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Organization of the United  
Nations**



**World Health Organization**



**World Organisation for Animal  
Health**

## **Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials**

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**Report of the FAO/WHO/OIE Expert meeting  
FAO, Rome, Italy  
26–30 November 2007**



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## ACRONYMS AND ABBREVIATIONS USED IN THE TEXT

ADI	Acceptable Daily Intake
CAC	Codex Alimentarius Commission
CCFH	Codex Committee on Food Hygiene
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration of the United States
HACCP	Hazard Analysis and Critical Control Point
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JEMRA	Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment
MIC	Minimum inhibitory concentration
OIE	Office international des epizooties (World Organisation for Animal Health)
PK/PD	Pharmacokinetic/Pharmacodynamic data integration
WHO	World Health Organization
WTO	World Trade Organization

## EXECUTIVE SUMMARY AND RECOMMENDATIONS

A Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials was held from 26 to 30 November 2007 in Rome, Italy. The meeting was convened as a continuation of the consultative process on antimicrobial resistance, arising from non-human use of antimicrobials in food-producing animal species, that was implemented jointly by the three Organizations in 2003 following recommendations of the Executive Committee of the Codex Alimentarius Commission in 2001 to discuss issues related to the use of antimicrobials in agriculture (including aquaculture) and veterinary medicine, taking into account the joint role played by antimicrobials as essential human and veterinary medicines.

The objectives of the expert meeting were to consider the WHO and OIE lists of critically important antimicrobials in order to:

- Find an appropriate balance between animal health needs and public health considerations, taking into account the overlap of the two lists;
- Identify as far as feasible, the current and potential hazards to public health resulting from this overlap;
- Identify the combinations—human-pathogen-antimicrobial use and animal species—that could be considered by risk managers as the priority combinations in terms of risk-benefit assessment for future consideration;
- Review current management strategies and options for maintaining the efficacy of critically important antimicrobials for humans and animals; and
- Provide recommendations on future FAO, OIE and WHO activities.

### ***Comparison of the WHO and OIE lists of critically important antimicrobials***

OIE has ranked veterinary antimicrobial agents as critically important, highly important or important to animal health, and WHO has ranked human antimicrobial agents as critically important, highly important or important to human medicine; most classes of antimicrobial agents have been ranked by both OIE and WHO in their lists.

However, when just the critically important antimicrobials were examined, some classes appear on the WHO list (carbapenems, ansamycins, glycopeptides, streptogramins and oxazolidinones), whereas other classes appear only on the OIE list (phenicols, sulfonamides, diaminopyrimidines and tetracyclines).

For a number of classes there is an overlap, where the class of antimicrobial agents is listed as critically important for human health by WHO and critically important for animal health by OIE. These are 3rd and 4th generation cephalosporins, quinolones (including fluoroquinolones), macrolides, penicillins and aminoglycosides. This overlap highlights the need to have in place antimicrobial resistance surveillance and to identify and implement appropriate management measures in order to mitigate resistance dissemination and maintain the efficacy of the drugs. Prudent use of all antimicrobials is considered essential.

### ***Risk assessment and prioritization***

A risk assessment, especially a quantitative assessment, can be time consuming and expensive, thus it is necessary to set priorities. This report suggests possible ways for risk managers to prioritize and rank combinations of drugs+animal species+pathogens for which to commission risk assessments.

The WHO and OIE lists of critically important antimicrobials should be considered when establishing priorities. The need for access to antimicrobials in both human and veterinary medicine was acknowledged.

The meeting identified key principles that a prioritization scheme for the risk assessment of antimicrobial resistance resulting from the use of antimicrobials in food animals could follow: objectivity and a simple and transparent approach are needed. In addition, any approach should be practical, adaptable to real life, be used as the basis for commissioning the risk assessment, be based on robust data where available, and could also serve to identify data gaps for targeted research. The

establishment of priorities is an iterative process and one that is revised at appropriate intervals as new data and knowledge become available

### **Risk management aspects**

The three classes of antimicrobial drugs that should be addressed as the highest priority for the development of risk management strategies with respect to antimicrobial resistance, as defined by the expert meeting, are: quinolones, 3rd and 4th generation cephalosporins, and macrolides. The bacteria of concern in terms of resistance to these groups of drugs are the foodborne pathogens *Salmonella* spp. and *Campylobacter* spp., and the commensal *Escherichia coli*.

The development and spread of antimicrobial resistance is a global public health problem that is affected by both human and non-human antimicrobial usage. All uses of antimicrobial agents lead to the emergence of antimicrobial-resistant micro-organisms and further promote the dissemination of resistant bacteria and resistance genes. Thus, a holistic approach is needed to best control the problems of antimicrobial resistance, one that takes into account the likely spread of resistant bacteria and resistance genes. This will involve not just the prudent use of antimicrobials, but also other actions such as hygiene measures, infection control, waste-water management and vaccination, all of which may decrease antimicrobial usage through prevention of infection and the disruption of spread of resistant bacteria.

The meeting identified and characterized preliminary risk management activities for antimicrobial resistance associated with food animals, and discussed the identification and selection of available risk management options. Such risks may be mitigated by health management measures such as infection control, good animal management practices, vaccination or development of alternatives to antimicrobials, and implementation of prudent use guidelines. Regulatory processes may need to be adjusted to consider antimicrobial resistance in the registration process for new antimicrobials or in cases where an extension of a therapeutic indication is being considered.

It was agreed that risk management decisions should be examined periodically when new scientific data become available, as well as when experience obtained from monitoring of risk management interventions warrants a review. This would include gathering and analysing data on antimicrobial use and antimicrobial resistance to provide a longitudinal review of food production and consumer health, and to determine the outcome of risk reduction measures taken.

### **Recommendations**

Recommendations to FAO, WHO, OIE and national governments were developed that address the risk analysis process of hazards related to antimicrobial resistance resulting from the use of antimicrobials in food animals:

1. Both lists of critically important antimicrobials should be revised on a regular basis (e.g. every second year) in a collaborative and coordinated approach by FAO, OIE and WHO.
2. When revising the lists of critically important antimicrobials, specific consideration should be given to a harmonized classification of cephalosporins, macrolides, aminoglycoside and tetracyclines, if possible to the compound level, taking into account that the resistance mechanism may be different for each generation of antimicrobial. With regard to the OIE list of critically important antimicrobials, it is suggested to further refine the categorization of critically important drugs with respect to their importance in the treatment of specific animal diseases.
3. The WHO and OIE lists of critical important antimicrobial agents and the considerations of the present expert meeting should be used when prioritizing drug+animal species+pathogen combinations for risk assessment.
4. If countries use an approach for risk prioritization as described in this document, it is recommended that they provide feedback to FAO, OIE and WHO on their success in implementing such a model, to assist in the further refinement and dissemination of these approaches at the national and international levels.
5. Antimicrobial resistance monitoring of foodborne pathogens and commensals (animal, human, food and commodity) should be implemented by all countries considering risk management

measures, to enable the detection of hazard and accurately assess the success of selected interventions. Ideally, quantitative standardized minimum inhibitory concentration methods should be applied.

6. Regions or countries lacking resources or experience for prioritization of critically important antimicrobial+animal species+pathogen combinations should seek cooperation with experienced regions or countries. The capacity of countries, particularly developing countries, needs to be enhanced to enable them to conduct surveillance of antimicrobial use and resistance, to implement intervention strategies to contain antimicrobial resistance, and to implement risk assessment approaches to support selection of risk management options. FAO, OIE and WHO should support such efforts.
7. Foodborne pathogens and commensals (in particular *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli*) linked to potential antimicrobial resistance to 3rd and 4th generation cephalosporins, quinolones and macrolides should be given special consideration for risk analysis.
8. The regulatory process should encompass elements that emphasize improvements in animal husbandry that lead to better animal health status and, consequently, decreases the need for antimicrobial use. When antimicrobial drugs are used, prudent use of these drugs should be promoted, particularly in respect of WHO and OIE identified critically important antimicrobials. Surveillance data for animals, humans and food are an integral part of ensuring correct regulatory policies and their effect in preventing and/or containing antimicrobial resistance.
9. Risk analysis of the release of human and animal effluents into aquatic environments, which serve as the growing grounds of fisheries, and aquaculture products needs to be performed, particularly with respect to the antimicrobials identified as critically important by WHO and OIE. Such risk analysis would determine the appropriate management options for where improved effluent management measures should be implemented (e.g. hospital effluents).
10. Risk assessment of antimicrobial resistance arising from the use of antimicrobials in animals should follow a structured approach comprising (i) release assessment; (ii) exposure assessment; and (iii) consequence assessment, as described in the OIE guidelines (Terrestrial Animal Health Code 2007, Appendix section 3.9.4). The existing international microbiological risk assessments (prepared by JEMRA) should be used in developing the exposure phase of the antimicrobial resistance risk assessment.
11. FAO, OIE and WHO are invited to strengthen their current collaboration to provide scientific advice in the field of antimicrobial resistance through the Joint FAO/WHO Expert meetings on Microbiological Risk Assessment (JEMRA) in collaboration with OIE.

## 1. PREAMBLE

A Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials was held from 26 to 30 November 2007 in Rome, Italy. This consultation was the fourth joint meeting of the three organizations since 2003.

The meeting was immediately preceded by a public stakeholders meeting, which was attended by representatives of organizations and institutions interested in the topic and by the participants of the expert meeting. The contributions given by representatives from the Danish Veterinary and Food Administration, the Federation of Veterinarians of Europe, the Institute of Food Technologists, the International Dairy Federation, the International Federation of Animal Health, and the World Veterinary Association have been made available through the FAO Website. See [http://www.fao.org/ag/agn/agns/micro\\_antimicrobial\\_en.asp](http://www.fao.org/ag/agn/agns/micro_antimicrobial_en.asp).

Mr Ezzeddine Boutrif, Director of the Nutrition and Consumer Protection Division of FAO, opened the meeting and welcomed the participants on behalf of the Director General of FAO. He stressed that FAO has contributed significantly to risk assessment and risk management in relation to antimicrobial resistance and food safety, and that this meeting was held as part of the joint FAO/WHO programme of work on the provision of scientific advice in food safety. The guidance obtained by this meeting would be used by the Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance. He emphasized that experts were asked to provide independent scientific advice and that they were acting in their own capacity and not on behalf of their institutions or governments.

Ms Awa Aidara-Kane, WHO, welcomed the participants on behalf of the Director General of WHO; she emphasized that antimicrobial resistance was a public health concern and that resistance to antimicrobial drugs had been addressed by WHO for many years. She highlighted the need for monitoring and containment of antimicrobial resistance, which requires a multi-sectoral approach. Emphasizing the role of critically important antimicrobials for human health, she underlined the need to keep them working while taking into consideration the needs for animals.

On behalf of the Director General of OIE, Ms Tomoko Ishibashi welcomed the experts and outlined the organization's expectations of the consultation, notably to provide recommendations on how OIE can best contribute to the overall objective of containment of antimicrobial resistance through controlling the use of antimicrobials in animals while fulfilling its responsibility to animal health and welfare, and through a steady supply of animal protein to humans.

Dr Scott McEwen was elected as Chairperson for the meeting, and Dr Paula Fedorka-Cray was appointed as Rapporteur.

### 1.1 Background

The Expert Meeting was convened as a continuation of the consultative process on this subject initiated jointly by FAO, OIE and WHO in 2003, following the recommendations of the 48th Session of the Executive Committee of the Codex Alimentarius Commission in 2001. The objective of this process was to discuss issues related to the use of antimicrobials in agriculture (including aquaculture) and veterinary medicine, taking into account the role played by antimicrobials as essential human and veterinary medicines. In response to this request, FAO, OIE and WHO organized three Expert Meetings: a first workshop on questions related to risk assessment was held in Geneva, Switzerland, in December 2003 (FAO/WHO/OIE, 2003), which was followed by a workshop on risk management options held in March 2004 in Oslo, Norway (FAO/WHO/OIE, 2004). The third consultation, specific to aquaculture, was held in Seoul, Republic of Korea, in June 2006 (FAO/WHO/OIE, 2006).

The concept of critically important antimicrobials was discussed by the first two workshops. The 2003 workshop, held in Geneva, concluded that antimicrobial classes that provide specific treatment or one of a limited number of treatments for serious human diseases or pathogens that cause foodborne diseases should be classified as 'critically important' and recommended that an expert clinical medical group appointed by WHO should define such antimicrobials. The 2004 workshop, convened in Oslo, recommended that the concept of critically important antimicrobials for human medicine should be developed by WHO, with a view to enabling specific resistance-preventive actions for these antimicrobials in the context of non-human use. It was also recommended that a similar list of

critically important antimicrobials for animals would be pursued by the OIE. A possible overlap of both critical lists for human and veterinary medicine would provide further information and allow an appropriate balance to be struck between animal health needs and public health considerations.

WHO organized a working group consultation in Canberra, Australia, in 2005 and issued lists of critically important, highly important and important antibacterial agents for human medicine (WHO, 2005). A second WHO Expert Meeting on critically important antimicrobials took place in Copenhagen in May 2007 to update the lists, as recommended in Canberra, taking into account recent developments in antimicrobial resistance and recommendations made by the WHO Expert Committee on the Selection and Use of Essential Medicine in March 2007 (WHO, 2007).

The OIE, through its *ad hoc* Group on antimicrobial resistance, organized a consultation involving all member countries and international organizations having signed a cooperation agreement with the OIE and, based on this consultation, issued a first list of antimicrobials of veterinary importance. A resolution was adopted during the General Session in May 2006 asking to refine the list. A refined list of veterinary important antimicrobials for food-producing animals was adopted by the OIE General Session in May 2007.

## 1.2 Objectives

The objectives of the expert meeting reported here were to consider both lists of critically important antimicrobials developed by WHO and OIE in order to:

- find an appropriate balance between animal health needs and public health considerations, taking into account the overlap of the two lists;
- identify, as far as feasible, the current and potential hazards to public health resulting from this overlap;
- identify the combinations of human pathogen+antimicrobial use+animal species that could be considered by risk managers as the priority combinations in terms of risk-benefit assessment for future consideration;
- review current management strategies and options for maintaining the efficacy of critically important antimicrobials for humans and animals; and
- provide recommendations on future FAO, OIE and WHO activities.

## 1.3 Organization of the Expert Meeting

The meeting was jointly organized by the Animal Production and Health Division, the Nutrition and Consumer Protection Division and the Fish Products and Industry Division of FAO, the Department of Food Safety, Zoonoses, and Foodborne Diseases of WHO, and the World Organisation for Animal Health (OIE). This process followed the principles of the joint FAO/WHO framework for the Provision of Scientific Advice on Food Safety and Nutrition (FAO/WHO, 2007), the rules for OIE scientific bodies, and other applicable rules of FAO, OIE and WHO for Expert Meetings.

The experts invited to the meeting were selected following standard procedures developed by FAO, OIE and WHO for selecting and designating experts that assure transparency, excellence and independence of the opinions expressed by these experts. Invited experts were asked to declare possible conflicts of interest; no such conflicts relevant to the discussions of the meeting were identified.

To ensure that the expert meeting had at its disposal all available and relevant information, FAO, OIE and WHO invited all interested parties to provide any relevant information and data, particularly information that might not be readily available in the public domain. Data on the following subjects were requested: (1) New developments of risk-benefit assessment of antimicrobial use in humans and animals; and (2) Management strategies and options to maintain the efficacy of critically important antimicrobials for humans and animals. Appendix G lists all documents submitted to the Joint Secretariat.

#### **1.4 Working procedures**

The expert meeting met in plenary sessions and in working groups. Before the meeting the Joint Secretariat had solicited topics for presentations from the meeting's participants; these papers were presented in plenary as outlined in the agenda (Appendix E) adopted at the beginning of the meeting.

The expert meeting addressed the issues in three working groups:

- Working group I: Critically important antimicrobials – the concept.  
Chair person: P. Collignon, and Rapporteur: S. Soback.
- Working group II: Identification of priority combinations for risk assessment.  
Chair person: R. Kroger, and Rapporteur: F. Aarestrup.
- Working group III: Review of and proposals for risk management measures.  
Chair person: P. Collignon, and Rapporteur: S. Soback.



## 2. CRITICALLY IMPORTANT ANTIMICROBIALS – THE CONCEPT

### 2.1 Scope

The expert meeting considered issues related to resistance to antimicrobials arising from transmission of such resistant micro-organisms from food and foodborne infections, and based its discussions on the results of previous meetings on the subject held within the joint FAO/WHO/OIE framework for discussions of antimicrobial resistance resulting from the non-human use of antimicrobials.

According to the meeting's terms of reference, only antimicrobial use in food-producing animals was considered; use in non-food-producing animals was excluded from the discussions. Antimicrobial use in non-food-producing animals should be subject to the prudent use provisions of the OIE Terrestrial Animal Health Code. The meeting recognized that some antimicrobials are used more broadly in agriculture in plant protection products. For example, streptomycin, gentamicin and oxytetracycline are used in many countries, and it was noted that there are no Codex standards addressing such use at the international level.

The expert meeting based its deliberations on the Report of the 2nd WHO Expert Meeting on critically important antimicrobials (Appendix A; WHO, 2007) and the list of veterinary important antimicrobials for food-producing animals, as adopted by the OIE General Session in May 2007 (Appendix B).

### 2.2 The WHO list of critically important antimicrobials

The WHO list of critically important antimicrobials was based on the following criteria for categorization as developed by two Expert Meetings (WHO, 2005; WHO, 2007):

- **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 caused by organisms that may acquire resistance genes from non-human sources.

The definitions of the different categories were as follows:

*Critically important* antimicrobials are those that meet criteria 1 and 2

*Highly important* antimicrobials are those that meet criteria 1 or 2

*Important antimicrobials* are those that meet neither criteria 1 nor 2

The detailed explanations of the reasoning of the WHO Expert Meetings were as follows.

#### 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 (as reproduced in Appendix A of this document) 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 bacteria in question. The panel included in the Comments section of the table (where appropriate; as reproduced in Appendix A of this document)

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 by the first WHO expert consultation 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 period 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.

The WHO panel had 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 was 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.

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

The antimicrobials and their categorization according to these criteria, as agreed by the 2nd WHO Expert Meeting in 2007, are listed in the first comprehensive table of Appendix A of this report. The following table (Table 1) is a condensed collation of the grouping of antimicrobial classes in the three categories.

**Table 1.** Categorization of antimicrobials used in human medicine according to importance in treatment of disease

Critically important antimicrobials	Highly important antimicrobials	Important antimicrobials
Aminoglycosides	Amidinopenicillins	Cyclic polypeptides
Ansamycins	Aminoglycosides	Fosfomycin
Carbapenems	Amphenicols	Fusidic acid
Cephalosporins (3rd & 4th generation)	Cephalosporins (1st & 2nd generation)	Lincosmides
Glycopeptides	Cephamecins	Mupirocin
Macrolides	Clofazimine	Nitrofurantoin
Oxazolidinones	Monobactams	Nitroimidazoles
Penicillins (natural, aminopenicillins & antipseudomonal)	Penicillins (antistaphylococcal)	
Quinolones	Polymyxins	
Streptogramins	Sulfonamides	
Tetracyclines		
Drugs used solely to treat tuberculosis or other mycobacterial diseases		

### 2.3 Prioritization within the WHO category of critically important antimicrobials

The 2nd WHO Expert Meeting, in 2007, was asked to prioritize the antimicrobial agents within the critically important category, in order to allow allocation of resources to those agents for which management of the risks from antimicrobial resistance are needed most urgently. The panel considered drugs of greatest priority when (1) there are relatively large absolute numbers of people affected with diseases for which the drug is the sole or one of few alternative therapies, (2) the overall frequency of

use of the drugs in human medicine for any use (whether appropriate or inappropriate) is relatively large, and (3) the drug is used to treat disease due to pathogens for which there is a greater degree of confidence in transmission of bacteria or their genes from non-human sources to humans (*E. coli*, *Campylobacter* spp. and *Salmonella* spp.).

In addition, given their charge to prioritize agents within the *critically important* category, the experts focused the two criteria developed by the previous expert consultation in Canberra (2005) 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 or 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** Antibacterial used to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused 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* spp.).

Those drugs that meet all three of criteria 1.1, 1.2 and 2.1 should be categorized according to the 2nd WHO Expert Panel as being of highest priority. Table A2 of Appendix A contains the result of this prioritization.

Prioritization resulted in designation of the following classes of antimicrobials for which comprehensive risk management strategies were needed most urgently (Table 2).

It was noted that the WHO Expert Panel had 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.

**Table 2.** Prioritized critically important antimicrobials

Cephalosporins (3rd & 4th generation)
Macrolides
Quinolones

## 2.4 The OIE list of critically important antimicrobials

Following a recommendation from the 2nd Joint FAO/WHO/OIE Expert Meeting in Oslo (2004), the OIE initiated the process of developing a list of critically important antimicrobials in veterinary medicine. The fundamental aim of this list is to safeguard the efficacy and availability of veterinary antimicrobial products for animal diseases where there are few or no alternatives. Additionally, the following utilities were expected:

- To help veterinarians in their choice of the appropriate therapeutic agent.
- To complement the OIE guidelines for responsible and prudent use of antimicrobial agents.
- To serve as a useful information base to support science-based risk assessment of antimicrobial resistance.

The critically important antimicrobials in veterinary medicine were defined as

“... antimicrobials used for the treatment, prevention and control of serious animal infections that may have important consequences on animal health and welfare, public health or important economic consequences and where there are few or no alternatives.”

## 2.5 Development of the OIE list

The work was assigned to the OIE *ad hoc* Group on Antimicrobial Resistance, consisting of experts,

which reports to the OIE Biological Standard Commission. The OIE list was developed on the basis of replies to a questionnaire sent to all 167 OIE member countries and four international organizations that have signed a cooperation agreement with OIE. This methodology was chosen to reflect, to the extent possible, the real use and need of antimicrobials under various conditions among OIE member countries worldwide.

In this questionnaire the following four basic topics were explored:

- Animal species.
- Disease treated and causative microbe:
  - Seriousness
  - Economic importance.
- Antimicrobials used:
  - Type of use (treatment/prevention/control)
  - Route
  - Accessibility of the product
  - Quality of the substance.
- Specific rules of usage for the country concerned.

It should be noted that the questionnaire also requested “justification” for each of the antimicrobials that a country considered critical (whether an alternative exists or not).

Replies were received from 62 member countries (including 46 developing countries) and four international organizations (66 in total). This response rate highlights the importance given to this issue by OIE member countries from all regions. These replies were analysed first by the OIE Collaborating Centre for Veterinary Drugs, and then discussed by the *ad hoc* Group. Finally, data from 60 member countries and 2 international organizations were included in the analysis. A list of proposed veterinary critically important antimicrobials was compiled and endorsed by the Biological Standards Commission, and circulated among member countries aiming for adoption by the OIE International Committee during the General Session in May 2006.

The list was submitted to the 74th International Committee, where active discussion took place among member countries. While many member countries appreciated the work, it was considered appropriate to continue refinement of the list, including further division into sub-categories. The list was therefore adopted as a preliminary list.

The *ad hoc* Group prepared its final recommendations of the list of antimicrobials of veterinary importance. Once again, this was examined and endorsed by the Biological Standards Commission, in its January 2007 meeting, and circulated among member countries. The refined list was submitted to the 75th International Committee during the General Session in May 2007, and adopted unanimously. The full list is presented as Appendix B of this report.

The following issues should be noted when referring to this list: the list refers only to antimicrobial use in food-producing animals (antimicrobial use in non-food-producing animals should be subject to the prudent use provisions of the OIE Terrestrial Animal Health Code); all compounds included in the list are used for treatment, prevention or control of disease in animals in at least one country, but for the majority in many countries worldwide; chloramphenicol and some other substances, use of which are banned in many countries in food-producing animals, are not included in the list; and antimicrobials used solely as growth promoters are not included in the list.

## 2.6 Criteria used for categorization of veterinary antimicrobials

In developing the list, it was agreed that any antimicrobial authorized for use in veterinary medicine according to the criteria of quality, safety and efficacy, as defined in the Terrestrial Animal Health Code (Appendix 3.9.3. Guidelines for the responsible and prudent use of antimicrobial agents in Veterinary Medicine) is *important*. Therefore, all antimicrobials used in food-producing animals were addressed to provide a comprehensive list, divided into *critically important*, *highly important* and *important* antimicrobials.

When defining the importance of veterinary antimicrobials, one very important difference between

the use of antimicrobials in humans and animals that needs to be considered is that in veterinary medicine many different animal species have to be treated. This is in contrast to human medicine, where only one species (humans) is treated.

The following criteria were selected to determine the degree of importance for classes of veterinary antimicrobials.

- Criterion 1** Response rate to the questionnaire regarding Veterinary Critically Important Antimicrobials.  
*This criterion was met when a majority of the respondents (more than 50%) identified the importance of the antimicrobial class in their response to the questionnaire.*
- Criterion 2** Treatment of serious animal disease and availability of alternative antimicrobials.  
*This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.*

On the basis of these criteria, the following three categories were established:

- Veterinary *critically important* antimicrobials are those that meet criteria 1 and 2
- Veterinary *highly important* antimicrobials are those that meet criteria 1 or 2
- Veterinary *important* antimicrobials are those that meet neither criteria 1 nor 2.

The following table (Table 3) is a condensed collation of the grouping of the three categories of antimicrobial agents.

**Table 3.** Categorization of antimicrobials used in veterinary medicine according to their importance in treatment of disease

<b>Veterinary critically important antimicrobials</b>	<b>Veterinary highly important antimicrobials</b>	<b>Veterinary important antimicrobials</b>
Aminoglycosides	Rifamycins	Bicyclomycin
Cephalosporins	Fosfomycin	Fusidic Acid
Macrolides	Ionophores	Novobiocin
Penicillins	Lincosamides	Orthosomycins
Phenicols	Pleuromutilins	Quinoxalines
Quinolones	Polypeptides	Streptogramins
Sulfonamides		
Tetracyclines		

It is to be noted that within the category of veterinary highly important antimicrobials, some classes are critically important for a particular animal species or for particular therapeutic indications.

The OIE list strives to address the complexity of veterinary medicine and avoid simplistic recommendation for diagnosis and treatment; to recognize the geographical diversity of the problems related to food animal production; to identify factors to be considered for risk analysis; to identify targets for strengthening implementation of the prudent use of antimicrobials; frame efforts to be made regionally for the responsible use of veterinary critically important antimicrobials with respect of the human and animal health and the containment of antimicrobial resistance; and to define the need for rules regulating antimicrobials authorization and coordination of such rules between countries.

## 2.7 Comparison of the WHO and OIE lists on the importance of antimicrobial classes

The comparison of the human and veterinary lists developed by WHO and OIE, respectively, shows

that most antimicrobial classes are used in both human and in veterinary medicine.

However, when just the *critically important* antimicrobials are examined (see Table 4) a number of classes appear only on the WHO list, namely carbapenems, ansamycins, glycopeptides, streptogramins and oxazolidinones, whereas the classes (compound groups) considered only as critically important for animal health by OIE were phenicols, sulfonamides and diaminopyrimidines, and tetracyclines. For a limited number of classes there is an overlap where both WHO and OIE have defined them as “critically important” for human and animal health, respectively. These are the 3rd and 4th generation cephalosporins, quinolones, macrolides, penicillins and aminoglycosides.

There is potential for confusion with the classes of tetracyclines, quinolones and cephalosporins, as they appear to have been defined in different ways by the WHO and OIE lists. The only tetracycline in the WHO critically important list is a glycylycylcline (tigecycline), the other class members are categorized as highly important. Due its resistance mechanisms, tigecycline is regarded as representing a different generation to other tetracyclines.

All quinolones and fluoroquinolones in the WHO list of critically important antimicrobials were grouped together in the same class, because when resistance develops to quinolones (e.g. nalidixic acid) then this is the first step in the development of high-level resistance in most bacteria to fluoroquinolones. In addition, when resistance is present to quinolones, this may result in reduced susceptibility to fluoroquinolones, resulting in antimicrobial treatment with fluoroquinolones being less effective and sometimes ineffective (e.g. Salmonellosis).

In the WHO list of critically important antimicrobials, the cephalosporins were separated into two different groups; 1st/2nd generation cephalosporins and 3rd/4th generation cephalosporins, based on the different resistance mechanisms in these two groups.

When viewed together, the WHO and OIE lists demonstrate that critically important antimicrobials are needed in both human and food animal therapy. Few of them are exclusively used in humans; others are used in both groups. This overlap highlights the need to have in place antimicrobial resistance surveillance and to identify and implement appropriate management measures in order to mitigate resistance dissemination and maintain the efficacy of the drugs. Prudent use of all antimicrobials is considered essential.

**Table 4.** Comparison of the human clinically important antimicrobials and veterinary clinically important antimicrobials lists

Critically important antimicrobials used in human medicine	Veterinary critically important antimicrobials
Aminoglycosides	Aminoglycosides
Cephalosporins (3rd and 4th generation)	Cephalosporins
Macrolides	Macrolides
Penicillins (natural, aminopenicillins and antipseudomonal)	Penicillins
Quinolones	Quinolones
Tetracyclines (only tigecycline)	Tetracyclines
Ansamycins	
Carbapenems	
Glycopeptides	
Oxazolidinones	
Streptogramins	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	Phenicols Sulfonamides

### 3. PRIORITIZING COMBINATIONS OF ANTIMICROBIAL AGENTS AND FOOD ANIMAL SPECIES FOR RISK ASSESSMENT

#### 3.1 Introduction and general comments

A risk assessment, especially a quantitative assessment, can be time consuming and expensive, thus it is necessary to set priorities. This report provides tools for risk managers to prioritize and rank combinations of drugs+animal species+pathogens for which to commission risk assessments.

At the national level, the competent national authority should always assess the possible impact on human safety with respect to antimicrobial resistance before granting approval of a new antimicrobial agent. For the purpose of this chapter, any human health concerns that might arise from approval and use of new antimicrobial classes for food-producing animals are therefore not considered.

The second WHO Expert Meeting on critically important antimicrobial for human use (WHO, 2007) recommended that three classes of antimicrobial drugs should be addressed as the highest priority for the development of risk management strategies with respect to antimicrobial resistance: quinolones, 3rd & 4th and fourth generation cephalosporins, and macrolides. Resistance against these groups of drugs is detected in foodborne pathogens, namely *Salmonella* spp. and *Campylobacter* spp., and the commensal *Escherichia coli*. Thus, the identification of these three classes is recognized as a first step to identify the priority groups of drugs and bacteria of concern. The considerations of the other critically important antimicrobials could warrant inclusion of commensal enterococci in the list of priorities.

The comparison of both lists discussed in the previous section made clear that there is an overlap for these three classes; all three are therefore an issue for prioritizing risk assessments.

The meeting agreed that the OIE guideline on risk assessment for antimicrobial resistance (OIE Terrestrial Animal code 2007, Appendix 3.9.4) could be used as a good basis for the initial prioritizing of areas where to perform risk assessments.

#### 3.2 Key principles to rank antimicrobial resistance hazards

The meeting identified key principles that any prioritization scheme for the risk assessment of antimicrobial resistance resulting from the use of antimicrobials in food animals should follow. These key principals include:

- Objectivity.
- A simple and transparent approach.
- The prioritization scheme should be practical and adaptable to real-life situations.
- Use for commissioning the risk assessment.
  - It should be based on robust data where available.
  - It should be used to identify data gaps for targeted research.
- An iterative process as new data and knowledge become available.
- Identification of hazards that should be used as a basis to start risk assessment.

#### 3.3 Data needs to identify priority combinations

Data needs for prioritizing foodborne risks have been provided by several guidelines from international organizations, such as Codex Alimentarius, FAO, OIE and WHO. The information used for prioritizing should be the most significant with regard to the hazard.

The fundamental requirement to begin any prioritizing process is surveillance data on the occurrence of antimicrobial resistant bacteria in the food chain causing infections in humans, and the most important food commodities and the extent of usage of antimicrobial agents for these food-producing animal species. Surveillance data on the prevalence of the foodborne bacteria in the

different food commodities from the origin animal species concerned should also be included.

The priority for collection of data should start from the WHO list of critically important antimicrobials. Thus, priority should be given to the collection data on resistance to fluoroquinolones and cephalosporins in *Salmonella* spp., and to fluoroquinolones and macrolides in *Campylobacter* spp.

It is important to identify the mechanism of resistance because some are more easily selected and disseminated in the foodborne bacteria than others. Ideally, surveillance and monitoring data should be based on determinations of the minimum inhibitory concentrations of the pathogen to the antimicrobial agents in question.

### 3.4 Criteria for establishing priorities

When prioritizing modes of use and animal species for risk assessment, focus should be on where data are available and on the appropriate combination of animal species+antimicrobial agent+foodborne pathogen.

When developing the criteria, the following questions and the answers to them are important:

- Is the antimicrobial agent used as a preferred treatment for foodborne pathogens in humans?
- What is the incidence of the foodborne disease?
- What is the severity of the foodborne disease?
- Is the antimicrobial agent a common treatment for a target pathogen?
- What is the animal species where the antimicrobial agent is used?
- What is the volume of antimicrobial used and route of administration?
- Are there monitoring data available on antimicrobial resistance?
- What is the frequency, extent and mode of use, including route of administration, dose scheme and duration of treatment?
- Is the drug used for a severe and common animal disease?
- Is there off-label use of the antimicrobial agent?
- Is the antimicrobial agent used without veterinary prescription?
- Is there evidence of emerging resistance in bacterial isolates from humans, food or animals?
- What is the prevalence of resistant bacteria among humans, food and animals?
- What is the volume of consumption of the food commodities from a given animal species?
- What is the extent of international trade in the food commodities?
- What is the prevalence of foodborne bacteria among the different foods?
- What is the potential environmental persistence of the antimicrobial agent and the resistant bacteria?
- What is the potential environmental dissemination?

Based on these questions, the following criteria for establishing priorities for risk assessment are proposed:

- Chemical, physical and pharmacological properties of the antimicrobial agent.
- Extent of veterinary use of the antimicrobial agent.
- Purpose of use.
- Route of administration.
- Prevalence of resistance in the primary production stage.
- Food consumption.

- Prevalence of bacteria in food.
- Antimicrobial resistance in bacteria isolated from food.
- Recommended treatment in humans.
- Incidence of the disease in humans.
- Severity of the disease in humans.

### **3.5 Using the criteria – three possible approaches**

There might be differences in the application of the abovementioned criteria by single countries and at the international or regional level. The meeting considered three different approaches that might be used to combine these criteria into a final prioritization process at the individual country level or at international level. The use of any approach should result in an output that prioritizes for risk assessment the combination of antimicrobial agent, the species of animal and the foodborne bacterium. The WHO and OIE lists of critically important antimicrobials should be considered when establishing priorities.

#### **Approach I**

Group the criteria into three main categories: *release*, *exposure* and *consequence*, as follows:

##### **Release**

- Chemical, physical and pharmacological properties of the antimicrobial agent.
- Extent of use of the antimicrobial in animal.
- Purpose of use (treatment, prevention...).
- Route of administration.
- Occurrence and prevalence of resistance in the target animal species (primary production stage).

##### **Exposure**

- Food consumption.
- Prevalence of bacteria in food.
- Prevalence of resistance in bacteria isolated from food.

##### **Consequence**

- Recommended treatment in humans.
- Incidence of the disease.
- Severity of the disease.

When using the categorization of the criteria, one possibility is to put a score for each category (e.g. 1, 2, 3; or high, medium, low). This approach can either put equal weight on each main category (release, exposure and consequence) or be adjusted to put more weight on the consequence estimates. It was noted that the abovementioned criteria are similar to some of the elements developed in FDA/CVM Guidance #152 (FDA, 2003).

#### **Approach II**

The criteria could be used in a decision tree. In this case, the prioritization is initially based on the observed consequences for human health.

##### **Consequence**

- Preferred antimicrobial treatment for infections caused by foodborne pathogens in humans.

- Incidence of the transmitted disease, based on surveillance data.
- Severity of the transmitted disease.

⇒ Take the antimicrobial+bacterium combination(s) of highest score and continue with the *exposure* category.

### Exposure

- Food consumption.
- Prevalence of bacteria in food.
- Prevalence of resistance in bacteria isolated from food.

⇒ Select the food commodities of main importance and continue with *release* category.

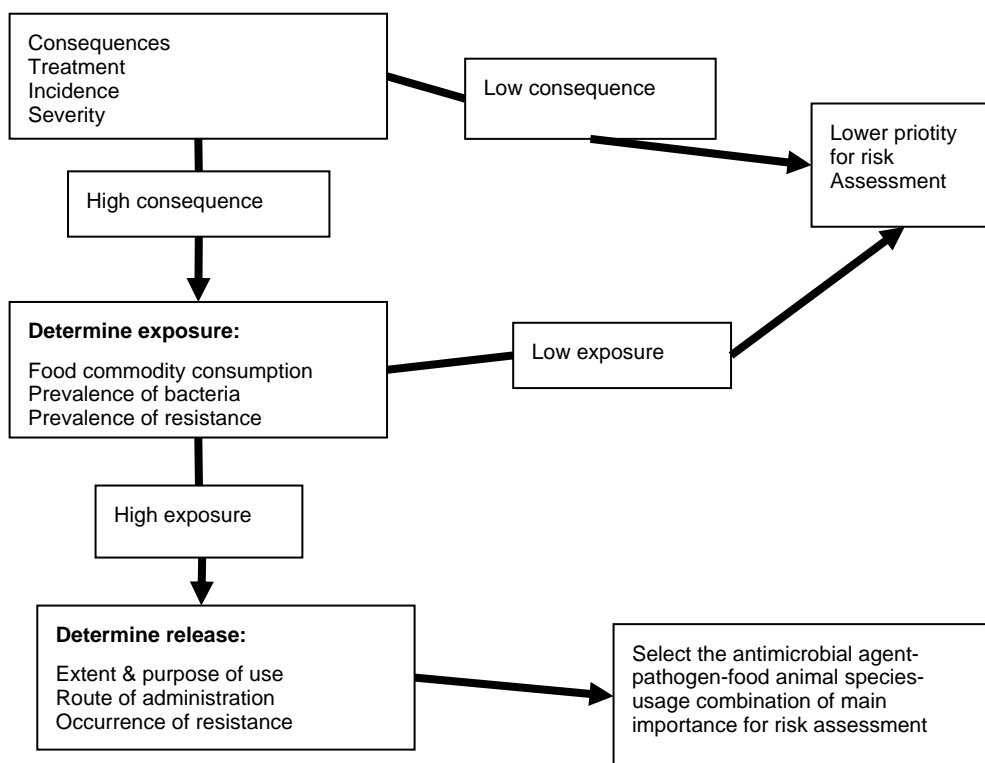
### Release

- Extent of use of the antimicrobial in animals.
- Purpose of use (treatment, prevention...).
- Route of administration.
- Occurrence and prevalence of resistance in the target animal species (primary production stage).

⇒ Select the antimicrobial agent+pathogen+food animal species+usage combination of main importance for risk assessment.

In this approach, only those combinations of antimicrobial resistance+animal species with the highest consequences for human health are examined further. For those combinations, information concerning exposure should be obtained. Subsequently, for food commodities responsible for the highest exposure to the hazard, data concerning the use of the drug in the relevant animal species should be collected.

The decision tree of Approach II is depicted below as a flow diagram.



### Approach III

Prioritization exercises could use the questions in Section 4.4 and further develop them into a shorter

list of criteria, which could then be used to set priorities at the national and international level. The meeting prepared an example of this approach.

### Criteria

1. Frequency and severity of human disease caused by hazard and preferred treatment for that hazard
2. Exposure to hazard through food
  - Consumption of food from a given animal species
  - Prevalence of foodborne bacteria in food
  - Prevalence of resistance in bacteria isolated from food
3. Frequency and severity of animal disease treated with the antimicrobial drug
  - Extent and diversity of use in the animal species
4. Extent of international spread of the hazard via traded food

The information available for each criterion may be summarized using a table that is formatted to reflect the antimicrobial drug being assessed in the first column, followed by the bacterial species of interest, then animal species. An application of the criterion is listed under rationale, and follows the criteria 1 through 4, as listed above. The meeting developed this approach further in Table 5. It should be noted that Table 5 is presented for example purposes only, as the meeting did not have the time necessary to review or have access to all relevant data sets to apply this approach comprehensively. Thus, Table 5 does not provide a rank or order of priority drug+bacteria+animal species, and is not intended to give recommendations.

This approach can be used to prioritize those combinations of antimicrobial agents and food animal species for which risk assessments should be done first at an international level.

**Table 5.** Example of Approach III for prioritization for risk assessment purposes of the combination of antimicrobial agent, the species of animal, and the foodborne bacterium

Drug	Bacterial species	Animal species	Rationale (available information for the four criteria) 1. Frequency and severity of human disease 2. Exposure to hazard through food 3. Frequency and severity of animal disease 4. International trade
Fluoro-quinolones	Salmonella	Poultry	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. One of the highest commodities consumed worldwide. The pathogen is frequently found in the food product and a high prevalence of resistance can be found in some countries. Microbiological risk assessment for the pathogen and commodity is available at the international level. 3. Common short-term treatment for <i>E. coli</i> in a wide number of countries and is administered to entire flocks through water. 4. Poultry traded to a large extent worldwide.
Fluoro-quinolones	Salmonella	Cattle	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. The food is frequently consumed and the pathogen is frequently found, primarily in ground product and less in whole meats in some countries. Resistance is not as frequent as in other commodities and may be particularly low in some countries. 3. Short-term treatment for a range of bovine diseases, which may vary between countries. Used to treat individual animals. 4. Beef traded to a large extent worldwide.

Drug	Bacterial species	Animal species	<b>Rationale (available information for the four criteria)</b> 1. Frequency and severity of human disease 2. Exposure to hazard through food 3. Frequency and severity of animal disease 4. International trade
Fluoro-quinolones	Salmonella	Pigs	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. Consumed worldwide. The pathogen is frequently found in ground product and less in whole meats. Resistance is low in most countries. 3. Used for short-term treatment for a range of porcine diseases, which may vary widely between countries. Used to treat individual animals. Is not licensed in some countries. 4. Pork traded to a large extent worldwide.
3rd and 4th generation Cephalosporins	Salmonella	Poultry	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. One of the highest commodities consumed worldwide. The pathogen is frequently found in the food product and a high prevalence of resistance can be found in some countries and is usually serovar dependent. Microbiological risk assessment for the pathogen and commodity is available at the international level. 3. Limited approved use for day-old chicks in some countries, but extensive extra-label use for eggs or day-old chicks in some countries. 4. Poultry traded to a large extent worldwide.
3rd and 4th generation Cephalosporins	Salmonella	Cattle	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. The food is frequently consumed. The pathogen is frequently found, primarily in ground product and less in whole meats in some countries, and resistance can be found in some countries and is usually serovar dependent. Resistance is not as frequent as in some other commodities. 3. Common short-term treatment for bovine mastitis in some countries. Used to treat individual animals for beef and more widely for other types of cattle. 4. Beef traded to a large extent worldwide.
3rd and 4th generation Cephalosporins	Salmonella	Pigs	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and the pathogen is known to cause severe diseases in humans, which may vary by serovar. 2. The food is frequently consumed. The pathogen is frequently found, primarily in ground product and less in whole meats in some countries, and resistance can be frequently found in some countries and is usually serovar dependent. 3. Used in pigs, primarily at the pen level. 4. Pork traded to a large extent worldwide.
Fluoro-quinolones	Campylobacter	Poultry	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequently occurring gastrointestinal disease. 2. One of the foods most consumed worldwide. The pathogen is very frequently found in the food product and a high prevalence of resistance can be found in some countries. 3. Common short-term treatment for <i>E. coli</i> in a wide number of countries and must be administered to entire flocks through the water. 4. Poultry traded to a large extent worldwide.
Fluoro-quinolones	Campylobacter	Cattle	1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequently occurring gastrointestinal disease. 2. The food is frequently consumed. The pathogen is frequently found. Resistance is not as frequent as in other commodities, and may be particularly low in some countries. 3. Short-term treatment for a range of bovine diseases, which may vary between countries. Used to treat individual animals. 4. Beef traded to a large extent worldwide.

Drug	Bacterial species	Animal species	Rationale (available information for the four criteria) <i>1. Frequency and severity of human disease</i> <i>2. Exposure to hazard through food</i> <i>3. Frequency and severity of animal disease</i> <i>4. International trade</i>
Fluoro-quinolones	Campylobacter	Pigs	<p>1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequently occurring gastrointestinal disease.</p> <p>2. The food is consumed worldwide. The <i>Campylobacter</i> species found in pigs is <i>C. coli</i>, which accounts for approximately 5% of human infection. Resistance is very frequent.</p> <p>3. Used for short-term treatment for a range of porcine diseases, which may vary widely between countries. Used to treat individual animals. Is not licensed in some countries.</p> <p>4. Pork traded to a large extent worldwide.</p>
Macrolides	Campylobacter	Poultry	<p>1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease.</p> <p>2. One of the foods most consumed worldwide. The pathogen is very frequently found in the food product and a high prevalence of resistance can be found in some countries. Resistant varies widely between countries.</p> <p>3. May be used in feed.</p> <p>4. Poultry traded to a large extent worldwide.</p>
Macrolides	Campylobacter	Cattle	<p>1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease.</p> <p>2. The food is frequently consumed. The pathogen is frequently found, primarily in ground product and less in whole meats in some countries. Resistance is not as frequent as in other commodities and may be particularly low in some countries</p> <p>3. Infrequently used in the individual animal.</p> <p>4. Beef traded to a large extent worldwide.</p>
Macrolides	Campylobacter	Pigs	<p>1. The antimicrobial agent is on the WHO list of critically important antimicrobials and is a preferred empiric treatment for a frequent gastrointestinal disease.</p> <p>2. The food is consumed worldwide. The <i>Campylobacter</i> species found in pigs is <i>C. coli</i>, which accounts for approximately 5% of human infection. Resistance is very frequent.</p> <p>3. Used for growth promotion and group treatment for a range of porcine diseases, which may vary widely between countries. Used in feeds.</p> <p>4. Pork traded to a large extent worldwide.</p>

### 3.6 Comparison of the three approaches

The meeting discussed briefly the pros and cons of each approach. While recognizing that further work is needed to develop them, the approaches described were considered to provide a good starting point. The selection and application of one of them should be undertaken taking into consideration the pros and cons listed below (Table 6). The experience gained in their application will be a valuable contribution to further work on developing an optimal approach.

Further work is needed to develop the Table 5 explained in Approach III. The experts did not believe that they had sufficient time and information to accurately rank the combinations. A similar approach and prioritization exercise in a related area undertaken by JEMRA for the Codex Committee on Food Hygiene required three months of data gathering and analysis prior to adoption of a final recommendation regarding the priority ranking.

**Table 6.** Comparing the pros and cons of the three approaches.

Approach	Pro	Con
I	Allows a semi-quantitative assessment based on data from all categories.	A disadvantage is that there is a need to have available data on all categories before risk prioritizations can be done. If equal weights are put on all categories, there is a risk that the outcome might either under- or over-estimate the human health consequences.
II	A decision tree has the advantage that only information from what is considered the most important animal species needs to be obtained	It has the disadvantage of potentially overlooking important factors in the entire picture.
III	It has the advantage of being simple, can be customized at the national level and can be performed when limited information is available. Is easily understandable and can be done immediately.	It may not be sufficiently robust to provide a ranking at a class level, and will require additional criteria at the drug level.

### 3.7 Analysis of current risk assessment models and examples

The experts reviewed examples of available qualitative and quantitative risk assessment models and approaches for the assessment of human health risks from the use of critically important antimicrobials in food-producing animals. Most of these assessments have focussed on resistance to critically important antimicrobials in *Salmonella* spp., *Campylobacter* spp. and enterococci. OIE has provided an extensive framework on how to perform a quantitative risk assessment for antimicrobial resistance (Appendix 3.9.4. of the Terrestrial Animal Health Code). Qualitative approaches adopted from these OIE guidelines are now being used by regulatory authorities in several countries to conduct pre-approval assessment of antimicrobials (e.g. FDA/CVM Guidance #152). It should be possible for most countries in the developed and developing world to adopt such qualitative pre-approval assessment approaches.

In addition, quantitative risk assessments have been conducted on antimicrobials currently approved for use in several countries (e.g. fluoroquinolones, streptogramins). One such assessment, conducted by FDA/CVM, was used in the decision to withdraw the approval of enrofloxacin for the therapy of bacterial infection in poultry. Other assessments were used to inform stakeholders of resistance risks where the drug remained authorized after the assessment. While informative, these quantitative risk assessments show that there are major gaps in available information, which severely limits their ability to accurately estimate the risks to human health from the use of critically important antimicrobials in food animals. It is apparent that undertaking such quantitative risk assessments is very demanding on human and financial resources. It is also clear that the expertise to conduct and independently review these assessments is scarce at the international level. Review of these assessments highlights the importance of transparency in presenting the outputs, and it was noted that, to be successful in guiding risk management, risk managers must provide assessors with clear, focused questions.

#### **Identified data gaps for risk assessment**

- Data on occurrence of antimicrobial resistant foodborne bacteria isolated from infections in humans, food commodities and food animals worldwide.
- Data on species-related drug usage with regard to the animal species treated, including indications.
- Application of available PK/PD data in the development of drug use that may vary on a regional level.
- Adoption of the methodology for, and harmonization of, the use of MICs is necessary for assessment of efficacy results.
- More specific information is needed on the frequency of transfer of genetic elements and the dissemination of resistant bacteria in the environment. This may require expanded efforts to assess reservoirs of bacteria and genetic elements.
- Information on the link between resistance, virulence and/or fitness of the bacterium, particularly for *Salmonella* spp. and *Campylobacter* spp.

Risk assessments should be conducted with a multidisciplinary approach and in an open and transparent manner. Most of the scientists currently working in the field of antimicrobial resistance, veterinary medicine and human medicine have only a basic understanding of the technical aspects of risk modelling, and few risk modellers are currently working in the field of antimicrobial resistance. Consequently, the meeting recognized the limitations of the recently performed quantitative risk assessments. Furthermore, it is probably beyond the capacity of all but a very small number of countries to conduct quantitative assessments on a regular and routine basis.

It was concluded that high quality risk assessments are needed to support risk management of use of critically important antimicrobials in food-producing animals. There is therefore an urgent need to improve risk assessment approaches, methodologies and resources at the international level. Risk assessment of chemical and microbiological hazards in food are currently conducted and reviewed at the international level by JECFA and JEMRA, respectively. Experience has shown that these expert bodies, composed of scientists from various disciplines and countries and based in academia, industry and government, can provide a very useful forum to pool scarce resources from around the world to conduct and review risk assessments. There is a need to extend such an approach to antimicrobial risk assessment. There is also a need at the international level for data to support risk assessment. When such data are incomplete, risk assessment models (qualitative and quantitative) must take resultant uncertainties into account. Data gaps occurring in a risk assessment process may be addressed using assumptions; the risk assessment output shall inform the risk manager about the uncertainties associated with these assumptions; and risk managers may, as part of a risk assessment policy, define whether conservative assumptions are necessary in order to protect public health. The data gaps identified in the box above should drive the need for research and surveillance and should serve as a guide for acquisition of resources and establishment of collaborations between the parties concerned.

In summary, there is a lack of coordinated effort for performing risk assessments for antimicrobial resistance. Global monitoring of antimicrobial resistance and drug use is required for the collection of robust data to be used for hazard identification, risk prioritization and risk assessment. This should be based on harmonized methods.



## 4. REVIEW OF AND PROPOSALS FOR RISK MANAGEMENT MEASURES

### 4.1 Introduction

Risk management options have been addressed at a number of previous meetings organized by FAO, OIE and WHO. The meeting held in Oslo in 2004 set out broad principles for the containment of antimicrobial resistance that may result from the use of antimicrobials in the non-human sector (FAO/WHO/OIE, 2004). These following principles were recommended:

- Establish a national surveillance programme on the non-human usage of antimicrobial agents.
- Establish a national surveillance programme on antimicrobial resistance in bacteria from food and animals.
- Implement strategies to prevent the transmission of resistant bacteria from animals to humans through the food production chain.
- Implement WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Foods, and follow OIE Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine (OIE Terrestrial Animal Health Code, Appendix Section 3.9.3).
- Implement specific management strategies to prevent the emergence and dissemination of bacteria resistant to critically important antimicrobial agents for people.
- Implement the risk assessment approaches that are needed to support selection of risk management options.
- Enhance the capacity of countries, particularly developing countries, to conduct surveillance of antimicrobial use and resistance, to implement intervention strategies to contain antimicrobial resistance, and to implement risk assessment approaches to support selection of risk management options.

The experts were asked to review the issue of risk management options for critically important antimicrobials, and in particular for situations where there was an overlap in those antimicrobials that were defined as such and that appeared in both the OIE and WHO lists of critically important antimicrobials. These involved the classes of quinolones, macrolides and 3rd & 4th generation cephalosporins. The micro-organisms with resistance to these agents that will be most relevant with respect to the risks to human health are the foodborne pathogens *Salmonella* spp. and *Campylobacter* spp., and commensal *Escherichia coli*.

The development and spread of antimicrobial resistance is a global public health problem that is affected by both human and non-human antimicrobial usage. All uses of antimicrobial agents lead to the emergence of antimicrobial resistant micro-organisms and further promote the dissemination of resistant bacteria and resistance genes. Furthermore, resistance genes neither respect phylogenetic, geographical nor ecological borders. Thus, the use of antimicrobials in one area (aquaculture, human or veterinary medicine) has an impact on the resistance situation in another area. Furthermore, resistance problems in one country can spread to other countries. Thus, a holistic approach is needed to best control the problems of antimicrobial resistance, one that takes into account the likely spread of resistant bacteria and resistance genes. This will involve not only the prudent use of antimicrobials, but also other actions (hygiene, infection control, waste-water management, vaccination, etc.), as these will help decrease the use of antimicrobials by prevention of infections, as well as interfering with the spread of resistant bacteria.

When discussing the need for a holistic approach, the meeting noted that effluents have been identified as sources of antimicrobial-resistant human pathogens as well as antimicrobials. This is a potential problem for animals (in particular aquaculture and capture fisheries) and public health. It is important to consider such additional sources when identifying the hazards related to antimicrobial resistance and antimicrobial sources in the food chain. Environmental sources and routes of contamination of foods (specifically from aquatic animals) with resistant foodborne pathogens require specific source-directed measures such as treatment of effluents, especially where they are present in higher amounts (e.g. hospitals, intensive animal farms). In addition, the processing of such food may

require specific considerations (e.g. HACCP).

## 4.2 Preliminary risk management activities

The meeting identified and characterized several preliminary risk management activities, such as identification of a food safety problem, establishment of a risk profile, ranking of the hazard for risk assessment and risk management priority, establishment of risk assessment policy for the conduct of the risk assessments, commissioning of the risk assessment, and consideration of the result of the risk assessment (FAO, 2006).

### 4.2.1 Identification of a food safety problem

The identification of the problem linked to antimicrobial resistant bacteria has been discussed in previous international consultations. The 2nd WHO Expert Meeting on critically important antimicrobials (WHO, 2007) highlighted groups of substances and bacteria of concern to be addressed most urgently in terms of risk management strategies for non-human use of antimicrobials.

For the purpose of this exercise, it is recommended that the food safety issues to be considered are foodborne diseases due to pathogenic *Salmonella* spp and *Campylobacter* spp. linked to potential antimicrobial resistance to 3rd and 4th generation cephalosporins, quinolones and macrolides. In addition, transmission of antimicrobial resistance associated with commensal *Escherichia coli* present in food should be considered.

The information that should be used for the identification of the safety problem can be obtained from the following sources:

- Food safety monitoring
- Environmental monitoring
- Laboratory investigations
- Epidemiological/clinical/toxicological studies
- Antimicrobial residue monitoring
- Antimicrobial resistance surveillance in animals and in foods of animal origin
- Antimicrobial usage surveys
- Animal and human disease surveillance
- Foodborne disease outbreaks
- Research on resistance transfer
- Other relevant information

### 4.2.2 Establishment of a risk profile

A risk profile of antimicrobial resistant bacteria in food was drafted by Codex Committee on Food Hygiene in 2000 (Doc. CX/FH 00/11). The 48th session of the Executive Committee of the Codex Alimentarius Commission agreed that consideration should be given to antimicrobial resistant micro-organisms in food within a risk analysis framework on a case-by-case basis as micro-organism+food combinations (CAC, 2001). According to the Executive Committee, more specific risk profiles identified in the ranking process as priorities should be drafted. These risk profiles should cover specific combinations of human pathogens+antimicrobial use+animal species.

The meeting proposed that a risk profile should include:

- A brief description of the situation.
- Consideration on the use of antimicrobials in animals.
- Identification of the resistant bacteria in food from animal origin.
- Information on pathways of transmission and commodities involved.
- Possible risks associated with that exposure.

### 4.2.3 Ranking of the hazard for risk assessment and risk management priority

The risk management activity of prioritizing risk assessments of antimicrobial resistance related to use of antimicrobials in food animals is addressed in Chapter 3.

#### 4.2.4 Establishment of a risk assessment policy

The expert meeting recommended that the OIE guideline on risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals (Terrestrial Animal Health Code 2007, Appendix 3.9.4) should be used to develop risk assessment policies to guide the conduct of risk assessments. The risk assessment part is divided into three parts: release, exposure and consequences.

The existing international microbiological risk assessments performed by the Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment (JEMRA) for *Salmonella* and *Campylobacter* should be used as part of the exposure phase of the risk assessment of antimicrobial resistance related to use of antimicrobials in food animals. Relevant risk assessments include those on *Salmonella* spp in eggs and broiler chickens (FAO/WHO, 2002) and *Campylobacter* spp. in broiler chickens (FAO/WHO, 2008).

#### 4.2.5 Commissioning of the risk assessment

In commissioning the risk assessment, risk managers should consider the following:

- risk management goals to be achieved;
- necessity and feasibility of the risk assessment; and
- cost-benefit analysis.

The commissioning of the risk assessment should follow the identification of the priorities as discussed in Chapter 3.

#### 4.2.6 Consideration of the result of the risk assessment

In judging the completeness of the risk assessment, risk managers would need to understand the nature, sources and extent of uncertainties and variability of the risk estimates expressed.

### **4.3 Risk management options and their implementation**

Under a general risk management framework, the identification and selection of risk management options should follow preliminary risk management activities as described in the previous section (see also the discussion and recommendations from FAO/WHO/OIE, 2004). The identification and description of the nature and characteristics of the food safety issue is an essential first task for risk managers. The initial description of the food safety issue provides the basis for the development of a risk profile, which in turn generates the context and scope of the problem and provides a guide for further action.

Identification and selection of available risk management options might include the following:

- Mitigate risks
- Health management measures or prevention
- Infection control policies
- Good animal management practices, including good hygiene practices
- Vaccination policies
- Infrastructure
- Development of alternatives to the use of antimicrobial treatment of infections
- Identify points in production-to-consumption where food safety measures could be implemented
- Prudent use guidelines
- Only approved products should be used
- All antimicrobials should be prescription-only medicines
- Information and education on prudent use

*Web links to examples for monitoring of risk management interventions*

DANMAP (Denmark)	<a href="http://www.danmap.org">http://www.danmap.org</a>
(WHO 2003)	<a href="http://whqlibdoc.who.int/hq/2003/WHO_CDS_CPE_ZFK_2003.1.pdf">http://whqlibdoc.who.int/hq/2003/WHO_CDS_CPE_ZFK_2003.1.pdf</a>
NARMS (USA)	<a href="http://www.fda.gov/cvm/narms_pg.html">http://www.fda.gov/cvm/narms_pg.html</a>
Public Health Agency of Canada (PHAC 2007)	<a href="http://www.phac-aspc.gc.ca/cipars-picra/heidelberg/heidelberg-eng.html">http://www.phac-aspc.gc.ca/cipars-picra/heidelberg/heidelberg-eng.html</a>

- Adjust regulatory processes
- Antimicrobial resistance should be considered as part of the authorization process for new antimicrobials or in cases where an extension of an indication is being considered
- Active review process for existing products
- Surveillance of antimicrobial resistance and antimicrobial usage

The experts recognized that prudent use guidelines have been written, endorsed and implemented by a number of groups in a number of countries. Risk management decisions are implemented by a variety of parties, including governments, food industry and the general public, alone or in collaboration. Industry commodity buying policies for animal food products are an example for incentive-based risk management options. The implementation of risk management decision should include effective risk communication strategies.

#### **4.4 Monitoring and review**

Risk management does not end when a decision has been taken and implemented. Risk managers should verify that the risk or hazard mitigation has achieved the intended results, and that there are no unintended consequences associated with the measures. Risk management decisions should be examined periodically when new scientific data become available, as well as when experience obtained from monitoring the impact of risk management interventions warrants a review. This important phase of risk management would include gathering and analysing data on foodborne antimicrobial resistance hazards such as antimicrobial use and antimicrobial resistance, to provide a longitudinal review of food safety and consumer health and to measure the outcome of risk measures taken.

It is important that the national public health infrastructure for the monitoring of the antimicrobial resistance in foodborne pathogens—*Campylobacter* spp. and *Salmonella* spp., and commensal *Escherichia coli*—is adequate to evaluate the extent of success of any risk management measures, as well as any unintended adverse consequences. This includes monitoring antimicrobial drug use and development of resistance to these antimicrobial in bacteria using standardized international methods (e.g. Minimum inhibitory concentrations (MICs) preferred). Monitoring of antimicrobials resistance has been performed in a number of countries to follow up effects of interventions targeted at the use of specific antimicrobials in food-producing animals (see Web links in box above).

MIC data are valuable because they enable reliable international comparison of reduced susceptibility or resistance in bacteria. MIC data can be generated in central laboratories using bacterial collections derived from countries in various parts of the world. Collaboration can be established between countries to ensure that infrastructure limitations and costs do not compromise collection of MIC data. Countries lacking the ability to build the necessary capacity to perform full-range MICs should consider making isolates available to laboratories with such capability.

Data from specific resistance monitoring programmes may in some cases be enhanced by data from other relevant sources, e.g. national surveillance networks of invasive human infections (bacteraemia).

Monitoring and review activities should be specifically designed to support management of foodborne risks and provide opportunity for multidisciplinary inputs in a risk-based food safety system. Monitoring could produce results that necessitate the commissioning of a new risk assessment or re-evaluation of an existing risk assessment, thus reducing previous uncertainties, or updating the analysis with new or additional research findings. Revised risk assessment results will lead to

reiteration of the entire risk management process, with possible changes in risk management goals and the risk management options. Regardless, a structured risk management programme must be applied with the outcomes (attainment of risk management goals) optimally assessed by a sensitive pre- and post-intervention monitoring programme. A 'generic risk management design' can be very helpful, but requires a significant commitment to multidisciplinary guidance, scientific process and impartial review of outcomes to become a usable tool for improving public health.

There are major differences between countries in laboratory capacity, technical skills and infrastructure available to implement the recommendations of this expert meeting. International support and cooperation will be needed to achieve the overall aim of containing antimicrobial resistance. Support is needed to monitor antimicrobial use and antimicrobial resistance and review intervention strategies. Special attention should be given to support developing countries through joint initiatives by FAO, OIE and WHO.

Future work on the risk assessment and management of resistance to antimicrobials in foodborne pathogens will require a structured and consolidated approach that ensures continuity of this and all previous consultations.'

***Information that could be used for monitoring the effects of risk management measures***

- Food consumption data (e.g. general population, at-risk host populations; very young, elderly, immuno-compromised)
  - Antimicrobial use statistics indexed by commodity (animal) and human illness type (e.g. gastroenteritis)
  - Compliance to treatment and laboratory utilization guidelines (Codes of Practice)
  - Compliance with prudent use guidelines (animal)
  - Data concerning targeted foodborne pathogens from invasive human infections (blood cultures)
  - National and regional surveillance of 'notifiable diseases' and other human and animal health monitoring data
  - Disease registries based on coded hospitalization and death records
  - Published investigations (which may include molecular epidemiology, genetics and gene context studies) comparing animal, food and human isolates
  - Risk factor studies of foodborne disease
  - Foodborne outbreak reports with attributable commodity source
  - Quality assurance and inspection records of food processing isolates using selected foodborne pathogens and commensals
- Number and content of the educational initiatives directed at all parties
- Results from similar surveillance and monitoring programmes in other geographical locations or nations



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## APPENDIX A

### WHO LIST OF CRITICALLY IMPORTANT ANTIMICROBIALS, AS PUBLISHED IN WHO, 2007.

**Table A1.** Listing and Categorization of Antimicrobials Used in Human Medicine

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

Critically Important Antimicrobials (continued)			
Drug name	Criterion 1	Criterion 2	Comments
<b>Macrolides</b> (including 14-, 15-, 16-membered compounds), <b>ketolides</b>	Y	Y	Limited therapy for <i>Legionella</i> , <i>Campylobacter</i> , and MDR <i>Salmonella</i> infections
azithromycin clarithromycin erythromycin midecamycin roxithromycin spiramycin telithromycin			Potential transmission of <i>Campylobacter</i> spp. from non-human sources
<b>Oxazolidinones</b>	Y	Y	Limited therapy for infections due to MDR <i>S. aureus</i> and <i>Enterococcus</i> spp.
linezolid			Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources
<b>Penicillins, (natural, aminopenicillins and antipseudomonal)</b>	Y	Y	Limited therapy for syphilis (natural penicillins) <i>Listeria</i> , <i>Enterococcus</i> spp. (aminopenicillins) and MDR <i>Pseudomonas</i> spp. (antipseudomonal)
penicillin G penicillin V ampicillin ampicillin/sulbactam amoxicillin amoxicillin/clavulanate piperacillin piperacillin/tazobactam azlocillin carbenicillin mezlocillin ticarcillin ticarcillin/clavulanate			Potential transmission of <i>Enterococcus</i> spp., <i>Enterobacteriaceae</i> including <i>E. coli</i> as well as <i>Pseudomonas aeruginosa</i> from non-human sources
<b>Quinolones</b>	Y	Y	Limited therapy for <i>Campylobacter</i> spp., invasive disease due to <i>Salmonella</i> spp., and MDR <i>Shigella</i> spp. infections
cinoxacin nalidixic acid pipemidic acid			Potential transmission of <i>Campylobacter</i> spp. and <i>Enterobacteriaceae</i> including <i>E. coli</i> and <i>Salmonella</i> spp. from non-human sources
ciprofloxacin enoxacin gatifloxacin gemifloxacin levofloxacin lomefloxacin moxifloxacin norfloxacin ofloxacin sparfloxacin			
<b>Streptogramins</b>	Y	Y	Limited therapy for MDR <i>Enterococcus faecium</i> and <i>S. aureus</i> infections
quinupristin/dalfo-pristin, pristinamycin			Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources

Critically Important Antimicrobials (continued)			
Drug name	Criterion 1	Criterion 2	Comments
<b>Tetracyclines (Glycylcyclines)</b>	Y	Y	Limited therapy for infections due to MDR <i>S. aureus</i>
tigecycline			
<b>Drugs used solely to treat tuberculosis or other mycobacterial diseases</b>	Y	Y	Limited therapy for tuberculosis and other <i>Mycobacterium</i> spp. disease and for many of these drugs, single drug therapy may select for resistance  Potential transmission of <i>Mycobacterium</i> spp. from non-human sources
cycloserine			
ethambutol			
ethionamide			
isoniazid			
para-aminosalicylic acid pyrazinamide			

Highly Important Antimicrobials			
Drug name	Criterion 1	Criterion 2	Comments
<b>Amidinopenicillins</b>	N <sup>†</sup>	Y	Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources.  *MDR <i>Shigella</i> spp. infections may be a regional problem
mecillinam			
<b>Aminoglycosides (Other)</b>	N	Y	Potential transmission of Gram negative bacteria that are cross resistant to streptomycin from non-human sources
kanamycin			
neomycin			
spectinomycin			
<b>Amphenicols</b>	N*	Y	*May be one of limited therapies for acute bacterial meningitis, typhoid fever and respiratory infections in certain geographic areas
chloramphenicol			
thiamphenicol			
<b>Cephalosporins, 1<sup>st</sup> generation</b>	N	Y	Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
cefazolin			
cephalexin			
cephalothin			
cephradine			
<b>Cephalosporins, 2<sup>nd</sup> generation</b>	N	Y	Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
cefaclor			
cefamandole			
cefuroxime			
loracarbef			
<b>Cephameycins</b>	N	Y	Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
cefotetan			
cefoxitin			
<b>Clofazimine</b>	Y	N	Limited therapy for leprosy

Highly Important Antimicrobials (continued)			
Drug name	Criterion 1	Criterion 2	Comments
<b>Monobactams</b>	N	Y	Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
aztreonam			
<b>Penicillins</b> (Antistaphylococcal)	N	Y	<i>S. aureus</i> including MRSA has been transferred to humans from animals
cloxacillin			
dicloxacillin			
flucloxacillin			
oxacillin			
naftillin			
polymyxins	Y	N	Limited therapy for MDR Gram negative bacterial infections, for example, those caused by <i>Acinetobacter</i> spp. and <i>Pseudomonas aeruginosa</i>
colistin			
polymyxin B			
<b>Sulfonamides</b> , 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 <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
para-aminobenzoic acid			
pyrimethamine			
sulfadiazine			
sulfamethoxazole			
sulfapyridine			
sulfisoxazole			
trimethoprim			
<b>Sulfones</b>	Y	N	Limited therapy for leprosy
dapsone			
<b>Tetracyclines</b>	Y	N	Limited therapy for infections due to <i>Chlamydia</i> spp. and <i>Rickettsia</i> spp.
chlortetracycline			
doxycycline			
minocycline			
oxytetracycline			
tetracycline			

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

NOTES: Other Classes of Antibacterial Drugs: drug classes that are not used in humans, and are currently only used in animal medicine, include arsenicals, bambamycins, ionophores, orthosomycins and quinoxalines.

**Table A2.** 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
<b>Aminoglycosides</b>	Low	Low	High	(Criterion 1) Limited therapy as part of treatment of enterococcal endocarditis and MDR tuberculosis  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp., <i>Enterobacteriaceae</i> (including <i>Escherichia coli</i> ), and <i>Mycobacterium</i> spp. from non-human sources
amikacin				
arbekacin				
gentamicin				
netilmicin				
tobramycin streptomycin				
<b>Ansamycins</b>	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 <i>Mycobacterium</i> spp. from non-human sources
rifabutin				
rifampin				
rifaximin				
<b>Carbapenems and other penems</b>	High	Low	High	(Criterion 1) Limited therapy as part of treatment of disease due to MDR Gram-negative bacteria  (Criterion 2) Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> and <i>Salmonella</i> spp. from non-human sources
ertapenem				
faropenem				
imipenem				
meropenem				
<b>Cephalosporins, (3rd and 4th generation)</b>	High	High	High	(Criterion 1) Limited therapy for acute bacterial meningitis and disease due to <i>Salmonella</i> spp. in children. Additionally, 4 <sup>th</sup> generation cephalosporins provide limited therapy for empirical treatment of neutropenic patients with persistent fever.  (Criterion 2) Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> and <i>Salmonella</i> spp. from non-human sources
cefixime				
cefotaxime				
cefepodoxime				
ceftazidime				
ceftizoxime				
cefoperazone				
cefoperazone/sulbactam				
ceftriaxone				
cefepime				
cefpirome				
cefoselis				
<b>Lipopeptides</b>	High	Low	Low	(Criterion 1) Limited therapy for infections due to MDR <i>Staphylococcus aureus</i>  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources
daptomycin				
<b>Glycylcycline (higher generation tetracycline)</b>	High	Low	High	(Criterion 1) Limited therapy for infections due to MDR <i>S. aureus</i> and MDR Gram negative bacteria  (Criterion 2) Potential transmission of <i>Enterobacteriaceae</i> including <i>E. coli</i> from non-human sources
tigecycline				
<b>Glycopeptides</b>	High	Low*	Low	(Criterion 1) Limited therapy for infections due to MDR <i>S. aureus</i> and <i>Enterococcus</i> spp.  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources
teicoplanin				
vancomycin				

Critically Important Antimicrobials (continued)				
Drug name	Criterion 1.1	Criterion 1.2	Criterion 2.1	Comments
<b>Oxazolidinones</b>	High	Low	Low	(Criterion 1) Limited therapy for infections due to MDR <i>S. aureus</i> and <i>Enterococcus</i> spp.  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources
linezolid				
<b>Penicillins, (natural, aminopenicillins and antipseudomonal)</b>	Low*	High	Low	(Criterion 1) Limited therapy for syphilis (natural) <i>Listeria</i> and <i>Enterococcus</i> spp. (aminopenicillins)  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp. from non-human sources
penicillin G				
penicillin V				
ampicillin				
ampicillin/sulbactam				
amoxicillin				
amoxicillin/clavulanate				
piperacillin				
piperacillin/tazobactam				
azlocillin				
carbenicillin				
mezlocillin				
ticarcillin				
ticarcillin/clavulanate				
<b>Macrolides</b> (including 14-, 15-, 16-membered compounds), <b>ketolides</b>	High	High	High	(Criterion 1) Limited therapy for <i>Legionella</i> , <i>Campylobacter</i> , and MDR <i>Salmonella</i> infections  (Criterion 2) Potential transmission of <i>Campylobacter</i> spp. from non-human sources
azithromycin				
clarithromycin				
erythromycin				
midecamycin				
roxithromycin				
spiramycin				
telithromycin				
<b>Quinolones</b>	High	High	High	(Criterion 1) Limited therapy for <i>Campylobacter</i> spp., invasive disease due to <i>Salmonella</i> spp., and MDR <i>Shigella</i> spp. infections  (Criterion 2) Potential transmission of <i>Campylobacter</i> spp. and Enterobacteriaceae including <i>E. coli</i> and <i>Salmonella</i> spp. from non-human sources
cinoxacin				
nalidixic acid				
pipemidic acid				
ciprofloxacin				
enoxacin				
gatifloxacin				
gemifloxacin				
levofloxacin				
lomefloxacin				
moxifloxacin				
norfloxacin				
ofloxacin				
Sparfloxacin				

Critically Important Antimicrobials (continued)				
Drug name	Criterion 1.1	Criterion 1.2	Criterion 2.1	Comments
<b>Streptogramins</b>	High	Low	Low	(Criterion 1) Limited therapy for MDR <i>Enterococcus faecium</i> and <i>S. aureus</i> infections  (Criterion 2) Potential transmission of <i>Enterococcus</i> spp. and MDR <i>S. aureus</i> from non-human sources
quinupristin/dalfo-pristin, pristinamycin				
<b>Drugs used solely to treat tuberculosis or other mycobacterial diseases</b>	High	High	Low	(Criterion 1) Limited therapy for tuberculosis and other <i>Mycobacterium</i> spp. disease and for many of these drugs, single drug therapy may select for resistance  (Criterion 2) Potential transmission of <i>Mycobacterium</i> spp. from non-human sources
cycloserine				
ethambutol				
ethionamide				
isoniazid				
para-aminosalicylic acid pyrazinamide				

NOTES: 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.

## APPENDIX B

### OIE LIST OF CRITICALLY IMPORTANT ANTIMICROBIALS AS PUBLISHED IN OIE, 2007.

#### CATEGORIZATION OF VETERINARY IMPORTANT ANTIMICROBIALS FOR FOOD-PRODUCING ANIMALS

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>AMINOGLYCOSIDES</b>								
AMINOCYCLITOL								
Spectinomycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
<b>AMINOGLYCOSIDES</b>								
Streptomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI		<p>The wide range of applications and the nature of the diseases treated make aminoglycosides extremely important for veterinary medicine.</p> <p>Aminoglycosides are of importance in septicaemias; digestive, respiratory and urinary diseases.</p> <p>Gentamicin is indicated for <i>Pseudomonas aeruginosa</i> infections, with few alternatives. Spectinomycin is used only in animals. Few economic alternatives are available.</p>	Y	Y	Y		
Dihydrostreptomycin	AVI, BOV, CAP, EQU, LEP, OVI, SUI	77.1%						
Framycetin	BOV, CAP, OVI							
Kanamycin	AVI, BOV, EQU, PIS, SUI							
Neomycin	API, AVI, BOV, CAP, EQU, LEP, OVI, SUI							
Paromomycin	CAP, OVI, LEP							
Apramycin	AVI, BOV, LEP, OVI, SUI							
Gentamicin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI							
Tobramycin	EQU							
Amikacin	EQU							
<b>ANSAMYCIN – RIFAMYCINS</b>								
Rifampicin	EQU	30%	<p>This antimicrobial class is authorized only in a few countries and with a very limited number of indications (mastitis) and few alternatives, e.g. treatment of <i>Rhodococcus equi</i> infections in foals.</p> <p><b>Rifampicin is critically important in equines.</b></p>	N	Y		Y	
Rifaximin	BOV, CAP, EQU, LEP, OVI, SUI							
<b>BICYCLOMYCIN</b>								
Bicozamycin	BOV, PIS	1.4%	Biclomycin is listed for digestive and respiratory diseases in cattle and septicaemias in fish.	N	N			Y

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>CEPHALOSPORINS</b>								
CEPHALOSPORIN 1G								
Cefacetrile	BOV							
Cefalexin	BOV, CAP, EQU, OVI, SUI							
Cefalotin	EQU							
Cefapyrin	BOV							
Cefazolin	BOV, CAP, OVI							
Cefalonium	BOV, CAP, OVI							
CEPHALOSPORIN 2G								
Cefuroxime	BOV							
CEPHALOSPORIN 3G								
Cefoperazone	BOV, CAP, OVI							
Ceftiofur	AVI, BOV, CAP, EQU, LEP, OVI, SUI							
Ceftriaxone	AVI, BOV, OVI, SUI							
CEPHALOSPORIN 4G								
Cefquinome	BOV, CAP, EQU, LEP, OVI, SUI							
<b>FOSFOMYCIN</b>								
Fosfomycin	AVI, BOV, PIS, SUI	7.1%	This antimicrobial is authorized only in a few countries. Fosfomycin has a limited number of alternatives in some fish infections. <b>Critically important for fish<sup>1</sup>.</b>	N	Y		Y	
<b>FUSIDIC ACID</b>								
Fusidic acid	BOV, EQU	1.4%	Fusidic acid is used in the treatment of ophthalmic diseases in cattle and horses.	N	N			Y

<sup>1</sup> Under study

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>IONOPHORES</b>								
Lasalocid	AVI, BOV, LEP, OVI	42.9%	Ionophores are essential for animal health because they are used to control intestinal parasitic coccidiosis. ( <i>Eimeria</i> spp.) where there are few or no alternatives available. <b>Ionophores are critically important in poultry.</b> <b>Ionophores are used only in animals</b>	N	Y		Y	
Maduramycin	AVI							
Monensin	API, AVI, BOV, CAP							
Narasin	AVI							
Salinomycin	AVI, LEP							
Semduramicin	AVI							
<b>LINCOSAMIDES</b>								
Pirlimycin	BOV	51.4%	Lincosamides are essential in the treatment of Mycoplasmal pneumonia, infectious arthritis and hemorrhagic enteritis of pigs.	Y	N		Y	
Lincomycin	API, AVI, BOV, CAP, OVI, PIS, SUI							
<b>MACROLIDES</b>								
<b>AZALIDE</b>		77.1%	Macrolides are used to treat Mycoplasmal infections in pig and poultry, hemorrhagic digestive disease in pigs and liver abscesses ( <i>Fusobacterium necrophorum</i> ) in cattle, where they have very few alternatives. Macrolides are also used for respiratory infections in cattle	Y	Y	Y		
Tulathromycin	BOV, CAP, LEP, OVI, SUI							
<b>MACROLIDES C14</b>								
Erythromycin	API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
<b>MACROLIDES C16</b>								
Josamycin	AVI, PIS							
Kitasamycin	AVI, SUI							
Spiramycin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
Tilmicosin	AVI, BOV, CAP, LEP, OVI, SUI							
Tylosin	API, AVI, BOV, CAP, LEP, OVI, SUI							
Mirosamycin	API, AVI, SUI							
Terdecamycin	AVI							
<b>NOVOBIOCIN</b>								
Novobiocin	BOV, CAP, OVI, PIS	31.4%	Novobiocin is used in the treatment of mastitis in the form of intramammary creams and in sepsis of fish. <b>Novobiocin is only used in animals</b>	N	N			Y

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>ORTHOSOMYCINS</b> Avilamycin	AVI, LEP	4.3%	Avilamycin is used for digestive diseases of poultry and rabbits, and is used to treat necrotic enteritis in chickens where available.  <b>The antimicrobial class is used only in animals.</b>	N	N			Y
<b>PENICILLINS</b> NATURAL PENICILLINS Benzylpenicillin Penethamate hydroxide Penicillin procaine AMDINOPENICILLINS Mecillinam AMINOPENICILLINS Amoxicillin Ampicillin Hetacillin AMINOPENICILLIN PLUS BETALACTAMASE INHIBITOR Amoxicillin_Clavulanic Acid CARBOXPENICILLINS Ticarcillin Tobicillin UREIDO PENICILLIN Aspoxicillin PHENOXPENICILLINS Phenoxyethylpenicillin Phenethicillin	AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI BOV, SUI BOV, CAM, CAP, EQU, OVI, SUI BOV, SUI AVI, BOV, CAP, EQU, OVI, PIS, SUI AVI, BOV, CAP, EQU, OVI, PIS, SUI BOV AVI, BOV, CAP, EQU, OVI, SUI EQU PIS BOV, SUI AVI, SUI EQU	87.1%	Penicillins are used in the treatment of septicaemias, respiratory and urinary tract infections.  They are very important in the treatment of many diseases in a broad range of animal species.  Few economical alternatives are available.	Y	Y	Y		

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>ANTISTAPHYLOCOCCAL PENICILLINS</b>								
Cloxacillin	BOV, CAP, EQU, OVI, SUI							
Dicloxacillin	BOV, CAP, OVI							
Nafcillin	BOV, CAP, OVI							
Oxacillin	BOV, CAP, EQU, OVI							
<b>PHENICOLS</b>								
Florphenicol	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI		Phenicols are of particular importance in treating some fish diseases, in which there are no or very few treatment alternatives.					
Thiamphenicol	AVI, BOV, CAP, OVI, PIS, SUI	51.4%	Phenicols also represent a useful alternative in respiratory infections of cattle, swine and poultry. Phenicols, and in particular florfenicol, are used to treat pasteurellosis in cattle and pigs.	Y	Y	Y		
<b>PLEUROMUTILINS</b>								
Tiamulin	AVI, CAP, LEP, OVI, SUI		Pleuromutilins are used exclusively in animals. The class of pleuromutilins is essential against respiratory infections in pigs and poultry.					
Valnemulin	AVI, SUI	48.6%	<b>This family is critically important against swine dysentery (<i>Brachyspira hyodysenteriae</i>)</b> because there are no alternatives in many regions.	N	Y		Y	
<b>POLYPEPTIDES</b>								
Enramycin	AVI, SUI							
Gramicidin	EQU							
Bacitracin	AVI, BOV, LEP, SUI	64.3%	Bacitracin is used against necrotic enteritis in poultry where available. Polypeptides are indicated in septicaemias, colibacillosis, salmonellosis and urinary infections. Cyclic polypeptides are widely used against Gram-negative digestive infections.	Y	N		Y	
<b>POLYPEPTIDES CYCLIC</b>								
Colistin	AVI, BOV, CAP, EQU, LEP, OVI, SUI							
Polymixin	BOV, CAP, EQU, LEP, OVI, AVI							

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>QUINOLONES</b>								
QUINOLONES 1G								
Flumequin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
Miloxacin	PIS							
Nalidixic acid	BOV							
Oxolinic acid	AVI, BOV, LEP, PIS, SUI							
QUINOLONES 2G (FLUORO-QUINOLONES)								
Ciprofloxacin	AVI, BOV, SUI	68.6%	Quinolones of the 1st and of 2nd generations are used in septicaemias and in infections such as colibacillosis, which cause serious losses in poultry, cattle, swine, fish and other species.	Y	Y	Y		
Danofloxacin	AVI, BOV, CAP, LEP, OVI, SUI		Fluoroquinolones have no equally efficacious alternative in the treatment of chronic respiratory disease in poultry ( <i>E. coli</i> ).					
Difloxacin	AVI, BOV, LEP, SUI							
Enrofloxacin	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
Marbofloxacin	AVI, BOV, EQU, LEP, SUI							
Norfloxacin	AVI, BOV, CAP, LEP, OVI, SUI							
Ofloxacin	AVI, SUI							
Orbifloxacin	BOV, SUI							
<b>QUINOXALINES</b>								
Carbadox	SUI	4.3%	Quinoxalines (carbadox) is used for digestive disease of pigs (e.g. swine dysentery).	N	N			Y

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>SULFONAMIDES</b>								
Sulfachlorpyridazine	AVI, SUI							
Sulfadiazine	BOV, CAP, OVI, SUI							
Sulfadimerazin	AVI, BOV, LEP							
Sulfadimethoxine	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
Sulfadimidine	AVI, BOV, CAP, EQU, LEP, OVI, SUI							
Sulfadoxine	EQU, SUI							
Sulfafurazole	PIS							
Sulfaguanidine	CAP, OVI							
Sulfamethazine	SUI							
Sulfadimethoxazole	AVI, BOV, SUI	70%	Several sulfonamides alone or in combination with diaminopyrimidines are very essential because of diseases covered (bacterial, coccidial and protozoal infections), and used in multiple animal species.	Y	Y	Y		
Sulfamethoxine	AVI, PIS, SUI							
Sulfamonomethoxine	AVI, PIS, SUI							
Sulfanilamide	BOV, CAP, OVI							
Sulfaquinoxaline	AVI, BOV, CAP, LEP, OVI							
<b>SULFONAMIDES- +DIAMINOPYRIMIDINES</b>								
Sulfamethoxy-pyridazine	AVI, BOV, EQU							
Trimethoprim+Sulfonamide	AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI							
<b>DIAMINOPYRIMIDINES</b>								
Baquiloprim	SUI							
Trimethoprim	AVI, BOV, CAP, EQU, LEP, OVI, SUI							
<b>STREPTOGRAMINS</b>								
Virginiamycin	AVI, BOV, OVI, SUI	5.7%	Virginiamycin is an important antimicrobial in the prevention of necrotic enteritis ( <i>Clostridium perfringens</i> )	N	N			Y

ANTIMICROBIAL FAMILY	SPECIES	% quotations	Specific comments	C1: Quotation > 50%	C2: Essential or Few alternatives	VCIA	VHIA	VIA
<b>TETRACYCLINES</b>								
Chlortetracycline	AVI, BOV, CAP, EQU, LEP, OVI, SUI	87.1%	Tetracyclines are very important in the treatment of many bacterial and chlamydial diseases in a broad range of animal species. There are no alternatives to tetracyclines in the treatment of animals against heartwater ( <i>Ehrlichia ruminantium</i> ) and anaplasmosis ( <i>Anaplasma marginale</i> ).  Few economical alternatives are available	Y	Y	Y		
Doxycycline	AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI							
Oxytetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI							
Tetracycline	API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI							

KEY TO ABBREVIATIONS used in the OIE table: Animal species in which these antimicrobials are used are AVI = avian; EQU = equine; API = bee; LEP = rabbit; BOV = bovine; OVI = ovine; CAP = caprine; PIS = fish; CAM = camel; SUI = swine.

The categories of microbials are: VCIA = Veterinary Critically Important Antimicrobials; VHIA = Veterinary Highly Important Antimicrobials; VIA = Veterinary Important Antimicrobials.

## APPENDIX C

### GLOSSARY

- antimicrobial agent** Any substance of natural, semi-synthetic, or synthetic origin that at *in vivo* concentrations kills or inhibits the growth of micro-organisms by interacting with a specific target.
- antimicrobial class** Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of antimicrobials within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.
- antimicrobial growth promoter** Antimicrobial agents used for the purpose of increasing the daily weight gain or feed efficiency (feed–weight gain ratio) of food-producing animals.
- antimicrobial resistance** The ability of a micro-organism to multiply or persist in the presence of increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.
- antimicrobial resistance genes** Genes in micro-organisms that confer resistance to antimicrobials. These are often located on mobile genetic elements, thereby enabling horizontal transmission from resistant to susceptible strains.
- containment of antimicrobial resistance** Infectious disease control measures that minimize the emergence and spread of antimicrobial-resistant micro-organisms.
- cross-resistance** A single resistance mechanism in a bacterium conferring resistance at various levels to all members of the class. The level of resistance depends on the intrinsic activity of the antimicrobial agent: in general the higher the activity, the lower the level of resistance. Cross-resistance implies cross-selection for resistance.
- co-resistance (associated resistance)** Various resistance mechanisms, each conferring resistance to an antimicrobial class, associated within the same bacterial host.
- extended co-resistance** A single mechanism conferring resistance to various antimicrobial classes. An example would be overexpression of an efflux pump with a broad substrate range.
- disease control** Activities aimed at preventing or curing disease in animals intended for food.
- empirical therapy** Therapy initiated on the basis of observation of clinical symptoms and patient history only, without confirmation of diagnosis by laboratory or other methods.
- food-producing animals** Animals raised for the purpose of providing food for humans. Most commonly this term refers to poultry, swine, cattle and sheep, but it does not exclude other domestically managed animals.
- good management/farming/veterinary practices** Routine practices that minimize risk from harmful antimicrobial-resistant bacteria or resistance genes through good prescribing and farm management and hygiene practices (e.g. optimal housing conditions and feeding strategies) and other non-antimicrobial disease preventive strategies, while maximizing the productivity of food animal production.
- Hazard Analysis and Critical Control Point (HACCP)** A science-based and systematic approach that identifies, evaluates, and controls hazards that are significant for food safety.
- pharmacokinetics** The ways in which antimicrobials (principally drugs/medicines) are absorbed by, move within, and are finally eliminated from animals, humans, etc.
- pharmacodynamics** The behaviour (e.g. quick, slow, short-term, long-term, etc.) of an antimicrobial at its receptor site (i.e. where it initiates its effect).
- prescribing practices** The behaviour of licensed medical or veterinary practitioners with regard to prescription of medicines, including such aspects as readiness to prescribe such medicines, readiness to delegate decisions on repeat prescriptions and other routine demands to staff who

are not medically qualified.

**prescription-only medicines** Medicines that are legally available to the “end user” only if they obtain a prescription from a licensed professional (e.g. veterinarian, medical doctor, dentist).

**prophylactic use** The administration of an antimicrobial to healthy animals in advance of an expected exposure to an infectious agent or following such an exposure but before onset of laboratory-confirmed clinical disease. Generally such usage is in a herd or flock situation and not in an individual animal.

**prudent use of antimicrobials** Usage of antimicrobials that maximizes therapeutic effect and minimizes the development of antimicrobial resistance.

**registration (licensing, authorization, approval)** The process of approving a drug for marketing in a country/region. Includes assessment based particularly on the criteria of safety, quality and efficacy. Because of inadequate local capacity, many developing countries rely on “third party certification”, i.e. granting market authorization to products already approved in certain developed countries.

**regulatory authority** A government agency responsible for codifying and enforcing rules and regulations as mandated by law.

**relevant authority** An authority with jurisdiction over relevant areas of concern in relation to use of antimicrobials in animals, including registration, licensing, sale, distribution, marketing and dispensing of antimicrobial agents.

**risk** A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard.

**risk-based evaluation** Evaluation of scientific and other relevant information with the aim of obtaining a qualitative and/or quantitative estimation of the probability of occurrence and severity of known or potential adverse public health effects.

**serovar** A subdivision of a species or subspecies distinguishable from other strains therein on the basis of antigenic character. Also called *serotype*.

**stakeholder** A person or group of persons, or an industry, association, organization, etc., with an economic or professional interest in/responsibility for an area or (involuntarily) affected by the developments in that same area. In the field of antimicrobial usage in food animals, farmers, veterinarians, animal feed manufacturers, food processors and distributors, retailers, relevant government organizations, pharmaceutical companies, consumers, public health officials, academic and other related groups are recognized as stakeholders.

**therapeutic use** Application of antimicrobials in curative doses in an adequate period of time to combat an established infection.

**zoonotic bacteria** Bacteria that are present in animal reservoirs and can be transferred to, and cause infections in, humans.

## APPENDIX D

### LIST OF PARTICIPANTS

#### Invited experts

AARESTRUP, Frank M.	Professor, National Food Institute, Technical University of Denmark, Copenhagen, Denmark
ALDAY-SANZ, Victoria	DVM/PhD, Consultant, Barcelona, Spain
COLLIGNON, Peter	Director, Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, and Professor, School of Clinical Medicine, Australian National University, Australia
COURVALIN, Patrice	Professor, Unité des Agents Antibactériens, Centre National de Référence de la Résistance aux Antibiotiques, Institut Pasteur, Paris France
ERRECALDE, Jorge Oscar	Full Professor of Pharmacology and Toxicology, Faculty of Veterinary Science, University of La Plata, La Plata, Argentina
FEDORKA CRAY, Paula J.	PhD, Richard Russell Research Center, Antimicrobial Resistance Research Unit, Athens, Georgia, USA
JONES Ronald N.,	Director, JMI Laboratories, North Liberty, Iowa, USA and Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA
KROKER, Reinhard	Professor, Federal Office for Consumer Protection and Food Safety, Berlin, Germany
MCEWEN, Scott	Professor, Department of Population Medicine, University of Guelph, Guelph, Ontario, Canada
MOULIN, Gérard	PhD, Head of Marketing Authorization Department, National Agency for Veterinary Medicinal Products (AFSSA/ANMV), La Haute Marche, Javené, Fougères, France
PALERMO NETO, João	Professor, School of Veterinary Medicine, Department of Pathology Applied Pharmacology and Toxicology Laboratory, São Paulo, SP, Brazil
PARK, Yong Ho	Professor, Department of Microbiology, College of Veterinary Medicine, Seoul National University, Seoul, Korea
SCHNEIDER, Herbert	DVM, AGRIVET International Consultants, Windhoek, Namibia
SOBACK, Stefan	Director, Food Safety Laboratories, Beit Dagan and Professor, Faculty of Agriculture, Hebrew University of Jerusalem, Israel
VALOIS, Angelo A.	PhD, Manager of Technical and International Policy Product Safety and Product Integrity, Animal and Plant Health, Australian Government Department of Agriculture, Fisheries and Forestry, Canberra, Australia

#### Resource persons

Name	Affiliation
ACAR, Jacques	OIE
ANGULO, Fred	WHO
CAHILL, Sarah	FAO
KRUSE, Hilde	WHO
LEE, Ym Shik	Codex Alimentarius Commission Secretariat
WENNBERG, Annika	FAO
WOO, Gun-Jo	Chair, Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance

#### Joint Secretariat

Name	Organization
ABELA-RIDDER, Bernadette	WHO
AIDARA-KANE, Awa	WHO
COSTARRICA, Maria de Lourdes	FAO
DE BALOGH, Katinka	FAO
ISHIBASHI, Tomoko	OIE
KARUNASAGAR, Iddya	FAO
LAMBERT, Catherine	OIE
LÜTZOW, Manfred	FAO



## APPENDIX E

### AGENDA OF THE MEETING

#### *Joint FAO / WHO / OIE Expert Meeting on Critically Important Antimicrobials*

Italy, Rome, 26–30 November 2007

<b>Time</b>	<b>Monday 26 November 2007</b>	<b>Speaker</b>
14.00 – 14.30	Opening and welcome by FAO Welcome address by WHO Welcome address by OIE Introduction of participants Election of a chairperson and a vice-chairperson Appointment of a rapporteur Adoption of the agenda	E. Boutrif A. Aidara-Kane T. Ishibashi E. Boutrif
14.30 – 14.45	Ten years after – antimicrobial resistance and the food chain	M. Lützow
14.45 – 15.00	Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance	G. Woo
15.00 — 15.30	Objectives and expected outputs of the meeting Proposed way of working – Working Groups	M. Costarrica
15.30 – 16.00	Coffee break	
16.00 – 16.45	List of critically important antimicrobials for human use - an introduction	A. Aidara-Kane P. Collignon
16.45-17.30	List of Veterinary Critically Important Antimicrobials – an introduction	J. Acar

<b>Time</b>	<b>Tuesday 27 November 2007</b>	
9.00- 10.30	Comparison of WHO and OIE lists of antimicrobials General aspects? Where to go during the following days? Critical elements	P. Collignon G. Moulin
10.30 – 11.00	Coffee break	
11.00 – 12:30	Criteria for establishment of risk assessment priorities	G. Moulin
12.30 – 13.30	Lunch	
13.30 – 15.30	Identification of priority combinations for consideration	Working groups
15.30 – 16.00	Coffee break	
16.00 – 17.30	Risk assessment of antimicrobial resistance – the principles	F. Aarestrup

<b>Time</b>	<b>Wednesday 28 November 2007</b>	<b>Speaker</b>
9.00-10.30	Risk Assessment Guidance – identification of policies and approaches – how to balance risks and benefits?	P. Fedorka Cray
10.30 – 11.00	Coffee break	
11.00 – 12.30	Risk Assessment Guidance – identification of possible data gaps for assessing risks and benefits	Working groups
12.30 – 13.30	Lunch	
13.30 – 15.30	Risk management options – review of national approaches Possible case studies: Korea, Australia, US, France, Germany, Israel, Denmark	R. Kroger/R. Jones Participants
15.30 – 16.00	Coffee break	
16.00 – 17.30	Critically Important Antimicrobials – Impact on food production Risk management options – the developing countries perspective Possible case studies: India, Brazil, Argentina	M. Lützw V. Alday Sanz Participants

<b>Time</b>	<b>Thursday 29 November 2007</b>	<b>Speaker</b>
9.00-10.30	Risk management – general principles	Working groups
10.30 – 11.00	Coffee break	
11.00 – 12.30	Consideration of Codex Taskforce Working Programme	Working groups
12.30 – 13.30	Lunch	
13.30 – 15.30	Conclusions and Recommendations	Plenary
15.30 – 16.00	Coffee break	
16:00 – 17:30	Rapporteur and Secretariat prepare the report	

<b>Time</b>	<b>Friday 30 November 2007</b>	<b>Speaker</b>
9.00 – 12:30	Report: finalization and adoption of the report	Plenary
12.30 – 13:30	Lunch	
13.30 – 16.30	Report: finalization and adoption of the report	Plenary

## APPENDIX F PAPERS PRESENTED

M. Lützow	Ten years after – antimicrobial resistance and the food chain
A. Aidara-Kane P. Collignon	List of critically important antimicrobials for human use – an introduction
J. Acar	List of Veterinary Critically Important Antimicrobials – an introduction
G. Moulin P. Collignon	Comparison of WHO and OIE lists of antimicrobials
M. Lützow	Critically Important Antimicrobials – Impact on food production
F. Aarestrup *	Risk assessment of antimicrobial resistance – the principles
G. Moulin *	Criteria for establishment of risk assessment priorities – Risk profiles
P. Fedorka Cray	Risk Assessment Guidance – identification of policies and approaches
J. Palermo Neto (Brazil)	
YH Park (Korea)	
I. Karunasagar (India)	
A. Valois (Australia)	
G. Moulin (France)	National case studies
R. Kroker (Germany)	
R. Jones (USA)	
J. Errecalde (Argentina)	
S. Soback (Israel)	
R. Jones R. Kroker	Risk management options – review of national approaches
V. Alday Sanz	Risk management options – the developing countries perspective

NOTES: \* The Experts were asked to develop papers in close coordination.

## APPENDIX G

### DOCUMENTS SUBMITTED IN RESPONSE TO THE CALL FOR DATA

- Comments on the Stakeholder Meeting and Data for Expert Meeting on CIAs, Rome, 26–30 Nov. 2007, by the National Reference Laboratory for antimicrobial resistance, Italy.
- Overview of report “Veterinary uses of antibiotics, antimicrobial resistance and consequences on human health”, French Food Safety Agency, January 2006.
- Lowrance et al. 2007. Changes in antimicrobial susceptibility in a population of *Escherichia coli* isolated from feedlot cattle administered ceftiofur crystalline-free acid. *American Journal of Veterinary Research*, 68(5): 501–507.
- IFT [Institute of Food Technologists]. 2006. Antimicrobial Resistance: Implications for the Food System. An Expert Report, Funded by the IFT Foundation. *Comprehensive Reviews in Food Science and Food Safety*, 5: 71–137
- Finland: Management strategies and options to maintain the efficacy of critically important antimicrobials for humans and animals. Ministry of Agriculture and Forestry. Department of Food and Health. June 2007.
- FARM 2003-2004. Rapport du programme français de surveillance de l’antibiorésistance des bactéries d’origine animale. French antimicrobial resistance monitoring in bacteria of animal origin. French Food Safety Agency, August 2006.
- Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI. VICH Topic GL36. CVMP/VICH/467/03-FINAL-corr. European Medicines Agency, April 2007-12-30
- Singer et al. 2007. Modelling the relationship between food animal health and human foodborne illness. *Preventive Veterinary Medicine* 79: 186–203.
- Singer, R.S., Ward, M.P., Maldonado, G. 2006. Can landscape ecology untangle the complexity of antibiotic resistance? *Nature Reviews Microbiology*, 4: 943–952.
- Committee for Medicinal Products for Veterinary Use (CVMP). Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobial Resistance. Call for data and information. EMEA/CVMP/253620/2007, 14 June 2007.
- Committee for Medicinal Products for Veterinary Use (CVMP). Public statement on the use of (fluoro)quinolones in food-producing animals in the European Union: development of resistance and impact on human and animal health. EMEA/CVMP/SAGAM/184651/2005, London, 15 February 2007.
- Committee for Medicinal Products for Veterinary Use (CVMP). Concept paper on how to evaluate the risk/benefit balance of veterinary medicinal products. EMEA/CVMP/377102/2006, London, 18 December 2006.
- Committee for Medicinal Products for Veterinary Use (CVMP). CVMP Strategy on antimicrobials 2006–2010 and status report on activities on antimicrobials. EMEA/CVMP/353297/2005, London, 20 March 2006.
- National Veterinary Assay Laboratory (NVAL), Ministry of Agriculture, Forestry and Fisheries in Japan. Response to the “Call for Data and Information”. Information for joint FAO/WHO/OIE Expert Meeting on critically important antimicrobials. June 2007.
- World Organisation for Animal Health (OIE). OIE list of antimicrobials of veterinary importance. November 2007.
- Karunasagar, I., Pai, R., Malathi, G.R. & Karunasagar, I. 1994. Mass mortality of *Penaeus monodon* due to antibiotic resistant *Vibrio harveyi* infection. *Aquaculture*, 128: 203–209.
- Karunasagar, I., Otta, S.K. & Karunasagar, I. 1996. Biofilm formation by *Vibrio harveyi* on surfaces. *Aquaculture*, 140: 241–245.
- Ali, A., Karunasagar, I. & Karunasagar, I. 1997. Effect of oxytetracycline on the immune response in *Labeo rohita* to *Aeromonas hydrophila* vaccine. pp. 187–191, in: T. Flegel et al. (editors). *Diseases in Asian Aquaculture III*. Asian Fisheries Society.
- Otta, S.K., Karunasagar, I. & Karunasagar, I. 1999. Bacterial flora associated with shrimp culture ponds growing *Penaeus monodon* in India. *Journal of Aquaculture in the Tropics*, 14(4): 309–318.
- Otta, S.K., Karunasagar, I. & Karunasagar, I. 2001. Bacteriological study of shrimp (*Penaeus monodon*) hatcheries in India. *Journal of Applied Ichthyology*, 17: 59–63.
- Kumar, H.S., Parvathy, A., Karunasagar, I. & Karunasagar, I. 2005. Prevalence of *Escherichia coli* in tropical seafood and their antibiotic resistance. *World Journal of Microbiology & Biotechnology*, 21: 619–623.
- Vinod, M.G., Shivu, M.M., Umesha, K.R., Rajeeva, B.C., Krohne, G., Karunasagar, I. & Karunasagar, I. 2006. Isolation of *Vibrio harveyi* bacteriophage with a potential for control of luminous vibriosis in hatchery environments. *Aquaculture*, 255: 117–124.
- Karunasagar, I., Shivu, M.M., Girisha, S.K., Krohne, G. & Karunasagar, I. 2007. Biocontrol of pathogens in shrimp hatcheries using bacteriophages. *Aquaculture*, 268: 288–292.