Critically important Antimicrobials for Human Medicine

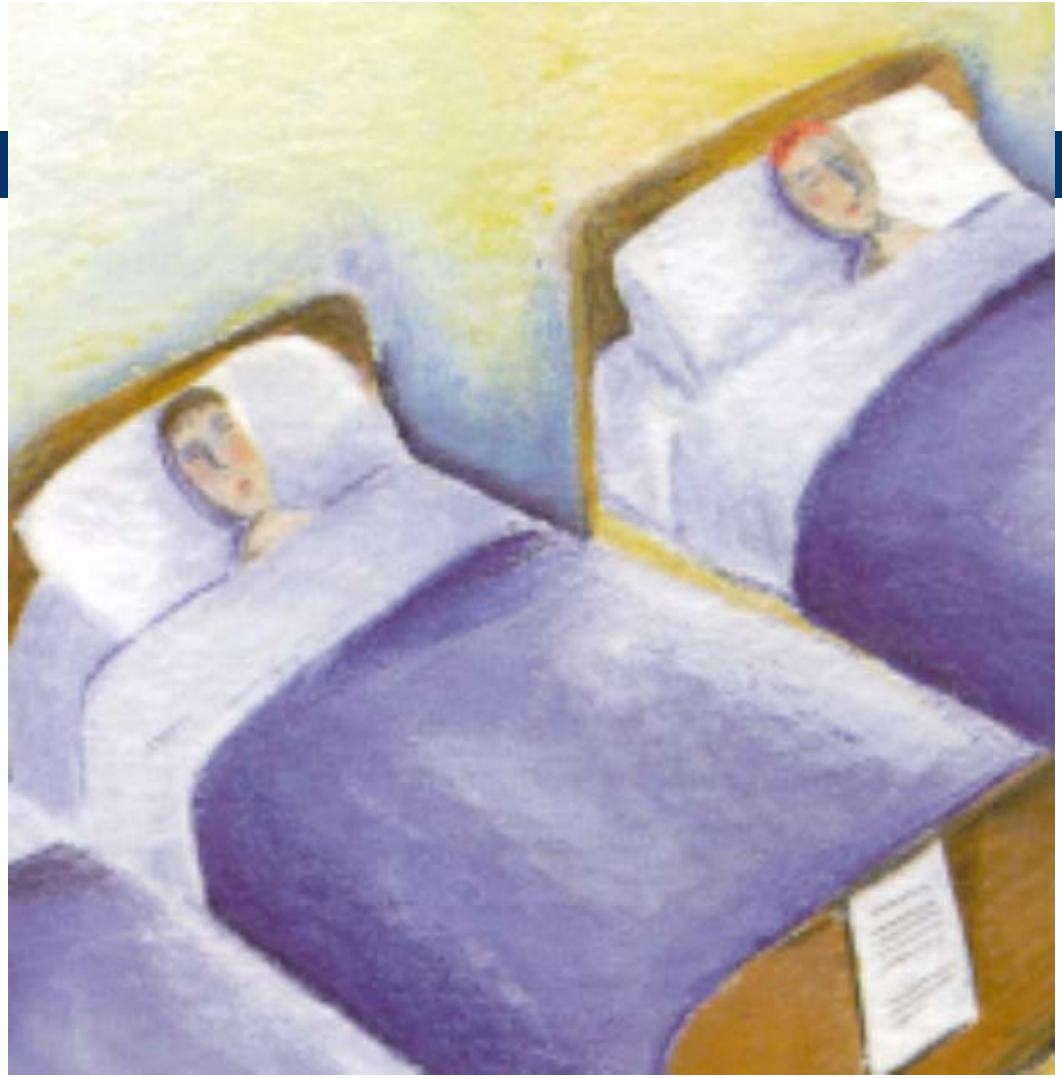
Report of a WHO working groups consultations and expert panels
Canberra, Australia. 2005
Copenhagen, Denmark 2007

Categorisation for the Development of Risk Management Strategies to contain Antimicrobial Resistance Due to Non-Human Antimicrobial Use

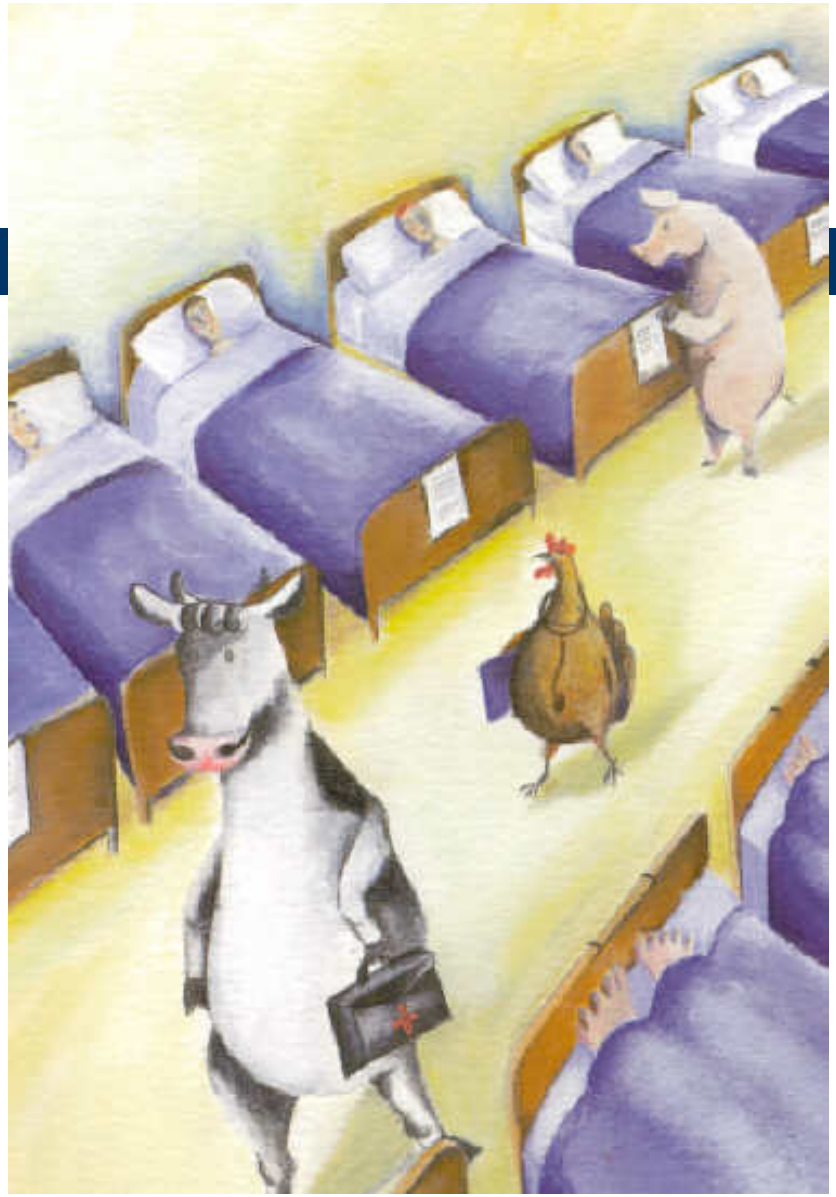
Prof Peter Collignon, Infectious Diseases and Microbiology,
The Canberra Hospital and Australian National University

Dr Awa Aidara-Kane, WHO Geneva

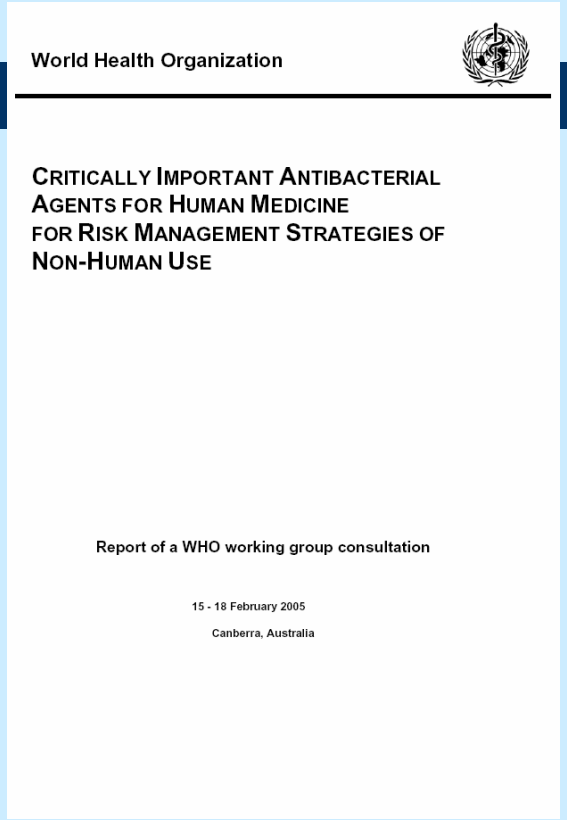
Antibiotic Resistance in people



Are animals involved?



Canberra and Copenhagen Expert Reports

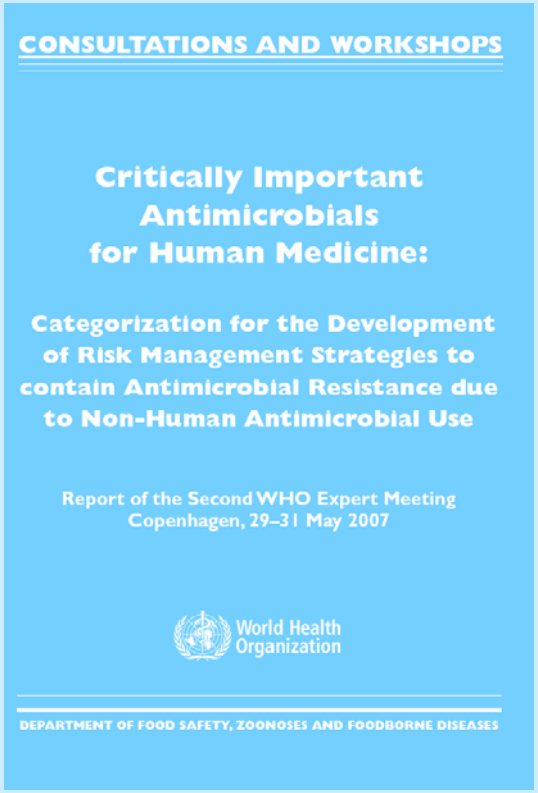

World Health Organization

CRITICALLY IMPORTANT ANTIBACTERIAL AGENTS FOR HUMAN MEDICINE FOR RISK MANAGEMENT STRATEGIES OF NON-HUMAN USE

Report of a WHO working group consultation

15 - 18 February 2005

Canberra, Australia


CONSULTATIONS AND WORKSHOPS

Critically Important Antimicrobials for Human Medicine:

Categorization for the Development of Risk Management Strategies to contain Antimicrobial Resistance due to Non-Human Antimicrobial Use

Report of the Second WHO Expert Meeting Copenhagen, 29–31 May 2007

World Health Organization

DEPARTMENT OF FOOD SAFETY, ZOONOSES AND FOODBORNE DISEASES

http://www.who.int/foodborne_disease/resistance/FBD_CanberraAntibacterial_FEB2005.pdf

http://www.who.int/foodborne_disease/resistance/antimicrobials_human.pdf

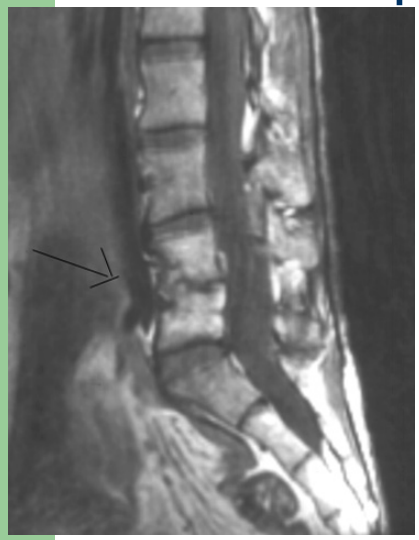
Purpose

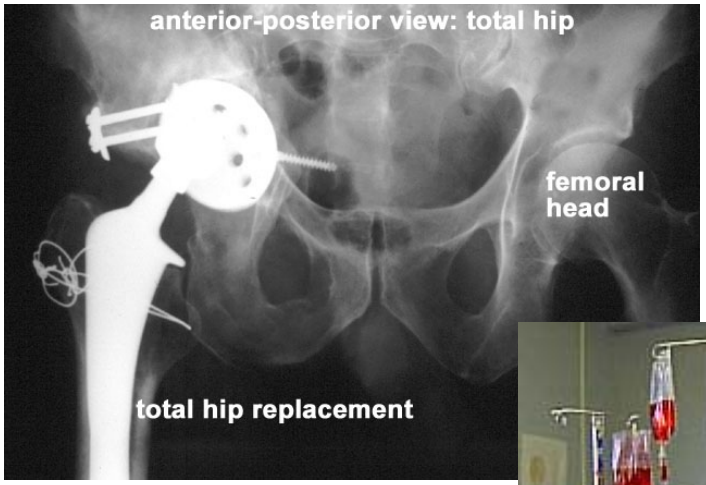
- Provide information on the human health consequences of antimicrobial resistance for use in the management of risk due to non-human use of antimicrobials.

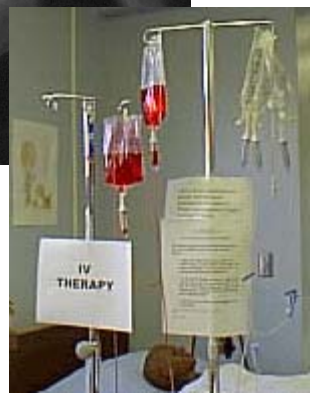
- This information should be used to support more comprehensive assessments of risk. Such comprehensive assessments should also include information on the potential development of resistance in pathogens in animals (release assessment) and the potential spread of resistant organisms or their genes from animals to humans (exposure assessment) and integrating these data into a comprehensive assessment of risk and strategies to manage that risk.

Infections cause serious morbidityand deaths

- Renal failure, osteomyelitis, prolonged antibiotic therapy etc







Why do this classification

- Some types of resistance worse that other
- Often might be No or few alternatives
  - Glycopeptide resistance in enterococcus (VRE),
  - 3rd generation cephalosporin and fluoroquinolone resistance in gram negatives
  - Macrolide resistance in campylobacter

Lists should help guide those not involved in human health

- Different perspectives
  - E.g. avoparcin in agriculture regarded as not very important (only used as growth promoter)
- Some lists already in place
  - Australia 1998
    - Jetacar (98); Class A, B and C
  - USA 2002
    - Their classifications/names used in WHO 2005 document but major differences in inclusions

Should antibiotics be used only for people?

- Then there would be No resistance through food chain or other pathways
- BUT this is not reasonable
  - Animals will also need some antibiotic therapy
- Thus need for some type of classification
    - Can’t have all antibiotics as critical!

“class” of drugs

- The term refers to agents with similar chemical structures that exert an effect on the same target in bacteria and may be affected by the same mechanisms of resistance (for example, ketolides are considered a variation on the macrolide class and not a separate class of drugs).

Only human use drugs in WHO tables

- But other antibiotics in same class but used in animals will have same resistance potential
- Therefore even if an antibiotic is not used in people it will have the same potential for resistance as others in same class but that are used in people.

The Criteria

- In developing the list, the panels considered that no antibacterial or class of antibacterials used in human medicine could be considered unimportant.

- Therefore, the panels decided to address all antibacterial drug classes used in human medicine to provide a comprehensive list divided into *Critically important*, *Highly important* and *Important* agents.

The criteria used for designating an antibacterial agent (or class) as critically important

- **Criterion 1**)
  - **Sole therapy or one of few alternatives to treat serious human disease**
- **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**

classification

- *Critically important* antimicrobials are those which meet criteria 1 AND 2.
- *Highly important* antimicrobials are those which meet criteria 1 OR 2.
- *Important* antimicrobials are those which meet neither criteria 1 nor 2.

Other factors for developing criteria

- The panels took into account how certain antibacterial agents are used in human medicine, the seriousness of the diseases treated with those agents and the availability of alternative therapies in the treatment of such diseases.
- In this way, the panels were able to assess the potential impact to human health of the potential loss of utility of antibacterial agents due to bacterial resistance to them.
- The panels also took into consideration pathogenic and commensal bacteria (or their genes) that may transfer to people from animals, food products, or the environment.

What happened since Canberra meeting in 2005?

- Short summary of the meeting presented at the WHO Expert Meeting on Selection and Use of Essential medicines in March 2005. For information
- WHO list of CIA submitted at the Expert committee in March 2007 for review
- 2nd WHO meeting on CIA in Copenhagen to review/update the Canberra list
- Updated in subsequent WHO expert panel Copenhagen and Guelph

2nd WHO meeting on Critically important antimicrobials for Human Health-Objectives; Copenhagen 2007; Outcomes

- Reviewed and updated the Canberra list taking into account
  - Controversies at Canberra meeting
  - Comments from the WHO Expert committee on selection and use of Essential Medicines
  - Recent developments in antimicrobial resistance

2nd WHO meeting on Critically important antimicrobials for Human Health-Objectives Outcomes

- Propose to WHO a list of antimicrobials that are "most critical" for human medicine with regards to antimicrobial resistance due to non-human use
- Give recommendations to WHO on future activities to be carried out for containment of foodborne antimicrobial

classification

- *Critically important* antimicrobials are those which meet criteria 1 AND 2.
- *Highly important* antimicrobials are those which meet criteria 1 OR 2.
- *Important* antimicrobials are those which meet neither criteria 1 nor 2.

Aminoglycosides and ansamycins (TB drugs)

CRITICALLY IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Aminoglycosides amikacin arbekacin gentamicin netilmicin tobramycin streptomycin	Y	Y	Limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis Potential transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*), and *Mycobacterium* spp. from non-human sources
Ansamycins rifabutin rifampin rifaximin	Y	Y	Limited therapy as part of therapy of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance Potential transmission of *Mycobacterium* spp. from non-human sources

Carbapenems and 3rd and 4th gen Cephs

Carbapenems and other penems ertapenem faropenem imipenem meropenem	Y	Y	Limited therapy as part of treatment of disease due to MDR Gram-negative bacteria Potential transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
Cephalosporins, (3rd and 4th generation) cefixime cefoperazone cefoperazone/sulbactam cefotaxime cefpodoxime ceftazidime ceftizoxime ceftriaxone cefepime cefoselis cefpirome	Y	Y	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. Potential transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources

Lipopeptides and Glycopeptides,

Critically Important Antimicrobials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Lipopeptides daptomycin	Y	Y	Limited therapy for infections due to MDR *S. aureus* Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources
Glycopeptides teicoplanin vancomycin	Y	Y	Limited therapy for infections due to MDR *Staphylococcus aureus* and *Enterococcus* spp. Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources

Macrolides and Oxazolinones

Macrolides (including 14-, 15-, 16-membered compounds), ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	Y	Y	Limited therapy for *Legionella*, *Campylobacter*, and MDR *Salmonella* infections Potential transmission of *Campylobacter* spp. from non-human sources (see Comments section immediately following this table for further explanation)
Oxazolidinones linezolid	Y	Y	Limited therapy for infections due to MDR *S. aureus* and *Enterococcus* spp. Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources

Penicillins

Penicillins, (natural, aminopenicillins and antipseudomonal)	Y	Y	Limited therapy for syphilis (natural penicillins) *Listeria, Enterococcus spp.(aminopenicillins)* and MDR *Pseudomonas spp.(antipseudomonal)* Potential transmission of *Enterococcus* spp., *Enterobacteriaceae* including *E. coli* as well as *Pseudomonas aeruginosa* from non-human sources (see Comments section immediately following this table for further explanation)
ampicillin ampicillin/sulbactam amoxicillin amoxicillin/clavulanate azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate			

Quinolones

Critically Important Antimicrobials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Quinolones	Y	Y	Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp., and MDR *Shigella* spp. infections Potential transmission of *Campylobacter* spp. and Enterobacteriaceae including *E. coli* and *Salmonella* spp. from non-human sources
cinoxacin nalidixic acid pipemidic acid			
ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin norfloxacin ofloxacin sparfloxacin			

Streptogramins, Tetracyclines (only glycylcyclines) and anti-TB drugs

Streptogramins quinupristin/dalfo-pristin, pristinamycin	Y	Y	Limited therapy for MDR *Enterococcus faecium* and *S. aureus* infections Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources (see Comments section immediately following this table for further explanation)
Tetracyclines (Glycylcyclines) tigecycline	Y	Y	Limited therapy for infections due to MDR *S. aureus*
Drugs used solely to treat tuberculosis or other mycobacterial diseases cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide	Y	Y	Limited therapy for tuberculosis and other *Mycobacterium* spp. disease and for many of these drugs, single drug therapy may select for resistance Potential transmission of *Mycobacterium* spp. from non-human sources

Highly Important antibiotics

HIGHLY IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Amidinopenicillins mecillinam	N*	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources. *MDR *Shigella* spp. infections may be a regional problem
Aminoglycosides (Other) kanamycin neomycin spectinomycin	N	Y	Potential transmission of Gram negative bacteria that are cross resistant to streptomycin from non-human sources
Amphenicols chloramphenicol thiamphenicol	N*	Y	*May be one of limited therapies for acute bacterial meningitis, typhoid fever and respiratory infections in certain geographic areas
Cephalosporins, 1st and 2nd generation cefaclor cefamandole cefuroxime cefazolin cephalexin cephalothin cephradine loracarbef	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Cephamycins cefotetan cefoxitin	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Clofazimine	Y	N	Limited therapy for leprosy
Monobactams aztreonam	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Penicillins (Antistaphylococcal) cloxacilllin dicloxacillin flucloxacillin oxacillin nafcillin	N	Y	*S.aureus* including MRSA can be transferred to people from animals
Polymyxins colistin	Y	N	Polymyxins may be the only available therapy for therapy of some MDR Gram-negative infections e.g. *Pseudomonas spp.*
polymyxin B	Y	N	Limited therapy for MDR Gram negative bacterial infections, for example, those caused by *Acinetobacter* spp. and *Pseudomonas aeruginosa*

Highly important antibiotics (Cont'd)

Highly Important Antimicrobials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Sulfonamides, DHFR inhibitors and combinations*	N*	Y	*May be one of limited therapies for acute bacterial meningitis and other infections in certain geographic areas Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
para-aminobenzoic acid pyrimethamine sulfadiazine sulfamethoxazole sulfapyridine sulfisoxazole trimethoprim			
Sulfones	Y	N	Limited therapy for leprosy
dapsone			
Tetracyclines	Y	N	Limited therapy for infections due to *Chlamydia* spp.and *Rickettsia* spp.
chlortetracycline doxycycline minocycline oxytetracycline tetracycline			

Important antimicrobials

IMPORTANT ANTIMICROBIALS			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Cyclic polypeptides bacitracin	N	N	
Fosfomycin	N*	N	*May be one of limited therapies for Shiga-toxin producing *E. coli* O157 in certain geographic areas
Fusidic acid	N*	N	*May be one of limited therapies to treat MDR *S. aureus* infections in certain geographic areas
Lincosamides clindamycin lincomycin	N	N	
Mupirocin	N	N	
Nitrofurantoins furazolidone nitrofurantoin	N	N	
Nitroimidazoles metronidazole tinidazole	N*	N†	*Evaluation based on antibacterial properties only †May be one of limited therapies for some anaerobic infections including *C. difficile* in certain geographic areas

prioritization of agents

- WHO charged the Copenhagen expert committee with prioritization of 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 Copenhagen expert panel considered drugs of greatest priority when 1) there are relatively large absolute numbers of people affected with diseases for which the drug is the sole or one of few alternative therapies, 2) the overall frequency of use of the drugs in human medicine for any use (whether appropriate or inappropriate) is relatively large, and 3) the drug is used to treat disease due to pathogens for which there is a greater degree of confidence in transmission of bacteria or their genes from non-human sources to humans (*E. coli*, *Campylobacter* spp. and *Salmonella* spp.)

This prioritization resulted in the designation of the classes for which comprehensive risk management strategies are needed most urgently:

- quinolones,
- 3rd/4th generation cephalosporins and
- macrolides.

- The expert panel also emphasized that the prioritization of these three classes of drugs should not minimize the importance of other drugs categorized as *critically important* on the list.

sense of urgency needed

- The expert panel pointed out that the development of this list is one part of a more comprehensive overall approach to the public health issues of antimicrobial resistance in both animals and humans.
- The expert panel emphasized that there should be a sense of urgency to the development of such risk management strategies, particularly for quinolones, 3rd/4th generation cephalosporins and macrolides.

THANK YOU !

MERCI !