# OIE Standards, Guidelines and Resolutions on Antimicrobial Resistance and the use of antimicrobial agents

WORLD ORGANISATION FOR ANIMAL HEALTH
*Protecting animals, preserving our future*

This publication has been prepared to support the Global Action Plan on Antimicrobial Resistance (AMR) that the World Health Organization (WHO) has developed in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the OIE.


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# Introduction

Antimicrobial Resistance (AMR) is now unanimously recognised as one of the major threats to human and animal health. At the World Organisation for Animal Health (OIE), discussions on AMR started as early as 1948, emphasising the long commitment of our organisation to this important One Health global challenge. Our 182 OIE Members are now fully engaged through *The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials*, and in October 2018 provided recommendations for our ongoing work programme during the 2nd OIE Global Conference on the Responsible and Prudent Use of Antimicrobial Agents for Animals.

As the standard-setting organisation on animal health, the OIE published international standards on AMR for terrestrial animals for the first time in 2003. These standards were updated several times since and extended to cover aquatic animals. More than ever, the implementation of our standards on responsible and prudent use of antimicrobials (Chapter 6.10. of the *Terrestrial Animal Health Code [Terrestrial Code]* and Chapter 6.2. of the *Aquatic Animal Health Code [Aquatic Code*]) is crucial to control AMR, ensuring the availability and efficacy of antimicrobials for future generations.

The *OIE List of Antimicrobial Agents of Veterinary Importance* was first published in May 2007 by adoption of Resolution No. XXVIII. This list was further updated several times and the latest version was adopted in May 2018 by the World Assembly of OIE Delegates.

Following the adoption of Resolution No. 14, *OIE's engagement in the One Health Global Effort to control Antimicrobial Resistance,* by the OIE World Assembly in May 2019, a Working Group on Antimicrobial Resistance was established, replacing the *ad hoc* Group on AMR which had its first meeting in March 2000. The OIE Working Group on AMR will support our work programme of standards and guidance development, including maintenance of the OIE List, and other important activities under the OIE strategy such as our system for monitoring and reporting antimicrobial usage in animals.

The OIE and its Members are working in One Health partnerships at global, regional and national levels to implement the *Global Action Plan on Antimicrobial Resistance*, developed by the World Health Organization (WHO) in collaboration with the OIE and the Food and Agriculture Organization of the United Nations (FAO), together

forming the Tripartite. United Nations Resolution No. 71/3 (adopted in 2016) calls the Tripartite to support the development and implementation of national action plans, and provide leadership in AMR through multi-stakeholder collaborations. The Monitoring and Evaluation framework for the Global Action Plan and the global Tripartite self-assessment survey of country progress in addressing AMR are examples of our joint work.

To further support countries in the implementation of OIE standards and guidelines, we compiled all standards, guidelines and recent OIE Resolutions in this updated booklet for easy reference. We hope you will find this second version of the *OIE Standards, Guidelines and Resolutions on antimicrobial resistance and the use of antimicrobial agents useful*. Further information on our AMR work programme can be found on our website at www.oie.int, and the communication materials we have developed on prudent use of antimicrobials are available at a dedicated site www.oie-antimicrobial.com. Should any further clarification be needed or to find out more about the OIE's work programme on AMR, do not hesitate to contact us via antimicrobialuse@oie.int.

Monique Éloit
Director General

# 1.
# Terrestrial Animal Health Code

CHAPTER 6.7.

# INTRODUCTION TO THE RECOMMENDATIONS FOR CONTROLLING ANTIMICROBIAL RESISTANCE

Article 6.7.1.

**Objective**

The purpose of Chapters 6.8., 6.9., 6.10. and 6.11. is to provide methodologies for Member Countries to appropriately address the emergence or spread of resistant bacteria from the use of *antimicrobial agents* in *animals* and to contain antimicrobial resistance through controlling the use of *antimicrobial agents*.

These chapters should be read in conjunction with the standards, codes of practice and guidelines on antimicrobial resistance developed by the Codex Alimentarius Commission.

*Antimicrobial agents* are essential drugs for human and animal health and welfare. The OIE recognises the need for access to *antimicrobial agents* in veterinary medicine: *antimicrobial agents* are essential for treating and controlling infectious *diseases* in *animals*. The OIE therefore considers that ensuring continued access to effective *antimicrobial agents* is important.

The OIE recognises that antimicrobial resistance is a global public and animal health concern that is influenced by the usage of *antimicrobial agents* in humans, *animals* and elsewhere. Those working in the human, animal and plant sectors have a shared responsibility to prevent or minimise pressures for the selection of antimicrobial resistance factors in humans and *animals*. Arising from its mandate for the protection of animal health and food safety, the OIE developed these chapters to provide guidance to Member Countries in regard to risks in all animal sectors.

The application of *risk assessment* measures should be based on relevant international standards on *risk analysis* and supported by sound data and information when available. The methodologies provided in these chapters should be consulted as part of the standard approach to prevent and reduce antimicrobial resistance.

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NB: FIRST ADOPTED IN 2009; MOST RECENT UPDATE ADOPTED IN 2014.

CHAPTER 6.8.

# HARMONISATION OF NATIONAL ANTIMICROBIAL RESISTANCE SURVEILLANCE AND MONITORING PROGRAMMES

Article 6.8.1.

**Objective**

This chapter provides criteria for the development of national antimicrobial resistance surveillance and monitoring programmes, and the harmonisation of existing national antimicrobial resistance surveillance and monitoring programmes in food-producing animals and in products of animal origin intended for human consumption.

Article 6.8.2.

**Purpose of surveillance and monitoring**

Active surveillance and monitoring are core parts of national antimicrobial resistance surveillance programmes. Passive surveillance and monitoring may offer additional information (refer to Chapter 1.4.). The OIE encourages cooperation among all Member Countries conducting antimicrobial resistance surveillance and monitoring.

Surveillance and monitoring of antimicrobial resistance is necessary to:

1) assess and determine the trends and sources of antimicrobial resistance in bacteria;
2) detect the emergence of new antimicrobial resistance mechanisms;
3) provide the data necessary for conducting *risk analyses* as relevant to animal and human health;
4) provide a basis for policy recommendations for animal and human health;
5) provide information for evaluating antimicrobial prescribing practices and for prudent use recommendations;
6) assess and determine effects of actions to combat antimicrobial resistance.

Article 6.8.3.

**General aspects of antimicrobial resistance surveillance and monitoring programmes**

Surveillance of antimicrobial resistance and monitoring of the prevalence of, and trends in, resistance in bacteria from *animals*, food, environment and humans, constitutes a critical part of animal health and food safety strategies aimed at limiting the spread of antimicrobial resistance and optimising the choice of *antimicrobial agents* used in therapy. *Feed* should also be considered according to national priorities.

Surveillance or monitoring of bacteria from products of animal origin intended for human consumption collected at different steps of the food chain, including processing, packing and retailing, should also be considered.

National antimicrobial resistance monitoring and surveillance programmes should be scientifically based and may include the following components:

1) statistically based surveys;
2) sampling and testing of food-producing animals on the farm, at live animal markets or at *slaughter*;
3) organised sentinel programme, for example targeted sampling of food-producing animals, *herds*, *flocks* and *vectors* (e.g. birds, rodents);
4) analysis of veterinary practice and diagnostic laboratory records;
5) sampling and testing of products of animal origin intended for human consumption;
6) sampling and testing of *feed ingredients* or *feed*.

Article 6.8.4.

**Sampling**

1. Sampling strategies

   *a)* Sampling should be conducted on a statistical basis. The sampling strategy should ensure:

   – the sample is representative of the population of interest and meets the objectives of the surveillance;

   – the robustness of the sampling method.

*b)* The following criteria are to be considered:

- sample source such as food-producing animal, food, animal feed;
- animal species;
- category of *animal* within species such as age group, production type;
- health status of the *animals* such as healthy, diseased;
- sample selection method such as targeted, systematic random, non-random;
- type of sample such as faeces, caeca, carcass, food product;
- sample size.

2. Sample size

The sample size should be large enough to allow detection or determine prevalence of, or trends in, existing and emerging antimicrobial resistance phenotypes.

The sample should avoid bias and be representative of the animal *population*, process, product or other unit of interest whilst taking into account the expected prevalence of the bacteria in the sample type, the expected prevalence of the resistance phenotype and the desired level of precision and confidence.

The sample size calculation should be based on independent samples. However, if there is any clustering at the *establishment* or animal level, the sample size should be adjusted accordingly. At low levels of expected prevalence, exact methods of sample size calculation should be preferred to approximate methods. Samples from which bacteria were not isolated cannot be used in the calculation of prevalence of the resistance phenotype.

3. Sample sources (Table 1)

Member Countries should examine their livestock production systems on the basis of available information and assess which sources are likely to contribute most to a potential *risk* to animal and human health.

*a)* Food-producing animals

Categories of food-producing animals considered for sampling should be relevant to the country's production system. Resource allocation should be guided by criteria such as production volume of the food-producing animal species and the prevalence of resistant bacteria.

*b)* Food

Member Countries should consider including products of animal origin intended for human consumption, produced locally or imported, in surveillance and monitoring programmes, as foodborne transmission is considered to be an important route for the transfer of antimicrobial resistance.

*c)* Feed

Member Countries should consider including *feed* in surveillance and monitoring programmes as they may become contaminated with antimicrobial resistant bacteria, e.g. *Salmonella.*

*d)* Environment

Member Countries should consider including the environment in surveillance and monitoring programmes as the environment of animals can be an important route for transfer or persistence of antimicrobial resistance.

4. Type of sample to be collected (Table 1)

Faecal samples should be collected in amounts sufficient for isolation of the resistant bacteria of concern (at least 5 g from bovine and porcine and whole caeca from *poultry*).

*Feed* samples representative of the batch should be collected in amounts sufficient for isolation of resistant bacteria of concern (at least 25 g) and should be linked to any pathogen *surveillance* programme that may be in place.

Existing food processing microbiological monitoring, risk-based management and other food safety programmes may provide useful samples for surveillance and monitoring of resistance in the food chain after *slaughter*.

**Table 1: Examples of sampling sources, sample types and output**

| Source | Type | Output | Additional information required or additional stratification |
|---|---|---|---|
| Herd or flock of origin | Faeces or bulk milk | Prevalence of resistant bacteria originating from animal populations (of different production types). Relationship between resistance and antimicrobial use | Age categories, production types, etc. Antimicrobial use over time |
| Slaughterhouse/ Abattoir | Faeces | Prevalence of resistant bacteria originating from animals at slaughter | |
| | Caeca or intestines | As above | |
| | Carcass | Prevalence of resistant bacteria after carcass dressing, representative of the hygiene of the process and the contamination during slaughter | |
| Processing, packing | Food products | Prevalence of resistant bacteria after processing, representative of the hygiene of the process and the contamination during processing and handling | |
| Point of sale (Retail) | Food products | Prevalence of resistant bacteria originating from food, exposure data for consumers | |
| Various origins | Animal feed | Prevalence of resistant bacteria originating from animal feed, exposure data for animals | |
| Various origins | Environment | Occurrence of resistant bacteria originating from the animal-immediate or the wider environment | |

Article 6.8.5.

**Bacteria subjected to surveillance and monitoring**

The following categories of bacteria may be included in surveillance and monitoring programmes:

1. Animal bacterial pathogens relevant to the countries' priorities

*a)* Surveillance and monitoring of antimicrobial resistance in animal bacterial pathogens are important to:

- detect emerging resistance that may pose a concern for animal and human health;
- detect changes in susceptibility patterns;
- provide information for *risk analysis;*
- provide data for *veterinarians* to inform their treatment decisions;
- provide information for epidemiological studies and trend analysis.

*b)* Information on the occurrence of antimicrobial resistance in animal bacterial pathogens is in general either derived from clinical material sent to veterinary diagnostic *laboratories* or from an active monitoring programme. Although antimicrobial resistance information provided by diagnostic *laboratories* is primarily for treatment purposes, it is also useful for identification of novel resistance patterns and can possibly assist in identifying emerging resistance. However, in order to estimate accurately the prevalence of antimicrobial resistance in the bacterial pathogen, in a larger population of animals, an active sampling programme should be implemented.

*c)* To promote a harmonised global approach to the selection of animal bacterial pathogens for inclusion in national surveillance and monitoring programmes, bacteria should be selected using one or more of the following criteria:

- impact on animal health and welfare;
- implication of antimicrobial resistance in the bacterial pathogen on therapeutic options in veterinary practice;
- impact on food security and on production (economic importance of associated diseases);
- bacterial diseases responsible for the majority of veterinary antimicrobial usage (stratified by usage of different classes or their importance);

– existence of validated susceptibility testing methodologies for the bacterial pathogen;

– existence of quality assurance programmes or other pathogen reduction options that are non-antimicrobial, such as vaccines and Good Agricultural Practices.

The table below, derived using the above criteria, lists suggested animal bacterial pathogens for inclusion in a surveillance or monitoring programme of food-producing animals. This list is not exhaustive and should be adapted according to the situation in the country.

**Table 2. Examples of target animal species and animal bacterial pathogens that may be included in resistance surveillance and monitoring programmes**

| Source | Respiratory pathogens | Enteric pathogens | Udder pathogens | Other pathogens |
|---|---|---|---|---|
| Cattle | *Pasteurella multocida* | *Escherichia coli* | *Staphylococcus aureus* | |
| | *Mannheimia haemolytica* | *Salmonella* spp. | *Streptococcus* spp. | |
| Pigs | *Actinobacillus pleuropneumoniae* | *Escherichia coli* | | *Streptococcus suis* |
| | | *Salmonella* spp. | | |
| Poultry | | *Salmonella* spp. | | *Escherichia coli* |

## 2. Zoonotic bacteria

### *a) Salmonella*

*Salmonella* should be sampled from food-producing animals, animal-derived food products and, if relevant, *feed*. For the purposes of consistency and harmonisation, animal samples should preferably be taken from healthy animals at the *slaughterhouse/abattoir* and *feed* samples should preferably be taken at the *feed* mill.

Surveillance and monitoring programmes may also include sampling of the environment at places where animals are kept or handled or bacterial isolates originating from other sources obtained from designated *laboratories*.

Isolation and identification of bacteria and bacterial strains should follow nationally or internationally standardised procedures.

Serovars of public health importance such as *S.* Typhimurium and *S.* Enteritidis should be included in surveillance and monitoring programmes. The inclusion of other relevant serovars will depend on the epidemiological situation in each country.

All *Salmonella* isolates should be characterised by serotype and, where appropriate, by genotype at designated *laboratories.*

*b) Campylobacter*

*Campylobacter* should be isolated from food-producing animals or associated food products. Isolation and identification of these bacteria should follow nationally or internationally standardised procedures. *Campylobacter* isolates should be identified to the species level.

*c)* Other bacteria that are pathogenic for humans

Other bacteria that are pathogenic for humans, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Listeria monocytogenes*, may be included in resistance surveillance and monitoring programmes.

*d)* Commensal bacteria

*E. coli* and *enterococci* (*Enterococcus faecium* and *E. faecalis*) may be sampled from feed, food-producing animals, their environment and products of animal origin intended for human consumption.

These bacteria are commonly used in surveillance and monitoring programmes as indicators, providing information on the potential reservoir of antimicrobial resistance genes, which may be transferred to pathogenic bacteria. For the purposes of consistency and harmonisation, these bacteria should preferably be isolated from healthy animals, at the *slaughterhouse/abattoir.*

Article 6.8.6.

**Storage of bacterial strains**

If possible, isolates should be preserved at least until reporting is completed. Preferably, appropriate isolates should be permanently stored. Bacterial strain collections, established by storage of all isolates from certain years, will provide the possibility of conducting retrospective studies.

Article 6.8.7.

**Antimicrobial susceptibility testing**

Clinically important *antimicrobial agents* or classes used in human and veterinary medicine should be included in antimicrobial resistance surveillance programmes. Member Countries should refer to the OIE list of antimicrobials of veterinary importance for surveillance and monitoring purposes, recognising that the number of tested *antimicrobial agents* may have to be limited according to financial resources.

Appropriately validated antimicrobial susceptibility testing methods should be used in accordance with Chapter 2.1.1. of the *Terrestrial Manual*, concerning laboratory methodologies for bacterial antimicrobial susceptibility testing. Antimicrobial susceptibility data should be reported not only qualitatively (susceptible or resistant), but also quantitatively (minimum inhibitory concentrations [MICs] or inhibition zone diameters).

Article 6.8.8.

**Recording, storage and interpretation of data**

1) Because of the volume and complexity of the information to be stored and the need to keep these data available for an undetermined period of time, careful consideration should be given to database design.
2) The storage of raw (primary, non-interpreted) data is essential to allow the evaluation in response to various kinds of questions, including those arising in the future.
3) Consideration should be given to the technical requirements of computer systems when an exchange of data between different systems (comparability or compatibility of automatic recording of laboratory data and transfer of these data between and within resistance surveillance and monitoring programmes)

is envisaged. Results should be collected in a suitable national database and recorded quantitatively:

*a)* as distributions of MICs in micrograms per millilitre;

*b)* or inhibition zone diameters in millimetres.

4) The information to be recorded should include, where possible, the following aspects:

*a)* sampling programme;

*b)* sampling date;

*c)* animal species and production type;

*d)* type of sample;

*e)* purpose of sampling;

*f)* type of antimicrobial susceptibility testing method used;

*g)* geographical origin (geographical information system data where available) of herd, flock or animal;

*h)* animal factors such as age, condition, health status, identification, sex;

*i)* exposure of animals to *antimicrobial agents*;

*j)* bacterial isolation rate.

5) The reporting of laboratory data should include the following information:

*a)* identity of laboratory,

*b)* isolation date,

*c)* reporting date,

*d)* bacterial species,

and, where relevant, other typing characteristics, such as:

*e)* serotype or serovar,

*f)* phage type,

*g)* antimicrobial susceptibility result or resistance phenotype,

*h)* genotype.

6) The number of isolates regarded as resistant should be reported as a proportion of the number of isolates tested, including the defined interpretive criteria used.

7) In the clinical setting, breakpoints are used to categorise bacterial strains as susceptible, intermediate or resistant. These clinical breakpoints may be elaborated on a national basis and may vary between Member Countries.

8) The bacterial isolation methods, antimicrobial susceptibility testing methods, standards and guidelines used should be recorded.

9) For surveillance and monitoring purposes, use of the microbiological breakpoint (also referred to as epidemiological cut-off point), which is based on the distribution of MICs or inhibition zone diameters of the specific bacterial species tested, is preferred. When using microbiological breakpoints, only the bacterial population with acquired resistance that clearly deviates from the distribution of the normal susceptible population will be designated as resistant. Clinical breakpoints, when available, should also be reported.

10) Ideally, data should be collected at the individual isolate level. This will allow antimicrobial resistance patterns to be recorded over time, along with, when available, relevant data on usage of *antimicrobial agents* and management practices.

Article 6.8.9.

**Reference laboratory and annual reports**

1) Member Countries should designate a national reference centre that assumes the responsibility to:
   *a)* coordinate the activities related to the antimicrobial resistance surveillance and monitoring programmes;
   *b)* coordinate and collect information from participating laboratories within the country;
   *c)* produce an annual report on the antimicrobial resistance situation in the country.

2) The national reference centre should have access to the:
   *a)* raw data;
   *b)* complete results of quality assurance and inter-laboratory calibration activities;
   *c)* inter-laboratory proficiency testing results;
   *d)* information on the structure of the surveillance or monitoring system;
   *e)* information on the chosen laboratory methods.

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NB: FIRST ADOPTED IN 2003; MOST RECENT UPDATE ADOPTED IN 2018.

CHAPTER 6.9.

# MONITORING OF THE QUANTITIES AND USAGE PATTERNS OF ANTIMICROBIAL AGENTS USED IN FOOD-PRODUCING ANIMALS

Article 6.9.1.

**Purpose**

The purpose of the recommendations in this chapter is to describe an approach to the monitoring of the quantities of *antimicrobial agents* used in food-producing animals.

In order to evaluate antimicrobial exposure in food-producing animals, quantitative information should be collected to monitor usage patterns by animal species, *antimicrobial agents* or class of *antimicrobial agents*, route of administration and type of use: veterinary medical (to treat, control or prevent infectious disease) or non veterinary medical (including growth promotion).

Article 6.9.2.

**Definitions**

For the purposes of the *Terrestrial Code*:

**Veterinary medical use of antimicrobial agents**: means the administration of an *antimicrobial agent* to an individual or a group of *animals* to treat, control or prevent infectious disease:

– **to treat**: means to administer an *antimicrobial agent* to an individual or a group of *animals* showing clinical signs of an infectious disease;

– **to control**: means to administer an *antimicrobial agent* to a group of *animals* containing sick *animals* and healthy *animals* (presumed to be infected), to minimise or resolve clinical signs and to prevent further spread of the disease;

– **to prevent**: means to administer an *antimicrobial agent* to an individual or a group of *animals* at risk of acquiring a specific *infection* or in a specific situation where infectious disease is likely to occur if the drug is not administered.

**Non veterinary medical use of antimicrobial agents**: means the administration of *antimicrobial agents* to *animals* for any purpose other than to treat, control or prevent infectious disease; it includes growth promotion.

**Growth promotion**: means the administration of *antimicrobial agents* to *animals* only to increase the rate of weight gain or the efficiency of feed utilisation.

Article 6.9.3.

## Objectives

The information provided in these recommendations is essential for antimicrobial resistance *risk analyses* and planning purposes and should be read in conjunction with Chapters 6.8. and 6.11. This information is necessary for interpreting antimicrobial resistance surveillance data and can assist in responding to problems of antimicrobial resistance in a precise and targeted way. The continued collection of this basic information will also help to give an indication of trends in the use of *antimicrobial agents* in animals over time and potential associations with antimicrobial resistance in animals. This information may also assist in *risk management* to evaluate the effectiveness of efforts to ensure responsible and prudent use and mitigation strategies (for example, by identifying changes in veterinary prescribing practices) and to indicate where change of antimicrobial usage practices might be appropriate. The publication of these data is important to ensure transparency and to allow all interested parties to assess trends, to perform *risk assessments* and for *risk communication* purposes.

Article 6.9.4.

## Development and standardisation of antimicrobial monitoring systems

Systems to monitor antimicrobial usage consist of the following elements:

1) Sources of antimicrobial data

*a)* Basic sources

Sources of data will vary from country to country. Such sources may include customs, import and export data, manufacturing and sales data.

*b)* Direct sources

Data from *veterinary medicinal product* registration authorities, wholesalers, retailers, pharmacists, *veterinarians*, *feed* stores, *feed* mills and pharmaceutical industry associations can be efficient and practical sources.

A possible mechanism for the collection of this information is to make the provision of appropriate information by pharmaceutical manufacturers to the regulatory authority one of the requirements of antimicrobial registration.

*c)* End-use sources (veterinarians and food animal producers)

This may be appropriate when basic or direct sources cannot be used for the routine collection of the information or when more accurate and locally specific information is required (such as off label use).

Periodic collection of this type of information may be sufficient.

Collection, storage and processing of data from end-use sources should be carefully designed, well managed and have the capability to produce accurate and targeted information.

*d)* Other sources

Non-conventional sources including Internet sales data related to *antimicrobial agents* could be collected where available.

Member Countries may wish to consider, for reasons of cost and administrative efficiency, collecting medical, food-producing animal, agricultural and other antimicrobial use data in a single programme. A consolidated programme would also facilitate comparisons of animal use with human use data for *risk analysis* purposes and help to promote optimal usage of *antimicrobial agents*.

2) Types and reporting formats of antimicrobial usage data

*a)* Type of antimicrobial use data

The data collected at minimum should be the weight in kilograms of the active ingredient of the antimicrobial(s) used in food-producing animals per year. It is possible to estimate total usage by collecting sales data, prescribing data, manufacturing data, import and export data or any combination of these.

The total number of food-producing animals by species, type of production and their weight in kilograms for food production per year (as relevant to the country of production) is essential basic information.

Information on dosage regimens (dose, dosing interval and duration of the treatment) and route of administration are elements to include when estimating antimicrobial usage in food-producing animals.

*b)* Reporting formats of antimicrobial use data

The *antimicrobial agents*, classes or sub-classes to be included in data reporting should be based on current known mechanisms of antimicrobial activity and antimicrobial resistance data.

Nomenclature of *antimicrobial agents* should comply with international standards where available.

For active ingredients present in the form of compounds or derivatives, the mass of active entity of the molecule should be recorded. For *antimicrobial agents* expressed in International Units, the factor used to convert these units to mass of active entity should be stated.

The reporting of antimicrobial use data may be further organised by species, by route of administration (specifically in-feed, in-water, injectable, oral, intramammary, intra-uterine and topical) and by type of use (veterinary medical or non veterinary medical).

Regarding data coming from end-use sources, further breakdown of data for analysis of antimicrobial use at the regional, local, *herd* and individual *veterinarian* or veterinary practice levels may be possible.

Article 6.9.5.

**Interpretation**

According to the OIE *risk assessment* guidelines (refer to Chapter 6.11.), factors such as the number or percentage of *animals* treated, treatment regimes, type of use and route of administration are key elements to consider.

When comparing antimicrobial use data over time, changes in the size and composition of animal populations should also be taken into account.

The interpretation and communication of results should take into account factors such as seasonality and disease conditions, animal species and age affected, agricultural systems (e.g. extensive range conditions and feedlots), animal movements, and dosage regimens with *antimicrobial agents*.

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NB: FIRST ADOPTED IN 2003; MOST RECENT UPDATE ADOPTED IN 2018.

CHAPTER 6.10.

# RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE

Article 6.10.1.

**Purpose**

This document provides guidance for the responsible and prudent use of *antimicrobial agents* in veterinary medicine, with the aim of protecting both animal and human health as well as the environment. It defines the respective responsibilities of the *Competent Authority* and stakeholders such as the veterinary pharmaceutical industry, *veterinarians*, animal *feed* manufacturers, distributors and food animal producers who are involved in the authorisation, production, control, importation, exportation, distribution and use of *veterinary medicinal products* (VMP) containing *antimicrobial agents*.

Responsible and prudent use is determined taking into account the specifications detailed in the marketing authorisation and their implementation when *antimicrobial agents* are administered to *animals* and is part of good veterinary and good agricultural practice.

Activities associated with the responsible and prudent use of *antimicrobial agents* should involve all relevant stakeholders.

Coordination of these activities at the national or regional level is recommended and may support the implementation of targeted actions by the stakeholders involved and enable clear and transparent communications.

Article 6.10.2.

**Objectives of responsible and prudent use**

Responsible and prudent use includes implementing practical measures and recommendations intended to improve animal health and *animal welfare* while preventing or reducing the selection, emergence and spread of antimicrobial-resistant bacteria in *animals* and humans. Such measures include:

1) ensuring the rational use of *antimicrobial agents* in *animals* with the purpose of optimising both their efficacy and safety;

2) complying with the ethical obligation and economic need to keep *animals* in good health;

3) preventing or reducing the transfer of resistant micro-organisms or resistance determinants within animal populations, the environment and between *animals* and humans;

4) contributing to the maintenance of the efficacy and usefulness of *antimicrobial agents* used in *animal* and human medicine;

5) protecting consumer health by ensuring the safety of food of animal origin with respect to residues of *antimicrobial agents*.

Article 6.10.3.

**Responsibilities of the Competent Authority**

1. Marketing authorisation

All Member Countries should combat the unauthorised manufacture, compounding, importation, advertisement, trade, distribution, storage and use of unlicensed, adulterated and counterfeit products, including bulk active ingredients, through appropriate regulatory controls and other measures.

The *Competent Authority* is responsible for granting marketing authorisation which should be done in accordance with the provisions of the *Terrestrial Code*. It has a significant role in specifying the terms of this authorisation and in providing the appropriate information to *veterinarians* and all other relevant stakeholders.

The *Competent Authority* should establish and implement efficient statutory registration procedures that evaluate the quality, safety and efficacy of VMP containing *antimicrobial agents*. According to Article 3.1.2., the *Competent Authority* should be free from any commercial, financial, hierarchical, political or other pressures which might affect its judgement or decisions.

Member Countries lacking the necessary resources to implement an efficient registration procedure for VMP containing *antimicrobial agents*, and which are importing them, should undertake the following measures:

*a)* evaluate the efficacy of administrative controls on the import of these VMP;

*b)* evaluate the validity of the registration procedures of the exporting and manufacturing country as appropriate;

*c)* develop the necessary technical co-operation with experienced relevant authorities to check the quality of imported VMP as well as the validity of the recommended conditions of use.

The *Competent Authorities* of *importing countries* should request the pharmaceutical industry to provide quality certificates prepared by the *Competent Authority* of the exporting and manufacturing country as appropriate.

Marketing authorisation is granted on the basis of the data submitted by the pharmaceutical industry or applicant and only if the criteria of safety, quality and efficacy are met.

Member Countries are encouraged to apply the existing guidelines established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

An evaluation of the potential risks and benefits to both *animals* and humans resulting from the use of *antimicrobial agents*, with particular focus on use in food-producing animals, should be carried out. The evaluation should focus on each individual *antimicrobial agent* and the findings should not be generalised to the antimicrobial class to which the particular active ingredient belongs. Guidance on usage should be provided for all target, route of administration, dosage regimens, withdrawal period and different durations of treatment that are proposed.

The *Competent Authority* should expedite the process for new *antimicrobial agents* in order to address a specific need for the treatment of animal *disease*.

## 2. Quality control of antimicrobial agents and VMP containing antimicrobial agents

Quality controls should be performed:

*a)* in compliance with the provisions of *good manufacturing practices*;

*b)* to ensure that analysis specifications of *antimicrobial agents* used as active ingredients comply with the provisions of registration documentations (such as monographs) approved by the relevant *Competent Authority*;

*c)* to ensure that the quality of *antimicrobial agents* in the marketed dosage forms is maintained until the expiry date, established under the recommended storage conditions;

*d)* to ensure the stability of *antimicrobial agents* when mixed with feed or drinking water;

*e)* to ensure that all *antimicrobial agents* and the VMP containing them are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

3. Assessment of therapeutic efficacy

*a)* Preclinical trials

*i)* Preclinical trials should:

– establish the spectrum of activity of *antimicrobial agents* against relevant pathogenic agents and non-pathogenic agents (commensals);

– assess the capacity of the *antimicrobial agents* to select for resistance *in vitro* and *in vivo*, taking into consideration intrinsically resistant and pre-existing resistant strains;

– establish an appropriate dosage regimen (dose, dosing interval and duration of the treatment) and route of administration necessary to ensure the therapeutic efficacy of the *antimicrobial agents* and limit the selection of antimicrobial resistance. Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal.

*ii)* The activity of *antimicrobial agents* towards the targeted microorganism should be established by pharmacodynamics. The following criteria should be taken into account:

– spectrum of activity and mode of action;

– minimum inhibitory and bactericidal concentrations against recent isolates;

– time- or concentration-dependent activity or co-dependency;

– activity at the site of *infection*.

*iii)* The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

– bio-availability in accordance with the route of administration;

– distribution of the *antimicrobial agents* in the treated *animal* and concentration at the site of *infection*;

– metabolism

– excretion routes.

Use of combinations of *antimicrobial agents* should be scientifically supported.

*b)* Clinical trials

Clinical trials in the target animal species should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

*i)* diversity of the clinical cases encountered when performing multi-centre trials;

*ii)* compliance of protocols with good clinical practice;

*iii)* eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;

*iv)* parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

4. Assessment of the potential of antimicrobial agents to select for resistance

Other studies may be requested in support of the assessment of the potential of *antimicrobial agents* to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered:

*a)* the concentration of either active *antimicrobial agents* or metabolites in the gut of the *animal* (where the majority of potential foodborne pathogenic agents reside) at the defined dosage level;

*b)* pathway for the human exposure to antimicrobial resistant microorganisms;

*c)* the degree of cross-resistance;

*d)* the intrinsic and pre-existing, baseline level of resistance in the pathogenic agents of human health concern in both *animals* and humans.

5. Establishment of acceptable daily intake (ADI), maximum residue limit (MRL) and withdrawal periods in food-producing animals

*a)* When setting the ADI and MRL for an *antimicrobial agent*, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.

*b)* The establishment of an ADI for each *antimicrobial agent*, and an MRL for each animal-derived food, should be undertaken before a VMP containing it is granted marketing authorisation.

*c)* For all VMP containing *antimicrobial agents*, withdrawal periods should be established for each animal species in order to ensure compliance with the MRLs, taking into account:

*i)* the MRLs established for the *antimicrobial agent* in the target *animal* edible tissues;

*ii)* the composition of the product and the pharmaceutical form;

*iii)* the dosage regimen;

*iv)* the route of administration.

*d)* The applicant should describe methods for regulatory testing of residues in food based on the established marker residues.

6. Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted.

7. Establishment of a summary of product characteristics for each VMP containing antimicrobial agents

The summary of product characteristics contains the information necessary for the appropriate use of VMP containing *antimicrobial agents* and constitutes the official reference for their labelling and package insert. This summary should contain the following items:

*a)* active ingredient and class;

*b)* pharmacological properties;

*c)* any potential adverse effects;

*d)* target animal species and, as appropriate, age or production category;

*e)* therapeutic indications;

*f)* target micro-organisms;

*g)* dosage regimen and route of administration;

*h)* withdrawal periods;

*i)* incompatibilities and interactions;

*j)* storage conditions and shelf-life;

*k)* operator safety;

*l)* particular precautions before use;

*m)* particular precautions for the proper disposal of un-used or expired products;

*n)* information on conditions of use relevant to the potential for selection of resistance;

*o)* contraindication.

## 8. Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, and any other relevant scientific data, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this, the following should be considered:

*a)* General epidemiological surveillance

The surveillance of animal microorganisms resistant to *antimicrobial agents* is essential. The relevant authorities should implement a programme in accordance with Chapter 1.4.

*b)* Specific surveillance

Specific surveillance to assess the impact of the use of a specific *antimicrobial agent* may be implemented after the granting of marketing authorisation. The surveillance programme should evaluate not only resistance in target animal pathogenic agents, but also in foodborne pathogenic agents, and commensals if relevant and possible. This will also contribute to general epidemiological surveillance of antimicrobial resistance.

## 9. Supply and administration of the VMP containing antimicrobial agents

The relevant authorities should ensure that all the VMP containing *antimicrobial agents* used in *animals* are:

*a)* prescribed by a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agents* in accordance with the national legislation and under the supervision of a *veterinarian*;

*b)* supplied only through licensed or authorised distribution systems;

*c)* administered to *animals* by a *veterinarian* or under the supervision of a *veterinarian* or by other authorised persons.

The relevant authorities should develop effective procedures for the safe collection and disposal or destruction of unused or expired VMPs containing *antimicrobial agents*. Their labels should have appropriate instructions for disposal and destruction.

10. Control of advertising

All advertising of *antimicrobial agents* should be compatible with the principles of responsible and prudent use and should be controlled by codes of advertising standards. The relevant authorities must ensure that the advertising of these products:

*a)* complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;

*b)* is restricted to a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agents* in accordance with the national legislation and under the supervision of a *veterinarian*.

11. Training on the usage of antimicrobial agents

The training on the usage of *antimicrobial agents* should include all the relevant organisations, such as the *Competent Authority*, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food animal owners and manufacturers of medicated animal *feed*. This training should focus on preserving the effectiveness of *antimicrobial agents* and include:

*a)* information on *disease* prevention, management and mitigation strategies;

*b)* the ability of *antimicrobial agents* to select for resistant microorganisms in *animals* and the relative importance of that resistance to public and animal health;

*c)* the need to observe responsible use recommendations for the use of *antimicrobial agents* in animal husbandry in agreement with the provisions of the marketing authorisations;

*d)* appropriate storage conditions, proper disposal of unused or expired VMP;

*e)* record keeping.

12. Research

The relevant authorities should encourage public- and industry-funded research, for example on methods to identify and mitigate the public health risks associated with specific *antimicrobial agent* uses, or on the ecology of antimicrobial resistance.

Article 6.10.4.

**Responsibilities of the veterinary pharmaceutical industry with regards to VMP containing antimicrobial agents**

1. Marketing authorisation

The veterinary pharmaceutical industry has responsibilities to:

*a)* supply all the information requested by the national *Competent Authority*;

*b)* guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;

*c)* implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance data.

2. Marketing and export

For the marketing and export of VMP containing *antimicrobial agents*:

*a)* only licensed and officially approved VMP containing *antimicrobial agents* should be sold and supplied, and then only through licensed/authorised distribution systems;

*b)* the pharmaceutical industry should provide quality certificates prepared by the *Competent Authority* of the exporting and manufacturing countries to the *importing country*;

*c)* the national regulatory authority should be provided with the information necessary to evaluate the amount of *antimicrobial agents* marketed.

3. Advertising

The veterinary pharmaceutical industry should respect principles of responsible and prudent use and should comply with established codes of advertising standards, including to:

*a)* distribute information in compliance with the provisions of the granted authorisation;

*b)* not advertise VMP containing *antimicrobial agents* directly to the food animal producer.

4. Training

The veterinary pharmaceutical industry should participate in training programmes as defined in point 11) of Article 6.10.3.

5. Research

The veterinary pharmaceutical industry should contribute to research as defined in point 12) of Article 6.10.3.

Article 6.10.5.

**Responsibilities of wholesale and retail distributors**

1) Distributors of VMP containing *antimicrobial agents* should only do so on the prescription of a *veterinarian* or other suitably trained person authorised to prescribe VMP containing *antimicrobial agents* in accordance with the national legislation and under the supervision of a *veterinarian*. All products should be appropriately labelled.

2) The recommendations on the responsible and prudent use of VMP containing *antimicrobial agents* should be reinforced by retail distributors who should keep detailed records of:
   *a)* date of supply,
   *b)* name of prescriber,
   *c)* name of user,
   *d)* name of product,
   *e)* batch number,
   *f)* expiration date,
   *g)* quantity supplied,
   *h)* copy of prescription.

3) Distributors should also be involved in training programmes on the responsible and prudent use of VMP containing *antimicrobial agents*, as defined in point 11) of Article 6.10.3.

Article 6.10.6.

**Responsibilities of veterinarians**

The *veterinarian*'s responsibility is to promote public health, animal health and *animal welfare*, including identification, prevention and treatment of animal *diseases*. The promotion of sound animal husbandry methods, hygiene procedures, *biosecurity* and *vaccination* strategies can help to minimise the need for antimicrobial use in food-producing animals.

*Veterinarians* should only prescribe *antimicrobial agents* for *animals* under their care.

1. Use of antimicrobial agents

The responsibilities of *veterinarians* are to carry out a proper clinical examination of the *animal(s)* and then:

*a)* administer or prescribe *antimicrobial agents* only when necessary and taking into consideration the OIE list of *antimicrobial agents* of veterinary importance;

*b)* make an appropriate choice of *antimicrobial agents* based on clinical experience and diagnostic laboratory information (pathogenic agent isolation, identification and antibiogram) where possible;

*c)* provide a detailed treatment protocol, including precautions and withdrawal times, especially when prescribing extra-label or off-label use.

2. Choosing antimicrobial agents

*a)* The expected efficacy of the treatment is based on:

*i)* the clinical experience of the *veterinarians*, their diagnostic insight and therapeutic judgement;

*ii)* diagnostic laboratory information (pathogenic agent isolation, identification and antibiogram);

*iii)* pharmacodynamics including the activity towards the pathogenic agents involved;

*iv)* the appropriate dosage regimen and route of administration;

*v)* pharmacokinetics and tissue distribution to ensure that the selected therapeutic agent is effective at the site of *infection*;

*vi)* the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogenic agents involved.

Should a first-line antimicrobial treatment fail or should the *disease* recur, a second line treatment should be based on the results of diagnostic tests. In the absence of such results, an appropriate *antimicrobial agent* belonging to a different class or sub-class should be used.

In emergencies, a *veterinarian* may treat *animals* without recourse to an accurate diagnosis and antimicrobial susceptibility testing, to prevent the development of clinical *disease* and for reasons of *animal welfare*.

*b)* Use of combinations of *antimicrobial agents* should be scientifically supported. Combinations of *antimicrobial agents* may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

3. Appropriate use of the VMP containing antimicrobial agents chosen

A prescription for VMP containing *antimicrobial agents* should indicate precisely the dosage regimen, the withdrawal period where applicable and the amount of VMP containing *antimicrobial agents* to be provided, depending on the dosage and the number of *animals* to be treated.

The extra-label or off-label use of VMP containing *antimicrobial agents* may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used, as applicable. It is the *veterinarian*'s responsibility to define the conditions of responsible use in such a case including the dosage regimen, the route of administration and the withdrawal period.

The use of compounded VMP containing *antimicrobial agents* and extra-label or off-label use of registered VMP containing *antimicrobial agents* should be limited to circumstances where an appropriate registered product is not available.

4. Recording of data

Records on VMP containing *antimicrobial agents* should be kept in conformity with the national legislation. Information records should include the following:

*a)* quantities of VMP used per animal species;

*b)* a list of all VMP supplied to each food-producing animal holding;

*c)* treatment schedules including animal identification and withdrawal period;

*d)* antimicrobial susceptibility data;

*e)* comments concerning the response of *animals* to treatment;

*f)* the investigation of adverse reactions to antimicrobial treatment, including lack of response due to possible antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

*Veterinarians* should also periodically review farm records on the use of VMP containing *antimicrobial agents* to ensure compliance with their directions or prescriptions and use these records to evaluate the efficacy of treatments.

5. Labelling

All VMP supplied by a *veterinarian* should be labelled in accordance with the national legislation.

6. Training and continued professional development

Veterinary professional organisations should participate in the training programmes as defined in point 11 of Article 6.10.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice recommendations on the responsible and prudent use of VMP containing *antimicrobial agents*.

Article 6.10.7.

**Responsibilities of food animal producers**

1) Food animal producers, with the assistance and guidance of a *veterinarian*, are responsible for implementing animal health and *animal welfare* programmes on their farms in order to promote animal health and food safety.

2) Food animal producers should:

*a)* draw up a health plan with the attending *veterinarian* that outlines preventive measures (e.g. feedlot health plans, mastitis control plans, endo- and ectoparasite control, *vaccination* programmes and *biosecurity* measures);

*b)* use VMP containing *antimicrobial agents* only on the prescription of a *veterinarian* or other suitably trained person authorised to prescribe VMP

containing *antimicrobial agents* in accordance with the national legislation and under the supervision of a *veterinarian*;

*c)* use VMP containing *antimicrobial agents* in accordance with product label instructions, including storage conditions, or the instructions of the attending *veterinarian*;

*d)* isolate sick *animals*, when appropriate, to avoid the transfer of pathogenic agents; dispose of dead or dying *animals* promptly under conditions approved by the relevant authorities;

*e)* address on-farm *biosecurity* measures and take basic hygiene precautions as appropriate;

*f)* comply with and record the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;

*g)* use VMP containing *antimicrobial agents* within the expiry date and dispose of unused and expired surplus VMP containing *antimicrobial agents* under conditions safe for the environment;

*h)* maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the *veterinarian* responsible for treating the *animals*;

*i)* keep adequate records of all VMP containing *antimicrobial agents* used, including the following:

  *i)* name of the product and active substance, batch number and expiry date;

  *ii)* name of prescriber and the supplier;

  *iii)* date of administration;

  *iv)* identification of the *animal* or group of *animals* to which the *antimicrobial agent* was administered;

  *v)* clinical conditions treated;

  *vi)* dosage;

  *vii)* withdrawal periods including the end-date of the withdrawal periods;

  *viii)* result of laboratory tests;

  *ix)* effectiveness of therapy;

*j)* inform the responsible *veterinarian* of recurrent *disease* problems.

3. Training

Food animal producers should participate in the training programmes as defined in point 11 of Article 6.10.3. It is recommended that food animal producer organisations work in cooperation with the veterinary professional organisations to implement existing guidelines for the responsible and prudent use of VMP containing *antimicrobial agents*.

Article 6.10.8.

**Responsibilities of animal feed manufacturers**

1) The supply of medicated feed containing *antimicrobial agents* to farmers keeping food-producing animals by animal *feed* manufacturers should be allowed only on the prescription of a *veterinarian*. Alternatively, such medicated *feed* may be prescribed by other suitably trained persons authorised to prescribe VMP containing *antimicrobial agents* in accordance with the national legislation and under the supervision of a *veterinarian*. Animal *feed* manufacturers preparing medicated *feed* should do so following rules put in place by the *Competent Authority* in accordance with the national legislation. All medicated *feed* and medicated premixes should be appropriately labelled.

2) The regulations and recommendations on the responsible and prudent use of VMP containing *antimicrobial agents* should be reinforced by animal *feed* manufacturers who should keep detailed records.

3) Use only approved sources of medications: Animal *feed* manufacturers preparing medicated *feed* should ensure that only approved sources of medications are added to *feed* at a level, and for a species and purpose as permitted by the drug premix label or a veterinary prescription.

4) Ensure appropriate labelling with product identification, direction for use and withdrawal time: Animal *feed* manufacturers preparing medicated *feed* should ensure that medicated animal *feed* are labelled with the appropriate information (e.g. level of medication, approved claim, intended species, directions for use, warning, cautions) so as to ensure effective and safe use by the producer.

5) Implement appropriate production practices to prevent contamination of other feed: Animal *feed* manufacturers preparing medicated *feed* should implement appropriate production practices to avoid unnecessary carry over and unsafe cross contamination of unmedicated *feed*.

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NB: FIRST ADOPTED IN 2003; MOST RECENT UPDATE ADOPTED IN 2014.

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 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 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, immune compromised 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.

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

# 2.
# Aquatic Animal Health Code

SECTION 6.

## ANTIMICROBIAL USE IN AQUATIC ANIMALS

CHAPTER 6.1.

# INTRODUCTION TO THE RECOMMENDATIONS FOR CONTROLLING ANTIMICROBIAL RESISTANCE

Article 6.1.1.

**Objectives**

The purpose of this section is to provide guidance for Member Countries to appropriately address the selection and dissemination of resistant microorganisms and antimicrobial resistance determinants from the use of *antimicrobial agents* in *aquatic animals*.

*Antimicrobial agents* are essential for human and animal health and welfare. The OIE recognises the need for access to *antimicrobial agents* in veterinary medicine: *antimicrobial agents* are essential for treating and controlling infectious *diseases* in *aquatic animals*. The OIE therefore considers that ensuring continued access to effective *antimicrobial agents* is important.

The OIE recognises that antimicrobial resistance is a global public and animal health concern that is influenced by the usage of *antimicrobial agents* in humans, animals and elsewhere. Those working in the human, animal and plant sectors have a shared responsibility to address the risk factors for the selection and dissemination of antimicrobial resistance. Arising from its mandate for the protection of animal health and food safety, the OIE developed these chapters to provide guidance to Member Countries in regard to risks in the animal sector.

The application of *risk assessment* and *risk management* measures should be based on relevant international standards on *risk analysis* and supported by sound data and information when available. The guidance provided in these chapters should be consulted as part of the standard approach to reduce the risk associated with the selection and dissemination of antimicrobial resistant microorganisms and antimicrobial resistance determinants.

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NB: FIRST ADOPTED IN 2010; MOST RECENT UPDATE ADOPTED IN 2011.

CHAPTER 6.2.

# PRINCIPLES FOR RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN AQUATIC ANIMALS

Article 6.2.1.

**Purpose**

These principles provide guidance for the responsible and prudent use of *antimicrobial agents* in *aquatic animals*, with the aim of protecting both animal and human health. The *Competent Authorities* responsible for the registration and marketing authorisation of products and the control of all organisations involved in the production, distribution and use of *antimicrobial agents* have specific obligations.

Article 6.2.2.

**Objectives of responsible and prudent use**

Responsible and prudent use includes a set of practical measures and recommendations intended to reduce the risk associated with the selection and dissemination of antimicrobial resistant microorganisms and antimicrobial resistance determinants in *aquatic animal* production to:

1) maintain the efficacy of *antimicrobial agents* both for veterinary and human medicine and to ensure the rational use of antimicrobials in *aquatic animals* with the purpose of optimising both their efficacy and safety;

2) comply with the ethical obligation and economic need to keep *aquatic animals* in good health;

3) prevent or reduce the transfer of both resistant microorganisms and resistance determinants from *aquatic animals* to humans and terrestrial animals;

4) prevent antimicrobial residues that exceed the established maximum residue limit (MRL) occurring in the food.

Article 6.2.3.

## Definition

**Pharmacovigilance of antimicrobial agent**: means the detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in *aquatic animals* and safety in people exposed to the products.

Article 6.2.4.

## Responsibilities of Competent Authorities

The *Competent Authorities* responsible for granting marketing authorisation for *antimicrobial agents* have a significant role in specifying the terms of the authorisation and in providing the appropriate information to the *veterinarian* or other *aquatic animal health professional* through product labelling and/or by other means, in support of prudent use of *antimicrobial agents* in *aquatic animals*.

It is the responsibility of *Competent Authorities* to develop up-to-date guidelines on data requirements for evaluation of *antimicrobial agent* applications.

*Competent Authorities* in cooperation with animal and public health professionals should adopt a proactive approach to promote prudent use of *antimicrobial agents* in *aquatic animals* as an element of a comprehensive strategy for the containment of antimicrobial resistance.

Elements of a comprehensive strategy should include good animal husbandry practices, vaccination policies and development of animal health care at the farm level, and consultation with a *veterinarian* or other *aquatic animal health professional*, all of which should contribute to reduction of the prevalence of animal *disease* requiring antimicrobial treatment.

*Competent Authorities* should expeditiously grant marketing authorisations when criteria of quality, efficacy and safety are met.

The examination of marketing authorisation applications should include an assessment of the risks to animals, humans and the environment resulting from the use of *antimicrobial agents* in *aquatic animals*. The evaluation should focus on each individual *antimicrobial agent* and take into consideration the class of antimicrobials to which the particular active substance belongs. The safety evaluation should include consideration of the potential impact of the proposed use in *aquatic animals* on human health, including the human health impact of antimicrobial resistance developing in microorganisms found in *aquatic animals*. An assessment of the impact of the proposed use on the environment should be conducted.

*Competent Authorities* should aim to ensure that advertising of *antimicrobial agents* complies with relevant legislation and marketing authorisations granted and discourage direct advertising other than to those legally entitled to prescribe the *antimicrobial agent*.

Information collected through pharmacovigilance programmes, including on lack of efficacy, should form part of the *Competent Authority's* comprehensive strategy to minimise antimicrobial resistance.

*Competent Authorities* should disseminate, to *veterinarians* or other *aquatic animal health professionals*, information on trends in antimicrobial resistance collected during surveillance programmes and should monitor the performance of susceptibility testing laboratories.

*Competent Authorities* and stakeholders should work together to provide for effective procedures for the safe collection and destruction of unused or out-of-date *antimicrobial agents*.

Article 6.2.5.

**Responsibilities of the veterinary pharmaceutical industry**

The veterinary pharmaceutical industry has responsibilities for providing information requested by *Competent Authorities* on the quality, efficacy and safety of *antimicrobial agents*. The responsibilities of the veterinary pharmaceutical industry cover pre- and post- marketing phases, including manufacturing, sale, importation, labelling, advertising and pharmacovigilance.

The veterinary pharmaceutical industry has the responsibility to provide the *Competent Authority* with the information necessary to evaluate the amount of *antimicrobial agents* marketed. The veterinary pharmaceutical industry should ensure that the advertising of *antimicrobial agents* directly to the *aquatic animal* producer is discouraged.

Article 6.2.6.

**Responsibilities of wholesale and retail distributors**

Distributors should ensure that their activities are in compliance with the relevant legislation.

Distributors should ensure that information for the appropriate use and disposal of the *antimicrobial agent* accompany all distributed products and should also be responsible for maintaining and disposing of the product in accordance with the manufacturer recommendations.

Article 6.2.7.

**Responsibilities of veterinarians and other aquatic animal health professionals**

Responsibilities of *veterinarians* or other *aquatic animal health professionals* include identifying, preventing and treating *aquatic animal diseases*, as well as the promotion of sound animal husbandry methods, hygiene procedures, vaccination and other alternative strategies to minimise the need for antimicrobial use in *aquatic animals*.

*Veterinarians* or other *aquatic animal health professionals* authorised to prescribe veterinary medicines should only prescribe, dispense or administer a specific course of treatment with an *antimicrobial agent* for *aquatic animals* under their care.

The responsibilities of *veterinarians* or other *aquatic animal health professionals* are to carry out a thorough clinical assessment of the *aquatic animal(s)*, including as appropriate: clinical examination, post-mortem examination, bacteriology with culture and sensitivity, and other laboratory tests to arrive at the most definitive *diagnosis* possible before initiating a specific course of treatment with an *antimicrobial agent*. Evaluation of environmental factors and husbandry at the production site (e.g. water quality) should be considered as potential primary factors leading to *infection* and should be addressed prior to prescribing a course of *antimicrobial agent* treatment.

If therapy with an *antimicrobial agent* is deemed necessary it should be initiated as soon as possible. The selection of the agent should be based on the knowledge and experience of the *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines.

As soon as possible, susceptibility testing of the target microorganism should be used to confirm the choice of treatment. Results of all susceptibility tests should be retained and should be available to the *Competent Authority*.

The *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines should indicate precisely to the *aquatic animal* producer the treatment regime, including the dose, the treatment intervals, the duration of the treatment, the withdrawal period and the amount of *antimicrobial agents* to be delivered, depending on the dosage and the number of *aquatic animals* to be treated.

The use of *antimicrobial agents* extra-label/off-label may be permitted in appropriate circumstances in conformity with the relevant legislation.

Records on the use of *antimicrobial agents* should be kept in conformity with the relevant legislation. *Veterinarians* or *aquatic animal health professionals* should also periodically review farm records on the use of the *antimicrobial agents* to

ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens. Suspected adverse reactions, including a lack of efficacy, should be reported to the *Competent Authority*. Associated susceptibility data should accompany the report of lack of efficacy.

Article 6.2.8.

**Responsibilities of aquatic animal producers**

*Aquatic animal* producers should implement health programmes on their farms in order to promote *aquatic animal* health and food safety. This can be done through adequate planning of culture strategies to maintain *aquatic animal* health through *biosecurity* programmes, husbandry, nutrition, vaccination, maintenance of good water quality, etc.

*Aquatic animal* producers should use *antimicrobial agents* only on the prescription of a *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines, and follow directions on the dosage, method of application, and withdrawal period.

*Aquatic animal* producers should ensure that *antimicrobial agents* are properly stored, handled, and disposed.

*Aquatic animal* producers should keep adequate records of *antimicrobial agents* used, bacteriological and susceptibility tests, and make such records available to the *veterinarian* or other *aquatic animal health professional*.

*Aquatic animal* producers should inform the *veterinarian* or other *aquatic animal health professional* of recurrent *disease* problems and lack of efficacy of *antimicrobial agent* treatment regimes.

Article 6.2.9.

**Training of users of antimicrobial agents**

The training of users of *antimicrobial agents* should involve all the relevant organisations, such as relevant regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, and veterinary professional organisations and other approved users such as *aquatic animal* owners.

Article 6.2.10.

**Research**

To address the significant lack of information for numerous species of *aquatic animals*, the relevant regulatory authorities and other stakeholders should encourage public-funded and industry-funded research.

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NB: FIRST ADOPTED IN 2011.

CHAPTER 6.3.

# MONITORING OF THE QUANTITIES AND USAGE PATTERNS OF ANTIMICROBIAL AGENTS USED IN AQUATIC ANIMALS

Article 6.3.1.

## Purpose

The purpose of these recommendations is to describe approaches to the monitoring of quantities of *antimicrobial agents* used in *aquatic animals*, including species reared for food and ornamental purposes.

These recommendations are intended for use in the collection of objective and quantitative information to evaluate usage patterns by antimicrobial class, route of administration and *aquatic animal* species in order to evaluate exposure of microorganisms to *antimicrobial agents*.

The collection of data on the use of *antimicrobial agents* in *aquaculture* may be constrained in some countries by the lack of available resources, lack of accurately labelled products, poorly documented distribution channels and lack of professional consultation or supervision. This chapter may therefore be seen as indicating the direction in which countries should develop with regard to collecting data and information on the use of *antimicrobial agents* in *aquatic animals*.

Article 6.3.2.

## Objectives

The information provided in these recommendations is essential for conducting *risk analyses* and for planning purposes. This information can be helpful in interpreting antimicrobial resistance surveillance data and can assist in the ability to respond to problems of antimicrobial resistance in a precise and targeted way. The continued collection of this basic information would help identify trends in the use of *antimicrobial agents* in *aquatic animals* and the potential association with antimicrobial resistance in *aquatic animal* bacteria, including potentially zoonotic bacteria. This information may also assist in *risk management* when evaluating the effectiveness of efforts to ensure responsible and prudent use and mitigation strategies and indicate where alteration of prescribing practices for *antimicrobial agents* in *aquatic animals* might

be appropriate. The publication of these data and their interpretation is important to ensure transparency and to allow all interested parties to assess trends, to perform *risk assessments* and for *risk communication* purposes.

Article 6.3.3.

**Development and standardisation of monitoring systems for antimicrobial agents**

*Competent Authorities* may, for reasons of cost and administrative efficiency, collect medical, agricultural, aquacultural and other *antimicrobial agents* use data in a single programme. Where livestock and *aquatic animal* industries are under multiple authorities in a single country, collaboration between the authorities to develop a coordinated monitoring system is necessary to facilitate the collection of data. Additionally, a consolidated programme would facilitate the comparison of *aquatic animal* use data with human use data necessary for a comprehensive *risk analysis*.

Systems to monitor usage of *antimicrobial agents* may consist of the following elements:

1. Sources of data on antimicrobial agents

   *a)* Basic sources

   Data from basic sources may include general information without specific attribution (such as, weight, quantity and class of *antimicrobial agents*).

   Sources of data will vary from country to country. Such sources may include customs, import, export, manufacturing and sales data.

   *b)* Direct sources

   Data from direct sources may include more specific information (such as target *aquatic animal* species, route of administration and active ingredient).

   Data from veterinary medicinal product registration authorities, manufacturers, wholesalers, retailers, *feed* stores and *feed* mills might be useful sources. A possible mechanism for the collection of this information is to make the provision of appropriate information by veterinary antimicrobial manufacturers to the registration authority one of the requirements of marketing authorisation (registration of the *antimicrobial agent*).

*c)* End-use sources

Data from end-use sources has the advantage of providing more detailed information on the type and purpose of use and can be complimentary to the other sources.

End-use sources of data may include *veterinarians*, *aquatic animal health professionals* and *aquatic animal* producers. End-use sources may be useful when more accurate and locally specific information is needed (such as extra-/off-label use).

Collection of this type of information can be resource intensive; therefore, periodic collection of this type of information may be sufficient. Data collection should be targeted to the most relevant period of use.

In some countries end-use sources may be the only practical source of information.

*d)* Other sources

Pharmaceutical industry associations and *aquatic animal* producer associations, veterinary and allied health professional associations, and other stakeholders with indirect knowledge of the quantities of *antimicrobial agents* used may be another source of this information.

Non-conventional sources including Internet sales data related to *antimicrobial agents* may be collected where available. Internet sales data may be particularly useful with respect to ornamental species.

2. Elements for data collection and reporting

*a)* Basic data to be collected should include:

*i)* the absolute amount in kilograms of the active ingredient of the *antimicrobial agent(s)* used per year, divided into antimicrobial class/subclass;

for active ingredients present in the form of compounds or derivatives, the mass of active entity of the molecule should be recorded; for *antimicrobial agents* expressed in International Units, the calculation required to convert these units to mass of active entity should be stated; it may be possible to estimate total usage by collecting sales data, prescribing data, manufacturing data, export/import data or any combination of these;

*ii)* the total number of *aquatic animals* treated and their weight in kilograms.

*b)* Additional data may be collected to further categorise the exposure of microorganisms to *antimicrobial agents* and may include:

*i)* species of fish, crustaceans, molluscs or amphibians treated;

*ii)* purpose e.g. *aquatic animals* for human consumption, use as ornamental species and baitfish;

*iii)* route of administration (medicated feed, bath treatment, parenteral delivery) and the method used to calculate the dose (biomass of *aquatic animals*, volume of water treated);

*iv)* indication for use.

The *antimicrobial agents*/classes/sub-classes to be included in data reporting should be based on current known mechanisms of antimicrobial activity / antimicrobial resistance mechanism.

Nomenclature of *antimicrobial agents* should comply with international standards where available.

When making information publically available, the *Competent Authority* should ensure confidentiality and anonymity of individual enterprises.

3. Considerations for data collection

Antimicrobial usage data may be collected on a routine basis and / or at a specific point in time depending on availability of resources and / or the need to monitor usage of *antimicrobial agents* or address a specific antimicrobial resistance problem.

Registration of products with labelling that accurately reflects the intended use of the *antimicrobial agent* will facilitate collection of information on the quantities and usage patterns.

Collection, storage and processing of data from end-use sources requires careful design but should have the advantage of producing accurate and targeted information.

Article 6.3.4.

**Elements for interpretation of data on the use of antimicrobial agents**

When available, the following information may support the interpretation of antimicrobial usage data and further characterisation of exposure pathways:

1) type of aquaculture system (extensive or intensive, ponds or tanks, flow-through or recirculating, hatchery or grow-out, integrated system);

2) animal movements (transfer between facilities or from wild to the facility, grading);

3) species, life stage, and/or stage of the production cycle;

4) environmental and culture parameters (seasonality, temperature, salinity, pH);

5) geographical location, specific rearing units;

6) weight/biomass, dosage regimes and duration of treatment with *antimicrobial agents*;

7) basis for treatment (historical, empirical, clinical, clinical with laboratory confirmation and sensitivity testing).

Factors such as the number/percentage of animals / culture units treated, treatment regimens, type of use and route of administration are key elements to consider for *risk assessment*.

When comparing use of *antimicrobial agents* over time, changes in size and composition of animal populations should also be taken into account.

Regarding data coming from end-user sources, analysis of the use of *antimicrobial agents* may be possible at the regional, local or farm level, and at the level of the individual *veterinarian* or other *aquatic animal health professional*.

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NB: FIRST ADOPTED IN 2012.

CHAPTER 6.4.

# DEVELOPMENT AND HARMONISATION OF NATIONAL ANTIMICROBIAL RESISTANCE SURVEILLANCE AND MONITORING PROGRAMMES FOR AQUATIC ANIMALS

Article 6.4.1.

**Purpose**

This chapter provides criteria relevant to *aquatic animals* and *aquatic animal products* intended for human consumption for:

1) the development of national antimicrobial resistance surveillance and monitoring programmes and

2) the harmonisation of existing national antimicrobial resistance surveillance and monitoring programmes.

Article 6.4.2.

**Objective of surveillance and monitoring programmes**

*Competent Authorities* should conduct active antimicrobial resistance surveillance and monitoring programmes for *aquatic animals*.

Surveillance and monitoring of antimicrobial resistance is necessary to:

1) establish baseline data on the prevalence of antimicrobial resistant microorganisms and determinants;

2) collect information on antimicrobial resistance trends in relevant microorganisms;

3) explore the potential relationship between antimicrobial resistance in *aquatic animal* microorganisms and the use of *antimicrobial agents*;

4) detect the emergence of antimicrobial resistance mechanisms;

5) conduct *risk analyses* as relevant to *aquatic animal* and human health;

6) provide recommendations on human health and *aquatic animal* health policies and programmes;

7) provide information to facilitate prudent use, including guidance for professionals prescribing the use of *antimicrobial agents* in *aquatic animals*.

Cooperation at a regional level between countries conducting antimicrobial resistance surveillance should be encouraged.

The findings of surveillance and monitoring programmes should be shared at the regional and international level to maximise understanding of the global risks to *aquatic animal* health and human health. The publication of these data and their interpretation is important to ensure transparency and to allow all interested parties to assess trends, to perform *risk assessments* and for *risk communication* purposes.

Article 6.4.3.

**General considerations for the design of surveillance and monitoring programmes**

Surveillance of antimicrobial resistance at targeted intervals or ongoing monitoring of the prevalence of resistance in microorganisms from *aquatic animals*, *aquatic animal products* intended for human consumption, and humans constitutes a critical part of *aquatic animal* health and public health strategies aimed at limiting the spread of antimicrobial resistance and optimising the choice of *antimicrobial agents* used in therapy.

For *aquaculture* it is important to conduct surveillance and monitoring of microorganisms that infect *aquatic animals* and microorganisms, including human pathogens, present on food derived from *aquatic animals*.

Article 6.4.4.

**Design of surveillance and monitoring programmes for antimicrobial susceptibility of microorganisms that infect aquatic animals**

An important consideration for the design of surveillance and monitoring programmes for antimicrobial susceptibility of microorganisms that infect *aquatic animals* is the lack of standardised and validated antimicrobial testing methods for a significant number of bacterial species of aquatic importance. When validated methods are available they should be used. Any deviations from standard methodology should always be clearly reported. For tests performed on bacterial species for which standard methods have not been developed full details of the methods used should be provided.

A preliminary requirement for the development of a surveillance and monitoring programme may be the identification and prioritisation of bacteria isolated from *aquatic animals* for methods development.

1. Selection of microorganisms

Information on the occurrence of antimicrobial resistance in microorganisms that infect *aquatic animals* should be derived from regular monitoring of isolates obtained from diagnostic laboratories. These isolates should have been identified as primary causal agents of significant disease epizootics in *aquatic animals*.

It is important that monitoring programmes focus on microorganisms that are associated with the commonly encountered *infections* of the major aquatic species farmed in the region / local growing area.

Selection should be designed to minimise bias resulting from over representation of isolates obtained from severe epizootics or epizootics associated with therapeutic failures.

Microorganisms belonging to a specific species or group may be selected for intensive study in order to provide information on a particular problem.

2. Methods used to analyse microorganism susceptibility to antimicrobial agents

Participating laboratories may perform disc diffusion, minimum inhibitory concentration (MIC) or other susceptibility tests to monitor frequencies of resistance. Protocols that have been standardised internationally and validated for application to the study of microorganisms isolated from *aquatic animals* should always be used.

3. Requirements for laboratories involved in monitoring resistance

Laboratories involved in national or regional monitoring of antimicrobial resistance should be of sufficient capability and have relevant expertise to comply with all the quality control requirements of the standardised test protocols. They should also be capable of participating in all necessary inter-laboratory calibration studies and method standardisation trials.

4. Choice of antimicrobial agents

Representatives of all major classes of *antimicrobial agents* used to treat *disease* in *aquatic animal* species should be included in susceptibility testing.

5. Reporting of results

The results of surveillance and monitoring programmes, including susceptibility data, should be published and made available for use by relevant stakeholders. Both primary quantitative data and the interpretive criteria used should be reported.

6. Surveillance and monitoring for epidemiological purposes

For epidemiological surveillance purposes, use of the epidemiological cut-off value (also referred to as microbiological breakpoint), which is based on the distribution of MICs or inhibition zone diameters of the specific microbial species tested, is preferred.

When reporting interpretations made by application of epidemiological cut-off values, the resultant categories should be referred to as wild type (WT) or non-wild type (NWT). When interpretations are made by the application of breakpoints the resultant categories should be referred to as sensitive, intermediate or resistant.

For microbial species and *antimicrobial agent* combinations, where internationally agreed epidemiological cut-off values have not been set, laboratories may establish their own laboratory-specific values provided the methods they use are clearly reported.

7. Surveillance and monitoring for clinical purposes

The application of clinical breakpoints may be appropriate when the aim of the programme is to provide information to facilitate prudent use, including guidance for professionals in prescribing *antimicrobial agents* in *aquatic animals*. Selecting *antimicrobial agents* for therapeutic administration on the basis of information gained from the application of validated clinical breakpoints to antimicrobial susceptibility test data for microorganisms isolated from *aquatic animals* is an important element in the prudent use of these agents.

Use of these clinical breakpoints allows microorganisms to be identified as unlikely to respond to the *in vivo* concentrations of *antimicrobial agents* achieved by a given standard therapeutic regime. In order to facilitate the development of these breakpoints, data is required that allows clinical correlation to be completed. For this purpose, where possible, data that relates *in vitro* susceptibility of isolates to the clinical outcome of treatments with specified dose regimes under specific environmental conditions should be collected and reported.

Valuable information with respect to setting clinical breakpoints can be gained from situations where therapeutic failure is reported. The *Competent Authority* should include, in a surveillance and monitoring programme, systems for capturing details of failed treatments and the laboratory susceptibility test of the microorganisms involved.

Article 6.4.5.

**Design of surveillance and monitoring programmes for microorganisms in or on aquatic animal products intended for human consumption**

For details of the sampling protocols and analytical procedures required for surveillance and monitoring programmes for antimicrobial resistance in microorganisms present in *aquatic animal products* intended for human consumption, Chapter 6.8. of the OIE *Terrestrial Animal Health Code* should be consulted.

It is important to note that the word 'commensal' as used in Chapter 6.8. of the OIE *Terrestrial Animal Health Code* has less relevance due to the transient nature of the intestinal microflora of *aquatic animals*. The inclusion of intestinal microflora in surveillance and monitoring programmes should only be considered when there is evidence that these are resident for sufficient time to be a risk factor affected by *antimicrobial agents*.

When designing a sampling programme it is important to consider that contamination of *aquatic animal products* with resistant microorganisms that are capable of infecting humans may arise from sources other than the *aquatic animal*. All sources of contamination should be taken into account, for example entry of raw manure into the aquatic environment. The number of such microorganisms associated with *aquatic animals* is much less than that found in terrestrial animals. However the following species should be included, as a minimum, in a surveillance and monitoring programme:

1) *Salmonella* spp.;

2) *Vibrio parahaemolyticus*;

3) *Listeria monocytogenes*.

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NB: FIRST ADOPTED IN 2012.

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 assessments*.

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 *pathogenic 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

NB: FIRST ADOPTED IN 2015.

# 3.
# Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

SECTION 2.1.

**LABORATORY DIAGNOSTICS**

CHAPTER 2.1.1.

# LABORATORY METHODOLOGIES FOR BACTERIAL ANTIMICROBIAL SUSCEPTIBILITY TESTING


## SUMMARY

*With the increase in bacterial resistance to traditionally used antimicrobials, it has become more difficult for clinicians to empirically select an appropriate antimicrobial agent. As a result,* in vitro *antimicrobial susceptibility testing* (*AST*) *of the relevant bacterial pathogens, from properly collected specimens, should use validated methods. Thus, AST is an important component of prudent antimicrobial use guidelines in animal husbandry worldwide and veterinarians in all countries should have these data available for informed decision-making.*

*Although a variety of methods exist, the goal of* in vitro *antimicrobial susceptibility testing are either to provide a reliable predictor of how an organism is likely to respond to antimicrobial therapy in the infected host or to assess for surveillance purposes whether there has been development of resistance. This type of information aids the clinician in selecting the appropriate antimicrobial agent, aids in developing antimicrobial use policy, and provides data for epidemiological surveillance. Such epidemiological surveillance data provide a base to choose the appropriate empirical treatment* (*first-line therapy*) *and to detect the emergence and/or the dissemination of resistant bacterial strains or resistance determinants in different bacterial species. The selection of a particular AST method is based on many factors such as validation data, practicality, flexibility, automation, cost, reproducibility, accuracy, standardisation and harmonisation.*

*The use of genotypic approaches for detection of antimicrobial resistance genes has also been promoted as a way to increase the speed and accuracy of susceptibility testing. Numerous DNA-based assays are being developed to detect bacterial antimicrobial resistance at the genetic level. These methods, when used in conjunction with phenotypic analysis, offer the promise of increased sensitivity,*

*specificity, and speed in the detection of specific known resistance genes and can be used in tandem with traditional laboratory AST methods.*

## INTRODUCTION

The spread of multiple antimicrobial-resistant pathogenic bacteria has been recognised by the World Organisation for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as a serious global human and animal health problem. The development of bacterial antimicrobial resistance is neither an unexpected nor a new phenomenon. It is, however, of increasing concern due to the frequency with which new emerging resistance phenotypes are occurring among many bacterial pathogens and commensal organisms, such as resistance to carbapenemases, colistin, linezolid, macrolids, etc.

Historically, many infections could be treated successfully according to the clinician's past clinical experience or because susceptibility could be reliably predicted (i.e. empirical therapy); however, this is becoming more the exception than the rule (Walker, 2007). Resistance has been observed to essentially all of the antimicrobial agents currently approved for use in human and veterinary clinical medicine. This, combined with the variety of antimicrobial agents currently available, makes the selection of an appropriate agent an increasingly challenging task. This situation has made clinicians more dependent on data from *in vitro* antimicrobial susceptibility testing, and highlights the importance of the diagnostic laboratory in clinical practice.

A number of antimicrobial susceptibility testing (AST) methods are available to determine bacterial susceptibility to antimicrobials. The selection of a method is based on many factors such as practicality, flexibility, automation, cost, reproducibility, accuracy, accessibility and individual preference. Standardisation and harmonisation of AST methodologies, used in epidemiological surveillance of antimicrobial drug resistance, are critical if data are to be compared among national or international surveillance/monitoring programmes of OIE Members. It is essential that AST methods provide reproducible results in day-to-day routine laboratory use and that the data be comparable with those results obtained by an acknowledged 'gold standard' reference method. Currently the reference AST method is the broth micro-dilution method that determines minimum inhibitory concentration (MIC) as described by the ISO (International Organization for Standardization, 2006). In the absence of standardised methods or reference procedures, susceptibility results from different laboratories cannot be reliably compared. The method used to select samples for inclusion in antimicrobial resistance surveillance programmes, as well as the methods used for primary bacterial isolation, are also important factors that should be standardised or harmonised to allow direct comparison of data between different regions; consideration of these issues is addressed in an OIE document (Dehaumont, 2004).

As the science of AST has progressed, a greater understanding of the multiple factors that could affect the overall outcome of susceptibility testing has become clearer (WHO, 2017). This document provides guidelines and standardisation for AST methodologies, and interpretation of antimicrobial susceptibility test results.

## 1. Test requirements

The following requirements should be applied to achieve standardisation of AST methods and comparability of AST results:

i) the use of standardised AST methods is essential, including the harmonisation of AST test parameters such as media, inoculum, incubation time, quality controls, choice of antimicrobial agents and subsequent interpretive criteria,

ii) standardised AST methods, including all critical specifications and interpretive criteria, should be clearly defined, documented in detail and used by all participating laboratories,

iii) all AST methods should generate accurate and reproducible data,

iv) quantitative susceptibility data (MIC) should be reported,

v) establishment of national or regional reference laboratories is essential for the coordination of AST methodologies, interpretations and appropriate operational techniques used to ensure accuracy and reproducibility (e.g. quality controls),

vi) microbiological laboratories should implement and maintain a formal quality management programme (see Chapter 1.1.5. *Quality management in veterinary testing laboratories*),

vii) laboratories should have acquired a third party accreditation that includes the AST methodologies to be used within the scope of that accreditation. The accreditation body should meet accepted international Laboratory Accreditation Cooperation [ILAC]) standards and guidelines regarding the standards used for the accreditation process. The accreditation standards used should include the requirement for participation in proficiency testing programmes,

viii) specific bacterial reference/quality control strains are essential for determining intra- and inter-laboratory quality control, quality assurance and proficiency testing.

## 2. Selection of antimicrobials for testing and reporting

Selecting the appropriate antimicrobials for susceptibility testing can be difficult given the vast numbers of agents available.

The following guidelines should be noted:

i) the FAO/OIE/WHO expert workshop on non-human antimicrobial usage and antimicrobial resistance recommends creating a list of veterinary and human critically important antimicrobials for susceptibility testing and reporting,

ii) selection of the most appropriate antimicrobials is a decision best made by each OIE Member in consultation with the appropriate bodies and organisations,

iii) antimicrobials in the same class may have similar *in vitro* activities against select bacterial pathogens. In these cases, a representative antimicrobial should be selected that predicts susceptibility to other members of the same class,

iv) certain microorganisms can be intrinsically resistant to particular antimicrobial classes; therefore it is unnecessary and misleading to test certain agents for activity *in vitro*. The type of intrinsic resistance has to be determined for these organisms via either the scientific literature or through testing,

v) the number of antimicrobials to be tested should comply with the guideline used (CLSI/EUCAST/ISO) and at least contain class representatives to ensure the relevance and practicality of AST (see also WHO, 2017).

Periodic review of microorganisms that are currently predictably susceptible to certain antimicrobial agents is recommended to ensure that emergent, unexpected resistance is detected. Emerging resistance may also be suspected following poor response to a standard antimicrobial treatment regime.

## 3. Antimicrobial susceptibility testing methodologies

The following requirements should be respected:

i) bacteria subjected to AST must be isolated in pure culture from the submitted sample,

ii) standard reference methods should be used for identification so that the subject bacteria are consistently and correctly identified to the genus and/or species level,

iii) bacterial isolates considered to be the most important and other selected isolates, should be stored for future analysis (either lyophilisation or cryogenic preservation at –70°C to –80°C).

The following factors influencing AST methods should be determined, optimised, and documented in a detailed standard operating procedure:

i) once the bacterium has been isolated in pure culture, a standardised concentration of the inoculum must be prepared using a nephelometer or spectrophotometer to ensure a defined number of colony forming units to obtain accurate and repeatable susceptibility results. Bacteria or other organisms used in AST testing should be from a fresh 24-hour culture,

ii) the composition and preparation of the agar and broth media used (e.g. pH, cations, thymidine or thymine, use of supplemented media) should comply with guidelines (CLSI/EUCAST/ISO). Performance and sterility testing of media lots should also be determined and documented as well as employed procedures,

iii) the content, range/interval and concentration of the antimicrobials used (microtitre plates, disk, strip, tablet), should follow guidelines (CLSI/EUCAST/ISO) and be relevant to the species tested,

iv) composition of solvents and diluents for preparation of antimicrobial stock solutions,

v) growth and incubation conditions (time, temperature, atmosphere e.g. $CO_2$),

vi) agar depth,

vii) the test controls to be used, including the reference organisms used,

viii) the subsequent interpretive criteria (clinical breakpoints, epidemiological cut-off values – ECOFFs).

For these reasons, special emphasis has to be placed on the use of documented procedures and validated, well documented methods, as sufficient reproducibility can be attained only through the use of such methodology.

## 4. Selection of antimicrobial susceptibility testing methodology

The selection of an AST methodology may be influenced by the following factors:

i) ease of performance,

ii) flexibility,

iii) adaptability to automated or semi-automated systems,

iv) cost,

v) reproducibility,

vi) reliability,

vii) accuracy,

viii) the organisms and the antimicrobials of interest in that particular OIE Member,

ix) availability of suitable validation data for the range of organisms to be susceptibility tested.

## 5. Antimicrobial susceptibility testing methods

The following three methods have been shown to consistently provide reproducible and repeatable results when followed correctly (Clinical and Laboratory Standards Institute (CLSI), 2008; Walker, 2007):

i) disk diffusion,

ii) broth dilution,

iii) agar dilution.

### 5.1. Disk diffusion method

Disk diffusion refers to the diffusion of an antimicrobial agent from a disk or tablet containing a specified concentration of the agent tablets into a solid culture medium (normally Müller–Hinton agar) that has been inoculated with a pure culture (see Section 3). The disk diffusion result is determined by measurement of the diameter of the inhibition zone around the disk, the diameter being proportional to the bacterial susceptibility to the antimicrobial present in the disk.

The diffusion of the antimicrobial agent into the culture media results in a gradient of the antimicrobial. When the concentration of the antimicrobial becomes so diluted that it can no longer inhibit the growth of the test bacterium, the zone of inhibition is demarcated. The diameter of this zone of inhibition around the antimicrobial disk is related to MIC for that particular bacterium/antimicrobial combination; the zone of inhibition correlates inversely with the MIC of the test bacterium. Generally, the larger the zone of inhibition, the lower the concentration of antimicrobial required to inhibit the growth of the organisms. However, this depends on the concentration of antimicrobial agent in the disk and its diffusibility. Antimicrobial agents that are very large molecules diffuse poorly in agar making disk diffusion methods unreliable for these compounds. For this reason disk diffusion methods are not recommended for example for the susceptibility testing of colistin/polymyxin (Matuschek *et al.*, 2018).

Note: Disk diffusion tests based solely on the presence or absence of a zone of inhibition without regard to the size of the zone of inhibition are not acceptable AST methodology.

### 5.1.1 Considerations for the use of the disk diffusion methodology

Disk diffusion is easy to perform, reproducible if standardised, and does not require expensive equipment. Its main advantages are:

i) low cost,

ii) ease in modifying test by changing antimicrobial disks when required,

iii) can be used as a screening test against large numbers of isolates,

iv) can identify a subset of isolates for further testing by other methods, such as determination of MICs.

v) the procedure is controlled by inclusion of appropriate control organisms for which a target zone size range is available (or has been derived) for each of the relevant antimicrobial agents being tested in the disk diffusion test procedure.

Manual measurement of zones of inhibition may be time-consuming. Automated zone-reading devices are available that can be integrated with laboratory reporting and data-handling systems.The disks should be distributed evenly on the agar surface so that the zones of inhibition around antimicrobial discs in the disc diffusion test do not overlap to such a degree that the zone of inhibition cannot be determined. Generally this can be accomplished if the discs are no closer than 24 mm from centre to centre, though this is dependent on disk concentration and the ability of the antimicrobial to diffuse in agar. Contamination of culture plates may be harder to detect using automated readers.

The diameter of the zone of inhibition obtained in disk diffusion tests is strongly influenced by the density of the bacterial inoculum applied, underlining the requirement to standardise the inoculum in accordance with guidelines (CLSI, EUCAST, ISO). A denser inoculum than intended will result in reduced zones of inhibition and a sparse inoculum will result in increased zones of inhibition (BSAC [British Society for Antimicrobial Chemotherapy], 2015).

## 5.2. Broth and agar dilution methods

The aim of the broth and agar dilution methods is to determine the lowest concentration of the antimicrobial that inhibits the visible growth of the bacterium being tested (MIC, usually expressed in µg/ml or mg/litre).The range of concentrations tested in broth and agar dilution methods generally includes the breakpoint (clinical or microbiological) with doubling dilutions either side of that value as considered appropriate. However, the MIC does not always represent exactly the concentration which was tested. The 'true' MIC is a point between the lowest test concentration that inhibits the growth of the bacterium

and the next lower test concentration. Therefore, MIC determinations performed using a dilution series may be considered to have an inherent variation of ±1 dilution.

Antimicrobial ranges should encompass both the interpretive criteria (susceptible, intermediate and resistant) for a specific bacterium/antibiotic combination and appropriate quality control reference organisms. Target MIC ranges should be available for each antimicrobial agent being tested.

Antimicrobial susceptibility dilution methods are more reproducible than agar disk diffusion which is why broth microdilution is the current reference test method. However, antibiotics are usually tested in doubling dilutions, which can produce inexact MIC data. The continuous range of zone diameter values obtained with disk diffusion can therefore be advantageous in certain circumstances, such as screening large numbers of susceptible isolates.

Any laboratory that intends to use a dilution method and set up its own reagents and antibiotic dilutions should have the ability to obtain, prepare and appropriately maintain stock solutions of reagent-grade antimicrobials, to account for the potency of the antimicrobial (supplied by the manufacturer) and to generate complex working dilutions on a regular basis. Published methods should be consulted. It is then essential that such laboratories use quality control organisms (see below) to assure accuracy and standardisation of their procedures.

**5.2.1 Broth dilution**

Broth dilution is a technique in which a suspension of bacterium of a predetermined optimal concentration is tested against varying concentrations of an antimicrobial agent (usually serial twofold dilutions) in a liquid medium of predetermined, documented formulation. The broth dilution method can be performed either in tubes containing a minimum volume of 2 ml (macrodilution) or in smaller volumes using microtitration plates (microdilution). Numerous microtitre plates containing lyophilised or dried prediluted antibiotics within the wells are commercially available. The use of the same batches of microdilution plates may assist in the minimisation of variation that may arise due to the preparation and dilution of the antimicrobials at different laboratories. The use of these plates, with a documented test protocol, including specification of appropriate reference organisms, will facilitate the comparability of results among laboratories.

Due to the fact that most broth microdilution antimicrobial test panels are prepared commercially, this method is less flexible than agar dilution or disk diffusion in adjusting to the changing needs of the surveillance/monitoring programme.

Because the purchase of antimicrobial plates and associated equipment may be costly, this methodology may not be feasible for some laboratories.

### 5.2.2 Agar dilution

Agar dilution involves the incorporation of varying concentrations of antimicrobial agent into an agar medium, usually using serial twofold dilutions, followed by the application of a defined bacterial inoculum to the agar surface of the plate. This method may be considered the most reliable for MIC determination for some antimicrobials (fosfomycin, mecillinam) and for certain bacteria where broth dilution methods are not well established.

The advantages of agar dilution methods include:

i) the ability to test multiple bacteria, except bacteria that swarm, on the same set of agar plates at the same time,

ii) the potential to improve the identification of MIC endpoints and extend the antibiotic concentration range,

iii) the possibility to semi-automate the method using an inoculum-replicating apparatus. Commercially produced inoculum replicators are available and these can transfer between 32 and 60 different bacterial inocula to each agar plate,

Agar dilution methods also have certain disadvantages, for example:

i) if not automated, they are very laborious and require substantial economic and technical resources,

ii) once the plates have been prepared, they normally should be used within 1–3 weeks depending in quality control (or less, depending on the stability of the antimicrobials tested),

iii) the endpoints are not always easy to read.

Agar dilution is often recommended as a standardised AST method for fastidious organisms (CLSI, 2015), such as anaerobes and *Helicobacter* species.

### 5.3. Other bacterial AST and specific antimicrobial resistance tests

Bacterial antimicrobial MICs can also be obtained using commercially available gradient strips that diffuse a predetermined antibiotic concentration. However, the use of gradient strips can be very expensive and MIC discrepancies can be found when testing certain bacteria/antimicrobial combinations compared with results of other methods (Ge *et al.*, 2002; Rathe *et al.*, 2009). Gradient strip methods are not recommended for testing the susceptibility of the antimicrobial agent colistin because of the large size of this molecule and its poor diffusion in agar (Matuschek *et al.*, 2018).

Regardless of the AST method used, the procedures should be documented in detail to ensure accurate and reproducible results, and appropriate reference and control organisms should always be tested every time AST is performed in order to ensure accuracy and validity of the data.

The appropriate AST choice can be dependent on the growth characteristics of the bacterium in question, as well as the objective of testing. In special circumstances, novel test methods and assays may be more appropriate for detection of particular resistance phenotypes. For example, chromogenic cephalosporin-based tests (CLSI, 2018) (e.g. nitrocefin) may provide more reliable and rapid results for beta-lactamase determination in certain bacteria, whereas inducible clindamycin resistance in *Staphylococcus* spp. may be detected using a disk diffusion method employing standard erythromycin and clindamycin disks in adjacent positions and measuring the resultant zones of inhibition (e.g. D-zone or D-test) (Zelazny *et al.*, 2005).

Similarly, extended-spectrum beta-lactamase (ESBL) (CLSI, 2018) activity in certain bacteria can also be detected by using standard disk diffusion susceptibility test methods incorporating specific cephalosporins (cefotaxime and ceftazidime) separately and in combination with a beta-lactamase inhibitor (clavulanic acid) and measuring the resulting zones of inhibition. Also penicillin-binding protein 2a (PBP 2a) can be detected in methicillin resistant staphylococci with a latex agglutination test (Stepanovic *et al.*, 2006). It is essential that testing of known positive and negative control strains occurs alongside clinical isolates to ensure accurate results.

Susceptibility testing may also be performed using breakpoint values specifically intended to detect particular mechanisms of bacterial resistance of clinical or public health importance, for example resistance to the carbapenems, which are used prudently to treat highly-resistant bacterial in humans (EUCAST [European Committee on Antimicrobial Susceptibility Testing], 2017).

## 5.4. Future directions in antimicrobial susceptibility/resistance detection

The use of genotypic approaches for detection of antimicrobial resistance genes has been promoted as a way to increase the rapidity and accuracy of susceptibility testing (Cai *et al.*, 2003; Chen *et al.*, 2005). Numerous DNA-based assays are being developed to detect bacterial antibiotic resistance at the genetic level. The newest and perhaps most state-of-the-art approach is to use genome sequencing to predict antimicrobial resistance phenotypes via identification and characterisation of the known genes that encode specific resistance mechanisms.

Methods that employ the use of comparative genomics, genetic probes, microarrays, nucleic acid amplification techniques (e.g. polymerase chain reaction [PCR]), and DNA sequencing offer the promise of increased sensitivity, specificity, and speed in the detection of specific known resistance genes (Cai *et al.*, 2003; Chen *et al.*, 2005; Perreten *et al.*, 2005). Genotypic methods have been successfully applied to supplement traditional AST phenotypic methods for other organisms including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and detection of fluoroquinolone resistance mutations (Cai *et al.*, 2003; Chen *et al.*, 2005; Perreten *et al.*, 2005). PCR methods have also been described for beta-lactamases, aminoglycoside inactivating enzymes, and tetracycline efflux genes (Cai *et al.*, 2003; Chen *et al.*, 2005; Frye *et al.*, 2010; Perreten *et al.*, 2005).

Technological innovations in DNA-based diagnostics should allow for the detection of multiple resistance genes and/or variants during the same test. The development of rapid diagnostic identification methods and genotypic resistance testing should help reduce the emergence of antimicrobial resistance, by enabling the use of the most appropriate antimicrobial when therapy is initiated. However, DNA techniques have to be demonstrated to be complementary to AST methods and results.

Additionally, new technological advances may facilitate the ability to probe bacterial species for large numbers of antimicrobial resistance genes quickly and cheaply, thereby providing additional relevant data for surveillance and monitoring programmes (Frye *et al.*, 2010). However, despite the new influx of genotypic tests, documented and agreed upon phenotypic AST methods will still be required in the near future to detect emerging resistance mechanisms among bacterial pathogens and to detect and characterise newly discovered mechanisms of resistance for the development and validation of genetic testing. A literature review (Ellington *et al.*, 2017) considered the role of whole genome sequencing (WGS) in antimicrobial susceptibility testing of bacteria and concluded there was insufficient published evidence to support the use of AST via WGS to replace phenotypic AST in clinical settings for all

bacterial species, although certain bacteria (e.g. *Salmonella, Staphylococcus aureus*) had been well characterised for that purpose. Subsequently several publications have added support to the use of genetic AST (e.g. McDermott *et al.*, 2016, Zhao *et al.*, 2016). The future of genetic testing in the detection of antimicrobial resistance is promising, but phenotypic testing will remain an important mainstay.

## 6. Antimicrobial susceptibility breakpoints and zone of inhibition criteria

The primary objective of *in-vitro* AST is to predict how a bacterial pathogen may respond to an antimicrobial agent *in vivo*. The results generated by bacterial *in-vitro* antimicrobial susceptibility tests, regardless of whether disk diffusion or dilution methods are used, are generally interpreted and reported as resistant, susceptible or intermediate to the action of a particular antimicrobial by applying clinical breakpoints. No single formula for selection of optimal breakpoints has been established. The process involves a review of existing data and is influenced by the methods used to select appropriate breakpoints.

Generally, antimicrobial susceptibility breakpoints are established by national standards organisations, professional societies or regulatory agencies. The relevant documents should be consulted. However, there can be notable differences in breakpoints for the same antimicrobial agent within and among countries due to differences between standards setting organisations and regulatory agencies and because of regional or national differences in dosing regimens (Brown & MacGowan, 2010; de Jong *et al.*, 2009; Kahlmeter *et al.*, 2006).

As mentioned previously, antimicrobial susceptibility testing results should be recorded quantitatively:

i) as distribution of MICs in milligrams per litre or µg/ml,

ii) or as inhibition zone diameters in millimetres.

The following two primary factors enable a bacterium isolate to be interpreted as susceptible or resistant to an antimicrobial agent:

i) The development and establishment of quality control ranges (CLSI, 2015), for disk diffusion or dilution testing, for quality control reference microorganisms.

   Establishment of quality control ranges for control organisms is essential for validating test results obtained using a specific AST method. The allowable interpretive category ranges for reference control organisms should be established in addition to determining breakpoints for susceptibility or resistance. The use of reference organisms is a quality control and quality assurance activity.

ii) The determination of the appropriate interpretive criteria regarding establishment of breakpoints (CLSI, 2015).

This involves the generation of three distinct types of data:

a) MIC population distributions of the relevant microorganisms,
b) pharmacokinetic parameters and pharmacodynamic indices of the antimicrobial agent,
c) results of clinical trials and the outcome of treatment of clinical cases of disease.

The development of a concept known as 'microbiological breakpoints', or 'epidemiological cut-off values' (the highest MIC value for the bacterium and antimicrobial agent under consideration, where the bacterium is devoid of any phenotypically expressed resistance to that antimicrobial agent), may be more appropriate for some antimicrobial surveillance programmes. Epidemiological cut-off values are derived by examining MIC population distributions for specific bacterial species and antimicrobials performed at several laboratories according to a standardised broth microdilution method. Bacterial isolates that possess any acquired phenotypic resistance (that is, have an MIC above the epidemiological cut-off value) and therefore deviate from the normal wild-type fully-susceptible population are designated as non-wild type (also termed or microbiologically resistant) and shifts in susceptibility to the specific antimicrobial/bacterium combination can thus be monitored (Kahlmeter, 2015; Kahlmeter *et al.*, 2006; Turnidge *et al.*, 2006). There is a great advantage in the recording of quantitative susceptibility data in that data may be analysed according to clinical breakpoints as well as by using epidemiological cut-off values.

The development of breakpoint criteria for disk diffusion tests usually involves comparing disk diffusion data against dilution data by creating a scattergram of the bacterial population distribution (representative bacterial isolates), by plotting the zone of inhibition against the logarithm to the base 2 of the MIC for each bacterial isolate for an individual bacterial species. The selection of breakpoints is then based on multiple factors, including regression line analysis that correlates MICs and zone diameters of inhibition, bacterial population distributions, error rate bounding, pharmacokinetics, and ultimately, clinical verification.

## 7. Antimicrobial susceptibility testing guidelines

A number of national standards and guidelines are currently available. International standards and guidelines for antimicrobial susceptibility testing and subsequent interpretive criteria throughout the world are:

– Clinical Laboratory and Standards Institute (CLSI, 2018),
– European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2017).

**Table 1: Phenotypic susceptibility testing methods available and their features**

| Susceptibility testing method | International standard available | Published methods available | Use in national surveillance programmes | Use in susceptibility testing for therapeutic purposes | Breakpoints that may be applied | Test output | Comparability of outputs | Features |
|---|---|---|---|---|---|---|---|---|
| Broth (micro) dilution MIC determination | Yes (ISO 20776-1), CLSI, EUCAST | Yes (CLSI, EUCAST) | Yes, broth microdilution MIC determination is preferred | Yes | Clinical breakpoints or epidemiological cut-off values (ECOFFs) | MIC | High | Current reference method. Recording MIC values allows interpretation of the test outputs using different breakpoints (e.g. clinical breakpoint or ECOFF), as well as re-evaluation of historical data if changes occur to breakpoints and evaluation of shifts in MIC. Numerous national surveillance programmes adopt this method. The MIC value can sometimes indicate the likely mechanism of resistance (e.g. high-level amikacin resistance and rRNA methylases) or provide an epidemiological marker. Currently, this is the only method suitable for determining susceptibility to colistin. |
| Agar dilution MIC determination | No | Yes (CLSI, EUCAST) | Not widely used | Yes | Clinical breakpoints or ECOFFs | MIC | Dependent on congruity of methods used | Reference method. The breakpoints appropriate for broth dilution may not be directly applicable to agar dilution. Currently used in particular for testing certain fastidious organisms. |
| Breakpoint method | No | Yes (scientific literature) | Not widely used | Yes | The test is performed at a set breakpoint | Resistant or susceptible at selected breakpoint | Dependent on congruity of methods used | Changes to breakpoints in this method result in the inability to interpret historical data. Shifts in susceptibility within the S or R categories cannot be detected. The breakpoint method relies on the growth or absence of growth of bacteria in broth or on agar containing an antimicrobial at a single (breakpoint) dilution. |
| Gradient strip method | No | Yes (manufacturer) | Not widely used | Yes | Clinical breakpoints or ECOFFs | MIC | High | Provide a convenient alternative method of determining MIC with minimal additional equipment required. |
| Disc diffusion test | No | Yes (CLSI, EUCAST) A number of different methods are available. These are not in general equivalent. | May be used, but broth microdilution MIC determination is preferred | Yes | Clinical breakpoints (ECOFFs are also available for the EUCAST disc diffusion method). | Diameter of zone of inhibition, interpreted as resistant or susceptible according to test guidelines | Dependent on congruity of methods used | Frequently used to provide an indication of susceptibility for therapeutic purposes. Versatile in that different discs can be used, according to the antimicrobials authorised for treatment. Different methods are not usually equivalent (zone sizes obtained using one method cannot be interpreted using criteria from another, different method). The collection of zone size data can allow shifts in susceptibility to be detected. Disc diffusion methods may be harmonised to a degree with other methods, by using the same breakpoint. |

The susceptibility testing method selected should provide details of the method, appropriate controls and quality control ranges and breakpoints. The comparability of outputs obtained in surveillance programmes is not only dependent on the laboratory methodology used but is also dependent on the target population of livestock included in the study and method of sampling.

At this time, only the CLSI has developed protocols for susceptibility testing of bacteria of animal origin and determination of interpretive criteria (CLSI, 2018). A veterinary sub-committee (VETCAST) has also been set up under the umbrella of EUCAST. However, protocols and guidelines are available from a number of standards organisations and professional societies, including those listed above for susceptibility testing for similar bacterial species that cause infections in humans. It is possible that such guidelines can be adopted for susceptibility testing for bacteria of animal origin, but each country must evaluate its own AST standards and guidelines. Additionally, efforts focusing on both standardisation and harmonisation of susceptibility/resistance breakpoints on an international scale are progressing. These efforts have primarily focused on the adoption of the standards and guidelines of CLSI and EUCAST, which provide laboratories with methods and quality control values enabling comparisons of AST methods and generated data (CLSI, 2018; Kahlmeter *et al.*, 2006). For those OIE Members that do not have standardised AST methods in place, the adoption of either set of standards would be an appropriate initial step towards acceptable methods and harmonisation.

Many bacteria that cause disease in aquatic animals require growth conditions (e.g. lower temperatures, supplemented or semisolid media) that may vary considerably as compared to terrestrial bacterial pathogens. This necessitated the need for the development of antimicrobial testing methods for bacteria isolated from aquatic species. Further information with regards to methods for disk diffusion or broth dilution antimicrobial susceptibility testing for bacteria isolated from aquatic animals can be referenced in two CLSI documents (CLSI, 2006; 2014b). Further information with regards to methods for disk diffusion or broth dilution antimicrobial susceptibility testing for infrequently isolated or certain fastidious bacteria (e.g. *Campylobacter*, *Pasteurella*) can also be referenced in the CLSI M45-A document (CLSI, 2015).

As a first step towards comparability of monitoring and surveillance data, Members should be encouraged to strive for harmonised and standardised programme design (Brown & MacGowan, 2010; Kahlmeter *et al.*, 2006; White *et al.*, 2001). Data from countries using different methods and programme design may otherwise not be directly comparable (Brown & MacGowan, 2010). Notwithstanding this, data collected over time in a given country may at least allow the detection of emergence of antimicrobial resistance or trends in prevalence of susceptibility/resistance in that particular country (Petersen *et al.*, 2003). However, if results achieved with different AST methods are to be compared, then comparability of results must be demonstrated and consensus on interpretation achieved. This will be best accomplished by the use of accurate and reliable documented AST methods used in conjunction with monitoring of AST performance while using well characterised reference microorganisms among participating laboratories.

## 8. Comparability of results

To determine the comparability of results originating from different surveillance systems, results should be reported quantitatively including information on the performance of the methods, the reference organisms and the antimicrobial.

AST data, consisting of cumulative and ongoing summary of susceptibility patterns (antibiograms) among clinically important and surveillance microorganisms should be created, recorded and analysed periodically at regular intervals (CLSI, 2014a). Data must also be presented in a clear and consistent manner so that both new patterns of resistance can be identified and atypical findings confirmed or refuted. This data should be available on a central data bank and published yearly.

Cumulative AST data will be useful in monitoring susceptibility/resistance trends in a region over time and assessing the effects of interventions to reduce antimicrobial resistance.

## 9. Quality control (QC) and quality assurance (QA)

Quality control/quality assurance systems should be established in accordance with Chapter 1.1.5. in laboratories performing AST:

i) quality control refers to the operational techniques that are used to ensure accuracy and reproducibility of AST,

ii) quality assurance includes, but is not limited to, monitoring, record keeping, evaluating, taking potential corrective actions if necessary, calibration, and maintenance of equipment, proficiency testing, training and QC. A QA programme helps ensure that testing materials and processes provide consistent quality results.

The following components should be determined and monitored:

i) precision of the AST procedure,

ii) accuracy of the AST procedure,

iii) qualifications, competence, and proficiency of the laboratory personnel, as well as the personnel that interpret the results and those that are involved in monitoring of antimicrobial resistance,

iv) performance of the appropriate reagents.

The following requirements should be respected:

i) Strict adherence to specified and documented techniques in conjunction with quality control (i.e. assurance of performance and other critical criteria) of media and reagents.

ii) Record keeping of:
   *a)* lot numbers of all appropriate materials and reagents,
   *b)* expiration dates of all appropriate materials and reagents,
   *c)* equipment calibration and monitoring,
   *d)* critical specifications for AST performance (reference results, time, temperature etc.).

iii) The appropriate reference microorganism(s) should always be used regardless of the AST method employed.

iv) Reference microorganisms are to be obtained from a reliable source for example, from the American Type Culture Collection (ATCC®), reliable commercial sources, or institutions with demonstrated reliability to store and use the organisms correctly.

v) Reference microorganisms should be catalogued and well characterised, including stable defined antimicrobial susceptibility phenotypes. Records regarding these reference organisms should include the established resistant and susceptible ranges of the antimicrobials to be assayed, and the reference to the method(s) by which these were determined.

vi) Laboratories involved in AST should use the appropriate reference microorganisms in all AST testing.

vii) Reference strains should be kept as stock cultures from which working cultures are derived and should be obtained from national or international culture collections. Reference bacterial strains should be stored at designated centralised or regional laboratories. Working cultures should not be subcultured from day to day as this introduces contamination and the method of producing working cultures should ensure that stock cultures are rarely used. This may be accomplished with the production of an intermediate stock of cultures derived from the original cultures that are used to crate day-to-day working cultures.

viii) The preferred method for analysing the overall performance of each laboratory should test the working stock of the appropriate reference microorganisms on each day that susceptibility tests are performed.

   Because this may not always be practical or economical, the frequency of such tests may be reduced if the laboratory can demonstrate that the results of testing reference microorganisms using the selected method are reproducible.

If a laboratory can document the reproducibility of the susceptibility testing methods used, testing may be performed on a weekly basis. If concerns regarding accuracy, reproducibility, or method validity emerge, the laboratory has a responsibility to determine the cause(s) and repeat the tests using the reference materials. Depending on the cause(s), daily reference material use and any other corrective action may be re-initiated.

ix) Reference microorganisms should be tested each time a new batch of medium or plate lot is used and on a regular basis in parallel with the microorganisms to be assayed.

x) Appropriate biosecurity issues should be addressed in obtaining and dispersing microorganisms to participating laboratories.

## 10. External proficiency testing

Laboratories should participate in external quality assurance and/or proficiency testing programmes in accordance with Chapter 1.1.5. Laboratories are also encouraged to participate in international inter-laboratory comparisons (e.g. WHO External Quality Assurance System) (Hendriksen *et al.*, 2009). All bacterial species subjected to AST should be included.

National reference laboratories should be designated with responsibility for:

i) monitoring the quality assurance programmes of laboratories participating in surveillance and monitoring of antimicrobial resistance,

ii) characterising and supplying to those laboratories a set of reference microorganisms,

iii) creating, managing, and distributing samples to be used in external proficiency testing,

iv) creating a central database available on the internet (e.g. European Antimicrobial Resistance Surveillance System [EARSS]) that contains the different susceptibility/resistance profiles for each bacterial species under surveillance.

## 11. Conclusion

Although a variety of methods exist, the goal of *in vitro* antimicrobial susceptibility testing testing for clinical veterinary purposes, surveillance and monitoring is the same: to provide a reliable predictor of how a microorganism is likely to respond to antimicrobial therapy in the infected host. This type of information aids the clinician in selecting the appropriate antimicrobial agent, provides data for surveillance, and aids in developing antimicrobial judicious use policies (World Organisation for Animal Health, 2018).

*In vitro* antimicrobial susceptibility testing can be performed using a variety of formats, the most common being disk diffusion, agar dilution, broth macrodilution, broth microdilution, and a concentration gradient test. Each of these procedures requires the use of specific testing conditions and methods, including media, incubation conditions and times, and the identification of appropriate quality control organisms along with their specific QC ranges. It is essential that AST methods provide reproducible results in day-to-day laboratory use and that the data be comparable with those results obtained by an acknowledged 'gold standard' reference method. In the absence of standardised methods or reference procedures, antimicrobial susceptibility/resistance results from different laboratories cannot be reliably compared.

The use of genotypic approaches for detection of antimicrobial resistance genes has also been promoted as a way to increase the rapidity and accuracy of susceptibility testing. New technological advances in molecular techniques (e.g. microarray) may facilitate the ability to probe bacterial species for large numbers of antimicrobial resistance genes quickly and cheaply, thereby providing additional relevant data into surveillance and monitoring programs (Ojha & Kostrzynska, 2008; Poxton, 2005). Standardised phenotypic AST methods will still be required to detect novel and emerging resistance mechanisms among bacterial pathogens and to validate their detection via genetic techniques (Ellington *et al.*, 2017).

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**NB**: There is an OIE Reference Laboratory for Antimicrobial resistance
(see Table in Part 4 of this *Terrestrial Manual* or consult the OIE Web site for the most up-to-date list:
www.oie.int/en/our-scientific-expertise/reference-laboratories/list-of-laboratories/ ).
Please contact the OIE Reference Laboratory for any further information on Antimicrobial resistance

FIRST ADOPTED IN 2004. MOST RECENT UPDATES IN 2019

# 4.
# OIE List of Antimicrobial Agents of Veterinary Importance

**(July 2019)**

## Introduction

The OIE[1] International Committee unanimously adopted the List of Antimicrobial Agents of Veterinary Importance at its 75th General Session in May 2007 (Resolution No. XXVIII).

### Background

Antimicrobial agents are essential drugs for human and animal health and welfare. Antimicrobial resistance is a global public and animal health concern that is influenced by both human and non-human antimicrobial usage. The human, animal and plant sectors have a shared responsibility to prevent or minimise antimicrobial resistance selection pressures on both human and non-human pathogens.

The FAO[2]/OIE/WHO[3] Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance held in Geneva, Switzerland, in December 2003 (Scientific Assessment) and in Oslo, Norway, in March 2004 (Management Options) recommended that the OIE should develop a list of critically important antimicrobial agents in veterinary medicine and that WHO should also develop such a list of critically important antimicrobial agents in human medicine.

Conclusion No. 5 of the Oslo Workshop is as follows:

> *The concept of 'critically important' classes of antimicrobials for humans should be pursued by WHO. The Workshop concluded that antimicrobials that are critically important in veterinary medicine should be identified, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE. The overlap of critical lists for human and veterinary medicine can provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.*

Responding to this recommendation, the OIE decided to address this task through its existing *ad hoc* Group on antimicrobial resistance. The terms of reference, aim of the list and methodology were discussed by the *ad hoc* Group since November 2004 and were subsequently endorsed by the Biological Standards Commission in its January 2005 meeting and adopted by the International Committee in May 2005. Thus, the work was officially undertaken by the OIE.

1 OIE: World Organisation for Animal Health

2 FAO: Food and Agriculture Organization of the United Nations

3 WHO: World Health Organization

## Scope

The OIE List of Antimicrobial Agents of Veterinary Importance:

- Addresses antimicrobial agents authorised for use in food-producing animals
- Does not include antimicrobial classes/sub classes only used in human medicine
- Does not include antimicrobial agents only used as growth-promoters
- Focuses currently on antibacterials and other important antimicrobials agents used in veterinary medicine

## Preparation of the draft list

The Director General of the OIE sent a questionnaire prepared by the *ad hoc* Group accompanied by a letter explaining the importance of the task to OIE Delegates of all Member Countries and international organisations having signed a Co-operation Agreement with the OIE in August 2005.

Sixty-six replies were received. This response rate highlights the importance given by OIE Member Countries from all regions to this issue. These replies were analysed first by the OIE Collaborating Centre for Veterinary Drugs, then discussed by the *ad hoc* Group at its meeting in February 2006. A list of proposed antimicrobial agents of veterinary importance was compiled together with an executive summary. This list was endorsed by the Biological Standards Commission and circulated among Member Countries aiming for adoption by the OIE International Committee during the General Session in May 2006.

## Discussion at the 74th International Committee in May 2006

The list was submitted to the 74th International Committee where active discussion was made among Member Countries. Concerns raised by Member Countries include: 1) the list includes substances that are banned in some countries; 2) some of the substances on the list are not considered 'critical'; 3) nature of the list – is this mandatory for Member Countries?; and 4) the use of antimicrobial agents as growth promotor is included. While many Member Countries appreciated the work, it was considered appropriate to continue refinement of the list. The list was adopted as a preliminary list by Resolution No. XXXIII.

## Refinement and adoption of the List of antimicrobial agents of Veterinary Importance

The *ad hoc* Group was convened in September 2006 to review the comments made at the 74th General Session of the OIE International Committee, and Resolution No. XXXIII adopted at the 74th General Session. Based on the further analysis provided by the OIE Collaborating Centre for Veterinary Medicinal Products, the *ad hoc* Group

prepared its final recommendations of the List of antimicrobial agents of veterinary importance together with an executive summary. Once again, this was examined and endorsed by the Biological Standards Commission in its January 2007 meeting and circulated among Member Countries. The refined List was submitted to the 75th International Committee during the General Session in May 2007 and adopted unanimously by Resolution No. XXVIII.

This list was further updated and adopted in May 2013, May 2015 and May 2018 by the World Assembly of OIE Delegates.

In July 2018, the *ad hoc* Group conducted a technical review of the List to improve coherence between the WHO and OIE List with respect to terminology used for antimicrobial classification, and this revision was endorsed by the Scientific Commission in February 2019. The report of the Scientific Commission to the OIE World Assembly of Delegates is detailed in the 86th General Session Final Report.

## Criteria used for categorisation of Veterinary Important Antimicrobial agents

In developing the list, the *ad hoc* Group agreed that any antimicrobial agent authorised for use in veterinary medicine according to the criteria of quality, safety and efficacy as defined in the *Terrestrial Animal Health Code* (Chapter 6.9. Responsible and prudent use of antimicrobial agents in veterinary medicine) is important. Therefore, based on OIE Member Country contributions, the Group decided to address all antimicrobial agents used in food-producing animals to provide a comprehensive list, divided into critically important, highly important and important antimicrobial agents.

In selecting the criteria to define veterinary important antimicrobial agents, one significant difference between the use of antimicrobial agents in humans and animals has to be accounted for: the many different species that have to be treated in veterinary medicine.

The following criteria were selected to determine the degree of importance for classes of veterinary antimicrobial agents.

Criterion 1. Response rate to the questionnaire regarding Veterinary Important Antimicrobial Agents

This criterion was met when a majority of the respondents (more than 50%) identified the importance of the antimicrobial class in their response to the questionnaire.

Criterion 2. Treatment of serious animal disease and availability of alternative antimicrobial agents

This criterion was met when compounds within the class were identified as essential against specific infections and there was a lack of sufficient therapeutic alternatives.

On the basis of these criteria, the following categories were established:

– Veterinary **Critically Important Antimicrobial Agents (VCIA)**: are those that meet **BOTH** criteria 1 **AND** 2

– Veterinary **Highly Important Antimicrobial Agents (VHIA)**: are those that meet criteria 1 **OR** 2

– Veterinary **Important Antimicrobial Agents (VIA)**: are those that meet **NEITHER** criteria 1 **OR** 2

## Revision of the list of antimicrobial agents of Veterinary Importance

The Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials held in Rome, Italy, in November 2007, recommended that the list of antimicrobial agents of Veterinary Importance should be revised on a regular basis and that the OIE further refine the categorisation of antimicrobial agents with respect to their importance in the treatment of specific animal diseases.

The OIE *ad hoc* Group on Antimicrobial Resistance met in July 2012 to review and update the OIE List of antimicrobial agents of veterinary importance (OIE List) taking into account the top three critically important antimicrobial agents of the WHO list of Critically Important Antimicrobials for Human Medicine.

The OIE *ad hoc* Group on Antimicrobial Resistance met in January 2018 to review and update the OIE List taking into account:

– the Global Action Plan on Antimicrobial Resistance supporting the phasing out of use of antibiotics for animal growth promotion in the absence of risk analysis;

– the Resolution No. 38 adopted by the OIE World Assembly of Delegates in May 2017;

– the fifth revision of the WHO list of Critically Important Antimicrobials for Human Medicine (2016) moving Colistin among the Highest Priority Critically Important Antimicrobials; and

– the OIE report on antimicrobial agents intended for use in animals (Second Report), in particular the antimicrobial agents used as growth promotors (english version, page 30, figure 5)

The Group made recommendations for the use of the updated OIE List.

## Recommendations

Any use of antimicrobial agents in animals should be in accordance with the OIE Standards on the responsible and prudent use laid down in the Chapter 6.9. of the *Terrestrial Animal Health Code* and in the Chapter 6.3. of the *Aquatic Animal Health Code.*

The responsible and prudent use of antimicrobial agents does not include the use of antimicrobial agents for growth promotion in the absence of risk analysis.

According to the criteria detailed above, antimicrobial agents in the OIE List are classified according to three categories, Veterinary Critically Important Antimicrobial Agents (VCIA), Veterinary Highly Important Antimicrobial Agents (VHIA) and Veterinary Important Antimicrobial Agents (VIA).

However, a specific antimicrobial/class or subclass may be considered as critically important for the treatment of a specific disease in a specific species (See specific comments in the following table of categorisation of veterinary important antimicrobial agents for food-producing animals).

For a number of antimicrobial agents, there are no or few alternatives for the treatment of some specified disease in identified target species as it is indicated in the specific comments in the OIE List. In this context, particular attention should be paid to the use of VCIA and of specific VHIA.

Among the VCIA in the OIE List, some are considered to be critically important both for human and animal health; this is currently the case for Fluoroquinolones and for the third and fourth generation of Cephalosporins. Colistin has been moved in 2016 to the WHO category of Highest Priority Critically Important Antimicrobials. Therefore these two classes and Colistin should be used according to the following recommendations:

– Not to be used as preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated;

– Not to be used as a first line treatment unless justified, when used as a second line treatment, it should ideally be based on the results of bacteriological tests; and

– Extra-label/off label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force; and

– Urgently prohibit their use as growth promotors.

The classes in the WHO category of Highest Priority Critically Important Antimicrobials should be the highest priorities for countries in phasing out use of antimicrobial agents as growth promotors.

The OIE List of antimicrobial agents of veterinary importance is based on expert scientific opinion and will be regularly updated when new information becomes available.

Antimicrobial classes / sub classes used only in human medicine are not included in this OIE List. Recognising the need to preserve the effectiveness of the antimicrobial agents in human medicine, careful consideration should be given regarding their potential use (including extra-label/off-label use) / authorisation in animals.

## Abbreviations

Animal species in which these antimicrobial agents are used are abbreviated as follows:

AVI: avian
API: bee
BOV: bovine
CAP: caprine
CAM: camel
EQU: equine
LEP: rabbit
OVI: ovine
PIS: fish
SUI: swine
VCIA: Veterinary Critically Important Antimicrobial Agents
VHIA: Veterinary Highly Important Antimicrobial Agents
VIA: Veterinary Important Antimicrobial Agents

## Categorisation of veterinary important antimicrobial agents for food-producing animals

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **AMINOCOUMARIN** | | Novobiocin is used in the local treatment of mastitis and in septicaemias in fish<br>This class is currently only used in animals | | | X |
| Novobiocin | BOV, CAP, OVI, PIS | | | | |
| **AMINOCYCLITOL** | | | | | |
| Spectinomycin | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | Used for respiratory infections in cattle and enteric infections in multiple species | X | | |
| **AMINOGLYCOSIDES** | | The wide range of applications and the nature of the diseases treated make aminoglycosides extremely important for veterinary medicine.<br>Aminoglycosides are of importance in septicaemias; digestive, respiratory and urinary diseases.<br>Gentamicin is indicated for *Pseudomonas aeruginosa* infections with few alternatives.<br>**Apramycin and Fortimycin are currently only used in animals.**<br>Few economic alternatives are available. | X | | |
| Dihydrostreptomycin | AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| Streptomycin | API, AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| **Aminoglycosides + 2 deoxystreptamine** | | | | | |
| Amikacin | EQU | | | | |
| Apramycin | AVI, BOV, LEP, OVI, SUI | | | | |
| Fortimycin | AVI, BOV, LEP, OVI, SUI | | | | |
| Framycetin | BOV, CAP, OVI | | | | |
| Gentamicin | AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI | | | | |
| Kanamycin | AVI, BOV, EQU, PIS, SUI | | | | |
| Neomycin | API, AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| Paromomycin | AVI, BOV, CAP, OVI, LEP, SUI | | | | |
| Tobramycin | EQU | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **AMPHENICOLS**<br>Florphenicol<br>Thiamphenicol | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI<br>AVI, BOV, CAP, OVI, PIS, SUI | The wide range of applications and the nature of the diseases treated make phenicols extremely important for veterinary medicine.<br>This class is of particular importance in treating some fish diseases, in which there are currently no or very few treatment alternatives.<br>This class also represents a useful alternative in respiratory infections of cattle, swine and poultry.<br>This class, in particular florfenicol, is used to treat pasteurellosis in cattle and pigs. | X | | |
| **ANSAMYCIN – RIFAMYCINS**<br>Rifampicin<br>Rifaximin | EQU<br>BOV, CAP, EQU, LEP, OVI, SUI | This antimicrobial class is authorised only in a few countries and with a very limited number of indications (mastitis) and few alternatives.<br>Rifampicin is essential in the treatment of *Rhodococcus equi* infections in foals. However it is only available in a few countries, resulting in an overall classification of VHIA. | | X | |
| **ARSENICAL**<br>Nitarsone<br>Roxarsone | AVI, SUI<br>AVI, SUI | Arsenicals are used to control intestinal parasitic coccidiosis. (*Eimeria* spp.). | | | X |
| **BICYCLOMYCIN**<br>Bicozamycin | AVI, BOV, PIS, SUI | Bicyclomycin is listed for digestive and respiratory diseases in cattle and septicaemias in fish. | | | X |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **CEPHALOSPORINS** | | Cephalosporins are used in the treatment of septicemias, respiratory infections, and mastitis. | | X | |
| **Cephalosporins first generation** | | | | | |
| Cefacetrile | BOV | | | | |
| Cefalexin | BOV, CAP, EQU, OVI, SUI | | | | |
| Cefalonium | BOV, CAP, OVI | | | | |
| Cefalotin | EQU | | | | |
| Cefapyrin | BOV | | | | |
| Cefazolin | BOV, CAP, OVI | | | | |
| **Cephalosporins second generation** | | | | | |
| Cefuroxime | BOV | | | | |
| **Cephalosporins third generation** | | The wide range of applications and the nature of the diseases treated make cephalosporin third and fourth generation extremely important for veterinary medicine. | X | | |
| Cefoperazone | BOV, CAP, OVI | | | | |
| Ceftiofur | AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| Ceftriaxone | AVI, BOV, OVI, SUI | | | | |
| **Cephalosporins fourth generation** | | Cephalosporins are used in the treatment of septicemias, respiratory infections, and mastitis.<br>Alternatives are limited in efficacy through either inadequate spectrum or presence of antimicrobial resistance. | | | |
| Cefquinome | BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| **FUSIDANE** | | Fusidic acid is used in the treatment of ophthalmic diseases in cattle and horses. | | | X |
| Fusidic acid | BOV, EQU | | | | |
| **IONOPHORES** | | Ionophores are essential for animal health because they are used to control intestinal parasitic coccidiosis (*Eimeria* spp.) where there are few or no alternatives available.<br>Ionophores are critically important in poultry.<br>**This class is currently only used in animals.** | | X | |
| Lasalocid | AVI, BOV, LEP, OVI | | | | |
| Maduramycin | AVI | | | | |
| Monensin | API, AVI, BOV, CAP | | | | |
| Narasin | AVI, BOV | | | | |
| Salinomycin | AVI, LEP, BOV, SUI | | | | |
| Semduramicin | AVI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **LINCOSAMIDES** | | Lincosamides are essential in the treatment of Mycoplasmal pneumonia, infectious arthritis and hemorrhagic enteritis of pigs. | | | |
| Lincomycin | API, AVI, BOV, CAP, OVI, PIS, SUI | | | X | |
| Pirlimycin | BOV, SUI, AVI | | | | |
| **MACROLIDES** | | The wide range of applications and the nature of the diseases treated make macrolides extremely important for veterinary medicine.<br><br>**Macrolides are used to treat Mycoplasma infections in pigs, haemorrhagic digestive disease in pigs (*Lawsonia intracellularis*) and liver abscesses (*Fusobacterium necrophorum*) in cattle, where they have very few alternatives**.<br><br>This class is also used for respiratory infections in cattle | X | | |
| **Macrolides C14-membered ring** | | | | | |
| Erythromycin | API, AVI, BOV,CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Oleandomycin | BOV | | | | |
| **Macrolides C15-membered ring** | | | | | |
| Gamithromycin | BOV | | | | |
| Tulathromycin | BOV, SUI | | | | |
| **Macrolides C16-membered ring** | | | | | |
| Carbomycin | AVI | | | | |
| Josamycin | AVI, PIS, SUI | | | | |
| Kitasamycin | AVI, SUI, PIS | | | | |
| Mirosamycin | API, AVI, SUI, PIS | | | | |
| Spiramycin | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Terdecamycin | AVI, SUI | | | | |
| Tildipirosin | BOV, SUI | | | | |
| Tilmicosin | AVI, BOV, CAP, LEP, OVI, SUI | | | | |
| Tylosin | API, AVI, BOV, CAP, LEP, OVI, SUI | | | | |
| Tylvalosin | AVI, SUI | | | | |
| **Macroslides C17-membered ring** | | | | | |
| Sedecamycin | SUI | | | | |
| **ORTHOSOMYCINS** | | Avilamycin is used for enteric diseases of poultry and rabbit.<br><br>**This class is currently only used in animals.** | | | X |
| Avilamycin | AVI, LEP, SUI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **PENICILLINS** | | | | | |
| **Natural penicillins (including esters and salts)** | | | | | |
| Benethamine penicillin | BOV | | | | |
| Benzylpenicillin | AVI, BOV, CAM, CAP, EQU, LEP, OVI, SUI | | | | |
| Benzylpenicillin procaine / Benzathine penicillin | BOV, CAM, CAP, EQU, OVI, SUI | **Penethamate (hydroiodide) is currently only used in animals** | | | |
| Penethamate (hydroiodide) | BOV | | | | |
| **Amdinopenicillins** | | The wide range of applications and the nature of the diseases treated make penicillins extremely important for veterinary medicine. | | | |
| Mecillinam | BOV, SUI | | | | |
| **Aminopenicillins** | | | | | |
| Amoxicillin | AVI, BOV, CAP, EQU, OVI, PIS, SUI | | | | |
| Ampicillin | AVI, BOV, CAP, EQU, OVI, PIS, SUI | | | | |
| Hetacillin | BOV | | | | |
| **Aminopenicillin + Betalactamase inhibitor** | | This class is used in the treatment of septicaemias, respiratory and urinary tract infections. | X | | |
| Amoxicillin + Clavulanic Acid | AVI, BOV, CAP, EQU, OVI, SUI | | | | |
| Ampicillin + Sulbactam | AVI, BOV, SUI | | | | |
| **Carboxypenicillins** | | This class is very important in the treatment of many diseases in a broad range of animal species. Few economical alternatives are available. | | | |
| Ticarcillin | EQU | | | | |
| Tobicillin | PIS | | | | |
| **Ureidopenicillin** | | | | | |
| Aspoxicillin | BOV, SUI | | | | |
| **Phenoxypenicillins** | | | | | |
| Phenethicillin | EQU | | | | |
| Phenoxymethylpenicillin | AVI, SUI | | | | |
| **Antistaphylococcal penicillins** | | | | | |
| Cloxacillin | BOV, CAP, EQU, OVI, SUI | | | | |
| Dicloxacillin | BOV, CAP, OVI, AVI, SUI | | | | |
| Nafcillin | BOV, CAP, OVI | | | | |
| Oxacillin | BOV, CAP, EQU, OVI, AVI, SUI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **PHOSPHONIC ACID DERIVATIVES** | | Fosfomycin is essential for the treatment of some fish infections with few alternatives however it is only available in a few countries, resulting in an overall classification of VHIA. | | | |
| Fosfomycin | AVI, BOV, PIS, SUI | | | X | |
| **PLEUROMUTILINS** | | The class of pleuromutilins is essential against respiratory infections in pigs and poultry. | | | |
| Tiamulin | AVI, CAP, LEP, OVI, SUI | | | | |
| Valnemulin | AVI, SUI | This class is also essential against swine dysentery *(Brachyspira hyodysenteriae)* however it is only available in a few countries, resulting in an overall classification of VHIA. | | X | |
| **POLYPEPTIDES** | | Bacitracin is used in the treatment of necrotic enteritis in poultry. | | | |
| Bacitracin | AVI, BOV, LEP, SUI, OVI | | | | |
| Enramycin | AVI, SUI | | | | |
| Gramicidin | EQU | | | | |
| **Polymyxins** | | This class is used in the treatment of septicaemias, colibacillosis, salmonellosis, and urinary infections. | | X | |
| Polymixin B | BOV, CAP, EQU, LEP, OVI, AVI | | | | |
| Polymixin E (colistin) | AVI, BOV, CAP, EQU, LEP, OVI, SUI | Polymyxin E (colistin) is used against Gram negative enteric infections. | | | |
| **QUINOLONES** | | | | | |
| **Quinolones first generation** | | Quinolones of the first generations are used in the treatment of septicaemias and infections such as colibacillosis. | | X | |
| Flumequin | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Miloxacin | PIS | | | | |
| Nalidixic acid | BOV | | | | |
| Oxolinic acid | AVI, BOV, LEP, PIS, SUI, OVI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **Quinolones second generation (fluoroquinolones)** | | | | | |
| Ciprofloxacin | AVI, BOV, SUI | The wide range of applications and the nature of the diseases treated make fluoroquinolones extremely important for veterinary medicine.<br><br>Fluoroquinolones are critically important in the treatment of septicaemias, respiratory and enteric diseases. | X | | |
| Danofloxacin | AVI, BOV, CAP, LEP, OVI, SUI | | | | |
| Difloxacin | AVI, BOV, LEP, SUI | | | | |
| Enrofloxacin | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Marbofloxacin | AVI, BOV, EQU, LEP, SUI | | | | |
| Norfloxacin | AVI, BOV, CAP, LEP, OVI, SUI | | | | |
| Ofloxacin | AVI, SUI | | | | |
| Orbifloxacin | BOV, SUI | | | | |
| Sarafloxacin | PIS | | | | |
| **QUINOXALINES** | | Quinoxalines (carbadox) is used for digestive disease of pigs (e.g. swine dysentery).<br>**This class is currently only used in animals**. | | | X |
| Carbadox | SUI | | | | |
| Olaquindox | SUI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **SULFONAMIDES** | | The wide range of applications and the nature of the diseases treated make sulfonamides extremely important for veterinary medicine.<br><br>These classes alone or in combination are critically important in the treatment of a wide range of diseases (bacterial, coccidial and protozoal infections) in a wide range of animal species. | X | | |
| Phthalylsulfathiazole | SUI | | | | |
| Sulfacetamide | AVI, BOV, OVI | | | | |
| Sulfachlorpyridazine | AVI, BOV, SUI | | | | |
| Sulfadiazine | AVI, BOV, CAP, OVI, SUI | | | | |
| Sulfadimethoxazole | AVI, BOV, SUI | | | | |
| Sulfadimethoxine | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Sulfadimidine (Sulfamethazine, Sulfadimerazin) | AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| Sulfadoxine | BOV, EQU, OVI, SUI | | | | |
| Sulfafurazole | BOV, PIS | | | | |
| Sulfaguanidine | AVI, CAP, OVI | | | | |
| Sulfamerazine | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Sulfamethoxine | AVI, PIS, SUI | | | | |
| Sulfamonomethoxine | AVI, PIS, SUI | | | | |
| Sulfanilamide | AVI, BOV, CAP, OVI | | | | |
| Sulfapyridine | BOV, SUI | | | | |
| Sulfaquinoxaline | AVI, BOV, CAP, LEP, OVI | | | | |
| **SULFAQUINOXALINE DIAMINOPYRIMIDINES** | | | | | |
| Ormetoprim+ Sulfadimethoxine | PIS | | | | |
| Sulfamethoxypyridazine | AVI, BOV, EQU, SUI | | | | |
| Trimethoprim+ Sulfonamide | AVI, BOV, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| **DIAMINOPYRIMIDINES** | | | | | |
| Baquiloprim | BOV, SUI | | | | |
| Ormetoprim | AVI | | | | |
| Trimethoprim | AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |

| Antimicrobial agents (class, sub-class, substance) | Species | Specific comments | VCIA | VHIA | VIA |
|---|---|---|---|---|---|
| **STREPTOGRAMINS** | | Virginiamycin is an important antimicrobial in the prevention of necrotic enteritis (*Clostridium perfringens*) | | | X |
| Virginiamycin | AVI, BOV, OVI, SUI | | | | |
| **TETRACYCLINES** | | The wide range of applications and the nature of the diseases treated make tetracyclines extremely important for veterinary medicine<br><br>This class is critically important in the treatment of many bacterial and chlamydial diseases in a wide range of animal species.<br><br>This class is also critically important in the treatment of animals against heartwater (*Ehrlichia ruminantium*) and anaplasmosis (*Anaplasma marginale*) due to the lack of antimicrobial alternatives. | X | | |
| Chlortetracycline | AVI, BOV, CAP, EQU, LEP, OVI, SUI | | | | |
| Doxycycline | AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Oxytetracycline | API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| Tetracycline | API, AVI, BOV, CAM, CAP, EQU, LEP, OVI, PIS, SUI | | | | |
| **THIOSTREPTON** | | This class is currently used in the treatment of some dermatological conditions. | | | X |
| Nosiheptide | AVI, SUI | | | | |

# 5.
# Resolutions

# Resolution No. 26

## Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals

**OIE General Session 2015**

Resolution No. 26

# COMBATING ANTIMICROBIAL RESISTANCE AND PROMOTING THE PRUDENT USE OF ANTIMICROBIAL AGENTS IN ANIMALS

Considering

1. That antimicrobial agents are essential tools for protecting animal health and welfare and also contribute to meeting the increasing global demand for safe meat, milk, fish and eggs, and other products of animal origin,

2. That antimicrobial resistance (AMR) is a significant global animal and human health threat that is influenced by the use of antimicrobial agents in some conditions,

3. That during the 77th General Session 2009, the World Assembly of Delegates (the Assembly) adopted Resolution No. 25 on Veterinary Products, which considered previous Resolutions on harmonisation of registration requirements for veterinary drugs, their responsible and prudent use and monitoring of resistance,

4. The recommendations of the OIE Global Conference on the responsible and prudent use of antimicrobial agents in animals, held in March 2013 in Paris, France, including recommendation No. 7 to collect harmonised quantitative data on the use of antimicrobial agents in animals with the view to establishing a global database,

5. The recent update and development of OIE standards and guidelines related to antimicrobial resistance, which include references to the relevant standards developed by Codex Alimentarius,

6. The tripartite agreement between FAO, OIE and WHO to address as a priority antimicrobial resistance and the important contribution of the OIE to the development and achievement of the WHO global action plan on antimicrobial resistance,

7. The network of OIE National Focal Points for Veterinary Products and its role in supporting the global implementation of the OIE standards regarding veterinary products,

8. The importance of the PVS pathway in supporting compliance of national

veterinary services with OIE standards including legislation, as a prerequisite to ensuring good governance covering production, registration, distribution and use of antimicrobial agents at the national level,

9. The importance of appropriate Veterinary Education and Veterinary Statutory Bodies in the promotion of veterinary oversight to ensure responsible use of antimicrobial agents in animals,

The Assembly recommends that

1. The OIE continue to develop and update standards and guidelines related to antimicrobial resistance and the prudent use of antimicrobial agents including updating regularly the OIE List of Antimicrobial Agents of Veterinary Importance.

2. The OIE, with support from relevant organisations and donors, work with Member Countries to support them to implement OIE standards and guidelines using the PVS pathway and other relevant OIE capacity building mechanisms, including twinning and regional seminars.

3. The OIE develop a procedure and standards for data quality for collecting data annually from OIE Member Countries on the use of antimicrobial agents in food-producing animals with the aim of creating an OIE global database to be managed in parallel with the World Animal Health Information System (WAHIS).

4. OIE Member Countries set up an official harmonised national system, based on OIE standards, for the surveillance of antimicrobial resistance and the collection of data on the use of antimicrobial agents in food-producing animals, and actively participate in the development of the OIE global database.

5. The participation of OIE Member Countries in the VICH Outreach Forum be facilitated with the aim of adopting and utilising harmonised international guidelines related to the technical requirements for registration of veterinary medicinal products.

6. OIE Member Countries improve veterinary legislation and education, where necessary, in order to facilitate implementation of OIE and Codex Alimentarius standards and guidelines related to antimicrobial resistance and veterinary oversight of the use of antimicrobial agents.

7. The OIE and OIE Member Countries encourage Veterinary Statutory Bodies and the veterinary profession as a whole to develop, implement and ensure compliance with ethics and codes of good veterinary practices, with particular reference to the prescription and delivery of antimicrobial agents by well-trained veterinarians or veterinary paraprofessionals under their direct oversight.

8. OIE Member Countries follow the guidance of the WHO Global Action Plan on Antimicrobial Resistance, developed with the support of the OIE in the spirit of the 'One Health' approach, in particular by developing national action plans, with the support of FAO and WHO where feasible and warranted, in respect of the use of antimicrobial agents in animals and ensuring their close collaboration with public health officials.

9. The OIE continue to seek donor support for the organisation of dedicated regional training seminars for OIE National Focal Points for Veterinary Products with the participation of FAO and WHO within the tripartite collaboration and invite other relevant partners to build capacity at the national and regional levels to enable the implementation of OIE and Codex Alimentarius intergovernmental standards to combat antimicrobial resistance and support the recommendations of the WHO Global Action Plan on Antimicrobial Resistance.

10. The OIE strengthen its collaboration with international organisations, such as the World Customs Organisation and Interpol, and stakeholders to combat counterfeit products with the aim of ensuring access to antimicrobial agents of proven quality.

11. Research be promoted to improve tools for rapid diagnostics for use in animals and to explore alternatives to antimicrobial use in animals, including the development of vaccines and other tools for priority diseases.

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(Adopted by the World Assembly of Delegates of the OIE on 26 May 2015
in view of an entry into force on 30 May 2015)

# Resolution No. 36

## Combating Antimicrobial Resistance through a One Health Approach: Actions and OIE Strategy

**OIE General Session 2016**

Resolution No. 36

# COMBATING ANTIMICROBIAL RESISTANCE THROUGH A ONE HEALTH APPROACH: ACTIONS AND OIE STRATEGY

Considering

1. That antimicrobial resistance (AMR) is both an animal and human health threat of growing concern which has been significantly considered by the OIE through the development and adoption of relevant and important standards and guidelines,

2. That during the 77th General Session (May 2009), the World Assembly of Delegates (the Assembly) adopted Resolution No. 25 on Veterinary Medicinal Products, which also considered previous Resolutions on the harmonising of registration requirements for veterinary drugs, their responsible and prudent use and the monitoring of resistance including recommended actions to be implemented,

3. The recommendations of the OIE Global Conference on the responsible and prudent use of antimicrobial agents in animals, held in March 2013 in Paris, France, including Recommendation No. 7 to collect harmonised quantitative data on the use of antimicrobial agents in animals with the view to establishing a global database, which was subsequently formally endorsed by the Assembly at the 83rd General Session (May 2015) through the adoption of Resolution No. 26,

4. The contribution of the OIE to the development of the World Health Organization's (WHO) Global Action Plan on Antimicrobial Resistance, under the framework of the Tripartite agreement between the Food and Agriculture Organization of the United Nations (FAO), the WHO and the OIE, which was adopted by the World Health Assembly of the WHO in May 2015,

5. The recommendation to Member Countries, to follow the guidance of the WHO Global Action Plan on Antimicrobial Resistance, in particular by developing national action plans, in respect of the use of antimicrobial agents in animals and ensuring close collaboration with public health officials, adopted through Resolution No. 26 of the 83rd General Session on Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals,

6. The importance of the capacities of the national Veterinary Services to comply with the relevant standards and the particular benefit of the OIE PVS Pathway in supporting the Member Countries to update their legislation, which is a prerequisite to ensure good governance covering registration, production, distribution, prescription and use as well as control and surveillance of antimicrobial agents at the national level,

7. The role of the network of the OIE National Focal Points for Veterinary Products in supporting the global implementation of the OIE standards regarding veterinary products,

8. The importance of appropriate veterinary and veterinary para-professional education in the promotion of veterinary oversight to ensure responsible use of antimicrobial agents in animals,

9. The action of OIE to raise the awareness of the health risk posed by antimicrobial resistance by developing communication materials and organising sub-regional, regional and international events,

And recognising

the importance and the relevance of the actions carried out by the OIE to date in the fight against antimicrobial resistance

The Assembly decides that

All the actions developed by the OIE according to the mandate approved by the Assembly, i.e.:

– The setting of standards and guidelines,

– The implementation of capacity building programmes for better governance with the aim of an improved veterinary stewardship of veterinary drugs in order to prevent the inappropriate use of antimicrobials,

– The establishment and the management of a database for the collection of data on the use of antimicrobial agents in animals as well as the development of interpretation indicators,

– The publication of and the contribution to the development of scientific knowledge, in particular on new technologies, including vaccines and alternatives to antimicrobials,

– The development of communication materials, to promote the prudent and responsible use of antimicrobials and to increase the public awareness,

Shall be compiled and consolidated within the OIE Strategy on antimicrobial resistance.

And recommends that

1. The OIE Strategy on antimicrobials be implemented through a stepwise approach, in close cooperation with WHO and FAO through a One Health approach as well as with other concerned partners and stakeholders, and that the OIE further promote intersectorial cooperation, coordination and interaction at regional and national levels.

2. The OIE advocate that policy makers act to preserve the efficacy of antimicrobial agents. These critical tools help to sustain animal health and welfare, contribute to food security and safety, protect human health from zoonotic disease threats and contribute to the economic prosperity of countries.

3. The OIE Strategy promote the responsible and prudent use of antimicrobials as well as approaches to decrease their use, such as the adoption of best practices for sanitation, OIE Terrestrial and Aquatic Code provisions for biosecurity to prevent disease, and good husbandry practices including vaccination programmes.

4. The OIE provide guidance on alternatives to the use of antimicrobials and on how to carry out risk analyses to demonstrate appropriate management to reduce the development of resistance and the protection of both animal and human health.

5. OIE Member Countries fulfil their commitment under the Global Action Plan to implement policies on the use of antimicrobials in terrestrial and aquatic animals, respecting OIE intergovernmental standards and guidelines on the use of critically important antimicrobial agents, and the phasing out of the use of antibiotics for growth promotion in the absence of risk analysis.

6. The OIE standards, guidelines and recommendations be actively communicated by the OIE to contribute to public discussion with full consideration of the multifactorial causes of antimicrobial resistance.

7. The OIE seek support to enable Member Countries to implement the OIE Strategy and their national action plans.

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(Adopted by the World Assembly of Delegates of the OIE on 26 May 2016
in view of an entry into force on 27 May 2016)

# Resolution No. 38

## Global action to alleviate the threat of antimicrobial resistance: progress and opportunities for future activities under the 'One health' initiative

**OIE General Session 2017**

Resolution No. 38

# GLOBAL ACTION TO ALLEVIATE THE THREAT OF ANTIMICROBIAL RESISTANCE: PROGRESS AND OPPORTUNITIES FOR FUTURE ACTIVITIES UNDER THE 'ONE HEALTH' INITIATIVE

Considering

1. The adoption of several Resolutions by the World Assembly of Delegates (the Assembly) to combat antimicrobial resistance (AMR), and in particular Resolution No. 25 of May 2009 on 'Veterinary products', which took into account previous Resolutions on harmonisation of requirements for registration of veterinary medicinal products, their responsible and prudent use and monitoring of AMR,

2. The adoption by the Assembly, in May 2015, of Resolution No. 26 on 'Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals' during the 83rd General Session, including the setting up by the OIE, in application of this Resolution, of a database to collect information on the use of antimicrobial agents in animals, as well as the follow up, by OIE Member Countries, of the principles of the WHO Global Acton Plan on Antimicrobial Resistance, developed with the support of the OIE to promote the 'One Health' concept, in particular through the development of national action plans,

3. The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials published in November 2016, in accordance with Resolution No. 36 adopted by the Assembly during the 84th General Session of the OIE (May 2016), which is based on the WHO Global Action Plan and outlines the objectives and the tactics used by the OIE to help Member Countries to combat AMR, by promoting the implementation of national action plans with a One Health approach and international standards at national level,

4. The willingness of OIE Member Countries to develop harmonised short-, medium- and long-term initiatives consistent with the OIE strategy, to combat AMR more effectively, notably through the action of OIE National Focal Points for Veterinary Products,

5. The organisation of regional training seminars for OIE National Focal Points for Veterinary Products their positive impact on the way Member Countries take into account the topics covered during these seminars,

6. That in order to promote veterinary supervision to ensure the responsible and prudent use of antimicrobial agents in animals, it is important that veterinarians and veterinary para professionals receive appropriate training and have relevant and updated information on AMR,

7. The measures taken by the OIE to make communication tools available to Member Countries to enable the organisation of awareness campaigns on the sanitary risks posed by AMR and on the need to adopt responsible and prudent use of antimicrobial agents,

8. OIE Member Countries' wish to have standards for the analysis of samples in order to be able to determine bacterial resistance and interpret the results in the context of AMR,

The Assembly recommends that

1. The OIE Member Countries fulfil their commitment under the Global Action Plan by applying OIE standards and guidelines, in particular those on responsible and prudent use of antimicrobial agents, which include specific recommendations on antimicrobials of critical importance, and the phasing out of the use of antibiotics for growth promotion in the absence of risk analysis.

2. OIE Member Countries continue their efforts regarding the collection of data on the use of antimicrobial agents in animals and send the information annually to the OIE using the questionnaire specifically developed for this purpose.

3. The Delegates of Member Countries and Focal Points interact at national level with their 'One Health' counterparts in particular with those participating in the Codex Alimentarius Commission, to ensure sustainable collaboration and coordination on the development of international standards on AMR.

4. The OIE promote approaches to reduce the need to use antibiotics by encouraging alternatives to antibiotics in particular the development of vaccines and best practice husbandry and hygiene.

5. The OIE continue to implement its work programme according to the four objectives of its Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials, in close collaboration with its Tripartite partners, WHO and FAO, with the help of other relevant partners and stakeholders, and to promote intersectoral coordination and cooperation at regional, sub-regional and national level.

6. The OIE support Member Countries in the implementation of a national action plan and international standards, especially with regard to responsible and prudent use of antimicrobial agents in order to combat AMR more effectively,

including the prescription and delivery of antimicrobial agents by well-trained veterinarians or suitably trained persons authorised in accordance with national legislation.

7. The OIE review the List of antimicrobial agents of veterinary importance including considering the purposes for use of antimicrobial agents in animals, in particular ionophores.

8. The OIE contribute to strengthening teaching on risks related to AMR and measures to be taken to control AMR in the core training curriculum and continuing education for veterinarians and veterinary para-professionals.

9. The OIE continue to organise training seminars at regional level for OIE National Focal Points for Veterinary Products (5th cycle), to improve awareness of its standards, guidelines and recommendations and the systems for improving the collection of data on the antimicrobial agents used in animals.

10. The OIE complement the specific standards and recommendations on laboratory methodologies for antimicrobial susceptibility testing to determine bacterial resistance and interpret the test results in the context of AMR, working with WHO and FAO to achieve integrated surveillance.

11. The OIE put in place tools to monitor the actions undertaken to implement its strategy on AMR, while also taking into account the evaluation developed in collaboration with its Tripartite partners and the future work of the United Nations interagency group to coordinate global action to fight antimicrobial resistance effectively and sustainably.

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(Adopted by the World Assembly of Delegates of the OIE on 25 May 2017
in view of an entry into force on 26 May 2017)

# Resolution No. 21

## List of antimicrobial agents of veterinary importance

**OIE General Session 2018**

Resolution No. 21

# LIST OF ANTIMICROBIAL AGENTS OF VETERINARY IMPORTANCE

Considering that

1. *Antimicrobial agent* is defined in the Glossary of the OIE *Terrestrial Animal Health Code* as "a naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition",

2. At the 74th General Session of the OIE in May 2006, the Assembly adopted Resolution No. XXXIII. This Resolution allowed the publication of a preliminary List of antimicrobial agents of veterinary importance based on the list compiled by the OIE from the answers received to the questionnaire sent to OIE Member Countries, and requested the OIE Director General to further refine the list and consider breaking it down into subcategories according to type of usage,

3. At the 75th General Session of the OIE in May 2007, the Assembly adopted Resolution No. XXVIII, which approved the List of antimicrobial agents of veterinary importance (OIE List) and mentioned that the OIE List will be regularly updated in accordance with new scientific information,

4. At the 81st General Session of the OIE in May 2013, the Assembly adopted Resolution No. 16 which approved the updated OIE List,

5. In 2015, the OIE List was updated by the OIE *ad hoc* Group on Antimicrobial Resistance the aim of which was to be consistent with the WHO List on *Critically important antimicrobials for human medicine* regarding the classification of antimicrobial agents and to specify, for some antimicrobial agents, the species for which they are currently used,

6. Revision of the recommendations of the OIE List was suggested by the OIE *ad hoc* Group on Antimicrobial Resistance and endorsed by the Scientific Commission for Animal Diseases at its February 2018 meeting to be proposed for adoption to the World Assembly of Delegates during the 86th General Session,

The Assembly resolves

1. To adopt the revised List of antimicrobial agents of veterinary importance presented as Appendix III of Annex 16 of the report of the meeting of the OIE Scientific Commission for Animal Diseases, February 2018 (Doc. 86 SG/12/CS3 B).

2. To request the Director General to publish the adopted OIE List on the OIE website.

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(Adopted by the World Assembly of Delegates of the OIE on 22 May 2018 in view of an entry into force on 25 May 2018)

# Resolution No. 14

## OIE's Engagement in the One Health Global Effort to Control Antimicrobial Resistance

**OIE General Session 2019**

Resolution No. 14

# OIE'S ENGAGEMENT IN THE ONE HEALTH GLOBAL EFFORT TO CONTROL ANTIMICROBIAL RESISTANCE

Considering

1. That antimicrobial resistance (AMR) is globally recognised as a growing political concern with serious social, economic, human health and animal health repercussions, as demonstrated by the United Nations (UN) General Assembly Resolution A-71/3 adopted in 2016,

2. The Second OIE Global Conference on antimicrobial resistance and prudent use of antimicrobial agents, putting standards into practice, organised in October 2018 in Marrakesh, Morocco, that confirmed commitment to supporting global strategies and initiatives developed under the leadership of the Tripartite (FAO, OIE, WHO) and recommended to further strengthen international collaboration and coordination including with the World Bank, the Organisation for Economic Co-operation and Development and other related institutions to build a stronger economic case for sustainable investment,

3. The ongoing AMR activities in the framework of the Tripartite, following the Memorandum of Understanding signed in 2018, and its joint workplan to support countries in implementing National Action Plans in support of the Global Action Plan on AMR,

4. The Monitoring and Evaluation framework developed by the Tripartite to measure country progress in the implementation of the Global Action Plan using a harmonised approach,

5. The AMR Multi-Partner Trust Fund "Combatting the rising global threat of AMR through a One Health Approach" on the verge of being established by the Tripartite to enable joint resource mobilisation for the implementation of the Tripartite workplans on AMR,

6. The Ad hoc Inter-agency Coordination Group on Antimicrobial Resistance (IACG) report, provided to the United Nations Secretary General in April 2019 after public consultation, and particularly its recommendations regarding global leadership and coordination on AMR, and calling on Member States to effectively address AMR by developing and implementing multisectoral One Health National Action Plans,

7. The upcoming UN Secretary General report prepared for the UN General Assembly in September 2019 in response to the Resolution A-71/3 to provide an update on progress made by Member States and the Tripartite on the implementation of the Political Declaration and recommendations emanating from the Ad-hoc Inter-Agency Coordination Group on Antimicrobial Resistance,

8. The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials developed following the adoption of Resolution No. 36 at the 84th General Session in May 2016, which also considered previous Resolutions related to AMR and the harmonisation of registration requirements for veterinary drugs,

9. The recommendation to OIE Member Countries, to follow the guidance of the Global Action Plan on Antimicrobial Resistance, particularly by developing National Action Plans, in respect of the use of antimicrobial agents in animals adopted through Resolution No. 26 at the 83rd General Session in May 2015,

10. The importance and the relevance of the OIE standards, guidelines, tools and interventions carried out by the OIE to date in the fight against AMR, and the need to maintain its active involvement in Tripartite activities and to reaffirm its role in the global leadership regarding the challenge of AMR for animal health and welfare,

And recognising

the need to urgently implement the Tripartite Workplan on AMR supported by the Multi-Partner Trust Fund to further scale up the global effort and support to the countries and to strengthen OIE's capacity to respond to the growing challenge and expectations in addressing AMR

The Assembly recommends that

1. The OIE continues to strengthen the central role of the Tripartite in engaging and coordinating all critical stakeholders at the global level through a Joint Tripartite Secretariat function, as well as through the AMR Multi-Partner Trust Fund, "Combatting the rising global threat of AMR through a One Health Approach" while taking into account the most effective use of current resources and work streams,

2. The OIE further contributes to the rapid implementation of the recommendations emanating from the work of IACG and the UNGA, in accordance with the GAP and the OIE Strategy on addressing AMR,

3. The OIE regularly informs its Member Countries of the global situation and progress made regarding the global use of antimicrobial agents in animals and the fight against AMR.

And decides that

The OIE Director General establishes a permanent Working Group on AMR supporting the implementation of the OIE Global Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials and the organisation's capacity to respond to global challenges according to its mandate.

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(Adopted by the World Assembly of Delegates of the OIE on 28 May 2019 in view of an entry into force on 31 May 2019)