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

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Preamble:

The World Health Organization convened an international expert Drafting Group on Critically Important Antimicrobials for Human Health from 15 to 18 February 2005 in Canberra, Australia.

The meeting was organized to follow up a FAO/WHO/OIE consultative process on Non-Human Antimicrobial Usage and Antimicrobial Resistance (1st Workshop on Scientific Assessment, December 2003 in Geneva, and 2nd Workshop on Management Options, March 2004 in Oslo).

After opening remarks by Ms Mary Murnane, Deputy Secretary Australian Department of Health and Ageing and Dr Awa Aidara Kane, World Health Organization, Geneva, Prof. Patrice Courvalin and Prof. John Turnidge were elected as chairperson and vice chairperson and Dr John Powers was appointed as rapporteur.

Background:

Antimicrobial agents are essential drugs for human health and animal health and welfare. Resistance to antimicrobials is a global public health concern that is impacted by both human and non human usage.

WHO's involvement with this issue dates back to 1997, when medical problems arising from the use of antimicrobials in livestock production were identified and concern was raised that drug-resistant pathogens could be transmitted to humans via the food-chain (The Medical Impact of the Use of Antimicrobials in Food Animals: Report and Proceedings of a WHO Meeting, Berlin, Germany, 13-17 October 1997, WHO/EMC/ZOO/97.4 http://www.who.int/emc/diseases/zoo/antimicrobial.html).

Following concern raised by the use of quinolones in food animals and emergence of quinolone-resistant enteric bacteria, a WHO consultation was held in June 1998 in Geneva to address the issue (Use of Quinolones in Food Animals and Potential Impact on Human Health: Report and Proceedings of a WHO Meeting, Geneva, Switzerland, 2-5 June 1998, WHO/EMC/ZDI/98.12). An important achievement was the publication in 2000 of the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (WHO Global principles for the containment of antimicrobial resistance in animals for food. Report of a WHO Consultation with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties, Geneva, Switzerland, 5-9 June 2000 http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm). Two years later, in 2002, WHO issued reports on the monitoring of antimicrobial usage (Monitoring antimicrobial usage in food animals for the protection of human health. Report of a WHO consultation. Oslo, Norway, 10-13 September 2001. http://www.who.int/emc/diseases/zoo/antimicrobial.html) and on the impact of termination of use of antimicrobials as growth promoters. (Impact of antimicrobial growth promoter termination in Denmark. The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark, 6-7 November 2002, Foulum, Denmark http://www.who.int/salmsurv/links/gssamrgrowthreportstory/en)

Antimicrobial resistance is a multi-factorial problem that requires a multi-disciplinary and a multi-agency approach. The Executive Committee of the Codex Alimentarius Commission at its 53rd session in 2001 recommended that FAO, WHO and the OIE

should consider hosting a joint meeting to discuss all issues of non-human usage of antimicrobials and antimicrobial resistance.

As a response to this recommendation, an FAO/OIE/WHO joint consultative process on non-human usage of antimicrobials and antimicrobial resistance was initiated. In accordance with the Codex Alimentarius risk analysis principles, it was decided to hold two workshops. The first workshop on scientific assessment was held in December 2003 in Geneva, and a second workshop on management options was held in March 2004 in Oslo.

The first expert workshop concluded that there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials: increased frequency of infections, increased frequency of treatment failures (in some cases death) and increased severity of infections, as documented for instance by fluoroquinolone-resistant human *Salmonella* infections. Evidence shows that the amount and pattern of non-human usage of antimicrobials affect the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria. The foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist. Far fewer data are available on the public health impact of antimicrobial usage in aquaculture, horticulture and companion animals.

The consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in humans. The workshop therefore recommended that an expert clinical medical group, appointed by WHO, define and provide a list of antimicrobials that are considered critically important in humans.

The second workshop also recommended that the concept of “critically important” classes of antimicrobials for people should be developed by WHO with a view to enabling specific resistance preventive actions for such antimicrobials related to non-human use. A list of critically important antimicrobials for humans would facilitate the process of implementing specific management strategies to prevent the emergence and dissemination of resistance to those agents. A similar list of critically important classes of antimicrobials for animals would be pursued by the Office Internationale des Epizooties (OIE).

As outlined in the Geneva and Oslo workshops, the main agents of disease that need to be considered are bacteria, especially those known to have the potential for transfer from food-producing animals to humans as either zoonotic pathogens or commensals (e.g. *E. coli*, *Salmonella* spp., *Campylobacter* spp. and *Enterococcus* spp.). Other bacteria that could potentially be transferred from non-human sources via food or the environment should also be taken into account. In addition, the transferability of resistance determinants between bacterial genera should be considered.

Overall objective and outcome:

The overall objective of this WHO international expert group is to first develop criteria for defining critically important antimicrobials for humans by class and /or subgroups, and then to propose a list. The list needs to take into account relevant bacteria (or their genes) that are likely to transfer to people from animals, food products, or the environment (both pathogens and commensals).

The report of the Drafting Group meeting will include:

1. criteria to define critically important antimicrobials for humans;

2. an explanation of the criteria that led to the selection of antimicrobials for this list; and

3. a draft list of critically important antimicrobials for humans.

Introduction:

At the present time the link between the potential spread of antimicrobial resistant pathogens or their genes from non-human antimicrobial use to humans appears most clear for bacteria.

Therefore, the list of antimicrobial agents considered critically important for human health (based on criteria defined below) is confined to antibacterial agents for which there is potential that their utility in man might be threatened by bacterial resistance resulting from their non-human use. However, the criteria drawn up to select this list would be applicable to any antibacterial agents for which the mechanisms of bacterial resistance have not yet been elucidated.

The first part of the table should be considered to be a core list of the most critical antibacterial agents globally. It is recommended that only an Expert panel appointed by WHO should make a decision to move an antibacterial from the first part (*Critically important*) to the lower parts (*Highly important* or *Important*) of the table. However, considerations such as costs and availability of antibacterials in various geographic areas as well as local resistance rates could cause the list of *Critically important* agents to be expanded for regional use (e.g. an antibacterial agent ranked *Highly important* may become *Critically important* in a particular region).

It is important to note that the *Critically important* list of antibacterials that has been developed differs from the WHO Essential Medicines list. The purpose of the *Critically important* list of antibacterial agents is for use in risk management strategies of non-human antibacterial use. The antibacterial agents that appear on the WHO Model List of Essential Medicines comprise those that satisfy the priority health needs of the population; they were selected with due regard to public health relevance, evidence on efficacy, and safety and comparative cost effectiveness. In contrast, cost was not a primary consideration in developing the list of *Critically important* antibacterial agents as there is little choice regarding cost when an antibacterial is the sole or one of few available alternatives to treat a disease. Most of the antibacterials in the WHO's Essential Medicine list also appear in the list of *Critically important* antibacterial agents. Those in the Essential Medicines list that have not been listed as critically important in this document are clindamycin, cloxacillin, metronidazole, chloramphenicol, nitrofurantoin, some sulfonamides, doxycycline and spectinomycin.

The list of *Critically important* antibacterials for human health has been developed separately from the list of *Critically important* antibacterial agents for animals that will be constructed by the OIE. It is anticipated that, once both lists have been developed and agreed, the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food will apply to any actions taken thereafter. Global principle number 6, in particular, states: "In the Evaluation of currently approved products, priority should be given to those products considered most important for human medicine. Characterization of the risk should include consideration of the

importance of the drug or members of the same class of drug to human medicine, the potential exposure to humans from antimicrobial-resistant bacteria and their resistant genes from food animals, as well as other appropriate scientific factors. Those antimicrobials judged to be essential for human medicine should be restricted and their use in food animals should be justified by culture and susceptibility testing."

Procedure

The panel that met in Canberra, Australia, first developed criteria to identify *Critically important* antibacterial agents and then applied the criteria to each drug or class of drugs. The term "class" of drugs as used here 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). In developing the criteria, the panel 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 panel was 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 panel also took into consideration pathogenic and commensal bacteria (or their genes) that may transfer to people from animals, food products, or the environment. The panel did not consider how this list will ultimately be used to formulate risk management strategies for use of antimicrobials in animals. This will be the focus and task of future meetings.

The Criteria

In developing the list, the panel considered that no antibacterial or class of antibacterials used in human medicine could be considered unimportant. Therefore, the panel 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. Comments were included in the table when it was recognized that regional factors might affect the ranking but these comments were not meant to be exhaustive, and other regional factors may be relevant.

The criteria used by the panel for designating an antibacterial agent (or class) as critically important are:

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

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.

Criterion 1: It is self-evident that antimicrobials that are the sole or one of few alternatives for treatment of serious infections in humans have an important place in

human medicine. 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. The panel 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 or have been proven to transmit from non-human source to humans.

Criterion 2: Antibacterial agents used to treat diseases caused by bacteria that may be transmitted to man from non-human sources are considered of higher importance. In addition, commensal organisms from non-human sources may transmit resistance determinants to human pathogens and the commensals may themselves be pathogenic in the immunosuppressed. The link between non-human sources and the potential to cause human disease appears greatest for the above bacteria. The panel included in the Comments section of the table (where appropriate) examples of the bacterial genera or species of concern. The panel did not consider that transmission of such organisms or their genes must be proven, but only the potential for such transmission to occur.

These criteria were developed solely with regard to the importance of these antibacterials in human medicine. The panel did not consider such issues as the likelihood of resistance to develop in non-human sources with non-human use of these drugs or the likelihood of exposure of humans to such organisms should such resistance develop. The history of the development of antimicrobial resistance shows that resistance may appear after a long periods of usage (e.g. vancomycin resistance in *Enterococcus faecium* was first detected after the drug had been in use for over 40 years). If resistance has not developed to date it does not assure that it will not develop in the future. In addition, the purpose of this list was to rank the drugs according to human use, not to develop risk management strategies for non-human use. This list would be one factor, but not the only factor, to consider in such risk management strategies. WHO plans to convene future meetings to discuss the issues of risk management strategies, using this list as one tool in developing such strategies.

The panel agreed that the list of *Critically Important* antibacterial agents should be updated regularly as new information becomes available, including data on resistance patterns, new and emerging diseases, and the development of new drugs.

The list below is meant to show examples of members in each drug class, 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.

Classification of Antibacterial Drugs

Critically Important Antibacterials			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Aminoglycosides amikacin arbekacin gentamicin kanamycin netilmicin neomycin tobramycin streptomycin	Y	Y	Limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis Potential transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *E. 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 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 generation cefixime cefotaxime cefpodoxime ceftazidime ceftizoxime cefoperazone cefoperazone/sul-bactam ceftriaxone	Y	Y	Limited therapy for acute bacterial meningitis and disease due to *Salmonella* in children Potential transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources

Critically Important Antibacterials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Cephalosporins 4th generation cefepime cefpirome cefoselis	Y	Y	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 daptomycin	Y	Y	Limited therapy for infections due to MDR *Staphylococcus aureus* Potential transmission of *Enterococcus* spp. 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. from non-human sources
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 (DANMAP, 2003; Engberg et al., 2001;WHO, 2003) (see Comments section immediately following this table for further explanation)
Oxazolidinones linezolid	Y	Y	Limited therapy for infections due to MDR *Staphylococcus aureus* and *Enterococcus* spp. Potential transmission of *Enterococcus* spp. from non-human sources

Critically Important Antibacterials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Penicillins, aminopenicillins ampicillin ampicillin/sulbactam amoxicillin amoxicillin/clavulanate piperacillin piperacillin/tazobactam*	Y	Y	Limited therapy for *Listeria* Potential transmission of *Enterococcus* spp. from non-human sources (see Comments section immediately following this table for further explanation)
Penicillins, natural penicillin G penicillin V	Y	Y	Limited therapy for syphilis Potential transmission of *Enterococcus* spp. from non-human sources
Quinolones cinoxacin nalidixic acid pipemidic acid ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin norfloxacin ofloxacin sparfloxacin	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* from non-human sources
Streptogramins quinupristin/dalfopristin, pristinamycin	Y	Y	Limited therapy for MDR *Enterococcus faecium* and *Staphylococcus aureus* infections Potential transmission of *Enterococcus faecium* from non-human sources (see Comments section immediately following this table for further explanation)

Critically Important Antibacterials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
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 Antibacterials			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Cephalosporins, 1st generation cefazolin cephalexin cephalothin cephradine	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Cephalosporins, 2nd generation cefaclor cefamandole cefuroxime 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

Highly Important Antibacterial (cont'd)			
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
Penicillins, antipseudomonal* azlocillin, carbenicillin mezlocillin ticarcillin ticarcillin/clavu-lanate	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* as well as *Pseudomonas aeruginosa* from non-human sources
Polymyxins colistin polymyxin B	Y	N	Limited therapy for MDR Gram negative bacterial infections, for example, those caused by *Acinetobacter* spp. and *Pseudomonas aeruginosa*
Spectinomycin	N	Y	Potential transmission of Gram negative bacteria that are cross resistant to streptomycin from non-human sources
Sulfonamides, DHFR inhibitors and combinations para-aminoben-zoic acid pyrimethamine sulfadiazine sulfamethoxazole sulfapyridine sulfisoxazole trimethoprim	N	Y	Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Sulfones dapsone	Y	N	Limited therapy for leprosy

Highly Important Antibacterials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Tetracyclines chlortetracycline doxycycline minocycline oxytetracycline tetracycline	Y	N	Limited therapy for infections due to *Chlamydia* spp. and *Rickettsia* spp.
Important Antibacterials			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
Amphenicols chloramphenicol thiamphenicol	N*	N	*May be one of limited therapies for acute bacterial meningitis and other infections in certain geographic areas
Cyclic polypeptides bacitracin	N	N	
Fosfomycin	N	N	
Fusidic acid	N*	N	*May be one of limited therapies to treat MDR *Staphylococcus aureus* infections in certain geographic areas
Lincosamides clindamycin lincomycin	N	N	
Mupirocin	N	N	
Nitrofurans furazolidone nitrofurantoin	N	N	
Nitroimidazoles metronidazole tinidazole	N*	N	*Evaluation based on antibacterial properties only
Penicillins, Antistaphylococcal	N	N	

* Piperacillin (with or without tazobactam) is not strictly an aminopenicillin; it is a ureidopenicillin. It has been included in the aminopenicillin group rather than the antipseudomonal penicillin group as it has significant activity against *Enterococcus* species, and is likely to exert similar selective pressure for resistance to aminopenicillins.

Drug classes that are not used in humans, and are currently only used in animal medicine include arsenicals, bambermycins, ionophores, orthosomycins, quinoxalines, and others.

Comments on the classification of some specific antibacterial agents:

Quinupristin/dalfopristin remains one of few available therapies for the treatment of infections due to multi-drug resistant *Enterococcus faecium*, particularly given the emergence of Linezolid-resistant strains. A related streptogramin, virginiamycin, is known to select for quinupristin/dalfopristin resistance in *Enterococcus faecium* in food animals (Hammerum et *al*., 1998; *FEMS Microbiol.Lett*. **168**, 145-151 Werner et *al*:,2000; *Microb.Drug Resist.* **6**, 37-47.).

Macrolides are widely used in food animal production and are known to select for macrolide-resistant *Campylobacter* spp. in animals.. 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*, the absolute number of serious cases is substantial. (DANMAP, 2003, Engberg et al., 2001; WHO, 2003)

Aminopenicillins and natural penicillins are among the few available therapies for invasive enterococcal and *Listeria* infections. In addition, in some parts of the world, there are few alternatives to the aminopenicillins for the outpatient management of acute lower respiratory tract infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae*. *Enterococcus* spp. are transmitted to humans from food animals via the food-chain. Therefore, according to the criteria used to develop the list of *Critically Important* antibacterial agents, the natural penicillins and aminopenicillins have been classified as as being critically important for human health.

The conclusions by the panel were unanimous on all the drug classifications with one exception. There was significant discussion regarding the classification of natural penicillins and aminopenicillins. After thorough discussion, the consensus was that these drugs are used as the sole therapy of serious human disease, including syphilis and invasive enterococcal infections. *Enterococcus* spp. may be transmitted to humans from non-human sources. Therefore, according to the criteria used to develop the list of Critically Important Drugs, antibacterials in these classes qualify as critically important.

Next steps:

As specified in the Oslo meeting of 2004, the WHO list of Critically Important antimicrobials for Human Health will be made publicly available and shared among member countries and other organizations, such as FAO and OIE.

A short summary of the report has been presented to the WHO Expert Committee on Selection and Use of Essential Medicines meeting in March 2005.

The draft list will be presented at this Expert Committee in March 2007.

Once the OIE list of Critically Important Antimicrobials for Animals published, WHO and OIE should consider convening a joint Expert Working Group to give recommendations on the appropriate balance to be struck between animal health needs and public health considerations.

The outcome of this process will be taken into account by Codex, for example within the Codex/OIE task force as recommended by the Oslo meeting, to define risk assessment policy and risk management options in relation to antimicrobial resistance.

Implementation of this concept at the national level will require that national considerations be taken into account.

The List should be updated at regular intervals since the rankings may change over time as resistance levels change and new drugs or therapeutic choices become available.

Annex 1: List of Participants

Dr Al-Bussaidy
Director
Department of Laboratories
Ministry of Health
P.O. Box 393
Postal Code 113
Muscat, Oman
Tel: +968 705943, Mobile: +968 9426288
E-mail: mohdl@omantel.net.om

Dr Tom Chiller
Chief National Antibiotic Resistance Monitoring System NARMS
Foodborne and Diarrheal Diseases Branch
National Centers for Infectious Diseases
Centre for Disease Control and Prevention
Mailstop D-63, 1600 Clifton Road
Atlanta, GA 30342, USA,
Tel: +1 404 3715406
Fax: +1 404 3715444
E-mail: tnc3@cdc.gov

Professor Peter Collignon
Director
Infectious Diseases Unit and Microbiology Department
The Canberra Hospital
PO Box 11, Woden, ACT 2607
Australia
Tel: +61 2 6244 2105
Fax: +61 2 6281 0349
E-mail: peter.collignon@act.gov.au

Professor Patrice Courvalin
Institut Pasteur
Unité des Agents Antibactériens
28, rue du Dr. Roux
75724 Paris Cedex 15, France
Tel:+33 1 4568 8320
Fax: +33 1 4568 8319
E-mail: pcourval@pasteur.fr

Dr Mohammad Iqbal Issack
Victoria Hospital, Central Health Laboratory, Candos, Mauritius
Tel: +230 4 271838
Fax: +230 4 245848
E-mail: missack@intnet.mu

Dr John Powers
Center for Veterinary Medicine
U.S. FDA Food and Drug Administration
Rockville, MD, USA
Tel: +1.301.8272350
E-mail: POWERSJOH@cder.fda.gov

Professor Jin Shaohong
Deputy Director
National Institute for the Control of Pharmaceutical & Biological Products,
People's Republic of China
Temple of Heaven
Beijing, 100050, China
Tel : +86 10 67017755-258 67054258
Fax : +86 10 67013755, 67018094
E-mail : jinshh@nicpbp.org.cn

Professor Kurien Thomas
Professor and Head
Department of Medicine Unit-2
Christian Medical College
Vellore 632004
TN, India
Mobile: +91 94432 45487 or +91 98430 54587
E-mail: kurien123@hotmail.com

Professor John Turnidge
Microbiology and Infectious Diseases,
Women's and Children's Hospital
72 King William Road
North Adelaide
SA 5006
Australia
Tel: +61 8 8161 6873
Tel: +61 8 8161 6189
E-mail: turnidgej@wch.sa.gov.au

Dr Haruo Watanabe
Director
Department of Bacteriology
National Institute of Infectious Diseases
Toyama 1-23-1
Shinjuku- ku
Tokyo 162-8640
Japan
Tel/Fax: +81 352851171
E-mail: haruwata@nih.go.jp

European Commission

Dr Mair Powell
European Medicines Agency (EMEA)
Contact address:
Medicines and Healthcare products Regulatory Agency (MHRA), Market Towers
1 Nine Elms Lane, London SW8 5NQ, United Kingdom
Tel: +44 207 084 2486
Fax : +44 207 084 2170
E-mail: Mair.Powell@mhra.gsi.gov.uk

OIE secretariat

Dr Jaques Acar
Marie Curie Université
22 Rue Emeriau, 75015 Paris
France
Tel: +33 1 4059 4241
Fax: +33 1 4567 0066
E-mail: jfacar7@wanadoo.fr or jfacar@hotmail.com

Australian Government Local Secretariat

Ms Fiona J Brooke
Director
Communicable Disease Management and Policy Biosecurity and Disease Control Branch
Department of Health and Ageing, Australian Government Department of Health
MDP 14 GPO Box 9848, Canberra ACT 2601
Tel: +61 2 6289 8847
Fax:61 2 6289 3677
Mob: +61 401 712 775
E-mail: fiona.brooke@health.gov.au

Dr Angelo A Valois
Director
Technical and International Policy
Product Safety and Integrity Product Integrity, Animal and Plant Health (DAFF), Australian Government Department of Agriculture Fisheries and Forestry
Tel: +61 2 6272 5566
Fax:+61 2 6272 5697
Mob: +61 0409 320 182
E-mail: angelo.valois@daff.gov.au

WHO secretariat

Dr Awa Aïdara-Kane
Strategy Development and Monitoring of Zoonoses,
Foodborne Diseases and Kinetoplastidae (ZFK)
Communicable Diseases Control Prevention and Eradication (CPE)
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland
Tel: +41 22 791 2403
Fax: +41 22 791 4893
E-mail: aidarakanea@who.int

Dr Phillip Jenkins
Policy, Access and Rational Use (PAR)
Essential Drugs and Medicines Policy (EDM)
Health Technology and Pharmaceuticals (HTP)
World Health Organization
20 Avenue Appia
1211 Geneva 27, Switzerland
Tel: +41 22 791 13572
E-mail: jenkinsp@who.int

Annex 2: Agenda

Time	Tuesday 15 feb. 2005	Speaker
09.30 – 10.00	• Opening • Election of Chairperson and Vice-Chairperson • Appointment of Rapporteur • Adoption of the agenda SESSION I: INTRODUCTIONARY PRESENTATION	Ms. Mary Murnane Dr A. Aidara-Kane
10.00 – 10.30	Emergence and dissemination of antibiotic resistance	Patrice Courvalin
10.30 – 11.00	Tea/Coffee break	
	SESSION I I: COUNTRY EXPERIENCES	
11.00 – 11.30	FDA criteria for assessing the importance of antimicrobial drugs in human medicine	John Powers
11.3 0 – 12.00	**Australian experience with classifying antibiotics used in Human Health**	Peter Collignon
12.30 - 13.00	Public Health Impact of Antimicrobial resistance in developing countries	Thomas Kurian
13.00 – 14.00	Lunch	
	SESSION III : CONSTITUTION OF WORKING GROUPS	
15.30 – 16.00	Coffee break	
16.00 – 17.30	• SESSION III : WORKING GROUPS	

Time	Wednesday 16 Feb 2005	
09.00 – 10.00	SESSION III Continued : WORKING GOUPS	
10.30 – 11.00	Coffee break	
11.00 – 13.00	SESSION III Continued : WORKING GOUPS	
13.00 – 14.00	Lunch	
14.00– 15.30	Plenary : Restitution WORKING GROUPS	
15.30 – 16.00	Coffee break	
16.00 – 18.00	SESSION III Continued : WORKING GROUPS	
18.00	Dinner (next to the meeting venue)	

Time	Thursday 17 Fed 2005	
09.00 – 09.30	SESSION III Continued : WORKING GROUPS	
10.30 – 11.00	Coffee break	
11.30 – 12.30	Plenary : Restitution WORKING GROUPS	
12.30 – 14.00	Lunch	
14.00 – 15.30	Report Finalisation	
15.30 – 16.00	Coffee break	
16.00 – 18.00	Adoption of Report and Closing Remarks	