Critically Important Antimicrobials for Human Medicine

3rd Revision 2011

World Health Organization

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

Critically Important Antimicrobials for Human Medicine

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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 2009, following a worldwide solicitation of experts from a variety of relevant fields, including human health and veterinary medicine, to serve as members. One agenda item of the 1st AGISAR meeting held in Copenhagen, 2009 was a follow-up of the two previous expert consultations on critically important antimicrobials. Experts at the 2009 meeting reviewed the Copenhagen 2007 list of CIA (the 1st revision of the CIA list) and produced the 2nd revision of the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and new drugs.

The 3rd AGISAR meeting was held in Oslo, Norway, in June 2011, and a further revision of the list included not only new drug developments and scientific information, but also focused on consolidating the suggestions on how the list might best be used to manage risks associated with antimicrobial use. Additional substances were added to the list according to their 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.

1.1 Contemporary context

Antimicrobials are used widely in agriculture. This includes non-therapeutic use such as for growth promotion. It also includes use as prophylaxis to try to prevent infections developing in food animals and therapeutic use to treat sick animals. However, this use also includes using agents defined by WHO as "critically important" for human medicine.

Bacteria (including those resistant to antimicrobials) that commonly transfer to people from food animals are *Salmonella* spp., *Campylobacter* spp., *Escherichia coli* and *Enterococcus* spp. More recently, emerging evidence has shown that *Staphylococcus aureus* (including MRSA) and *Clostridium difficile* also occur in food animals and can later be found in food products and environments shared with humans. More details and background information can be found in the previous edition of the 1st AGISAR report at www.agisar.org.

Resistant Gram negative bacteria (e.g., *E. coli*) have become a major and rapidly increasing problem. There are no new classes of antimicrobials in the pipeline and so it is unlikely that any new classes of effective antimicrobials will be available for 10 years or more to treat infections caused by resistant Gram negative bacteria.

Recently, we have seen the development and spread of bacteria carrying metallo-betalactamase genes that are resistant to carbapenems (and all beta-lactams). One of the most concerning aspects is the recent intercontinental spread of a multi-resistant strain of E.coli (New Delhi metallo- betalactamase or NDM strain) which are resistant to carbapenems and nearly all other antimicrobials (including non-betalactam classes). These types of multi-resistant bacteria have caused infections not only in hospitals, but also in the community. They have also spread within hospitals in Britain and elsewhere. The genes encoding for the metallo-betalactamases have been transferred to many other genera of bacteria (e.g., *Klebsiella*, *Vibrio* and *Providentia*). These increasingly commonly isolated bacterial isolates have necessitated using therapy with intravenous polymyxin; which, as an "old" antimicrobial had previously been discarded from systemic clinical use because of toxicity and other problems. In many cases it is now the only agent with proven

activity against many of these multi-resistant isolates. Notwithstanding this, some bacterial strains carrying the NDM gene are resistant to all antimicrobials, including the polymyxins. The end of the age of the miracle drug may indeed be upon us.

In The Netherlands the same genes encoding for ESBL (extended spectrum beta-lactamases) in *E. coli* isolates are found in both food animal isolates (especially poultry) and in those causing serious infections in people. On a global scale, *E. coli* is the most important human pathogen and causes substantially many more infections than *Salmonella* and *Campylobacter* combined. Thus, the importance of resistance in *E. coli*, typically considered a benign commensal, should not be underestimated.

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.

Of special importance, risk managers should carefully consider that fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been categorized as being of highest priority for risk management among those antimicrobials.

Carbapenems, lipopeptides and oxazolidinones currently have no veterinary equivalent. WHO recommends that these classes as well as any new class of antimicrobial developed for human therapy should not be used in animals, plants, or in aquaculture.

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:
An antimicrobial agent which is the sole, or one of limited available therapy, 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* severely limits options in the treatment of invasive infections such as pneumonia and blood stream infections and alters the clinical outcome (increased morbidly and mortality). However for skin lesions such as abscesses, incision and drainage alone are often effective without the use of an antimicrobial. Nevertheless, antimicrobials are often used for early treatment of MRSA skin lesions so that they do not progress to abscess formation.

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, especially for those with life threatening infections. Participants have 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 to humans from non-human sources or, (2) human 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; 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., *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 themselves may also 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; rather, it is considered sufficient that the potential for such transmission exists.

5. Interpretation of categorization

Critically Important
Those antimicrobials which meet both Criterion 1 and Criterion 2 are termed: *critically important* for human medicine.

Highly Important
Those antimicrobials which meet either Criterion 1 or Criterion 2 are termed: *highly important* for human medicine.

Important
Those antimicrobials those which meet neither Criterion 1 nor Criterion 2 are termed: *important* for human medicine.

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

Comments are included in the table when it is recognized that regional factors could affect the ranking; however, these comments are not meant to be exhaustive and other regional factors could be relevant in shifting an antimicrobial's importance. While countries or regions may choose to shift one drug, or class of drug, importance upwards (e.g., based on cost or availability); however, it is imperative that countries not elect to unilaterally

move a drug classification downwards. Only a WHO panel of experts are authorized to move drug classification in that direction.

In this 3rd revision of the WHO list, the following drugs and classes were shifted for the following reasons:

Over the last few years there have been dramatic increases in multi-resistant Gram negative infections both in the community and in hospitals. Therapy of many of these Gram negative infections (e.g. with multi-resistant *E. coli*) have become much more limited and agents such as colistin (a polymyxin) are now being used as often are no other alternatives. Thus classes of drugs active against Gram negatives such as phosphonic acid derivatives (e.g., fosfomycin), polymyxins (e.g., colistin) and monobactams (e.g., aztreonam) have been reclassified as "Critically Important".

In contrast, for Gram positive infections more antimicrobials have become available (e.g., lipopeptides, oxazolidinones and additional glycopeptides). Thus, streptogramins that were previously classified as Critically Important are now classified as "Highly Important" as there are more effective agents that cause less side effects now available to treat these infections. On the other hand, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals and the very serious consequences of treatment failures in such cases, this class was re-classified as being of highest priority in this revision of the List.

Tetracyclines are re-categorised now as "Highly Important". In the previous edition they were reclassified as "critically important" because tetracyclines are the main therapy for *Brucella* infections which are most often acquired by people from animals. However, there are many countries where *Brucella* infections have been eradicated from food animals. However, in areas of the world where *Brucella* species are still likely to be transmitted from food production animals, tetracyclines should continue to be classified as "critically important."

As sole therapy for certain conditions (e.g., endocarditis) and because cross resistance occurs, all aminoglycosides have been consolidated into the critically important category, including kanamycin and neomycin which were previously listed as highly important.

Lincosamides (e.g., clindamycin and lincomycin) have been moved to highly important because human infection may result from transmission of *Enterococcus* spp. and *Staphylococcus* aureus including MRSA from non-human sources.

Table 1. Listing and categorization of antimicrobials used in human medicine. Examples of veterinary use only drugs are listed at the end of each category for easy reference.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Aminoglycosides amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin sisomicin streptoduocin streptomycin tobramycin *Veterinary use only::* apramycin framycetin	Yes	Yes	(Criterion 1) Sole or 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.
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	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.

**This list does not necessarily include all drugs in a class using in human medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef *Veterinary use only:* cefovecin cefquinome ceftiofur	Yes	Yes	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children. Limited therapy for infections due to Multi-Drug Resistant *Enterobacteriaceae*, which are increasing in incidence worldwide. 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.
Cyclic esters fosfomycin	Yes	Yes	(Criterion 1) Limited therapy for ESBL *E.coli* causing UTI. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Fluoro- and other quinolones	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.
cinoxacin ciprofloxacin enoxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin oxolinic acid pazufloxacin pefloxacin pipemidic acid piromidic acid prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin trovafloxacin *Veterinary use only:* danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin orbifloxacin			

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary use only:* Avoparcin	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 MDR *Enterobacteriaceae*. Limited therapy for infections due to MRSA. (Criterion 2) May result from transmission of MRSA and *Enterobacteriaceae* 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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin *Veterinary use only:* gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin	Yes	Yes	(Criterion 1) Limited therapy for *Legionella*, *Campylobacter* and MDR *Salmonella* and *Shigella* infections. (Criterion 2) May result from transmission of *Campylobacter* spp. and *Salmonella* from non-human sources.
Monobactams aztreonam carumonam	Yes	Yes	(Criterion 1) Limited therapy for infections with MDR Gram negatives, especially with limited other options including for ESBLs. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
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.
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin ampicillin azidocillin azlocillin bacampicillin carbenicillin carindacillin clometocillin epicillin hetacillin metampicillin meticillin mezlocillin penamecillin penicillin G (=benzylpenicillin) penicillin V (=phenoxymethylpenicillin) pheneticillin piperacillin pivampicillin propicillin sulbenicillin sultamicillin talampicillin temocillin ticarcillin *Veterinary use only:* penethamate hydroiodide	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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Polymyxins colistin polymyxin B	Yes	Yes	(Criterion 1) Limited therapy for infections with MDR *Enterobacteriaceae* (e.g. *Klebsiella* spp., *E. coli, Acinetobacter*, *Pseudomonas* spp.). (Criterion 2) May result from transmission of *Enterobacteriaceae* from non-human sources.
Rifamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	Yes	Yes	(Criterion 1) Limited therapy as part of treatment 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 and multi-drug resistant *Staphylococcus aureus* through the food chain.
Drugs used solely to treat tuberculosis or other mycobacterial diseases calcium aminosalicylate capreomycin cycloserine ethambutol ethionamide isoniazid morinamide para-aminosalicylic acid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Amdinopenicillins mecillinam pivmecillinam	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.
Amphenicols chloramphenicol thiamphenicol *Veterinary use only:* florfenicol	No[#]	Yes	(Criterion 1[#]) 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. (Criterion 2) May result from transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* from non-human sources.

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HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Cephalosporins (1st and 2nd generation) and cephamycins cefaclor cefacetrile cefadroxil cefaloridine cefalexin cefalotin cefamandole cefapirin cefatrizine cefazedone cefazolin cefbuperazone cefmetazole cefminox cefonicid ceforanide cefotetan cefotiam cefoxitin cefprozil cefradine cefroxadine ceftezole cefuroxime flomoxef loracarbef *Veterinary use only:* cefalonium	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.
Lincosamides clindamycin lincomycin *Veterinary use only:* pirlimycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus* including MRSA from non-human sources.

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HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
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.
Pseudomonic acids mupirocin	No[#]	Yes	(Criterion 1[#]) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for topical *Staphylococcus aureus* infections. (Criterion 2) May result from transmission of MRSA from non-human sources.
Riminofenazines clofazimine	Yes	No	(Criterion 1) Limited therapy for leprosy.
Steroid antibacterials 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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Streptogramins quinupristin/dalfopristin pristinamycin *Veterinary use only:* virginiamycin	No	Yes	(Criterion 2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources
Sulfonamides, Dihydrofolate reductase inhibitors and combinations brodimoprim iclaprim pyrimethamine sulfadiazine sulfadimethoxine sulfadimidine sulfafurazole (=sulfisoxazole) sulfaisodimidine sulfalene sulfamazone sulfamerazine sulfamethizole sulfamethoxazole sulfamethoxypyridazine sulfametomidine sulfametoxydiazine sulfametrole sulfamoxole sulfanilamide sulfaperin sulfaphenazole sulfapyridine sulfathiazole sulfathiourea tetroxoprim trimethoprim *Veterinary use only:* ormosulfathiazole phthalylsulfathiazole	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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Sulfones dapsone aldesulfone	Yes	No	(Criterion 1) Limited therapy for leprosy.
Tetracyclines chlortetracycline clomocycline demeclocycline doxycycline lymecycline metacycline minocycline penimepicycline rolitetracycline oxytetracycline tetracycline	Yes	^No	(Criterion 1) Limited therapy for infections due to *Brucella, Chlamydia* spp. and *Rickettsia* spp. (Criterion 2^) Transmission of *Brucella* spp. from non-human sources. ^Countries where human brucellosis 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

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

IMPORTANT ANTIMICROBIALS			
Drug name*	**C1**	**C2**	**Comments**
Aminocyclitols spectinomycin	No	No^	(Criterion 2^) May result from transmission of *Enterobacteriaceae* including *E. coli* from non-human sources. No demonstrated transmission from *E. coli to Gonococcus*
Cyclic polypeptides bacitracin	No	No	
Nitrofurantoins furazolidone nitrofurantoin nifurtoinol nitrofural *Veterinary use only:* furaltadone	No	No	
Nitroimidazoles metronidazole tinidazole ornidazole	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*.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

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. As a result of this prioritization, the list was re-examined during the 1st AGISAR meeting (Copenhagen, 2009) and then further re-categorized during the Oslo (2011) meeting.

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 their 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 resistant 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 of resistant bacteria from non-human sources is already occurring, or has occurred previously.

Table 2. Prioritization of antimicrobials categorized as *Critically Important* in human medicine. Examples of veterinary use only drugs are listed at the end of each category for easy reference.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Aminoglycosides amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin sisomicin streptoduocin streptomycin tobramycin *Veterinary use only:* apramycin framycetin	No	No	Yes	(Application 2.1) Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*) and *Mycobacterium* spp. from non-human sources.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	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 use in human medicine. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef *Veterinary use only:* cefovecin cefquinome ceftiofur	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 use in human medicine. (Application 2.1) Transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources.
Cyclic esters fosfomycin	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.

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PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Fluoro- and other 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 use in human medicine. (Application 2.1) Transmission of *Campylobacter* spp. and Enterobacteriaceae including *E. coli* and *Salmonella* spp. from non-human sources
cinoxacin ciprofloxacin enoxacin fleroxacin flumequine garenoxacin gatifloxacin gemifloxacin grepafloxacin levofloxacin lomefloxacin moxifloxacin nalidixic acid norfloxacin ofloxacin oxolinic acid pazufloxacin pefloxacin pipemidic acid piromidic acid prulifloxacin rosoxacin rufloxacin sitafloxacin sparfloxacin temafloxacin trovafloxacin *Veterinary use only:* danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin orbifloxacin				

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary use only:* avoparcin	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 use in human medicine. (Application 2.1) Transmission of vancomycin resistant enterococcus (VRE) has occurred in past when avoparcin was used in food animals.
Glycylcyclines tigecycline	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.
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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin *Veterinary use only:* gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin	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 use in human medicine. (Application 2.1) Transmission of *Campylobacter* spp. from non-human sources.
Monobactams aztreonam carumonam	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.
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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Penicillins (natural, aminopenicillins and antipseudomonal) amoxicillin ampicillin azidocillin azlocillin bacampicillin carbenicillin carindacillin clometocillin epicillin hetacillin metampicillin meticillin mezlocillin penamecillin penicillin G (=benzylpenicillin) penicillin V (=phenoxymethylpenicillin) pheneticillin piperacillin pivampicillin propicillin sulbenicillin sultamicillin talampicillin temocillin ticarcillin *Veterinary use only:* penethamate hydroiodide	No[#]	Yes	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 use in human medicine. (Application 2.1) Transmission of *Enterococcus* spp. and *Enterobacteriaceae* (including *Salmonella spp* and *Escherichia coli*)
Polymyxins colistin polymyxin B	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.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name*	**1.1**	**1.2**	**2.1**	**Comments**
Rifamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	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 use in human medicine.
Drugs used solely to treat tuberculosis or other mycobacterial diseases calcium aminosalicylate capreomycin cycloserine ethambutol ethionamide isoniazid morinamide para-aminosalicylic acid protionamide pyrazinamide sodium aminosalicylate terizidone tiocarlide	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 use in human medicine.

**This list does not necessarily include all drugs in a class that are used in human or veterinary medicine; however, the major examples are included here*

7. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (1.1, 1.2 and 2.1): Fluoroquinolones, 3rd and 4th generation cephalosporins, Macrolides, and Glycopeptides.

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

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

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

Glycopeptides are known to select for glycopeptides-resistant *Enterococcus* spp. in food animals (e.g., when avoparcin was used as a growth promoter, vancomycin resistant enterococcus (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals and the very serious consequences of treatment failures in such cases, this class was re-classified as being of highest priority in the 3rd revision of the List.

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