参考資料２

CHAPTER 6.11.

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

Article 6.11.1.

Recommendations for analysing the risks to animal and human health from antimicrobial resistant microorganisms of animal origin

1. Introduction

Antimicrobial resistance is a naturally occurring phenomenon influenced by many factors. However, problems related to antimicrobial resistance are inherently related to *antimicrobial agent* use in any environment, including human , animal and other uses.

Antimicrobial resistance associated with the use of *antimicrobial agents* for therapeutic and non-therapeutic purposes has led 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*.

2. Objective

For the purpose of this chapter, the principal aim of *risk analysis* is to provide Member 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 of resistance arising from the use of *antimicrobial agents* in *animals*.

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

3. The risk analysis process

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.

4. Hazard identification

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 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 pathogenic agent, fall ill and then be treated with an *antimicrobial agent* that is no longer effective.

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 an *antimicrobial agent*, or more particularly, dissemination 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 likelihood of exposure;

c) the consequences of exposure in terms of *risks* to human and animal health.

The general principles of *risk assessment* apply equally to both *qualitative* and *quantitative risk assessment*. At a minimum, a *qualitative risk assessment* should always be undertaken.

Article 6.11.2.

Analysis of risks to human health

1. Definition of the risk

The infection of humans with microorganisms that have acquired resistance due to antimicrobial usage 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* in *animals*.
– Microorganisms having obtained a resistance determinant from other microorganisms which have acquired resistance arising from the use of an *antimicrobial agent* in *animals*.

The identification of the *hazard* should include consideration of the class or subclass of the *antimicrobial agent*. This definition should be read in conjunction with point 4) of Article 6.11.1.

3. Release assessment

A release assessment describes the biological pathways that may lead to the release of resistant microorganisms or resistance determinants into a particular environment due to the use of a specific *antimicrobial agent* in *animals*. It also estimates 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, entertainment or companion animal, and, where appropriate, production type such as veal calves or dairy cattle, broilers or laying hens, treated with the *antimicrobial agent* in question;
– number of *animals* treated and their age, geographical distribution and, where appropriate, sex;
– 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 extra-label or off-label use;
– methods and routes of administration of the *antimicrobial agent*;
– dosage regimen (dose, dosing interval and duration of the treatment);
– pharmacokinetics and relevant pharmacodynamics of the *antimicrobial agent*;
– prevalence of pathogenic agents that are likely to develop resistance in an animal species;
– prevalence of commensal bacteria which are able to transfer resistance to human pathogenic agents;
– mechanisms and pathways of direct or indirect transfer of resistance;
– potential linkage of virulence attributes and resistance;
– cross-resistance 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.

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, species and other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

– human demographics, including population subgroups, and food consumption patterns, including traditions and cultural practices with respect to the preparation and storage of food;
– prevalence of resistant microorganisms in food at the point of consumption;
– microbial load in contaminated food at the point of consumption;
– environmental contamination with resistant microorganisms;

- occurrence in animal *feed* of resistant microorganisms that have the capacity to become established in the *animals*, thus leading to contamination of food of animal origin;
- transfer of resistant microorganisms and their resistance determinants between humans, *animals* and the environment;
- measures taken for microbial decontamination of food;
- survival capacity and dissemination of resistant microorganisms during the food production process (including slaughtering, processing, storage, transportation and retailing);
- disposal practices for waste products and the likelihood for human exposure to resistant microorganisms or resistance determinants through those waste products;
- 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 to treat humans;
- pharmacokinetics, such as metabolism, bioavailability and distribution to the gastrointestinal 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 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 and subsequent host response interactions;
- 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 food consumption patterns due to loss of confidence in the safety of food products and any associated secondary *risks*;
- interference with antimicrobial therapy in humans;
- importance of the *antimicrobial agent* in human medicine;
- prevalence of resistance in human bacterial pathogenic agents 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 with antimicrobial resistant microorganisms;
- adverse effects on vulnerable human sub-population (children, immunocompromised persons, elderly, pregnant, etc.);
- increased severity or duration of infectious disease;
- number of person/days of illness per year;
- deaths (total per year; probability per year or reduced life expectancy for a random member of the population or a member of a specific sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;
- severity of the disease caused by the target resistant microorganisms;
- availability and cost of alternative antimicrobial therapy;
- potential impact of switching to an alternative *antimicrobial agent* (e.g. alternatives with potential increased toxicity);
- occurrence of antimicrobial resistance in target pathogenic agents observed in humans;
- consequences of the overall *risk* impacts (e.g. illness and hospitalisation).

7. Risk management components

The OIE defines *risk management* as consisting of the steps described below.

a) *Risk* evaluation - the process of comparing the *risk* estimated in the *risk assessment* with the reduction in *risk* expected from the proposed *risk management* measures.

b) Option evaluation

A range of *risk management* options is available to minimise the emergence and dissemination of antimicrobial resistance and these include both regulatory and non-regulatory options, such as the development of codes of practice 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 animal diseases can have the dual benefits of reducing *risks* to human health associated with both the bacterial pathogenic agent under consideration and antimicrobial resistance.

c) Implementation

Risk managers should develop an implementation plan that describes how the decision will be implemented, by whom and when. *Competent Authorities* should ensure an appropriate regulatory framework and infrastructure.

d) Monitoring and review

Risk management options 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 6.11.3.

Analysis of risks to animal health

1. Definition of the risk

The *infection* of *animals* with microorganisms that have acquired resistance due to antimicrobial usage in *animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal *infection*.

2. Hazard identification

– Microorganisms that have acquired resistance (including multiple resistance) arising from the use of an *antimicrobial agent* in *animals*;
– microorganisms having obtained a resistance determinant from another microorganism which has acquired resistance arising from the use of an *antimicrobial agent* in *animals*.

The identification of the *hazard* should include considerations of the class or subclass of the *antimicrobial agent*. This definition should be read in conjunction with point 4) of Article 6.11.1.

3. Release assessment

The following factors should be considered in the release assessment:

– animal species, category such as food producing, zoo, entertainment or companion animal and, where appropriate, production type, such as veal calves or dairy cattle, broilers or laying hens treated with the *antimicrobial agent* in question;
– number of *animals* treated, and their age, geographical distribution and, where appropriate, sex;
– 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 extra-label or off-label use;
– dosage regimen (dose, dosing interval and duration of the treatment);
– methods and routes of administration of the *antimicrobial agent*;
– the pharmacokinetics and relevant pharmacodynamics of the *antimicrobial agent*;
– site and type of *infection*;

- development of resistant microorganisms;
- mechanisms and pathways of resistance transfer;
- cross-resistance 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.

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 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 and movement of *animals*);
- number or percentage of *animals* treated;
- quantity and trends of *antimicrobial agents* used in *animals*;
- survival capacity and dissemination of resistant microorganisms;
- exposure of *wildlife* to resistant microorganisms;
- disposal practices for waste products and the likelihood of animal exposure to resistant microorganisms or resistance determinants through those products;
- capacity of resistant microorganisms to become established in *animals*;
- exposure to resistance determinants from other sources such as water, effluent, waste pollution, etc.;
- pharmacokinetics, such as metabolism, bioavailability, distribution to the gastrointestinal flora;
- transfer 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 and subsequent host response interactions;
- 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;
- importance of the *antimicrobial agent* in animal health (see OIE list of antimicrobial agents of veterinary importance).

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;
- deaths (total per year; probability per year or reduced life expectancy for a random member of the population or a member of a specific sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;
- availability and cost of alternative antimicrobial therapy;
- potential impact of switching to an alternative *antimicrobial agent*, e.g. alternatives with potential increased toxicity.

7. Risk management components

The relevant provisions in point 7) of Article 6.11.2. apply.

8. Risk communication

The relevant provisions in point 8) of Article 6.11.2. apply.

NB: FIRST ADOPTED IN 2004; MOST RECENT UPDATE ADOPTED IN 2015.