

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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CONTENTS

Preamble	1
Background:	1
ntroduction:	3
Procedure	4
The Criteria	4
Classification of Antibacterial Drugs	6
Comments on the classification of some specific antibacterial agents: 1	2
Next steps: 1	2
Annex 1: List of Participants 1	3
Annex 2: Agenda 1	5

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 guinolones 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 Report of a WHO consultation. Oslo, Norway, 10-13 September 2001. health. 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 6-7 in Denmark, 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 nonhuman 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 clindamycin, cloxacillin, metronidazole, this document are 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

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