REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 12–14 December 2011

1. Opening

The OIE ad hoc Group on Antimicrobial Resistance met from 12 to 14 December 2011 at the OIE Headquarters in Paris, France. Dr Elisabeth Erlacher-Vindel, Deputy Head of the Scientific and Technical Department, welcomed the participants on behalf of the Director General of the OIE, Dr Bernard Vallat.

The overall objective of the Group was to revise the relevant OIE Terrestrial Animal Health Code (Terrestrial Code) chapters relating to the use of antimicrobials and the containment of antimicrobial resistance in veterinary medicine (contained in Section 6 of this Terrestrial Code) using, as far as possible, user-friendly text while taking into note of the draft guidelines and the definitions developed by the FAO1/WHO2 Codex Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance.

The specific objective of this third meeting of the Group was to continue with the revision of the Terrestrial Code started at the first meeting by addressing Chapter 6.10. Risk assessment for antimicrobial resistance arising from the use of antimicrobials, and considering the comments received from OIE Member Countries on the proposed updated version of Chapter 6.9. of the Terrestrial Code drafted at the second meeting of the Group.

A presentation was given by Dr David White from the United States Food and Drug Administration (FDA) comparing and contrasting the antimicrobial resistance risk analysis approaches taken by OIE, Codex and the FDA (see Appendix IV). The OIE risk analysis framework was based on the Covello-Merkhofer model and included four components: hazard identification; risk assessment; risk management; and risk communication, whereas the Codex framework includes three main components: risk assessment; risk management (which includes risk assessment policy), and risk communication. The OIE risk assessment components were release assessment, exposure assessment, consequence assessment, and risk estimate, whereas the Codex risk assessment components were hazard identification, hazard characterisation, exposure assessment, and risk characterisation.

The OIE also circulated to the Group a related paper [Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin; Vose et al. (2001). Rev. sci. tech. Off. Int. Epiz. 20 (3), 811–827] (see Appendix V). The appendix C of this paper provided comparison between the Codex and the OIE approaches in greater details.

2. Appointment of chairperson and rapporteur

The meeting was chaired by Dr Herbert Schneider and Mr Christopher Teale acted as rapporteur.

3. Adoption of the Agenda

The adopted Agenda, List of Participants, and Terms of Reference are presented in Appendices I, II and III of this report, respectively.

1 FAO: Food and Agriculture Organization of the United Nations
2 WHO: World Health Organization

The Group was reminded that Chapter 6.10. of the *Terrestrial Code* had been adopted in 2003. Further revision was deemed necessary to take into account the Codex Guidelines on Risk Analysis of Foodborne Antimicrobial Resistance (CAC/GL 77-2011) developed by the *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance. The chapter was therefore revised with a primary focus on animal health and welfare while taking into account the Codex Guidelines that relate primarily to food.

The Group agreed that further discussion would be useful to clarify the practical application of both sets of guidelines (OIE and Codex), particularly for the overlapping areas of risk analysis process.

The title of the chapter was changed from risk assessment to risk analysis as the Group expanded the sections on risk management and risk communication; Chapter 6.6 would need to accommodate this change.

The Group was of the opinion that a reference in Chapter 6.10. to the article of Vose *et al.* (2001), mentioned above, would be useful to OIE Member Countries. It was also suggested that this article, which was published ten years before being updated.

5. **Review of and reply to the technical comments received from OIE Member Countries on the proposed updated version of Chapter 6.9. of the Terrestrial Animal Health Code**

Comments received from OIE Member Countries were reviewed and taken into consideration in finalising Chapter 6.9. of the *Terrestrial Code*.

6. **Finalisation of definitions of the terms identified at the second meeting**

Owing to time constraint, the Group was not able to discuss this agenda item.

7. **Discussion on the way forward to update the OIE list of antimicrobials of veterinary importance**

The Group discussed briefly the OIE list of antimicrobials of veterinary importance and agreed to address fully this matter at its next meeting.

8. **Next meeting**

Proposed dates of the next meeting: 2–4 July 2012 at the OIE Headquarters, Paris, France.

The main tasks for the next meeting would be:

- to review the OIE list of antimicrobials of veterinary importance and update it, if needed.
- to finalise definitions of the terms identified at the second meeting of the Group and to discuss the need for new definitions to be included in the glossary of the *Terrestrial Code*.
- to address the OIE Member Country comments received on the proposed revisions to Chapter 6.10. drafted at the third meeting.

9. **Other matters**

The Group noted that a global conference on antimicrobial resistance would be organised by the OIE on 13-15 March 2013, in Paris, France.
Appendix I

MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE
Paris, 12–14 December 2011

Agenda

1. Opening
2. Adoption of agenda
3. Appointment of chairperson and rapporteur
4. Review and update of Chapter 6.10.: “Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals” of the Terrestrial Animal Health Code taking into account the guidelines for risk analysis of foodborne antimicrobial resistance developed by the ad hoc Intergovernmental Task Force on Antimicrobial Resistance of the Codex Alimentarius
5. Review of and reply to the technical comments received from OIE Member Countries on the proposed updates to Chapter 6.9.: “Responsible and prudent use of antimicrobial agents in veterinary medicine” of the Terrestrial Animal Health Code drafted at the last meeting of the ad hoc Group
6. Finalisation of definitions of the terms identified at the second meeting (if time allows)
7. Discussion on the way forward to update the OIE list of antimicrobials of veterinary importance (if time allows)
8. Next meeting
9. Other matters
10. Adoption of report
MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 12–14 December 2011

List of Participants

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MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE  
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Terms of Reference

Review and update the chapters of the *Terrestrial Animal Health Code* related to antimicrobials and antimicrobial resistance in the following order:

- Chapter 6.8.: Monitoring of the quantities of antimicrobials used in animal husbandry;
- Chapter 6.7.: Harmonisation of national antimicrobial resistance surveillance and monitoring programmes;
- Chapter 6.9.: Responsible and prudent use of antimicrobial agents in veterinary medicine;
- Chapter 6.10.: Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals
Appendix (contd)  

AHG on Antimicrobial Resistance/December 2011

Appendix IV

**OIE, CODEX and FDA Risk Analysis Strategies**

**Codex Alimentarius**
- An international inter-governmental body that develops food standards and guidelines to promote consumer protection and facilitate world trade
- CAC created the Ad-Hoc Intergovernmental Task Force on Antimicrobial Resistance at its 29th (2006) session
  - Hosted by Republic of Korea
  - Limited existence – 4 meetings (2007-2010)
- **CTFAMR**
  - Assess the risks to human health associated with the presence in food and feed including aquaculture and the transmission through feed and food of AMR microbes and resistance genes and to develop appropriate risk management strategies

**CTFAMR**
- Goal was to develop a Codex AMR risk analysis approach that allows countries or regions to implement actions based upon identified and prioritized needs and available resources

- Chapter 6.7 Harmonization of national antimicrobial resistance surveillance and monitoring programs
- Chapter 6.8 Monitoring of the quantities of antimicrobials used in animal husbandry
- Chapter 6.9 Responsible and prudent use of antimicrobial agents in veterinary medicine
- Chapter 6.10 Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals

- Provide a transparent, objective and scientifically defensible method of assessing and managing the human and animal health risks associated with the development of resistance arising from the use of antimicrobials in animals

**OIE Risk Analysis Methodology**
- The Ad hoc Group of experts on antimicrobial resistance, appointed by OIE, has developed an objective, transparent and defensible risk analysis process, providing a valid basis for risk management decisions in respect to antimicrobial resistance. The components of risk analysis and of different possible approaches in risk assessment (qualitative, semi-quantitative, and quantitative) are defined. The Ad hoc Group recommended the following: an independent risk assessment based on scientific data, an iterative risk analysis process; a qualitative risk assessment systematically undertaken before considering a quantitative approach; the establishment of a risk assessment policy; and the availability of technical assistance for developing countries.

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Contrast Components of Food and Animal RA Models

The Components of Risk Analysis: a comparison of the systems used by the Codex Alimentarius and the Office International des Epizooties (OIE)

<table>
<thead>
<tr>
<th>Codex Alimentarius</th>
<th>OIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Assessment</td>
<td>Hazard Identification</td>
</tr>
<tr>
<td>Hazard Identification</td>
<td>Risk Assessment</td>
</tr>
<tr>
<td>Hazard Characterization</td>
<td>Risk Release Assessment</td>
</tr>
<tr>
<td>Exposure Assessment</td>
<td>Exposure Assessment</td>
</tr>
<tr>
<td>Risk Characterization</td>
<td>Consequence Assessment</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Risk Estimate</td>
</tr>
<tr>
<td>Risk Communication</td>
<td>Risk Communication</td>
</tr>
</tbody>
</table>

Definition of the Risk

The infection of humans with microorganisms that have acquired resistance to a specific antimicrobial used in animals, and resulting in loss of benefit of antimicrobial therapy used to manage the human infection

Difference between OIE and Codex

Place of hazard identification in the models

- OIE – Identification of “risk agents” (hazards) and the conditions under which they might potentially produce adverse consequences
- 2 types of hazards exist
  - Bacteria that have acquired resistance due to the use of a particular antimicrobial in animals
  - Resistance determinants selected as a result of the use of a particular antimicrobial in animals

Release Assessment

- Describes the biological pathways necessary for the use of a specific antimicrobial in animals to lead to the release of resistant microorganisms or resistance determinants into a particular environment
  - Estimates either qualitatively or quantitatively the probability of that complete process happening

Exposure Assessment

- Describes the biological pathways necessary for exposure of humans to the resistant microorganisms or resistance determinants released from a given antimicrobial use in animals
  - Estimates the probability of the exposures occurring

Consequence Assessment

- Describes the relationship between specified exposures to resistant microorganisms or resistant determinants and the consequences of those exposures
  - Describes the potential consequences of a given exposure and estimates the probability of them occurring

Risk Estimation

- Integrates the results from the risk assessment, exposure assessment and consequence assessment to produce overall estimates of risks associated with hazards
  - Takes into account the whole risk pathway from hazard identification to unwanted consequences
Risk Management and Communication

- Have to be continuously monitored and reviewed in order to ensure that objectives are being achieved

  - OIE Terrestrial Code Articles
    - 2.1.5 Principles of Risk Management
    - 2.1.6 Risk Management Components
    - 2.1.7 Principles of Risk Communication

Qualitative Risk Assessment

- Release assessment
  - Describes factors related to an antimicrobial drug and its use in animals that contribute to the emergence of resistant bacteria or resistant determinants in the animal

- Exposure assessment
  - Describes likelihood of human exposure to resistant bacteria or resistance determinants through animal-derived food
  - Evaluation based on relative consumption and contamination of those commodities

- Consequence assessment
  - Describes human health consequence of exposure to resistant bacteria (or determinants) based on importance of drug (or related drugs) to humans

Hazard Identification

The hazard has been defined as human illness, (that is):
- caused by an antimicrobial-resistant bacterium;
- attributable to an animal-derived food commodity, and;
- treated with a human antimicrobial drug of concern.

Release Assessment

- Probability that resistant bacteria will emerge in the target animals

<table>
<thead>
<tr>
<th>Relevant parameters</th>
<th>Extent to which relevant factors favor emergence of resistant bacteria</th>
<th>Release H, M, or L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>Spectrum of activity</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>Resistance mechanisms</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>Resistance transfer</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
<tr>
<td>OTHER</td>
<td>- Cautions (important)</td>
<td>- Moderate (important)</td>
</tr>
</tbody>
</table>

FDA/CVM Regulatory Approach

- Microbial Food Safety Risk Assessment
  - Part of the human food safety evaluation that assesses the impact of the use of an antimicrobial drug on the development of resistance among pathogenic zoonotic bacteria of human health concern
  - October 23, 2003
  - Approach applies to antimicrobial drugs intended for food-producing animals
  - Human exposure through ingestion of animal-derived food

Qualitative risk assessment approach

- Based on the process described by the OIE Ad Hoc Group on Antimicrobial Resistance

GFI152 - Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern

Step 2: Exposure Assessment

- Describes likelihood of human exposure to food-borne bacteria of human health concern through animal-derived food products

Hazard Characterization

Qualitative Risk Assessment

Step 1: Release Assessment

- Describes factors related to an antimicrobial drug and its use in animals that contribute to the emergence of resistant bacteria or resistant determinants in the animal

Risk Management

Could include advisory committee review, post-approval monitoring, label restrictions, adaptation and evaluation, or decline of drug approval application
**Exposure Assessment**

- Probability that humans consuming animal derived foods will be exposed to resistant bacteria of public health concern
- Evaluation based on relative consumption and contamination of those commodities
- Variety of data sources – all welcome to better address the concern
  - NARMS, CIPARS, DANMAP, etc

**Probability of food commodity contamination**

<table>
<thead>
<tr>
<th>Probability of food commodity contamination</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Medium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Evaluation based on relative consumption of commodities and relative contamination of those commodities**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Per capita consumption (pounds per capita per year)</th>
<th>Qualitative Ranking (High, Medium, Low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>62.4</td>
<td>High</td>
</tr>
<tr>
<td>Chicken</td>
<td>60.4</td>
<td>High</td>
</tr>
<tr>
<td>Pork</td>
<td>46.5</td>
<td>High</td>
</tr>
<tr>
<td>Fish and shellfish</td>
<td>16.5</td>
<td>Medium</td>
</tr>
<tr>
<td>Turkey</td>
<td>13.3</td>
<td>Medium</td>
</tr>
<tr>
<td>Lamb and mutton</td>
<td>0.9</td>
<td>Low</td>
</tr>
<tr>
<td>Veal</td>
<td>0.4</td>
<td>Low</td>
</tr>
<tr>
<td>Total meat</td>
<td>199.7</td>
<td></td>
</tr>
</tbody>
</table>

Source: USDA Economic Research Service, boneless trimmed equivalent

**Consequence Assessment**

**Probability that human exposure to resistant bacteria results in an adverse health consequence**

<table>
<thead>
<tr>
<th>Critical Importance</th>
<th>Important 1st &amp; 2nd generation cephalosporins, monobactams, quinolones</th>
<th>Highly Important 4th generation cephalosporins, aminoglycosides, clindamycin</th>
<th>Critically Important 3rd generation cephalosporins, macrolides, fluoroquinolones</th>
</tr>
</thead>
</table>

**Criteria for Ranking**

1. Antimicrobial drugs used to treat enteric pathogens that cause food-borne disease
2. Side therapy or one of few alternatives to treat serious disease or drug is essential component among many antimicrobials in the treatment of human disease
3. Antimicrobials used to treat enteric pathogens in non-food-borne disease
4. No cross-resistance within drug class and absence of linked resistance with other drug classes
5. Difficulty in transmitting resistance elements within or across genera and species of organisms

- Critically important: Meet **BOTH** criteria 1 and 2
- Highly important: Meet either 1 or 2
- Important: Meet either criteria 3, 4, or 5

**Qualitative Risk Integration**

Risk estimation integrates results from release, exposure and consequence assessments to produce overall measure of risk associated with hazards.

**Risk Estimation**

<table>
<thead>
<tr>
<th>Release</th>
<th>Exposure</th>
<th>Consequence</th>
<th>Risk Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Important</td>
<td>Low</td>
</tr>
<tr>
<td>Medium</td>
<td>Medium</td>
<td>Highly Important</td>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>Critically Important</td>
<td>High</td>
</tr>
</tbody>
</table>
Possible risk management steps range from denying the drug approval application to approving the application under various use conditions that assure the safe use of the product.

Examples of Possible Risk Management Strategies Based on the Level of Risk (H, M, or L)

<table>
<thead>
<tr>
<th>Approval conditions</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketing status</td>
<td>Category 1 (H)</td>
</tr>
<tr>
<td>Extra-label use</td>
<td>Rx</td>
</tr>
<tr>
<td>Post-approval tracking</td>
<td>NARMS</td>
</tr>
<tr>
<td>Advisory committee review</td>
<td>YES</td>
</tr>
</tbody>
</table>

Possible process for ranking (High, Medium, Low) of extent of antimicrobial drug use in animals based on duration and method of administration (GFI#152, Table 7, Page 23)

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Individual animals</th>
<th>Flock or herd of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short (&lt;6 days)</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>Medium (6-21 days)</td>
<td>L</td>
<td>M</td>
</tr>
<tr>
<td>Long (&gt;21 days)</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin


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This report, prepared by the OIE Ad hoc Group of experts on antimicrobial resistance, has not yet received the approval of the International Committee of the OIE.

Summary
The Ad hoc Group of experts on antimicrobial resistance, appointed by the Office International des Epizooties, has developed an objective, transparent and defensible risk analysis process, providing a valid basis for risk management decisions in respect to antimicrobial resistance. The components of risk analysis and of different possible approaches in risk assessment (qualitative, semi-quantitative and quantitative) are defined. The Ad hoc Group recommended the following: an independent risk assessment based on scientific data; an iterative risk analysis process; a qualitative risk assessment systematically undertaken before considering a quantitative approach; the establishment of a risk assessment policy; and the availability of technical assistance for developing countries.

Keywords
Appendix (contd)

AHG on Antimicrobial Resistance/December 2011

Introduction

This document presents the concept of risk analysis, comprising the components of hazard identification, risk assessment, risk management and risk communication, as applicable to antimicrobial resistance. The inter-relationship of these components is described and the respective distinct responsibilities of risk assessors and risk managers are identified. An example of a risk analysis methodology is given both in relation to animal health and to human health.

Background

Use of antimicrobials in animals for therapeutic, preventative and growth promotion purposes can reduce the therapeutic value of antimicrobials used in animal and human medicine because of losses in susceptibility of pathogenic bacteria. This risk may be represented by the loss of therapeutic value of one or several antimicrobial drugs and includes the emergence of multi-resistant bacteria.

The principal aim of risk analysis of antimicrobial resistance in bacteria from animals is to provide Member Countries of the Office International des Epizooties (OIE) with an objective and defensible method of assessing the risk to human health associated with the development of resistance due to the use of antimicrobial drugs in animals. The procedure should be transparent and clearly separate responsibilities in risk assessment and risk management. Risk assessment must be based on available scientific data and should be objective and subject to peer review. Risk management should be structured and evidence-based and should consider the use of the OIE International Animal Health Code (IAHCC) as a framework for action, including the control of the use of antimicrobial drugs in animals and the provision of clear guidelines for the use of antimicrobials in animals.

A policy framework for the authority regulating antimicrobials should be established to provide risk managers and risk assessors with a consistent set of legal, regulatory and administrative tools within which risk analyses must be conducted.

This Guideline explains the recommendations of the OIE Ad hoc Group on antimicrobial resistance for guidelines and principles for conducting transparent, objective and defensible risk analyses to control the impact of using antimicrobials in animals, and provides recommended definitions of terms used in risk analysis.

Two principal sets of terminology are currently in use in risk analysis related to this topic, namely: the United States (US) National Academy of Science (NAS) system on which the Codex Alimentarius Commission (Codex) approach is based, developed for food safety issues, and the Czebelo-Merkloher system on which the OIE International Animal Health Code risk analysis is based. Beyond their apparent differences, both systems are very similar and largely contain the same components. The way these components are ordered in each of these two systems has evolved because of the type of risks that are being addressed. The terminology presented in this document follows the Czebelo-Merkloher system. Comparison between the two systems and definitions of terms are given in Appendix B.

The risk analysis process

Risk analysis is defined in the OIE code as ‘The process composed of hazard identification, risk assessment, risk management and risk communication’. It is a term frequently used to describe the complete process of properly addressing a risk issue. It encompasses assessing and managing the risk together with all the appropriate communication between risk assessors, stakeholders and risk managers. A typical risk analysis proceeds as detailed below:

a) A policy framework will previously have been established by risk managers that describes the types of risk that need to be addressed, implying, among other things, the ranking of these risks among other risk issues. In consultation with technical experts and risk assessors, a strategy for the assessment of the risk is then formulated. The policy framework also provides an explanation of the type of risk management options that can be considered under the legislative and regulatory framework of the country. Finally, the policy framework should explain the risk decision-making process, including methods of evaluating and quantifying risks and the level of risk deemed to be acceptable.

b) A risk issue and plausible risk management action that could be taken to reduce or eliminate the risk are identified by management.

c) In consultation with technical experts, risk assessors and other stakeholders, a strategy for a preliminary assessment of the risk is formulated, including precisely how the risk is to be evaluated.

d) Risk assessors execute a preliminary qualitative assessment (scoping study) and advise management on the feasibility of assessing quantitatively the risk and on the identified risk management strategies. This report is made public.

e) Managers will determine from this scoping study whether the risk is sufficiently severe to warrant further action, including whether resources (which could be very limited) can be dedicated to the issue. If the risk is considered sufficiently important, and if feasible, risk managers may then instruct risk
Risk management

Risk management policy

Risk management policy is a new term defined as 'The regulatory policy framework for monitoring, measuring, assessing and managing risks involved in the use of antimicrobials in food producing animals'. A critical precursor to the risk analysis process is the development and public explanation of such a policy framework. This framework, aimed at providing guidelines for conducting an appropriate risk assessment, has to be developed by the risk managers with the technical support of the scientific experts in charge of the risk assessment.

The policy framework explains the philosophy behind monitoring and controlling risks involved in the use of antimicrobials in food producing animals. It should explain methods for involving risk assessment in the approval of new drug use, the various restrictions of use that might be applied to control and reduce any adverse impact, and the procedure for retesting apparent use of the drug. It must also explain how the human or animal impact due to resistance will be measured, what level of impact will be considered unacceptable, and how this information is used in the registration of new drugs.

The policy framework may also address the additional importance of certain antimicrobial drugs needed to treat infectious diseases in human medicine for which there are no effective alternative therapies. Furthermore, it should explain the range of risk reduction actions that management can select within legislative and regulatory restrictions.

The framework should explain the impact of uncertainty on the risk management decision. It should also address what actions will be taken in the event of identifying an unquantifiable risk due to antimicrobial use.

The establishment of a population of resistant bacteria as a result of the use of an antimicrobial in animals means that the human or animal health impact may continue long after the animal use of an antimicrobial has ceased. The policy framework should therefore address how to manage a long-term impact, and may include some cut-off period or discount factor that recognizes the reduced value of a therapeutic drug as new drugs become available.

However, the policy framework should not necessarily restrict risk management from considering potential risk management options that may be outside the current domain of the
regulatory authority. Clear explanation of these conditions allows the pharmaceutical and agricultural industries and the veterinary and healthcare professional bodies to plan and test current and future antimicrobial products in a predictable environment and modify their use to achieve clear objectives.

Clearly stating the policy framework ensures transparency during the risk management phase of a risk analysis. People react to risk in very different and often emotional ways: a clear policy on how to measure risk and what is deemed acceptable implicitly recognizes that a zero risk policy is unachievable and greatly reduces any suspicion of false argument.

Risk management components

Risk management is conducted by risk managers who have a comprehensive understanding of policy and an appropriate level of technical background to communicate effectively with the risk assessors. The OIE defines risk management as consisting of the steps described below.

Risk evaluation

The process of comparing the risk estimated in the risk assessment with the appropriate level of protection of the Member Country.

Option evaluation

The process of identifying, evaluating the efficiency and feasibility of, and selecting measures in order to reduce the risk associated with an importation in line with the appropriate level of protection of the Member Country. The efficacy is the degree to which an option reduces the likelihood and/or magnitude of adverse biological and economic consequences. Evaluating the efficacy of the options selected is an iterative process that involves their incorporation into the risk assessment followed by comparison of the resulting level of risk with that considered acceptable. The evaluation for feasibility normally focuses on technical, operational and economic factors affecting the implementation of the risk management options.

Implementation

The process of following through with the risk management decision and ensuring that the risk management measures are in place.

Monitoring and review

The ongoing process by which the risk management measures are continually assessed to ensure that they are achieving the results intended.

Risk decision when data are insufficient or inadequate

In the event that insufficient or inadequate data are available to reasonably assess the importance of a potential risk issues, and it is considered that the risk is potentially of such severity that one cannot wait for sufficient data before taking action, it is reasonable for the risk managers to take a temporary risk avoidance action that minimizes any exposure to the risk. There are five extremely important considerations when faced with this situation, as follows:

a) A risk assessment must first be attempted, and all reasonable efforts made to acquire the necessary data, within the allowable timeframe, before taking the temporary risk avoidance action.

b) the risk avoidance action must be chosen to provide the required level of protection in the manner least restrictive to trade.

c) the risk avoidance action should be commensurate with the potential severity of the risk.

d) in all cases, particularly in international trade, the risk avoidance action should be taken in conjunction with a commitment to acquire the necessary data, within a reasonably short and defined time, to help assess the severity of the risk and the most appropriate risk reduction strategy.

e) the process must remain transparent.

Risk assessment

Risk assessment is defined in the OIE Code as ‘The evaluation of the likelihood and the biological and economic consequences of entry, establishment, or spread of a pathogenic agent within the territory of an importing country’. There are a number of approaches to assessing the magnitude of a risk and the value of potential risk reduction options. These can be broadly categorised into three types: qualitative, semi-quantitative and quantitative risk assessments. Whichever approach is taken, the risk assessment must be designed to address the specific question posed by the risk managers.

The risk assessment process is usually sub-divided into four components: risk release assessment; exposure assessment; consequence assessment; and risk estimation. Their meanings are described below and examples of factors that may be considered in each component are listed in Appendices A and B.

Release assessment

Defined in the OIE Code as ‘Description of the biological pathways necessary for the use of an antimicrobial in animals to release resistant bacteria or resistance determinants into a particular environment, and estimating the probability of that complete process occurring either qualitatively or quantitatively’.

Exposure assessment

Defined in the OIE Code as ‘Describing the biological pathways necessary for exposure of animals and humans to the hazards released from a given source, and estimating the probability of the exposure occurring, either qualitatively or quantitatively’.
Consequence assessment

Defined in the OIE Code as ‘Description of the relationship between specified exposures to a biological agent and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of their occurring. This estimate may be either qualitative or quantitative’.

Risk estimation

Defined in the OIE Code as ‘Integration of the results from the release assessment, exposure assessment, and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. Thus risk estimation takes into account the whole of the risk pathway from hazard identified to unwanted outcome’.

The policy framework will provide guidelines to the risk assessors on how to assess the complete impact of any risk issue and risk reduction strategies. For example, removing an antimicrobial from veterinary use may mean that another antimicrobial is used in its place with potentially worse consequences. Unless these secondary impacts, whether positive or negative, are addressed, the risk management strategy may be sub-optimal.

The initial planning stages of a risk assessment can be performed as described below:

a) The risk issue in question is formally expressed to ensure that all participants agree on the problem to be addressed. The potential mechanisms and pathways via which the hazard can result in an adverse effect are also described. This system, as understood by the risk assessment team, can be explained using one or more flow diagrams. At this point, the diagram is purely conceptual and there is therefore no need for data. The purpose of such diagrams is to focus thought on what data would be useful, what possible risk management options exist, and to integrate and review the level of knowledge about the system in general. It is advisable to involve a broad participation in the exercise and to circulate widely to stakeholders and relevant experts.

b) A preliminary data search is conducted to assess what components of the system might be adequately quantified. Components might include, for example, the prevalence of resistant bacteria in flocks, water or carcasses; the distribution by animal species, season and geographical region of use of an antimicrobial; the frequency of the use of the antimicrobial in human medicine and the health status of those receiving the antimicrobial. At this stage, it is sufficient to know of the availability of data. Requests for data that might help quantify the components of the system can also be made to stakeholders and relevant experts. Strong consideration should also be given to useful data that may not be immediately available, but that could become available within a reasonable period, perhaps with some research effort. The interpretation of what constitutes a reasonable period will reflect the importance and severity of the risk issue in question. It may be appropriate to consider completing a risk assessment rapidly to help decision makers identify the immediate actions to be taken, recognising that a re-evaluation of the risk issue when more data become available may lead the decision maker to alter the preliminary actions that were taken.

c) A review of the system, as perceived by the risk assessment team, together with the data available to quantify the components of that system can provide important guidance. It can illustrate which risk management options can be properly assessed for their effectiveness. It can also guide the risk assessor regarding the production of a quantitative risk assessment, if required, that would be based on data as well as supplying guidance as to whether such a model could be validated in some way. It is the combination of feasible risk management options, together with the data that could be available to assess those options, that should direct the risk assessment team towards the form of their assessment. If the system is not sufficiently well understood, or insufficient data are available to meaningfully quantify the model, it may only be possible to produce a qualitative risk analysis. However, quantification of certain aspects of the system may also be possible, which could enable the evaluation of a restricted number of risk management options. The risk assessment model can be kept as simple as possible to support the range of risk management decisions being considered. The model structure may not include a complete pathway analysis of the risk scenario if there are limited risk reduction strategies the benefits of which could be addressed in a far simpler model. Flexibility in the approach to modelling will reduce the effort required to produce the assessment and limit the number and type of assumptions that may have to be made in the model. However, the model may not then be useful in addressing other questions that arise over the same risk issue and may not help other stakeholders contribute to efficiently managing the risk. It may also be difficult to demonstrate consistency between models where different model structures have been used together with quite different assumptions.

A full assessment of the risk to human and animal health from antimicrobial-resistant bacteria resulting from use of antimicrobials in food-producing animals can be divided into three parts, as follows:

a) Production of the resistant bacteria of interest as a result of antimicrobial use, or more particularly, production of the resistant determinants if transmission is possible between bacteria. (If it is the use of the antimicrobial in animals that is being considered as the hazard, there may be several different species of bacteria to consider.)
b) consideration of the realistic pathways via which humans can become exposed to these resistant bacteria or resistance determinants; together with the possible range of bacterial load ingested at the moment of exposure.

c) consideration of the response of the person to the exposure.

Risk assessment of antimicrobial issues can be technically difficult, and it is essential that the assessment is the work of a team of professionals with broad expertise in risk analysis, modelling, microbiology, veterinary medicine and animal husbandry, human healthcare and medicine, chemistry and any other relevant disciplines. Published chemical, microbial and genetic risk assessments can provide useful generic illustrations for modelling components of the risk assessment.

**Qualitative risk assessment**

A qualitative risk assessment is defined in the OIE Code as 'An assessment where the outputs on the likelihood of the outcome or the magnitude of the consequence are expressed in qualitative terms such as high, medium, low or negligible'. A qualitative risk assessment is always completed first as part of a preliminary evaluation (scoping study), whether or not one progresses to a semi-quantitative or fully quantitative assessment. It is the collection of all available information that will enable the determination of the probability and impact of the risk to a question. A qualitative risk assessment discuss the steps necessary for the risk to occur, which pathways are feasible and which can be logically discounted. In a risk assessment of a human health impact due to use of a specific antimicrobial in food producing animals, for example, factors would include patterns of use of the antimicrobial, rate of resistance acquisition in exposed bacteria, the ecology of these resistant bacteria, pathways via which these bacteria may directly or indirectly transfer resistance to pathogens that infect humans, and the rates at which antimicrobial analogues to the animal antimicrobials are prescribed for the infected humans.

A qualitative risk assessment would also need to discuss the level of loss of benefit of the human medicine antimicrobial. All of these factors constitute a risk scenario on which one can overlay possible risk reduction strategies and discuss the benefits they might provide. Appendices A and B list factors that may be useful in an assessment. At this stage, a risk may be determined to be logically insignificant because, for example, the biological pathway is not possible or the risk is logically less severe than another for which a full analysis has been completed and determined to be acceptably small. As more risk assessments are conducted on antimicrobial issues, there may be broad agreement concerning the likely risks associated with particular hazards. In such cases, a qualitative assessment may frequently be the sole requirement. Qualitative assessment does not require mathematical modelling skills and so will often be the type of assessment used for routine decision-making.

When all easily-obtainable information has been collected, a preliminary report to the risk managers is necessary to advise of any further information that will be needed to complete the picture, or perhaps any additional information that will be necessary to complete a more quantitative analysis. It should also be apparent at this stage whether data are or can be made available to assess each risk reduction strategy and communicating this to the risk managers enables them to assess which risk reduction strategies are worth pursuing in greater depth.

**Quantitative risk assessment**

Quantitative risk assessment is defined in the OIE Code as 'An assessment where the outputs of the risk assessment are expressed numerically'. The purpose of quantitative risk assessment is to numerically evaluate the probability and impact(s) associated with a risk issue. Two principal mathematical approaches are feasible: the most common is to use a Monte Carlo simulation model to describe the risk event (the development of the hazard into an actual impact), together with its uncertainty (lack of knowledge) and variability (inherent randomness); the second method is to use the algorithms of probability theory to produce a formalistic model of the risk event. Monte Carlo simulation is almost always preferred over algebraic methods because it is far simpler to execute, particularly with modern software. It offers greater modelling flexibility and is easy to understand, check and explain, and less prone to human error in model development. However, Monte Carlo simulation of rare events can become onerous, in which case a combination of calculating some simpler parts of a risk scenario and simulating the remainder may sometimes prove more efficient.

A quantitative risk assessment produces a mathematical model that simulates the effect of possible risk management actions. It may be desired that any possible action between and including production of the food animal and the final human health effect be evaluated qualitatively. If so, the quantitative risk assessment model must simulate all important microbial pathways between the farm and the exposed human or animal in sufficient detail to evaluate possible changes in the system as a result of a risk management action. For risk management purposes, it may only be necessary to evaluate changes in the human or animal health impact as a result of a risk management action, not the underlying box health risk, although it may be informative to be able to estimate the base health risk for other purposes.

Thus, a full risk assessment model may need to consider a wide range of pathways. For example, *Enterococcus faecium* is a hardy organism that can survive for long periods outside its original host. Possible pathways may include, for example, run off from manure lagoons or fields sprayed with manure entering waterways used by swimmers, or the consumption of vegetables that have been grown in fields sprayed with manure. By contrast, these pathways would not be important for Campylobacter which succumb rapidly to changes in their environment. Failure to appreciate the range of pathways...
could lead to a misvaluation of the effect of some risk management action. For example, irradiation of poultry carcasses may be effective against Campylobacter if consumption of meat were to be considered the primary exposure pathway. However, irradiation might prove ineffective for E. faecium if the primary exposure pathway was from consumption of raw vegetables.

Microbial food safety risk assessments have for some time attempted to model very similar risk issues to those posed by antimicrobial resistance. A variety of modelling techniques exists for microbial risk assessments, based around the principles of stochastic simulation of risk scenarios (14, 18, 19, 22). Spreadsheet models are generally used together with Monte Carlo simulation add-ins to create simulations of the entire ‘farm-to-fork’ continuum, finishing with the way in which the consumer is affected by consumption of the bacteria. Other commercially available dynamic simulation applications can achieve much the same effect. There are a variety of formula-based models available from the field of predictive microbiology to estimate the growth and attenuation of various bacteria when exposed for different amounts of time to different environments, particularly level of moisture, temperature and pH. Thus, a quantitative risk assessment combines probability mathematics (11, 17), usually from the binomial and Poisson processes, with empirical curve-fitting equations and sometimes theoretically based formulae from predictive microbiology, to attempt to characterise the exposure events. Microbial food safety models consider the redistribution, growth and attenuation of bacteria during the various actions in slaughtering, processing, food handling and cooking. For example, the microbial load on contaminated carcasses will be reduced drastically through correct handling, removal of the most contaminated parts of the carcass, scaling and washing. In contrast, cross-contamination between carcasses through aerosols, splashing, vectors, etc., can mean that the proportion of contaminated carcasses leaving the slaughter plant is greater than the proportion of contaminated animals entering the plant. Much of the modelling principles necessary in antimicrobial resistance risk assessment parallels those used in microbial food safety risk assessment. At the time of writing (November 2000), very few antimicrobial resistance risk assessments have been published (http://www.fda.gov/ cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html; http://www.fda.gov/cvm/dis/mappges/antiofc.html); but a significant number of microbial food safety risk assessments have been completed which provide practical illustrations of the techniques employed (2, 8; http://www.fsis.usda.gov/index.htm; http://www.foodinclearinghouse.umd.edu/risk_assessments.htm; http://www.fsis.usda.gov/DIN/cutlisk/home.htm; http://www.m-udsa.gov/tractfoodborne/risk.htm).

Microbial risk assessments typically use logarithmic scales in estimating the microbial load because of the range of numbers that can be involved and the multiplying nature of bacterial growth and attenuation. Subsequent estimations of the probability of infection, illness or perhaps death from specific exposures are made through dose-response equations to produce a final estimate of the total human health impact. Risk assessments that model the complete microbial pathway from the farm to final ingestion are sometimes called ‘farm-to-fork’ or ‘farm-to-table’ risk assessments, though these are potentially misleading terms in cases where significant exposure pathways are associated with ingestion via other means (e.g. consumption of vegetables, ingestion through soil or water, and human to human or animal to human transmission). A full ‘farm-to-fork’ model invariably contains a host of potentially contestable assumptions because of the inherent complexity of the system being modelled and the gaps in knowledge of that system. It also relies on a great deal on the validity of a dose-response model, the weaknesses of which are well known (21).

In general, a risk assessment model should only be as complex as necessary to evaluate the risk management options available to the regulatory authority; therefore a full ‘farm-to-fork’ model may not be necessary. For example, the risk assessment completed by the United States Food and Drug Administration Center for Veterinary Medicine (USFDA-CVM) on the human health effect of fluoroquinolone-resistant Campylobacter (http://www.fda.gov/cvm/dis/mappges/antiofc.html) considered only the effect of removal of fluoroquinolone use in poultry. This assessment avoided any modelling of the ‘farm- to-fork’ pathways. It estimated the number of human cases of campylobacteriosis that would have been affected by the fluoroquinolone-resistance from poultry, to provide an estimate of the current risk. The argument was that removing fluoroquinolone from poultry would have the effect of reducing the human impact by this amount, which was supported by the low survivability of Campylobacter outside its host, so resistance would rapidly disappear. The assessment then related this risk to the level of prevalence of fluoroquinolone-resistant Campylobacter contaminated chicken carcasses at the end of the slaughter plant. The argument then presented was that changes in that prevalence and/or the load on the contaminated carcasses can be mapped to a corresponding change in the human health impact. The structure of models like this can be used very effectively in other countries, using data appropriate to that country, where similar assumptions would apply.

All parameters in a quantitative risk assessment model must be quantified. The most transparent approach, least likely to attract criticism, is to use published data from peer-reviewed papers. However, such data will frequently not be available and reasonable surrogates may be used in their place, together with supporting arguments for the surrogacy. Expert opinion may also be used, but it is more transparent if any data from which the expert has based his or her opinion can be used in its place (12). Unpublished data from reliable sources may also be used. Regardless of the source, all data used in the risk assessment must be critically reviewed.
A quantitative risk assessment must explicitly model the uncertainty associated with the model parameters using techniques like the bootstrap (5, 6), Bayesian inference (9, 20) and classical statistics (1, 10, 13). Bayesian inference is particularly useful at explicitly stating the contribution arising from observations, interpretation of those observations and any subjective estimation. Bayesian inference also allows the analyst to combine information from different sources, such as two different random surveys of a population for contamination with different test sensitivities and specificities.

The results of the risk assessment are presented as a report to the risk managers, explaining the methods used, characterising the risk in appropriate terms according to policy, together with the benefits of any risk reduction strategies that could be assessed. All quantified terms should be reported with their uncertainties in an easily understandable form. The relative frequency distribution provides an excellent visual representation of the level of uncertainty, whilst cumulative distribution plots allow the risk manager to evaluate the risk at any desired level of confidence. Sensitivity analyses should be performed to determine the key uncertainty parameters of the model and illustrated using techniques such as spider plots and tornado charts. Key assumptions must also be explicitly described, together with a balanced argument of the reasoning for the assumptions and a discussion of the inaccuracy of the predictions of the model should those assumptions be false. This model uncertainty must be clearly analysed, and possible methods of validating assumptions must be considered, perhaps through scientific experiments or comparisons with the experience of other nations. Inclusion and discussion of all types of uncertainty in the risk assessment report allow the risk managers to apply the appropriate level of conservatism in valuing the risk and any risk reduction options. It should be emphasised that failure to properly address uncertainty in the risk assessment report equates to an implicit value judgement of the risk that is not the remit of the risk assessor.

Semi-quantitative risk assessment

Semi-quantitative risk assessment is a new term defined as 'An assessment where estimates of the likelihood of the outcome and the magnitude of the consequences are expressed in semi-quantitative terms via some scoring mechanism. It will frequently not be possible to perform a complete quantitative risk assessment on each item in a portfolio of risk issues facing risk managers because of lack of appropriate data. In such circumstances, it would nonetheless be useful to have a method for comparing the magnitude of risks and the benefits of risk reduction strategies for those risks. Semi-quantitative risk assessment, when properly executed, is a transparent approach that supports the efficient management of a portfolio of risk issues without requiring complete quantification of the risks or excessive risk avoidance. Semi-quantitative risk assessment techniques are commonly used for risk analysis in commercial projects, but are currently not widely accepted in international risk issues because of the difficulty in retaining transparency and because the process is open to abuse without proper guidelines.'

The principle of semi-quantitative risk assessment (22) is initially to estimate the probability and size of the potential consequences into broad, but well-defined categories, then convert these estimates using a scoring system to produce a severity score for the risk. Various risk management options can be evaluated according to the degree to which they would reduce the severity score of the risk. The technique has a number of advantages, as follows:

- the risks can be compared in a systematic fashion
- a severity threshold can be set for unacceptable risk
- an efficient and consistent policy framework can be developed which minimises the total severity scores for all risks given the resources available.

Risk communication

As defined in the OIE Code, 'Risk communication is the interactive exchange of information on risk among risk assessors, risk managers and other interested parties. There are many aspects to risk communication. Failure to pay proper attention to risk communication may easily result in failure of the risk analysis process. Both risk managers and risk assessors should be well versed in the concepts of risk analysis. The risk assessors should have a clear understanding of policy. Similarly, the risk managers should be fully conversant with the terminology and terminology of risk assessment and appreciate the level of effort and variety of disciplines involved in producing a reliable risk assessment. The goals of risk communication are the following:

- to promote awareness and understanding of the specific issues under consideration during the risk analysis process, by all participants
- to promote consistency and transparency in arriving at and implementing risk management decisions
- to provide a sound basis for understanding the risk management decisions proposed or implemented
- to improve the overall effectiveness and efficiency of the risk analysis process
- to strengthen working relationships and mutual respect among all participants
- to promote the appropriate involvement of all stakeholders in the risk communication process
- to exchange information on the knowledge, attitudes, values, practices and perceptions of stakeholders concerning the risks in question.'
The joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Consultation on the application of risk communication to food standards and safety measures, held in 1998 in Rome, provides an in-depth discussion on the subject (7).

**Communication between assessors and managers**

Management must provide clear instructions for the risk issue that is to be analyzed, together with the preferred method(s) of characterization (e.g., percent days of illness per year). Assessors must ensure that the managers have reasonable expectations of the assessment and may also advise of other potential information the assessment may provide that would help the management in their decision-making. There should be communication between the risk assessors and risk managers throughout the assessment process to ensure that the assessment is completed in a timely fashion and that the required resources are made available.

**Communication between assessors and stakeholders**

It is extremely helpful to widely publicize the intended method of assessment, including model structure and assumptions at the earliest possible opportunity, together with an expression of flexibility in the eventuality of any new information or ideas. This allows stakeholders to provide input, improve transparency of the process and improve support for the assessment and any resultant risk management decision.

**Communication between managers and stakeholders**

Risk managers will usually need to advise stakeholders of the intention to perform a risk analysis at the beginning of the project. At this stage, communication with stakeholders is an important opportunity to gather political and scientific support for the risk assessment, as well as a data gathering exercise. When the risk assessment has been completed, it is advisable to make the report publicly available with a reasonable comment period to ensure that there are no major errors in the assessment or additional data available. The World Wide Web is an excellent means for maximizing the availability of the assessment and may include downloadable, self-contained versions of the risk assessment. Publishing comments received, together with any responses from the risk assessment and risk management teams, underlines the transparency of the process. These can be included in the final risk analysis document that explains the results of the risk assessment together with the risk management decision that has been made.

**Recommendations**

To effectively manage antimicrobial resistance risk issues, the OIE Ad hoc Group recommends that:

- risk analysis should be conducted in an objective and defensible manner;
- the risk analysis process should be transparent and consistent;
- risk analysis should be conducted as an incentive and continuous process;
- risk management and risk assessment functions should be kept separate to ensure the independence of decision-making and evaluation of the risk;
- risk management should be conducted in reference to a policy framework setting out the domain of the regulator and the range of risk reduction actions that may be considered;
- the risk assessment should be based on sound science and conducted according to a strategy established by the risk managers in co-operation with the risk assessors;
- risk assessment requires a multidisciplinary team and should be conducted in broad consultation with available scientific expertise;
- qualitative risk assessment should always be undertaken, and provides information on whether progression to full quantitative risk assessment is feasible and/or necessary;
- risk assessment of antimicrobial resistance issues requires very specific, technical skills that may not be available to developing countries. The OIE and its Member Countries should work towards helping these countries to develop or access these skills, to ensure that risk assessment itself does not become a barrier to trade;
- communication between managers, assessors and stakeholders is essential. Effort should be made to establish such communication early in the process, to allow opportunity for responses, and should be continued throughout the risk analysis process.
Appendix (contd)

Antibiorésistance :
méthodologie d’analyse du risque appliquée à l’impact potentiel sur la santé publique des bactéries d’origine animale résistantes aux antibiotiques

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H.C. Wegener & M.L. Costarica

Résumé
Le Groupe Ad hoc d’experts sur l’antibiorésistance créé par l’Office international des épizooties a élaboré une procédure d’analyse du risque à la fois objective, transparente et justifiée, offrant une base valable pour les décisions de gestion du risque relatives à l’antibiorésistance. Les auteurs définissent les éléments constitutifs de l’analyse du risque et les différentes approches possibles de l’évaluation du risque (qualitative, semi-quantitative et quantitative). Les recommandations du Groupe ad hoc portent sur les points suivants : évaluation du risque indépendante basée sur des données scientifiques ; processus itératif d’analyse du risque ; réalisation systématique d’une évaluation qualitative du risque avant toute approche quantitative ; élaboration d’une politique d’évaluation du risque ; enfin, préstation d’une assistance technique pour les pays en développement.

Mots-clés

Resistencia a los antimicrobianos:
metodología de análisis de riesgos para determinar la eventual incidencia en la salud pública de bacterias de origen animal resistentes a los antimicrobianos

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Resumen
El Grupo Ad hoc de expertos sobre la resistencia de las bacterias a los productos antimicrobianos, creado por la Oficina Internacional de Epizootias, ha elaborado un proceso de análisis de riesgos objetivo, transparente y defendible, brindando con ello una sólida base para tomar decisiones de gestión de riesgos ligados a la
Appendix A

Risk assessment of human health impact due to the use of antimicrobials in animals

The following list, although not exhaustive, describe factors that may need consideration in a risk assessment of human health impact.

Definition of the risk

The infection of humans with bacteria that have acquired resistance to the use of a specific antimicrobial in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the human infection.

Hazard identification

Two types of hazard exist, as follows:

1. Bacteria that have acquired resistance due to the use of a particular antimicrobial in animals;
2. Resistance determinants selected as a result of the use of a particular antimicrobial in animals.

The identification of the hazard must include considerations on the class or subclasses of antimicrobial.

Release assessment

Release assessment consists of describing the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring, either qualitatively or quantitatively. The release assessment describes the probability of the release of each of the potential hazards under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures. Examples of the kind of inputs that may be required in the release assessment are as follows:

- Species of animal treated with the antimicrobial in question
- Number of animals treated, geographical distribution of these animals
- Variation in methods of administration of the antimicrobial
- Bacteria developing resistance as a result of the antimicrobial use
- Mechanisms of direct or indirect transfer of resistance
- Capacity of resistance transfer (chromosomes, plasmids)
- Cross-resistance and/or co-resistance with other antimicrobials
- Surveillance of animals, animal products and waste products for the existence of resistant bacteria.

Exposure assessment

Exposure assessment consists of describing the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring, either qualitatively or quantitatively. The probability of exposure to the identified hazards is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed. Examples of the kind of inputs that may be required in the exposure assessment are as follows:

- Human demographics and consumption patterns, including traditions and cultural practices
- Prevalence of feed and/or the animal environment contaminated with resistant bacteria
- Prevalence of animal feed contaminated with resistant bacteria

Palabras clave

— microbial load in contaminated food at the point of consumption
— survival capacity and redistribution of resistant bacteria during the agrofood process (including slaughtering, processing, storage, transportation and retailing)
— disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in these waste products
— point of consumption of food derived from the food-producing animal (professional catering, home cooking)
— variation in consumption and food-handling methods of sub-populations
— capacity of resistant bacteria to settle in human intestinal flora
— human-to-human transmission of the bacteria under consideration
— capacity of resistant bacteria to transfer resistance to human commensals
— exposure to resistance determinants from other sources
— amount of antimicrobials used in response to human illness
— dose, route of administration (oral, injection) and duration of human treatment
— pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

Consequence assessment
Consequence assessment consists of describing the relationship between specified exposures to resistant bacteria or resistance determinants and the consequences of these exposures. A causal process must be believed to exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring. This estimate may be either qualitative or quantitative. Examples of consequences include the following:
— dose-response relationships
— variation in susceptibility of sub-populations
— variation and frequency of human health effects resulting from loss of efficacy of antimicrobials
— changes in human medicine practices resulting from reduced confidence in antimicrobials
— changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks
— associated costs
— interference with a classical first line antibiotic therapy in humans
— perceived future of the drug (time reference).

Risk estimation
Risk estimation consists of integrating the results from the release assessment, exposure assessment and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. Thus, risk estimation takes into account the whole of the risk pathway from the hazard identified to the unwanted outcome. For a quantitative assessment, the final outputs may include the following:
— number of people falling ill
— increased severity or duration of disease
— number of person-days of illness per year
— deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)
— importance of the pathology caused by the bacteria
— absence of alternate antimicrobial therapy
— level of resistance observed in humans
— any arbitrary scale of impact to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).

Risk management options to evaluate
The following risk management measures could be implemented:
— decision not to grant a licence for use of a new antimicrobial
— review of licence authorisation and label indications
— revoking of licence
— restrict use of antimicrobial (e.g. in particular industries, therapeutic only)
— review of prudent use guidelines
— establish monitoring of veterinary use of antimicrobials
— revision of treatment guidelines.

Appendix B

Risk assessment of impact on animal health due to the use of antimicrobials in animals

The following list, though not exhaustive, describe factors that may need consideration in a risk assessment of animal health impact.

Definition of the risk
The infection of animals with bacteria that have gained resistance from the use of a specific antimicrobial in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal infection.
Hazard identification
Possible hazards are as follows:

– bacteria that have acquired resistance due to the use of a particular antimicrobial in animals
– resistance determinants selected as a result of the use of a particular antimicrobial in animals.

The identification of the hazard must include consideration of:

– bacteriological and/or sub-class of antimicrobial.

Release assessment
Examples of the type of inputs that may be required in the release assessment are as follows:

– species of animal treated with the antimicrobial in question
– number of animals treated, geographical distribution of those animals
– variation in methods of administration of the antimicrobial
– bacteria developing resistance as a result of the antimicrobial use
– mechanism of direct or indirect transfer of resistance
– capacity of resistance transfer (chromosomes, plasmids)
– cross-resistance and/or co-resistance with other antimicrobials
– surveillance of animals, animal products and waste products for the existence of resistant bacteria.

Exposure assessment
The following are examples of the type of input that may be required in the exposure assessment:

– prevalence of resistant bacteria in all animals
– prevalence of food and/or the animal environment contaminated with resistant bacteria
– animal-to-animal transmission of the bacteria under consideration
– number/percentage of animals treated with the particular antimicrobial
– dissemination of resistant bacteria from animals (animal husbandry, method, movement of animals)
– prevalence of animal food contaminated with resistant bacteria
– amount of antimicrobial used in animals
– treatment (dose, route of administration, duration)
– microbial food in contaminated food at point of consumption
– survival capacity of resistant bacteria (competition of mixed population; survival in the environment; contamination cycles
including potentially the following elements: animals, humans, animal food, environment, food, non-food producing animals, wildlife)
– dissemination of resistant bacteria and resistance determinants
– disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in these waste products
– capacity of resistant bacteria to become established in animal intestinal flora
– exposure to resistant determinants from other sources
– dose, route of administration (e.g., injection) and duration of human treatment
– pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

Consequence assessment
Examples of consequences include the following:

– dose-response relationships
– variation in susceptibility of sub-populations
– variation and frequency of animal health effects resulting from loss of efficacy of antimicrobials
– changes in veterinary medicine practices resulting from reduced confidence in antimicrobials
– associated costs
– perceived future of the drug (time reference).

Risk estimation
For a quantitative assessment, the final outputs may include the following:

– number of therapeutic failures due to resistant bacteria
– animal suffering (level and increase)
– economic cost (treatment with antibiotics, veterinary services, husbandry, reduced income, loss of market)
– deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)
– level of resistance observed in animals.

Risk management options to evaluate
The following risk management measures could be implemented:

– decision not to grant a licence for use of a new antimicrobial
– review of licence authorisation and label indications
– revocation of licence for antimicrobials already used
– restrict use of antimicrobial (e.g. in particular industries, therapeutic only)
– review of prudent use guidelines
– establish monitoring of veterinary use of antimicrobials
– revision of treatment guidelines.
Appendix C

Comparison of systems and terms used by the Codex Alimentarius and the Office International des Epizooties

The terms used in this document comply with the OIE terminology, as defined in Section 1.4. of the Gak (16) based on the Covello-Merkhofer system (4). The Codex Alimentarius (3) uses a different, but equally valid system, designed by the US NAS (15). The issue of antimicrobial resistance arising from the use of antimicrobials in food-producing animals bridges the domain of OIE for animal husbandry and that of the FAO for food safety. It is therefore useful to compare these two systems and define terms used in this paper, to help integrate the two approaches.

Two risk analysis terminology systems: description

Table I summarises the components of risk analysis in the OIE and Codex models.

<table>
<thead>
<tr>
<th>Components of risk analysis system</th>
<th>Codex Alimentarius</th>
<th>OIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk assessment</td>
<td>Hazard identification</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>Risk management</td>
<td>Risk management</td>
<td>Risk management</td>
</tr>
<tr>
<td>Risk communication</td>
<td>Risk communication</td>
<td>Risk communication</td>
</tr>
</tbody>
</table>

Table I summarises the components of risk analysis in the OIE and Codex models.

Table II summarises the components of risk assessment in the OIE and Codex models.

<table>
<thead>
<tr>
<th>Components of risk assessment model</th>
<th>Codex Alimentarius</th>
<th>OIE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard identification</td>
<td>Risk release assessment</td>
<td>Risk release assessment</td>
</tr>
<tr>
<td>Hazard characterisation</td>
<td>Exposure assessment</td>
<td>Exposure assessment</td>
</tr>
<tr>
<td>Exposure assessment</td>
<td>Consequence assessment</td>
<td>Consequence assessment</td>
</tr>
<tr>
<td>Risk characterisation</td>
<td>Risk estimate</td>
<td>Risk estimate</td>
</tr>
</tbody>
</table>

In a system based on the NAS model (called the ‘Codex system’ here), there are only three components of risk analysis, whereas in the system based on the Covello-Merkhofer model (called the ‘OIE system’ here), four components are present. Both systems include risk assessment, risk management and risk communication as components of risk analysis. However, the OIE system also includes hazard identification as a component of risk analysis, whereas the Codex system includes hazard identification as a sub-component of risk assessment. The terms risk management and risk communication are equivalent under both systems.

The NAS system was initially developed to assess the risks to health from exposure to chemicals. Codex has adapted this system for food safety purposes. The Covello-Merkhofer system was initially developed to assess a wide range of risks from any potential hazard, the specific wording of the explanations in Table III reflects these differences.

The first difference centres around the place of hazard identification in the models. The initial report of the NAS model (15), describes hazard identification as a major undertaking. The definition relates specifically to chemicals, and even in this case, NAS indicates that it includes weighting the available evidence relevant to cause and effect, as well as evidence relating to the magnitude of effect for the specified chemical. It is essentially a qualitative process of considerable magnitude. Given the number of potential pathogens hazards present in animals and animal products, the OIE risk analysis system, with a separate hazard identification step, is more adapted to pathogenic risk management.

The second difference is the presence in the OIE system of a step called release assessment, absent in the Codex system. Covello and Merkhofer argue that this is necessary for describing the probability of a given system (e.g. an individual, complex, a meat processing plant or another risk source) to release risk agents into the environment of interest. They believe this to be an essential step in obtaining an accurate understanding of risk. From a practical standpoint, this is an essential explicit step to either assess the risks due to a particular hazard from a specific source or process, or to undertake a cost-benefit analysis of putting in place release reduction safeguards for that source or process.

Release comes before the possibility of exposure in actual exposure events. Thus, the Covello-Merkhofer system follows release assessment by assessing the probability of exposure for each potential exposure route of interest. The third difference between the models is that the NAS system places exposure assessment after the dose response (hazard characterization) step. The precise definitions are also slightly different.

The fourth difference is in the place and meaning of consequences in the two models. Exposure can then lead to consequences – unwanted consequences when considering a hazard. Thus, the Covello-Merkhofer system places consequences assessment after exposure assessment, and defines it broadly (as any consequences that can occur can be considered, and their probability assessed). However, the NAS system looks only at the consequences of variation in dose of the chemical being considered (i.e. a dose-response assessment, also called hazard characterization).
<table>
<thead>
<tr>
<th>Term</th>
<th>Office International des Epizooties definition or equivalent</th>
<th>Codex Alimentarius definition or equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acceptable risk</td>
<td>Risk level judged by Member Countries to be compatible with the protection of animal and public health within their country</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Consequence assessment</td>
<td>Description of the relationship between exposure to a biological agent and the consequences of those exposures. A causal process must exist by which exposure produces adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of these consequences occurring. The estimate may be either qualitative or quantitative.</td>
<td>Consequence assessment</td>
</tr>
<tr>
<td>Dose-response assessment</td>
<td>DQE equivalent: consequence assessment</td>
<td>The determination of the relationship between the magnitude of exposure (DQE) for a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response) – see Hazard characteristics</td>
</tr>
<tr>
<td>Exposure assessment</td>
<td>Describing the biological pathways necessary for exposure of animals and humans to the hazards released from a given source, and estimating the probability of the exposure occurring, either qualitatively or quantitatively.</td>
<td>The qualitative and/or quantitative evaluation of the likely etiology of biological, chemical and physical agents via food, as well as exposures from other sources if relevant</td>
</tr>
<tr>
<td>Hazard</td>
<td>In the context of this Code, any pathogenic agent that could produce adverse consequences on the importation of a commodity.</td>
<td>A biological, chemical or physical agent is, or condition of, food with the potential to cause an adverse health effect.</td>
</tr>
<tr>
<td>Hazard characterization</td>
<td>Embedded in the ‘consequence assessment’ in the DQE system</td>
<td>The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical and physical agents that may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are available.</td>
</tr>
<tr>
<td>Hazard identification</td>
<td>The process of identifying the pathogenic agents which could potentially be introduced to the commodity considered for importation.</td>
<td>The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.</td>
</tr>
<tr>
<td>Implementation</td>
<td>The process of following through with the risk management decision and ensuring that the risk management measures are in place.</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Monitoring and review</td>
<td>The ongoing process by which the risk management measures are continually assessed to ensure that they are achieving the results intended.</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Option evaluation</td>
<td>The process of identifying, evaluating the efficiency and feasibility of, and selecting measures in order to reduce the risk associated with an importation is done at the appropriate level of protection of the Member Country. The efficacy is the degree to which an option reduces the likelihood and/or magnitude of adverse biological and economic consequences. Evaluating the efficacy of the options selected is an iterative process that involves their incorporation into the risk assessment and then comparing the resulting level of risk with that considered acceptable. The evaluation for feasibility normally focuses on technical, operational and economic factors affecting the implementation of the risk management options.</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Quantitative risk assessment</td>
<td>An assessment in which the outputs of the risk assessment are expressed in quantitative terms.</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Quantitative risk assessment</td>
<td>An assessment in which the outputs of the risk assessment are expressed numerically.</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>Description of the biological pathways necessary for the use of an antimicrobial in animal or plant resistance determinants and the overall probability of that process occurring, either qualitatively or quantitatively.</td>
<td>The likelihood of the occurrence and the likely magnitude of the consequences of an adverse event to animal or human health in the importing country during a specified time period.</td>
</tr>
</tbody>
</table>
### Table III (contd)

<table>
<thead>
<tr>
<th>Term</th>
<th>Office International des Epizooties definition or equivalent</th>
<th>Codex Alimentarius definition or equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk analysis</td>
<td>The process composed of hazard identification, risk assessment, risk management and risk communication</td>
<td>A process consisting of three components: risk assessment, risk management and risk communication</td>
</tr>
<tr>
<td>Risk assessment</td>
<td>The evaluation of the likelihood and the biological and economic consequences of entry, establishment, or spread of a pathogenic agent within the territory of an importing country</td>
<td>A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment and (iv) risk characterization</td>
</tr>
<tr>
<td>Risk characterisation</td>
<td>OIE equivalent, risk estimation</td>
<td>The qualitative and/or quantitative estimation, including uncertainies, of the probability of occurrence and severity of known or potential zoonotic health effects in a given population based on a hazard identification, hazard characterization and exposure assessment</td>
</tr>
<tr>
<td>Risk communication</td>
<td>Risk communication is the interactive exchange of information on risk among risk assessors, risk managers and other interested parties</td>
<td>The interactive exchange of information and openness throughout the risk analysis process concerning hazards and risks, risk-related factors and risk perceptions, among assessors, risk managers, consumers, industry, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions</td>
</tr>
<tr>
<td>Risk estimation</td>
<td>Integration of the results from the risk assessment, exposure assessment and consequence assessment to produce overall measures of risks associated with the hazards identified at the outset. This, risk estimation takes into account the entire risk pathway from the hazard identified to the annoyed outcome</td>
<td>OIE equivalent, risk characterisation</td>
</tr>
<tr>
<td>Risk evaluation</td>
<td>The process of comparing the risk estimate in the risk assessment with the appropriate level of protection of the Member Country</td>
<td>Embedded in 'risk management' in the Codex system</td>
</tr>
<tr>
<td>Risk management</td>
<td>The process of identifying, selecting and implementing measures that can be applied to reduce the level of risk</td>
<td>The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and if needed, selecting appropriate prevention and control options</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>The process of examining the impact of the variation in individual model inputs on the model output in a quantitative risk assessment</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Transparency</td>
<td>Comprehensive documentation of all data, information, assumptions, methods, results, discussions and conclusions used in the risk analysis. Conclusions should be supported by an objective and logical discussion and the document should be fully referenced</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>The lack of precise knowledge of the input values which is due to measurement error or to lack of knowledge of the steps required, and the pathways from hazard to risk, when building the scenario (or being assessed)</td>
<td>No equivalent defined</td>
</tr>
<tr>
<td>Variability</td>
<td>A real-world complexity in which the value of an input is not the same for each case due to natural diversity in a given population</td>
<td>No equivalent defined</td>
</tr>
</tbody>
</table>

### Table IV

**Definition of new terms introduced in this document**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk management policy</td>
<td>The regulatory policy framework for the monitoring, measuring, assessing and managing of risks involved in the use of antimicrobials in food-producing animals</td>
</tr>
<tr>
<td>Semi-quantitative risk assessment</td>
<td>An assessment where estimates of the likelihood of the outcome and the magnitude of the consequences are expressed in semi-quantitative terms via a scoring mechanism</td>
</tr>
</tbody>
</table>
References


