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

DEPARTMENT OF FOOD SAFETY, ZOONOSES AND FOODBORNE DISEASES

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Preamble

The World Health Organization convened an Expert Meeting on Critically Important Antimicrobials for Human Medicine, in Copenhagen, Denmark, from 29 to 31 May 2007.

The meeting was organized to follow up a consultative process on critically important antibacterial agents for human health risk management strategies of non-human use (First WHO Expert Meeting on Critically Important Antibacterial Agents for Human Medicine, Canberra, February 2005), and a FAO/OIE/WHO consultative process on non-human antimicrobial usage and antimicrobial resistance (1st Workshop on Scientific Assessment, Geneva, December 2003, and 2nd Workshop on Management Options, Oslo, March 2004).

Following opening remarks delivered by Dr Jørgen Schlundt and Dr Awa Aidara Kane, of the World Health Organization, Dr Henrik Wegener welcomed participants on behalf of the National Food Institute, Technical University of Denmark. Professor Peter Collignon, of the Canberra Hospital, Australia, and Dr Ezra Barzilay, of the Centers for Disease Control and Prevention (CDC), Atlanta, USA, were elected as Chairperson and Rapporteur respectively.

Executive Summary

Antimicrobial resistance is a global public health concern that is impacted by both human and non-human antimicrobial use. The consequences of antimicrobial resistance are particularly important when pathogens are resistant to antimicrobials that are *critically important* in the treatment of human disease. WHO therefore convened a meeting of experts in Canberra, Australia, on 15 and 16 February 2005, to develop a list and categorization of drugs according to their importance in human medicine. Participants in that meeting categorized antimicrobial drugs as *critically important*, *highly important*, and *important* based on two criteria. When using these two criteria, participants categorized antimicrobials as critically important if they were: (i) sole therapies or one of few alternatives to treat serious human disease, and (ii) 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.

WHO convened the second WHO Expert Meeting on Critically Important Antimicrobials for Human Medicine in Copenhagen, Denmark, from 29 to 31 May 2007. Participants reviewed comments on the Canberra document that had been received from various parties including the WHO Expert Committee the Selection and Use of Essential Medicines. Comments indicated that the title of the document should include an explanation regarding the purpose of this list, so participants modified the title accordingly to indicate that the purpose of this list is for consideration as part of developing risk management strategies for antimicrobial resistance due to non-human antimicrobial use. The wording in the title was also modified from "antibacterials" to "antimicrobials" in order to be consistent with OIE listings and the concept that this list at present includes antibacterials but in the future may expand to include other agents.

The purpose of both the Canberra report and this report is to provide information on the human health consequences of antimicrobial resistance for use in the management of risk due to non-human use of antimicrobials. In addition, this information should be used to support more comprehensive assessments of risk. Such comprehensive assessments should 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.

Participants reviewed the two criteria used to classify human antimicrobials at the first meeting held in Canberra and decided that these criteria remained appropriate. Participants then used those criteria to re-examine the categorization of all human antibacterial classes in light of new drug development and scientific information since 2005. On the basis of this re-examination, relatively few changes were needed to update the categorization of antimicrobials.

Participants were requested to prioritize agents within the *critically important* category in order to allow allocation of resources on the agents for which management of the risks from antimicrobial resistance are needed most urgently. For this, a more detailed application of the two original criteria was used than that employed to develop the Canberra list. Participants considered drugs of greatest priority when (i) there are relatively large absolute numbers of people affected with diseases for which the drug is the sole or one of few alternative therapies, (ii)) the overall frequency of use of the drugs in

human medicine for any use (whether appropriate or inappropriate) is relatively large, and (iii) 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, $3^{rd}/4^{th}$ generation cephalosporins and macrolides. Participants 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.

Recommendations were provided to WHO on various aspects related to antimicrobial resistance in order to protect human health. It was pointed out that there are important gaps in our knowledge and that there is a need for better data on various factors that impact the assessment of risks from antimicrobial resistance due to non-human use as well as human use. There is a need for more and better information on burden of illness in relation to antimicrobial resistance attributable to non-human use of antimicrobials. There is also a need for data on antimicrobial utilization in both humans and animals, data on factors that lead to development and spread of antimicrobial resistance in various pathogens in animals and humans, and better data on the benefits of antimicrobials in both animals and humans in order to balance the benefits as well as the risks of antimicrobial use.

Participants also pointed out that the development of this list is part of a more comprehensive approach to the public health issue of antimicrobial resistance in both animals and humans. It was emphasized that there should be a sense of urgency to the development of such risk management strategies, particularly for quinolones, $3^{rd}/4^{th}$ generation cephalosporins and macrolides.

NOTE: In this document the word "list" refers to the entire listing of all antimicrobial classes used in human medicine. The term "category" refers to the characterization of various antimicrobials into the groupings of *critically important*, *highly important*, or *important*. 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

1. BACKGROUND

1.1 WHO in the wider global context of containing antimicrobial resistance (AMR)

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

Effectiveness of critically important antimicrobials for human medicine should not be compromised by inappropriate over-use and/or misuse in the non-human sector. Agreeing a list of antimicrobials whose use should be controlled/limited in the non-human sector is only one of many risk management strategies to contain the problem of antimicrobial resistance. There have been a number of recent different WHO initiatives and approaches to containing antimicrobial resistance in the human sector. Activities aiming at containing antimicrobial resistance in humans due to non-human antimicrobial use have also been carried out in WHO since the late 1990s.

1.2 Containing antimicrobial resistance due to human use of antimicrobials

WHO's Global Strategy for Containment of Antimicrobial Resistance was published in 2001 (http://www.who.int/drugresistance) and recommends a multisectoral approach to the problem. The main recommendation is to establish national task forces to coordinate interventions aimed at:

- strengthening surveillance of use and resistance
- improving use of antimicrobial drugs
- improving access to appropriate antimicrobials
- reducing the disease burden and spread of infection
- enforcing regulation and legislation related to containing antimicrobial resistance
- developing appropriate new drugs and vaccines.

Much of the above evidence was presented at the 2nd International Conference on Improving the Use of Medicines, in 2004, where 472 participants from 70 countries presented studies on intervention impact on drug use (http://www.icium.org). An analysis of all the studies presented was undertaken and a main recommendation made for countries to establish national programmes to improve the use of medicines with long-term in-built monitoring systems and coordinated multifaceted interventions. Specific recommendations for AMR containment included: strengthening surveillance; evaluating intervention impact; avoidance of perverse financial incentives; and focus on high priority areas such as infection control, surgical prophylaxis, use by drug sellers, regulation to restrict antimicrobial over-the-counter (OTC) availability and inclusion of AMR in undergraduate and postgraduate curricula. These recommendations made in 2004 are very similar to those of WHO's Global Strategy on Containment of AMR published in 2001. A further specific recommendation of the Conference was to develop surveillance systems and regulation to control non-human antimicrobial use.

A summary of this evidence was presented to the World Health Assembly in 2005, resulting in the adoption of resolution WHA58.27 on *Improving Antimicrobial Resistance*. Further evidence was presented to the World Health Assembly in 2007, resulting in the adoption of resolution WHA60.16, on *Rational Use of Medicines*. The WHO Secretariat

has drafted a plan of action to implement both resolutions based on establishing a global team within WHO dedicated to facilitating the bringing together of stakeholders at country level – including governments, professions and civil society – in order to form national scaled-up plans of action. This plan of action, endorsed by WHO's 15th Expert Committee for the Selection and Use of Essential Medicines, in March 2007, follows the single most important recommendation made by multiple sources. It has only been possible to make progress on the issue of antimicrobial resistance containment in humans since the introduction of systematic collection of global data on actual drug use, intervention impact on use, and policy implementation, followed by publication of the evidence. As at least half of all antimicrobial drug consumption is estimated to occur in the non-human sector, and resistance can transfer between animals and humans, any effective strategy to contain antimicrobial resistance must involve the non-human sector. It is therefore very important that data similar to that already collected in the human sector (on drug use, impact intervention and policy implementation) be collected also in the non-human sector and the evidence be published.

1.3 Containing antimicrobial resistance due to non-human use of antimicrobials

The widespread use of antimicrobials not only for therapeutic purposes but also for prophylactic and growth promotion purposes in livestock production has intensified the risk for the emergence and spread of resistant microorganisms. This raises particular concern since the same classes of antimicrobials are used both in humans and animals. The emergence and spread of antimicrobial resistance in bacteria poses a threat to human health and presents a major financial burden. Moreover, few new antibiotics are being developed to replace those becoming ineffective through resistance. Food is generally considered to be the most important vector for spread of resistance between humans and animals.

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 expressed 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/foodborne_disease/resistance/en).

Following concern expressed on the use of quinolones in food animals and the emergence of quinolone-resistant enteric bacteria, a WHO consultation to address this issue was held in Geneva, in June 1998 (*Use of Quinolones in Food Animals and Potential Impact on Human Health*: Report and Proceedings of a WHO Meeting, Geneva, 2-5 June 1998, WHO/EMC/ZDI/98.12).

Concerned about the extensive use of antibiotics in food production, which could further accelerate the development of antimicrobial resistance and thus render treatment ineffective, the World Health Assembly adopted in 1998 a resolution on antimicrobial resistance (WHA51.17) urging Member States to encourage the reduced and rational use of antimicrobials in food-animal production.

This 1998 World Health Assembly resolution was followed by the development of 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, 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 Atimicrobial Growth Promoter Termination in Denmark.* The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark. Foulum, Denmark, 6-7 November 2002. http://www.who.int/salmsurv/links/gssamrgrowthreportstory/en)

Recognizing that antimicrobial resistance is a multifactorial 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, OIE and WHO should consider hosting a joint meeting to discuss all issues related to the non-human use of antimicrobials and antimicrobial resistance.

As a response to this recommendation, an FAO/OIE/WHO joint consultative process on non-human use 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 Geneva, in December 2003, and a second workshop on management options was held in Oslo, in March 2004.

As recommended during the Oslo workshop, a WHO meeting on Critically Important Antimicrobials for Human Medicine was organized in Canberra, in February 2005. To complement this process a Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance was held in Seoul, Korea, in June 2006. This focused on the use of antimicrobials in aquaculture and the public health impact of such use, an issue that had not been addressed thoroughly in earlier consultations. It also evaluated usage patterns and the public health impact of this use, in order to develop strategies to minimize any risk. (All reports available at : http://www.who.int/foodborne_disease/resistance/en/).

The main outcomes of this process were two-fold:

1. The recent establishment of a Codex Task Force on Non-Human Use of Antimicrobials and Antimicrobial Resistance. The output of this Task Force is expected to be relevant to the setting of international standards in support of prevention and containment of antimicrobial resistance.

2. The global development of the concept of *Critically Important Antimicrobials* (CIA) for humans. This will be followed by proposed strategies for the specific limitation or ban of their use in animals in order to prevent/contain resistance to those antimicrobials. Management options should be proposed taking into account the list of critically important antimicrobials for animals developed by OIE. An appropriate balance should be struck between animal health needs and human health considerations – human health being, however, paramount compared to animal health (WHO Global Principle Number 6).

2. OVERALL OBJECTIVES AND OUTCOME OF THE MEETING

The 1st WHO Expert Meeting on Critically Important Antimicrobials for Human Medicine, held in Canberra, Australia, in February 2005, had categorized antimicrobial drugs as being *critically important, highly important* or *important.* It was recommended at that meeting that WHO should update the list at regular intervals as ranking could vary over time as resistance levels changed, or as new drugs or therapeutic choices became available.

The overall aim of the Copenhagen meeting was to update that WHO list of critically important antimicrobials for human medicine and to define which antimicrobials were to be considered – and in which priority – in order to prevent the potential emergence of antimicrobial resistance in humans due to non-human antimicrobial use.

The specific aims of this meeting were therefore:

1. To update the WHO list of critically important antimicrobials for human medicine, taking into account new scientific information and comments from the review recently undertaken by the WHO Expert Committee for the Selection and Use of Essential Medicines.

2. To develop criteria for prioritization of antimicrobials within the updated category of critically important agents for human medicine.

3. To apply these criteria to prioritize the critically important antimicrobials for developing risk-management strategies in order to preserve their effectiveness in human medicine.

4. To provide recommendations to FAO, OIE and WHO, as well as the Codex Alimentarius Commission, on current and future activities regarding non-human use of antimicrobials.

The expected outcome of the meeting was a report including an updated list of critically important antimicrobials for consideration for risk management strategies of antimicrobial resistance due to non-human antimicrobial for use at (a) the first session of the Codex Task Force on Antimicrobial Resistance, to be held in Seoul, Republic of Korea, from 23 to 26 October 2007, and the FAO/OIE/WHO Expert Consultation on Critically Important Antimicrobials, to be held in Rome, Italy, from 26 to 30 November 2007.

3. INTRODUCTION

There is a need for internationally recognized principles for risk assessment (the probability of occurrence and the severity of adverse health outcomes) related to antimicrobial resistance owing to non-human use of antimicrobials. The purpose of this list is to function as part of, but not the sole part of risk assessments of non-human antimicrobial use and their potential impact on human health. This list focuses primarily on the *consequences* of the potential loss of effectiveness of various antibacterials in the treatment of human disease. This list does not focus on other components of risk assessments such as the potential for development of resistant organisms in animals owing

to animal use of antimicrobials (*release assessment*), and the potential spread of resistant organisms from animals to humans (*exposure assessment*). An overall assessment of risk involves the release exposure and consequence assessment integrated into the overall risk estimate. Prioritization among the classes of antimicrobials in the critically important category of the list should not be used to minimize the importance of other critically important antimicrobials in the same category.

3.1 What should the list be used for?

- To prioritize the antimicrobials characterized as *critically important* for most urgent development of risk management strategies in order to preserve their effectiveness in human medicine.
- To include in current and future comprehensive assessments of risk.

3.2 What should the list not be used for?

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

At present the link between the potential spread of antimicrobial resistant pathogens and/or their genes from non-human antimicrobial use to humans appears most clear for bacteria. The list of antimicrobial agents considered *critically important* for human health (based on criteria defined below) is therefore 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.

3.3 Important considerations

- Cost, availability of drugs and burden of illness may cause local health authorities to expand the category of critically important drugs.
- This list differs in purpose and content from the WHO Model List of Essential Medicines.

The first part of Table 1 (see page 15) should be considered a core list of the most critical antibacterial agents globally. It is recommended that decisions regarding the move of an antibacterial from a more important category (*Critically Important*) to a category of lesser importance (*Highly Important* or *Important*) be restricted to groups of experts appointed by WHO. However, considerations such as cost 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).

3.4 Geographical considerations

The list of critically important antimicrobials is based upon two criteria: whether an antimicrobial is the sole or one of the few treatments available for serious human infection

(criterion 1), and whether an antimicrobial treats pathogens that have the potential to transfer from animals to humans (criterion 2). The availability of certain antimicrobials and the burden of disease may vary significantly in different regions of the world and as such may result in the need for countries to reclassify certain antimicrobials as *critically important.* For example, in many low-income countries, there is a lack of availability of quinolones and 3rd/4th generation cephalosporins to treat infections that are common and that often have serious consequences to human health (e.g. urinary tract infections, shigellosis, pneumonia, meningitis). These regions may therefore wish to reclassify an antimicrobial (e.g. trimethoprim-sulfamethoxazole) as a *critically important* antimicrobial if in that region the antimicrobial in question is the sole treatment available for serious infections (criterion 1). Another example, is the combination of rifampicin and fusidic acid, which is frequently used in Australia as oral therapy for multi-drug resistant *S. aureus* infections. Fusidic acid constitutes the sole or one of the few alternative therapies available for the treatment of multiresistant *S. aureus* (criterion 1). If fusidic acid was used in animals and resistance developed in animal staphylococcal strains (criterion 2), fusidic acid could be classified in Australia as *critically important.*

It should be noted that the second criterion for categorizing antimicrobials is based on the likelihood of transmission of organisms from animals to humans. In some parts of the world, there are few alternatives to aminopenicillins for the outpatient management of common respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (criterion 1). Yet there is no evidence at present to suggest the transmission of *Streptococcus pneumoniae* and *Haemophilus influenzae* from animals to humans. For this reason, antimicrobials such as trimethoprime-sulfamethoxazole, which are widely used in developing countries to treat acute lower respiratory tract infections, are not categorized as *critically important* when considered to be alternative therapy for the treatment of bacteria such as *E.coli* (criterion 1) which are transmitted via the food chain (criterion 2).

3.5 WHO Model List of Essential Medicines

It is important to note that the list of antimicrobials presented here differs from the WHO Model List of Essential Medicines. The purpose of this list of antimicrobial agents is for use as part of risk management strategies of non-human antibacterial use. The antimicrobial 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 regard to public health relevance, and evidence of efficacy, safety and comparative cost effectiveness. In contrast, cost was not a primary consideration in developing the list of antimicrobials for this current document 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 Model List of Essential Medicines also appear in this list. Those in the list of essential medicines that have not been listed as *critically important* in this document are chloramphenicol, clindamycin, cloxacillin, doxycycline, metronidazole, nitrofurantoin, spectinomycin and sulfonamides.

4. UPDATING THE CANBERRA LIST

4.1 Elements for consideration to update the Canberra list

The panel updated the Canberra list taking into account recent developments in antimicrobial resistance and the comments received from WHO**.**

4.1.1 Recent developments in antimicrobial resistance

New antimicrobials
A new antimicrobial, tigecycline, has been approved for treatment of Gram-negative and *S. aureus* infections in humans. Tigecycline is structurally related to the tetracyclines, but with enhanced activity. Tigecycline could be important for treatment of infections with MDR *S. aureus*. No similar compound is currently approved for treatment of infections in animals.

Extended Spectrum Beta-lactamase (ESBL) producing enzymes
The prevalence of ESBL positive *Enterobacteriaceae,* including Salmonella and *E. coli,* from food animals have continued to increase and has also emerged in more countries. More evidence that ESBL-genes and ESBL-harbouring clones spread through the food chain has also become available.

Methicillin-resistant* Staphylococcus aureus *in animals
From being almost exclusively a health-care-associated pathogen, Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged during the last two decades into the community and has recently also caused infections in and colonized pets and production animals. MRSA has been detected in cattle, chickens, horses, pigs, dogs, rabbits, seals, birds and cats. The colonization in animals has in several cases been implicated in infections in humans. It is important, however, to distinguish between the epidemiology of MRSA in relation to livestock, where a new clone (ST398) is seemingly emerging, to those of pet animals that are infected with classical human variants of MRSA. ST398 was first detected in 2004 in The Netherlands and has so far not been found among strains isolated prior to 2003.

Based on our current knowledge, some strains of MRSA should now be considered a zoonosis. Pet animals can act as a reservoir for the bacterium from where it can transfer to humans and cause infection. In infection control, pet animals should probably be treated in the same way family members would be treated. However, in livestock, the situation is different. Thus, it seems likely that a single clone (ST398) has adapted itself to colonize livestock animals (pigs, chickens and cattle) from where it can spread to humans. The importance for human health and the implications for infection control are currently unclear and will need to be reviewed as more information becomes available.

Transferable low-level resistance fluoroquinolone resistance in Enterobacteriaceae
Until recently, chromosomal mutations in different genes involved in DNA-transcription and replication were considered the main mechanisms of quinolone resistance in *Enterobacteriaceae*. A new and transferable mechanism was described in 1998 in a *Klebsiella pneumoniae* isolate obtained from a patient in 1994 in Alabama, USA. This mechanism named *qnrA* encodes a protein that blocks the action of fluoroquinolones. Since then two other *qnr*-genes (*qnrB* and *qnrS*) and a number of different variants have been identified. Plasmid mediated quinolone resistance was originally found very rarely, but seems to have spread more rapidly than expected and is now found in several species, including *Salmonella spp*. and *E. coli* in Africa, Asia, Europe and USA. The genes are often located on transferable plasmids together with other resistance genes especially genes encoding resistance to cephalosporins. Presence of the *qnr* genes alone does not necessarily mediate full resistance to nalidixic acid and thus makes it uncertain to use

nalidixic acid for screening for fluoroquinolone resistance. This is in contrast to the mutation-mediated resistance where one mutation encodes low-level resistance to fluoroquinolones and full resistance to nalidixic acid. Low-level fluoroquinolone resistance is difficult to detect in routine diagnostic laboratories and these isolates might easily be considered susceptible, especially when using diffusion testing.

In 2006 another mechanism of transferable quinolone resistance was reported. The *cr* variant of *aac(6')Ib* encodes an aminoglycoside acetyltransferase that confers resistance to ciprofloxacin by N-acetylation of its piperazinyl amine. This mechanism was described in *E. coli* isolates from Shanghai, but has since been found among *Enterobacteriaceae* strains from several countries worldwide. As for *qnr* this new fluoroquinolone resistance mechanism seems to be located on multiple resistance plasmids which commonly also encode cephalosporin resistance.

Ease of global spread of resistant bacteria

More evidence has become available that antimicrobial resistant bacteria will spread globally and that the selection for antimicrobial resistance among food animals in one country can cause human health problems in other countries. This has occurred with a number of different *Salmonella spp*. (e.g. *Salmonella* Schwartzengrund, *Salmonella* Typhimurium DT104, *Salmonella* Virchow)

4.1.2 WHO Expert Committee for the Selection and Use of Essential Medicines

WHO's 15th Expert Committee for the Selection and Use of Essential Medicines considered, in March 2007, the report on *Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-Human Use*, that had been produced by the WHO working group consultation in Canberra, Australia, in 2005. This Expert Committee is a formal body established by the World Health Assembly in 1977 that meets every two years and works in accordance with WHO's Regulations for Expert Committees. Members of Expert Committees are selected from WHO's Expert Advisory Panels applying the Organization's principles of regional representation and gender balance. Applications for items to be included in the agenda of the Expert Committee must be received several months ahead of the meeting with supporting justification or evidence in order to be placed on the WHO web site for public comment. Such applications are reviewed by two members of the Expert Committee whose observations are also placed on the web site for public comment. Following this expert review and public comment, items are then considered by the Expert Committee and recommendations made.

The Expert Committee for the Selection and Use of Essential Medicines endorsed the concept of *Critically Important Antibiotics* which members understood to mean "identifying antibiotics that should not be used for non-human use". They noted how this concept is different from that of Essential Medicines. They felt, however, that the labels of *critically important* and *highly important* could be confusing and that the full definitions of these categories should be used instead. This implies modifying the terms to clearly indicate the purpose of the list and adding some statements about the use of *Critically Important Antibiotics* being restricted in the non-human sector. The Expert Committee also recommended establishing a WHO Advisory Group, involving FAO and OIE, to meet regularly to update the list of *Critically Important Antibiotics* and to consider what recommendations are needed for the non-human use of antibiotics that are considered essential but not critically important

4.2 Changes in this document compared to the Canberra document

4.2.1 Change in title

Participants in the Copenhagen meeting agreed that the title of the document should be modified from "antibacterials" to "antimicrobials" in order to be consistent with the OIE list. They also agreed that in future this list should be expanded from only including antibacterials to including other agents. Comments on the previous document indicated that the title should include an explanation of the purpose of this list. Participants therefore modified the title to indicate that the purpose of this list is for consideration for risk management strategies of antimicrobial resistance due to non-human antimicrobial use.

4.2.2 Re-examination of the list of all antimicrobial classes used in human medicine and categorizatioin of antimicrobials

At the Canberra meeting, in 2005, participants created a list of all antimicrobial classes used in human medicine and categorized antimicrobials into three groups of *critically important*, *highly important*, and *important* based on criteria developed during the meeting.

Firstly, participants developed criteria to categorize all antimicrobial classes in human medicine and then applied those 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). In developing such criteria, participants took into account how certain antimicrobials are used in human medicine, the availability of data from randomized trials on the safety and effectiveness of various drugs in the treatment of particular diseases, the seriousness of the diseases treated with those agents and the availability of similarly effective therapies in the treatment of such diseases. Participants were then able to assess the potential consequences to human health of the potential loss of effectiveness of antibacterial agents due to bacterial resistance. Participants also took into consideration pathogenic and commensal bacteria (or their genes) that may transfer to people from animals, food products or the environment.

At the Copenhagen meeting, in May 2007, participants reviewed the two criteria used to classify human antimicrobials at the Canberra meeting. Participants in the Copenhagen meeting decided that these criteria remained valid, and then applied them to re-examine the classification of all human antimicrobial classes in light of new drug development and scientific information since 2005.

Criteria

In developing these classifications, participants considered that no antibacterial or class of antibacterials used in human medicine could be considered unimportant. Partipants therefore 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. Participants included in the *Comments* section of the table examples of the diseases for which the given antibacterial (or class of selected agents within a class) was considered one of the sole or limited therapies for specific infection(s). This criterion does not consider the likelihood that such pathogens may transmit, or have been proven to transmit, from non-human 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. Participants did not consider such issues as the likelihood of resistance developing in non-human sources with non-human use of these drugs, or the likely exposure of humans to such organisms should such resistance develop. The history of the development of antimicrobial resistance shows that resistance may appear after 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). Because resistance has not developed to date there is no guarantee 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 became available, including data on resistance patterns, new and emerging diseases, and the development of new drugs.

The list in Table 1 (see page 15) 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.

Other classes of antibacterial drugs not used in humans

Classes of drugs that are not used in humans and which are currently only used in animal medicine include arsenicals, bambermycins, ionophores, orthosomycins, quinoxalines, and others.

Comments on the classification of some specific antibacterial agents

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.

Aminopenicillins and natural penicillins are among the few available therapies for invasive enterococcal and *Listeria* infections. *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 being critically important for human medicine.

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.

Changes in antimicrobial categorization

On the basis of this re-examination, relatively few changes were needed to update the classification tables.

- Tigecycline (a new tetracycline derivative with activity against multi-resistant *S. aureus* and gram negative bacteria) was released in 2005 and was categorized as *critically important.*
- All penicillins (other than anti-staphylococcal penicillins) were grouped together and remain as *critically important*.
- The anti-staphylococcal penicillins were moved from *important* to *highly important* as there is now more evidence of the potential transfer of *S. aureus*, including MRSA, from food production animals to humans.

- Because of the evidence of transfer of *flo* genes and chloramphenicol-resistant *Salmonella* from animals to humans, the amphenicols were moved from *important* to *highly important.*
- Because of different resistance mechanisms, the aminoglycosides were divided into two groups. As a result, two aminoglycosides (kanamycin, neomycin) were moved from *critically important* to *highly important.*
- The classification of 3rd and 4th generation cephalosporins was not changed but these were combined in the tables as the mechanisms for antimicrobial resistance are similar and the criteria for their classifications were the same. The 1st and 2nd generation cephalosporins were also combined in the tables for similar reasons. This is consistent with the grouping of other classes like quinolones.

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

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 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
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

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
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, (natural, aminopenicillins and antipseudomonal) ampicillin ampicillin/sulbactam amoxicillin amoxicillin/clavulanate azlocillin carbenicillin mezlocillin penicillin G penicillin V piperacillin piperacillin/tazobactam ticarcillin ticarcillin/clavulanate	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)

Critically Important Antimicrobials (cont'd)			
Drug name	**Criterion 1**	**Criterion 2**	**Comments**
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* spp. from non-human sources
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 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 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			
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

5. PRIORITIZATION WITHIN THE *CRITICALLY IMPORTANT* CATEGORY

In addition, given their mandate to prioritize agents within the *critically important* category, the Copenhagen panel of experts focused on the two criteria developed by the Canberra panel to prioritize agents within the *critically important* category:

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

- *Criterion 1.1* – High absolute number of people affected by all diseases for which the antimicrobial is the sole/one of few therapies available.

- *Criterion 1.2* – High frequency of any use of the antimicrobial in human medicine regardless of indication given that usage for any reason may result in selection pressure for resistance.

Focusing criterion 2: Antibacterials 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.

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

Those drugs categorized as highest priority met all three of criteria 1.1, 1.2 and 2.1.

Amoxicillin is categorized as *critically important* but has not been ranked in this report as treating a large absolute number of people with serious disease based on the incidence of *Listeria* and enterococcal infections (criterion 1.1). However, in low-income countries, amoxicillin may be extensively used for many infections (*criterion 1.2*) and its main use may be for serious infections such as pneumonia which have a high disease burden. Such countries may wish to re-rank amoxicillin as high for criterion 1.1.

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

Critically Important Antimicrobials				
Drug name	**Criterion 1.1**	**Criterion 1.2**	**Criterion 2.1**	**Comments**
Aminoglycosides	Low	Low	High	(Criterion 1) Limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis (Criterion 2) Potential transmission of *Enterococcus* spp., *Enterobacteriaceae* (including *Escherichia coli*), and *Mycobacterium* spp. from non-human sources
amikacin arbekacin				
gentamicin netilmicin tobramycin streptomycin				
Ansamycins	High	High	Low	(Criterion 1) Limited therapy as part of therapy of mycobacterial diseases including tuberculosis and single drug therapy may select for resistance (Criterion 2) Potential transmission of *Mycobacterium* spp. from non-human sources
rifabutin rifampin rifaximin				
Carbapenems and other penems	High	Low	High	(Criterion 1) Limited therapy as part of treatment of disease due to MDR Gram-negative bacteria (Criterion 2) Potential transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
ertapenem faropenem imipenem meropenem				
Cephalosporins, (3rd and 4th generation)	High	High	High	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to *Salmonella spp.* in children. Additionally, 4th generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever. (Criterion 2) Potential transmission of *Enterobacteriaceae* including *E. coli* and *Salmonella* spp. from non-human sources
cefixime cefotaxime cefpodoxime ceftazidime ceftizoxime cefoperazone cefoperazone/sulbactam ceftriaxone				
cefepime cefpirome cefoselis				
Lipopeptides	High	Low	Low	(Criterion 1) Limited therapy for

daptomycin				infections due to MDR *Staphylococcus aureus* (Criterion 2) Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources

Critically Important Antimicrobials (continued)				
Drug name	**Criterion 1.1**	**Criterion 1.2**	**Criterion 2.1**	**Comments**
Glycylcycline (higher generation tetracycline) tigecycline	High	Low	High	(Criterion 1) Limited therapy for infections due to MDR *S. aureus* and MDR Gram negative bacteria (Criterion 2) Potential transmission of *Enterobacteriaceae* including *E. coli* from non-human sources
Glycopeptides teicoplanin vancomycin	High	Low*	Low	(Criterion 1) Limited therapy for infections due to MDR *S. aureus* and *Enterococcus* spp. (Criterion 2) Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources
Oxazolidinones Linezolid	High	Low	Low	(Criterion 1) Limited therapy for infections due to MDR *S. aureus* and *Enterococcus* spp. (Criterion 2) Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources
Penicillins, (natural, aminopenicillins and antipseudomonal) penicillin G penicillin V ampicillin ampicillin/sulbactam amoxicillin amoxicillin/clavulanate piperacillin piperacillin/tazobactam azlocillin carbenicillin mezlocillin ticarcillin ticarcillin/clavulanate	Low*	High	Low	(Criterion 1) Limited therapy for syphilis (natural) *Listeria* and *Enterococcus spp.* (aminopenicillins) (Criterion 2) Potential transmission of *Enterococcus* spp. from non-human sources
Macrolides (including 14-, 15-, 16-membered compounds), ketolides azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin	High	High	High	(Criterion 1) Limited therapy for *Legionella*, *Campylobacter,* and MDR *Salmonella* infections (Criterion 2) Potential transmission of *Campylobacter* spp. from non-human sources

Critically Important Antimicrobials (continued)				
Drug name	**Criterion 1.1**	**Criterion 1.2**	**Criterion 2.1**	**Comments**
Quinolones cinoxacin nalidixic acid pipemidic acid ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin norfloxacin ofloxacin Sparfloxacin	High	High	High	(Criterion 1) Limited therapy for *Campylobacter* spp., invasive disease due to *Salmonella* spp., and MDR *Shigella* spp. infections (Criterion 2) Potential transmission of *Campylobacter* spp. and Enterobacteriaceae including *E. coli* and *Salmonella* spp. from non-human sources
Streptogramins quinupristin/dalfo-pristin, pristinamycin	High	Low	Low	(Criterion 1) Limited therapy for MDR *Enterococcus faecium* and *S. aureus* infections (Criterion 2) Potential transmission of *Enterococcus* spp. and MDR *S. aureus* from non-human sources

Critically Important Antimicrobials (continued)				
Drug name	**Criterion 1.1**	**Criterion 1.2**	**Criterion 2.1**	**Comments**
Drugs used solely to treat tuberculosis or other mycobacterial diseases	High	High	Low	(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) Potential transmission of *Mycobacterium* spp. from non-human sources
cycloserine ethambutol ethionamide isoniazid para-aminosalicylic acid pyrazinamide				

6. CONCLUSIONS

Participants reviewed all the agents used in human medicine and came to conclusions regarding the classification of drugs which were very similar to those of the previous meeting in 2005.

The prioritization of classes of antimicrobials to be addressed most urgently in terms of risk management strategies for non-human use of antimicrobials resulted in the selection of three groups of drugs: quinolones, 3rd /4th generation cephalosporins, and macrolides. These drugs meet both criteria 1 and 2 from the previous document (one of sole or few therapies of serious disease in humans and used to treat diseases caused by organisms that may be transmitted or acquire resistance genes from non-human sources). In addition, these drugs are used widely and the absolute numbers of people affected by the diseases for which they are the sole therapies are relatively common. These drugs also are used to treat diseases due to organisms where there is the greatest degree of confidence of a non-human source of bacteria or genes.

The antimicrobials listed as those of highest priority for risk management strategies is identical to those mentioned in the list developed at the joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance, held in Geneva, from 1 to 5 December 2003, and are to be included on any priority list. The evidence presented at that meeting indicated that the list of critically important classes of antimicrobials should include quinolones and 3rd generation cephalosporins for Salmonella and other Enterobacteriaceae, as well as quinolones and macrolides for Campylobacter spp. (see page 18 of the report : http://www.who.int/foodborne_disease/resistance/en/).

7. RECOMMENDATIONS

1. The prioritization of antimicrobials categorized as *critically important* developed by the Copenhagen meeting should be used as part of the development of risk management strategies for the containment of antimicrobial resistance in humans due to non-human use of antimicrobials. In the first instance, this should be quinolones, 3rd/4th generation cephalosporins and macrolides.

2. WHO should, at regular intervals, revise the list of *Critically Important Antimicrobials* for human medicine as appropriate to incorporate new scientific information on resistance and on new antimicrobial agents.

3. More information including, but not limited to, volume of drug use, usage patterns, evidence on the benefit of drug usage for animals, emergence, occurrence and spread of antimicrobial resistant bacteria and resistance genes, animals and human hygiene practices should be obtained in different countries and regions. These data should be collected in a harmonized way and used to monitor and promote changes in practice as well as to determine the human health risk from different food animals reservoirs.

4. Burden of illness studies should be pursued in relation to antimicrobial resistance and the proportion of resistance attributable to non-human use of antimicrobials.

5. Individual Member States or regions should consider factors such as cost and availability of antimicrobials in specific geographic areas, as well as local resistance rates and burden of illness, that may cause the list of *Critically Important*

Antimicrobials to be expanded. Only an expert panel appointed by WHO has the right to move an antimicrobial agent from a more important category to a category of lesser importance.

6. Should a new class of antimicrobials be developed that may be used in human medicine or selected for resistance to antimicrobials used in human medicine, this class should be placed on the *critically important* category on the list.

7. The rational use of *Critically Important Antimicrobials* in human medicine should be encouraged and the use of such antimicrobials be reserved for the treatment of serious disease.

8. Harmonized, internationally recognized and accepted principles for risk assessment related to antimicrobial resistance due to non-human use of antimicrobials should be developed.

9. FAO/OIE/WHO should continue working together to support the implementation by Member States of recommendations, guidelines and codes of practice developed by the Codex Alimentarius Commission to minimize and contain antimicrobial resistance owing to non-human use of antimicrobials.

8. NEXT STEPS

As specified during the Oslo meeting in 2004, the updated list of WHO's Critically Important Antimicrobials for Human Medicine will be made available as widely as possible and shared among Member States and other organizations such as FAO and OIE.

The WHO list will be presented to the next meeting of the WHO Expert Committee for the Selection and Use of Essential Medicines.

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

The list should be updated at regular intervals since ranking may require modification over time as resistance levels change and new drugs or therapeutic choices become available.

The list of antimicrobials for human health has been developed separately from the list of antimicrobial agents for animals established by OIE. Experts will be invited to participate in a meeting scheduled to take place in Rome, in November 2007, to consider these two lists.

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

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Annex 1

WHO Expert Meeting on Critically Important Antimicrobials for Human Medicne
Copenhagen, 29-31 May 2007

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Annex 2

WHO Expert Meeting on Critically Important Antimicrobials for Human Medicine
Copenhagen, 29-31 May 2007

AGENDA

TUESDAY, 29 MAY 2007		
09.00 – 09.30	• Opening • Election of Chairperson and Vice-Chairperson • Appointment of Rapporteur • Adoption of the agenda	**Jørgen Schlundt,** Director Department of Food Safety, Zoonoses and Foodborne Disease Surveillance, WHO Geneva **Dr Henrik Wegener** Director, National Food Institute, Technical University of Denmark
09.30 – 10.00	**SESSION I: INTRODUCTIONARY PRESENTATIONS** Antimicrobial resistance in foodborne bacteria : recent developments	**Frank Aarestrup** National Food Institute Technical University of Denmark
10.00 – 10.30	Tea/Coffee break	
	SESSION I: INTRODUCTIONARY PRESENTATIONS (continued)	
10.30 – 11.00	**WHO strategy for containment of antimicrobial resistance from a Human perspective**	**Kathy Holloway** WHO Geneva
11.0 0 – 11.30	WHO list of CIA developed during Canberra meeting in 2005	**Peter Collignon** , Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, Australia, and **Awa Aidara-Kane**, WHO, Genev
11.30 - 12.00	**WHO list of Essential Medicines and output of the Expert Committee for Selection and Use of Essential Medicines after consideration of the WHO list of CIA**	**Kathy Holloway** WHO Geneva
12.00 – 13.00	Lunch	
13.00-15.30	**SESSION II: UPDATE OF WHO LIST OF CIA FOR HUMANS** **I**ssues raised by The WHO Expert Committee on the selection and use of Essential Medicines	
15.30 – 16.00	Coffee break	

16.00 – 17.30	**SESSION II: UPDATE OF WHO LIST OF CIA FOR HUMANS (continued)**	
WEDNESDAY, 30 MARCH 2003		
09.00 – 10.30	**SESSION III: PRIORITY SETTING** Rationale and Principle for Prioritization Defining combination antimicrobial/animal species to be considered in priority for development of guidelines and standard-setting	
10.30 – 11.00	Coffee break	
11.00 – 12.00	SESSION III: PRIORITY SETTING (continued)	
12.00 – 13.00	Lunch	
13.00– 15.30	**SESSION IV: RECOMMENDATIONS** Recommendations to WHO on future work for containment of foodborne antimicrobial resistance	
15.30 – 16.00	Coffee break	
16.00 – 18.00	**SESSION V: REPORT** Finalization and adoption of the report	
18.00	Dinner	
THURSDAY, 31 MAY 2007		
09.00 – 10.30	SESSION V: REPORT (continued) Finalization and adoption of the report	
10.30 – 11.00	Coffee break	
11.00 – 13.00	**REVIEW PANEL** Guidelines for rational use of antimicrobials in animals, integrating the concept of critically- important antimicrobials in humans in Denmark	
12.30 – 14.00	Lunch	
14.00 – 15.30	**Closing remarks**	

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