World Health Organization

# WHO Medically Important Antimicrobial List

**(Previously known as the WHO Critically Important Antimicrobial List)**

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

## 7th Revision 2023

# Contents

# 1. Background

Globally there is a need to preserve the efficacy of antimicrobial agents and minimize the risk of antimicrobial resistance (AMR). AMR develops and transfers within and amongst all sectors and there is a need to engage in a One Health approach to minimize risk of emergence and transmission of AMR. It is important to improve the responsible and prudent use of antimicrobial agents, thus decreasing the inappropriate use of these agents in all sectors particularly for medically important antimicrobial agents*.

To support this goal, the World Health Organization (WHO) in 2005 first developed the List of Critically Important Antimicrobials (CIAs). The list categorizes antimicrobial classes authorized in both humans and animals based on the importance of the antimicrobial class in human medicine and the contribution of non-human use to the risk of transmission of AMR to humans.

Through the Global Action Plan on AMR (GAP) adopted in 2015, WHO, the Food and Agriculture Organization of the United Nations (FAO), the United Nations Environmental Program (UNEP) and the World Organisation for Animal Health (WOAH) through the Quadripartite collaboration developed tools and guidance to support countries in the implementation of 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 and the last revision (6$^{th}$ revision) was published in 2018[1].

* The term antimicrobial refers to antibacterials in this document. Other lists of antimicrobials such as antifungals will be developed in the future to complement this list.

In 2019, Member States made a request to the WHO Director-General to maintain and systematically update the WHO CIA List[2] (Now renamed herein as the WHO Medically Important Antimicrobial List -WHO MIA List).

As AMR is a multi-sector problem, many national and international guidelines exist aiming to mitigate AMR risks to human and animal health. For example, the WHO AWaRe classification[3] supports appropriate access to antimicrobials based on their availability and intends to help policymakers develop antimicrobial stewardship guidelines regarding their appropriate use in human medicine. The AWaRe classification provides three groupings of antimicrobials, (Access, Watch and Reserve), which considers the impact of different antimicrobials and antimicrobial classes on AMR, together with their importance, availability and affordability in treating human infections globally.

Further, the WHO AWaRe (Access, Watch, Reserve) antibiotic book[4] provides guidance for countries to optimize the use of antimicrobials in humans and provides recommendations on the choice of antibiotic, dose, route of administration and duration of treatment for common infectious syndromes. The AWaRe classification is built into the WHO EML antibiotic book. The WHO MIA List is the only WHO document that is intended to provide guidance to countries for establishing principles and guidelines for the responsible and prudent use of antimicrobials in non-human sectors, in order to minimise risks for the development and transfer of resistant bacteria from non-human sectors to humans. This document also supports the implementation of NAPs by promoting the optimal use of antimicrobials in both humans and animals (4$^{th}$ GAP strategic objective). The WHO MIA List is based on specific criteria, categorizations and groupings of each class of antimicrobial, based on its medical importance for treatment of serious disease in humans and the potential transmission of AMR from bacterial microorganisms to humans due to use of these agents in non-human sectors.

For the purposes of this document, 'non-human' use refers to food animal use only. It is also recognized that antimicrobial use (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[5,6]. AMU is also influenced by how the antimicrobial is administered (e.g., parenteral administration in individual animal vs medicated feed or water in groups of animals), and the types of animals treated such as terrestrial and aquatic, food animals, companion animals, fibre and fur bearing animals, laboratory animals, conservation animals and working animals. Further, based on the current limitations of data regarding AMU on plants, and any potential impact of AMR on human health; 'non-human' use in this document does not include the use of antimicrobials on plants at this time.

## 2. Purpose of the WHO MIA List

This list aims to support WHO Member States to:

1) Categorize antimicrobial classes that are authorized for use in humans, in both humans and animals, and not authorized in humans, based on their medical importance in human medicine while considering the potential risk of the development and spread of resistance.
2) Assist in the risk management of AMU and AMR in non-human sectors.

## 3. Target audience

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

- National Regulators and policymakers in the Ministry of Health and Ministry of Agriculture or equivalent authorities responsible

for the regulation, monitoring and assuring the prudent use of antimicrobials

- Veterinarians, veterinary paraprofessionals and aquatic animal/plant/crop health professionals and prescribers of antimicrobials
- National AMR steering or coordinating committees responsible for the development, implementation and monitoring of the national action plans, policies and standards for mitigating AMR at the national level

# 4. Explanation of changes included in the WHO MIA List 7TH Revision

## 4.1 Introduction of "Authorized for use in humans only" Medically important' and "Not medically important" groups

These groups described in table 1 were created to provide a more comprehensive pathway to assess all antimicrobial classes that are used in humans only (authorized for use in humans only), animals only (not authorized in human medicine) or both (authorized for use in both in humans and animals), while recognizing that antimicrobial classes that are used in both humans and animals are the focus of this document with regards to mitigating AMR risk to human health.

### 4.1.1 Introduction of "Authorized for use in humans only"

This group is not intended to mean that these antimicrobials are not high priority. Indeed, they should be considered to be of additional concern, aligning with the WHO best practices statement (section 5.3.1) that antimicrobial classes not currently authorized in food animals should not be used in food animals in the future. This also creates a pathway whereby any new antimicrobial classes that are authorized for use only in humans in the future would automatically be added to this category, without the need to wait for review in a future edition of this list.

### 4.1.2 Introduction of "Not medically important for humans" group

This group was added to the main decision-making process, as opposed to placing a selection of these drugs in Annex 2 as per 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 medically important antimicrobials. This group was added to try to ensure that all antimicrobials used in animals came under scrutiny as part of the standard evaluation approach, so that they would not be placed in a low priority category by default, without a proper assessment of the potential risk of AMR in humans.

### 4.2 Changes to prioritization factors

In the previous edition, CIAs were further assessed using three prioritization factors. The first two related to the number of people that might need to be treated and the second related to the frequency of and the intensity of antimicrobial use in humans. However, it was apparent that the previous prioritization factors 1 and 2 were somewhat confusing and potentially overlapping. Since those prioritization factors were designed to assess the importance of the antimicrobial in humans, it was decided to use the WHO Essential Medicines List and the WHO AWaRe classification, established systems that indicate the importance of individual antimicrobials (Essential Medicines List) and categorize antimicrobial drugs into Access, Watch and Reserve categories based on their importance and AMR concerns (AWaRe Classification). Since these are classified at the individual drug, and not at class level, it was necessary to determine how to address situations where drugs within a class were distributed to different AWaRe ranking. The two lists were used together to assess two different aspects of importance. If an antimicrobial drug was both on the Essential Medicines List and categorized as Watch or Reserve on the

AWaRe list, the corresponding class or subclass was deemed to have fulfilled PF1.

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

The new PF2 was a slight modification of the previous P3, and an added assessment of the degree of evidence of the impact of antimicrobial use in animals on the treatment of serious and life-threatening diseases in humans (e.g., the frequency of blood-stream infections).

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

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 to 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 only conferred by a specific resistance mechanism (16S methyltransferases) compared to other aminoglycosides. As the only aminoglycoside in the AWaRe Reserve category and also only authorized for use in humans, plazomicin was classified as “Aminoglycosides (Reserve)”.

Based on this separation, all of these 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 for treatment of campylobacteriosis, most cases are self-limiting and antibiotic therapy is not advised and *Campylobacter* rarely causes 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 for treatment of enterococcal infections and listeriosis. However, new antimicrobial options for enterococci are available in many regions. While aminopenicillins remain important for treatment of listeriosis, there are other treatment options, and it was determined that C1 no longer applied. This resulted in recategorization of this drug class as 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 animals and the limited therapeutic options to treat 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 as fulfilling the C1 criterion in some geographical settings only. However, since therapeutic options to treat anaerobic infections, including *Clostridium difficile* infection, are limited worldwide, they 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 3.2). Antimicrobial classes were divided into sub-classes for categorization only if justified based on mechanisms of resistance. For example, there are sufficient differences in mechanisms of resistance to the cephalosporin groups to separate the 1st and 2nd generation from the 3rd to 5th generation cephalosporins for the purposes of categorization. Additionally, there were situations where it was deemed that an antimicrobial agent was sufficiently different from other members of a class or subclass, based on factors such as resistance mechanisms or AWaRe list ranking.

Therefore, antimicrobials were assessed at the class level, unless there were reasons to separate 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., beta-lactam, beta-lactamase inhibitor)
- Presence of different resistance mechanisms compared to other members within the class/subclass

- Presence on 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 above.

Antimicrobial classes that are only authorized for topical use were not considered unless they are frequently used for treatment of 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.

## 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 Critically Important, Highly Important or Important Antimicrobials.

**Criterion 1 (C1):** ***Sole or one of limited available therapies, to treat serious bacterial infections in humans***

**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 bacterial agent, serious infections are overall more likely to result in increased morbidity or mortality if left untreated because few or no effective antibacterial agents are available.

It is of high importance that the effectiveness of such antimicrobial agents be preserved, as loss of efficacy of these antimicrobials 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):** ***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 because these infections are most amenable to risk management strategies related to non-human use of antimicrobials. The organisms that cause disease need not be drug-resistant at the present time. However, the potential for transmission shows the path for acquisition of resistance now or in the future. The evidence for a link between non-human sources and transmission to humans is greatest for certain bacteria (e.g., non-typhoidal *Salmonella* spp., *Campylobacter* spp., *Escherichia coli*, *Enterococcus* spp. and *Staphylococcus aureus*). Commensal organisms from non-human sources may also transmit resistance determinants to human pathogens. Commensals may also be pathogenic in immunosuppressed hosts. It is important to note that the transmission of such organisms or their genes do not need to be demonstrated; rather, it is considered sufficient that the potential for such transmission is identified through risk assessment.

### 5.2.2 Prioritization

Antimicrobials within the critically important (CIA) category by virtue of fulfilling both above criteria 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 Essential Medicines List[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 those classes of antimicrobials included in the WHO EML list and considered Watch or Reserve in the AWaRe list. While the WHO EML list and AWaRe list categorize drugs with different methods and for different purposes than this list, 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 disease, as those have the greatest impact on 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, are rare.

### 5.3 Authorization status

Antimicrobial groups were evaluated based on their current authorization status. Antimicrobials were considered authorized for human and/or non-human use if authorized for use in any country.

### 5.3.1 Antimicrobials "Authorized for use in humans only"

The agents authorised for use in humans only are not authorised for use in animals, and as such there is little or no data available to properly assess Prioritization Factor 2, thus the criteria for categorization (HPCIA, CIA, HIA, IA) were not applied. These drug classes mainly contain newer antimicrobials that are very important for treatment of serious multidrug resistant infections in humans. Most of these classes were previously classified as "Critically Important" in the 6th revision[2]; however, if approved for use in food 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 above.

The group of antimicrobials authorized only for use in human includes aminomethylcycline, anti-pseudomonal penicillins with and without β-lactamase inhibitors, carbapenems with or without inhibitors, 3rd, 4th and 5th generation cephalosporins with and without β-lactamase inhibitors, siderophore cephalosporin, fluorocycline, glycopeptides and lipoglycopeptides, glycylcyclines, ketolides, lipopeptides, 18 membered-ring macrolides, monobactams, nitrofurans derivatives, 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".

- For implementation purposes, drugs within classes* in the group of "Authorized for use in humans only" should be approached as HPCIA category and should not be authorized in the future for use in food animals, crops or plants unless potential risks to human health have been evaluated through procedures consistent with a risk-based approach (see Codex Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011[8]).

### 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 Highest Priority Critical Important (HPCIA) or Critically Important Antimicrobial (CIA).

If only one or none of the two criteria were fulfilled, classes within this group were categorized as Highly Important (HIA) or Important (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 below do not apply. These are classified as "not medically important for humans" and would remain as such, unless in the future substantial evidence becomes available that use of an antimicrobial agent in this group can result in resistance to a medically important antimicrobial.

## 5.4. Decision tree

A decision tree is used to facilitate the categorization of the classes of antimicrobials based on the use in humans and non-human sectors (Figure 1).

Table 1 summarize the categorization of all classes of antimicrobials included in the WHO MIA List. Table 2 includes all classes of antimicrobials categorized as “Authorized only for use in humans”. Table 3 includes all classes of antimicrobials categorized as “authorized for use in both humans and animals” and table 4 includes all classes of antimicrobials categorized as “not authorized in human medicine”.

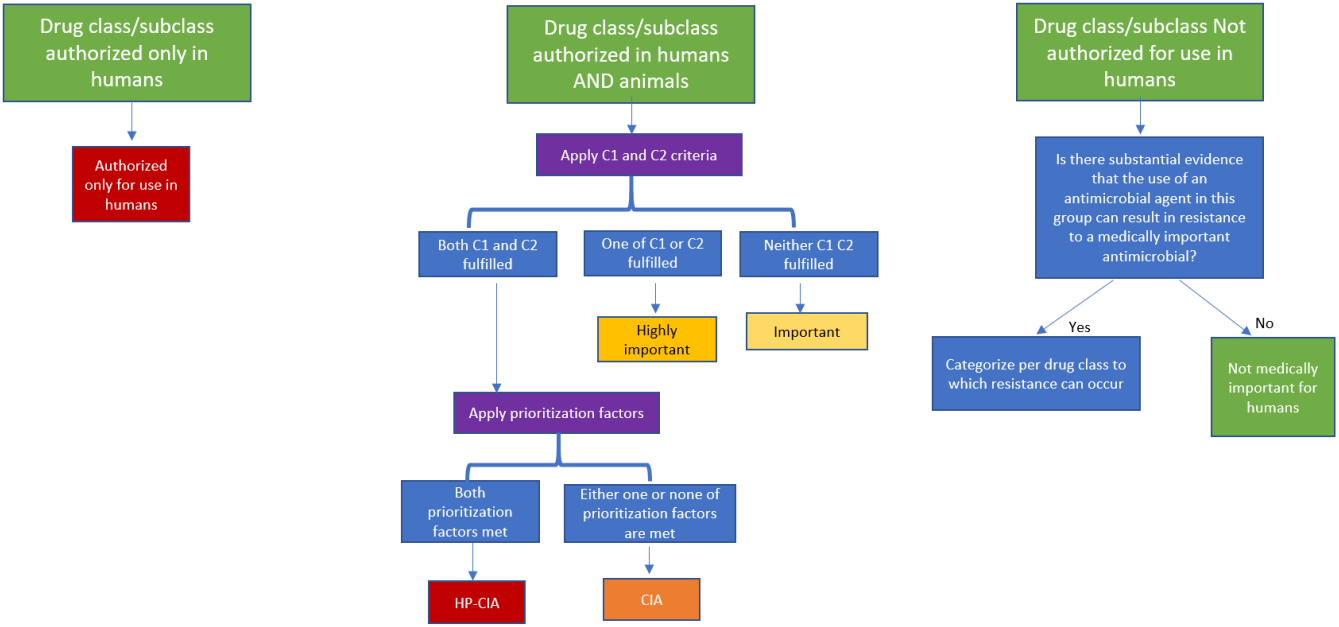


**Figure 1. Decision tree to categorize all antimicrobials**

## 6. Implementation activities

The *WHO MIA List* should be used to help with risk-based decisions to minimise the 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 from the use of antimicrobials in non-human sectors on human health. The document is intended to be used in conjunction with other relevant documents (Codex Guidelines for risk analysis of foodborne antimicrobial resistance, Codex Code of practice to minimize and contain foodborne antimicrobial resistance, Codex Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance[9], and the WOAH List of Antimicrobials of Veterinary Importance), as well as national and regional differences in antimicrobial resistance, disease prevalence and antimicrobial access.

Considering the WHO Model List of Essential Medicines[7], the EML (Essential Medicines List) Antibiotic book[2], and AWaRe Classification[3], as well as national surveillance of AMR and AMU, will allow for prioritization of risk management strategies in the human sector, the animal sector, in agriculture (crops) and horticulture for future planning, through a coordinated multisectoral One Health approach.

Some examples of use of the document include:

| 1. Enhance regulations and optimize the use of antimicrobials at national and regional levels |
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| 1. Use by competent authorities, the pharmaceutical industry, veterinarians, veterinary paraprofessionals and aquatic animal/plant/crop health professionals for the prioritization of risk management strategies for antimicrobials categorized as medically important to preserve their effectiveness |
| 2. Use in conjunction with Codex AMR texts (Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance (CXG 94-2021) and the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011), Code of practice to minimize and contain foodborne AMR (CXC 61-2021) for prioritizing risk profiling and hazard analysis for mitigating foodborne AMR risks |
| 3. Developing responsible and prudent use and treatment guidelines in non-human sectors in conjunction of existing international guidelines such as the WOAH List of Antimicrobials of Veterinary Importance |
| 4. Developing of national and regional policies to support the responsible and prudent use of medically important antimicrobials across sectors |
| 5. 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, 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 "HPCIA" group followed by agents in "CIA" group, then "HI", then "I". The least risk and impact to human |

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| health is associated with agents that are "Not Medically important for humans" |
| 6. Assisting efforts to eliminate the use of medically important antimicrobials for non-veterinary medical purpose, such as growth promotion and in crop production and agri-food systems for non-phytosanitary purposes. |
| 7. Assisting with policies to limit use of HPCIA across sectors |
| 8. Informing the development of guidelines for responsible antimicrobial use, integrated AMU and AMR surveillance and reporting strategies following a One Health approach; |

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| 2. Surveillance, monitoring and evaluation |
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| 1. As part of a One Health approach, ensuring that medically important antimicrobials are included in antimicrobial resistance and use monitoring/surveillance programmes |
| 2. Use in conjunction with Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance (CXG 94-2021) |
| 3. Informing the development of targeted research projects to address data gaps on existing or future medically important antimicrobials |

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| 3. Strengthen risk management in non-human sectors |
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| 1. Developing of risk management measures such as restricted use, labelling, limiting or prohibiting off-label or extra-label |

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| use, and making antimicrobial agents available by prescription only |

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| 4. Strengthen communication of risks |
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| 1. Communicating risks to the public, prescribers and users of antimicrobials in non-human sectors |

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## Table 1. Antimicrobial Grouped according to Authorized Use

| Medically Important Antimicrobials | | | | | | Not Medically Important |
|---|---|---|---|---|---|---|
| AUTHORIZED FOR USE IN HUMANS ONLY* | | AUTHORIZED FOR BOTH HUMAN AND ANIMAL | | | | NOT AUTHORIZED IN HUMANS |
| | | CATEGORIZATION OF ANTIMICROBIALS | | | | |
| | | HPCIA | CIA | HIA | IA | |
| Aminoglycoside (Plazomicin) | Glycylcyclines | Cephalosporins (3rd, 4th generation) | Aminoglycosides | Amphenicols | Aminocyclitols | Aminocoumarins |
| Macrolide 18 membered ring (Fidaxomicin) | Lipopeptides | Quinolones | Ansamycins | Cephalosporins (1st and 2nd Generation) and cephamycins | Cyclic polypeptides | Arsenicals |
| Aminomethylcycline | Monobactams | Polymyxins | Macrolides (14, 15, 16 membered-ring) | Lincosamides | Heterocyclic compound | Bicyclomycins |
| Anti-pseudomonal penicillins (Carboxypenicillin and Ureidopenicillin) | Nitrofurans derivatives | Phosphonic acid derivatives | | Nitroimidazoles | Hydroxyquinoline | Orthosomycins |
| | | | | Tetracyclines | | |
| Anti-pseudomonal penicillins with B-lactamase inhibitors | Oxazolidinones | | | Penicillins (amidinopenicillins and aminopenicillins) | Pleuromutilins | Phosphoglycolipids |
| Carbapenems with or without B-lactamase inhibitor | Riminofenazines | | | Penicillins (aminopenicillins with beta- lactamase inhibitors) | | Ionophores (including polyethers) |
| Cephalosporins (3rd ,4th and 5th generation cephalosporins with B-lactamase inhibitors) | Sulfones | | | Penicillins (anti-staphylococcal) | | Quinoxalines |
| 5th generation cephalosporins | Glycopeptides and lipoglycopeptid | | | Penicillins (narrow spectrum) | | |
| Siderophore cephalosporin | Pseudomonic acids (mupirocin) | | | Streptogramins | | |
| Fluorocycline | Phenol derivatives (clofoctol) | | | Sulfonamides, dihydrofolate reductase inhibitors and combinations | | |
| Drugs used solely to treat tuberculosis or other mycobacterial diseases | | | | Fusidanes | | |

## Table 2[1]. Antimicrobials "Authorized only for use in humans"

| Antimicrobial class | Antimicrobial | Comments |
|---|---|---|
| **AUTHORIZED FOR USE IN HUMANS ONLY** | | |
| Aminoglycosides: Plazomicin | plazomicin | Specific mechanisms of resistance compared to other aminoglycosides. Classified as "reserve" in WHO AWaRe list. |
| Aminomethylcycline | omadacycline | This is a new antimicrobial class derived from modifications to a tetracycline scaffold. |
| Anti-pseudomonal penicillins (Carboxypenicillin and Ureidopenicillin) | azlocillin<br>carbenicillin<br>carindacillin<br>mezlocillin<br>piperacillin<br>sulbenicillin<br>ticarcillin | Categorized as CIA in previous revisions |
| Anti-pseudomonal penicillins with B-lactamase inhibitor | piperacillin-tazobactam<br>ticarcillin-clavulanic-acid | |
| Carbapenems with or without inhibitors | biapenem<br>doripenem<br>ertapenem<br>faropenem<br>imipenem<br>meropenem<br>panipenem | Categorized as CIA in previous revisions |

[1] 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

| | | |
|---|---|---|
| | imipenem/cilastatin<br>imipenem-relebactam<br>meropenem-vaborbactam | |
| 3rd ,4th and 5th generation cephalosporins with B-lactamase inhibitor | cefoperazone-sulbactam<br>ceftazidime-avibactam<br>ceftriaxone-sulbactam<br>ceftolozane-tazobactam | Categorized as HPCIA in previous revisions |
| 5th generation cephalosporins | ceftaroline<br>ceftobiprole | |
| Siderophore cephalosporin | cefiderocol | This is a new antimicrobial class derived from modifications to a cephalosporin scaffold. |
| Fluorocycline | eravacycline | This is a new antimicrobial class derived from modifications to a tetracycline scaffold. |
| Glycopeptides and lipoglycopeptides | dalbavancin<br>oritavancin<br>ramoplanin<br>teicoplanin<br>telavancin<br>vancomycin | Categorized as HPCIA in previous revisions |
| Glycylcyclines | tigecycline | Categorized as CIA in previous revisions |
| 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<br>carumonam | Categorized as CIA in previous revisions |

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| Nitrofurans derivatives | furaltadone<br>furazolidone<br>furazidin<br>nifuroxazide<br>nifurtoinol<br>nitrofural<br>nitrofurantoin | Categorized as IA in previous revisions |
| Oxazolidinones | cadazolid<br>linezolid<br>radezolid<br>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 in this MIA list |
| Riminofenazines | clofazimine | Categorized as HIA in previous revisions |
| Sulfones | aldesulfone sodium<br>dapsone | Categorized as HIA in previous revisions |
| Drugs used solely to treat tuberculosis or other mycobacterial diseases | aminosalicylate calcium<br>bedaquiline<br>capreomycin<br>cycloserine<br>delamanid<br>ethambutol<br>ethionamide<br>isoniazid<br>morinamide<br>para-aminosalicylic-acid<br>pretomanid<br>protionamide<br>pyrazinamide<br>sodium aminosalicylate<br>terizidone<br>tiocarlide | Categorized as CIA in previous revisions |

421 **Table 3. Categorization of "Antimicrobials authorized for use in both**
422 **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<br>cefdinir<br>cefditoren<br>cefepime<br>cefetamet<br>cefixime<br>cefmenoxime<br>cefodizime<br>cefoperazone<br>cefoselis<br>cefotaxime<br>cefovecin<br>cefozopran<br>cefpiramide<br>cefpirome<br>cefpodoxime<br>cefquinome<br>cefsulodin<br>ceftazidime<br>ceftibuten<br>cefteram-pivoxil<br>ceftiofur<br>ceftizoxime<br>ceftolozane<br>ceftriaxone<br>latamoxef | Yes | Yes | Yes | Yes | (C1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* spp. in children.<br>Limited therapy for infections due to MDR Enterobacterales, which are increasing in incidence worldwide. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever.<br><br>(C2) May result from transmission of Enterobacterales.<br><br>(PF1) One or more members of the drug class are included in the EML and are classified as Watch or Reserve on the AWaRe classification.<br>(PF2) Transmission resistant Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources |

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

| | | | | | | |
|---|---|---|---|---|---|---|
| Polymyxins | colistin[2]<br>polymyxin B | Yes | Yes | Yes | Yes | (C1) Limited therapy for infections with MDR Enterobacterales (e.g., *Klebsiella* spp., *E. coli, Acinetobacter, Pseudomonas* spp.).<br><br>(C2) May result from transmission of Enterobacterales from non-human sources.<br><br>(PF1) One or more members of the drug class are included in the EML and are classified as Watch or Reserve on the AWaRe classification.<br><br>(PF2) Colistin resistant bacteria and the *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.<br><br>(C2) May result from transmission of Enterobacterales, including *E. co*li, from non-human sources.<br><br>(PF1) Oral formulation is in the EML and is classified as Watch and IV formulation is in the EML and is classified as Reserve in AWaRe classification<br><br>(PF2) Emergence of plasmid-mediated fosfomycin-resistant *E. coli* in food animals has been reported |

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

| CRITICALLY IMPORTANT ANTIMICROBIALS (CIA) | | | | | | |
|---|---|---|---|---|---|---|
| **Antimicrobial class** | **Antimicrobial agent** | **C1** | **C2** | **PF1** | **PF2** | **Comments** |
| Aminoglycosides | amikacin<br>apramycin<br>arbekacin<br>astromicin<br>bekanamycin<br>dibekacin<br>dihydrostreptomycin<br>framycetin<br>gentamicin<br>isepamicin<br>kanamycin<br>micronomicin<br>neomycin<br>netilmicin<br>paromomycin<br>ribostamycin<br>sisomicin<br>streptoduocin<br>streptomycin<br>tobramycin | Yes | Yes | No | Yes | (C1) Sole or limited therapy as part of treatment of enterococcal endocarditis and multidrug-resistant (MDR) tuberculosis and MDR Enterobacterales.<br><br>(C2) May result from transmission of *Enterococcus* spp., Enterobacterales (including *E. coli*)<br><br>(PF2) Transmission of *Enterococcus* spp., Enterobacterales (including *E. coli)*<br><br>**NOTE:** (PF1) While streptomycin is a Watch drug on the AWaRe list and is on the EML list, it is the only aminoglycoside that fulfills that. Further, its placement on the AWaRe list was for treatment of multidrug resistant 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<br>rifampicin<br>rifamycin<br>rifapentine<br>rifaximin | Yes | Yes | Yes | No | (C1) Limited therapy as part of treatment of mycobacterial diseases including tuberculosis; single drug therapy may select for resistance.<br><br>(C2) May result from transmission of MDR *Staphylococcus aureus* through the food chain. |

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|---|---|---|---|---|---|---|
| Macrolides (14, 15, 16 membered-ring) | azithromycin<br>cethromycin<br>clarithromycin<br>dirithromycin<br>erythromycin<br>flurithromycin<br>gamithromycin<br>josamycin<br>kitasamycin<br>midecamycin<br>miocamycin<br>oleandomycin<br>rokitamycin<br>roxithromycin<br>spiramycin<br>tildipirosin<br>tilmicosin<br>troleandomycin<br>tulathromycin<br>tylosin<br>tylvalosin | Yes | Yes | Yes | No | (C1) Limited therapy for *Legionella*, *Campylobacter*, and MDR *Salmonella* spp. and *Shigella* infections.<br><br>(C2) May result from transmission of *Campylobacter* spp. and *Salmonella* spp. from non-human sources.<br><br>(PF1) One or more members of the drug class are classified as Watch or Reserve on the AWaRe list.<br><br>(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 blood stream or sterile site infections, are rare. |
| **HIGHLY IMPORTANT ANTIMICROBIALS (HIA)** | | | | | | |
| **Antimicrobial class** | **Antimicrobial agent** | **C1** | **C2** | **Comments** | | |
| Amphenicols | chloramphenicol<br>florfenicol<br>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.<br><br>(C2) May result from transmission of Enterobacterales, including *E. coli* and *Salmonella* spp., from non-human sources. | | |

| | | | | |
|---|---|---|---|---|
| Cephalosporins (1st and 2nd Generation) and cephamycins | cefacetrile<br>cefaclor<br>cefadroxil<br>cefalexin<br>cefalonium<br>cefaloridine<br>cefalotin<br>cefamandole<br>cefapirin<br>cefatrizine<br>cefazedone<br>cefazolin<br>cefbuperazone<br>cefmetazole<br>cefminox<br>cefonicid<br>ceforanide<br>cefotetan<br>cefotiam<br>cefoxitin<br>cefprozil<br>cefradine<br>cefroxadine<br>ceftezole<br>cefuroxime<br>flomoxef<br>loracarbef | No | Yes | (C2) May result from transmission of Enterobacterales, including *E. coli*, from non-human sources |
| Lincosamides | clindamycin<br>lincomycin<br>pirlimycin | No | Yes | (C2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus*, including MRSA, from non-human sources. |
| Nitroimidazoles | metronidazole<br>ornidazole<br>secnidazole<br>tinidazole | Yes | No | (C1) Limited therapies for anaerobic infections including *C. difficile*. |
| Penicillins (amidinopenicillins) | mecillinam<br>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.<br><br>(C2) May result from transmission of Enterobacterales, including *E. coli*, from non-human sources. |

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|---|---|---|---|---|
| Penicillins (aminopenicillins) | amoxicillin<br>ampicillin<br>azidocillin<br>bacampicillin<br>epicillin<br>hetacillin<br>metampicillin<br>pivampicillin<br>sultamicillin<br>talampicillin<br>temocillin | No* | Yes | (C1*) In certain settings, Criterion 1 may be met: the class is one of limited therapies for Listeria and *Enterococcus* spp.<br><br>(C2) May result from transmission of *Enterococcus* spp., Enterobacterales, including *E. coli* from non-human sources |
| Penicillins (aminopenicillins with beta-lactamase inhibitors) | amoxicillin-clavulanic acid<br>ampicillin-sulbactam | No* | Yes | ((C2) May result from transmission of *Enterococcus* spp., Enterobacterales, including *E. coli* from non-human sources |
| Penicillins (anti-staphylococcal) | cloxacillin<br>dicloxacillin<br>flucloxacillin<br>meticillin (=methicillin)<br>nafcillin<br>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*).<br><br>(C2) May result from transmission of *S. aureus*, including MRSA, from non-human sources. |
| Penicillins (narrow spectrum) | benzathine-benzylpenicillin<br>benethamine-benzylpenicillin<br>benzylpenicillin (=penicillin G)<br>clometocillin<br>penamecillin<br>penethamate hydriodide<br>pheneticillin | 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.<br><br>(C2) May result from transmission of penicillin-resistant *Staphylococcus aureus*, from non-human sources. |
| Streptogramins | pristinamycin<br>quinupristin-dalfopristin<br>virginiamycin | No | Yes | (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources. |

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

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|---|---|---|---|---|
| Tetracyclines | chlortetracycline<br>clomocycline<br>demeclocycline<br>doxycycline<br>lymecycline<br>metacycline<br>minocycline<br>oxytetracycline<br>penimepicycline<br>rolitetracycline<br>sarecycline<br>tetracycline | Yes | No* | (C1) Limited therapy for infections due to *Brucella* spp., *Chlamydia* spp., and *Rickettsia* spp.<br><br>(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 agent** | **C1** | **C2** | **Comments** |
| Aminocyclitols | spectinomycin | No* | No* | (C1*) In some areas spectinomycin may be one of limited antimicrobials still active against *Neisseria gonorrhoeae*.<br><br>(C2*) May result from transmission of Enterobacterales, including *E. coli*, from non-human sources, but there is no demonstrated transmission from *E. coli* to *Neisseria gonorrhoeae* |
| Cyclic | bacitracin | No | No | |
| Heterocyclic compound | methenamine hippurate<br>methenamine mandelate | No | No | |
| Hydroxyquinoline | halquinol<br>nitroxoline | No | No | |
| Pleuromutilins | lefamulin<br>retapamulin<br>tiamulin<br>valnemulin | No | No | |

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**Table 4. Categorization of Antimicrobials "Not authorized for use in humans"**

| NOT AUTHORIZED FOR USE IN HUMANS<br>Not Medically Important for Humans | |
|---|---|
| Aminocoumarins | novobiocin |
| Arsenicals | roxarsone, nitarsone |
| Bicyclomycins | bicozamycin |
| Orthosomycins | avilamycin |
| Phosphoglycolipids | bambermycin (=flavomycin)<br>flavophospholipol<br>moenomycin |
| Ionophores (including polyethers) | laidlomycin<br>lasalocid,<br>maduramicin<br>monensin,<br>narasin,<br>salinomycin<br>semduramicin |
| Quinoxalines | carbadox, olaquindox |

## 7. References


1. Critically Important Antimicrobial for Human Medicine, 6th revision 2018 https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1

2. Seventy second World Health Assembly item 11.8 https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R5-en.pdf
3. 2021 AWaRe Classification https://www.who.int/publications/i/item/2021-aware-classification
4. The WHO AWaRe (Access, Watch, Reserve) antibiotic book https://www.who.int/publications/i/item/9789240062382
5. WOAH Terrestrial Animal Health Code https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-code-online-access/?id=169&L=1&htmfile=chapitre_antibio_monitoring.htm

6. Codex Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance, CXC 61-2005, Adopted in 2005. Amended in 2021. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXC%2B61-2005%252FCXC_061e.pdf
7. WHO Model Lists of Essential Medicines. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists
8. Codex Guidelines for risk analysis of foodborne antimicrobial resistance CXG 77-2011 https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXG%2B77-2011%252FCXG_077e.pdf

9. Compendium of Codex AMR texts s to address foodborne AMR https://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/en/c/1472643/

# Annex 1. Development of the WHO MIA List 7th Revision

## Establishment of the Advisory Group on Critically Important Antimicrobials for Human Medicine -AG CIA-

WHO established in 2021 an Advisory Group on Critically Important Antimicrobials for Human Medicine through an open call inviting experts from the different disciplines to provide expertise in the revision and development of the WHO MIA List.

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

## Development of the WHO CIA List 7th revision

The AG CIA agreed to establish three Working Groups (WGs) to revise, update and develop the 7th revision.

The three working groups established were

1. WG1 Revision of National and Regional MIA list and comparison with the WHO MIA List
2. WG2 Revision of Macrolides
3. WG3 Revision of the prioritization factors on the MIA list

The AGCIA group worked regularly through virtual meeting to discuss and agree on the different steps to develop the 7th revision.

# Annex 2. History of the WHO MIA List

## Background of the WHO MIA List

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

The first expert workshop recognized that AMR 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 firstly that there was a clear evidence of adverse human health consequences due to resistant organisms from non-human usage of antimicrobials. It was documented increase frequency of infections, treatment failures (in some cases death) and increased severity of infections, example is fluoroquinolone-resistant *Salmonella* infections in humans. Secondly, the amount and pattern of non-human usage of antimicrobials affected the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria. Thirdly, the consequences of 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 considered critically important in humans.

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

The experts recognized that the implementation of the concept at national level 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 inform risk assessments, specifically for assessing consequences on human health associated with use of antimicrobials in non-human sectors
- to develop risk management options that involve restriction of use in a country

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

A third FAO/OIE/WHO expert meeting met in Rome in 2007 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.

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

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 AMR were needed most urgently. The classes of drugs that met all prioritization criteria were called Highest Priority Critically Important Antimicrobials.

Subsequently, a WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) was formed in 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 third AGISAR meeting held in Oslo, Norway in 2011, the *WHO CIA List* was updated with additional information. Veterinary drugs falling in the same classes of antimicrobials as those in the human medicine list were also listed in the tables. This was done to help risk managers more readily identify those drugs and classes that were analogous to those used in human medicine and thus had greater potential to impact AMR to the critically important antimicrobials for human medicine.

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

The 6th revision[2] of the *WHO CIA List* took place at the eight AGISAR meeting held in Utrecht, The Netherlands in 2018. It was decided on the basis of resistance mechanisms and availability of alternative therapies, 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 "Highly Important" from "Critically Important". Changes in prioritization criteria 2 (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. Separate listing in Annex 1 of antimicrobials used in human and veterinary medicine was removed; they are now listed together. To accurately distinguish those products used only in humans from those also used in one or more types of animals (e.g., food-producing, companion) or plants requires a level of complexity and information on possible off-label use (particularly in companion animals) not needed for the WHO CIA List.

## Annex 3. Glossary of terms

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

**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 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):** 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 the World Health Organization in December of 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 the disease.

**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 and include bacteria such as *Klebsiella* spp and *E. coli*.

**Criterion 1 (C1):** Sole, or one of limited available therapies, to treat serious bacterial infections in people

**Criterion 2 (C2):** 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 (CIA):** 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 to only 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 (Codex text on foodborne antimicrobial resistance, 2021).

**Highly important antimicrobials**: 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:** Antimicrobial classes used in humans that meet the two new revised prioritization criteria (PF1 and PF2).

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

***mcr* genes:** 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 agent.

**Medically important antimicrobial:** 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 (*Magiorakos A-P et al., 2012*)

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

**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. (Codex texts on foodborne antimicrobial resistance, 2021).

**Prioritization factor 1 (PF1):** The class contains at least one antimicrobial that is BOTH on the Essential Medicines List and 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, 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. (Codex texts on foodborne antimicrobial resistance, 2021).

**Veterinarian paraprofessional:** means a person who, for the purposes of the Terrestrial Code, is authorized by the veterinary statutory body to carry out certain designated tasks (dependent upon 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. (WOAH Terrestrial Animal Health Code, Thirtieth edition, 2022).