



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

**CODEX**  
**ALIMENTARIUS**  
INTERNATIONAL FOOD STANDARDS

# FOODBORNE ANTIMICROBIAL RESISTANCE

COMPENDIUM OF STANDARDS





# **FOODBORNE ANTIMICROBIAL RESISTANCE**

**COMPENDIUM OF STANDARDS**

Food and Agriculture Organization of the United Nations  
World Health Organization  
Rome, 2022

Required citation:

FAO and WHO. 2022. *Foodborne antimicrobial resistance: Compendium of Codex standards*. Rome. <https://doi.org/10.4060/cb8554en>

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ISBN [FAO] 978-92-5-135734-7

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# FOODBORNE ANTIMICROBIAL RESISTANCE

COMPENDIUM OF STANDARDS

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# Foreword

Antimicrobial resistance (AMR) is a serious global health threat and a food safety issue of primary concern. Following COVID-19, it is being called the silent pandemic. To combat AMR, governments and international organizations such as the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO) and the World Organisation for Animal Health (OIE) have recognized that the issue has to be approached in a multidisciplinary manner. This means addressing animal, plant and human health as well as the environment through a so-called “One Health” approach.

The Codex Alimentarius Commission is the international reference body for food safety under the Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization. Within the Codex mandate to protect consumer health and ensure fair practices in the food trade, Codex has addressed the risk posed by AMR transmitted through food by developing three Codex texts dealing with foodborne AMR. These texts contribute to Goal 3: “Good Health and Well-being” of the UN Sustainable Development Goals, and address current, emerging and critical food safety issues in a timely manner, in line with Goal 1 of the Codex Strategic Plan (2020–2025).

The *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*, adopted in 2011, are a major reference text providing a science-based framework on processes and methodology for risk analysis and its application to foodborne AMR. The *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance (CoP)* was revised in 2021 and the *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance (GLIS)*, completed in the same year, together stand as key references for risk management and risk assessment of foodborne AMR.

The addition of the CoP and GLIS to the 2011 risk analysis guidelines, marks a major step in the Codex response to risk analysis of foodborne AMR. It is expected that these texts will become vital tools that can be widely applied to assess and manage the risk of foodborne AMR. They will also support national, regional and international level efforts to control this issue providing practical measures to solve the global threat of AMR through the “One Health” approach.

**Yong Ho Park, DVM, PhD**

Chairperson, CODEX *Ad hoc* Intergovernmental Task Force  
on Antimicrobial Resistance (TFAMR)





# Introduction

This publication brings together the three Codex texts that support governments in designing and running a successful strategy to tackle foodborne antimicrobial resistance (AMR).

The first Codex text on AMR was completed in 2005. The *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CXC 61-2005) was developed, by the Codex Committee on Residues of Veterinary Drugs in Foods, to minimize the potential adverse impact on public health resulting from the use of antimicrobial agents in food-producing animals.

The 2011 *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011) provide a structured risk analysis framework to address the risks to human health associated with the presence of antimicrobial resistant microorganisms in food and animal feed. Developed by the Ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance (TFAMR) between 2007 and 2010, the guidelines were a further Codex response to an issue that was already becoming a global health concern.

In 2015, the World Health Assembly adopted a global action plan on AMR, which included in its key objectives, strengthening the knowledge and evidence base on AMR through surveillance and research, and optimizing the use of antimicrobial medicines in human and animal health. This work led Codex to consider gaps in its response to AMR and where revision to established texts may be required.

In 2017, when the Codex Alimentarius Commission re-established TFAMR to begin an ambitious programme of work in response to global priorities, one part of the mandate was therefore to revise the 2005 code of practice.

The updated version presented here takes into account developments in food safety along the food chain and advances in AMR risk management tools. It now addresses the risks of foodborne AMR from production right through to consumption in line with the mandate of Codex.

The publication of the global action plan had also led to the conclusion in Codex that guidance was needed on monitoring and surveillance of foodborne AMR.

The third and new text in this publication is the *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance* (CXG 94-2021). TFAMR was mandated by the Commission to consider developing these guidelines also taking into consideration work by the World Health Organization (WHO) and the World Organisation for Animal Health (OIE). The text is a remarkable achievement and was completed in just four sessions of the task force; a testament to the ability of Codex to build consensus. It will assist governments in the design and implementation of integrated monitoring and surveillance programmes on AMR, providing flexible options based on the resources, infrastructure, capacity and priorities of individual countries.

The *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* appear first in this publication as the overarching risk analysis document. The GLIS feeds monitoring and surveillance data into this text to support the risk assessment and the COP provides risk-based guidance on management measures and practices along the food chain to minimize and contain foodborne AMR.

**Codex Secretariat**

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## Note

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*All Codex texts are available free of charge for download on the Codex website in Arabic, Chinese, English, French, Russian and Spanish.*

# Acknowledgements

The Codex Alimentarius Commission gratefully acknowledges the contribution of the Government of the Republic of Korea in hosting TFAMR. It further acknowledges the commitment and leadership of Chairperson Professor Yong Ho Park, the Chairpersons of the working groups, Rosa Peran (Netherlands) and Donald Prater (United States of America) and the experts and co-Chairpersons from Canada, Chile, China, Kenya, New Zealand and the United Kingdom of Great Britain and Northern Ireland in the development and finalization of the 2021 texts.

# Acronyms and abbreviations

<b>ALOP</b>	appropriate level of protection
<b>AMR</b>	antimicrobial resistance / antimicrobial resistant
<b>AMU</b>	antimicrobial use
<b>AST</b>	antimicrobial susceptibility testing
<b>CIA</b>	Critically Important Antimicrobials
<b>CLSI</b>	Clinical and Laboratory Standards Institute
<b>CXG</b>	Codex Alimentarius Commission / Guidelines
<b>CXC</b>	Codex Alimentarius Commission / Code of Practice
<b>ECOFF</b>	epidemiological cut-off value
<b>EUCAST</b>	European Committee on Antimicrobial Susceptibility Testing
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>FSO</b>	food safety objective
<b>GHP</b>	good hygiene practices
<b>GMP</b>	good manufacturing practices
<b>GVP</b>	good veterinary practices
<b>HACCP</b>	hazard analysis and critical control point
<b>IPM</b>	integrated pest management
<b>MICs</b>	minimal inhibitory concentrations
<b>OIE</b>	World Organisation for Animal Health
<b>PC</b>	performance criterion
<b>PD</b>	pharmacodynamic
<b>PK</b>	pharmacokinetic
<b>PO</b>	performance objective
<b>RMO</b>	risk management option
<b>WHO</b>	World Health Organization
<b>WTO/SPS</b>	World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures



# GUIDELINES FOR RISK ANALYSIS OF FOODBORNE ANTIMICROBIAL RESISTANCE



TYPE  
**GUIDELINES**  
CXG 77- 2011

EDITION  
ADOPTED  
2011



# GUIDELINES FOR RISK ANALYSIS OF FOODBORNE ANTIMICROBIAL RESISTANCE

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# 1. Introduction

Antimicrobial resistance (AMR – also used for “antimicrobial resistant” in this document) is a major global public health concern and a food safety issue. When pathogens become resistant to antimicrobial agents they can pose a greater human health risk as a result of potential treatment failure, loss of treatment options and increased likelihood and severity of disease. Problems related to AMR are inherently related to antimicrobial use in any environment, including human and non-human uses. The use of antimicrobial agents in food-producing animals/crops provides a potentially important risk factor for selection and dissemination of AMR microorganisms and determinants from animals/food crops to humans via the consumption of food.

In accordance with Codex principles, risk analysis is an essential tool in assessing the risk to human health from foodborne AMR microorganisms and determining appropriate risk management strategies to control those risks. Over the past decade, there have been significant developments with respect to the use of risk analysis approaches in addressing AMR. A series of FAO/OIE/WHO expert consultations on AMR have led to agreement that foodborne AMR microorganisms are potential microbiological food safety hazards. Consequently, the need for the development of a structured and coordinated approach for AMR risk analysis has been emphasized.<sup>1, 2, 3, 4</sup> WHO/FAO and OIE guidelines on risk analysis provide broad, structured approaches to address the potential public health impact of AMR microorganisms of animal/crop origin via food.<sup>5, 6</sup> However, a consolidated framework specific to foodborne AMR risk analysis was considered necessary, due to the biological complexity of AMR, the multidisciplinary aspects of AMR within the entire food production to consumption continuum and the need to identify appropriate risk management strategies.

More specifically, these guidelines provide a structured risk analysis framework to address the risks to human health associated with the presence in food and animal feed, including aquaculture, and the transmission through food and animal feed, of AMR microorganisms or determinants linked to non-human use of antimicrobial agents.

1 FAO/OIE/WHO. 2003. First Joint FAO/OIE/WHO Expert Workshop on Non-human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment, Geneva, Switzerland, 1-5 December 2003.

2 FAO/OIE/WHO. 2004. Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management options, Oslo, Norway, 15-18 March 2004.

3 FAO/OIE/WHO. 2006. Joint FAO/OIE/WHO Expert Meeting on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, Seoul, Republic of Korea, 13-16 June 2006.

4 FAO/OIE/WHO. 2008. Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials Report of the FAO/WHO/OIE Expert meeting, FAO, Rome, Italy, 26-30 November 2007, Appendix C Glossary.

5 FAO/WHO. 2006. Food safety risk analysis: A guide for national safety authorities. (FAO Food and Nutrition Paper 87).

6 OIE. *Terrestrial Animal Health Code* (Section Veterinary Public Health).

The initial part of the risk analysis framework consists of a group of tasks collectively referred to as “preliminary risk management activities”, which are carried out by the risk managers. This allows the risk manager to decide what action to take. This may involve the establishment of a risk assessment policy and the commissioning of a risk assessment or another appropriate action. If it is decided to commission a risk assessment, the preliminary risk management activities will provide some of the basic information required by risk assessors undertaking this task. The risk analysis framework includes the identification, evaluation, selection and implementation of appropriate risk management actions to, if necessary, minimize and contain the identified risk to human health. Risk managers are responsible for verifying that the risk management measures implemented are achieving the intended results, that unintended consequences associated with the measures are limited and that the risk management goals can be achieved. Good communication among risk assessors, managers and interested parties is essential for a transparent and informed risk analysis.

These guidelines present components of foodborne AMR risk analysis in a chronological order of the risk analysis process. For better readability, the “Foodborne AMR risk communication” and “Surveillance of use of antimicrobial agents and AMR microorganisms and determinants” sections are placed at the end of the document, recognizing that the activities identified within these sections are applicable throughout the process.

This document should be read in conjunction with the *Working Principles for Risk Analysis for Food Safety for Application by Governments* (CXG 62-2007), the *Principles and Guidelines for the Conduct of Microbiological Risk Assessment* (CXG 30-1999), the *Principles and Guidelines for the Conduct of Microbiological Risk Management* (CXG 63-2007), the *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CXC 61-2005), the *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance* (CXG 94-2021), the *Code of Hygienic Practice for Meat* (CXC 58-2005), the *Code of Hygienic Practice for Milk and Milk Products* (CXC 57-2004) and the *Code of Hygienic Practice for Eggs and Eggs Products* (CXC 15-1976). Risk analysis of AMR on animal feeds may also consider the *Code of Practice on Good Animal Feeding* (CXC 54-2004), as well as *Animal Feed Impact on Food Safety*<sup>7</sup> and the chapters related to the control of AMR in the *OIE Terrestrial Animal Health Code*.<sup>8</sup>

7 FAO/WHO. 2008. *Animal Feed Impact on Food Safety*. Report of the FAO/WHO Expert Meeting FAO Headquarters, Rome 8-12 October 2007.

8 See note 6 above.

## 2. Scope

The scope of these guidelines is to provide science-based guidance on processes and methodology for risk analysis and its application to foodborne AMR related to non-human use of antimicrobial agents. The guidelines aim to assess the risk to human health associated with the presence in food and animal feed, including aquaculture, and the transmission through food and animal feed, of AMR microorganisms and determinants, to provide advice on appropriate risk management activities to reduce such risk. The guidelines will further address the risk associated with different sectors of antimicrobial agent use such as veterinary applications, plant protection or food processing.

As there are existing Codex or internationally recognized guidelines, the following areas related to antimicrobial agents or AMR are outside the scope of this document: residues of antimicrobial agents in food; AMR marker genes in recombinant-DNA plants and recombinant-DNA microorganisms;<sup>9</sup> non-genetically modified microorganisms (for example, starter cultures) intentionally added to food with a technological purpose,<sup>10</sup> and certain food ingredients, which could potentially carry AMR genes, such as probiotics.<sup>11</sup>

## 3. Definitions

The following definitions are included to establish a common understanding of the terms used in this document. The definitions presented in the *Codex Procedural Manual and the Principles and Guidelines for the Conduct of Microbiological Risk Assessment* (CXG 30-1999) are applicable to this document.

### **Adverse health effect**

An undesirable or unwanted outcome in humans. In this document, this refers to the human infections caused by AMR microorganisms and determinants in food or acquired from food of animal/crop origin as well as increased frequency of infections and treatment failures, loss of treatment options, and increased severity of infections manifested by prolonged duration of disease, increased hospitalization and mortality.<sup>12</sup>

9 The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA plants is addressed in the *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* (CXG 45-2003).

10 The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA microorganisms is addressed in the *Guideline for the Conduct of Food Safety Assessment of Foods Produced Using Recombinant-DNA Microorganisms* (CXG 46-2003).

11 The food safety assessment on the use of probiotics in foods is addressed in a Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Foods (FAO/WHO, 2002).

12 See Note 1 above.

**Antimicrobial agent**

Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of microorganisms by interacting with a specific target.<sup>13</sup>

**Antimicrobial class**

Antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of antimicrobial agents within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties.

**Antimicrobial resistance (AMR)**

The ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.

**Antimicrobial resistance determinant**

The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial agent. They are located either chromosomally or extra-chromosomally and may be associated with mobile genetic elements such as plasmids, integrons or transposons, thereby enabling horizontal transmission from resistant to susceptible strains.

**Commensal**

Microorganisms participating in a symbiotic relationship in which one species derives some benefit while the other is unaffected. Generally, commensal microorganisms are considered to be non-pathogenic in their normal habitat but may, in certain circumstances, become opportunistic pathogens.

**Co-resistance**

The ability of a microorganism to multiply or persist in the presence of different classes of antimicrobial agents due to possession of various resistance mechanisms.

**Cross-resistance**

The ability of a microorganism to multiply or persist in the presence of other members of a particular class of antimicrobial agents or across different classes due to a shared mechanism of resistance.

**Extra- or off-label use**

The use of an antimicrobial agent that is not in accordance with the approved product labelling.

**Foodborne pathogen**

A pathogen present in food, which may cause human disease(s) or illness through consumption of food contaminated with the pathogen and/or the biological products produced by the pathogen.

**Food-producing animals**

Animals raised for the purpose of providing food to humans.

<sup>13</sup> See Note 4 above.

**Interpretive criteria**

These are specific values such as minimal inhibitory concentrations (MICs) or inhibition zone diameters based on which bacteria can be assigned to categories of either 'susceptible', 'intermediate' or 'resistant'.

**Pathogen**

A microorganism that can cause infection, illness or disease.

**Risk management option (RMO)**

A specific action that could be implemented to mitigate risk at various control points throughout the food production to consumption continuum.

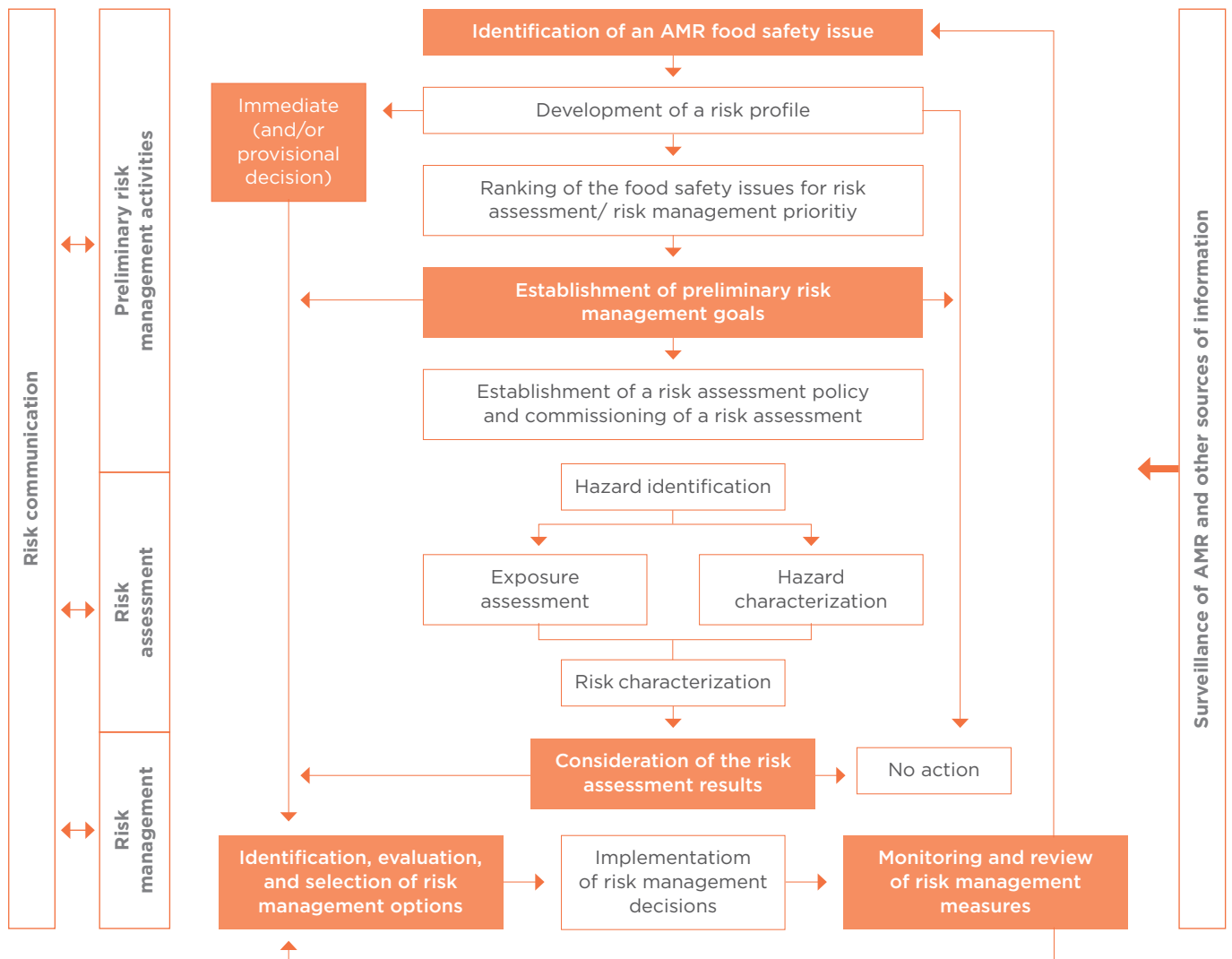
## 4. General principles for foodborne AMR risk analysis

*The Working Principles for Risk Analysis for Food Safety for Application by Governments (CXG 62-2007) shall apply to all aspects of foodborne AMR risk analysis. General principles specific to foodborne AMR risk analysis are as follows.*

- Principle 1** Foodborne AMR risk analysis should consider the impact of foodborne AMR on human health as a result of non-human use of antimicrobial agents.
- Principle 2** Foodborne AMR risk analysis should consider the selection and dissemination of foodborne AMR through the food production to consumption continuum.
- Principle 3** Foodborne AMR risk analysis should consider relevant international documents (for example, recommendations of the "Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials") for setting priorities for risk assessment and/or risk management activities.
- Principle 4** Foodborne AMR risk analysis should consider national and regional differences in the use of antimicrobial agents, human exposure to and prevalence of foodborne AMR microorganisms and determinants, as well as available RMOs.
- Principle 5** Foodborne AMR risk analysis should build on Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CXG 30-1999) and Principles and Guidelines for the Conduct of Microbiological Risk Management (CXG 63-2007) and, in addition, needs to consider factors relating to the antimicrobial susceptibility of the microorganism(s) in question and related consequences to treatment of human disease resulting from exposure to AMR microorganisms.
- Principle 6** Foodborne AMR risk analysis should focus on clearly defined combinations of the food commodity, the AMR microorganism and determinants and the antimicrobial agent(s) to which resistance is expressed. Co-resistance and cross-resistance should be considered in certain situations.

- Principle 7** Monitoring and surveillance of the use of antimicrobial agents and prevalence of AMR microorganisms and determinants are critical to evaluating and determining the effectiveness of implemented risk management measures and informing all levels of risk analysis.
- Principle 8** Evaluation of pre-harvest foodborne AMR RMOs should include, whenever appropriate, animal health aspects relevant to food safety. Foodborne AMR risk analysis when considering such animal health aspects should take into account relevant OIE standards.

**Figure 1**  
 Framework for  
 foodborne AMR risk  
 analysis



Note: the boxes in orange highlight the key decision points in the framework of foodborne AMR risk analysis

## 5. Framework for foodborne AMR risk analysis

Figure 1 provides an overview of the framework for foodborne AMR risk analysis as presented in this document. The diagram is intended to aid risk managers by identifying decision points and placing the components of risk analysis in relation to one another, such as: i) sequencing of steps that are included in preliminary risk management activities; ii) steps for conducting risk assessment; iii) the process for identification, evaluation, selection, implementation and monitoring and review of RMOs; and iv) elements and activities used throughout the process, including risk communication and surveillance of the use of antimicrobial agents and AMR. Surveillance, while not a conventional component of risk analysis, is considered integral to each step of the foodborne AMR risk analysis.

## 6. Preliminary foodborne AMR risk management activities

A potential food safety issue may arise when AMR microorganisms or determinants are present in, and/or transmitted to, humans from food. Foodborne exposure to these AMR microorganisms or determinants may adversely impact human health. The risk manager initiates the risk management process with the preliminary risk management activities to determine the scope and magnitude of the food safety issue and, where necessary, to commence activities to manage the identified risk.

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### 6.1 Identification of an AMR food safety issue

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This is the initial step in which risk managers identify and briefly describe the AMR food safety issue, i.e. the defined combination of the hazard(s) (AMR microorganisms and/or determinant(s)), the antimicrobial agent(s) to which resistance is expressed and the food commodity in which the hazard is identified. AMR food safety issues may be identified on the basis of information arising from a variety of sources, as described in Section 7.1.

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## 6.2

### Development of a foodborne AMR risk profile

The foodborne AMR risk profile is a description of a food safety problem and its context. This risk profile presents, in a concise form, the current state of knowledge related to the food safety issue, describes current control measures and RMOs that have been identified to date and the food safety policy context that will influence further possible actions. It is important to note that the risk profile is a scoping exercise to describe and define the pertinent factors that may influence the risk posed by the hazard. It is not intended to be an abbreviated version of a risk assessment. The risk profile is usually developed by personnel with specific scientific expertise on the food safety issue of concern and understanding of AMR risk assessment techniques. Interested parties who are familiar with the relevant food production chain and related production techniques should be consulted.

The depth and breadth of the foodborne AMR risk profile may vary depending on the needs of the risk managers and the complexity and urgency of the food safety issue. A list of elements for consideration in a foodborne AMR risk profile is described in Appendix 1 of this document. Additional risk profile elements can be found in the *Principles and Guidelines for the Conduct of Microbiological Risk Management* (CXG 63-2007). In addition, it is important to consider critically important antimicrobial agent lists developed by international organizations and national/regional authorities (see Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, Rome 2008).<sup>14</sup>

Consideration of the information given in the risk profile may result in options leading to a range of initial decisions, such as determining that no further action is needed, commissioning a foodborne AMR risk assessment, establishing additional information gathering pathways or implementing immediate risk mitigation management.

When there is evidence that a risk to human health exists but scientific data are insufficient or incomplete, it may be appropriate for risk managers to make a provisional decision, while obtaining additional information that may inform and, if necessary, modify the provisional decision. In those instances, the provisional nature of the decision and the timeframe or circumstances under which the provisional decision will be reconsidered (e.g. after the completion of a risk assessment) should be communicated to all interested parties when the decision is initially made.

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## 6.3

### Ranking of the food safety issues and setting priorities for risk assessment and management

Given the potentially high resource costs associated with conducting risk assessments and/or implementing risk management decisions, the AMR risk profile provides the principal resource that should be used by risk managers in risk ranking or prioritization of this AMR food safety issue among numerous other food safety issues.

Beyond the description of the AMR food safety issue provided by the risk profile, other criteria may be used for ranking or prioritization. These are generally determined by the risk managers in conjunction with interested parties and in consultation with risk assessors on scientific aspects of the issues.

<sup>14</sup> WHO List of Critically Important Antimicrobials (CIA) at: [www.who.int/foodborne\\_disease/resistance/cia/en](http://www.who.int/foodborne_disease/resistance/cia/en); OIE List of Antimicrobials of Veterinary Importance at: [http://www.oie.int/download/Antimicrobials/OIE\\_list\\_antimicrobials.pdf](http://www.oie.int/download/Antimicrobials/OIE_list_antimicrobials.pdf)



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## 6.4

### Establishment of preliminary risk management goals

Following development of the risk profile and the ranking of the AMR food safety issues for risk assessment/risk management priority, risk managers should decide on the preliminary risk management goals that determine the next steps to be taken, if any, to address the identified AMR food safety issue.

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## 6.5

### Establishment of a risk assessment policy

Following a decision as to the need for a risk assessment, risk assessment policy should be established by risk managers in advance of commissioning the risk assessment. The risk assessment policy should be developed in consultation with risk assessors and all other interested parties. This procedure aims at ensuring that the risk assessment is systematic, complete, unbiased and transparent. The mandate given by risk managers to risk assessors should be as clear as possible and provide guidance as to the scope of the risk assessment, the need to address uncertainty and what assumptions to use when the available data are inconsistent or incomplete. Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different RMOs.

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## 6.6

### Commission a foodborne AMR risk assessment

Risk managers may commission a risk assessment to provide a transparent, systematic evaluation of relevant scientific knowledge to help make an informed decision regarding appropriate risk management activities.

Information that may be documented in the commissioning of the risk assessment includes:

- a description of the specific AMR food safety issue (as defined in the AMR risk profile);
- the scope and purpose of the risk assessment;
- the specific questions to be answered by the risk assessment;
- the preferred type (e.g. quantitative or qualitative) of risk assessment to be conducted;
- the expertise and resources required to carry out the risk assessment; and
- timelines for milestones and completion of the risk assessment and its review.

## 7. Foodborne AMR risk assessment

The foodborne AMR risk assessment guidelines described in this section provide a transparent science-based approach to identify and assess a chain of events that affect the frequency and amount of AMR microorganisms to which humans are exposed through the consumption of food and to describe the magnitude and severity of the adverse health effects from that exposure. An AMR risk assessment addressing the specific risk to the defined population will examine the load and likelihood of contamination of all foods (domestic and imported) by AMR microorganisms and/or determinants and, to the extent possible, the factors that are relevant and could influence their prevalence in food.

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### 7.1 Sources of information

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Given the fact that multiple data sources are likely to be required for a foodborne AMR risk assessment and that these data can be limited, their strengths, limitations, discrepancies and gaps should be clearly described.

Possible sources of information:

- surveillance programmes (see Section 9);
- epidemiological investigations of outbreaks and sporadic cases associated with AMR microorganisms;
- clinical studies including case reports on the relevant foodborne infectious disease incidence, primary and secondary transmission, antimicrobial therapy and impacts of resistance on disease frequency and severity;
- national/regional treatment guidelines for foodborne microorganisms, including information on the medical importance of, and potential impacts of, increased resistance in target or other microorganisms to alternative treatments;
- studies on interaction between microorganisms and their environment through the food production to consumption continuum (e.g. litter, water, faeces and sewage);
- investigations of the characteristics of AMR microorganisms and determinants (and *in vivo*);
- research on properties of antimicrobial agents, including their resistance to selection potential (in vitro and in vivo), and transfer of genetic elements and the dissemination of AMR microorganisms in the environment;
- studies on the link between resistance, virulence and/or fitness (e.g. survivability or adaptability) of the microorganism;
- studies on the pharmacokinetics / pharmacodynamics associated with selection of AMR in any given setting;
- laboratory and/or field animal/crop trials addressing the link between antimicrobial agent usage and resistance (particularly regional data);
- science-based expert opinion; and
- existing microbiological and AMR risk assessments.

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## 7.2

### Process of foodborne AMR risk assessment

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At the outset, the risk assessor should consider the risk profile, information documented during commissioning the risk assessment and the risk assessment policy. In addition, risk assessors may require a preliminary investigation phase to define and map the work to be undertaken within the framework of the AMR risk assessment.

Foodborne AMR risk assessment is composed of hazard identification, exposure assessment, hazard characterization and risk characterization. Details of suggested elements for consideration of each component can be found in Appendix 2. Exposure assessment and hazard characterization can be conducted in parallel (Figure 1).

The general principles of a foodborne AMR risk analysis apply equally to both qualitative and quantitative risk assessment. While the design differences may yield different forms of output, both approaches are complementary. The selection of a qualitative or quantitative approach should be made based on the purpose or the type of questions to be answered and data availability for a specific AMR risk assessment. In accordance with the *Working Principles for Risk Analysis for Food Safety for Application by Governments* (CXG 62-2007), quantitative data should be used to the greatest extent possible without discounting the utility of available qualitative information.

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## 7.3

### Hazard identification

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The purpose of hazard identification is to describe the foodborne AMR hazard of concern (Appendix 2). Risk assessors should review literature and information from surveillance programmes to identify specific strains or genotypes of foodborne microorganisms that may pose risks by a particular combination of food commodity, AMR microorganism and/or determinants and antimicrobial agents to which resistance is expressed. Additionally, the biology of AMR microorganisms and/or determinants within different environments/niches (e.g. interactions in animal feeds or aquaculture environment as well as in food matrices) and information on the susceptible strains of the same organisms or related AMR microorganisms and/or determinants will be useful. When necessary, science-based opinions on hazard identification can be sought from relevant experts.

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## 7.4

### Exposure assessment

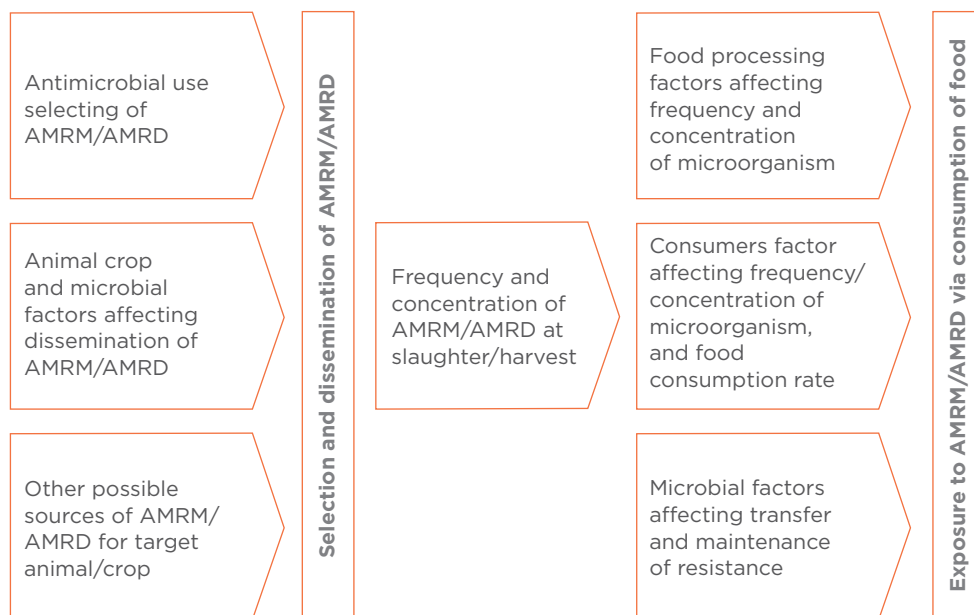
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Use of antimicrobial agents occurs in different agricultural sectors and at different stages of production, including animal feed, in food-producing animals, crop production and/or during food processing. Following antimicrobial use, selection of AMR microorganisms and determinants may occur, which then could be disseminated between these sectors, such as between animal feed and food-producing animals, or food-producing animals' waste being spread on crops, etc. Other risk/preventive factors may affect either selection or dissemination of resistance.

The fundamental activities in exposure assessment should include: (a) clear depiction or drawing of the exposure pathway; (b) detailing the necessary data requirements based on the pathway; and (c) summarizing the data. Considerations related to exposure assessment are illustrated in Figure 2a.<sup>15</sup>

<sup>15</sup> The exposure assessment covers the release and exposure assessments of the OIE risk assessment scheme (OIE. *Terrestrial Animal Health Code* (Risk assessment for AMR arising from the use of antimicrobials in animals)).

**Figure 2a**  
 Considerations for exposure assessment in a foodborn AMR risk assessment – the exposure pathway



**The objective is to arrive at an estimate of the magnitude of exposure to AMRM/AMRD. Consider all relevant pathways and risk factors required to address the risk management question.**

AMRM = antimicrobial resistant microorganism; AMRD = antimicrobial resistant determinant;

Section 2.1 of Appendix 2 includes suggested pre-harvest factors for estimating the likelihood of selection and dissemination of resistance within animal or crop populations. A possible output from the pre-harvest component of exposure assessment is an estimate or probability of the influence of the use of antimicrobial agents on the prevalence of AMR microorganisms and/or determinants in the target animals or crops. Section 2.2 of Appendix 2 considers possible post-harvest factors related to the human exposure to food containing AMR microorganisms and/or determinants. A possible output from the post-harvest component of exposure assessment is an estimate of the likelihood and level of contamination of the food product with resistant microorganisms at the time of consumption.

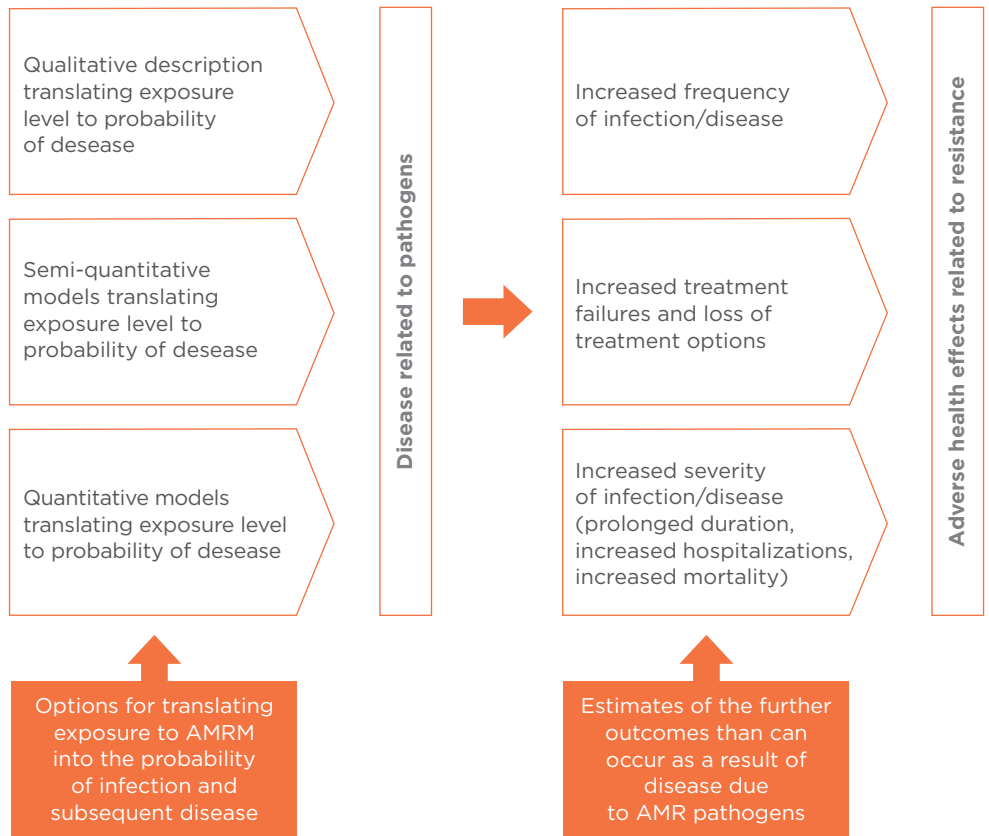
When the hazard of interest is AMR determinants alone, including in commensal microorganisms, then an exposure assessment should consider whether these AMR determinants can transfer to human pathogens that subsequently become resistant. Assessment of the exposure through animal feed should also consider resistance selection in microorganisms present in animal feed due to exposure to in-feed antimicrobial agents and their transmission to food-producing animals, including aquaculture species (refer to the *Code of Practice on Good Animal Feeding* – CXC 54-2004). Particular environmental reservoirs of AMR determinants may need to be considered in the foodborne AMR risk assessment.

## 7.5 Hazard characterization

The hazard characterization step considers the characteristics of the hazard, food matrix and host in order to determine the probability of disease in humans upon exposure to the hazard. A foodborne AMR hazard characterization also includes the characteristics of the acquired resistance so as to estimate the additional consequences that can occur when humans are exposed to resistant pathogens, such as increased frequency and severity of disease. Possible factors that can have an impact on the hazard characterization are included in Section 3 of Appendix 2.

The output from the hazard characterization, including the dose-response relationship where available, assists in translating levels of exposure to a likelihood of an array of adverse health effects or outcomes. The approach for conducting hazard characterization will be guided by the risk question(s) and the risk manager's needs. Figure 2b includes examples of different options (e.g. qualitative descriptions, semi-quantitative and quantitative models) that could be used to link exposure to AMR microorganisms to infection and subsequent disease and depicts the further adverse health effects caused by an AMR pathogen.

**Figure 2b**  
Considerations  
for hazard  
characterization  
in a foodborne AMR  
risk assessment



**The objective is to arrive at an estimate of the adverse health effects related to resistance conditional on disease and infection with AMRM.**

AMRM = antimicrobial resistant microorganism

Determining the number of cases with a particular foodborne disease based on exposure is similar to non-AMR microbiological risk assessment, except that potential increased virulence of resistant microorganisms and selection effects in patients treated with the antimicrobial agents of concern should be incorporated into the assessment. The risk outcome in an AMR risk assessment, like microbiological risk assessments will focus on diseases except, in this case, the focus is specifically on disease attributed to resistant microorganisms. The risk outcome considers the subsequent risk of treatment failure or other complications as a result of infection from microorganisms that have acquired resistance. It should also be noted that hazard characterization for AMR microorganisms and determinants, when appropriate, may be informed by hazard characterization for non-AMR microorganisms. Thus, compared to a non-AMR hazard characterization, these outcomes can be a series of additional consequences that occur following the initiating infection event. The hazard characterization step estimates the probability of infection and then, conditional to this event, the probability of disease. The other consequences that occur because infection is from a resistant microorganism are additional conditional probabilities, as disease is conditional on infection.

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## 7.6 Risk characterization

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Risk characterization considers the key findings from the hazard identification, exposure assessment and hazard characterization to estimate the risk. The form that the risk characterization takes and the outputs it produces will vary from assessment to assessment as a function of the risk management request. This section provides guidance on the general types of outputs that may be informative in the risk characterization but specific outputs may need to be established at the onset of the assessment process based on the risk question(s) and the risk manager's needs. Suggested elements for risk characterization are included in Section 4 of Appendix 2.

Additional outputs of risk characterization, which would have been defined in the purpose of an AMR risk assessment, may include scientific evaluation of RMOs within the context of the risk assessment.<sup>16</sup>

The adverse human health effects of concern in a foodborne AMR risk assessment include the severity and likelihood of the human infections associated with the resistant microorganisms. The risk estimate may be expressed by multiple risk measures, for example in terms of individual risk, population (including relevant subgroups) risk, per-meal risk or annual risk based on consumption. Health effects may be translated into burden of disease measurements. The selection of the final risk measures should generally have been defined within the purpose of the foodborne AMR risk assessment, during the commissioning of the AMR risk assessment, in order to determine the appropriate exposure assessment and hazard characterization outcomes for risk characterization.

<sup>16</sup> FAO/WHO. 2006. The use of microbial risk assessment outputs to develop practical risk management strategies: metrics to improve food safety. Report, Kiel, Germany, 3-7 April, 2006,9,11,27.

Other elements to consider in association with risk characterization, depending upon the purpose of the risk assessment and the details necessary to adequately characterize the risk, are:

- Sensitive sub-populations (i.e. human populations with special vulnerability) and whether the potential risks/exposures/health impacts are adequately characterized.
- Key scientific assumptions used (stated in clear and readily understandable language) and their impact on the assessment's validity.
- An explicit description of the variability and uncertainty. The degree of confidence in the final estimation of risk will depend on the variability, uncertainty and assumptions identified in all previous steps.<sup>17</sup> Risk assessors must be sure that risk managers understand the impacts of these aspects on the risk characterization.
- Sensitivity and uncertainty analysis. Quantitative uncertainty analysis is preferred, however, it may be arrived at through professional and/or expert advice. In the context of quality assurance, uncertainty analysis is a useful tool for characterizing the precision of model predictions. In combination with sensitivity analysis, uncertainty analysis also can be used to evaluate the importance of model input uncertainties in terms of their relative contributions to uncertainty in the model outputs.
- Strengths and weaknesses/limitations of the risk assessment – what parts are more or less robust. Particularly for a complex issue such as the risk posed by AMR microorganisms, discussion of the robustness of data used, i.e. weight of evidence, will enhance the credibility of the assessment. Weaknesses linked to the limited number of microbial species considered or for which resistance data are available should be made clear.
- Alternatives to be considered, i.e. to what extent are there plausible alternatives or other opinions? Does the AMR risk assessment adequately address the questions formulated at the outset of the work? What confidence do the assessors have about whether the conclusions can be relied upon for making decisions?
- Key conclusions as well as important data gaps and research needs.

Appendix 3 provides examples of the outputs from a qualitative foodborne AMR risk assessment. This appendix is not intended to imply that a qualitative AMR risk assessment is the preferred approach but merely to illustrate ways in which qualitative findings can be presented. Quantitative risk assessments can be divided into two types, deterministic or probabilistic, which will have different forms of output.<sup>18</sup>

The AMR risk assessment may also identify areas of research needed to fill key gaps in scientific knowledge on a particular risk or risks associated with a given combination of the food commodity(ies), the AMR microorganism(s) and/or determinant(s) and antimicrobial agent(s) to which resistance is expressed. The conclusions of the risk assessment including a risk estimate, if available, should be presented in a readily understandable and useful form to risk managers and made available to other risk assessors and interested parties so that they can review the assessment.

<sup>17</sup> FAO/WHO. 1999. *Principles and guidelines for the conduct of microbiological risk assessment* (CXG 30-1999).

<sup>18</sup> FAO/WHO Kiel Report, 10.

## 8. Foodborne AMR risk management

The purpose of this section of the guidelines is to provide advice to risk managers on approaches to manage the risk of foodborne AMR microorganisms and/or determinants linked to the non-human use of antimicrobial agents.

Risk managers should consider both non-regulatory measures and regulatory controls. Risk management decisions should be proportionate to the level of risk, whether an intervention is a single RMO or a combination of RMOs.

Once a decision has been made to take action, RMOs should be identified, evaluated, selected, implemented, monitored and reviewed, with adjustments made when necessary.

It is implicit in the recommended approach to AMR risk management that good agricultural practices, Good Veterinary Practices (GVP) and Good Hygienic Practices (GHP) should be in place along the food production to consumption continuum and that relevant Codex codes of practices are implemented as fully as possible:

- *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance* (CXC 61-2005);
- *Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals* (CXG 71-2009);
- *Principles and Guidelines for the Conduct of Microbiological Risk Management* (CXG 63-2007);
- *Code of Practice on Good Animal Feeding* (CXC 54-2004);
- *International Code of Practice General Principles of Food Hygiene* (CXC 1-1969);
- *Code of Hygienic Practice for Meat* (CXC 58-2005);
- *Code of Hygienic Practice for Milk and Milk Products* (CXC 57-2004);
- *Code of Hygienic Practice for Eggs and Eggs Products* (CXC 15-1976);
- *Code of Hygienic Practice for Fresh Fruits and Vegetables* (CXC 53-2003); and
- *Principles for the Establishment and Application of Microbiological Criteria for Foods* (CXG 21-1997).

Additionally, relevant sections of the OIE *Terrestrial Animal Health Code*,<sup>19</sup> the FAO *Responsible Use of Antibiotics in Aquaculture*<sup>20</sup> and the WHO *Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*<sup>21</sup> should be consulted.

<sup>19</sup> See note 6 above.

<sup>20</sup> FAO. 2005. *Responsible Use of Antibiotics in Aquaculture*.

<sup>21</sup> WHO. 2000. *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food*.



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## 8.1

### Consideration of the foodborne AMR risk assessment results

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The risk manager should consider the strengths and weaknesses of foodborne AMR risk assessment results. The responsibility for resolving the impact of uncertainties and assumptions described in the risk assessment lies with the risk manager and not with the risk assessors.

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## 8.2

### Identification of foodborne AMR RMOs

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When identifying RMOs to control an AMR food safety issue, risk managers should consider a range of points along the food production to consumption continuum, both in the pre-harvest and post-harvest stages, where control measures may be implemented and the interested parties, who have responsibility to implement such measures. In general, it is valuable to identify initially as broad a range of possible options as practicable and then select the most promising and applicable interventions for more detailed evaluation.

To identify RMOs to address an AMR food safety issue, risk managers should ensure the previously listed Codex Codes of Practice, OIE and WHO documents are considered (Section 8), as they may contain sources of RMOs that can be adapted to a particular AMR food safety issue. In certain instances, the RMOs therein may pertain only to specific commodities or circumstances in the food production to consumption continuum. Their applicability to foodborne AMR risks should be considered by risk managers as they may identify points at which foodborne microbiological hazards can be controlled, including those that potentially contribute to the selection and dissemination of AMR microorganisms and determinants.

Risk assessors, scientists, food policy analysts and other interested parties play important roles in identifying RMOs based on their expertise and knowledge. Specific RMOs may also be identified or developed during the process of constructing a risk profile and/or risk assessment.

The potential to combine one or more RMOs or integrate them into a comprehensive food safety approach, based on a generic system such as hazard analysis and critical control points (HACCP),<sup>22</sup> should be considered.

Table 1 provides examples of RMOs for the control of foodborne AMR risks, inclusive but not exhaustive of existing Codex Codes of Practice, and RMOs specific to foodborne AMR. The table is divided into pre-harvest RMOs, which include measures to reduce the risk related to the selection and dissemination of foodborne AMR microorganisms and/or determinants and post-harvest RMOs, which include measures to minimize the contamination of food by AMR microorganisms and/or determinants.

<sup>22</sup> Hazard analysis and critical control points (HACCP) - A system which identifies, evaluates, and controls hazards which are significant for food safety.

**Table 1**  
Examples  
of foodborne AMR  
risk management  
options

**PRE-HARVEST OPTIONS**

<b>Animal feed production</b>	<p>Implement programmes to minimize the presence in feed and feed ingredients of AMR microorganisms and/or determinants and the transmission of these through feed.</p> <p>Prohibit or restrict the addition of feed ingredients containing AMR microorganisms and/or determinants identified as contributing to a specific food safety problem.</p>
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**Examples of regulatory controls on conditions of use of veterinary antimicrobial agents and additives:**

- marketing status limitation;
- restrict extra-/off-label use;
- extent of use limitation;
- major label restriction; and
- withdrawal of the marketing authorization.

**Examples of non-regulatory controls on condition of use of veterinary antimicrobial agents and additives:**

<b>Food animal production</b>	<p>Develop and implement national or regional treatment guidelines<sup>23</sup> targeting a specific AMR food safety issue.</p> <p>Develop and regularly update antimicrobial responsible use guidelines<sup>24</sup> written by professional bodies or internationally recognized entities, such as OIE.</p> <p>Promote use of and improve availability, speed, and accuracy of diagnostic microbiological tests.</p> <p>Disseminate and use international standards for:</p> <ul style="list-style-type: none"> <li>• Bacterial culture and antimicrobial susceptibility testing;<sup>25</sup> and</li> <li>• Interpretive criteria.</li> </ul> <p>Implement biosecurity and animal health and infection control programmes to minimize the presence and transmission of foodborne AMR microorganisms and/or determinants between animals, to/from animals to humans and between flocks/herds.</p>
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(...)

23 National/Regional Treatment Guidelines (non-regulatory control) – An animal or crop species-specific guidelines developed to address a specific disease or infection and could be implemented as a voluntary step prior to regulatory controls such as withdrawing an antimicrobial drug or making significant label restrictions.

24 Responsible Use Guidelines – Judicious use, responsible use, and prudent use guidelines are all documents that contain broad principles with respect to the administration of antimicrobials; some may be species-specific. For the purposes of this document, these guidelines will be referred to as responsible use guidelines. Guidance on Responsible Use can be found in the *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance* (CXC 61-2005) and *OIE Terrestrial Animal Health Code* (Section Veterinary Public Health).

25 *OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (Laboratory Methodologies for Bacterial Antimicrobial Susceptibility Testing).

(...)

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## PRE-HARVEST OPTIONS

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### Examples of regulatory controls on conditions of use of antimicrobial agents on crops:

- pre-market assessment and approval;
- marketing status limitation;
- restrict extra-/off-label use;
- extent of use limitation;
- limit use to conditions when crops are known to be at risk of developing disease; and
- withdrawal of the marketing authorization.

Evaluate the safety of viable microorganisms used in food and feed crop production for their potential to introduce and spread AMR.

### Examples of non-regulatory controls of use:

Implement the use of alternative strategies for specific diseases:

#### Food crop production

- Substitution of use of antimicrobial agent with non-antimicrobial treatments (chemical and non-chemical) and, if not feasible, use antimicrobial agents in combination with alternative treatments.<sup>26</sup>
- Treating only specific developmental stages where the treatment is likely to be most effective, rather than treating at all developmental stages.

Development and implementation of national or regional treatment guidelines targeting a specific AMR food safety issue.

Promote the use of and improve availability, speed and accuracy of diagnostic microbiological tests.

Develop, disseminate and use international standards for:

- bacterial culture and antimicrobial susceptibility testing; and
- interpretive criteria.

Implement biosecurity and infection control programmes to prevent the presence and transmission of foodborne AMR microorganisms and determinants between crops and from crops to humans.

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#### Waste management

Implement control measures to limit the spread of AMR microorganisms and/or determinants through other sources of contamination, by assuring the appropriate use of human and animal waste (biosolids, wastewater, manure, other waste-based fertilizers) in fields for food and animal feed production:

Design treatment procedures to control AMR microorganisms and/or antimicrobial agents that could lead to their emergence in biosolids, wastewater, manure and other waste-based fertilizers identified as contributing to a specific food safety problem.

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## POST-HARVEST OPTIONS

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Prevent food containing AMR microorganisms from reaching the consumer when identified as constituting a risk to public health that requires urgent action. If already placed in the market, it may be appropriate to withdraw such food on the market for reprocessing or destruction.

Develop and check compliance with microbiological criteria, which define the acceptability of a product or a food lot in accordance with *Principles for the Establishment and Application of Microbiological Criteria for Foods* (CXG 21-1997) and regulate action to be taken in cases of non-compliance at the level of:

- sorting;
  - reprocessing;
  - rejection; and
  - further investigation.
- 

<sup>26</sup> While the use of alternative treatments and those targeting specific developmental stages could be considered a non-regulatory option, the treatment products (chemical or non-chemical) are likely to require approval from regulatory authorities.

## 8.3

### Evaluation of foodborne AMR RMOs

After a range of RMOs have been identified, the next step is to evaluate one or more options with respect to their ability to reduce risk and thereby achieve an ALOP<sup>27</sup> or a public health goal. For AMR, an example of an ALOP might be a specific target for the incidence of cases of resistant foodborne infectious diseases. A variety of approaches to setting ALOPs or public health goals are described in FAO Food and Nutrition Paper 87 “*Food safety risk analysis – A guide for national food safety authorities*”.<sup>28</sup> The process by which options are evaluated may vary depending on the specific RMOs and their impact on different control points in the food production to consumption continuum. The option of not taking any action should also be evaluated.

Ideally, the following information should be available for evaluating individual or combinations of possible RMOs. Risk managers may ask risk assessors to develop this information as part of the risk assessment:

- estimates of risk that would result from application of different risk management measures (either singly or in combination), expressed either qualitatively or quantitatively;
- technical information on the feasibility and practicality of implementing different options; and
- tools and resources to verify the correct implementation of the RMOs.

Any positive or negative impacts of RMOs on public health should be considered when evaluating RMOs. Risk managers should also consider whether alternatives exist, such as alternative antimicrobial agents, non-antimicrobial treatments or changes in livestock husbandry or food production practices. RMOs describing alternatives to using an antimicrobial agent should always be considered.

Consideration should be given to how cross-resistance or co-resistance will affect the outcomes of different RMOs. For example, the use of an alternative antimicrobial agent may select co-resistance to an antimicrobial agent critically important to human health.

Food safety approaches/systems, such as HACCP, include the concept of risk-based targets for control of hazards at particular steps in the food production chain. An ability to develop specific quantitative food safety metrics, such as food safety objective (FSO), performance objective (PO) and performance criterion (PC), will assist in evaluating RMOs.

RMOs for AMR should be evaluated according to their impact on the specific combination of the food commodity, the AMR microorganism and/or determinants and the antimicrobial agents to which resistance is expressed at a given control point in the entire food production to consumption continuum. Depending on the nature of the specific hazard, the RMO may be more or less effective at meeting a designated PO or FSO. The relative contribution of RMOs towards achieving a given FSO will provide criteria for risk managers to use when selecting RMOs.

<sup>27</sup> Appropriate Level of Protection (ALOP) – The level of protection deemed as appropriate by the member establishing sanitary and phytosanitary measures to protect human, animal, or plant life or health within its territory (World Trade Organization, Agreement on the Application of Sanitary and Phytosanitary Measures (WTO SPS)).

<sup>28</sup> See note 5 above.

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## 8.4

### Selection of foodborne AMR RMOs

Information obtained from the evaluation of RMOs (relative to the specific combination of the food commodity, the AMR microorganisms and/or determinants and the antimicrobial agent(s) to which resistance is expressed) can be used to determine the most efficient approach to achieving the desired goal or ALOP.

An important means of reducing human exposure to AMR microorganisms through the entire food production to consumption continuum is to ensure, as far as possible, that good hygienic practice and HACCP are being followed (*Code of Practice – General Principles of Food Hygiene* – CXC 1-1969). Over and above what can be put in place as good hygienic practice, specific RMOs can address AMR issues.

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## 8.5

### Implementation of foodborne AMR risk management decision(s)

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

To effectively execute food safety control measures, parties involved in the food production chain generally implement complete food control systems using comprehensive approaches such as good agricultural practices, GVP, Good Manufacturing Practices (GMP), GHP and HACCP systems. These approaches should be expanded to incorporate risk management measures specific to foodborne AMR.

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## 8.6

### Monitoring and review of foodborne AMR risk management measures

Risk managers should establish a process to monitor and review whether the risk management measures have been properly implemented and whether or not an outcome has been successful. This should also include the monitoring and review of provisional decisions. Effectiveness of the risk management measures should be evaluated against specific food safety metrics, the ALOP and/or public health goals. Possible end points include:

- prevalence of foodborne AMR microorganisms and/or determinants at farm level;
- prevalence of foodborne AMR microorganisms and/or determinants in food products at slaughter/harvest;
- prevalence of foodborne AMR microorganisms and/or determinants in food products at retail level;
- prevalence of foodborne AMR microorganisms and/or determinants in human clinical isolates;
- number of human cases (or incidence rates) associated with adverse health effects such as treatment failure, loss of treatment options and/or severity of infections (e.g. prolonged duration of disease, increased frequency of bloodstream infections, increased hospitalization and mortality) attributable to foodborne AMR microorganisms and/or determinants; and
- trends in non-human use of antimicrobial agents, including critically-important antimicrobial agents.

National surveillance programmes, designed to monitor the presence of AMR microorganisms and the use of antimicrobial agents, can help establish a baseline against which the effectiveness of risk management measures can be evaluated.

Monitoring/control points related to implemented risk management decisions should be measured to assess the effectiveness and need for potential adjustment. Additional monitoring/control points may be measured to identify new information on the specific food safety issue. Risk managers are responsible for verifying the effectiveness and appropriateness of the risk management measures and for monitoring potential unintended consequences.

## 9. Surveillance of use of antimicrobial agents, AMR microorganisms and determinants

Surveillance programmes on the use of antimicrobial agents and prevalence of foodborne AMR provide information including baseline data that is useful for all parts of the risk analysis process. Data can be used to explore potential relationships between antimicrobial agent use and the prevalence of AMR microorganisms in humans, food-producing animals, crops, food, feed, feed ingredients and biosolids, wastewater, manure and other waste-based fertilizers, as input for risk profiling and risk assessment, to measure the effect of interventions and to identify trends.

Methodology of surveillance programmes should be internationally harmonized to the extent possible. The use of standardized and validated antimicrobial susceptibility testing methods and harmonized interpretive criteria are essential to ensure that data are comparable.

Surveillance of use of antimicrobial agents should, to the extent possible, include all antimicrobial agents used in food-producing animal and crop production. Ideally, such surveillance should provide data per animal species or crop. National/regional authorities may use guidelines such as those described in the OIE *Terrestrial Animal Health Code*, “Monitoring of the quantities of antimicrobial agents used in animal husbandry” and relevant WHO guidance.

Surveillance of AMR in microorganisms originating from food-producing animals, crops and food should ideally be integrated with programmes that monitor resistance in humans. Consideration may also be given to inclusion of animal feed, feed ingredients and biosolids, wastewater, manure and other waste-based fertilizers in such programmes. National/regional authorities may use established guidelines such as those published in the OIE *Terrestrial Animal Health Code* “Harmonisation of national AMR surveillance and monitoring programmes” and relevant WHO guidance to describe key elements of programmes to monitor the prevalence of foodborne AMR microorganisms in animals.

## 10. Foodborne AMR risk communication

To better define the food safety issue, the risk manager may need to pursue information from sources that have specific knowledge pertaining to the issue. An open process, in which the food safety issue is clearly identified and communicated by the risk managers to risk assessors as well as affected consumers and industry, is essential to promote both an accurate definition and a well-understood and common perception of the issue.

Communication with all interested parties should be promoted at the earliest opportunity and integrated into all phases of a risk analysis (see Figure 1). This will provide all interested parties, including risk managers, with a better understanding of risks and risk management approaches. Risk communication should be also well documented.

Mechanisms may be established for engaging interested parties routinely in food safety decision-making at the national/regional level. For foodborne AMR risk analysis, communication should bring industry (producer, food processor, pharmaceutical, etc.), consumer representatives, government officials and other interested parties (public health experts, medical professionals, etc.) together to discuss problems, priorities and strategies.

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### 10.1 Foodborne AMR risk communication as a risk management tool

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Information on antimicrobial agents should be made available by the pharmaceutical or other relevant industries in the form of labelling, data sheets or leaflets to ensure the safe and effective use of antimicrobial agents, in compliance with national regulations.

The food industry is responsible for developing and applying food safety control systems for effective implementation of risk management decisions. Depending on the nature of the decision, this may require risk communication activities, such as effective communication across the entire food supply chain, including consumers as appropriate, and training or instruction of its staff and internal communication.

Guideline documents, training programmes, technical bulletins and other information developed by industry (pharmaceutical, food producer, food processor, etc.) associations may assist to decrease foodborne AMR.

Training involving all relevant professional organizations, regulatory authorities, the pharmaceutical and other relevant industries, veterinary sectors, research institutes, professional associations and other approved users is of importance to ensure consumer safety and, therefore, the protection of public health.

Public education programmes, appropriate labelling and public interest messages are important tools to enable consumers to limit their health risks by following food safety-related instructions. Consumer organizations play a significant role in communicating this information to consumers.

Where risk management measures include consumer information, outreach programmes are often required, for example, by enlisting health care providers in disseminating the information. Messages aimed to inform and engage specific audiences need to be presented in appropriate media.



# Appendix I

## ELEMENTS FOR CONSIDERATION IN A FOODBORNE AMR RISK PROFILE

The objective of a foodborne AMR risk profile is to present prerequisite scientific information on the identified food safety issue to inform risk managers prior to decision-making. A risk profile should be 'fit for purpose' and in some situations will be an elemental exercise. This list is provided for illustration and is not intended to be exhaustive and not all elements may be applicable in all situations. The risk profile should incorporate, to the extent possible, information on the following:

**1.**  
**DESCRIPTION  
OF THE AMR  
FOOD SAFETY  
ISSUE**

The AMR food safety issue is a defined combination of:

- AMR hazard(s) of concern i.e. the AMR microorganism(s) and/or determinant(s);
- the antimicrobial agent(s) to which resistance is expressed; and
- the food commodity in which the AMR hazard(s) is identified.

**2.**  
**INFORMATION  
ON AMR  
MICROORGANISM(S)  
AND/OR  
DETERMINANT(S)**

- Characteristics of the identified foodborne microorganism(s):
  - Sources and transmission routes
  - Pathogenicity of particular strains
  - Growth and survivability of foodborne AMR microorganism(s) in the food commodity production to consumption continuum
  - Virulence and linkages to resistance
  - Inactivation in foods (e.g. D-value, minimum pH for growth, etc.)
  - Distribution, frequency and concentrations of the AMR hazard(s) in the food chain
- Characteristics of the resistance expressed by the AMR microorganism(s) and/or determinant(s)
  - Resistance mechanisms and location of AMR determinants
  - Cross-resistance and/or co-resistance to other antimicrobial agents
  - Transferability of resistance determinants between microorganisms

**3.  
INFORMATION  
ON THE  
ANTIMICROBIAL  
AGENT(S)  
TO WHICH  
RESISTANCE  
IS EXPRESSED**

- i. Class of the antimicrobial agent(s)
- ii. Non-human uses of the antimicrobial agent(s):
  - Formulation of the antimicrobial agent(s).
  - Distribution, cost and availability of the antimicrobial agent.
  - Purpose and use of antimicrobial agent(s) in feed, food animals, crop production and/or during food processing.
  - Methods, routes of administration of the antimicrobial agent(s) (individual/mass medication, local/systemic application) and frequency.
  - Potential extra-label/off-label, use of approved antimicrobial agent(s) and use of non-approved antimicrobial agent(s).
  - Potential role of cross-resistance or co-resistance with use of other antimicrobial agent(s) in food production.
  - Trends in the use of the antimicrobial agent(s) in the agricultural and aquaculture sectors and information on emerging resistance in the food supply.
  - Information on the relationship between the use of the antimicrobial agent(s) and the occurrence of AMR microorganisms or determinants in the food commodity of concern.
- iii. Human uses of the antimicrobial agent(s):
  - Spectrum of activity and indications for treatment.
  - Importance of the antimicrobial agent(s) including consideration of critically important antimicrobial lists.
  - Distribution, cost and availability.
  - Availability of alternative antimicrobial agent(s).
  - Trends in the use of the antimicrobial agent(s) in humans and information on emerging diseases due to microorganism(s) resistant to the antimicrobial agent(s) or classes.

**4.  
INFORMATION  
ON FOOD  
COMMODITY(IES)**

- iv. Source(s) (domestic or imported), production volume, distribution and per capita consumption of foods or raw materials identified with the AMR hazard(s) of concern:
  - Characteristics of the food product(s) that may impact risk management (e.g. further processed, consumed cooked, pH, water activity, etc.).
  - Description of the food production to consumption continuum (e.g. primary production, processing, storage, handling, distribution and consumption) and the risk factors that affect the microbiological safety of the food product of concern.

**5.  
INFORMATION  
ON ADVERSE  
PUBLIC HEALTH  
EFFECTS**

- v. — Characteristics of the disease caused by the identified foodborne AMR microorganism(s) or by pathogens that have acquired resistance determinants via food:
- Trends in AMR foodborne disease.
  - Frequency and severity of effects including case-fatality rate, hospitalization rate and long-term complications.
  - Susceptible populations and risk factors.
  - Epidemiological pattern (outbreak or sporadic).
  - Regional, seasonal and ethnic differences in the incidence of foodborne disease due to the AMR hazard(s).
  - Additional information on the relationship between the presence of the AMR microorganisms or determinants in the food commodity and the occurrence of the adverse health effect(s) in humans.

- vi. — Consequences of AMR on the outcome of the disease:
- Loss of treatment options and treatment failures.
  - Increased frequency and severity of infections, including prolonged duration of disease, increased frequency of bloodstream infections, hospitalization and mortality.

**6.  
RISK  
MANAGEMENT  
INFORMATION**

- vii. — Identification of risk management options to control the AMR hazard along the production to consumption continuum, both in the pre-harvest and post-harvest stages:
- Measures to reduce the risk related to the selection and dissemination of foodborne AMR microorganism(s).
  - Measures to minimize the contamination and cross-contamination of food by AMR microorganism(s).

- viii. — Effectiveness of current management practices in place based on surveillance data or other sources of information.

**7.  
EVALUATION  
OF AVAILABLE  
INFORMATION  
AND MAJOR  
KNOWLEDGE  
GAPS**

- ix. — Uncertainty of available information.
- x. — Areas where major gaps of information exist that could hamper risk management activities, including, if warranted, the conduct of a risk assessment.

# Appendix II

## SUGGESTED ELEMENTS FOR CONSIDERATION IN A FOODBORNE AMR RISK ASSESSMENT

This appendix lists suggested elements to include in an AMR risk assessment; the level of detail of the data may vary on a case-to-case basis. This list is for illustration and is not intended to be exhaustive and not all elements may be applicable in all situations.

### 1. HAZARD IDENTIFICATION

#### 1.1 Identification of hazard of concern: foodborne AMR microorganisms and/or determinants

#### 1.2 Microorganisms and resistance related information

- Potential human pathogens (phenotypic and genotypic characterization) that are likely to acquired resistance in non-human hosts.
- Commensals with AMR determinants (phenotypic and genotypic characterization) and the ability to transfer them to human pathogens.
- Mechanisms of AMR, location of AMR determinants, frequency of transfer and prevalence among human and non-human microflora.
- Co- and cross-resistance and importance of other antimicrobial agents whose efficacy is likely to be compromised.
- Pathogenicity, virulence and their linkage to resistance.

#### 1.3 The antimicrobial agent and its properties

- Description of the antimicrobial agent - name, formulation, etc.
- Class of antimicrobial agent.
- Mode of action and spectrum of activity.
- Pharmacokinetics of the antimicrobial agent.
- Existing or potential human and non-human uses of the antimicrobial agents and related drugs.

**2.**  
**EXPOSURE**  
**ASSESSMENT**

**2.1**

**Pre-harvest factors affecting prevalence of hazard**

- Resistance selection pressure:
  - Attributes of antimicrobial agent use at the population level:
    - Number of animals or extent of crops exposed to the antimicrobial agent in the defined time period.
    - Geographical distribution of antimicrobial agent use and/or number of farms using the antimicrobial agent.
    - Prevalence of infection/disease that the antimicrobial agent is indicated for in the target (animal/crop) population.
    - Potential extra-label/off-label and use of approved antimicrobial agent(s) and use of non-approved antimicrobial agent(s).
    - Data on trends in antimicrobial agent use and information on emerging diseases, changes in farm production system or other changes that are likely to impact antimicrobial agent use.
  - Attributes of antimicrobial agent use at the individual level
    - Methods and routes of administration of the antimicrobial agent (individual/mass medication, local/systemic application).
    - Dosing regimen and duration of use.
    - Pharmacokinetics and pharmacodynamics in animals.
    - Time from antimicrobial agent administration to harvest of animal or crop products.
    - Cumulative effects of use of other antimicrobial agents in the defined time period.
- Target animal or crop and microbial factors affecting resistance development and spread
  - Temporal and seasonal changes in foodborne AMR microorganism prevalence.
  - Duration of infection/shedding of foodborne AMR microorganism(s) (zoonotic and/or commensal).
  - Rate of resistance development in commensal and zoonotic microorganisms in targets after administration of an antimicrobial agent.
  - Resistance mechanisms, location of and occurrence of AMR determinants and resistance transfer rates between microorganisms.
  - Cross-resistance and/or co-resistance to other antimicrobial agents based on phenotypic or genotypic characterization.
  - Prevalence of commensals and zoonotic microorganisms in targets and proportion resistant to the antimicrobial agent.
  - Transmission of AMR microorganisms and/or determinants between target animals/crops and from animals/crops to environment and back to target animals/crops.
  - Animal management factors.
  - Food crop production/management factors.

- Other possible sources of foodborne AMR microorganisms for the target animal/crop
  - Non-target animal/plant species.
  - Animal feed and feed ingredients.
  - Soil, water, animal and human waste products (biosolids, wastewater, manure and other waste-based fertilizers).

## 2.2

### **Post-harvest factors affecting frequency and concentration of the AMR microorganism in food**

- Initial level of contamination of the food product
  - Frequency and concentration of foodborne AMR microorganisms and/or determinants at harvest of animal or crop products.
  - Frequency and concentration of foodborne AMR microorganisms and/or determinants present in retail food.
  - Food matrix factors (food product formulation).
- Food processing factors
  - The level of sanitation and process control in food processing and likely environmental contamination.
  - Methods of processing (including sanitation and process controls such as GMP, GHP and HACCP).
  - Cross-contamination points.
  - Probable use of additives and preservatives (due to their activities or impacts on growth or numbers of microorganisms).
  - Packaging.
  - Distribution and storage.
  - Catering and food services.
- Consumer factors
  - Human demographic data.
  - Storage, cooking and handling of food.
  - Overall human per capita consumption of the food identified with the hazard.
  - Patterns of consumption and socio-economic, cultural, ethnic and regional differences.
  - Place of food consumption (home, commercial establishment or elsewhere).
- Microbial factors
  - Capacity of foodborne AMR microorganisms to transfer resistance to human commensal and/or pathogenic microorganisms.
  - Growth and survival characteristics and fate of AMR microorganisms along the food production to consumption continuum.
  - Microbial ecology of food: survival capacity and redistribution of foodborne AMR microorganism in the food production to consumption continuum.

**3.**  
**HAZARD**  
**CHARACTERIZATION**

3.1

**Human host and adverse health effects**

- Host factors and susceptible population.
- Nature of the infection, disease.
- Diagnostic aspects.
- Epidemiological pattern (outbreak or sporadic).
- Antimicrobial therapy and hospitalization.
- Importance of the antimicrobial agents in human medicine.
- Increased frequency of infections and treatment failures.
- Increased severity of infections, including prolonged duration of disease, increased frequency of bloodstream infections, increased hospitalization and increased mortality.
- Persistence of hazards in humans.

3.2

**Food matrix related factors that can influence the survival capacity of the microorganisms while passing through the gastrointestinal tract**

3.3

**Dose-response relationship: mathematical relationship between the exposure and probability of adverse outcome (e.g. infection, disease and treatment failure)**

**4.**  
**RISK**  
**CHARACTERIZATION**

4.1

**Factors for consideration in risk estimation**

- Number of people falling ill and the proportion of that number with AMR microorganisms attributable to a foodborne source.
- Effects on sensitive subpopulations.
- Increased frequency of infections, frequency of treatment failures, severity or duration of infectious disease, rates of hospitalization and mortality with AMR microorganisms compared to susceptible microorganisms due to resistance.
- Number of person-days of disease per year.
- Deaths (total per year, probability per year or lifetime for a random member of the population or a member of a specific more-exposed or more-vulnerable subgroup) linked to AMR microorganisms attributable to a foodborne source.
- Importance of pathology caused by the target microorganisms.
- Existence or absence of therapeutic alternatives.
- Potential impact of switching to an alternative antimicrobial agent (e.g. alternatives with potential increased toxicity).
- Methods to allow weighted summation of different risk impacts including consequences (e.g. disease and hospitalization).

4.2

**Evaluation of RMOs**

- Comparison of public health burden before and after interventions.
- Potential effect on animal health relevant to food safety.

4.3

**Sensitivity analysis**

- Effect of changes in model input values and assumption on model output.
- Robustness of model results (output).

4.4

**Uncertainty and variability analysis**

- Range and likelihood of model predictions.
- Characterize the precision of model prediction.
- Relative contributions of uncertainties in model input to uncertainty in the model output.



## Appendix III

# EXAMPLES OF QUALITATIVE FOODBORNE AMR RISK ASSESSMENT

Although quantitative risk assessments are encouraged, qualitative risk assessments are often preferred due to their potential lower data demands. The level of scrutiny, review and standards of logic and reasoning to which a qualitative approach should be held are, however, no less than those to which a quantitative approach is subjected.

The following examples illustrate potential approaches that can be used to conduct a qualitative risk assessment. However, these should not be viewed as recommended or accepted default approaches for adoption. The thought process and discussions that surround the development of categories for the exposure or the hazard characterization (e.g. “rare,” “high,” etc.), as well as how these categories translate into the ultimate risk outcome, are a key part of the decision-making and risk management process. The essential parts of developing a qualitative risk assessment can be grouped into three basic tasks:

- the development of qualitative statements or scores to describe the exposure assessment (e.g. “high,” “medium”, etc.) with careful consideration given to the implications and interpretation of these categorizations;
- the development of qualitative statements or scores to describe the hazard characterization (e.g. “mild”, “moderate”, “severe” etc.) with careful consideration given to the implications and interpretation of these categorizations; and
- the process through which the different exposure and hazard characterization categories or scores are combined and integrated into overall risk levels (e.g. what does a “low” in exposure and a “high” in hazard characterization translate to and is it different from a “medium” in both).

There are currently no pre-defined hazard characterization or exposure assessment categories that can be used and different categories may be more suitable for certain situations. The approach used to integrate the exposure assessment and hazard characterization can also vary.

## EXAMPLE 1

### Illustrative exposure assessment scoring

Typically, in a qualitative risk assessment, the probability of the population being exposed to the hazard is translated into a series of qualitative statements. The qualitative risk assessment requires expert opinions or other formalized, transparent and documented process to take the existing evidence and convert it into a measure of the probability of exposure. To illustrate, the probability has been converted into the following categories and scores:

- negligible (0) – Virtually no probability that exposure to the hazard can occur;
- moderate (1) – Some probability for exposure to occur; and
- high (2) – Significant probability for exposure to occur.

The assignment of both a statement reflecting the exposure probability as well as a corresponding score is done in this example to facilitate the process through which the exposure and hazard characterization will subsequently be combined. The description of the categorical statements includes an assessment providing greater detail as to the interpretation behind each of the categories.

### Illustrative hazard characterization scoring

The hazard characterization translates the outcomes of this step into qualitative statements that reflect the implications of exposure to a hazard. The following is an example of categories that might be useful in the case of foodborne zoonotic disease:

- negligible (0) – probability of disease upon exposure to AMR microorganisms is the same as for susceptible organisms and the outcomes as a result of disease are not different;
- mild (1) – probability of disease upon exposure to AMR microorganisms is the same as for susceptible organisms, but the outcomes following disease are more serious requiring hospitalization;
- moderate (2) – probability of disease upon exposure to AMR microorganisms is higher and outcomes following disease are more serious requiring hospitalization; and
- severe (3) – probability of disease upon exposure to AMR microorganisms is higher and outcomes following disease are very serious requiring hospitalization as well as creating the potential for treatment failures requiring lengthy hospitalization.

### Illustrative risk characterization output

Ultimately, the exposure assessment and hazard characterization need to be integrated in the risk characterization in order to estimate the risk. By assigning each of the qualitative categories (e.g. “high,” “medium,” etc.) with a numerical score (e.g. 0, 1, 2), the results can be produced in a transparent way by simply multiplying the scores. The resulting risk characterization score can then be translated into meaningful qualitative risk categories. In this example, the products of the exposure assessment and hazard characterization are assigned the following categories:

- No additional risk:** Value of 0
- Some additional risk:** Value between 1 and 2
- High additional risk:** Value between 3 and 4
- Very high additional risk:** Value between 5 and 6

The results could also be presented graphically as shown below, providing a clear picture of how outcomes are judged to be “very high additional risk” or “no additional risk,” for example.

		Exposure assessment		
		Negligible	Moderate	High
Hazard characterization	Negligible	0	0	0
	Mild	0	1	2
	Moderate	0	2	4
	Severe	0	3	6

Legend	
Negligible	0 = No additional risk
Mild	1-2 = Some additional risk
Moderate	3-4 = High additional risk
Severe	6 = Very high additional risk

## EXAMPLE 2

### Illustrative exposure assessment scoring

The rankings of “Negligible,” “Low,” “Medium,” “High” and “Not Assessable” may be used for qualitative determination of the probability of human exposure to a given AMR microorganism in a given food or feed commodity, animal species or plant. The different ranking is defined below:

- Negligible – The probability of exposure for susceptible people is extremely low;
- Low (Unlikely) – The probability of exposure for susceptible people is low but possible;
- Medium (Likely/Probable) – The probability of exposure for susceptible people is likely;
- High (Almost Certain) – The probability of exposure for susceptible people is certain or very high;
- Not assessable – The probability of exposure for susceptible people cannot be assessed.

### Illustrative hazard characterization scoring

The AMR-related adverse human health effects (i.e. risk endpoints) may be ranked qualitatively as below.<sup>1</sup> In this example, it is considered that adverse health effects associated with the microorganisms that are resistant to critically important antimicrobials in human medicine are likely to have a more severe consequence than those with microorganisms resistant to other antimicrobial agents:

- negligible – no adverse human health consequences or within normal limits;
- mild – symptoms are minimally bothersome and no therapy is necessary;
- moderate – symptoms are more pronounced or of a more systemic nature than mild symptoms but not life threatening; some form of treatment is usually indicated;
- severe – symptoms are potentially life threatening and require systematic treatment and/or hospitalization; increase severity may occur due to the foodborne AMR microorganism; and
- fatal – directly or indirectly contributes to the death of the subject; treatment failure is likely expected due to the foodborne AMR microorganism.

### Illustrative risk characterization scoring

In a qualitative risk assessment, the risk estimate may be integrated into the qualitative (descriptive) considerations of “Negligible,” “Low,” “Medium,” “High,” and “Very High” from the outputs of the Exposure Assessment and Hazard Characterization steps. An example of integration is presented in Table 2.

<sup>1</sup> Modified after National Cancer Institute, 2006. Common Terminology Criteria for Adverse Events v3.0. [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

**Table 1**  
Integration  
of the outputs  
of hazard  
characterization  
and exposure  
assessment into  
the qualitative  
risk characterization

<b>Exposure Assessment Probability of Exposure</b>	<b>Hazard Characterization Severity of Adverse Health Effect</b>	<b>Qualitative Risk Characterization</b>
Negligible	Negligible	Negligible
Low (Unlikely)	Negligible	Negligible
Medium (Possible)	Negligible	Low
High (Almost Certain)	Negligible	Low
Negligible	Low (Mild)	Low
Low (Unlikely)	Low (Mild)	Low
Medium (Possible)	Low (Mild)	Medium
High (Almost Certain)	Low (Mild)	Medium
Negligible	Medium (Moderate)	Low
Low (Unlikely)	Medium (Moderate)	Low
Medium (Possible)	Medium (Moderate)	High/Medium
High (Almost Certain)	Medium (Moderate)	High
Negligible	High (Severe)	Low
Low (Unlikely)	High (Severe)	Medium
Medium (Possible)	High (Severe)	High
High (Almost Certain)	High (Severe)	Very High
Negligible	Very High (Fatal)	Medium/Low
Low (Unlikely)	Very High (Fatal)	High
Medium (Possible)	Very High (Fatal)	Very High
High (Almost Certain)	Very High (Fatal)	Very High



# GUIDELINES ON INTEGRATED MONITORING AND SURVEILLANCE OF FOODBORNE ANTIMICROBIAL RESISTANCE



TYPE  
**GUIDELINES**  
CXG 94- 2021

EDITION  
ADOPTED  
2021



# GUIDELINES ON INTEGRATED MONITORING AND SURVEILLANCE OF FOODBORNE ANTIMICROBIAL RESISTANCE

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# 1. Introduction and purpose

Antimicrobial resistance (AMR) is a global public health threat at the human, animal and environmental interface which necessitates a “One Health” approach. Monitoring and surveillance of foodborne AMR contributes to the food safety component of such an approach.

For the purpose of these Guidelines, monitoring refers to the collection and analysis of foodborne AMR, antimicrobial use (AMU)<sup>1</sup> and related data and information. Surveillance is the systematic, continuous or repeated, measurement, collection, collation, validation, analysis and interpretation of data and trends from defined populations to inform risk analysis. These data may enable the measurement of the impact of risk management measures.

Ideally the integrated monitoring and surveillance programme(s) includes the coordinated and systematic collection of data or samples at appropriate stages along the food chain and within the food production environment, and the testing, analysis and reporting of data. The integrated programme(s) includes the alignment and harmonization of sampling, testing, analysis and reporting methodologies and practices, as well as the integrated analysis of relevant epidemiological information from humans, animals, foods, plants/crops and the food production environment.

National priorities, AMR food safety issues and scientific evidence, capabilities and available resources should guide the development of integrated monitoring and surveillance programme(s) which should undergo continuous improvement as resources permit. This does not imply that a country needs to implement both monitoring and surveillance in all stages or areas covered by the programme(s).

The data generated by integrated monitoring and surveillance programme(s) provide valuable information for the risk analysis (risk assessment, risk management and risk communication) of foodborne AMR. These data may also be useful for trend analysis, epidemiological studies, food source attribution studies and research.

While this document’s focus is on foodborne AMR, there is an implicit connection between the goal of addressing foodborne AMR with the goal of reducing foodborne illness, and thus a connection to the national food safety control system.

These Guidelines are intended to assist governments in the design and implementation of integrated monitoring and surveillance programme(s). They provide flexible options for implementation and expansion, considering resources, infrastructures, capacity, and priorities of countries. Each monitoring and surveillance programme should be designed to be relevant for national, and when appropriate, regional circumstances. While these Guidelines are primarily aimed at action at the national level, countries may also consider creating or contributing to international, multinational or regional, monitoring and surveillance programme(s) to share laboratories, data management and other necessary resources.

<sup>1</sup> See description of AMU in Section 22 on components of integrated monitoring and surveillance programme(s) for AMU.

The design and implementation of monitoring and surveillance programme(s) should be assessed or re-assessed based on their relevance to foodborne AMR priorities at the national and, when appropriate, at the international level.

Continuous improvement of the monitoring and surveillance programme(s) should take into account identified priorities and broader capacity issues. Continuous improvement may include: collecting more information or having new sources of data on AMU and AMR in humans, animals and/or plants/crops, availability of food consumption, agriculture and aquaculture production data, and improvement in cross-sector laboratory proficiency and quality assurance and reporting.

Data generated from national monitoring and surveillance programme(s) on AMR in food should not be used to generate unjustified barriers to trade.

These Guidelines should be applied in conjunction with the *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CXC 61-2005) and the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011). Design and implementation aspects of these Guidelines should also take into account other relevant Codex texts including the *Principles and Guidelines for National Food Control Systems* (CXG 82-2013) and the *General Guidelines on Sampling* (CXG 50-2004).

Where appropriate, the standards of other international standard setting organizations, including the standards of the World Organization for Animal Health (OIE standards) should be considered. These Guidelines may also be used taking into consideration guidance already developed by other advisory bodies including the World Health Organization (WHO) Advisory Group on Integrated Surveillance of AMR (WHO-AGISAR) *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach*.

## 2. Scope

These Guidelines cover the design and implementation of integrated monitoring and surveillance programme(s) for foodborne AMR and AMU along the food chain and the food production environment.

Although these Guidelines do not cover the design and implementation of monitoring and surveillance of AMR and AMU in humans, an integrated programme within the context of overall risk management of AMR (One Health Approach) may be informed by data, trends, methodology and epidemiology regarding AMR and AMU in humans.

The microorganisms covered by these Guidelines are foodborne pathogens of public health relevance and indicator bacteria.

Antimicrobials used as biocides including disinfectants, are excluded from the scope of these Guidelines.

## 3. Definitions

The definitions presented in the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011) and *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance* (CXC 61-2005) are applicable to these Guidelines.

The following definitions are included to establish a common understanding of the terms used in these Guidelines.

### **Antimicrobial agent**

Any substance of natural, semi-synthetic or synthetic origin that at in vivo concentrations kills or inhibits the growth of microorganisms by interacting with a specific target.<sup>2</sup>

### **Antimicrobial resistance (AMR)**

The ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.<sup>3</sup>

### **Food chain**

Production to consumption continuum including, primary production (food-producing animals, plants/crops, feed), harvest/slaughter, packing, processing, storage, transport, and retail distribution to the point of consumption.

### **Foodborne pathogen**

A pathogen present in food, which may cause human disease(s) or illness through consumption of food contaminated with the pathogen and/or the biological products produced by the pathogen.<sup>4</sup>

### **Food production environment**

The immediate vicinity of the food chain where there is relevant evidence that it could contribute to foodborne AMR.

### **Hazard**

For the purpose of these Guidelines, the term “hazard” refers to antimicrobial resistant microorganism(s) and/or resistance determinant(s).<sup>5</sup>

### **One Health approach**

A collaborative, multisectoral and trans-disciplinary approach working with the goal of achieving optimal health outcomes, recognizing the interconnection between humans, animals, plants and their shared environment.

### **Plants/Crops**

A plant or crop that is cultivated or harvested as food or feed.

2 *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011), Section 3.

3 See Note 2 above.

4 See Note 2 above.

5 See Note 2 above.

## 4. Principles

- Principle 1** A One Health approach should be applied whenever possible and applicable when establishing monitoring and surveillance programmes for foodborne AMR; contributing to the food safety component of such an approach.
- Principle 2** Monitoring and surveillance programme(s) are an important part of national strategy(ies) to minimize and contain the risk of foodborne AMR.
- Principle 3** Risk analysis should guide the design, implementation and evaluation of monitoring and surveillance programme(s).
- Principle 4** Monitoring and surveillance programme(s) should be designed to generate data on AMR and AMU, in relevant sectors to inform risk analysis.
- Principle 5** Monitoring and surveillance programme(s) should be tailored to national priorities and should be designed and implemented to allow continuous improvement as resources permit.
- Principle 6** Priority for implementation of monitoring and surveillance programme(s) should be given to the most relevant foodborne AMR and/or AMR food safety issues (which are the defined combinations of the food commodity, the AMR microorganism and determinants and the antimicrobial agent(s) to which resistance is expressed as described in CXG 77-2011) from a public health perspective, taking into account national priorities.
- Principle 7** Monitoring and surveillance programme(s) should incorporate, to the extent practicable, the identification of new and emerging foodborne AMR or trends and should be designed to inform epidemiological investigation.
- Principle 8** Laboratories involved in monitoring and surveillance should have effective quality assurance/management systems in place.
- Principle 9** Monitoring and surveillance programme(s) should aim to harmonize laboratory methodology, data collection, analysis and reporting across sectors according to national priorities and resources as part of an integrated approach. Use of internationally recognized, standardized and validated methods and harmonized interpretative criteria, where available, contributes to the comparability of data, facilitates the multisectoral exchange and analysis of data and enhances an integrated approach to data management, analysis and interpretation.

## 5. Risk-based approach

For the purpose of these Guidelines, a risk analysis approach – as described in the framework for foodborne AMR risk analysis (CXG 77-2011) – may inform the development, implementation and evaluation of monitoring and surveillance programme(s) with data and scientific knowledge regarding the likely occurrence of foodborne AMR hazards along the food chain and their potential to pose risks to human health.

Information from monitoring and surveillance programme(s) and available data from other sources, are important for risk assessment and may inform decisions on the appropriateness of control measures to minimize and contain foodborne AMR.

When information or data of foodborne AMR within a country is limited, monitoring and surveillance programme(s) may initially be designed according to the relevant data and/or scientific knowledge that is available on AMR hazards and their potential to result in public health risks. AMR food safety issues may be identified on the basis of information arising from a variety of sources, as described in the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011).

## 6. Regulatory framework, policy and roles

Integrated monitoring and surveillance programme(s) requires good governance by the competent authorities. As part of national action plans (NAPs) for AMR, the competent authorities responsible for the monitoring and surveillance activities along the food chain, including the food production environment, should ensure collaboration with human health, animal health, plant/crop health, environment and other relevant authorities.

Activities related to monitoring and surveillance programme(s) should involve a wide range of relevant stakeholders who may contribute to the development, implementation and evaluation of integrated monitoring and surveillance.

Sharing of knowledge and monitoring and surveillance results with international organizations on a voluntary basis, should be encouraged since it may improve the global understanding of foodborne AMR and inform risk analysis.

It is important for competent authorities to have access to all available sources of relevant data in their country.

## 7. Preliminary activities for the implementation of an integrated monitoring and surveillance programme(s) for foodborne AMR

Preliminary activities for implementation are part of the framework for monitoring and surveillance programme(s). Undertaking pilot studies and testing provide valuable insights into the design of monitoring and surveillance programme(s).

Countries should strive for continuous improvement of monitoring and surveillance activities and progress according to country-specific objectives, priorities, infrastructure, technical capability, resources and new scientific knowledge.

## 8. Establishing the monitoring and surveillance objectives

The establishment of monitoring and surveillance objectives should be done in a consultative manner by the competent authorities and stakeholders and should take into consideration existing food safety programmes, the AMR NAPs, relevant information on AMR and AMU in the country, as well as any existing activities to address AMR in the different sectors (human, animal, plant/crop, food and the environment). Competent authorities should identify the challenges they currently face during the implementation of these activities.

The following aspects should be considered:

- The primary reasons for the data collection (e.g. to evaluate trends over time and space; to provide data useful for risk assessments; to obtain baseline information).
- The representativeness of the data collection (e.g. randomized samples; systematic sampling).
- The setting of proposed timelines for sampling and reporting.
- A description of how and to whom the information will be reported and communicated.



## 9. Considerations for prioritization

When establishing monitoring and surveillance priorities, the competent authorities should consider the epidemiology and public health implications of foodborne AMR, AMU patterns and available information on food production systems, food distribution, food consumption patterns and food exposure pathways.

Monitoring and surveillance priorities for microorganisms and resistance determinants, antimicrobial agents and sample sources should be informed by national, regional and international public health data and scientific knowledge where it exists. Competent authorities should identify existing data sources and data gaps on foodborne AMR and AMU including data required for risk analysis or results of risk analysis.

## 10. Infrastructure and resources

Once objectives and priorities have been established, competent authorities should determine the infrastructure, capacity and resources required to meet the objectives.

Implementation of AMR monitoring and surveillance may proceed at a different rate than that of AMU monitoring and surveillance and vice versa. As both types of data benefit from a joint analysis, it is useful if the components of the programme(s) are aligned during development to allow for integrated analysis. The evolution of integrated monitoring and surveillance programme(s) does not need to strictly follow the order described in these Guidelines.

As part of initial planning, the competent authorities should also consider where harmonization and standardization are required to meet monitoring and surveillance objectives. In order to optimize resources and efforts, the competent authorities should consider the possibilities of expansion and/or integration of monitoring and surveillance activities with other ongoing activities.

The competent authorities should also consider coordination of sampling and laboratory testing, collaboration with relevant stakeholders, and development of a plan for receiving, analysing, reporting and archiving data. When possible, a central repository facilitates data management and could improve the efficiency of data analysis.

# 11. Key design elements to be established before initiating the monitoring and surveillance activities

When designing the monitoring and surveillance programme(s), the following elements should be considered:

AMR:

- the highest priority microorganisms, panels of antimicrobials and sample sources to be targeted;
- points in the food chain and frequency of sampling;
- representative sampling methods, sampling plans, laboratory analysis and reporting protocols; and
- standardized and/or harmonized methodologies for sampling, testing and reporting.

AMU:

- antimicrobial distribution chains from manufacturing or import to end-user including sales/use data providers;
- identification of the appropriate points of data collection and the stakeholders that can provide the data;
- an assessment of the need to establish a legal framework before initiating collection and reporting of antimicrobial sales and use data in food producing animals and plants/crops may be useful; and
- the collection of AMU data may be started on a voluntary basis in agreement with stakeholders who have these data.

Consideration should be given to additional information provided in the OIE Terrestrial Animal Health Code and Aquatic Animal Health Code.

## 12. Components of integrated monitoring and surveillance programme(s) for AMR

This section is intended to provide an enabling framework which countries can utilize to establish integrated monitoring and surveillance of foodborne antimicrobial resistance appropriate to their national situation, and which includes considerations of available resources. As such, integrated monitoring and surveillance may vary between countries.

Integrated monitoring and surveillance programme(s) for foodborne AMR should consider the following elements:

- sampling design;
- sampling plans;
- sample sources;
- target microorganisms and resistance determinants;
- antimicrobials to be tested;
- laboratory testing methodologies and quality assurance systems; and
- data management activities.

The initial scope and design of the monitoring and surveillance programme(s) for AMR should consider previous research or surveillance findings, national priorities or national and/or international experience and agreed recommendations. As the AMR programme develops, the scope and design may be adjusted based on one or more of the following factors:

- monitoring and surveillance findings;
- epidemiology of antimicrobial-resistant microorganisms as available;
- risk profile and risk assessment findings; and
- evaluation of the integrated monitoring and surveillance programme(s).

## 13. Sampling design

The design of monitoring and surveillance programme(s) for AMR may build on or be integrated with existing monitoring and surveillance programme(s) or may involve development of new infrastructures and activities specifically for the purpose of foodborne AMR data collection. If data are collected through existing programmes designed for another purpose, this will need to be specified and the methodologies, data limitations and data interpretation should be described.

The sampling design should consider temporal and geographical coverage of data collection.

Once a sampling design is established, consistency in sample types and methodology is desirable to achieve long-term, comparability and accurate interpretation of results, especially when new methodologies are added and the programme is adjusted.

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### 13.1 Sampling plan

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The sampling plan should describe the following:

- The procedure to collect a sample from the selected sample source(s) at the selected point(s) in the food chain.
- Sample size, statistical methods and underlying assumptions (e.g. representativeness, frequency of recovery, the initial or expected prevalence of AMR in that microorganism and the size of the population to be monitored) of the data used to calculate the number of samples and isolates.
- Statistical power, precision and objectives of testing.
- Strengths and limitations that affect data interpretation.

The following elements should be considered in the sampling plan:

- Whether the sampling strategy is active (i.e. designed for AMR surveillance) or passive (i.e. using a system already in place).
- Target animal or plant/crop species, food commodities or food production environment.
- Point(s) in the food chain where the samples will be taken and sample type.
- Strata (levels) or risk clusters (groups) to best meet surveillance objectives.
- Opportunities to collect metadata if available.
- Target microorganisms, resistance phenotypes and resistance determinants.
- Frequency of sampling.
- Prevalence and seasonality of the microorganisms under study, if known.

- Standard operating procedures for sample collection:
  - who should collect the samples;
  - procedures for collection of samples in accordance with the defined sampling strategy and to guarantee that traceability, biosecurity and quality assurance are maintained from collection through to analysis and storage; and
  - procedures for storing and transporting the samples in order to maintain sample integrity for testing.

Initial implementation of the sampling plan may include a limited selection of sample sources at one or more specific points along the food chain.

As the programme(s) develop, and implementation advances according to priorities and resources, the sample sources within the sampling plan may be broadened. This may include additional animal or plant/crop species, production types, or food commodities or stages in the food chain to gradually be more representative of the populations of interest.

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## 13.2

### Sample sources

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When identifying the sample sources to be included in the monitoring and surveillance programme(s), consideration should be given to the major direct and scientifically relevant indirect food exposure pathways.

The selection of samples should reflect production and consumption patterns in the population and the likely prevalence of foodborne AMR. The prevalence of the bacterial species should be considered to maximize the likelihood of detection.

The integrated programme(s) should reflect food production in the country and cover samples from relevant stages of the food chain where there is science-based evidence that they could contribute to foodborne AMR. For integration, samples should be collected from the same species at the different but relevant points along the food chain. Samples should be, to the greatest extent possible, representative of the target animals and plants/crops species and the epidemiological unit being targeted. Possible sample sources are:

- **Food-producing animals**

Samples taken from healthy animals may be collected on-farm or at slaughter. Collection of samples from animals not immediately entering the food chain may provide additional information on foodborne AMR at the population-level but may be a lower priority than those animals directly entering the food supply.

- At the farm-level, samples may include faeces, feed, water, or other relevant food production inputs.

Consideration may be given to samples described in the *OIE Terrestrial Animal Health Code and Aquatic Animal Health Code*, specifically the chapters on *Harmonisation of National Antimicrobial Resistance Surveillance and Monitoring Programmes* and the *Development and Harmonisation of National Antimicrobial Resistance Surveillance and Monitoring Programmes for Aquatic Animals*.

- At slaughter, samples may include carcass swabs, caecal contents or lymph nodes. In some animal species, caecal contents or lymph nodes may be representative of the pre-slaughter environment and may or may not provide an estimate of AMR arising at the farm-level. Samples collected after slaughter (e.g. carcass) may provide an estimate of contamination arising from the slaughterhouse.

- **Food**

Food product samples may be collected at processing plants, packaging plants, wholesale or retail.

The place where the food samples are collected should reflect the production system in the country and the purchasing habits of the consumer (e.g. sampling open markets or chain stores).

At the retail-level, food samples may include raw meat, fish or seafood, dairy products, other edible tissues, raw produce, and minimally processed food products. Food selection may be modified periodically in order to capture multiple commodities, seasonality, or where products have been identified as high risk.

- **Plants/crops**

The selection of plants/crops should be risk-based and/or guided by the relevant standard setting bodies where available.

Samples may be collected from farms, pre-harvest or post-harvest.

- **Food production environment**

The selection of samples from the food production environment should be risk-based and relevant to the food production system.

Samples may be collected from the immediate environment of food-producing animals and plants/crops, processing plants, wholesale facilities or retail outlets.<sup>6</sup>

- **Target microorganisms and resistance determinants**

Selection of the target microorganisms and resistance determinants should be considered based on their relevance to food safety and public health.

Bacterial species may include:

- Foodborne pathogens such as *Salmonella*, *Campylobacter* or other food borne pathogens depending on national or regional epidemiology and risks.
- Indicator bacteria such as *Escherichia coli* and *enterococci* (e.g. *Enterococcus faecium* and *Enterococcus faecalis*), which can contaminate food and harbour transferable resistance genes.

Target microorganisms from aquatic animals and food of non-animal origin may be determined based on available scientific evidence and/or relevance to public health.

<sup>6</sup> E.g. soil, water, litter and bedding, organic fertilizers, sewage or manure.

The selection of target microorganisms should consider the presence of high priority AMR genes or mobile genetic elements and horizontal gene transfer in a given bacterial population.

Monitoring and surveillance programme(s) may begin with phenotypic susceptibility testing for AMR in representative foodborne pathogens and/or indicator bacteria. Options for expansion may include a broader range of foodborne pathogens, or indicator bacteria, testing for genetic determinants of resistance, virulence and mobile genetic elements.

Whenever possible, the characterization of bacterial isolates to the species-level and, as feasible, molecular analysis of particular isolates that may present a public health concern should be undertaken.

## 14. Laboratories

Laboratories participating in the monitoring and surveillance programme(s) should consider:

- a. Bacterial isolation, identification (to species and serotype level, where relevant), typing and antimicrobial susceptibility testing (AST) using standardized and validated methods performed by trained personnel.
- b. Laboratories should have quality assurance/management systems in place, or accreditation in accordance with national or international guidance.
- c. Participating in external quality assurance/management system testing including proficiency testing in identification, typing and AST of the microorganisms included in the monitoring and surveillance programme(s).
- d. Being equipped with facilities and having procedures to maintain sample integrity including appropriate storage temperatures and records that track the time between sample reception and analysis and ensure traceability.
- e. Storing isolates and reference strains using methods that ensure viability and absence of change in the characteristics and purity of the strain.
- f. Access to a national reference laboratory or an international laboratory that can provide technical assistance if necessary and carry out molecular characterization.

## 15. Antimicrobial susceptibility testing

Methods that are standardized and validated by nationally or internationally recognized organizations should be used where available.

## 16. Methods and interpretative criteria

Quality control strains of bacteria should be included and used according to international standards where available to support validation of results and data harmonization.

Interpretation of results for minimum inhibitory concentration (MICs) or disk diffusion, should be undertaken consistently according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) tables or the Clinical and Laboratory Standards Institute (CLSI) standards, and should include quantitative results (i.e. inhibition zone diameters including the disk content or MIC values). When neither tables nor standards are available, programme-specific interpretive criteria or categories may be used.

Categorization of the isolate and reporting of results may be undertaken based on the epidemiological cut-off values (ECOFFs) which should be reported as wild type, non-wild type or by clinical breakpoint which should be reported according to the interpretive category. The use of ECOFFs as interpretive criteria will allow for optimum sensitivity for detection of acquired resistance, temporal analysis of trends and comparability between isolates from different origins. Clinical breakpoints may differ between animal species and countries or regions. The interpretive criteria or category used should be included in the analysis and reporting of the data.

Raw quantitative data should be maintained in order to allow comparability of results, for early recognition of emerging AMR or reduced susceptibility in order to maximize the ability to analyse and compare results across sample sources.

Quantitative results are necessary for the analysis of resistance patterns over time and when retrospective data analysis is needed due to changes in clinical breakpoints or ECOFFs. Quantitative results are necessary for quantitative microbiological risk assessment.

## 17. The panel of antimicrobials for susceptibility testing

The panel of antimicrobials for phenotypic susceptibility testing should be harmonized within national monitoring and surveillance programme(s) as to ensure continuity and comparability of data. Attempts should be made to use the same antimicrobial class representatives across sample sources, geographic regions, and over time.

The antimicrobials included in the panel should depend on the target bacteria, the clinical or epidemiological relevance of these antimicrobials and should allow for the tracking of isolates with particular patterns of resistance.



The antimicrobials included may take into account the classes and uses in the relevant animal and/or plant/crop production sectors, as well as their influence in the selection or co-selection of resistance. Antimicrobials that would give the best selection of cross-resistance profiling should be considered for inclusion in the panel. Other antimicrobials which have the potential for co-selection of resistance due to gene linkage may also be included even if they are not used in animal and/or plant/crop production sectors.

Antimicrobials to be tested may be prioritized based on their higher priority ranking for human health, the national context, and/or their influence on the selection or co-selection of resistance.

## 18. Concentration ranges of antimicrobials

The concentration ranges used should ensure that both ECOFFs and clinical breakpoints, when available, are included to allow for the comparability of results with human data. The concentration range of each antimicrobial agent should also cover the full range of allowable results for the quality control strain(s) used for each antimicrobial agent.

## 19. Molecular testing

Whenever possible, molecular testing should be conducted for the detection and characterization of resistance determinants and for epidemiological analysis according to country-specific scenarios and resources.

Molecular testing may be useful in addressing or confirming inconclusive phenotypic results and may be used for the early detection or detection of resistant microorganisms of high public health importance.

For the rapid identification of resistance clusters and outbreak investigations, molecular characterization may be used. Molecular characterization in conjunction with epidemiological information, informs the determination of source and transmission chains, the detection of emergence and investigation of the spread of new resistant strains or resistance determinants, and source attribution by linking to molecular monitoring of pathogens or resistant microorganisms or resistance determinants across sectors.

Sequence data generated and stored with appropriate metadata may be used for retrospective and prospective surveillance.

Molecular methods may allow for the integration of resistance data with other relevant public health data (e.g. virulence determinants, AMR determinants).

## 20. Collection and reporting of resistance data

The information collected and recorded may differ depending on the stage of sampling along the food chain, sampling design and the specific monitoring and surveillance objectives. To ensure consistency, sampling information should be recorded at the isolate and sample level.

Information for each individual sample should include:

- a. reference to the general description of the sampling design and plan;
- b. specific information about the origin of the sample such as from what, where and when the sample was collected;
- c. general information to identify the isolate, bacterial species, serotype, other subtyping information as appropriate; and
- d. specific information about the isolation of the bacteria and the AST (e.g. date of testing, method used, quantitative results). In the case of qualitative results, the interpretative criteria should be recorded.

Reporting of results from the monitoring and surveillance programme(s) should be timely.

Sample sources, analytical methods, AST methods, and interpretive criteria should be clearly described, and differences transparently explained to show where data may not be directly comparable.

## 21. Components of integrated monitoring and surveillance programme(s) for AMU

For the purpose of these Guidelines, “antimicrobial use” and its abbreviation “AMU” are used to refer to antimicrobials intended for use as it relates to sales, prescriptions/orders, manufacturing, imports and exports, information on actual administration or application, or any combination of these antimicrobials used for food-producing animals or plants/crops. It is also important to note that antimicrobial sales data represent a summary of the volume of product sold or distributed through various outlets by the manufacturer intended for sale to the end user, not the volume of product ultimately purchased by the end user for administration to food-producing animals or application to plants/crops.

This section is intended to provide an enabling framework which countries can utilize to establish monitoring and surveillance of AMU appropriate to their national situation, and which includes considerations of available resources. As such, monitoring and surveillance activities and the data collection may vary between countries.

For the monitoring and surveillance of AMU, including sources of data and the collection and reporting of AMU data in food-producing animals, the OIE's *Terrestrial Animal Health and Aquatic Animal Health Codes* should be considered.

## 22. Design of an integrated monitoring and surveillance programme(s) for antimicrobial agents intended for use in food-producing animals or plants/crops

Each country may decide to collect different types of data, sales and/or use, according to their monitoring and surveillance objectives. The antimicrobial sales data collection may evolve into the collection of use data. The competent authority should consider the limitations of each type of data. Some aspects of data collection or reporting need to be specified for sales versus other types of use data; this is reflected below.

AMU data is important information to be considered during the interpretation of the results from the AMR monitoring and surveillance programme(s), along with other relevant epidemiological data.

Sales data may be used to monitor trends although sales data do not always reflect the real use, administration or application of antimicrobials.

The collection of data on the use of antimicrobials at farm/primary producer level, although it may be challenging and resource demanding, should be considered, as it can provide information on the magnitude of species-specific use and on how and why antimicrobials are being administered.

The choice of units of measurement<sup>7</sup> and/or indicators<sup>8</sup> for AMU should be established depending on method and scope of the data collection and the monitoring and surveillance objectives.

<sup>7</sup> Unit of measurement (i.e. numerator): a metric that expresses the quantities of antimicrobial agents.

<sup>8</sup> Indicator of AMU: a metric which combines a numerator with a denominator to contextualize the quantities of antimicrobial agents measured.

The following elements should be considered when deciding on the approach to collect sales and/or use data.

- a. Identification of the scope of the data to be captured (e.g. the antimicrobial agents, classes or sub-classes). The scope may also consider mechanisms of antimicrobial action, relevant resistance data and reporting requirements.
- b. Development of a protocol to collect qualitative (e.g. types of antimicrobials on farm) and/or quantitative information on the antimicrobials intended for use in food-producing animals or plants/crops.
- c. Harmonization of the nomenclature of antimicrobial agents with international standards, where available.
- d. Identification of the plant/crop type and/or species of food-producing animals for which the antimicrobials were intended to be used.
- e. Identification of the level of detail required to meet the surveillance requirements (e.g. production type, route of administration or reason for use).
- f. Information on antimicrobial dose, dosing interval and duration.
- g. Technical units of measurement for reporting antimicrobial sales or use.

## 23. Sources of AMU data

Sources of data may include:

- a. Sales data: may be collected from registration authorities, marketing authorization holders, wholesalers, veterinarians, retailers, pharmacies, feed mills, farm shops/agricultural suppliers, pharmaceutical associations, cooperatives or industry trade associations or any combination of these.
  - Import data: may be collected from the competent authorities in charge of registration of medicinal products, the marketing authorization holder or customs. Care must be taken to avoid double counting with sales data in the country and take into account that some imported antimicrobials may not be intended for use within the country.
- b. Use data: may be collected from farm/plant health professional records, livestock/plant production company records or estimated from veterinary prescriptions or farm surveys.

Data on quantities of antimicrobials sold or used within a country may differ. Differences may include loss during transport (package damage), storage (due expiry date) and administration (whole package not administered), stock purchased and held for future use, and fluctuations in animal or plant/crop populations.

## 24. Collection and reporting of AMU

### 24.1 Collection of data

The numerator may be an expression qualitatively describing AMU (e.g. classes of antimicrobials agents) or may be the antimicrobial quantity representing the amount of antimicrobial agents sold or used in food-producing animals and/or plants/crops. The calculation of the numerator should consider the quantities of antimicrobial agents which may be reported in different units of measurement according to monitoring and surveillance objectives and the types of data collected.

To interpret and/or analyse the data, considerations for the numerator may include identification of the antimicrobial agent or product, the quantity of packages sold or used, and the strength per unit.

The denominator, when used, is the total food-producing animal population or plant/crop area or quantities harvested that may be exposed to the antimicrobials reported during the monitoring and surveillance period. Relevance to the food production systems in the country may be considered. The denominator may provide the context for reporting and analysing the sales and/or use data.

Additional considerations for the denominator may include the characteristics of the population of food-producing animals or plants/crops treated with the relevant antimicrobial during the monitoring and surveillance period (e.g. species, type, number, body weight, age).

### 24.2 Reporting of data

Multiple units of measurement and/or indicators for reporting of sales and/or use may be appropriate depending on the national situation and the monitoring and surveillance objectives.

## 25. Integrated analysis and reporting of results

### 25.1 Management of data

To facilitate the management of data, database(s) should be structured, and where feasible, centralized or coordinated to allow for the appropriate and easy extraction of data when required and to accommodate expansion as the integrated monitoring and surveillance programme(s) improves.

A confidentiality and data management policy should be put in place. Data should be collected and stored to maintain data integrity and to protect the confidentiality of personal and proprietary information.

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## 25.2

### Analysis of results

To facilitate the management of data, ongoing or regular validation of the data should be considered.

A description of the sampling design(s) and sampling plan(s), such as stratification and randomization procedures, for the food-producing animals, plants/crops, food production environment or food categories, should be recorded to link data within and across monitoring and surveillance components.

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The data from the integrated monitoring and surveillance programme(s) may be analysed as described in CXG 77-2011 for risk assessment purposes and to inform the development and implementation of risk management options and policies to drive responsible and prudent use of antimicrobials to address foodborne AMR.

Analysis of data from the integrated monitoring and surveillance programme(s) may include the assessment within or between sectors across the One Health spectrum, to evaluate temporal or geographical trends over time, across host species, across bacterial species or antimicrobial classes. When available, other contextual information such as epidemiological data may be considered.

The detailed methodology and the epidemiological context of the monitoring and surveillance programme(s) should be considered for the analysis. Where data are available, exposure pathways among people, food-producing animals, plants/crops and their shared environment connecting resident bacterial populations may be incorporated into the analysis.

Data may originate from different monitoring and surveillance programme(s), so comparability is an important consideration. The choice of analytic approaches, when possible, should allow the investigation of relationships between AMU and AMR within or across food producing animals, plants/crops and human populations, provided that AMR and AMU data are representative of the target population. Integrated monitoring and surveillance of foodborne AMR should be harmonized, when possible, across these sectors to assist in the understanding of relationships between AMR and AMU, including other factors that may influence the emergence and spread of AMR.

AMR data from relevant human isolates may be considered for inclusion in the analysis and reporting based on information from significant foodborne pathogens according to national epidemiological information and, whenever possible, indicator flora.

Integration of data from surveillance of human clinical isolates should facilitate the ability to identify trends in resistance to specific antimicrobials important for use in human medicine, as well as to identify trends in the occurrence of resistance between humans, food-producing animals, plants/crops and/or food.

Statistical analysis should be used to ensure proper interpretation of results.

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## 25.3

### Reporting of results

Results of integrated monitoring and surveillance programme(s) should be reported regularly, where resources allow.

Whenever possible, reports on the integrated monitoring and surveillance programme(s) data across humans, animals, plants/crops, food and the food production environment should be made publicly available.

Transparent and open communication for the reporting of the results between the competent authorities and the different stakeholders including the public should be considered.

## 26. Evaluation of the integrated monitoring and surveillance programme(s)

Evaluation of the integrated monitoring and surveillance programme(s) provides assurance that the data and information reported are robust and the programme objectives are being met. The evaluation will also guide the best use of data collection resources.

Potential foodborne AMR risks to human health are subject to change over time. Evaluation and review should be undertaken at a frequency appropriate to integrate evolving monitoring and surveillance methodologies, identification of new resistance patterns, new exposure pathways along the food chain and changing patterns of AMU in humans, animals and plants/crops, and to respond to changing national priorities.

Competent authorities should develop a framework and plan to facilitate the evaluation and review of monitoring and/or surveillance activities, which may include the following:

- identify the skills needed by evaluators;
- describe the monitoring and surveillance programme(s) to be evaluated, including the objectives and desired outcomes. This may involve a specific or single component of the entire programme(s) (e.g. the sample collection, laboratories, analysis and reporting);
- identify relevant stakeholders for the evaluation;
- identify key performance criteria to be evaluated;
- collect data to facilitate evaluation based on the key performance criteria;
- consider relevant stakeholder input/feedback;
- report results of evaluation;
- draw conclusions on components of the evaluation;

- identify or provide identification of relevant monitoring and surveillance programme adjustments; and
- share evaluation outcomes with stakeholders.

If the design of the monitoring and surveillance programme(s) changes or expands, adjustments should ensure the ability of the programme(s) to identify trends over time remains, that historical data are maintained and that the programme continues to meet the established objectives.

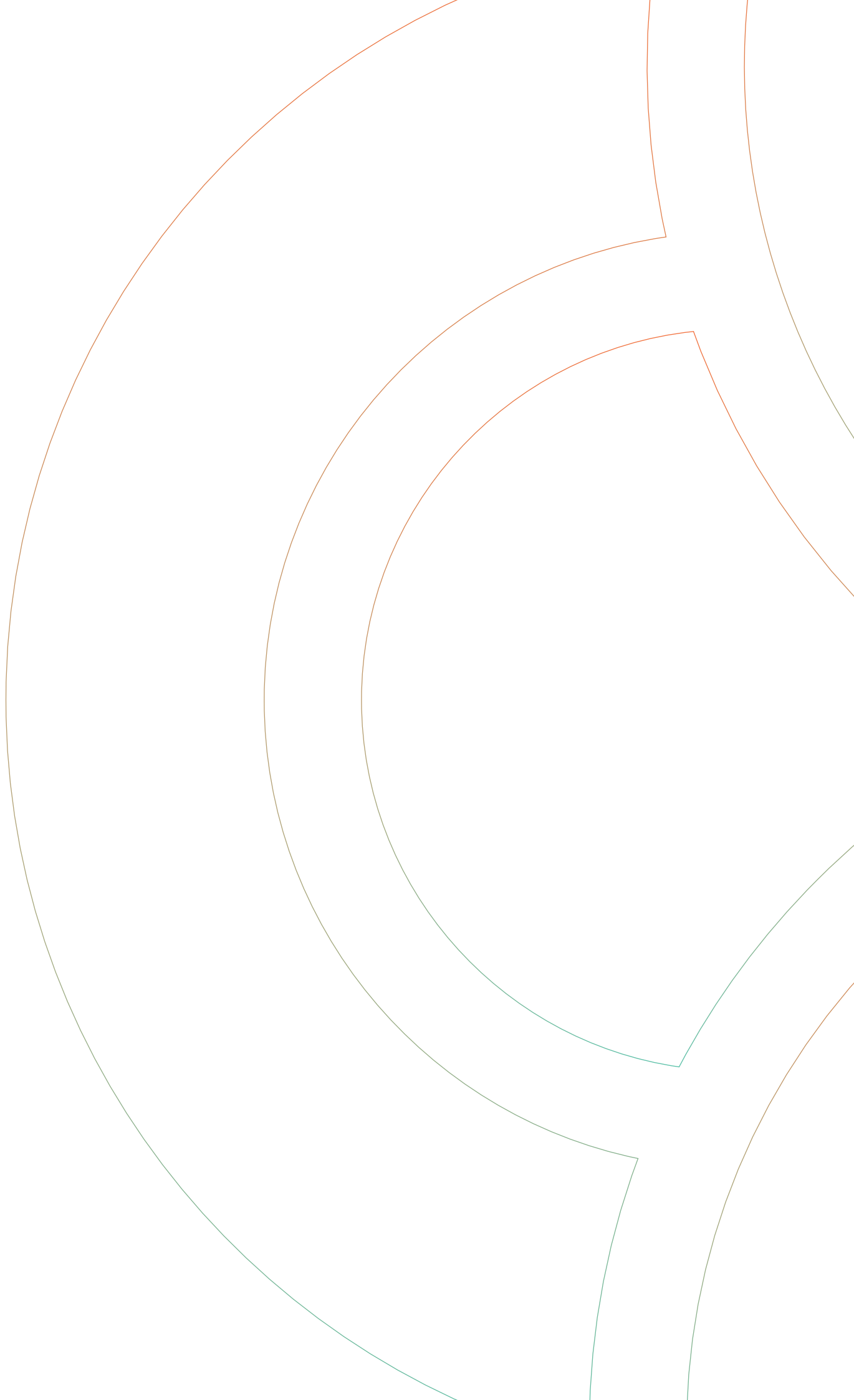
## 27. Training and capacity-building

Training and capacity-building are important components of the integrated monitoring and surveillance programme(s) and should be supported where possible, by the competent authorities.

Training of the relevant competent authorities should include different aspects of the monitoring and surveillance programme(s) (e.g. collection, analysis, interpretation and reporting of the data).

Training of relevant stakeholders at the national level on different aspects of the monitoring and surveillance programme(s) is recommended.







# CODE OF PRACTICE TO MINIMIZE AND CONTAIN FOODBORNE ANTIMICROBIAL RESISTANCE



TYPE

**CODE OF PRACTICE**  
CXC 61-2005

EDITION

ADOPTED 2005  
REVISED 2021





# CODE OF PRACTICE TO MINIMIZE AND CONTAIN FOODBORNE ANTIMICROBIAL RESISTANCE

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# 1. Introduction

Antimicrobial resistance (AMR) poses an important, complex, and priority global public health challenge. Along the food chain, there is a need to address the risks associated with development, selection and dissemination of foodborne resistant microorganisms and resistance determinants. Responsible and prudent use of antimicrobial agents in all sectors following a One Health approach and strategies for best management practices in animal production (terrestrial and aquatic), plant/crop production and food/feed processing, packaging, storage, transport, and wholesale and retail distribution should form a key part of multisectoral national action plans to address risks of foodborne AMR.

This Code of Practice addresses the responsible and prudent use of antimicrobial agents by participants in the food chain, including, but not limited to, the role of competent authorities, the pharmaceutical industry, veterinarians, and plant/crop health professionals, and food producers and processors. It provides guidance on measures and practices at primary production, and during processing, storage, transport, wholesale and retail distribution of food to prevent, minimize and contain foodborne AMR in the food supply. It also identifies knowledge gaps and provides guidance on communication strategies to consumers.

In keeping with the Codex mandate, this Code of Practice addresses antimicrobial use along the food chain. It is recognized that the use of antimicrobial agents along the food chain may result in exposure to antimicrobial resistant bacteria or their determinants in the food production environment. As part of a One Health approach to minimize and contain foodborne AMR, only authorized products should be used and best practices in the food production sector should be followed to minimize the occurrence/persistence in the food production environment of antimicrobials and their metabolites from food production related activities, and to minimize the risks associated with the selection and dissemination of resistant microorganisms and resistance determinants in the food production environment.

This Code of Practice is an integral part of risk analysis focusing on risk management options and should be read in conjunction with other Codex texts including the *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance* and the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* (CXG 77-2011). In addition, the *Code of Hygienic Practice for Fresh Fruits and Vegetables* (CXC 53-2003), the *Code of Practice on Good Animal Feeding* (CXC 54-2004), and the *Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes associated with the Use of Veterinary Drugs in Food Producing Animals* (CXG 71-2009) are particularly relevant for use of agricultural chemicals on plants/crops, animal feed, and veterinary drugs, respectively.

This Code of Practice provides risk management advice, including the responsible and prudent use of antimicrobial agents that can be applied proportionately to the risks identified through the risk analysis process described in the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*. Risk managers are responsible for prioritizing and assessing foodborne AMR risks appropriate to the country and determining how best to reduce risk and protect public health.

The *Principles and Guidelines for the Conduct of Microbiological Risk Management* (CXG 63-2007) contains guidance for developing and implementing risk management measures. Setting priorities and identifying risk management measures should take into account the following:

- *WHO Guidance on Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria, application of a One Health approach*;
- *WHO List of Critically Important Antimicrobials for Human Medicine*, specifically the Annex with the complete list of antimicrobials for human use, categorized as critically important, highly important and important;
- relevant chapters of the *OIE Terrestrial and Aquatic Animal Health Codes* and the *OIE List of Antimicrobial Agents of Veterinary Importance*; and
- national lists of important antimicrobials for humans and animals where they exist.

Where available, national and local guidelines to prevent, minimize and contain foodborne AMR should be taken into consideration. Best management practices and guidelines on the responsible and prudent use of antimicrobials developed by governmental and professional organizations should also be considered.

This document is designed to provide a framework, for the development of measures to mitigate the risk of foodborne AMR that countries may implement, as part of their national strategy on AMR, in accordance with their capabilities, based on their national priorities and capacities, and within a reasonable period of time. A progressive implementation may be used by some countries to properly apply elements in this document proportionate to the foodborne AMR risk and should not be used to generate unjustified barriers to trade.

## 2. Scope

This Code of Practice provides risk management guidance to address the risk to human health of the development and transmission of antimicrobial resistant microorganisms or resistance determinants through food. It provides risk-based guidance on relevant measures and practices along the food chain to minimize and contain the development and spread of foodborne AMR, including guidance on the responsible and prudent use of antimicrobial agents in animal production (terrestrial and aquatic) plant/crop production, and references other best management practices, as appropriate.

This document includes guidance for all interested parties involved in the authorization, manufacture, sale and supply, prescription and use of antimicrobial agents in the food chain together with those involved in the handling, preparation, food processing, storage, transport, wholesale and retail distribution and consumption of food who have a role to play in ensuring the responsible and prudent use of antimicrobial agents and/or who have a role with limiting the development and spread of foodborne antimicrobial resistant microorganisms and resistance determinants.



Most of the recommendations in this Code of Practice focus on antibacterials, however some recommendations may also be applicable to antiviral, antiparasitic, antiprotozoal, and antifungal agents, where there is scientific evidence of foodborne AMR risk to human health.

As there are existing Codex or internationally recognized guidelines, the following areas related to antimicrobial agents or AMR are outside the scope of this document: residues of antimicrobial agents in food; AMR marker genes in recombinant DNA plants/crops<sup>1</sup> and recombinant DNA microorganisms,<sup>2</sup> non-genetically modified microorganisms (for example, starter cultures) intentionally added to food with a technological purpose; certain food ingredients, which could potentially carry AMR determinants, such as probiotics;<sup>3</sup> and biocides. In addition, AMR from non-food animals, non-food plants/crops, or non-food routes are also outside the scope of this document.

### 3. Definitions

The relevant definitions presented in the Codex Procedural Manual, *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*, *General Principles of Food Hygiene* (CXC 1-1969), *Principles and Guidelines for the Conduct of Microbiological Risk Assessment* (CXG 30-1999) and *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance* are applicable to this document.

The following definitions are included to establish a common understanding of the terms used in this document:

**Antibacterial**

A substance that acts against bacteria.

**Antimicrobial agent**

Any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of microorganisms by interacting with a specific target.

**Antimicrobial resistance (AMR)**

The ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species.

1 The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA plants is addressed in the *Guidelines for the Conduct of Food Safety Assessment of Foods derived from Recombinant-DNA Plants* (CXG 45-2003).

2 The food safety assessment on the use of antimicrobial resistance marker genes in recombinant-DNA microorganisms is addressed in the *Guideline for the Conduct of Food Safety Assessment of Foods produced using Recombinant-DNA Microorganisms* (CXG 46-2003).

3 The food safety assessment on the use of probiotics in foods is addressed in the Report of the Joint FAO/WHO Working Group on drafting *Guidelines for the Evaluation of Probiotics in Foods* (FAO/WHO, 2002).

**Antimicrobial resistance determinant**

The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial agent. They are located either chromosomally or extra-chromosomally and may be associated with mobile genetic elements such as plasmids, integrons or transposons, thereby enabling horizontal transmission from resistant to susceptible strains.

**Control of disease/metaphylaxis**

Administration or application of antimicrobial agents to a group of plants/crops or animals containing sick and healthy individuals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease.

**Extra- or off-label use**

The use of an antimicrobial agent that is not in accordance with the approved product labelling.

**Food chain**

Production to consumption continuum including, primary production (food-producing animals, plants/crops, feed), harvest/slaughter, packing, processing, storage, transport, and distribution to the point of consumption.

**Food-producing animals**

Animals raised for the purpose of providing food to humans.

**Food production environment**

The immediate vicinity of the food chain where there is relevant evidence that it could contribute to foodborne AMR.

**Growth promotion**

Administration of antimicrobial agents to only increase the rate of weight gain and/or the efficiency of feed utilization in animals. The term does not apply to the use of antimicrobials for the specific purpose of treating, controlling, or preventing infectious diseases.

**Marketing authorization**

Process of reviewing and assessing a dossier to support an antimicrobial agent to determine whether to permit its marketing (also called licensing, registration, approval, etc.), finalized by granting of a document also called marketing authorization (equivalent: product licence).

**Medically important antimicrobials**

Antimicrobial agents important for therapeutic use in humans, taking into account the WHO List of Critically Important Antimicrobials for Human Medicine, including the classes described in the Annex of the “List of Medically Important Antimicrobials, categorized as Critically Important, Highly Important, and Important”, or equivalent criteria established in a national list, where available. It does not include ionophores or other agents determined not to be a foodborne AMR risk consistent with the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance.

**One Health approach**

A collaborative, multisectoral, and trans-disciplinary approach working with the goal of achieving optimal health outcomes recognizing the interconnection between humans, animals, plants/crops, and their shared environment.

### **Pharmacovigilance**

The collection and analysis of data on how products perform in the field after authorization and any interventions to ensure that they continue to be safe and effective. These data can include information on adverse effects to humans, animals, plants or the environment; or lack of efficacy.

### **Plants/crops**

A plant or crop that is cultivated or harvested as food or feed.

### **Plant/crop health professional**

An individual with professional or technical training, knowledge and experience in plant/crop health and protection practices.

### **Prevention of disease/prophylaxis**

Administration or application of antimicrobial agents to an individual or a group of plants/crops or animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the antimicrobial agent is not administered or applied.

### **Veterinary medical use<sup>4,5</sup>/phytosanitary use<sup>6</sup> (food-producing animals or plants/crops)**

Administration or application of antimicrobial agents for the treatment, control/metaphylaxis or prevention/prophylaxis of disease.

### **Treatment of disease**

Administration or application of antimicrobial agents to an individual or group of plants/crops or animals showing clinical signs of infectious disease.

## **4. General principles to minimize and contain foodborne antimicrobial resistance**

### **Principles on AMR Risk Management (generally)**

- Principle 1** A One Health approach should be applied, wherever possible and applicable, when identifying, evaluating, selecting, and implementing foodborne AMR risk management options.
- Principle 2** Considering that this document is to provide risk management guidance to address foodborne AMR risks to human health, for animal health and plant health aspects, relevant OIE and IPPC standards should be considered.

4 See also OIE Terrestrial Animal Health Code, specifically the chapter on Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals.

5 Also recognized as therapeutic use in some jurisdictions/organizations.

6 See also IPPC International Standard for Phytosanitary Measures, Glossary of Phytosanitary Terms.

- Principle 3** Foodborne AMR risk management measures should be implemented in a way that is proportionate to the risk and reviewed on a regular basis as described in the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*. Risk managers should consider potential unintended consequences to humans, animal, and plant health of recommended risk management measures.
- Principle 4** The *WHO List of Critically Important Antimicrobials for Human Medicine*, the *OIE List of Antimicrobial Agents of Veterinary Importance*, or national lists, where available, should be considered when setting priorities for risk assessment and risk management to minimize and contain AMR. The lists should be regularly reviewed and updated as necessary when supported by scientific findings as new scientific data emerges on resistance patterns.
- Principle 5** On a continuous and progressive implementation of risk management measures along the food chain to minimize and contain the possible risks associated with foodborne AMR, priority should be given to the most relevant elements from a public health perspective.

#### **Principle on preventing infections and reducing the need for antimicrobials**

- Principle 6** Biosecurity, appropriate nutrition, vaccination, animal and plant/crop best management practices, and other alternative tools where appropriate, and that have been proven to be efficacious and safe, should be considered to reduce the need for use of antimicrobial agents.

#### **Principles on the responsible and prudent use of antimicrobials (generally)**

- Principle 7** The decision to use antimicrobial agents should be based on sound clinical judgement, experience, and treatment efficacy. Where feasible and appropriate the results of bacterial cultures and integrated resistance surveillance and monitoring should also be considered.
- Principle 8** Medically important antimicrobials should be prescribed, administered, or applied only by, or under the direction of, veterinarians, plant/crop health professionals, or other suitably trained persons authorized in accordance with national legislation.
- Principle 9** Antimicrobial agents should be used as legally authorized and following all applicable label directions; except where specific legal exemptions apply.
- Principle 10** The choice of which antimicrobial agent to use should take into consideration relevant professional guidelines, where available, results of antimicrobial susceptibility testing of isolates from the production setting, where appropriate, and make adjustments to the antimicrobial agent selection based on clinical outcomes or when foodborne AMR risks become evident.
- Principle 11** Science-based species or sector-specific responsible and prudent antimicrobial use guidelines should be developed, implemented, and reviewed on a regular basis to maintain their effectiveness in minimizing the risk of foodborne AMR. Such guidelines could be included as a part of national action plans or stakeholder-led plans on AMR with development and dissemination shared among countries and organizations.

### **Principles on the use of antimicrobials in specific circumstances**

- Principle 12** Responsible and prudent use of antimicrobial agents does not include the use for growth promotion of antimicrobial agents that are considered medically important. Antimicrobial agents that are not considered medically important should not be used for growth promotion unless potential risks to human health have been evaluated through procedures consistent with the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*.
- Principle 13** Medically important antimicrobial agents should only be used for veterinary medical use/phytosanitary use (treatment, control/metaphylaxis or prevention/prophylaxis of disease).
- Principle 14** Medically important antimicrobials should only be administered or applied for prevention/prophylaxis where professional oversight has identified well-defined and exceptional circumstances, appropriate dose and duration, based on clinical and epidemiological knowledge, consistent with the label, and in line with national legislation. Countries could use additional risk management measures for medically important antimicrobials considered highest priority critically important as described in the *WHO List of Critically Important Antimicrobials for Human Medicine*, the *OIE List of Antimicrobial Agents of Veterinary Importance*, or national lists, where available, including restrictions proportionate to risk and supported by scientific evidence.
- Principle 15** When used for the control of disease/metaphylaxis, medically important antimicrobial agents should only be used on the basis of epidemiological and clinical knowledge and a diagnosis of a specific disease and follow appropriate professional oversight, dose, and duration.

### **Principle on surveillance of antimicrobial resistance and use**

- Principle 16** Monitoring and surveillance of the use of antimicrobial agents and the incidence or prevalence, and in particular trends, of foodborne AMR microorganisms and resistance determinants are among the critical factors to consider when developing risk management measures and evaluating the effectiveness of implemented risk management measures. Use of antimicrobial agents in humans, food-producing animals, and plants/crops and transmission of pathogens and resistance genes between humans, food-producing animals, plants/crops, and the environment are additional factors to consider, through the foodborne AMR risk analysis process described in the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*.

## 5. Responsible and prudent use of antimicrobial agents

The *OIE Terrestrial and Aquatic Animal Health Codes* and the *OIE List of Antimicrobial Agents of Veterinary Importance* contain detailed information with respect to the control of veterinary medicines for use in food-producing animals and aquaculture.

For more information on the data requirements for authorization of antimicrobial agents for food-producing animals see relevant national guidelines or internationally harmonized guidelines.

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### 5.1 Responsibilities of the competent authorities

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The competent authorities, including the authority responsible for granting the marketing authorization for antimicrobials for use along the food chain, have a significant role in specifying the terms of the authorization and in providing appropriate information to the veterinarian and plant/crop health professionals, or other suitably trained persons authorized in accordance with national legislation and producers through product labelling and/or by other means, in support of the responsible and prudent use of antimicrobial agents along the food chain. It is the responsibility of competent authorities to develop up-to-date guidelines on data requirements for evaluation of antimicrobial agent applications, as well as ensuring that antimicrobial agents used in the food chain are used in accordance with national legislation.

National governments in cooperation with animal, plant/crop, and public health professionals should adopt a One Health approach to promote the responsible and prudent use of antimicrobial agents along the food chain as an element of a national strategy to minimize and contain AMR. Good animal production (terrestrial and aquatic) and best management practices for plant/crop production, vaccination and biosecurity policies and development of animal and plant/crop health programmes at the farm level contribute to reduce the prevalence of animal and plant/crop disease requiring antimicrobial administration and can be incorporated into national strategies to complement activities in human health.

National action plans may include recommendations to relevant professional organizations to develop species or sector-specific guidelines.

In order to promote responsible and prudent use of antimicrobial agents, it is important to encourage the development, availability, and use of validated, rapid, reliable diagnostic tools, where available, to support veterinarians and plant/crop health professionals in diagnosing the disease and selecting the most appropriate antimicrobial, if any, to be administered/applied.

The competent authorities should determine appropriate labelling, including the conditions that will minimize the development of foodborne AMR while still maintaining efficacy and safety.

### **Quality control of antimicrobial agents**

Competent authorities should ensure that quality controls are carried out in accordance with national or international guidance and in compliance with the provisions of good manufacturing practices.

### **Assessment of efficacy**

Assessment of efficacy is important to assure adequate response to the administration of antimicrobial agents. As part of the marketing authorization process, the assessment should include the efficacy with optimal dosages and durations, supported by clinical trials, microbiological data (including antimicrobial susceptibility testing), pharmacokinetic (PK) data, and pharmacodynamic (PD) data.

### **Assessment of the potential antimicrobial agents to select for resistant microorganisms**

The competent authorities should assess the potential of medically important antimicrobial agents used along the food chain to select for foodborne AMR taking into account the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*, the *WHO List of Critically Important Antimicrobials for Human Medicine*, the *OIE List of Antimicrobial Agents of Veterinary Importance*, or national lists, where available.

### **Assessment of the impact on the food production environment**

In accordance with their national guidelines, competent authorities should consider results of foodborne AMR risk assessment of sources that contribute to the food production environment, e.g. reuse of wastewater for irrigation, and use of manure, and other waste-based fertilizers for soil fertilization. When a foodborne AMR risk is determined through the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance* the need for monitoring and proportionate risk management measures should be considered.

### **Establishment of a summary of characteristics for each antimicrobial product**

Competent authorities should establish a Summary of Product Characteristics or similar document for each authorized antimicrobial product. The information in these documents can be utilized in labelling and as a package insert. Such information may include:

- brand/chemical/drug name;
- product description;
- indications for use;
- dosage forms/strengths/application rates;
- duration of treatment or application interval;
- contraindications; warnings;
- adverse reactions/phytotoxicity/incompatibilities;
- product interactions and uses in specific populations for each authorized antimicrobial product, when available;
- withdrawal periods or pre-harvest intervals; and
- storage conditions.

### **Monitoring and surveillance programmes**

Competent authorities should establish systems for the monitoring and surveillance of foodborne AMR and antimicrobial use (AMU) following the *Codex Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance* and *OIE standards for monitoring of antimicrobial resistance and use in animals*.

Competent authorities should have in place a pharmacovigilance programme for the monitoring and reporting of suspected adverse reactions to veterinary antimicrobial agents, including lack of the expected efficacy that could be related to foodborne AMR. The information collected through the pharmacovigilance programme can contribute to a comprehensive strategy to minimize and contain foodborne AMR along the food chain.

In cases where the assessment of data collected from pharmacovigilance and from other post-authorization surveillance including, if available, targeted surveillance of foodborne AMR in veterinary or plant/crop pathogens, suggests that the conditions of use of the given antimicrobial agent marketing authorization should be reviewed, competent authorities shall endeavour to achieve this re-evaluation.

### **Distribution of antimicrobial products**

Competent authorities should make sure antimicrobial products are distributed through licensed/authorized distribution systems in accordance with national legislation.

Competent authorities should prevent illegal medicines and unapproved formulations from entering distribution systems.

### **Control of advertising**

Competent authorities should ensure that advertising and promotion of antimicrobial products is done in accordance with national legislation or policies.

Advertising and promotion of antimicrobial agents should be done in a manner consistent with specific regulatory recommendations for the product.

### **Training on foodborne antimicrobial resistance and the responsible use of antimicrobial agents**

Training should be supported, to the extent possible, by the competent authorities on topics related to minimizing AMR and encouraging the responsible use of antimicrobial agents. Training may take the form of communication and outreach and should be relevant to veterinarians and plant/crop health professionals, manufacturers and marketing authorization holders, wholesale and retail distributors, food animal and plant/crop producers, and other participants along the food chain as appropriate. Training and communication may broadly address other public health-related activities.



Relevant information may include, but is not limited to:

- information on disease prevention and management strategies to reduce the need to use antimicrobial agents;
- relevant information to enable the veterinarians and plant/crop health professionals to use or prescribe antimicrobial agents responsibly and prudently;
- the need to adhere to responsible and prudent use principles and using antimicrobial agents in production settings in agreement with the provisions of the marketing authorizations and professional advice;
- utilizing the *WHO List of Critically Important Antimicrobials for Human Medicine*; the *OIE List of Antimicrobial Agents of Veterinary Importance*, and national lists where they exist;
- information on appropriate storage conditions for antimicrobial agents before and during use and the safe disposal of unused and out-of-date antimicrobials;
- understanding relevant risk analysis of antimicrobial agent products and how to use that information;
- national action plans, if available, and international strategies to fight and control AMR;
- good AMU practices, antimicrobial prescription writing and establishment of withdrawal period;
- training in new methodologies for molecular analysis of resistance; understanding methods and results of susceptibility testing of antimicrobials and molecular analysis;
- the ability of antimicrobial agents to select for resistant microorganisms or resistance determinants that may contribute to animal, plant/crop, or human health problems;
- understanding the process of identifying, evaluating, implementing, and monitoring the effectiveness of risk management options; and
- the collection and reporting of AMR and AMU monitoring and surveillance data.

### **Knowledge gaps and research**

To further elucidate the risk from foodborne AMR, the relevant authorities could encourage public and private research in the following areas and not limited to:

- improve the knowledge about the mechanisms of action, pharmacokinetics and pharmacodynamics of antimicrobial agents to optimize the dosage regimens for veterinary medical use/phytosanitary use and their efficacy;
- improve the knowledge about the mechanisms of transmission, selection, co-selection, emergence and dissemination of resistance determinants and resistant microorganisms along the food chain;
- develop practical models for applying the concept of risk analysis to assess the public health concern precipitated by the development of foodborne AMR;
- further develop protocols to predict, during the authorization process, the impact of the proposed use of the antimicrobial agents on the rate and extent of foodborne AMR development and spread;

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## 5.2

### Responsibilities of manufacturers and marketing authorization holders

- assess the primary drivers leading to use of antimicrobials at the farm, sub-national, and national levels, and the effectiveness of different interventions to change behaviour and reduce the need to use antimicrobial agents in food production;
- improve the knowledge on behaviour change and on cost-effective interventions to reduce the need of antimicrobial agents;
- develop safe and effective alternatives to antimicrobial agents, new antimicrobial agents, rapid diagnostics, and vaccines; and
- improve knowledge on the role of the environment on the persistence of antimicrobial agents, and the emergence, transfer and persistence of foodborne AMR determinants and resistant microorganisms.

#### Collection and disposal of unused or out-of-date antimicrobial agents

The competent authorities should develop effective procedures for the safe collection and disposal of unused, substandard and falsified drugs, illegally marketed, or out-of-date antimicrobial agents.

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#### Marketing authorization of antimicrobial agents

It is the responsibility of the antimicrobial agent marketing authorization holders to:

- supply all the information requested by the national competent authority in order to establish objectively the quality, safety and efficacy of antimicrobial agents;
- ensure the quality of this information based on the implementation of procedures, tests and trials in compliance with the provisions of good manufacturing, good laboratory and good clinical practices; and
- utilize manufacturing standards/practices and comply with national regulations in order to minimize contamination of the food production environment.

#### Marketing and export of antimicrobial agents

Only officially licensed/authorized antimicrobial agents should be marketed, and then only through distribution systems in accordance with national legislation.

Only antimicrobial agents meeting the quality standards as specified in the legislation of the importing country should be exported.

The amount of antimicrobial agents marketed should be provided to the national competent authority when requested, and in addition, when feasible, information on estimated of types of use (e.g. treatment, control, prevention), route of administration and target species.

Package size and the concentration and composition of antimicrobial formulations should be adapted, as far as possible, to the approved indications of use in order to avoid improper dosing, overuse, and leftovers.

### **Advertising**

It is the responsibility of manufacturers and marketing authorization holders to advertise antimicrobial agents in accordance with the provisions of Section 5.1, and not to inappropriately advertise antimicrobial agents directly to producers.

Manufacturers and marketing authorization holders should not provide incentives that have a financial value to prescribers or suppliers for the purpose of increasing the use or sales of medically important antimicrobials.

### **Training**

It is the responsibility of the marketing authorization holders to support training on topics related to foodborne AMR and the responsible use of antimicrobial agents as described in Section 5.1, as appropriate.

### **Research**

It is the responsibility of the marketing authorization holders to supply required data to register antimicrobial agents including data regarding the safety and efficacy of products as appropriate.

Research on the development of new antimicrobials, safe and effective alternatives to the use of antimicrobials, rapid diagnostics and vaccines are encouraged.

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## **5.3 Responsibilities of wholesale and retail distributors**

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Wholesalers and retailers distributing medically important antimicrobial agents should only do so on the prescription of a veterinarian or order from a plant/crop health professional or other suitably trained person authorized in accordance with national legislation. All distributed products should be appropriately labelled.

Distributors should keep records of medically important antimicrobials supplied according to the national regulations and may include, for example:

- date of supply;
- name of responsible veterinarian or plant/crop health professional or other suitably trained and authorized person;
- name of medicinal product, formulation, strength and package size;
- batch number;
- quantity supplied;
- expiration dates;
- manufacturer name and address; and
- target species.

Distributors should support training, as appropriate, on topics related to foodborne AMR and the responsible use of antimicrobial agents using information provided by the competent authorities, manufacturers and marketing authorization holders, veterinarians and plant/crop professionals and other relevant entities as described in Section 5.1, as appropriate.

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## 5.4

### Responsibilities of veterinarians<sup>7</sup> and plant/crop health professionals

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Veterinarians and plant/crop health professionals should identify new or recurrent disease problems and develop strategies in conjunction with competent authority to prevent, control, or treat infectious disease at the national level. These may include, but are not limited to, biosecurity, improved production practices, proper animal nutrition and safe and effective alternatives to antimicrobial agents, including vaccination or integrated pest management practices where applicable/available.

Professional organizations should be encouraged to develop species or sector-specific guidelines on the responsible and prudent use of antimicrobial agents.

Antimicrobial agents should only be prescribed or administered when necessary, only as long as required, and in an appropriate manner.

- A prescription, order for application, or similar document for medically important antimicrobial agents should indicate the dose, the dosage intervals, route and the duration of the administration, the withdrawal period, when appropriate, and the amount of antimicrobial agent to be delivered, depending on the dosage and the characteristics of the individual or population to be treated, in accordance with national legislation. Prescriptions or orders should also indicate the owner and the location of the food-producing animals or plants/crops to which the antimicrobials are to be administered.
- All medically important antimicrobial agents should be prescribed or applied and used according to label directions and/or the direction of a veterinarian or consultation with a plant/crop health professional, and the conditions stipulated in the national legislation.
- Protocols for monitoring use to allow for data collection or for quality assurance purposes should be considered as recommended in the *Guidelines on Integrated Monitoring and Surveillance of Foodborne Antimicrobial Resistance*.

For food-producing animals, the appropriate use of medically important antimicrobial agents in veterinary practices is a clinical decision that should be based on the experience of the prescribing veterinarian, and epidemiological and clinical knowledge and, if available, based on adequate diagnostic procedures. When a group of food-producing animals may have been exposed to pathogens, they may need to be treated without recourse to a laboratory confirmed diagnosis based on antimicrobial susceptibility testing to prevent the development and spread of clinical disease.

For plant/crop production, the appropriate use of medically important antimicrobial agents to manage disease/pests should be based on the principles of integrated pest management (IPM), consultation with a plant/crop health professional, historical and epidemiological knowledge of the disease/pest situation and monitoring of the current disease/pest status. Only authorized products should be used following label directions. Alternatives to medically important antimicrobials should be considered when available and their safety and effectiveness has been determined. Medically important antimicrobial agents should only be used to the extent necessary for a specific disease and follow appropriate professional oversight, dose, and duration.

<sup>7</sup> Under some circumstances, this may refer to a suitably trained person authorized in accordance with national legislation, for example an Aquatic Animal Health Professional.

54. Determination of the choice of an antimicrobial agent should be based on:

- The expected efficacy of the administration based on:
  - the expertise and experience of the veterinarian, plant/crop health professional or suitably trained and authorized person;
  - the spectrum of the antimicrobial activity towards the pathogens involved;
  - the history of the production unit particularly in regard to the antimicrobial susceptibility profiles of the pathogens involved. Whenever possible, the antimicrobial susceptibility profiles should be established before the commencement of the administration. If this is not possible, it is desirable for samples to be taken before the start of the administration to allow for, if necessary, adjustment of therapy based on susceptibility testing. Should a first antimicrobial administration fail, or should the disease recur, the use of a second antimicrobial agent should ideally be based on the results of microbiological susceptibility tests derived from relevant samples;
  - the appropriate route of administration;
  - results of initial administration;
  - previous published scientific information on the treatment of the specific disease and available scientific knowledge on AMU and resistance;
  - evidence-based therapeutic guidelines, such as species or sector-specific guidelines on the responsible and prudent use of antimicrobial agents, if available; and
  - the likely course of the disease.
- The need to minimize the adverse health effect from the development of AMR based on:
  - the choice of the activity spectrum of the antimicrobial agent. Narrow-spectrum antimicrobials should be selected whenever possible/appropriate;
  - the targeting of specific microorganism;
  - known or predictable susceptibilities using antimicrobial susceptibility testing whenever possible;
  - optimized dosing regimens;
  - the route of administration;
  - the use of fixed combinations of antimicrobial agents (i.e. only combinations contained in authorized veterinary medicinal products) which are effective against the target pathogens; and
  - the importance of the antimicrobial agents to human and veterinary medicine.
- If the label conditions allow for flexibility, the veterinarian or plant/crop health professional should consider a dosage regimen that is long enough to allow an effective treatment but is short enough to limit the selection of resistance in foodborne and/or commensal microorganisms.

### **Off-label use**

For food-producing animals, the off-label use of a veterinary antimicrobial agent may be permitted in appropriate circumstances and should comply with the national legislation including the use of approved or appropriate withdrawal periods. It is the veterinarian's responsibility to define the conditions of use including the dosage regimen, the route of administration, and the duration of the administration and the withdrawal period.

Human health risk related to foodborne AMR should be an important factor when considering the off-label use of veterinary antimicrobial agents in food-producing animals.

Medically important antimicrobials should not be used off-label for plants/crops, except off-label use for emerging disease control, in accordance with national legislation.

### **Record keeping and recording**

For food-producing animals and plants/crops, records on antimicrobial agent prescription or application should be kept in conformity with national legislation or best management practice guidelines.

In particular, for investigation of AMR, veterinarians and plant/crop health professionals or suitably trained persons authorized in accordance with national legislation should:

- record the antimicrobial susceptibility testing results; when genomic information, when available; and
- record the antimicrobial used, the dosage and the duration; investigate adverse reactions to antimicrobial agents, including lack of expected efficacy, and report it, as appropriate, to the competent authorities (through a pharmacovigilance system, if available).

Veterinarians and plant/crop health professionals should also periodically review farm records on the use of antimicrobial agents to ensure compliance with their directions.

Veterinarians and plant/crop health professionals may have a role to play assisting the competent authorities in monitoring and surveillance programmes related to AMU and AMR as appropriate.

### **Training**

Professional or other organizations should support the development and/or delivery of training on issues related to AMR and the responsible use of antimicrobial agents as described in Section 5.1, as appropriate.

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## 5.5 Responsibilities of food animal and plant/crop producers

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Producers are responsible for implementing health programmes on their farms to prevent and manage disease outbreaks with assistance of veterinarians, plant/crop health professionals, or other suitably trained persons authorized in accordance with national legislation. All participants involved in primary production of food have an important role to play in preventing disease and reducing the need to use antimicrobials agents to minimize and contain the risk of foodborne AMR.

Producers of food animals and plants/crops have the following responsibilities:

- to use antimicrobial agents only when necessary, under the supervision of a veterinarian or plant/crop health professional when required, and not as a replacement for good management and farm hygiene practices, or other disease prevention methods;
- to implement a health plan in cooperation with the veterinarian, plant/crop health professional, or other suitably trained person authorized in accordance with national legislation that outlines measures to prevent disease;
- to use antimicrobial agents in the species, for the uses and at the doses on the approved labels and in accordance with the prescription, product label instructions or the advice of a veterinarian, plant/crop health professional or other suitably trained person authorized in accordance with national legislation familiar with the food-producing animals or the plant/crop production site;
- to isolate sick and dying animals, dispose of dead animals, diseased plants/crops promptly under approved condition by competent authorities;
- to comply with the storage conditions of antimicrobial agents according to the approved product labelling;
- to comply with the recommended withdrawal periods or pre-harvest intervals;
- to not use out-of-date antimicrobial agents and to dispose of all unused or out-of-date antimicrobial agents in accordance with the provisions on the product labels and national legislation;
- to inform the veterinarian, plant/crop health professional, or other suitably trained person authorized in accordance with national legislation in charge of the production unit of recurrent disease problems or suspected lack of efficacy of antimicrobial applications;
- to maintain or have their veterinarian, plant/crop health professional, or other suitably trained individual maintain all clinical and laboratory records of microbiological diagnosis and susceptibility testing. These data should be made available to the professional in charge of the administration in order to optimize the use of antimicrobial agents;

- to keep adequate records of all antimicrobial agents used, including, for example, the following:
  - copy of the prescription, order for application or other documentation, when available;
  - name of the antimicrobial agent/active substance and batch number;
  - name of supplier;
  - date of administration; species and number of animals or plants/crops;
  - identification of the production unit to which the antimicrobial agent was administered;
  - disease treated, prevented, or controlled;
  - relevant information on animals or plants/crops treated (number, age, weight);
  - quantity/dose and duration of the antimicrobial agent administered;
  - withdrawal periods or pre-harvest intervals;
  - result of treatment, in consultation with the veterinarian or plant/crop health professional; and
  - name of the prescribing veterinarian, plant/crop health professional or other suitably trained person authorized in accordance with national legislation.
- to ensure sound management of wastes and other materials to minimize dissemination of excreted antimicrobial agents, resistant microorganisms and resistance determinants into the environment where they may contaminate food;
- to address on-farm biosecurity measures and take infection prevention and control measures as appropriate and as provided in the *OIE Terrestrial and Aquatic Animal Health Codes*;
- to participate in training on issues related to AMR and the responsible use of antimicrobial agents as described in Section 5.1, as appropriate; and
- to assist the relevant authorities in surveillance programmes related to AMU and AMR, as appropriate.

The responsible and prudent use of antimicrobial agents should be supported by continuous efforts in disease prevention to minimize infection during production. Efforts should aim to improve health, thereby reducing the need for antimicrobial agents. This can be achieved by, for example, improving hygiene, biosecurity, health management on farms, improving animal and plant/crop genetics, and implementing national or international good animal production (terrestrial and aquatic), and plant/crop production practices.

Disease prevention through the use of vaccines, and other measures that have been clinically proven to be safe and efficacious for supporting animal health, such as adequate nutrition can be considered and applied when appropriate and available.

Prevention and reduction of the incidence and severity of plant pests and diseases should be implemented by applying good agricultural practices, such as crop rotation, accurate and timely diagnosis and monitoring of diseases, use of disease resistant crop varieties, exclusionary practices that prevent introduction of pathogens into a crop, careful site selection IPM strategies and biological controls when appropriate and available.



## 6. Practices during production, processing, storage, transport, retail and distribution of food

Concerted efforts of all stakeholders along the food chain are required to minimize and contain foodborne illness, including illness related to foodborne AMR. While this Code focuses on responsible and prudent use of antimicrobial agents in primary production at the farm level, the later phase of the food chain also plays an important role in preventing foodborne AMR infection and illness.

The food processing industry and food retailers should refer to the *Principles and Guidelines for the Conduct of Microbiological Risk Management*.

Food should be produced and handled in such a way as to minimize the introduction, presence and growth of microorganisms, which apart from having the potential to cause spoilage and foodborne illnesses can also disseminate foodborne AMR. Slaughterhouses and processing plants should follow good manufacturing practices and the Hazard Analysis and Critical Control Points (HACCP) principles. The *General Principles of Food Hygiene* is a useful reference in this respect.

Food business operators should provide training on good hygienic practices, including those for minimizing cross-contamination. The *WHO Five Keys to Safer Food* contains useful information for food handlers to minimize the transmission of foodborne illness, including resistant infections.

## 7. Consumer practices and communication to consumers

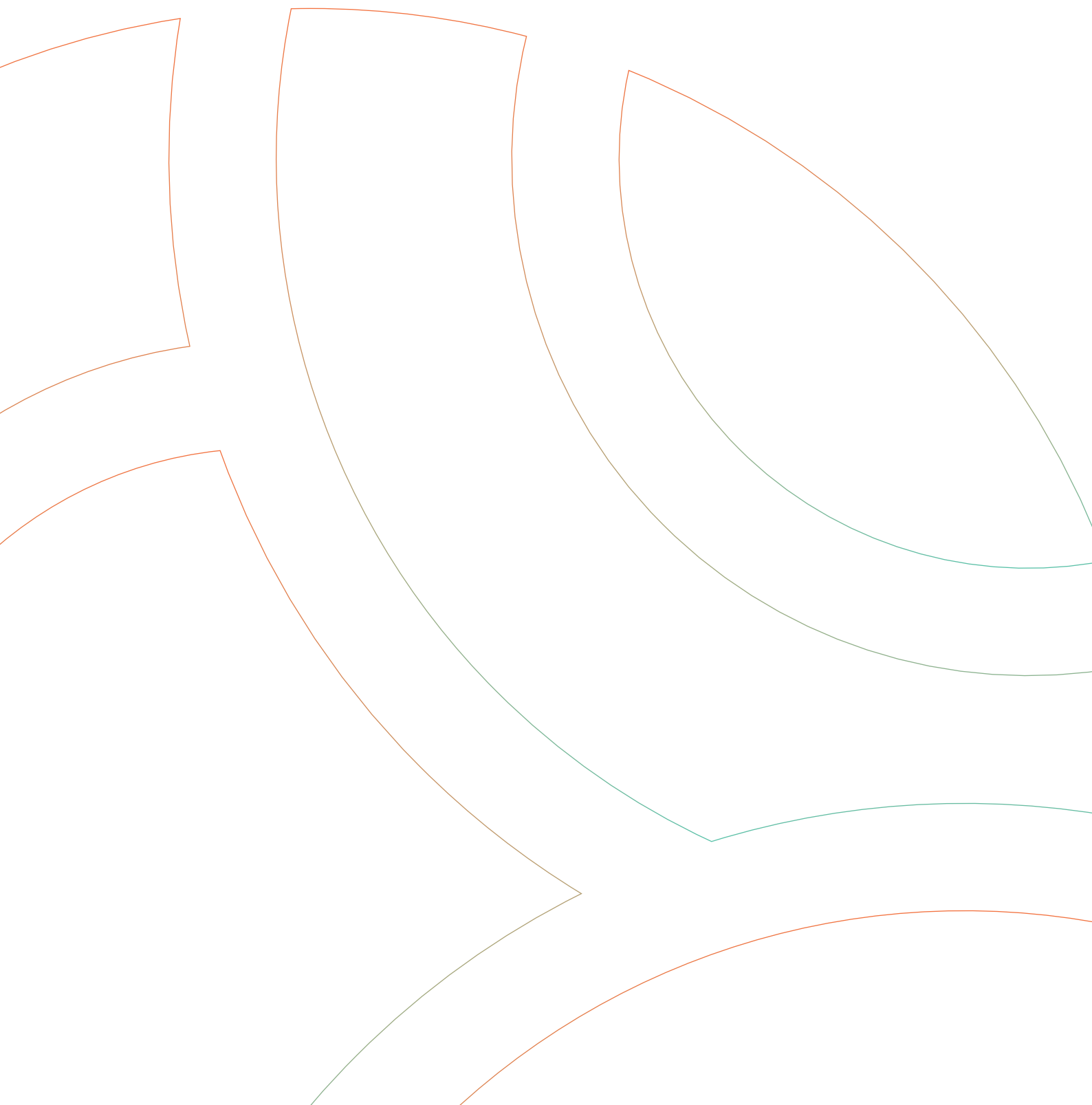
Government, food industry and other stakeholders along the food chain should inform and educate consumers on the risks of foodborne illness, including infections with resistant microorganisms and ways to minimize the risk of infection.

Some aspects to consider when communicating to consumers are:

- identifying all the stakeholders and having a common message;
- providing information that is science-based, clear, accessible, and targeted to a non-scientific audience; and
- considering local characteristics that affect how risks are perceived (e.g. religious belief, traditions).

Various manuals from international organizations, such as the FAO, WHO and OIE can be used as tools to assist in awareness-raising for consumers on how to minimize foodborne bacteria in their food.

For more information on risk communication refer to *WHO Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria, Application of a One Health approach*; *FAO/WHO Risk Communication applied to Food Safety Handbook*, and the *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011)*.











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