CHAPTER 6.5.

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

Article 6.5.1.

Recommendations for analysing the risks to aquatic animal health and human health from antimicrobial resistant microorganisms of aquatic 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 and non-human 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 *antimicrobial agents*.

2. Objective

For the purposes 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 *aquatic animal* health risks associated with the selection and dissemination of resistance arising from the use of *antimicrobial agents* in *aquatic 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. Definitions

For the purposes 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 *aquatic 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 *aquatic animals* could become exposed to an antimicrobial resistant pathogen, fall ill and then be treated with an *antimicrobial agent* that is no longer effective.

For the purposes of this chapter, risk to *aquatic animal* health relates to the *infection* of *aquatic animals* with microorganisms in which resistance has emerged due to *antimicrobial agent* usage in *aquaculture*, and resulting in the loss of benefit of antimicrobial therapy used to manage *aquatic animal diseases*.

For the purposes of this chapter, risk to human health relates to the *infection* of humans with microorganisms in which resistance has emerged due to *antimicrobial agent* usage in *aquatic animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the human *infection*.

4. 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.

5. Risk assessment

The assessment of the risk to human and *aquatic animal* health from antimicrobial resistant microorganisms resulting from the use of *antimicrobial agents* in *aquatic 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) all pathways and their contribution to the likelihood of humans and *aquatic animals* being exposed to these resistant microorganisms or resistance determinants;

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

The general principles of *risk assessment* as defined in Article 2.1.3. apply equally to both qualitative and quantitative *risk assessment*.

Article 6.5.2.

Special considerations for conducting antimicrobial resistance risk analysis in aquaculture

1. Introduction

Antimicrobial resistance (AMR) *risk analysis* in *aquaculture* is challenged by a variety of factors that impact both *risk assessment* and *risk management*, including the diversity of *aquaculture*, relative lack of methods for culture and antimicrobial susceptibility testing (AST), relative lack of information on use of drugs, and potential for the development of a reservoir of resistant microorganisms and resistance determinants with a potential for horizontal transmission.

Nevertheless, the fundamental principles of *risk analysis* (*risk assessment*, *risk management*, *risk communication*) provide a framework just as valuable for *aquaculture* as for terrestrial animal production.

2. Data needs

Special care is required in the design of data collection programmes for *risk assessment* to take account of possible confounding factors.

Because many types of *aquaculture* operations (in particular, open systems) intersect with terrestrial animal production and human environments, it is especially important to clearly identify the risk to be assessed. The selection and dissemination of resistant microorganisms or resistant determinants may be associated with the use of *antimicrobial agents* on *aquatic animals* or it may be the result of antimicrobial use in nearby terrestrial animal production operations or the presence of *antimicrobial agents* in human waste water.

3. Diversity of aquaculture

The range of species under culture, the number and type of different culture systems, and the range of *antimicrobial agents* and their routes of administration impact elements of the *risk assessment*, particularly the entry assessment. Therefore, careful attention should be used when grouping seemingly similar sectors of the *aquaculture* industry.

Identification, selection and monitoring of *risk management* options are also influenced by the diversity of *aquaculture*.

4. Lack of standardised methods for antimicrobial susceptibility testing

Currently, standardised methods for antimicrobial susceptibility testing (AST) for many relevant *aquaculture* species are lacking resulting in inability to quantify specific risks. Standardised AST methods should be used where available; or when standardised methods are not available, well-described and scientifically sound approaches should be applied.

5. Lack of approved drugs

The small number of approved *antimicrobial agents* for use in *aquaculture* challenges *risk analysis*, both in terms of *risk assessment* and *risk management*.

The collection and use of thorough information on the types and quantities of *antimicrobial agents* that are in use in *aquaculture* and relevant to the *risk assessment* is important. In some circumstances legal extra or off-label and illegal uses may also need to be considered. See Chapter 6.3.

For *risk management*, the small number of approved drugs in combination with a range of regulatory and *aquatic animal* health infrastructure in countries engaged in *aquaculture* presents additional challenges. *Risk management* options should be practical and take into account the ability for enforcement and compliance.

For monitoring and *surveillance* programmes, a lack of approved drugs means systems for collection of data and information on the quantities of *antimicrobial agents* used may need to consider not only licensed distribution of approved drugs, but information on the use of unapproved drugs.

6. Potential for development of a reservoir (horizontal transmission)

Microorganisms inhabiting the environment represent the fundamental reservoir of resistant determinants in the biosphere. This reservoir represents the basic origin of all *antimicrobial agent* resistance determinants encountered in human and veterinary medicine. The frequency of resistance determinants in environmental microorganisms is maintained by intrinsic, non-anthropogenic factors; all human uses of *antimicrobial agents*, including in *aquaculture*, have the potential to increase the size of the reservoir.

There is a risk that the use of *antimicrobial agents* in *aquaculture* will result in a rise in the frequency of resistance determinants in the environmental microbiome. This may result in an increase in the frequency with which determinants are transferred to microorganisms capable of infecting humans, animals or *aquatic animals*.The assessment and management of this risk are extremely complex. The biological pathways both for the entry assessment and the exposure assessment are myriad and at present no specific guidelines can be offered.

Article 6.5.3.

Analysis of risks to human health

1. Definition of the risk

The *infection* of humans with microorganisms in which resistance has emerged due to *antimicrobial agent* usage in *aquatic animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the human *infection*.

2. Hazard

– Microorganisms that have acquired resistance (including multiple resistance) arising from the use of an *antimicrobial agent* in *aquatic animals*.

– Microorganisms having obtained a resistance determinant from other microorganisms which have acquired resistance arising from the use of an *antimicrobial agent* in *aquatic 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 3 of Article 6.5.1.

3. Entry assessment

An entry assessment describes the biological pathways by which the use of a specific *antimicrobial agent* in *aquatic animals* leads to the entry of resistant microorganisms or resistance determinants into a particular environment. This assessment includes estimating qualitatively or quantitatively the probability of that complete process occurring. The entry assessment describes the probability of the entry of each of the *hazards* under each specified set of conditions with respect to amounts and timing.

The following factors should be considered in the entry assessment:

– species of *aquatic animals* treated with the *antimicrobial agent(s)* in question;

– *aquaculture* production system (intensive or extensive, net pens, tanks, raceways, ponds, other);

– number of *aquatic animals* treated, their age and their geographical distribution;

– prevalence of *disease* for which the *antimicrobial agent* is indicated or is used in the target *aquatic animal* population;

– data on trends in *antimicrobial agent* use and changes in *aquaculture* production systems;

– data on potential 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*;

– site and type of *infection*;

– development of resistant microorganisms;

– prevalence of *pathogenic agents* that are likely to develop resistance in an *aquatic animal* species;

– 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 *aquatic animals* and *aquatic animal products* and waste products.

The following confounding factors should be considered in the entry assessment:

– resistant microorganisms or resistant determinants associated with *aquatic animals* or *aquatic animal products* that are a result of terrestrial contamination of the aquatic environment, *feed* contamination or contamination during post-harvest processing.

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 agent*'s use in *aquatic animals*, and estimates the probability of 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 other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

– human demographics, including population subgroups, food consumption patterns, and 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;

– transfer of resistant microorganisms and their resistance determinants between humans, *aquatic 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, distribution to the gastrointestinal flora;

– level of direct contact of workers in the *aquaculture* or processing industries to the antimicrobial resistant organisms.

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 (e.g. illness and hospitalisation);

– 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 animal health and human health (see OIE List of Antimicrobial Agents of Veterinary Importance and WHO List of Critically Important Antimicrobials);

– prevalence of resistance in human bacterial pathogens under consideration.

6. Risk estimation

A risk estimation integrates the results from the entry 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.

7. Risk management

Risk management consists of the steps described below.

a) Risk evaluation

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 *aquaculture*.

Risk management decisions need to consider fully the implications of these different options for human health and *aquatic animal* health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of *aquatic animal diseases* can have the dual benefits of reducing the risks to human health associated with both the bacterial pathogen 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 *risk analysis*. This will provide all interested parties, including risk managers, with a better understanding of *risk management* approaches. *Risk communication* should be also well documented.

Article 6.5.4.

Analysis of risks to aquatic animal health

1. Definition of the risk

The *infection* of *aquatic animals* with microorganisms in which resistance has emerged due to antimicrobial usage in *aquatic animals*, and resulting in the loss of benefit of antimicrobial therapy used to manage the *aquatic animal infection*.

2. Hazard

– Microorganisms that have acquired resistance (including multiple resistance) arising from the use of an *antimicrobial agent* in *aquatic animals*.

– Microorganisms having obtained a resistance determinant from another microorganism which has acquired resistance arising from the use of an *antimicrobial agent* in *aquatic 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 3 of Article 6.5.1.

3. Entry assessment

The following factors should be considered in the entry assessment:

– *aquatic animal* species treated with the *antimicrobial agent* in question;

– *aquaculture* production system (intensive or extensive, net pens, tanks, raceways, ponds, other);

– number of *aquatic animals* treated, and their age, geographical distribution and, where appropriate, sex;

– prevalence of *disease* for which the *antimicrobial agent* is indicated or is used in the target *aquatic animal* population;

– data on trends in *antimicrobial agent* use or sales and changes in *aquaculture* production systems;
– data on potential 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);
– the pharmacokinetics and pharmacodynamics of the *antimicrobial agent*;
– type and site of *infection*;
– development of resistant microorganisms;
– prevalence of *pathogenic agents* that are likely to develop resistance in an *aquatic animal* species;
– mechanisms and pathways of direct or indirect transfer of resistance;
– cross-resistance or co-resistance with other *antimicrobial agents*;
– data on trends and occurrence of resistant microorganisms obtained through *surveillance* of *aquatic animals*, *aquatic animal products* and waste products.

The following confounding factors should be considered in the entry assessment:

– resistant microorganisms or resistant determinants associated with *aquatic animals* or their products that are a result of terrestrial contamination of the aquatic environment, *feed* contamination or contamination during post-harvest processing.

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 *aquatic animals*;
– prevalence of resistant microorganisms in *feed* and in the *aquatic animal* environment;
– animal-to-animal transmission of the resistant microorganisms and their resistance determinants (*aquatic animal* husbandry practices, movement of *aquatic animals*);
– number or percentage of *aquatic animals* treated;
– quantity and trends of *antimicrobial agent* used in *aquatic animals*;
– survival capacity and spread of resistant microorganisms;
– exposure of wildlife to resistant microorganisms;
– disposal practices for waste products and the likelihood for *aquatic animal* exposure to resistant microorganisms or resistance determinants through those products;
– capacity of resistant microorganisms to become established in *aquatic animals*;
– exposure to resistance determinants from other sources such as water, effluent, waste pollution, etc.;
– pharmacokinetics, such as metabolism, bioavailability, distribution to relevant flora - considering the gastrointestinal flora of many aquatic species may be transient;
– transfer of resistant microorganisms and resistance determinants between humans, *aquatic 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 *aquatic 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 *aquatic animal* health and human health (see OIE List of Antimicrobial Agents of Veterinary Importance and WHO List of Critically Important Antimicrobials);
– 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 *aquatic animal* welfare;
– estimation of the economic impact and cost on *aquatic animal* health and production;
– deaths (total per year; probability per year for a random member of the population or a member of a specific more exposed sub-population) linked to antimicrobial resistant microorganisms when compared with deaths linked to sensitive microorganisms of the same species;

– availability of alternative antimicrobial therapy;
– potential impact of switching to an alternative *antimicrobial agent* e.g. alternatives with potential increased toxicity.

6. Risk estimation

A risk estimation integrates the results from the entry 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.

7. Risk management

The relevant provisions in point 7 of Article 6.5.3. apply.

8. Risk communication

The relevant provisions in point 8 of Article 6.5.3. apply.