

TERRESTRIAL ANIMAL HEALTH STANDARDS  
COMMISSION

FEBRUARY 2012 REPORT

CHAPTER 6.10.

RISK ANALYSIS ASSESSMENT FOR  
ANTIMICROBIAL RESISTANCE ARISING FROM  
THE  
USE OF ANTIMICROBIAL AGENTS IN ANIMALS

Article 6.10.1.

Recommendations for analysing the risks to animal and human public health from antimicrobial resistant micro-organisms of animal origin

1. Introduction

Problems related to antimicrobial resistance are inherently linked to antimicrobial use in any environment, including human and non-human usages. However, the emergence of antimicrobial resistance can occur through factors other than use of antimicrobial agents.

The use of antimicrobial agents for therapy therapeutic and non therapeutic purposes, prophylaxis and growth promotion in *animals* can reduce their efficacy in animal and human medicine, through the development of antimicrobial resistant strains of pathogenic micro-organisms. This *risk* may be represented by the loss of therapeutic efficacy of one or several antimicrobial agents drugs and includes the selection and dissemination of antimicrobial resistant micro-organisms emergence of multi-resistant micro-organisms.

2. Objective

The principal aim of *risk analysis*, for the purpose of this chapter, for antimicrobial resistance in micro-organisms from animals is to provide OIE Member Countries with 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 antimicrobial agents in *animals*.

3. The risk analysis process

The principles of *risk analysis* are described in Chapter 2.1, Section of this *Terrestrial Code*. The components of risk analysis described in this chapter are hazard identification, risk assessment, risk management and risk communication.

A qualitative risk assessment should always be undertaken. Its outcome will determine whether progression to a quantitative risk assessment is feasible and/or necessary.

4. Hazard identification

Hazard identification is defined under the OIE *Terrestrial Code* Chapter 2.1.

For the purpose of this chapter, the *hazard* is the resistant micro-organism or resistance determinant that emerges as a result of the use of a specific antimicrobial agent in *animals*. This definition reflects the development of resistance in a species of pathogenic micro-organisms, as well as the development of a resistance determinant that may be passed from one species of micro-organisms to another. The conditions under which the *hazard* might produce adverse consequences include any scenarios through which humans or *animals* could become exposed to a pathogen which contains that

resistance determinant, fall ill and then be treated with an antimicrobial **agent** that is no longer effective because of the resistance.

#### 5. Risk assessment

The *assessment of the risk* to human and animal health from antimicrobial-resistant micro-organisms resulting from the use of antimicrobials in *animals* should examine:

- a) the likelihood of emergence of resistant micro-organisms arising from the use of antimicrobial(s), or more particularly, **dissemination production** of the resistance determinants if transmission is possible between micro-organisms;
- b) consideration of all pathways and their importance, by which humans could be exposed to these resistant micro-organisms or resistance determinants, together with the **possible degree likelihood** of exposure;
- c) the consequences of exposure in terms of *risks* to human and ~~or~~ animal health.

**The general principle of risk assessment as defined in Chapter 2.1. of the *Terrestrial Code* applies equally to both qualitative and quantitative risk assessment. At a minimum, a qualitative risk assessment should always be undertaken.**

Article 6.10.2.

### **Analysis of risks to human health**

#### 1. Definition of the risk

The *infection* of humans with micro-organisms that have acquired resistance to a specific antimicrobial **agent due to the use** in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the human *infection*.

#### 2. Hazard identification

- Micro-organisms that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial **agent(s)** in *animals*.
- Micro-organisms having obtained a resistance determinant(s) from other micro-organisms which have acquired resistance arising from the use of an antimicrobial **agent(s)** in *animals*.

The identification of the *hazard* must include consideration of the class or subclass of the antimicrobial **agent(s)**. This definition should be read in conjunction with point 4) of Article 6.10.1.

#### 3. Release assessment

A release assessment describes the biological pathways necessary for the use of a specific antimicrobial **agent** in *animals* to lead to the release of resistant micro-organisms or resistance determinants into a particular environment, and estimating either qualitatively or quantitatively the probability of that complete process occurring. 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.

The following factors should be considered in the release assessment:

- species of animal treated with the antimicrobial agent(s) in question;
- number of *animals* treated, sex, age and their geographical distribution ~~of those *animals*~~;
- prevalence of infection or disease for which the antimicrobial agent is indicated in the target animal population;
- data on trends in antimicrobial agent use and changes in farm production systems;
- potential extra-label or off-label use;
- variation in methods and routes of administration of the antimicrobial agent(s);
- dosage regimen including duration of use;
- the pharmacokinetics or pharmacodynamics/pharmacokinetics of the antimicrobial agent(s);
- micro-organisms developing resistance as a result of the antimicrobial(s) use pathogens that are likely to acquire resistance in animal host;
- commensal bacteria which are able to transfer resistance to human pathogens;
- mechanisms and pathways of direct or indirect transfer of resistance;
- potential linkage of virulence attributes and resistance;
- cross-resistance and/or co-resistance with other antimicrobial agents;
- data on occurrence of resistant micro-organisms through surveillance of *animals*, products of animal origin and animal waste products for the existence of resistant micro-organisms.

#### 4. Exposure assessment

An exposure assessment describes the biological pathways necessary for exposure of humans to the resistant micro-organisms or resistance determinants released from a given antimicrobial use in *animals*, and estimating the probability of the exposures occurring. 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.

The following factors should be considered in the exposure assessment:

- human demographics and food consumption patterns, including traditions and cultural practices in respect to the preparation and storage of food;
- prevalence of resistant micro-organisms in food at the point of consumption;
- microbial load in contaminated food at the point of consumption for quantitative risk assessment;
- environmental contamination with resistant micro-organisms;
- prevalence of animal feed contaminated with resistant micro-organisms;
- transfer cycling of resistant micro-organisms between humans, *animals* and the environment;

- steps measures taken for of microbial decontamination of food;
- microbial load in contaminated food at the point of consumption;
- survival capacity and spread redistribution—of resistant micro-organisms during the food production process (including slaughtering, processing, storage, transportation and retailing);
- disposal practices for waste products and the opportunity for human exposure to resistant micro-organisms or resistance determinants in those waste products;
- point of consumption of food (professional catering, home cooking);
- variation in consumption and food-handling methods of exposed populations and subgroups of the population;
- capacity of resistant micro-organisms to become established in humans;
- human-to-human transmission of the micro-organisms under consideration;
- capacity of resistant micro-organisms to transfer resistance to human commensal micro-organisms and zoonotic agents;
- amount and type of antimicrobials used in response to human illness;
- pharmacokinetics (such as metabolism, bioavailability and access to intestinal flora).

##### 5. Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant micro-organisms or resistance determinants 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 them occurring.

The following factors should be considered in the consequence assessment:

- microbial dose—host response relationships;
- variation in susceptibility of exposed populations or subgroups of the population;
- variation and frequency of human health effects resulting from loss of efficacy of antimicrobial agents and associated costs;
- potential linkage of virulence attributes and resistance;

- ~~– changes in human medicinal 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 first line/choice antimicrobial therapy in humans;
- ~~– importance of the antimicrobial agent in human medicine perceived future usefulness of the antimicrobial (time reference);~~
- prevalence of resistance in human bacterial pathogens under consideration.

## 6. Risk estimation

A *risk* estimation integrates the results from the release assessment, exposure assessment and consequence assessment to produce overall estimates of *risks* associated with the *hazards*. Thus, *risk* estimation takes into account the whole of the *risk* pathway from *hazard identification* to the unwanted consequences.

The following factors should be considered in the *risk* estimation:

- number of people falling ill and the proportion of that number affected with antimicrobial resistant strains of micro-organisms;
  - ~~– adverse effects on vulnerable human sub-population (children, immuno-compromised persons, elderly, etc.);~~
  - increased severity or duration of infectious disease;
  - number of person~~s~~ or 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 severity of the pathology infection caused by the target micro-organisms;
  - existence or absence of alternative antimicrobial therapy;
  - ~~– potential impact of switching to an alternative antimicrobial agent (e.g. alternatives with potential increased toxicity);~~
  - occurrence incidence of antimicrobial resistance in target pathogens observed in humans;
  - consequences of the overall to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).
- ## 7. Risk management components options and risk communication

~~The OIE defines risk management as consisting of the steps described below. Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.~~

- a) Risk evaluation - the process of comparing the risk estimated in the risk assessment with the Member Country's appropriate level of protection.

b) Option evaluation.

A range of risk management options is available to minimise the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. Risk management decisions need to consider fully the implications of these different options for human health and animal health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial diseases of animals will have the dual benefit of reducing the risks linked to antimicrobial resistance, in cases where the bacterial disease under consideration has also developed antimicrobial resistance.

c) Implementation

Risk managers should develop an implementation plan that describes how the decision will be implemented, by whom and when. National or regional authorities should ensure an appropriate regulatory framework and infrastructure.

d) Monitoring and review

Risk management options have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

8. Risk communication

Communication with all interested parties be promoted at the earliest opportunity and integrated into all phasis of a risk analysis. This will provide all interested parties, including risk managers, with the better understanding of risk management approaches. Risk communication should be also well documented.

Article 6.10.3.

**Analysis of risks to animal health**

1. Definition of the risk

The *infection of animals* with micro-organisms that have acquired resistance ~~to from the use of~~ a specific antimicrobial agent(s) due to the use in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal *infection*.

2. Hazard identification

- mMicro-organisms that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial agent(s) in *animals*.
- mMicro-organisms having obtained a resistance determinant(s) from another micro-organisms which have acquired resistance arising from the use of an antimicrobial agent(s) in *animals*.

The *identification of the hazard* must include considerations of the class or subclass of the antimicrobial agent(s). This definition should be read in conjunction with point 4) of Article 6.10.1.

### 3. Release assessment

The following factors should be considered in the release assessment:

- animal species treated with the antimicrobial agent in question;
- number of *animals* treated, sex, age and their geographical distribution;
- dosage regimen including amounts used and duration of treatment use;
- variation in methods and routes of administration of the antimicrobial agent(s);
- the pharmacokinetics or pharmacodynamics / pharmacokinetics of the antimicrobial agent(s);
- site and type of *infection*;
- development of resistant micro-organisms;
- mechanisms and pathways of resistance transfer;
- cross-resistance and/or co-resistance with other antimicrobial agents;
- data on occurrence of resistant micro-organisms through surveillance of animals, products of animal origin and animal waste products for the existence of resistant micro-organisms.

### 4. Exposure assessment

The following factors should be considered in the exposure assessment:

- prevalence and trends of resistant micro-organisms in clinically ill and clinically unaffected *animals*;
- prevalence of resistant micro-organisms in feed / the animal environment;
- animal-to-animal transmission of the resistant micro-organisms (animal husbandry methods, movement of animals);
- number / or percentage of *animals* treated;
- dissemination of resistant micro-organisms from animals (animal husbandry methods, movement of animals);
- quantity and trends of antimicrobial agent(s) used in *animals*;
- treatment regimens (dose, route of administration, duration);
- survival capacity of resistant micro-organisms and spread of resistant micro-organisms;
- exposure of *wild-life* to resistant micro-organisms;
- disposal practices for waste products and the opportunity for animal exposure to resistant micro-organisms or resistance determinants in those products;

- capacity of resistant micro-organisms to become established in *animal* intestinal flora;
- exposure to resistance determinants from other sources such as water, effluent, waste pollution, etc.;
- dose, route of administration and duration of treatment;
- pharmacokinetics, such as (metabolism, bioavailability, access to intestinal flora);
- transfer cycling of resistant micro-organisms between humans, animals and the environment.

#### 5. Consequence assessment

The following factors should be considered in the consequence assessment:

- microbial dose - host response relationships;
- variation in disease susceptibility of exposed populations and subgroups of the populations;
- variation and frequency of animal health effects resulting from loss of efficacy of antimicrobial agents and associated costs;
- potential linkage of virulence attributes and resistance;
- changes in practices resulting from reduced confidence in antimicrobials;
- associated cost;
- perceived future importance/ usefulness of the drug antimicrobial agent in animal health (see OIE list of antimicrobials of veterinary importance) (time reference).

#### 6. Risk estimation

The following factors should be considered in the *risk* estimation:

- additional burden of disease due to antimicrobial resistant micro-organisms;
- number of therapeutic failures due to antimicrobial resistant micro-organisms;
- increased severity and duration of infectious disease;
- *animal welfare*;
- economic cost;
- 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);
- existence or absence of alternative antimicrobial therapy;
- potential impact of switching to an alternative antimicrobial agent e.g. alternatives with potential increased toxicity;
- estimation of the economic impact and cost on animal health and production;
- incidence of resistance observed in animals;

#### 7. Risk management options/ components and risk communication

The relevant provisions contained in Article 6.9.7. do apply.

Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

The relevant recommendations (Articles 2.1.5., 2.1.6. and 2.1.7.) in the *Terrestrial Code* apply.

A range of *risk management* options is available to minimize the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory *risk management* options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. *Risk management* decisions need to consider fully the implications of these different options for human health and animal health and *welfare* and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial *diseases* of *animals* will have the dual benefit of reducing the *risks* linked to antimicrobial resistance, in cases where the bacterial *disease* under consideration has also developed antimicrobial resistance. Appropriate communication with all stakeholders is essential throughout the *risk assessment* process.

#### 8. Risk communication

The relevant provisions contained in Article 6.9.8. do apply.