

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 microorganisms of animal origin

1. Introduction

Antimicrobial resistance is a naturally occurring phenomenon. However, problems related to antimicrobial resistance are inherently linked to antimicrobial agent use in any environment, including human and non-human usages. However, the selection emergence or dissemination of antimicrobial resistance can occur or be influenced by through factors other than the use of antimicrobial agents.

Antimicrobial resistance associated with the use of antimicrobial agents for therapeutic and non-therapeutic purposes may lead to the selection and dissemination of antimicrobial resistant microorganisms, with a resulting loss of therapeutic efficacy in animal and human medicine of one or several 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 microorganisms. 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

For the purpose of this chapter, the principal aim of risk analysis, for the purpose of this chapter, for antimicrobial resistance in micro-organisms from animals is to provide Members Countries with a transparent, objective and scientifically defensible method of assessing and managing the human and animal health risks associated with the selection and dissemination development of resistance arising from the use of antimicrobial agents in animals.

Guidance on the issue of foodborne antimicrobial resistance related to the non-human use of antimicrobial agents is covered by the Codex Guidelines for risk analysis of foodborne antimicrobial resistance (CAC/GL77-2011).

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.

The chapter includes factors to be considered at various steps of the risk analysis process. These factors are not intended to be exhaustive and not all elements may be applicable in all situations.

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

Annex XII (contd)

4. Hazard identification

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

For the purpose of this chapter, the *hazard* is the resistant microorganism 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 potential for resistant microorganisms to cause adverse health effects, as well as the potential for horizontal transfer of genetic determinants between microorganisms. The conditions under which the *hazard* might produce adverse consequences include any scenarios through which humans or *animals* could become exposed to an antimicrobial resistant 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 microorganisms resulting from the use of *antimicrobial agents* in *animals* should examine:

- a) the likelihood of emergence of resistant microorganisms arising from the use of *antimicrobial agent(s)*, or more particularly, dissemination ~~production~~ of the resistance determinants if transmission is possible between microorganisms;
- b) consideration of all pathways and their importance, by which humans and animals could be exposed to these resistant microorganisms 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 principles 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 microorganisms that have acquired resistance to a specific antimicrobial agent due to the antimicrobial usage used in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the human *infection*.

2. Hazard identification

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

The identification of the *hazard* ~~must~~ should 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 that may lead to the release of resistant microorganisms or resistance determinants into a particular environment due to for the use of a specific antimicrobial agent in animals to lead to the release of resistant microorganisms or resistance determinants into a particular environment. It also estimates 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:

- animal species, category such as food producing, zoo or companion animal, and, where appropriate, production type (e.g. such as veal calves or dairy cattle, broilers or laying hens), of animal treated with the antimicrobial agent(s) in question;
- number of *animals* treated, sex, age and their geographical distribution of these *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;
- = data on potential extra-label or off-label use;
- variation in methods and routes of administration of the antimicrobial agent(s);
- dosage regimen (dose, dosing interval and duration of the treatment) including duration of use;
- the pharmacokinetics and relevant of pharmacodynamics/pharmacokinetics of the *antimicrobial agent(s)*;
- micro-organisms developing resistance as a result of the antimicrobial(s) use prevalence of pathogens that are likely to develop acquire resistance in animal host;
- = prevalence of 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 trends and occurrence of resistant microorganisms obtained 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 microorganisms or resistance determinants released from a given antimicrobial use in *animals*, and estimates 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.

Annex XII (contd)

The following factors should be considered in the exposure assessment:

- human demographics, including population subgroups, and food consumption patterns, including traditions and cultural practices in respect to the preparation and storage of food;
- prevalence of resistant microorganisms in food at the point of consumption or other exposure;
- microbial load in contaminated food at the point of consumption or other exposure for quantitative risk assessment;
- environmental contamination with resistant microorganisms;
- occurrence of resistant microorganisms in animal feed prevalence of animal feed contaminated with resistant microorganisms;
- transfer cycling of resistant microorganisms and their resistance determinants 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 dissemination spread redistribution of resistant microorganisms during the food production process (including slaughtering, processing, storage, transportation and retailing);
- disposal practices for waste products and the likelihood opportunity for human exposure to resistant microorganisms or resistance determinants in through 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 microorganisms to become established in humans;
- human-to-human transmission of the microorganisms under consideration;
- capacity of resistant microorganisms to transfer resistance to human commensal microorganisms and zoonotic agents;
- amount and type of *antimicrobial agents* used in response to treat humans illness;
- pharmacokinetics, such as metabolism, bioavailability and distribution to the gastrointestinal access to intestinal flora.

5. Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant microorganisms or resistance determinants and the consequences of those exposures. A causal process must should 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;

Annex XII (contd)

- 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 or /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 infected ~~affected~~ with antimicrobial resistant strains of microorganisms;
- adverse effects on vulnerable human sub-population (children, immunocompromised persons, elderly, etc.);
- increased severity or duration of infectious *disease*;
- number of person ~~/ 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) linked to antimicrobial resistant microorganisms;
- importance severity of the pathology disease infection caused by the target microorganisms;
- availability 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).

Annex XII (contd)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 dissemination spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning for the use of antimicrobial agents 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 pathogen 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 Competent Authorities should ensure an appropriate regulatory framework and infrastructure.

d) Monitoring and review

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

8. Risk communication

Communication with all interested parties should be promoted at the earliest opportunity and integrated into all phases 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 health1. Definition of the risk

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

2. Hazard identification

- mMicroorganisms that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial agent(s) in animals;
- mMicroorganisms having obtained a resistance determinant(s) from another microorganisms which ~~has~~ acquired resistance arising from the use of an antimicrobial agent(s) in animals.

The *identification of the hazard* ~~must~~ should 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, category such as food producing, zoo or companion animal and, where appropriate, production type, (e.g. such as veal calves or dairy cattle, broilers or laying hens), treated with the antimicrobial agent(s) in question;
- number of *animals* treated, sex, age and their geographical distribution;
- = 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;
- 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 and relevant pharmacodynamics/ ~~pharmacokinetics~~ of the *antimicrobial agent(s)*;
- site and type of *infection*;
- development of resistant microorganisms;
- mechanisms and pathways of resistance transfer;
- cross-resistance and/or co-resistance with other antimicrobial agents;
- data on trends and occurrence of resistant microorganisms obtained 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 microorganisms in clinically ill and clinically unaffected *animals*;
- occurrence ~~prevalence~~ of resistant microorganisms in feed and in/ the animal environment;
- animal-to-animal transmission of the resistant microorganisms and their resistance determinants (animal husbandry practices methods and 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*;

Annex XII (contd)

- treatment regimens (dose, route of administration, duration);
- survival capacity of resistant micro-organisms and dissemination spread of resistant microorganisms;
- exposure of *wildlife* to resistant microorganisms;
- disposal practices for waste products and the likelihood opportunity for animal exposure to resistant microorganisms or resistance determinants in through those products;
- capacity of resistant microorganisms to become established in *animals* 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, distribution to the gastrointestinal flora, access to intestinal flora;
- transfer cycling of resistant microorganisms and their resistance determinants 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 antimicrobial agents 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 microorganisms;
- number of therapeutic failures due to antimicrobial resistant microorganisms;
- = increased severity and duration of infectious disease;
- impact on animal welfare;
- = estimation of the economic impact and cost on animal health and production;
- = economic cost;

Annex XII (contd)

- 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) linked to antimicrobial resistant microorganisms;
- = availability 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 point 7 of Article 6.9.7. 6.10.2. 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 point 8 of Article 6.9.8. 6.10.2. do apply.

 — Text deleted