Critically Important Antimicrobials for Human Medicine

4th Revision 2013

World Health Organization

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

Critically Important Antimicrobials for Human Medicine

4th Revision 2013

WHO Library Cataloguing-in-Publication Data

Critically important antimicrobials for human medicine – 4th rev.

1.Anti-infective agents - classification. 2.Anti-infective agents - adverse effects. 3.Drug resistance, microbial - drug effects. 4.Risk management. 5.Humans. I.World Health Organization.

ISBN 978 92 4 151146 9 (NLM classification: QV 250)

Printed by the WHO Document Production Services, Geneva, Switzerland

CONTENTS

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.

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.

As an outcome of this 4th revision, fluoroquinolones, 3rd and 4th generation cephalosporins, macrolides and glycopeptides have been categorized as being highest-priority critically important antimicrobials. Special attention should be paid to carbapenems, lipopeptides and oxazolidinoses that are last resort antimicrobials for treatment of serious infectious diseases in human that have no veterinary equivalent.

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.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Aminoglycosides	Yes	Yes	(C1) Sole or limited therapy as part of treatment of enterococcal endocarditis and multidrug resistant (MDR) tuberculosis. (C2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *E. coli*), and *Mycobacterium* spp. from non-human sources.
amikacin arbekacin bekanamycin dibekacin dihydrostreptomycin framycetin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin tobramycin streptomycin			
Veterinary only: apramycin			

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Ansamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	Yes	Yes	(C1) Limited therapy as part of treatment of mycobacterial diseases including tuberculosis; single drug therapy may select for resistance. (C2) May result from transmission of *Mycobacterium* spp. from non-human sources and MDR *Staphylococcus aureus* through the food chain.
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Yes	Yes	(C1) Limited therapy for infections due to MDR *Enterobacteriaceae*. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli* and *Salmonella*, from non-human sources.
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozopran cefpiramide cefpirome cefpodoxime cefsulodin	Yes	Yes	(C1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children. Limited therapy for infections due to MDR *Enterobacteriaceae*, which are increasing in incidence worldwide. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (C2) May result from transmission of *Enterobacteriaceae*, including *E.*

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef *Veterinary only:* ceftiofur cefovecin cefquinome			*coli* and *Salmonella*, from non-human sources.
Phosphonic acid derivatives fosfomycin	Yes	Yes	(C1) Limited therapy for ESBL *E. coli* causing urinary tract infections. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources.
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin *Veterinary only:* avoparcin	Yes	Yes	(C1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Glycylcyclines tigecycline	Yes	Yes	(C1) Limited therapy for infections due to MDR *Enterobacteriaceae*. Limited therapy for infections due to MRSA. (C2) May result from transmission of MRSA and *Enterobacteriaceae* from non-human sources.
Lipopeptides daptomycin	Yes	Yes	(C1) Limited therapy for infections due to MDR MRSA. (C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources.
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin	Yes	Yes	(C1) Limited therapy for *Legionella*, *Campylobacter*, and MDR *Salmonella* and *Shigella* infections. (C2) May result from transmission of *Campylobacter* spp. and *Salmonella* from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Veterinary only: gamithromycin kitasamycin tildipirosin tilmicosin tulathromycin tylosin tylvalosin			
Monobactams aztreonam carumonam	Yes	Yes	(C1) Limited therapy for infections with MDR Gram-negatives, especially with limited other options including for ESBLs. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources.
Oxazolidinones linezolid	Yes	Yes	(C1) Limited therapy for infections due to MDR MRSA and MDR *Enterococcus* spp. (C2) 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 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 only:* penethamate hydriodide	Yes	Yes	(C1) Limited therapy for syphilis (natural penicillins), *Listeria*, *Enterococcus* spp. (aminopenicillins), and MDR *Pseudomonas* spp. (antipseudomonal). (C2) May result from transmission of *Enterococcus* spp., *Enterobacteriaceae*, including *E. coli*, as well as *Pseudomonas aeruginosa* from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Polymyxins colistin polymyxin B	Yes	Yes	(C1) Limited therapy for infections with MDR *Enterobacteriaceae* (e.g. *Klebsiella* spp., *E. coli, Acinetobacter*, *Pseudomonas* spp.). (C2) May result from transmission of *Enterobacteriaceae* from non-human sources.
Quinolones 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	Yes	Yes	(C1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella*, and MDR *Shigella* spp. infections. (C2) May result from transmission of *Campylobacter* spp. and *Enterobacteriaceae*, including *E. coli* and *Salmonella*, from non-human sources.

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	C1	C2	Comments
Veterinary only: danofloxacin difloxacin enrofloxacin ibafloxacin marbofloxacin orbifloxacin			
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	(C1) Limited therapy for tuberculosis and other *Mycobacterium* spp. disease; for many of these drugs, single drug therapy may select for resistance. (C2) May result from transmission of *Mycobacterium* spp. from non-human sources.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Amidinopenicillins mecillinam pivmecillinam	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MDR *Shigella* spp. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources.
Amphenicols chloramphenicol thiamphenicol	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may represent one of the limited therapies for acute bacterial meningitis, typhoid and non-typhoid fever, and respiratory infections. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli* and *Salmonella*, from non-human sources.
Veterinary only: Florfenicol			

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Cephalosporins (1st and 2nd generation) and cephamycins	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for sepsis in children. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources.
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 only: cefalonium			
Lincosamides	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and *Staphylococcus aureus*, including MRSA, from non-human sources.
clindamycin lincomycin			
Veterinary only: pirlimycin			

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Penicillins (antistaphylococcal) cloxacilllin dicloxacillin flucloxacillin oxacillin nafcillin	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for staphylococcal infections (*S. aureus*). (C2) May result from transmission of *S. aureus*, including MRSA, from non-human sources.
Pleuromutilins retapamulin *Veterinary only:* tiamulin valnemulin	No	Yes	(C2) May result from transmission of *S. aureus*, including MRSA, from non-human sources.
Pseudomonic acids mupirocin	No*	Yes	(C1*) In certain geographic settings, Criterion 1 may be met: the class may be one of limited therapies for topical *Staphylococcus aureus* infections. (C2) May result from transmission of MRSA from non-human sources.
Riminofenazines clofazimine	Yes	No	(C1) Limited therapy for leprosy.
Steroid antibacterials fusidic acid	No*	Yes	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for infections with MRSA. (C2) May result from transmission of MRSA from non-human sources.
Streptogramins quinupristin/dalfopristin pristinamycin *Veterinary only:* virginiamycin	No	Yes	(C2) May result from transmission of *Enterococcus* spp. and MRSA from non-human sources

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
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 only:* formosulfathiazole phthalylsulfathiazole	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* infections, and other infections. (C2) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources.
Sulfones dapsone aldesulfone	Yes	No	(C1) Limited therapy for leprosy.

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Tetracyclines[†] chlortetracycline clomocycline demeclocycline doxycycline lymecycline metacycline minocycline penimepicycline rolitetracycline oxytetracycline tetracycline	Yes	*No	(C1) Limited therapy for infections due to *Brucella* spp., *Chlamydia* spp., and *Rickettsia* spp. (C2*) Countries where transmission of brucellosis from non-human sources to humans is common should consider making tetracycline a critical antibiotic, as there is considerable concern regarding the availability of effective products where *Brucella* spp. are endemic. [†]There are differences in activity and resistance mechanisms in tetracyclines (e.g., minocycline, doxycycline compared to chlortetracycline) against some bacteria such as *Acinetobacter*. In future editions, the tetracycline class may need to be separated into different groups.

IMPORTANT ANTIMICROBIALS			
Drug name	**C1**	**C2**	**Comments**
Aminocyclitols spectinomycin	No	No*	(C2*) May result from transmission of *Enterobacteriaceae*, including *E. coli*, from non-human sources, but there is no demonstrated transmission from *E. coli* to *Gonococcus.*
Cyclic polypeptides bacitracin	No	No	
Nitrofurantoins furazolidone nitrofurantoin nifurtoinol nitrofural *Veterinary only:* furaltadone	No	No	
Nitroimidazoles metronidazole tinidazole ornidazole	No*	No	(C1*) In certain geographic settings, criterion 1 may be met: the class may be one of limited therapies for anaerobic infections including *C. difficile*.

6. Prioritization within the Critically Important category

Antimicrobials within the critically important category are prioritized to assist in allocating resources towards agents for which risk-management strategies are needed most urgently (see Table 5). The following three criteria are used for prioritization:

Prioritization criterion 1 (P1): *High absolute number of people affected by diseases for which the antimicrobial class is the sole or one of few alternatives to treat serious infections in humans.*

Prioritization criterion 2 (P2): *High frequency of use of the antimicrobial class for any indication in human medicine, since use may favour selection of resistance.*

Prioritization criterion 3 (P3): *The antimicrobial class is used to treat infections in people for which there is evidence of transmission of resistant bacteria (e.g., non-typhoidal Salmonella and Campylobacter spp.) or resistance genes (high for E. coli and Enterococcus spp.) from non-human sources.*

Explanation: The first two prioritization criteria are relate to the AMU volume in humans. Increased volume of use directly relates to the development of resistance and, therefore, poses a greater threat to their use 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.

The third prioritization criterion relates to transmission. Risk-management strategies are most urgently needed in situations where evidence suggests that the transmission of resistant bacteria or resistance genes from non-human sources is already occurring, or has occurred previously.

Highest-priority critically important antimicrobials:

Antimicrobial classes that meet all three prioritization criteria (P1, P2, and P3) are considered the *highest priority critically important antimicrobials*.

Changes in prioritization criteria 2 (P2) were made for aminoglycosides, cyclic esters, and polymyxins.

Table 2. Prioritization of antimicrobials categorized as critically important in human medicine.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**P1**	**P2**	**P3**	**Comments**
Aminoglycosides amikacin apramycin arbekacin bekanamycin dibekacin dihydrostreptomycin gentamicin isepamicin kanamycin neomycin netilmicin ribostamycin sisomicinstreptoduocin tobramycin streptomycin	No	Yes	Yes	(P2) High frequency of use in human medicine. (P3) Transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *E. coli*), and *Mycobacterium* spp. from non-human sources.
Ansamycins rifabutin rifampicin (=rifampin) rifaximin rifapentine rifamycin	Yes	Yes	No	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**P1**	**P2**	**P3**	**Comments**
Carbapenems and other penems biapenem doripenem ertapenem faropenem imipenem meropenem panipenem	Yes	Yes	No*	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3*) Still very limited transmission of carbapenem-resistant *Enterobacteriaceae*, including *E. coli* and *Salmonella*, from non-human sources but spread of carbapenem-resistant *Salmonella* is increasing.
Cephalosporins (3rd and 4th generation) cefcapene cefdinir cefditoren cefepime cefetamet cefixime cefmenoxime cefodizime cefoperazone cefoselis cefotaxime cefozoprancefpiramide cefpirome cefpodoxime cefsulodin ceftaroline ceftazidime ceftizoxime ceftobiprole ceftibuten ceftriaxone latamoxef	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of Enterobacteriaceae, including E. coli and Salmonella, from non-human sources

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**P1**	**P2**	**P3**	**Comments**
Cyclic esters Fosfomycin	Yes	Yes	No*	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3*) There are concerns that in some countries high volumes of fosfomycin are used in food animals.
Glycopeptides dalbavancin oritavancin teicoplanin telavancin vancomycin	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of vancomycin-resistant enterococci (VRE) has occurred in past when avoparcin was used in food animals.
Glycylcyclines tigecycline	Yes	No	No	(P1) 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	**P1**	**P2**	**P3**	**Comments**
Lipopeptides Daptomycin	Yes	No	No	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.
Macrolides and ketolides azithromycin clarithromycin erythromycin dirithromycin flurithromycin josamycin midecamycin miocamycin oleandomycin rokitamycin roxithromycin spiramycin telithromycin troleandomycin	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of *Campylobacter* spp. from non-human sources.
Monobactams aztreonam carumonam	Yes	No	No	P1) 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	(P1) 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	**P1**	**P2**	**P3**	**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	No*	Yes	Yes	(P1*) In certain geographic settings, this criterion 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. (P2) High frequency of use in human medicine. (P3) Transmission of *Enterococcus* spp. and *Enterobacteriaceae* (including *Salmonella* and *E. coli*)
Polymyxins colistin polymyxin B	Yes	Yes *	No	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2*) In some countries there are high levels of topical use in people

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**P1**	**P2**	**P3**	**Comments**
Quinolones 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	Yes	Yes	Yes	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine. (P3) Transmission of *Campylobacter* spp. and *Enterobacteriaceae*, including *E. coli* and *Salmonella*, from non-human sources.

PRIORITIZATION OF CRITICALLY IMPORTANT ANTIBIOTICS				
Drug name	**P1**	**P2**	**P3**	**Comments**
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	(P1) High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available. (P2) High frequency of use in human medicine.

7. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (P1, P2, and P3): quinolones, third- and fourth-generation cephalosporins, macrolides and ketolides, and glycopeptides.

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

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

Macrolides and ketolides 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, for 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 glycopeptide-resistant *Enterococcus* spp. in food animals (e.g. when avoparcin was used as a growth promoter, vancomycin-resistant enterococci (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, glycopeptides are classified as being of the highest priority.

World Health Organization