to treat multidrug-resistant pathogens in humans.

5.3.1 Antimicrobials authorized for use in humans only

Placement of these classes in a separate category is not intended to mean that these antimicrobials are not high priority. Indeed, they should be considered by default to be the most critical and to have the highest AMR risk (like HPCIA agents), as several of these drug products are considered to be last resort or sole therapy for treating serious multidrug-resistant infections in humans (Table 2).

The agents authorized for use in humans only are not authorized for systemic use in animals, and as such there are few or no data available to properly assess PF2. Thus, the criteria for categorization (HPCIA, CIA, HIA, IA) were not applied. These drug classes mainly contain newer antimicrobials that are very important in treating serious multidrug-resistant infections in humans. Most of these classes were classified as critically important in the 6th Revision *(3)*; however, if approved for use in food-producing animals in the future, any agent from this group would by default be categorized as critically important and be subject to further prioritization, as described in section 5.2.2.

The group of antimicrobials authorized only for use in humans includes plazomicin, aminomethylcycline, anti-pseudomonal penicillins with and without β-lactamase inhibitors, carbapenems with or without inhibitors, 3rd-, and 4th-generation cephalosporins with β-lactamase inhibitors, 5th-generation cephalosporins with and without β-lactamase inhibitors, siderophore cephalosporins, fluorocyclines, glycopeptides and lipoglycopeptides, glycylcyclines, ketolides, lipopeptides, 18-membered-ring macrolides, monobactams, oxazolidinones, pseudomonic acids, riminofenazines, sulfones, drugs used solely to treat tuberculosis and other mycobacterial diseases and phenol derivatives (clofoctol).

The following best practices statements are aligned with the position of the Quadripartite organizations (FAO, UNEP, WHO and WOAH) and are critical to preserving the effectiveness of these agents in humans:

- Any new antimicrobial class that is authorized only in humans will automatically be placed in the authorized for use in humans only category.
- For implementation purposes, drugs within classes in the group of authorized for use in humans only should not be authorized in the future for use in food-producing animals, crops or plants.

5.3.2 Antimicrobials authorized for use in both in humans and animals

Antimicrobials in this group are currently authorized for use in both humans and animals. If an antimicrobial class fulfilled the two criteria (C1 and C2) explained in section 5.2.1, two prioritization factors (section 5.2.2) were applied to categorize the class as HPCIA or CIA.

If only one or none of the two criteria were fulfilled, classes within this group were categorized as HIA or IA antimicrobials, respectively.

5.3.3 Antimicrobials not authorized for use in humans

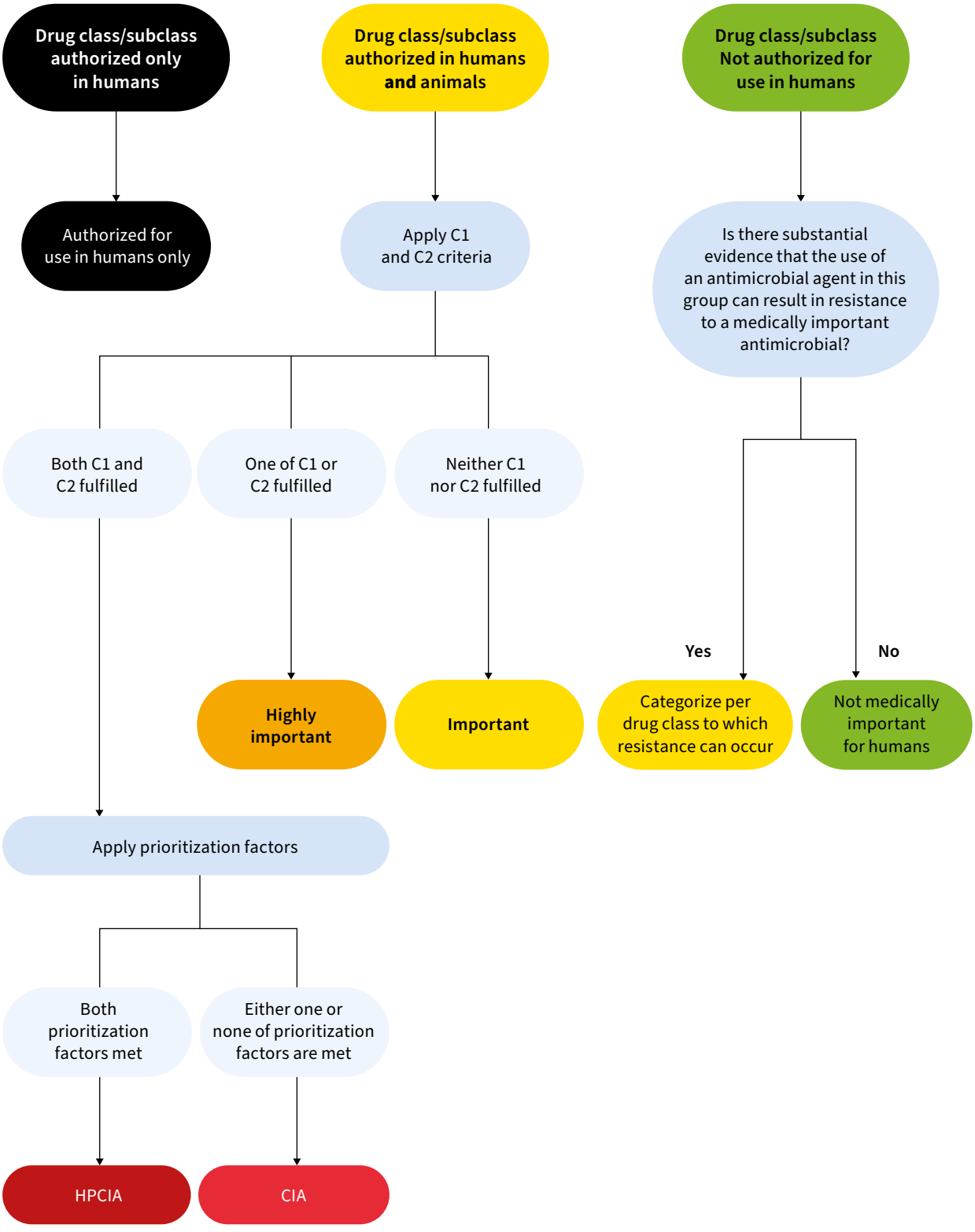
These antimicrobials are not currently authorized for use in humans; therefore, the two evaluation criteria listed in section 5.2.1 do not apply. These are classified as not medically important for humans and will remain as such unless new substantial evidence becomes available that use of an agent in this group can result in resistance to a medically important antimicrobial or if a drug from the class becomes authorized for use in humans.

5.4 Decision tree

A decision tree was used to facilitate categorization of the classes of antimicrobials based on use in humans and non-human sectors (Fig. 2).

Table 1 summarizes the categorization of all classes of antimicrobials included in the WHO MIA List. Table 2 includes all classes of antimicrobials authorized only for use in humans. Table 3 includes all classes of antimicrobials authorized for use in both humans and animals, and Table 4 includes all classes of antimicrobials not authorized in human medicine.

Fig. 2. Decision tree used to categorize antimicrobials



C1: criterion 1; C2: criterion 2; CIA: critically important antimicrobial; HP-CIA: highest priority critically important antimicrobial.

6. Implementation activities

The WHO MIA List should be used to help with risk-based decisions to minimize any adverse impact of AMU in animals on AMR in humans.

The WHO MIA List is intended to guide international, national and subnational (local, state, provincial) antimicrobial stewardship efforts by providing categorization of antimicrobials based on the risk and implications of AMR for human health from AMU in non-human sectors. The document is intended to be used in conjunction with other relevant documents (*Codex Guidelines for risk analysis of foodborne antimicrobial resistance, Code of practice to minimize and contain foodborne antimicrobial resistance* and *Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance (8)*, and the WOAH list of antimicrobials of veterinary importance *(8)*), as well as national and regional differences in AMR, disease prevalence and antimicrobial access.

Considering the WHO EML *(10)*, the AWaRe antibiotic book *(6)* and the AWaRe classification *(5)* as well as national surveillance of AMR and AMU will help to prioritize risk management strategies in the human sector, the animal sector, agriculture (crops) and horticulture for future planning, through a coordinated multisectoral One Health approach. Box 1 lists examples of use of WHO MIA List.

Box 1. Intended uses of the WHO MIA List

1. Enhanced regulations and optimized use of antimicrobials at the national and regional level

- Use by competent authorities, the pharmaceutical industry, veterinarians, veterinary paraprofessionals and aquatic animal/plant/crop health professionals to prioritize risk management strategies for antimicrobials categorized as medically important to preserve their effectiveness.
- Use in conjunction with Codex AMR texts – *Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance* (CXG 94-2021) and *Guidelines for risk analysis of foodborne antimicrobial resistance* (CXG 77-2011), *Code of practice to minimize and contain foodborne AMR* (CXC 61-2021) – to prioritize risk profiling and hazard analysis for mitigating foodborne AMR risks.
- Developing responsible and prudent use and treatment guidelines in non-human sectors in conjunction with existing international guidelines such as the WOAH *List of antimicrobials of veterinary importance*.
- Developing national and regional policies to support the responsible and prudent use of medically important antimicrobials across sectors.
- Guiding approaches to reduce or restrict the use of certain antimicrobials in non-human sectors. These should be prioritized based on categorization of antimicrobial agents and risk to human health being highest with use of agents from the authorized for use in humans only group. This risk and impact on human health lessens progressively with use of agents from the HPCIA group followed by agents in the CIA group, then HI, then I. The least risk and impact to human health is associated with agents that are not medically important for humans.
- Assisting efforts to eliminate the use of medically important antimicrobials for non-veterinary medical purposes, such as growth promotion, and in crop production and agri-food systems for non-phytosanitary purposes.
- Assisting with policies to limit the use of HPCIA across sectors.
- Informing the development of guidelines for responsible AMU, integrated AMU and AMR surveillance and reporting strategies following a One Health approach.

Box 1 (continued). Intended uses of the WHO MIA List

2. Surveillance, monitoring and evaluation

- As part of a One Health approach, ensuring that medically important antimicrobials are included in AMR and AMU monitoring/surveillance programmes.
- Use in conjunction with Codex *Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance* (CXG 94-2021).
- Informing development of targeted research projects to address data gaps in existing or future medically important antimicrobials.

3. Strengthen risk management in non-human sectors

- Developing risk management measures such as restricted use, labelling, limiting unregulated off-label or extra-label use and making antimicrobial agents available by prescription only.

4. Strengthen communication of risks

- Communicating risks to the public, prescribers and users of antimicrobials in non-human sectors.

AMR: antimicrobial resistance; AMU: antimicrobial use and consumption; CIA: critically important antimicrobial; HIA: highly important antimicrobial; HPCIA: highest priority critically important antimicrobial; IA: important antimicrobial; MIA: medically important antimicrobial; WOAH: World Organisation for Animal Health (formerly OIE).

Table 1. Antimicrobials grouped according to authorized use

Medically important antimicrobials						Not medically important
Authorized for use in humans only		Authorized for both humans and animals				Not authorized in humans
Class	Class	Categorization of categorization of antimicrobials antimicrobials				
		HPCIA	CIA	HIA	IA	
Aminoglycosides (plazomicin)	Lipopeptides	Cephalosporins (3rd, 4th generation)	Aminoglycosides	Amphenicols	Aminocyclitols	Aminocoumarins
Aminomethycyclines	Macrolides 18-membered ring (fidaxomicin)	Quinolones	Ansamycins	Cephalosporins (1st- and 2nd-generation) and cephamycins	Cyclic polypeptides	Arsenicals
Anti-pseudomonal penicillins (carboxypenicillin and ureidopenicillin)	Monobactams	Polymyxins	Macrolides (14-, 15-, 16-membered ring)	Lincosamides	Heterocyclic compounds	Bicyclomycins
Anti-pseudomonal penicillins with β-lactamase inhibitors	Oxazolidinones	Phosphonic acid derivatives		Nitroimidazoles	Hydroxyquinoline	Orthosomycins
				Tetracyclines		
Carbapenems with or without β-lactamase inhibitors	Riminofenazines			Penicillins (amidinopenicillins and aminopenicillins)	Pleuromutilins	Phosphoglycolipids
Cephalosporins (3rd-, 4th- and 5th-generation with β-lactamase inhibitors)	Sulfones			Penicillins (aminopenicillins with β-lactamase inhibitors)	Nitrofuran derivatives	Ionophores (including polyethers)
Cephalosporins (5th-generation)	Glycopeptides and lipoglycopeptides			Penicillins (anti-staphylococcal)		Quinoxalines

Table 1 (continued). Antimicrobials grouped according to authorized use

Medically important antimicrobials						Not medically important
Authorized for use in humans only		Authorized for both humans and animals				Not authorized in humans
Class	Class	Categorization of categorization of antimicrobials antimicrobials				
		HPCIA	CIA	HIA	IA	
Cephalosporins (Siderophore)	Pseudomonic acids (mupirocin)			Penicillins (narrow spectrum)		Halogenated 8-hydroxyquinolines
Fluorocyclines	Phenol derivatives (clofoctol)			Streptogramins		
Glycylcyclines	8-hydroxy-5-nitroquinoline			Sulfonamides, dihydrofolate reductase inhibitors and combinations		
Drugs used solely to treat tuberculosis or other mycobacterial diseases				Fusidanes		

CIA: critically important antimicrobials; HIA: highly important antimicrobials; HPCIA: highest priority critically important antimicrobials; MIA: medically important antimicrobials.

Table 2. Antimicrobials authorized only for use in humans[a]

Antimicrobial class	Antimicrobial	Comments
Authorized for use in humans only		
Aminoglycosides: plazomicin	plazomicin	Specific mechanisms of resistance compared to other aminoglycosides. Classified as Reserve on the WHO AWaRe list.
Aminomethylcyclines	omadacycline	This is a new antimicrobial class derived from modifications to a tetracycline scaffold.
Anti-pseudomonal penicillins (carboxypenicillins and ureidopenicillins)	azlocillin carbenicillin carindacillin mezlocillin piperacillin sulbenicillin ticarcillin	Categorized as CIA in previous revisions.
Anti-pseudomonal penicillins with β-lactamase inhibitors	piperacillin-tazobactam ticarcillin-clavulanic acid	
Carbapenems with or without inhibitors	biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Categorized as HPCIA in previous revisions.
	Imipenem-cilastatin imipenem-relebactam meropenem-vaborbactam	
3rd-, 4th- and 5th-generation cephalosporins with β-lactamase inhibitors	cefoperazone-sulbactam ceftazidime-avibactam ceftolozane-tazobactam ceftriaxone-sulbactam	Categorized as HPCIA in previous revisions.
5th-generation cephalosporins	ceftaroline ceftobiprole	
Siderophore cephalosporins	cefiderocol	This is a new antimicrobial class derived from modifications to a cephalosporin scaffold.
Fluorocyclines	eravacycline	This is a new antimicrobial class derived from modifications to a tetracycline scaffold.
Glycopeptides and lipoglycopeptides	dalbavancin oritavancin ramoplanin teicoplanin telavancin vancomycin	Categorized as HPCIA in previous revisions.
Glycylcyclines	tigecycline	Categorized as CIA in previous revisions.
8-Hydroxy-5-nitroquinolines	nitroxoline	

Table 2 (continued). Antimicrobials authorized only for use in humans[a]

Antimicrobial class	Antimicrobial	Comments
Authorized for use in humans only		
Ketolides	telithromycin	Categorized as HPCIA in previous revisions.
Lipopeptides	daptomycin	Categorized as CIA in previous revisions.
18-Membered-ring macrolides	fidaxomicin	Categorized as HPCIA in previous revisions.
Monobactams	aztreonam carumonam	Categorized as CIA in previous revisions.
Oxazolidinones	cadazolid linezolid radezolid tedizolid	Categorized as CIA in previous revisions.
Phenol derivatives	clofoctol	This is an antibiotic active against Gram-positive bacteria. It was not previously classified in the WHO CIA lists.
Pseudomonic acids	mupirocin	This is a topical antimicrobial used in the control of MRSA and was categorized as HIA in previous revisions. It is the only topical antimicrobial included on this MIA list.
Riminofenazines	clofazimine	Categorized as HIA in previous revisions.
Sulfones	aldesulfone sodium dapsone	Categorized as HIA in previous revisions.
Drugs used solely to treat tuberculosis or other mycobacterial diseases	aminosalicylate calcium bedaquiline capreomycin cycloserine delamanid ethambutol ethionamide isoniazid morinamide *para*-aminosalicylic acid pretomanid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	

AWaRe: Access, Watch, Reserve; CIA: critically important antimicrobial; HIA: highly important antimicrobial; HPCIA: highest priority critically important antimicrobial; MIA: medically important antimicrobial; WHO: World Health Organization.

[a] Antimicrobial classes now listed in this revision as authorized for use in human only would be classified as critically important if ever authorized for use in food animals.

Table 3. Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial agent					Comments
Highest priority critically important antimicrobials (HPCIA)						
Antimicrobial class	**Antimicrobial**	**C1**	**C2**	**PF1**	**PF2**	**Comments**
Cephalosporins (3rd, 4th generation)	cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefovecin cefozopran cefpiramide cefpirome cefpodoxime cefquinome cefsulodin ceftazidime cefteram pivoxil ceftibuten ceftiofur ceftizoxime ceftolozane ceftriaxone latamoxef	Yes	Yes	Yes	Yes	(C1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* spp. in children. Limited therapy for infections due to MDR Enterobacterales, which are increasing in incidence worldwide. Additionally, 4th-generation cephalosporins are limited options for empirical treatment of neutropenic patients with persistent fever. (C2) May result from transmission of Enterobacterales. (PF1) One or more members of the drug class are included in the EML and are classified as Watch or Reserve in the AWaRe classification. (PF2) Transmission-resistant Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	PF1	PF2	Comments
Quinolones	besifloxacin cinoxacin ciprofloxacin danofloxacin delafloxacin difloxacin enoxacin enrofloxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin ibafloxacin lascufloxacin levofloxacin levonadifloxacin lomefloxacin marbofloxacin moxifloxacin nadifloxacin nalidixic acid nemonoxacin norfloxacin ofloxacin orbifloxacin oxolinic acid ozenoxacin pazufloxacin pefloxacin pipemidic acid piromidic acid pradofloxacin prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin trovafloxacin	Yes	Yes	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 Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources. (PF1) One or more members of the drug class are included in the EML and are classified as Watch or Reserve in the AWaRe classification. (PF2) Transmission-resistant Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	PF1	PF2	Comments
Polymyxins	colistin[a] polymyxin B	Yes	Yes	Yes	Yes	(C1) Limited therapy for infections with MDR Enterobacterales (e.g., *Klebsiella* spp., *E. coli*, Acinetobacter, Pseudomonas spp.). (C2) May result from transmission of Enterobacterales from non-human sources. (PF1) One or more members of the drug class are included in the EML and are classified as Watch or Reserve in the AWaRe classification. (PF2) Colistin-resistant bacteria and *mcr* family genes can be transmitted via the food chain.
Phosphonic acid derivatives	fosfomycin	Yes	Yes	Yes	Yes	(C1) Limited therapy for urinary tract infections. (C2) May result from transmission of Enterobacterales, including *E. coli*, from non-human sources. (PF1) Oral formulation is on the EML and is classified as Watch in the AWaRe classification, and IV formulation is on the EML and is classified as Reserve in the AWaRe classification. (PF2) Emergence of plasmid-mediated fosfomycin-resistant *E. coli* in food animals has been reported.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Critically important antimicrobials (CIA)						
Antimicrobial class	**Antimicrobial**	**C1**	**C2**	**PF1**	**PF2**	**Comments**
Aminoglycosides	amikacin apramycin arbekacin astromicin bekanamycin dibekacin dihydrostreptomycin framycetin gentamicin isepamicin kanamycin micronomicin neomycin netilmicin paromomycin ribostamycin sisomicin streptoduocin streptomycin tobramycin	Yes	Yes	No	Yes	(C1) Sole or limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis and MDR Enterobacterales. (C2) May result from transmission of *Enterococcus* spp., Enterobacterales (including *E. coli*). (PF2) Transmission of *Enterococcus* spp., Enterobacterales (including *E. coli*). NOTE: (PF1) While streptomycin is a Watch drug on the AWaRe list and is on the EML, it is the only aminoglycoside that fulfils PF1. Further, its placement on the AWaRe list was for treatment of MDR tuberculosis, a disease that would not be influenced by use of streptomycin in animals. Therefore, it was determined that it did not justify determining the drug class fulfilled PF1.
Ansamycins	rifabutin rifampicin rifamycin rifapentine rifaximin	Yes	Yes	Yes	No	(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 MDR *S. aureus* through the food chain.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	PF1	PF2	Comments
Macrolides (14, 15, 16-membered ring)	azithromycin cethromycin clarithromycin dirithromycin erythromycin flurithromycin gamithromycin josamycin kitasamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin tildipirosin tilmicosin troleandomycin tulathromycin tylosin tylvalosin	Yes	Yes	Yes	No	(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. (PF1) One or more members of the drug class are classified as Watch or Reserve in the AWaRe list. (PF2) While resistance to macrolides in *Campylobacter* spp. can occur after macrolides are used in animals, life-threatening infections with *Campylobacter* spp., as defined by bloodstream or sterile site infections, are rare.
Highly important antimicrobials (HIA)						
Antimicrobial class	**Antimicrobial**	**C1**	**C2**			**Comments**
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 Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	Comments
Cephalosporins (1st and 2nd generation) and cephamycins	cefacetrile cefaclor cefadroxil cefalexin cefalonium cefaloridine 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 Enterobacterales, including *E. coli*, from non-human sources
Lincosamides	clindamycin lincomycin pirlimycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and *S. aureus*, including MRSA, from non-human sources.
Nitroimidazoles	metronidazole ornidazole ronidazole secnidazole tinidazole	Yes	No	(C1) Limited therapies for anaerobic infections, including C. *difficile*.
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 Enterobacterales, including *E. coli*, from non-human sources.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	Comments
Penicillins (aminopenicillins)	amoxicillin ampicillin azidocillin bacampicillin epicillin hetacillin metampicillin pivampicillin sultamicillin talampicillin temocillin	No*	Yes	(C1*) In certain settings, criterion 1 may be met: the class is one of limited therapies for Listeria and *Enterococcus* spp. (C2) May result from transmission of *Enterococcus* spp., Enterobacterales, including *E. coli*, from non-human sources.
Penicillins (aminopenicillins with β- lactamase inhibitors)	amoxicillin-clavulanic acid ampicillin-sulbactam	No*	Yes	(C1*) In certain settings, criterion 1 may be met: the class is one of limited therapies for Listeria and *Enterococcus* spp. (C2) May result from transmission of *Enterococcus* spp., Enterobacterales, including *E. coli*, from non-human sources.
Penicillins (anti-staphylococcal)	cloxacillin dicloxacillin flucloxacillin meticillin (= methicillin) nafcillin oxacillin	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)	benethamine-benzylpenicillin benzathine-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, leptospirosis, yaws and syphilis. (C2) May result from transmission of penicillin-resistant *S. aureus* 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.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	Comments
Sulfonamides, dihydrofolate reductase inhibitors and combinations	brodimoprim formosulfathiazole iclaprim ormetoprim phthalylsulfathiazole pyrimethamine sulfachlorpyridazine sulfadiazine sulfadimethoxine sulfadimidine sulfafurazole (= sulfisoxazole) sulfaguanidin sulfaisodimidine sulfalene sulfamazone sulfamerazine sulfamethazine sulfamethizole sulfamethoxazole sulfamethoxypyridazine sulfametomidine sulfametoxydiazine sulfametrole sulfamoxole sulfanilamide sulfaperin sulfaphenazole sulfapyridine sulfaquinoxaline sulfathiazole sulfathiourea tetroxoprim trimethoprim	No*	Yes	(C1*) In certain geographic settings, C1 may be met: the class may be one of limited therapies for acute bacterial meningitis, systemic non-typhoidal *Salmonella* spp. infections and other infections.
Fusidanes	fusidic acid	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited combination oral therapies for infections with MRSA. (C2) May result from transmission of MRSA from non-human sources.

Table 3 (continued). Categorization of antimicrobials authorized for use in both humans and animals

Antimicrobial class	Antimicrobial	C1	C2	Comments
Tetracyclines	chlortetracycline clomocycline demeclocycline doxycycline lymecycline metacycline minocycline oxytetracycline penimepicycline rolitetracycline sarecycline 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.
Important antimicrobials (IA)				
Antimicrobial class	**Antimicrobial**	**C1**	**C2**	**Comments**
Aminocyclitols	spectinomycin	No*	No*	(C1*) In some areas spectinomycin may be one of limited antimicrobials still active against *Neisseria gonorrhoeae*. (C2*) May result from transmission of Enterobacterales, including *E. coli*, from non-human sources, but there is no demonstrated transmission from *E. coli* to *N. gonorrhoeae*.
Cyclic polypeptides	bacitracin enramycin (=enduramycin)	No	No	
Heterocyclic compounds	methenamine hippurate methenamine mandelate	No	No	
Nitrofuran derivatives	furaltadone furazidine furazolidone nifuroxazide nifurtoinol nitrofural nitrofurantoin	No	No	
Pleuromutilins	lefamulin retapamulin tiamulin valnemulin	No	No	

AWaRe: Access, Watch, Reserve; C1: criterion 1; C2: criterion 2; EML: Essential Medicines List; IV: intravenous; MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; PF1: prioritization factor 1; PF2: prioritization factor 2; spp.: species.

[a] Colistin, also known as polymixin E, includes colistin sulfate and colistin methanesulfonate

Table 4. Categorization of antimicrobials not authorized for use in humans

NOT AUTHORIZED FOR USE IN HUMANS Not medically important for humans	
Aminocoumarins	novobiocin
Arsenicals	nitarsone, roxarsone
Bicyclomycins	bicozamycin
Halogenated 8-hydroxyquinolines	halquinol
Ionophores (including polyethers)	laidlomycin lasalocid maduramicin monensin narasin salinomycin semduramicin
Orthosomycins	avilamycin
Phosphoglycolipids	bambermycin (= flavomycin) flavophospholipol moenomycin
Quinoxalines	carbadox, olaquindox

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Annex 1. Development of the WHO MIA List

A1.1 Establishment of the Advisory Group on Critically Important Antimicrobials for Human Medicine

In 2021 WHO established in 2021 an Advisory Group on Critically Important Antimicrobials for Human Medicine (AG CIA) through an open call inviting experts from the different disciplines to provide expertise in revising and developing the WHO MIA List.

Seventeen members were selected from the six WHO regions and from the human, animal, agriculture and environment sectors.

A1.2 Development of the WHO MIA List

The AG CIA agreed to establish three working groups (WGs) to revise, update and develop the WHO MIA List

- WG1, Revision of National and Regional MIA List and Comparison with the WHO MIA List;
- WG2, Revision of Macrolides; and
- WG3, Revision of the Prioritization Factors on the MIA List.

The AG CIA conducted the development of the WHO MIA List through the revision of the existing national and regional lists of critically important antimicrobials for human medicine, revision of new evidence on the use of all classes of antimicrobials to treat infection diseases in humans.

The AG CIA group worked regularly through virtual meetings to discuss and agree on the different steps needed to develop the WHO MIA List.

A1.3 Declaration of interests of experts

Declarations of interest (DOIs) were collected and reviewed following WHO standard operating procedures. All members of the WHO AG-CIA submitted written disclosures of competing interests relevant to participate as members of the advisory group. All members did not disclose any conflict of interest as a result the WHO technical unit granted their participation in the development of the WHO MIA List.

Annex 2. History of the WHO MIA List

A2.1 Background of the WHO MIA List

The WHO list of medically important antimicrobials for human medicine (previously known as the WHO list of critically important antimicrobials for human medicine) was originally developed following recommendations from two consecutive expert meetings organized by FAO, OIE (now the WOAH) and WHO. The first workshop was convened in Geneva in December 2003 and the second in Oslo in March 2004 to address public health consequences associated with the use of antimicrobial agents in food-producing animals *(1,2)*.

The first expert workshop recognized that AMR is 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 are frequently the same, or closely related to those used in human medicine.

The first expert workshop concluded, first, that there was clear evidence of adverse human health consequences due to resistant organisms from non-human use of antimicrobials. It was shown to increase the frequency of infections, to result in treatment failures (in some cases death) and to increase the severity of infections, for example fluoroquinolone-resistant *Salmonella* infections in humans. Second, the amount and pattern of non-human use of antimicrobials affected the occurrence of resistant bacteria in animals and in food commodities and thereby human exposure to these resistant bacteria. Third, the consequences of AMR 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 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 disease and microbiology), first to develop criteria for defining critically important antimicrobials for humans 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."*(2)*.

The experts recognized that implementing the concept at the national level would require considering national priorities and consequently that lists may vary from country to country. Moreover, 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 inform risk assessments, specifically of the consequences on human health associated with the use of antimicrobials in non-human sectors; and
- to develop risk management options that involve restricting 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 to consider the WHO and OIE lists of critically important antimicrobials and to begin to address the overlap of the two lists, for example the potential hazards to public health resulting from this overlap and combinations of pathogens, antimicrobials and animal species of greatest concern *(3)*. 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.

A2.2 History of the WHO CIA List

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

The 1st 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.

The 2nd 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, considering new drug development and scientific information since 2005. Participants were also requested to prioritize agents within the critically important category to allow allocation of resources towards the agents for which management of risks from AMR were needed most urgently. The classes of drugs that met all prioritization criteria were categorized as highest priority critically important antimicrobials.

Subsequently, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was formed in 2008, 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 3rd 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 drugs and classes that were analogous to those used in human medicine and thus had greater potential to impact AMR to the critically important antimicrobials for human medicine.

A further revision of the WHO CIA List took place at the 5th AGISAR meeting held in Bogotá, Colombia, in 2013. The WHO CIA List was again updated following the 7th AGISAR meeting in Raleigh, North Carolina, 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 health care 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 use 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 to date 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, this group was moved to "the important" category.

The 6th Revision of the WHO CIA List took place at the 8th AGISAR meeting held in Utrecht, Netherlands, in 2018 *( )*. Based on resistance mechanisms and the availability of alternative therapies, it was decided to group penicillins into six groups for classification: narrow-spectrum penicillins (e.g., benzylpenicillin), amidinopenicillins (e.g., mecillinam), anti-staphylococcal penicillins (e.g., flucloxacillin), aminopenicillins (e.g., ampicillin), extended-spectrum penicillins (e.g., amoxicillin-clavulanic acid) and antipseudomonal penicillins (e.g., piperacillin). In the case of simple penicillins, since there are now alternative therapies available for syphilis and enterococcal infections, this group was moved to the highly important category from the critically important category. Changes in P2 were made for aminoglycosides, phosphonic acid derivatives, and polymyxins, and 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 C1 and C2. In the interests of clarity, minor changes to the wording of P1–P3 were also made. A separate listing in Annex 1 of antimicrobials used in human and veterinary medicine was removed; they are now listed together. To accurately distinguish products used only in humans from those also used in one or more types of animals (e.g., food-producing animals, companion animals) 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.

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Annex 3. Glossary

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

Antibiotic: An agent or substance that is produced from microorganisms that 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: Antimicrobials are agents used to prevent, control and treat infectious diseases in humans, animals and plants. They include antibiotics, fungicides, antiviral agents and parasiticides. Disinfectants, antiseptics, other pharmaceuticals and natural products may also have antimicrobial properties.

Antimicrobial class: Antimicrobial class refers to 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 because of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.

Antimicrobial resistance (AMR): AMR occurs when bacteria, viruses, fungi and parasites no longer respond to antimicrobial agents. As a result of drug resistance, antibiotics and other antimicrobial agents become ineffective, and infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness and death.

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

Control of disease/metaphylaxis: Administration or application of antimicrobial agents to a group of plants/crops or animals containing sick and healthy individuals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of disease *(1)*.

Class: Refers to the antimicrobial class with subagents or subclasses of antimicrobials with a similar structure and mechanism of action.

CRE: Carbapenem-resistant Enterobacterales are resistant to the carbapenem class of antibiotics. CRE include bacteria such as *Klebsiella* spp. and *E. coli*.

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 caused by bacteria *(1)* possibly transmitted from non-human sources or *(2)* with resistance genes from non-human sources.

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

Growth promotion/growth promoter: Administration of antimicrobial agents only to increase the rate of weight gain and/or the efficiency of feed utilization in animals. The term does not apply to the use of antimicrobials for the specific purpose of treating, controlling or preventing infectious diseases *(1)*.

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

Highest priority critically important antimicrobials (HPCIAs): Antimicrobial classes used in humans that meet the two new revised prioritization criteria (PF1 and PF2).

Important antimicrobials (IAs): Antimicrobial classes used in humans which meet neither C1 nor C2 are categorized as important for human medicine.

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

Marketing authorization: Process of reviewing and assessing a dossier to support an antimicrobial agent to determine whether to permit its marketing (also called licensing, registration, approval, etc.), finalized by granting of a document also called marketing authorization (equivalent: product licence) *(1)*.

Medically important antimicrobial (MIA): Antimicrobial authorized for use 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.

Multidrug resistance (MDR): Non-susceptibility to at least one agent in three or more antimicrobial categories *(3)*.

Non-human use: While non-human use encompasses use of antimicrobials in animals, crops and plants, for the purposes of this document, non-human use refers to antimicrobial use in animals. While most of the currently available data and concerns pertain to antimicrobial use in food-producing animals, there are parallel issues in companion, working, conservation and fur/fibre-bearing species. Unless specifically noted, in this document, "animals" refers to the broad population of non-human animal species.

One Health: One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change and contributing to sustainable development.

Prevention of disease/prophylaxis: Administration or application of antimicrobial agents to an individual or a group of plants/crops or animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the antimicrobial agent is not administered or applied *(1)*.

Prioritization factor 1 (PF1): The class contains at least one antimicrobial that is BOTH on the EML and classified as Watch or Reserve in the AWaRe classification list.

Prioritization factor 2 (PF2): 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.) or resistance genes (e.g., *E. coli*, *S. aureus* and *Enterococcus* spp.) for the particular antimicrobial from non-human sources, and these infections are frequent causes of invasive and life-threatening infections.

Treatment of disease: Administration or application of antimicrobial agents to an individual or group of plants/crops or animals showing clinical signs of infectious disease *(1)*.

Veterinarian paraprofessional: A person who, for the purposes of the Terrestrial Code, is authorized by the veterinary statutory body to carry out certain designated tasks (depending on the category of veterinary paraprofessional) in a territory and delegated to them under the responsibility and direction of a veterinarian. The tasks for each category of veterinary paraprofessional should be defined by the veterinary statutory body depending on qualifications and training, and in accordance with need *(2)*.

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