Critically Important Antimicrobials for Human Medicine

4th Revision 2013

World Health Organization

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

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1. History of the current document

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

The 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark, in May 2007. During the second meeting, participants reviewed the two criteria and re-examined the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. Participants were also requested to prioritize agents within the critically important category in order to allow allocation of resources towards the agents for which management of the risks from antimicrobial resistance are needed most urgently. These antimicrobial classes were fluoroquinolones, 3rd and 4th generation cephalosporins and macrolides.

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 in part of AGISAR's terms of Reference. At the 3rd AGISAR meeting held in Oslo, Norway, in June 2011, additional information was added to the list such as ATC codes (per the WHO Collaborating Centre for Drug Statistics), to ensure a more complete listing of products. Veterinary drugs falling in the same classes of antimicrobials as those in the human medicine list are now also listed in the tables to help risk managers more readily identify those drugs and classes that are analogous to human medicines and with greater potential to impact resistance among the critically important antimicrobials for human medicine.

The current revision took place at the 5th AGISAR meeting held in Bogota, Colombia, in 2013.

2. Purpose

This document is intended for public health and animal health authorities, practicing physicians and veterinarians, and other interested stakeholders

involved in managing antimicrobial resistance to ensure that critically important antimicrobials are used prudently both in human and veterinary medicine.

3. Use of the document

The list of Critically Important Antimicrobials should be used as a reference to help formulate and prioritize risk assessment and risk management strategies for containing antimicrobial resistance due to human and non-human antimicrobial use. Some examples of appropriate use of the document include:

- Prioritizing for most urgent development of risk management strategies those antimicrobials characterized as *critically important* in order to preserve their effectiveness in human medicine.
- Ensuring that critically important antimicrobials are included in antimicrobial susceptibility monitoring programmes.
- Refining and prioritizing risk profile and hazard analysis activities for interventions by species or by region.
- Developing risk management options such as restricted use, labelling, limiting or prohibiting extra-label use, and making antimicrobial agents available by prescription only.
- For the development of prudent use and treatment guidelines in humans and animals.
- To direct special research projects to address prevalence data gaps on existing or potential future CIAs.
- Communicating risks to the public

This list should not be considered as the sole source of information to guide a risk management approach; instead, there are some basic overarching principles that should guide future decisions regarding antimicrobials, including:

- when a new class of drug comes on the market, it should be considered critically important from the outset unless strong evidence suggests otherwise,
- existing drugs such as carbepenems, linezolid, and daptomycin, which are not currently used in food production, should likewise

not be used in the future in animals, plants, or in aquaculture , and in regions of the world where at least one criterion for critically important status is met, and limited alternative therapies are available for a given condition, then the class should by default be considered critically important

4. The criteria

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

Explanation: It is evident that antimicrobials that are the sole or one of few alternatives for the treatment of serious bacterial infections in humans; therefore, they occupy an important place in human medicine. Serious infections are likely to result in significant morbidity or mortality if left untreated. Seriousness of disease may relate to the site of infection (e.g. pneumonia, meningitis) or the host (e.g. infant, immunosuppression). Even though multidrug resistance alone may or may not always influence patient outcomes, in general it is associated with poorer outcomes.

It is of prime importance, then, that the use of such antibacterial agents be preserved, as loss of efficacy in these drugs due to the emergence of resistance would have a significant impact on human health, especially for people with life-threatening infections. The *Comments* sections of the tables include examples of the diseases for which the given antibacterial agent or class was considered the sole or one of limited therapies. This criterion does not consider the likelihood that these pathogens may be transmitted, or have been transmitted, from non-human sources to humans.

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

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

5. Interpretation of categorization

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

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

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