Critically Important Antimicrobials for Human Medicine

3rd Edition

World Health Organization

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

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3rd Edition

Department of Food Safety and Zoonoses

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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 this meeting, participants considered the list of all antimicrobial classes used in human medicine and categorized antimicrobials into three groups of *critically important, highly important,* and *important* based on criteria developed.

The 2nd WHO Expert Meeting on Critically Important Antimicrobials for Human Health was held in Copenhagen, Denmark, in May 2007. In this 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 on the agents for which management of the risks from antimicrobial resistance are needed most urgently.

The 1st AGISAR meeting held in Copenhagen, 2009 was a follow-up of these two previous expert consultations. Experts from the meeting reviewed the Copenhagen 2007 list of CIA (2nd edition of the CIA list) and came up with the 3rd edition of the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and new drugs.

2. What should the list be used for?

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

- Prioritization of the antimicrobials characterized as *critically important* for most urgent development of risk management strategies in order to preserve their effectiveness in human medicine.

- Elevating the categorization of specific antimicrobials in regions/countries where it is warranted

- Designing antimicrobial susceptibility testing platforms for use in national programmes to monitor antimicrobial resistance

- Informing national policies related to antimicrobial resistance
- Developing appropriate new drugs and vaccines that will preserve critically important antimicrobial agents

3. What should the list NOT be used for?

- As the sole source of information for developing risk management strategies.
- As the sole source of treatment guidelines for either animals or humans.
- To minimize the importance of other critically important antimicrobials in the same category.

4. The criteria

Criterion 1:
Antimicrobial agent is used as sole therapy or one of few alternatives to treat serious human disease.

Explanation: It is self-evident that antimicrobials that are the sole or one of few alternatives for treatment of serious infectious diseases in humans have an important place in human medicine. Serious disease refers to those illnesses which, if left untreated, are likely to result in irreversible morbidity or mortality. Seriousness of disease may relate to the site of infection or the host (e.g. pneumonia, meningitis). Multidrug resistance alone may or may not influence patient outcomes. For instance, multidrug resistance in *S. aureus* limits options in the treatment of pneumonia, but incision and drainage alone appears effective without antimicrobials in the treatment of skin abscesses. Therefore drug resistance does not influence the treatment of patient outcomes in skin abscesses.

It is of prime importance that the utility of such antibacterial agents should be preserved, as loss of efficacy in these drugs due to emergence of resistance would have an important impact on human health. Participants included in the *Comments* section of the table examples of the diseases for which the given antibacterial (or class of selected agents within a class) was considered one of the sole or limited therapies for specific infection(s). This criterion does not consider the likelihood that such pathogens may transmit, or have been proven to transmit, from non-human sources to humans.

Criterion 2:
Antimicrobial agent is used to treat diseases caused by either: (1) organisms that may be transmitted via non-human sources or (2) diseases causes by organisms that may acquire resistance genes from non-human sources.

Explanation: Antimicrobial agents used to treat diseases caused by bacteria that may be transmitted to man from non-human sources are considered of higher importance, because these are most amenable to risk-management strategies related to non-human antimicrobial use. The organisms that cause disease need not be drug-resistant at the present time, but the potential for transmission shows the potential path for transmission 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. *S. aureus*, *Enterococcus* spp., *E. coli*, *Campylobacter* spp. and *Salmonella* spp.). Commensal organisms from non-human sources (animals, water, food or the environment) also may transmit resistance determinants to human pathogens and the commensals may themselves be pathogenic in immunosuppressed hosts. The *Comments* section of the table includes examples of the bacterial genera or species of concern. It is important to note that transmission of such organisms or their genes need not be demonstrated, the potential for such transmission remains.

5. Interpretation of categorization

Critically Important
Those antimicrobials which meet both criteria 1 and 2.

Highly Important
Those antimicrobials those which meet either criterion 1 or 2.

Important
Those antimicrobials those which meet neither criterion 1 nor 2.

The list below is meant to show examples of members of each class of drugs, and is not meant to be inclusive of all drugs. Not all drugs listed in a given class have necessarily been proven safe and effective for the diseases listed.

Comments were included in the list table when it was recognized that regional factors could affect the ranking, but these comments were not meant to be exhaustive and other regional factors could be relevant.

Table 1. Listing and categorization of antimicrobials used in human medicine.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Aminoglycosides amikacin arbekacin gentamicin netilmicin tobramycin streptomycin	Yes	Yes	(Criterion 1) Limited therapy as part of treatment of enterococcal endocarditis and Multi-Drug Resistant (MDR) tuberculosis. (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources.
Ansamycins rifabutin rifampin rifaximin	Yes	Yes	(Criterion 1) Limited therapy as part of therapy of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance. (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources.
Carbapenems and other penems doripenem ertapenem faropenem imipenem meropenem	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR *Enterobacteriaceae*. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.
Cephalosporins (3rd and 4th generation) cefepime cefixime cefoperazone cefoperazone/sulbactam cefoselis cefotaxime cefpirome cefpodoxime ceftazidime ceftizoxime ceftobiprole ceftriaxone	Yes	Yes	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Glycopeptides teicoplanin vancomycin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. And MRSA from non-human sources.
Glycylcyclines tigecycline	Yes	Yes	(Criterion 1) Limited therapy for infections due to MRSA. (Criterion 2) May result from transmission of MRSA from non-human sources.
Lipopeptides daptomycin	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.
Macrolides and ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	Yes	Yes	(Criterion 1) Limited therapy for *Legionella*, *Campylobacter* and MDR *Salmonella* infections. (Criterion 2) May result from transmission of *Campylobacter* spp. and Salmonella from non-human sources.
Oxazolidinones Linezolid	Yes	Yes	(Criterion 1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin amoxicillin/clavulanate ampicillin ampicillin/sulbactam azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate	Yes	Yes	(Criterion 1) Limited therapy for syphilis (natural penicillins) *Listeria*, *Enterococcus* spp. *(aminopenicillins)* and MDR *Pseudomonas* spp. *(antipseudomonal).* (Criterion 2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* including *E. coli* as well as *Pseudomonas aeruginosa* from non-human sources.
Quinolones cinoxacin ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin pipemidic acid sparfloxacin	Yes	Yes	(Criterion 1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp. and MDR *Shigella* spp. infections. (Criterion 2) May result from transmission of *Campylobacter* spp. and *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.
Streptogramins quinupristin/dalfopristin, pristinamycin	Yes	Yes	(Criterion 1) Limited therapy for MDR *Enterococcus faecium* and MRSA infections. (Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Tetracyclines chlortetracycline doxycycline minocycline oxytetracycline tetracycline	Yes	Yes	(Criterion 1) Limited therapy for infections due to *Brucella*, *Chlamydia* spp. and *Rickettsia* spp. (Criterion 2) Transmission of *Brucella* spp. from non-human sources.
Drugs used solely to treat tuberculosis or other mycobacterial diseases cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide	Yes	Yes	(Criterion 1) Limited therapy for tuberculosis and other *Mycobacterium* spp. disease and for many of these drugs, single drug therapy may select for resistance. (Criterion 2) May result from transmission of *Mycobacterium* spp. from non-human sources.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Amdinopenicillins mecillinam	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MDR *Shigella* spp. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Aminocyclitols spectinomycin	No	Yes	(Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Aminoglycosides (Other) kanamycin neomycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp., and *Enterobacteriaceae* including *E. coli* and Salmonella from non-human sources.
Amphenicols chloramphenicol thiamphenicol	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, typhoid and non-typhoid fever and respiratory infections. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* from non-human sources.
Cephalosporins (1st and 2nd generation) cefaclor cefamandole cefazolin cefuroxime cephalexin cephalothin cephradine loracarbef	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Cephamycins cefotetan cefoxitin	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Fusidic acid	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MRSA. (Criterion 2) May result from transmission of MRSA from non-human sources.
Monobactams aztreonam	No	Yes	(Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Pseudomonic acids Mupirocin	No	Yes	(Criterion 2) May result from transmission of MRSA from non-human sources.
Penicillins (Antistaphylococcal) cloxacilllin dicloxacillin flucloxacillin oxacillin nafcillin	No*	Yes	(Criterion 1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for staphylococcal infections (*S. aureus*). (Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources.
Pleuromutilins retapamulin	No	Yes	(Criterion 2) May result from transmission of *S. aureus* including MRSA from non-human sources.
Polymyxins colistin polymyxin B	Yes	No	(Criterion 1) Limited therapy for infections with MDR *Enterobacteriaceae* (e.g. *Klebsiella* spp., *E. coli, Acinetobacter, Pseudomonas* spp.).
Riminofenazines Clofazimine	Yes	No	(Criterion 1) Limited therapy for leprosy.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Sulfonamides, DHFR inhibitors and combinations[*] para-aminobenzoic acid pyrimethamine sulfadiazine sulfamethoxazole sulfapyridine sulfisoxazole trimethoprim	No[*]	Yes	(Criterion 1[*]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for acute bacterial meningitis, systemic non-typhoidal salmonella infections and other infections. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Sulfones apsone	Yes	No	(Criterion 1) Limited therapy for leprosy.

IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Cyclic polypeptides bacitracin	No	No	
Cyclic ethers fosfomycin	No[*]	No	(Criterion 1[*]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for Shiga-toxin producing *E. coli* O157.
Lincosamides clindamycin lincomycin	No	No	
Nitrofurantoins furazolidone nitrofurantoin	No	No	
Nitroimidazoles metronidazole tinidazole	No[*†]	No	(Criterion 1[*]) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for anaerobic infections including *C. difficile*. [†]Evaluation based on its use as an antimicrobial agent.

6. Prioritization within the Critically Important category

Given the mandate to prioritize agents within the *Critically Important* category, the Copenhagen panel (2007) focused on the two criteria developed by the Canberra panel (2005) to prioritize agents within the *critically important* category. The list was re-examined in the 1st AGISAR meeting (Copenhagen, 2009).

Focusing criterion 1:
Sole therapy or one of few alternatives to treat serious human disease

- Application 1.1 – High absolute number of people affected by diseases for which the antimicrobial is the sole or one of few alternatives to treat serious human disease.

- Application 1.2 – High frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance.

Explanation: In order to apply criterion 1 in a focused manner, the panel developed two applications, both of which related to volume of antimicrobial usage. Increased volume of usage directly relates to development of resistance and therefore poses a greater threat to the utility as sole therapies. Furthermore, humans receiving antimicrobials for any indication have a greater susceptibility to acquiring infection by a foodborne pathogen resistant to those antimicrobial agents.

Focusing criterion 2:
Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases causes by organisms that may acquire resistance genes from non-human sources.

- Application 2.1 – Greater degree of confidence that there are non-human sources that result in transmission of bacteria (*Campylobacter* spp.) or their resistance genes to humans (high for *Salmonella* spp., *Escherichia* coli and *Enterococcus* spp.).

Explanation: In order to apply criterion 2 in a focused manner, the panel developed one application. Risk-management strategies are most urgently

needed in situations where evidence suggests that transmission from non-human sources is already occurring.

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

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**1.1**	**1.2**	**2.1**	**Comments**
Aminoglycosides amikacin arbekacin gentamicin netilmicin streptomycin tobramicina	No	No	Yes	(Application 2.1) Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources.
Ansamycins rifabutin rifampin Rifaximin	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance.
Carbapenems and other penems doripenem ertapenem faropenem imipenem meropenem	Yes	No	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**1.1**	**1.2**	**2.1**	**Comments**
Cephalosporins (3rd and 4th generation) cefepime cefixime cefoperazone cefoperazone/sulbactam cefoselis cefotaxime cefpirome cefpodoxime ceftazidime ceftizoxime ceftobiprole ceftriaxone	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Glycopeptides teicoplanin vancomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Glycylcyclines tigecycline	Yes	No	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.
Lipopeptides daptomycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**1.1**	**1.2**	**2.1**	**Comments**
Macrolides and ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Campylobacter* spp. from non-human sources.
Oxazolidinones Linezolid	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin amoxicillin/clavulanate ampicillin ampicillin/sulbactam azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate	No*	Yes		(Application 1.1*) In certain geographic settings, application 1.1 may be met: there may be a high absolute number of people affected by all disease for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* from non-human sources.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**1.1**	**1.2**	**2.1**	**Comments**
Quinolones	Yes	Yes	Yes	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Campylobacter* spp. and *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Streptogramins quinupristin/dalfopristin, pristinamycin	Yes	No	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Tetracyclines chlortetracycline doxycycline minocycline oxytetracycline tetracycline	No	Yes	Yes	(Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**1.1**	**1.2**	**2.1**	**Comments**
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Yes	Yes	No	(Application 1.1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (Application 1.2) High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance.
cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide				

7. The top three Critically Important Antimicrobials

Those drugs categorized as highest priority met all three applications (1.1, 1.2 and 2.1): Quinolones, 3rd and 4th generation cephalosporins and Macrolides.

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

3rd and 4th generation cephalosporins are widely used in food animal production and are known to select for cephalosporin-resistant *Salmonella* spp. in animals. At the same time, 3rd and 4th generation cephalosporins are one of few available therapies for serious Salmonella infections, particularly in children. Given the high incidence of human disease due to *Salmonella* spp., the absolute number of serious cases is substantial.

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