codex alimentarius commission

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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

Agenda Item 4 **CX/AMR 09/3/4**
June 2009

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

***AD HOC* CODEX INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE**

Third Session

Jeju, Republic of Korea, 12-16 October 2009

PROPOSED DRAFT GUIDELINES FOR RISK ANALYSIS OF FOODBORNE ANTIMICROBIAL RESISTANCE (N01-2008, N02-2008, N03-2008)

At Step 3

(prepared by the electronic Working Group led by the United States of America)

Governments and international organizations in Observer status with the Codex Alimentarius Commission wishing to submit comments at Step 3 on the proposed draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (Annex I to this document) are invited to do so **no later than 1 September 2009** as follows: Secretariat, *Ad Hoc* Codex Intergovernmental Task Force on Antimicrobial Resistance, Food Microbiology Division, Korea Food and Drug Administration, Eunpyeonggu, Seoul, 122-704, Republic of Korea (Telefax: + 82-2-355-6036, E-mail: kwakhyos@kfda.go.kr ***preferably***), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (Telefax: +39 06 5705 4593; E-mail: Codex@fao.org - ***preferably***).

BACKGROUND

1. The 2nd Session of the Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance (2nd TFAMR) made significant progress on the development of three documents, one each on risk assessment, risk profiling, and risk management, but noted that some sections in these documents and in the proposed structure were not complete and required further development. The Task Force agreed to establish an electronic working group (eWG), hosted by the U.S., open to all Members and Observers and working in English only, to prepare a consolidated document entitled, "Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (AMR)."

PROCEEDING OF THE WORKING GROUP

2. Twenty-six Members /Observers (Argentina, Australia, Belize, Canada, Costa Rica, Denmark, European Community, France, Germany, Ireland, Japan, Korea, Mexico, New Zealand, Norway, United Kingdom, Poland, Spain, Sweden, and United States, Consumers International, European Medicines Agency, International Dairy Federation, International Commission on Microbiological Specifications for Foods, International Federation for Animal Health and World Organization for Animal Health) either expressed an interest in or participated in the eWG. Subsequent to the 2nd TFAMR, Circular Letter CL2008/33-AMR (CL) was issued along with the report from the meeting and call for comments by February 28. These comments were forwarded by the Codex Secretariat to the U.S. In May 2009, the U.S. distributed to the eWG a draft consolidated document incorporating all comments that were submitted in response to the CL and solicited additional comments on the consolidated document. Based on comments to the May draft, the U.S. has prepared for further consideration by the Task Force the attached "Proposed Draft Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (AMR)".

GENERAL COMMENTS ON THE DRAFT DOCUMENT

3. The eWG is very appreciative of the many constructive comments received from Members and Observers through both the February 2009 comment period, as well as through the May 2009 comment period of the eWG. All comments have resulted in an improved document, even though the inclusion and reconciliation of some of the comments have resulted in significant modifications of the pre-existing text in some sections.

4. The eWG tried to preserve previously agreed language as much as possible, except where there were obvious repetitions or inaccuracies. Members and Observers are encouraged to resubmit any comments that they believe might need to be reconsidered for the next meeting of the Task Force.

5. In order to present a readable draft guideline, the eWG has removed all brackets from the text because 1) it believed the comments received have adequately resolved the issues, or 2) the brackets were no longer meaningful in the context of the revisions to the text. Readers may wish to review Appendix II of the CL to identify bracketed text from the 2nd TFAMR.

DETAILED DISCUSSION ON THE DRAFT DOCUMENT

Introduction and Scope

6. As part of creating a consolidated document, it was determined by the 2nd TFAMR that a single Introduction should be drafted. The eWG noted that each of the three original documents also contained a "Scope"; however, the information provided in each of the "Scope" sections was specific for each original portion of the risk analysis process. Consequently, a new "Scope" section was drafted for the consolidated document and should be reviewed by the Task Force. The heading "Scope" was dropped from the individual sections, but the information was retained in each section for further discussion and possible deletion.

General Principles

7. There was a consensus at the 2nd TFAMR to combine the General Principles into a single section that applies to AMR Risk Analysis. In an effort to remove redundancy with existing Codex documents, those General Principles inherent to all Codex risk analysis were replaced by an introductory paragraph referencing such work. The remaining General Principles are those that specifically apply to AMR risk analysis.

8. The eWG noted that some delegations proposed a new General Principle to address animal health and welfare, and that others agreed that animal health, animal welfare, and environmental factors are important, but are likely outside the mandate of this Task Force. The Codex Procedural Manual states that risk management "…decisions should be based on risk assessment, and take into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in food trade…." Therefore, the eWG elected not to include these areas as a General Principle for AMR Risk Analysis, but to address such concerns in the risk management section, specifically as a factor to be considered by risk managers in the evaluation of Risk Management Options (RMOs) (see paragraph 108).

Organization of Risk Management Activities

9. Two approaches that have been considered for the organization of the consolidated document: 1) provide a chronological approach, in which the risk analysis activities are discussed on a step-by-step basis in the same order in which they would be carried out by risk managers; or 2) group the activities by function in which the two main activities are grouped into risk management and risk assessment. There are pros and cons to each approach. The first approach (step-by-step discussion) may be easier to follow for users of the document; the second approach (function-based discussion) may provide less redundancy and overlap concerning coordination of risk management activities that are performed throughout the process. A preference for the second approach was expressed at the 2nd TFAMR. However, during harmonization of the document and in light of comments from multiple delegations, the first approach was utilized by the eWG. The merits of the two approaches should be discussed at the next Task Force meeting after members have reviewed the consolidated document.

Long document/specific to AMR vs. short document/more general

10. In the course of consolidating and harmonizing the guideline and considering the responses to the CL, the eWG noted that the length of the document was long compared with similar Codex guidelines. It

believes the reason for the length is the considerable detail that this draft contains (e.g., Appendix 1 and 2), as well as overlap with existing Codex texts. Some overlap is unavoidable and even necessary to adapt risk analysis methodology to AMR, and to make the guideline complete and coherent. Also, a guideline with additional detail may provide risk managers with more useful information in addressing AMR food safety issues. To that end, a balance was sought between a need for brevity without compromising the utility of the document. The eWG chose to eliminate redundant text in some cases, but maintained text specific to AMR or adapted some text to be specific to AMR. However, pending discussions in the Task Force, further condensation and focus on AMR-specific issues may be beneficial.

Risk Communication

11. Although there is little debate concerning the importance of risk communication in all risk analysis activities, it is difficult to develop a section on risk communication specific to AMR. The current text in the document provides an excellent summary of the principles of risk communication in food safety risk analysis; it is general in nature and not specific to AMR risk analysis. Further, the current text is similar to text in adopted Codex guidelines on risk communication/risk analysis. The Task Force should consider the overall approach to the comprehensiveness of the guideline (see paragraph above) and determine whether the existing text on risk communication should be revised to make it more AMR specific.

References

12. Many in the eWG agreed that references should be eliminated in the document and retained in a separate section at the end of the document, but some requested that references be retained both in the appropriate locations in the document as well as in a later section. For now, references are retained both within the document and in a section at the end of the document for further consideration by the Task Force.

Elements of a Risk Profile

13. Comments received in response to the CL, as well as those received from Members of the eWG, revealed much confusion about the scope and content of a risk profile. To address these comments, the risk profile section was modified to reinforce the concept that a risk profile is an information-gathering exercise and not an "abbreviated" risk assessment. These changes included eliminating the concept of an "abbreviated" risk profile, and replacing Appendix 1 (which contributed to the confusion by having significant overlap with the listed elements for a risk assessment that were provided in Appendix 2) with a list of five bullet points describing the fundamental elements of a risk profile. These five points were previously those listed as the key elements for an abbreviated risk profile. The listing of fundamental elements for a risk profile provides additional emphasis on the point that a risk profile must be flexible to fit the nature of the food safety issue, yet still provide sufficient information to inform decision-making on the next actions to be taken by risk managers. The Task Force should consider whether this approach clarifies the concept of a risk profile and if there remains a role for an abbreviated risk profile.

Broad Risk Management Goals

14. There was significant discussion concerning the role of this step in preliminary risk management activities. The eWG believes the setting of risk management goals should not be limited to this step, but be part of risk management decision-making throughout the risk analysis process. Goal setting should occur at steps before the risk profile; during preliminary risk management activities; and prior to the onset of the identification, selection, and evaluation of risk management options. The intent of establishing goals at this particular step is to incorporate the information gathered up to this point in time and refine existing goals to determine the most appropriate activities to address the food safety issue. In response to many conflicting comments, the eWG retained much of the language that was in the document, pending additional discussion at the next Task Force meeting.

Figure 2, Schematic showing the scope and relationship of the components of AMR risk assessment

15. Some delegations suggested deleting the bottom portion of Figure 2; others supported the current figure with some added revisions and language for the legend. The key issue is whether Figure 2 adequately illustrates the relationship between the four general steps (Codex) of risk assessment (shown in the top part of the figure) and aspects of resistance selection and dissemination (shown in the bottom part of the figure). The intent of the original figure was to show the Codex risk assessment process tailored to AMR, as well as to emphasize the need for considering the factors in the "release assessment" of the OIE risk assessment process. Based on comments received in the eWG, a modified version of the figure was drafted by the U.S.

and included in the current version of the document. The Task Force should consider whether the new version of the Figure meets the intent, or whether the original figure should be restored.

Figure 3, Schemes for hazard characterization in AMR risk assessment

16. Some delegations suggested deleting this figure because they believe it does not adequately describe this portion of the risk assessment. At this time, the figure is retained with minor revisions. A decision on Figure 3 should be made at the next meeting of the Task Force.

Placement of supplemental RMOs

17. Since the initial draft of the risk management document, a long list of supplemental RMOs has been embedded within the section on "Identification of risk management options." Identification of RMOs is one of five steps described for risk managers in Food Safety Risk Analysis (FAO #87) along with evaluation, selection, implementation, and monitoring and review. There was discussion at the 2nd TFAMR and in comments received to the CL and eWG about the need to provide a better description of the process for identifying, evaluating, selecting, implementing, and monitoring and review of RMOs with emphasis on aspects related to AMR. Several comments indicate the presence of a substantial list of options within one of the five sections impedes the flow of describing the process. Solutions to this problem include: moving the RMOs to an appendix, placing them in a table, and finding another way to set them apart from the description of the process. After discussions in the eWG, the U.S. drafting group adopted a table proposed by the EC with brief descriptions of each RMO and placed it in the main body of the text prior to the description of the process. The Task Force should consider whether the brief descriptions adequately describe the RMOs or whether additional detail is needed. If additional detail is required, the use of an appendix may need to be re-evaluated to maintain readability of the document.

Monitoring of RMOs vs. surveillance of AMR

18. Comments to the CL and the eWG continue to indicate confusion about the difference between monitoring and review of RMOs and monitoring and surveillance of antimicrobial usage and AMR microorganisms and resistance determinants. RMOs described in the draft document from the 2nd TFAMR blur this distinction. As a result, the U.S. drafting group retained text specific to the monitoring and review of RMOs in Section 8.5 and developed a new section to address monitoring and surveillance of antimicrobial usage and AMR microorganisms and resistance determinants. The eWG believes that the latter activity is fundamentally different from the component of risk management and overlaps areas of risk analysis, including risk assessment. The Task Force should review this new section.

RECOMMENDATIONS TO THE 3rd SESSION OF THE TASK FORCE

19. The revised document (included in Annex I) should be distributed to the Codex members and observers for comments at Step 3, further consideration at the Third Session of the Task Force and be advanced through the step procedure of Codex.

Annex I

PROPOSED DRAFT GUIDELINES FOR RISK ANALYSIS OF FOODBORNE ANTIMICROBIAL RESISTANCE
(N01-2008, N02-2008, N03-2008)

At Step 3 of the Procedure

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INTRODUCTION

1. Antimicrobial resistance (AMR) is a major global public health concern and a food safety issue. When pathogens become resistant to antimicrobials, 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. AMR is inherently related to antimicrobial use in any environment, including human and non-human uses. The use of antimicrobials in food-producing animal/crops provides a potentially important risk factor for development and spread of resistant microorganisms and AMR determinants from animals/food crops to humans via the consumption of food.

2. In accordance with Codex principles, risk analysis is an essential tool in assessing the overall risk to human health from foodborne antimicrobial resistant microorganisms and determining appropriate risk mitigation 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 concurred that antimicrobial resistant foodborne microorganisms are possible microbiological food safety hazards. Consequently, the need for the development of a structured and coordinated approach for AMR risk analysis has been emphasized (FAO/OIE/WHO, 2003, 2004, 2006, and 2008). The WHO/FAO and OIE guidelines on risk analysis provide broad, structured approaches to address the potential public health impact of antimicrobial resistant microorganisms of animal origin *via* food (WHO/FAO, 2006, and OIE, 2008). However, 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 mitigation strategies, this guideline document presents a consolidated framework specific to AMR risk analysis.

3. More specifically, this guideline provides a structured risk analysis framework to address the risks to human health associated with the presence in food and animal feed, and the transmission through food and animal feed, of antimicrobial resistant microorganisms or resistance determinants linked to non-human use of antimicrobials. This document describes the steps to be used by Codex or national/regional authorities in conducting risk analysis activities as they relate to AMR.

4. The initial phase of the framework consists of a group of tasks collectively referred to as preliminary risk management activities. A systematic preliminary risk management process brings the food safety issues into focus and provides a guide for further actions. The second phase of the framework is the conduct of a risk assessment that provides a transparent, science-based approach that characterizes the exposure pathways, the adverse health effects, and the human health impact associated with specific foodborne exposures to the antimicrobial resistant microorganisms of concern. The third phase of the framework includes identification, selection, and implementation of appropriate risk management actions to minimize and contain the identified human health risks. Good communication between risk assessors and managers as well as with other interested parties should be in place for a transparent and informed risk analysis.

5. This document should be read in conjunction with the Working Principles for Risk Analysis for Food Safety for Application by Governments (CAC/GL 62-2007), the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999), the Principles and Guidelines for the Conduct of Microbiological Risk Management (CAC/GL 63 - 2007), and the Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005). Risk analysis of AMR on animal feeds may also consider Codex Code of Practice on Good Animal Feeding (CAC/RCP 54-2004), as well as Animal Feed Impact on Food Safety (FAO/WHO, 2008a) and the chapters 6.5 to 6.8 related to the control of AMR for the Terrestrial Animal Health Code (OIE).

SCOPE

6. The scope of this guideline is to provide science-based guidance on methodology and processes for risk analysis and its application to non-human use of antimicrobials. The intent of the guideline is to address the risks to human health associated with the presence in food and feed including aquaculture and the transmission through food and feed of antimicrobial resistant microorganisms and AMR determinants and to develop appropriate risk management advice based on that assessment to reduce such risk. The guideline will further address the risks associated with different areas of use of antimicrobials such as veterinary applications, plant protection or food processing.

7. As there are existing Codex or internationally recognized guidelines, the following uses of antimicrobials are outside the scope of the guideline: residues of antimicrobials in food; AMR marker genes in recombinant-DNA plants and recombinant DNA microorganisms; non-genetically modified microorganisms (for example, starter cultures) intentionally added to food with a technological purpose; and certain food ingredients which could potentially carry AMR genes such as probiotics.

DEFINITIONS

8. The following definitions are included to establish a common understanding of the terms used in this document. The definitions presented in the Principles and Guidelines for the Conduct of Microbiological Risk Assessment (CAC/GL 30-1999) are applicable to this document. Definitions established by Codex appear in *italics*. Definitions cited from existing FAO/OIE/WHO documents are referenced as appropriate.

Adverse Health Effect – An undesirable or unwanted outcome in humans. In this document, this refers to the human infections or their frequency caused by antimicrobial resistant microorganisms and resistance determinants in food or acquired from food of animal/plant origin as well as the 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 increased mortality (FAO/OIE/WHO, 2003).

Antimicrobial – 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 (FAO/OIE/WHO, 2008).

Antimicrobial Class – Antimicrobials 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 antimicrobials 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 relative to the susceptible counterpart of the same species (FAO/OIE/WHO, 2008).

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 (WTO, SPS Agreement).

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 rare circumstances, become opportunistic pathogens should they be present and replicate in other host body site(s) (e.g., blood).

Co-Resistance – Various resistance mechanisms, each conferring resistance to an antimicrobial class, associated within the same microbiological host (FAO/OIE/WHO, 2008).

Cross-Resistance – A single resistance mechanism in a bacterium conferring resistance at various levels to other members of the class or to different classes. The level of resistance depends on the intrinsic activity of the antimicrobial, in general the higher the activity, the lower the level of resistance. Cross-resistance implies cross-selection for resistance (FAO/OIE/WHO, 2008).

Dose-Response Assessment – *The determination of the relationship between the magnitude of exposure (dose) to a chemical, biological or physical agent and the severity and/or frequency of associated adverse health effects (response).*

Exposure Assessment – *The qualitative and/or quantitative evaluation of the likely intake of biological, chemical, and physical agents via food as well as exposures from other sources if relevant.* In this document, it is the evaluation of the amount and frequency of exposure of humans to antimicrobial-resistant microorganisms and resistance determinants through the consumption of food.

Extra- and Off-Label Use – The non-human use of an antimicrobial that is not in accordance with the approved product labeling. Such uses may be allowed under certain national regulations.

Food – *Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation or treatment of "food," but does not include cosmetics or tobacco or substances used only as drugs.*

Food Chain Partners – All relevant entities involved in the minimization of AMR in the production to consumption continuum **(**regulatory authorities, veterinary pharmaceutical industry, wholesale and retail distributors, veterinarians, food animal producers and crop growers, food producers, food distributors) (RCP 61).

Food Safety Objective (FSO) – *The maximum frequency and/or concentration of a hazard in a food at the time of consumption that provides or contributes to the appropriate level of protection (ALOP).*

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.

Hazard Analysis and Critical Control Points (HACCP) – *A system which identifies, evaluates, and controls hazards which are significant for food safety.*

Hazard – *A biological, chemical, or physical agent in, or condition of, food with the potential to cause an adverse health effect.* In this document, hazard includes antimicrobial resistant microorganisms and resistance determinants (derived from food, animal feed, animals, and plants).

Hazard Characterization – *The qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical, and physical agents which may be present in food. For chemical agents, a dose-response assessment should be performed. For biological or physical agents, a dose-response assessment should be performed if the data are obtainable.*

Hazard Identification – *The identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods.*

Intrinsic Resistance – Inherent resistance to certain antimicrobials resulting from structural or biochemical characteristics common to the wild-type microorganisms of a genus or subspecies.

National Treatment Guideline (non-regulatory control) – An animal species-specific guideline developed to address a specific disease and implemented as a voluntary step prior to regulatory controls such as withdrawing an antimicrobial drug or making significant label restrictions.

Pathogen – A microorganism that causes illness or disease.

Performance Criterion (PC) – *The effect in frequency and/or concentration of a hazard in a food that must be achieved by the application of one or more control measures to provide or contribute to a PO or an FSO.*

Performance Objective (PO) – *The maximum frequency and/or concentration of a hazard in a food at a specified step in the food chain before the time of consumption that provides or contributes to an FSO or ALOP, as applicable.*

Post-Harvest – The stage of food animal or plant production from the time of slaughtering or harvesting, which often includes cooling, cleaning, sorting, packing and other processes.

Pre-Harvest – The stage of food animal or plant production until slaughtering or harvesting (including transport and lairage).

Prevention and Prophylactic Use – Use of an antimicrobial(s) in healthy animals and plants considered to be at risk of infection or prior to the onset of clinical infectious disease. This treatment includes control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and prevention of an infectious disease that has not yet been clinically diagnosed.

Resistance Determinant – The genetic element(s) encoding for the ability of microorganisms to withstand the effects of an antimicrobial. 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.

Responsible Use Guidelines – Judicious use, responsible use, prudent use, clinical practice guidelines, and guidelines for prudent use are all terms that refer to 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.

Risk – *A function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard(s) in food.*

Risk Analysis – *A process consisting of three components: risk assessment, risk management, and risk communication.*

Risk Assessment – *A scientifically based process consisting of the following steps: (i) hazard identification, (ii) hazard characterization, (iii) exposure assessment, and (iv) risk characterization.*

Risk Assessment Policy – *Documented guidelines on the choice of options and associated judgments for their application at appropriate decision points in the risk assessment such that the scientific integrity of the process is maintained.*

Risk Characterization – *The qualitative and/or quantitative estimation, including attendant uncertainties, of the probability of occurrence and severity of known or potential adverse health effects in a given population based on hazard identification, hazard characterization and exposure assessment.*

Risk Communication – *The interactive exchange of information and opinions throughout the risk analysis process concerning risk, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, industry, the academic community, and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.*

Risk Manager – A national or international governmental organization with responsibility for AMR risk management activities.

Risk Management – *The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.*

Risk Management Option (RMO) – A specific action taken to mitigate risk at various control points throughout the food production to consumption continuum.

Risk Estimate – *The quantitative estimation of risk resulting from risk characterization.*

Risk Profile – *The description of the food safety problem and its context.*

Weight of Evidence – A measure that takes into account the nature and quality of scientific studies intended to examine the risk of a hazard. Uncertainties that result from the incompleteness and unavailability of scientific data frequently require scientists to make inferences, assumptions, and judgments in order to characterize a risk.

GENERAL PRINCIPLES FOR AMR-RISK ANALYSIS

9. The Working Principles for Risk Analysis for Food Safety for Application by Governments CAC/GL62 shall apply to all aspects of AMR-risk analysis. As AMR-risk analysis is a specific form of microbiological food safety risk analysis, the General Principles for microbiological risk assessment CAC/GL30 and microbiological risk management CAC/GL 63 also apply to AMR-risk analysis. General Principles specific to AMR-risk analysis follow.

Principle 1: AMR-risk analysis should consider the impact of AMR on the treatment effectiveness/efficacy of antimicrobials used in human medicine.

Principle 2: AMR-risk analysis should consider the selection and dissemination of AMR through the food production to consumption continuum.

Principle 3: AMR-risk analysis should give consideration to all relevant international documents (for example, recommendations of the "Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials") for setting priorities for further risk assessment and/or risk management activities.

Principle 4: AMR-risk analysis should consider national and regional differences in antimicrobial usage, human exposure, prevalence and pattern of resistant microorganisms, foodborne antimicrobial resistant microorganisms, and genetic determinants of resistance, as well as available RMOs.

Principle 5: AMR-risk analysis should build on existing microbiological risk analysis guidelines 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.

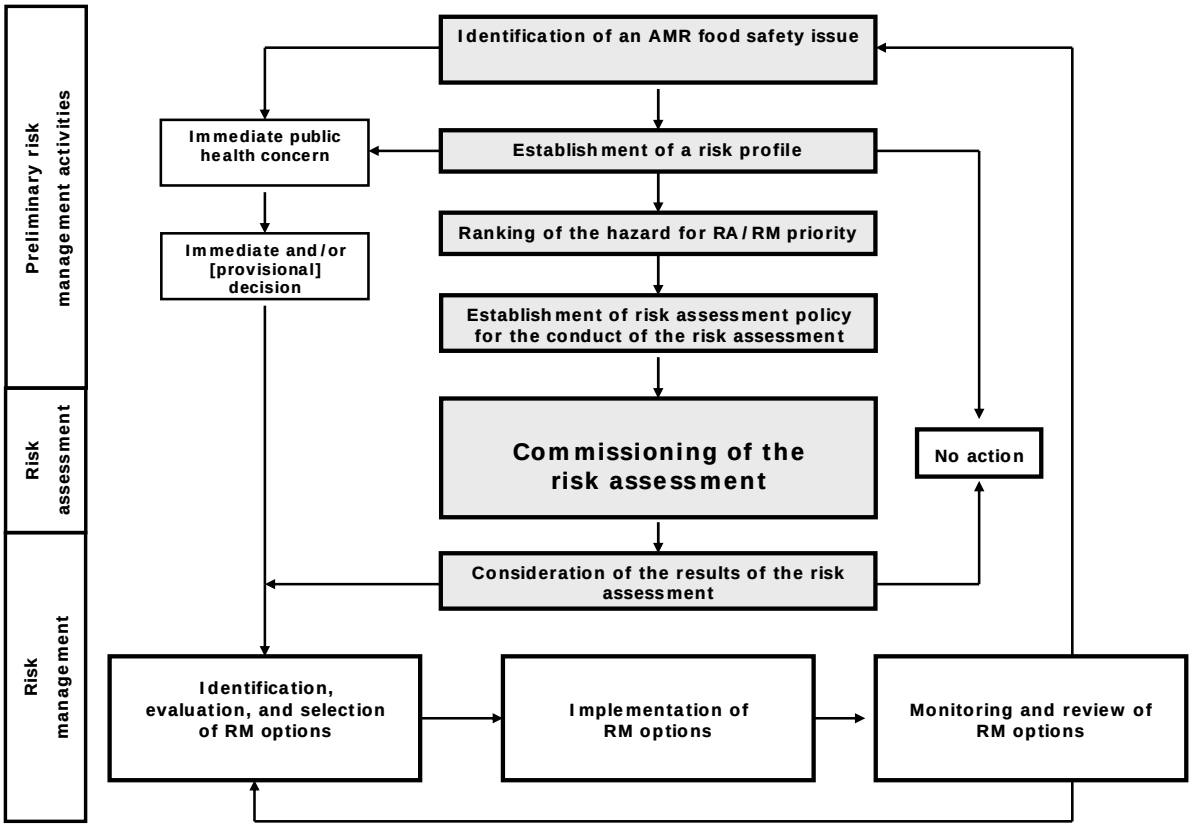
Principle 6: AMR-risk analysis should focus on clearly defined combinations of the food, antimicrobial drug(s), antimicrobial use pattern, and resistant foodborne microorganisms/or genetic determinants of resistance with consideration of co-resistance in certain situations.

Principle 7: Monitoring and surveillance of antimicrobial usage and prevalence of AMR microorganisms and resistance determinants are critical to evaluating and determining the effectiveness of implemented RMOs and informing all levels of risk analysis.

FRAMEWORK FOR AMR-RISK ANALYSIS

10. Figure 1 provides an overview of the framework for AMR-risk analysis as presented in this document. The diagram is intended to aid risk managers by placing the components of risk analysis in relation to one another and providing a frame of reference for the elements such as: i) sequencing of steps prior to risk assessment (preliminary risk management activities); ii) the process for identification, selection, implementation, and monitoring and review of RMOs; and iii) describing the process for implementing and reviewing a provisional decision.

Figure 1. Framework for AMR-Risk Analysis



11. Following the identification of an AMR food safety issue, risk managers must make decisions about the immediacy of a public health concern. A decision to take RMOs prior to the establishment of a risk profile or risk assessment should only be undertaken when there is clear evidence of an immediate risk to human health.

12. The establishment of a risk profile greatly aids the risk manager in assessing the scope and context of the AMR food safety issue. This step should be followed by a ranking of hazards for risk assessment and risk management priority. Understanding the relative significance of the AMR food safety issue with respect to concurrent risks from other food safety issues will help the risk manager allocate resources in a manner that optimally protects public health.

13. Each of the activities described in the framework involves risk communication, not only between risk managers and risk assessors, but also with other interested parties, particularly those that have the ability to impact various control points and entities that may be affected by the implementation of RMOs.

PRELIMINARY AMR-RISK MANAGEMENT ACTIVITIES

14. A potential food safety issue may arise when antimicrobial resistant microorganisms or resistance determinants are present or transmitted in food and/or animal feed, including aquaculture. Foodborne exposures to resistant microorganisms or resistance determinants may adversely impact human health. The risk manager initiates the risk management process, beginning with the preliminary risk management activities, to evaluate the scope and magnitude of the food safety issue and, where necessary, to commence activities to manage the identified risk. In the course of implementing these preliminary risk management activities, the risk managers should consider the different areas of use of antimicrobials, such as in food animals (including aquatic species) and in plants.

Identification of an AMR food safety issue

15. AMR food safety issues may be identified on the basis of information arising from a variety of sources, such as AMR surveillance in animals and in foods of animal origin, food safety monitoring, antimicrobial usage surveys, animal and human surveillance data (including post-marketing surveillance data on approved antimicrobials), epidemiological or clinical studies, laboratory studies, research on resistance transfer, scientific, technological or medical advances, environmental monitoring, recommendations of experts and interested parties, etc. Information on AMR microorganisms and resistance determinants related to plant production and food processing should be included. Additional potential sources of information are provided in the Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005).

Development of an AMR-risk profile

16. The AMR risk profile is a description of a food safety problem and its context that 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, if any, 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 and 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 production chain and related production techniques should be consulted.

17. The depth and breadth of the AMR risk profile may vary depending on the needs of the risk managers and the complexity and urgency of the food safety issue. The fundamental elements that comprise a risk profile include:

- Description of the hazard and public health problem (the AMR food safety issue);
- Identification and characterization of the food commodity + antimicrobial resistant microorganisms + antimicrobial use combination;
- Consideration of critically important antimicrobial lists developed by national and international groups (e.g., see Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials, Rome 2008);
- Description of usage (extent and nature) of antimicrobials in food production, when available (such as veterinary applications, aquaculture, plant protection or food processing); and
- Identification of major knowledge gaps.

18. When there is evidence of an immediate public health concern, it may be necessary to limit the scope of the risk profile in response to the urgency of the food safety issue.

19. 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 an AMR risk assessment, establishing additional information gathering pathways, or implementing immediate risk mitigation for those food safety issues that require an immediate action[1] by the risk manager without further scientific consideration (e.g., requiring withdrawal/recall of contaminated products).

20. 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 select 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 should be communicated to all interested parties and the timeframe or circumstances under which the provisional decision will be reconsidered (e.g., reconsideration after the completion of a risk assessment) should be articulated when the decision is initially communicated.

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

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

22. 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 mangers in conjunction with stakeholders, and in consultation with risk assessors on scientific aspects of the issues. Other criteria that could be used to rank this ARM food safety issue among other food safety issues include:

- Perceived relative level of risk to consumers;
- Capability to implement effective food safety control measures; and
- Potential international trade implications associated with food safety control measures.

Establishment of broad risk management goals

23. Following development of the risk profile and the risk ranking/prioritization, risk managers should decide on the preliminary risk management goals that determine the next steps to be taken, if any, to address the identified food safety issue. These goals should be established through an interactive process between the risk managers, scientific experts, and other interested parties.

24. Risk management goals should have as their primary objective the protection of the health of consumers. Other considerations in selecting appropriate risk management goals include the potential impact on trade, as well as the feasibility of implementation, enforcement, and compliance of the risk mitigation measures associated with the goals.

25. Often critical in establishing and achieving risk management goals is to determine the need, or the feasibility, of a risk assessment. Factors that may increase the desirability of a risk assessment include:

- The nature and magnitude of the risk are not well characterized by the available information;
- The risk is connected to economic, social, and cultural considerations, including consequences for animal health and welfare; and
- The risk management activities have major trade implications.

26. Other practical issues that impact the decision as to whether a risk assessment is needed include:

- The availability of resources;
- The urgency of the food safety issue; or
- The availability of scientific information.

[1] The International Health Regulation (2005) Agreement gives provisions for appropriate measures in case of public health emergencies, including food related events (www.who.int/csr/ihr/ihrwha58_3-en.pdf). The Principles and Guidelines for the Exchange of Information in Food Safety Emergency Situation (CAC/GL 19-1995) defines a food safety emergency as a situation whether accidental or intentional that is identified by a competent authority as constituting a serious and as yet uncontrolled foodborne risk to public health that requires urgent action. Emergency measures may be part of immediate action.

Establishment of risk assessment policy

27. Following a decision as to the need for a risk assessment, risk assessment policy should be established by risk managers in advance of 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. Where necessary, risk managers should ask risk assessors to evaluate the potential changes in risk resulting from different RMOs.

Commission the AMR-risk assessment

28. Based on the established risk management goals, 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. The nature and scope of the risk assessment may vary, depending on the food safety issue of concern, but it is important to ensure that:

- A clear mandate is given to risk assessors that communicates the purpose and scope of the risk assessment, the risk assessment policy, and the form of the desired output;
- All aspects of the commissioning and conduct of the risk assessment are documented and transparent;
- Sufficient resources and a realistic timetable are provided;
- The risk assessment team has appropriate expertise and is free from conflicts of interest and undue biases;
- A functional separation between the risk assessors and risk managers is maintained to the extent practicable;
- There are effective and iterative communication pathways between the risk assessors and risk managers during the risk assessment process; and
- The risk assessment be adequately reviewed by the scientific community and, if appropriate, the public.

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

- A description of the specific food safety issue (as defined in the 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, 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.

Consideration of results of AMR-risk assessment

30. 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. The responsibility for resolving the impact of uncertainties described in the risk assessment on RMOs lies with the risk manager and not with the risk assessors.

31. 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 hazard – combination of food, antimicrobial drug(s), antimicrobial use pattern, and resistant foodborne microorganisms/or genetic determinants of resistance.

RISK ASSESSMENT

32. The 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 antimicrobial

resistant microorganisms to which humans are exposed by the consumption of food and to describe the magnitude and severity of the adverse effects of 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 resistant microorganisms and/or resistance determinants and to the extent possible the factors that are relevant and could influence their prevalence in food.

Sources of information

33. Given the fact that multiple data sources are likely required for an AMR-risk assessment and that these data can be limited, their strengths, limitations, discrepancies, and gaps should be clearly presented using a weight-of-evidence approach.

34. Possible sources of information:

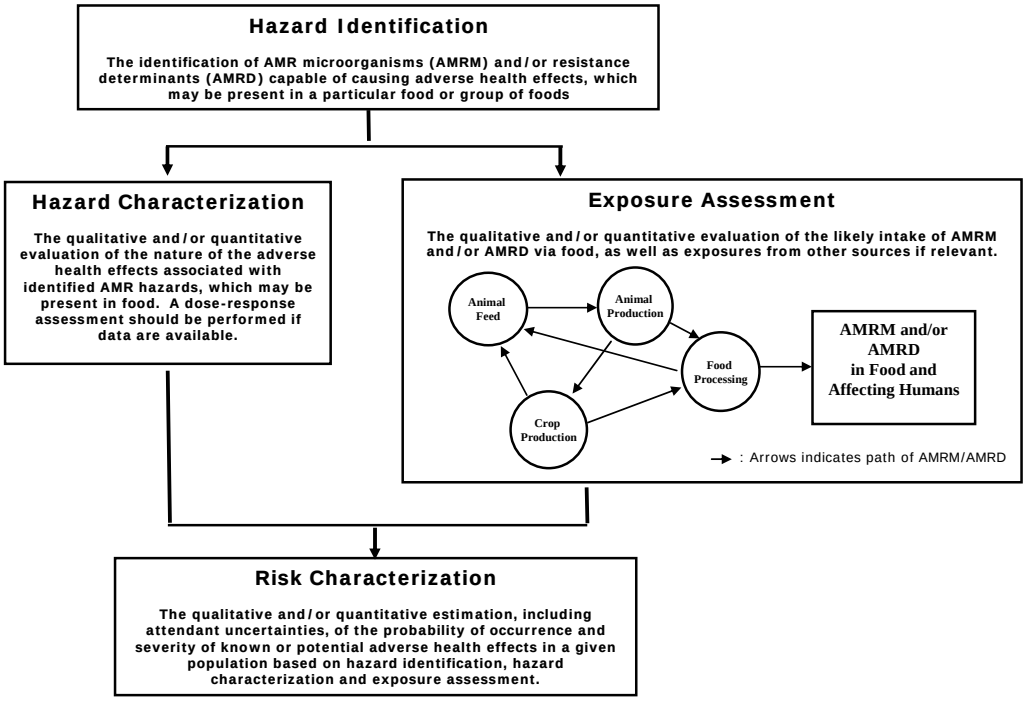
- Monitoring and surveillance programs (phenotypic and if applicable genotypic information) for resistant microorganisms derived from humans, food, animal feed, animals, or plants taking into consideration epidemiologic and microbiological breakpoints.
- Epidemiological investigations of outbreaks and sporadic cases associated with resistant 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 production to consumption continuum (litter, water, feces, and sewers). The difficulty of distinguishing human as well as non-human sources should be considered when attributing the origin of AMR from environmental data.
- Non-human antimicrobial use data such as quantity of antimicrobial drugs used at national and regional levels, route of administration, daily dosage and duration, species-specific (including animals and plants), and other distinguishing animal production factors such as animal production class or system.
- Investigations of the characteristics of resistant microorganisms and resistance determinants (in vitro and in vivo studies), transfer of genetic elements, and the dissemination of resistant microorganisms and resistance determinants in the food chain and in the relevant environment.
- Research on properties of antimicrobials including their resistance selection (in vitro and in vivo) potential.
- Laboratory and/or field animal/crop trials addressing the linkage of antimicrobial usage and resistance.
- 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.

Process of AMR-risk assessment

35. At the beginning of the work, risk assessment may require a preliminary investigation phase to define and map the work to be undertaken within the framework of the AMR-risk assessment.

36. Figure 2 shows the Codex risk assessment process with respect to addressing AMR. The process of an AMR-risk assessment is composed of hazard identification, exposure assessment, hazard characterization, and risk characterization. Details of elements for each component may be found in Appendix 1. Exposure assessment and hazard characterization can be conducted in parallel.

Figure 2. Codex AMR-Risk Assessment and Possible Pathways for Selection and Dissemination of AMR in Food In Relation to Exposure Assessment



Note: Circles indicate where antimicrobial drug use can occur. AMRM: antimicrobial resistant microorganism; AMRD: antimicrobial resistance determinant. See Appendix 2 for detailed information for each component of the Codex risk assessment scheme.

37. The principles of an AMR-risk assessment 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 CAC/GL 62-2007 (FAO/WHO, 2007), quantitative data should be used to the greatest extent possible without discounting the utility of available qualitative information.

Hazard identification

38. The purpose of hazard identification is to identify the AMR concern with food. Risk assessors should review literature and information from surveillance programs to identify specific strains or genotypes of foodborne microorganisms that pose risks by particular antimicrobial-microorganism-food commodity combination. Additionally, interaction of resistant microorganisms or resistance determinants with the appropriate environment (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 resistant microorganisms (or resistance determinants) will be useful. When necessary, opinions on hazard identification can be sought from relevant experts and consideration given to using studies on surrogate microorganisms.

Exposure assessment

39. The exposure assessment will address all the pathways of selection and dissemination of resistant microorganisms and resistance determinants to humans via the consumption of food as a consequence of non-human uses of antimicrobials. This step covers the release assessment and exposure assessment of the OIE risk assessment scheme (OIE, Terrestrial Animal Health Code, Chapter 6.8). The exposure assessment component in Figure 2 describes possible aspects that may result in the presence of antimicrobial resistant microorganisms and/or resistance determinants in food. The fundamental activities in this step should therefore include: (a) clear depiction or drawing of the exposure pathway; (b) detailing the necessary data requirements based on this pathway; and (c) summarizing the data.

40. The nature and the scope of the risk question posed to the risk assessor(s) will affect the types of data required for the exposure assessment. For example, risk manager(s) can pose questions about AMR

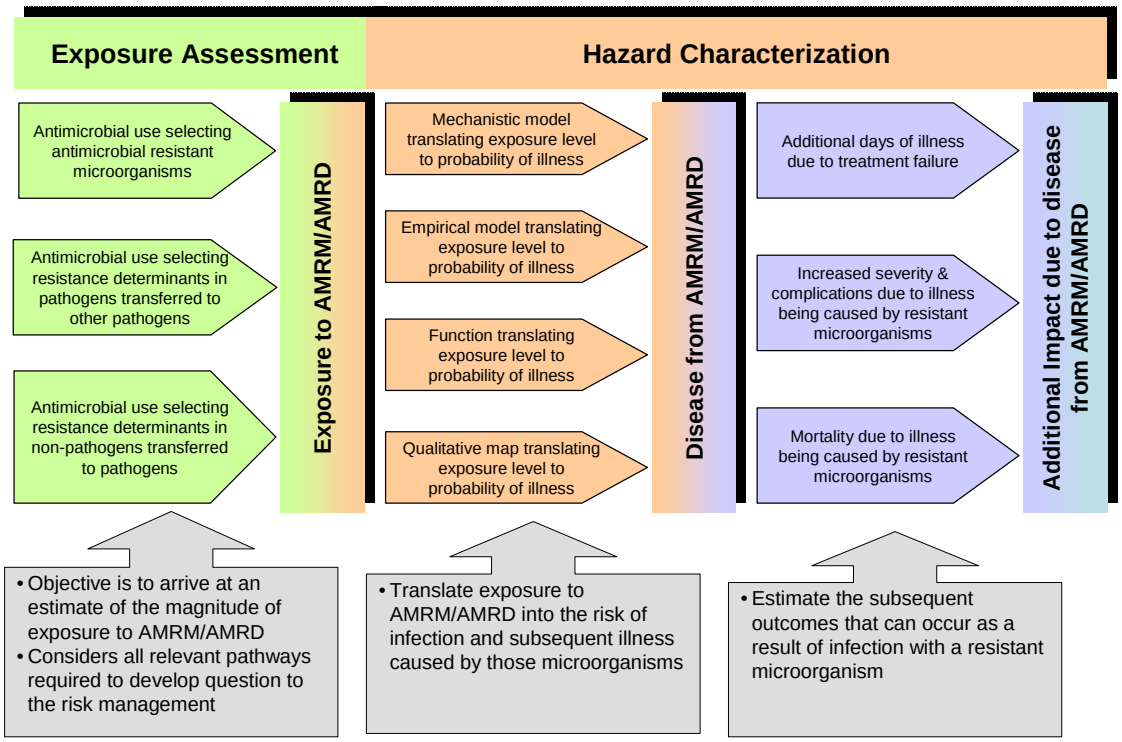
development or about exposure to known antimicrobial resistant microorganisms/resistant determinants found on food. Section 3.1 of Appendix 1 (Exposure assessment – pre-harvest factors) includes possible factors for modeling the likelihood of selection and dissemination of resistance within animal or plant populations. A possible output from pre-harvest exposure assessment is an estimate or probability of the influence of the use of antimicrobials on the prevalence of resistant microorganisms in the target animal or crop. Section 3.2 of Appendix 1 considers possible factors related to the human exposure to food containing antimicrobial resistant microorganisms and/or resistant determinants (post-harvest factors). A possible output from post-harvest exposure assessment is an estimate of the likelihood and level of contamination of the food product with resistant microorganisms at the time of consumption and attendant uncertainty.

41. When the hazard of interest is the resistance determinant alone, including those in commensal microorganisms, then an exposure assessment should consider whether these resistance determinants can be transferred to human pathogens that subsequently become resistant. Assessing the exposure through animal feed should also consider resistance selection in microorganisms in animal feed due to exposure to in-feed antimicrobials and their transmission to food animals, including aquaculture species (Refer to the Code of Practice on Good Animal Feeding [AC/RCP 54-2004]). Particular environmental reservoirs of resistance determinants may need to be considered in the AMR-risk assessment.

Hazard characterization

42. The hazard characterization step considers the characteristics of the hazard, matrix, and host in order to determine the probability of disease upon exposure to the hazard. An AMR-risk assessment 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, including increased frequency and severity of disease. Possible factors that can have an impact on the hazard characterization are included in Section 4 of Appendix 1.

Figure 3. Example of Modeling Approaches for Hazard Characterization and Exposure Assessment in AMR-Risk Assessment



43. 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 choice of a modeling approach will be guided by the risk question(s) and the risk manager's needs. Figure 3

describes examples of different types of models (e.g., mechanistic models, empirical models, functions, or qualitative mapping) that could link exposure to diseases. A comprehensive model with high quality data will offer a higher degree of confidence about the estimates of adverse health effects. Consideration will need to be given to how exposures are converted into risks, as well as the scales used.

44. 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 antimicrobials of concern must 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 antimicrobial resistant microorganisms and resistance determinants, when appropriate, may be informed by hazard characterization for non-antimicrobial resistant microorganisms. Thus, compared to a non-AMR-risk assessment, these outcomes are just a series of additional consequences that can 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.

Risk characterization

45. The risk characterization step integrates the information from the preceding components of the risk assessment and synthesizes overall conclusions about risk that are complete, informative, and useful for risk managers. The purpose of risk characterization is to answer the original questions posed by risk managers and to put into context the findings from the risk assessment process including uncertainties and other findings that could have an impact on the risk management decision. As a result, 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 guidelines on the types of outcomes that may be informative in the risk characterization, but specific outputs – such as if the risk outcome is to be measured using number of additional cases, other public health measures like disability adjusted life years (DALYs), or preventable fraction – will need to be established at the onset of the assessment process in conjunction with risk managers.

46. Additional outcomes 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 (FAO/WHO, 2006b).

47. The adverse human health effects of concern in an AMR-risk assessment encompass 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(s), per-meal risk, or annual risk based on consumption. Health effects may be translated into burden of disease measurements such as DALYs. The selection of the final risk measures must generally have been defined within the purpose of the 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.

48. The risk characterization considers the key findings from the hazard identification, exposure assessment, and hazard characterization to estimate the risk. Other elements to consider, depending upon the purpose of the risk assessment and the detail 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 language and understandable by non-mathematicians) 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 (FAO/WHO, 1999). 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 subjectively. 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.
- Existing microbial and AMR-risk assessments.
- 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 antimicrobial resistant 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 microorganisms species considered or for which resistance data is 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?
- Important data gaps and research needs.

49. The potential points for consideration in the risk characterization are presented in Section 5 of Appendix 1.

50. Appendix 2 provides examples of the outputs from a qualitative AMR-risk assessment. The 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 (FAO/WHO 2006b).

RISK MANAGEMENT

51. The purpose of this section of the guideline is to provide advice to national and regional authorities on risk management specific to reduce the risk of foodborne antimicrobial resistant microorganisms and resistance determinants arising from the non-human use of antimicrobials that may be necessary following risk profiling and/or risk assessment. Guidelines on the identification, evaluation, and selection of RMOs will be provided. In addition, consideration will be given to the implementation of RMOs and how to measure and monitor the effectiveness of the selected RMOs, including establishing a baseline against which subsequent changes can be compared.

52. National/regional authorities, in implementing these guidelines, should consider a continuum of possible interventions throughout the food chain, each step of which can reduce risk by minimizing and containing AMR microorganisms and resistance determinants.

53. When considering RMOs to address an AMR food safety issue, risk managers should ensure that Codex Codes of Practices that cover the production to consumption continuum are being implemented as fully as possible. The Codes of Practice contain RMOs that impact control points at which foodborne microbiological hazards exist, including those that potentially contribute to the selection and dissemination AMR microorganisms.

- Codex *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC/RCP 61-2005).
- Codex Recommended International *Code of Practice for Control of the Use of Veterinary Drugs* (CAC/RCP 38-1993).
- Codex *Principles and Guidelines for the Conduct of Microbiological Risk Management* (CAC/GL 63-2007).
- Recommended International *Code of Practice General Principles of Food Hygiene* (CAC/RCP 1-1969).
- Codex *Code of Practice on Good Animal Feeding* (CAC/RCP 54-2004).
- Codex *Code of Hygienic Practice for Fresh Fruits and Vegetables* (CAC/RCP 53-2003).

- *Principles for the Establishment and Application of Microbiological Criteria for Foods* (CAC/GL 21- 1997).

54. Additionally, relevant sections of the OIE Terrestrial Animal Health Code (2008), Responsible Use of Antibiotics in Aquaculture (T 469) FAO, Rome, 2006; and WHO, Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food should be consulted.

55. RMOs described in Table 1 are intended to be examples of supplemental RMOs specific for AMR that may be implemented at the discretion of national/regional authorities and in a manner that is proportional to the level of risk.

56. Once a decision has been made to take action as a result of a provisional decision, risk profile, and/or risk assessment, the following process should be used to identify, evaluate, select, implement and monitor one or more RMOs. Although many RMOs may be considered as impacting either the pre- or post-harvest section of the production-to-consumption continuum, some RMOs are better thought of in terms of the contributions of relevant food chain partners. The important concept is to follow a structured process in evaluating, selecting, and implementing the RMOs followed by a systematic process for monitoring their effectiveness and making adjustments when necessary.

57. Any regulatory measures must be able to be enforced on the basis of the national framework of legal and regulatory authorities. However, in some countries, good results have been achieved by referring to measures that are voluntary (non-regulatory controls) rather than legally binding.

Table 1. Examples of Risk Management Options Supplemental to Codex Codes of Practice

PRE-HARVEST OPTIONS	
Animal feed production	Implement programs to minimize the presence in feed and feed ingredients of antimicrobial resistant microorganisms and resistance determinants of microorganisms and the transmission of these through feed. Monitor feed and feed ingredients for resistant microorganisms and resistance determinants: • Consider antimicrobial resistance when assessing the microbiological safety of feed ingredients. • Set maximum limits on resistant microorganisms for feed and feed ingredients. Prohibit or restrict the addition of ingredients with impact on AMR in animal feed.
Food animal production	Regulatory controls on conditions of use: • marketing status limitation, • extra-/off-label prohibition, • extent of use limitation, • avoid or limit use of antimicrobial agents or a specific agent for disease prevention/prophylaxis in healthy animal not considered to be at risk of infection, • major label restriction, and • withdrawal of authorization. Development and implementation of treatment guidelines targeting a specific AMR problem supported nationally or regionally on a voluntary basis prior to regulatory control. Development and regular update of species-specific responsible use guidelines by professional bodies.

	Improve accuracy of microbiological diagnosis by national authorities in the development, dissemination, and use of international standards for • culture and susceptibility testing, and • breakpoints and interpretive criteria. Implement biosecurity and animal health and infection control programs to minimize the presence and transmission of foodborne microorganisms and resistance determinants between animals, to/from animals to humans and between flocks/herds: • Active control programs to reduce zoonotic infections without using antimicrobials. • Changes in production systems to minimize commingling of naïve animals with other animals and ensuring of appropriate stocking density of animals. • Improved housing/ventilation systems to prevent respiratory infections. • Improved waste management systems to minimize exposure of animals to manure. • Implement quality assurance programs as part of good production practice. • Improved hygiene, sanitary measures (disinfection between "growouts," rodent controls, use of disinfectants, etc. • Vaccination when appropriate to prevent disease. • Training of personnel in the improvement of specific husbandry practices.
Food crop production	Regulatory controls on conditions of use: • marketing status limitation, • extra-/off-label prohibition, • extent of use limitation, • discourage or limit prophylactic use on healthy crops, • limit use to conditions when crops are known to be at risk of developing disease, and • withdrawal of authorization. Implement use of alternative strategies for specific diseases: • Substitution of antimicrobial use with non-antimicrobial treatments (chemical and non-chemical) and, if not feasible, use antimicrobials in combination with alternative treatments. • 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 crop-specific responsible use guidelines targeting a specific AMR problem supported nationally and regionally on a voluntary basis prior to regulatory control. Improve accuracy of microbiological diagnosis by national authorities in the development, dissemination, and use of international standards for: • culture and susceptibility testing, and • breakpoints and interpretive criteria. Implement biosecurity and infection control programs to prevent the presence and transmission of foodborne resistant AMR microorganisms and resistance

	determinants between crops and from crops to humans.
Waste management	Control the spread of AMR microorganisms through other possible sources of contamination: • Avoid direct use in agriculture of human and animal waste (biosolids, manure), and • Use proper treatment procedures that are designed to reduce or eliminate pathogens in biosolids, manure, and other natural fertilizers. Implement control measures to limit the spread of antimicrobial resistant microorganisms and resistance determinants of microorganisms through other possible sources of contamination, such as direct use in agriculture of human and animal waste (biosolids, manure): • Handling and storage systems where biosolids, manure or other natural fertilizers are used on crops or pastures, • Proper treatment procedures designed to reduce or eliminate pathogens in biosolids, manure, or other natural fertilizers, • Appropriate time between applying biosolids, manure, or other natural fertilizers and grazing or forage harvesting (silage and hay making) to allow the applied material to decompose and to minimize contamination, • Proper use and application of biosolids, manure, compost, or other natural fertilizers and plant nutrients, • Monitor biosolids, manure, or other natural fertilizers used in feed production for resistant microorganisms and resistance determinants, and • Prohibit the use of biosolids, manure, or other natural fertilizers in food and feed production that exceeds limits on resistant microorganism.
POST-HARVEST OPTIONS	
	Prevent food containing AMR microorganisms and AMR determinants that constitute a risk for human health, from reaching the consumer. If already placed in the market, withdraw such food from 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 (CAC/GL 21-1997) and regulate action to be taken in cases of non-compliance at the level of: • Sorting, • Reprocessing, • Rejection, and • Further investigation.

Identification of AMR-RMOs

58. Risk managers will generally identify a range of RMOs with the capacity to resolve the food safety issue at hand. In general, to the extent practicable, it is valuable to consider initially a relatively broad range of possible options, then to select the most promising alternatives for more detailed evaluation.

59. The approach to the identification of options specific to AMR should keep in mind two aspects: 1) the range of points along the food chain where options may be implemented, and 2) the food chain partners who

have responsibility and act in various areas of food production. The first aspect seeks to identify areas of the production to consumption continuum that may be amenable to certain measures to reduce risk, such as animal/crop production or the processing of harvested food. Targeted interventions at various stages of these production areas should be considered by risk managers. The second aspect seeks to identify measures that can be developed and/or implemented by various food chain partners.

60. By looking at options to reduce specific risks described in the risk profile and/or risk assessment with respect to both the food production chain and the partners involved, additional, complementary RMOs may be derived. This approach assumes that good agricultural practices and basic food hygiene practices are in place all along the food production chain and that opportunities exist to identify and implement targeted risk-reducing measures at relevant points along the continuum.

61. Existing Codes of Practice contain RMOs that should be implemented as fully as possible. In certain instances, the RMOs described in existing Codes of Practice pertain only to specific commodities or circumstances in the production to consumption continuum. However, the applicability of these RMOs to AMR risks and control points should also be considered by risk managers. Table 1 contains examples of RMOs specific for AMR that may take concepts from related Codes of Practice and apply them to ARM risks.

62. In addition, risk assessors, scientists, food policy analysts, economists, and other stakeholders also play important roles in identifying options based on their expertise and knowledge. Specific RMOs may 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 HACCP, should be considered.

63. Pre-harvest RMOs include measures to reduce the risks associated with the use of antimicrobials as related to the risk of selection/spread of AMR during the production of food. These may include reducing the extent of use of antimicrobials, such as in circumstances where alternative production methods are available, and/or where therapeutic benefits are not established or are no longer expected. Post-harvest RMOs include measures to minimize the contamination of food by resistant microorganisms.

Evaluation of AMR-RMOs

64. 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. The process by which options are evaluated may vary depending on the specific RMOs and their impact on different control points in the production to consumption continuum. The option of not taking any action should also be evaluated.

65. In the ideal situation, 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.

- A “menu” of estimates of risk that would result from application of potential risk management measures (either singly or in combination), expressed either qualitatively or quantitatively.
- Technical information on the feasibility and practicality of implementing different options.
- Benefit-cost analysis of different potential measures, including both magnitude and distribution (i.e., who benefits, who pays the costs).
- WTO SPS implications of different options in international trade situations.

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

67. Because antimicrobials play a major role in animal health, animal health should be considered when evaluating RMOs, but this must be considered secondary to human health protection. Consideration of animal health and welfare could be factors in evaluating RMOs in circumstances where the options are “equally effective” in protecting the health of the consumer.

68. 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 may select co-resistance to an antimicrobial critically important to human health.

69. Outcome-driven approaches, 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 FSO, PO, and PC, will assist in evaluating RMOs.

70. RMOs for AMR should be evaluated based on their impact on the specific food/microorganism/antimicrobial use combination at a given control point in the food chain. 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 toward achieving a given FSO will provide criteria for risk managers to use when selecting RMOs.

Selection of AMR-RMOs

71. In order to select the best RMO or combination of RMOs to address an AMR food safety issue, risk managers should first determine an ALOP or public health goal. Once the goal is established, information obtained from the evaluation of RMOs (relative to the specific AMR combination of food/microorganism/antimicrobial use) can be used to determine the most efficient approach to achieving the desired goal. For AMR, an example of an ALOP might be a specific target for the incidence of resistant infections. A variety of approaches to setting ALOPs or public health goals are described in FAO Food and Nutrition Paper 87 (2006).

72. In addition to establishing the ALOP or public health goal and evaluating the effectiveness of RMOs, risk managers must weigh those impacts against other factors that influence decision-making, including the feasibility and practicality of potential measures, cost-benefit considerations, stakeholder concerns, ethical considerations, availability of alternatives (therapeutic agents or husbandry practices), and creation of countervailing risks such as decreases in the availability or nutritional quality of foods.

73. An important means of reducing human exposure to antimicrobial resistant organisms through the food chain is to ensure as far as possible that good hygienic practice and HACCP are being followed (Codex Recommended International Code of Practice – General Principles of Food Hygiene). Over and above what can be put in place as good hygienic practice, specific RMOs can address AMR issues.

74. It is difficult to define strict rules about how to select the best RMOs. A combination of measures may be necessary. These measures should be adapted to the level of risk as defined by the risk assessment**.** Regarding specific measures about AMR, cross-resistance, co-resistance issues should be considered.

75. In case of high level of risk, the following measures may be considered:

- Do not use these drugs at all,
- Restrict the use of the antimicrobial drugs in some species or some routes of administration or specific production processes,
- Use only in individual animals based on culture results and lack of alternative drugs,
- Use only in individual animals, and
- Restrict extra and/or off-label use.

Implementation of AMR-RMOs

76. Risk managers should develop an implementation plan that describes how the options will be implemented, by whom, and when. Risk management decisions are implemented by a variety of parties, including government officials, the food chain partners, and consumers. How to implement AMR-RMOs varies according to the food safety issue and its risk characterization, the specific circumstances, and the parties involved.

77. National/regional authorities should ensure an appropriate regulatory framework and infrastructure. Monitoring and surveillance should be supported by regulation and the enforcement of control measures.

78. To effectively execute control measures, food producers and processors generally implement complete food control systems using comprehensive approaches such as Good Manufacturing Practices (GMP), Good

Hygiene Practices (GHP), and HACCP systems. These approaches provide a platform to implement specific food safety RMOs as identified and selected by risk managers.

Monitoring and review of AMR-RMOs

79. National/regional authorities or food chain partners should evaluate the effectiveness of RMOs regularly, at a predetermined moment in time, and/or following the emergence of significant new evidence that has the potential to alter the approach to address the AMR food safety issue. This should also include the monitoring and review of the provisional decisions.

80. Monitoring/control points related to specifically implemented RMOs 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 (e.g., emerging hazard, virulence of a pathogen, change in AMR patterns, prevalence and microbial load in foods, sensitivity of sub-populations, or changes in dietary intake patterns).

81. Governments should define an evaluation process to assess whether the RMOs have been properly implemented and an assessment whether or not an outcome has been successful.

MONITORING AND SURVEILLANCE OF ANTIMICROBIAL USE AND ANTIMICROBIAL RESISTANT MICROORGANISM AND DETERMINANTS

82. Monitoring of the use of antimicrobials is essential to try to establish the link between the use of an antimicrobial and the prevalence of resistant microorganisms and determinants. For making harmonization in results from assessing the efficacy and comparing the effectiveness of new antimicrobials, referring to a set of standard methods is recommended, or at least it should be stated in the paragraph that standard and valid methods have to be used.

- Monitoring should, to the extent possible, include all antimicrobials used in food animal and crop production.
- Monitoring of antimicrobial usage in animals should be compatible with existing monitoring programs taking into account relevant aspects of the drug/microorganisms/animal species/food relationship, approved label indications and if appropriate include data collection at the species level and/or category of animal within species. The level of detail of data collection could be implemented in a stepwise fashion proportionate to the risk, as needed to obtain a consumer protection or food safety goal, or as needed to assess the effectiveness of RMOs.
- Authorities should preferably plan the collection and analysis of data on the dissemination of AMR and on antimicrobial usage.
- AMR data should be analyzed with AM usage data together with other relevant data to assess possible relationships.

83. A minimum level of monitoring should be established in order to measure usage and risk management effects.

84. Monitoring schemes should be harmonized (CAC/RCP 61-2005 & GL 63) between countries, to the extent possible.

85. International guidelines such as those published in the OIE Terrestrial Animal Health Code, Chapter 6.5., “Harmonisation of national AMR surveillance and monitoring programmes,” describe key elements of programs to monitor the prevalence of AMR microorganisms. Standardized and validated testing methods are also essential to the ability to use information from programs designed to monitor the presence of AMR microorganisms. Information from these programs can help establish a baseline against which the effectiveness of RMOs can be measured. Appendix 3 contains suggested endpoints that may be monitored for RMOs. The effectiveness of the RMOs should be assessed against the specific food safety metrics and the ALOP or public health goals.

86. Understanding the linkage between antimicrobial use and the prevalence of AMR microorganisms in food and feed will allow risk managers the opportunity to further refine or develop new RMOs. National/regional authorities may use established guidelines such as those described in the OIE Terrestrial Animal Health Code, Chapter 6.6., “Monitoring of the quantities of antimicrobials used in animal

husbandry," to collect data on antimicrobial usage. Monitoring antimicrobial use is important in exploring any relationships between antimicrobial use and the prevalence of AMR microorganisms in food and feed, measuring the effect of interventions aimed at reducing antimicrobial use, and identifying trends.

RISK COMMUNICATION

General Considerations

87. 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.

88. Risk communication decision-makers can obtain vital information, provide information, and solicit feedback from interested parties. Communication with all interested parties promotes better understanding of risks and greater understanding on risk management approaches. The great value that communication adds to any risk analysis justifies expanded efforts to ensure that it is an effective part of the process.

89. Communication between interested parties should be integrated into all phases of a risk analysis at the earliest opportunity.

90. Mechanisms may be established for engaging interested parties in food safety decision-making at the national/regional level in a general, ongoing way. For AMR risk analysis, communication should bring industry (producer, food processor, pharmaceutical, etc.), consumer representatives and government officials together to discuss problems, priorities, and strategies in collegial, non-adversarial settings; seeking common ground may also be achieved by fostering direct communication between industry and consumer representatives.

During Preliminary Risk Management Activities

91. Risk communication at this stage should consider the key elements of the preliminary risk management activities by the risk managers through the effective interaction with the interested parties. The scope and the extent of the specific AMR food safety issues including the impact on public health should be clearly determined with open communication among all the parties. It is important to obtain the information from multiple sources regarding the specific AMR risk issues including the known and unknown as well as the perception. Communication is also critical among the risk mangers, risk assessors, and the interested parties for activities on development of a risk profile and/or commissioning of a risk assessment in order to provide evidence-based preliminary RMOs, which are also to be communicated timely to the interested and affected parties.

During Risk Assessment

92. Risk communication during risk assessment should be a continuous interactive process involving risk managers, risk assessors and interested parties. Throughout the process of AMR risk assessment, there should be an effective communication between risk assessors and risk managers to establish the scientific facts and the unknowns on the nature and magnitude of AMR risks as well as to identify options to minimize the estimated risks. Similarly, communication should be maintained between risk assessors and interested parties for gathering relevant input or data and maintaining the transparency of the risk assessment process. This should be guided by understanding current thinking, goals and choices of the interested and affected parties, and developing strategies that are sensitive to their perspectives while ensuring the main objective being public health protection. The outcome of risk assessment should be communicated to all interested parties and the general public in a timely fashion.

During the Implementation of RMOs

93. Risk managers should communicate decisions (including the rationale) on RMOs to all interested parties and how those affected will be expected to implement them, where appropriate.

94. Risk management decisions are implemented by a variety of parties, including governments, veterinary drug industry, veterinarians, farmers, food processing industry, wholesale and retail food distributors and the general public, alone or in collaboration. The implementation of risk management decision(s) should include effective risk communication strategies.

Public Education on Food Safety Related to AMR

95. Public education on food safety requires risk communication skills, but the two endeavors are distinct. Education is an activity in which the expert authorities have knowledge to pass on to the public.

96. Risk communication in the area of AMR should create, or raise, public awareness on the nature of the risk, the existence of different routes of dissemination, and the relative importance of the food chain for human exposure, measures that have been put in place to mitigate the risks and what consumers can do to lower the risks.

Risk Communication as a Risk Management Tool

97. Ranking RMOs should be a broadly participatory process in which relevant stakeholder groups affected by the decisions should participate. Decisions on issues such as risk distribution and equity, economics, cost-effectiveness, and arriving at an ALOP are often the crux of risk management.

98. Information on veterinary antimicrobial products considered essential by the national authority to ensure their safe and effective use, in compliance with national regulations, should be made available by the veterinary drug industry, in the form of labeling, data sheets, or leaflets.

99. Food industry is responsible for developing and applying food safety control systems for effective implementation of risk mitigation measures. Depending on the nature of the option, this may require risk communication activities such as effective communication with suppliers, customers and/or consumers, as appropriate, training or instruction of its staff and internal communication.

100. Industry (pharmaceutical, food producer, food processor, etc.) associations may find it beneficial to develop and provide guideline documents, training programs, technical bulletins and other information that assists industry.

101. Training should be undertaken to ensure the safety to the consumer of animal derived food and therefore the protection of public health. Training should involve all the relevant professional organizations, regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes, professional associations and other approved users.

102. Consumers can enhance both their personal and the public's health by being responsible for, adhering to, keeping informed of and following food safety-related instructions. Multiple means of providing this information to consumers should be undertaken, such as public education programs, appropriate labeling, and public interest messages. Consumer organizations can play a significant role in getting this information to consumers. Information to promote food safety should be disseminated.

103. When RMOs include consumer information, outreach programs are often required, for example to enlist health care providers in disseminating the information. When the goal is to inform and engage the public, messages intended for specific audiences need to be presented in media the audiences pay attention to.

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APPENDIX 1. SUGGESTED ELEMENTS FOR CONSIDERATION IN AMR-RISK ASSESSMENT

This appendix lists suggested elements to include in an AMR-risk assessment; the level of details of the data may vary on a case-to-case basis.

1. Purpose and Scope

2. Hazard Identification

2.1. Identification of hazard of concern: antimicrobial resistant microorganisms and resistance determinants in food and animal feed

2.2. The antimicrobial and its properties

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

2.3. Microorganisms and resistance related information

- Potential human pathogens (species/strain) that likely acquire resistance in non-human hosts
- Commensals (species/strain) with resistance determinants and the possibility to transmit them to human pathogens
- Mechanisms of antimicrobial resistance, location of resistance determinants, frequency of transfer and prevalence among human and non-human microflora
- Co- and cross-resistance and/or multiple resistance, and importance of other antimicrobials whose efficacy is likely to be compromised

2.4 Potential adverse effects in humans

- Increased frequency of treatment failures
- Increased severity of infections including prolonged duration of disease, increased frequency of bloodstream infections, increased hospitalization, and increased mortality

2.5 Relationship of presence of antimicrobial resistant microorganisms or determinants in/on food and potential adverse human health impacts

- Clinical reports/case studies
- Epidemiological studies and surveillance
- Laboratory investigations

3. Exposure Assessment

3.1. Pre-harvest factors affecting prevalence of hazard on-farm

- Resistance selection pressure:
    - Extent of antimicrobial use or proposed use
        - Number of animal, crop, or target farms exposed to the antimicrobial in the defined time period
        - Geographical distribution of use and/or farms
        - Prevalence of disease that the antimicrobial is indicated for in the target (animal/crop) population
        - Potential extra-label, off-label, and non-approved use of antimicrobial

        - Data on trends in antimicrobial use and information on emerging diseases, changes in farm production system, or other changes that are likely to impact antimicrobial use
    - Parameters of non-human use of antimicrobials
        - Methods and routes of administration of the antimicrobial (individual/mass medication, local/systemic application)
        - Dosing regimen and duration of use
        - Pharmacokinetics and pharmacodynamics in animals
        - Time from antimicrobial administration to harvest
        - Cumulative effects of use of other antimicrobials in the defined time period
- Target animal or crop and microbial factors affecting resistance development and spread
    - Temporal and seasonal changes in microorganism prevalence
    - Duration of infection/shedding of resistant microorganism(s) (zoonotic and/or commensal) of interest
    - Rate of resistance development in commensal and zoonotic microorganisms in targets after administration of an antimicrobial
    - Resistance mechanisms, location of resistance determinants, occurrence and rate of transfer of resistance between microorganisms
    - Cross-resistance and/or co-selection for resistance to other antimicrobials (phenotypic or genotypic description)
    - Prevalence of commensals and zoonotic microorganisms in targets and proportion resistant to the antimicrobial (and minimal inhibitory concentration levels)
    - Transmission of resistant microorganisms/determinants between target animals/crops, and from animals/crops to environment and back to target animals/crops
    - Animal management factors affecting immunity
    - Food crop production/management
- Other possible sources of resistant microorganisms for the target
    - Prevalence of microorganisms of interest in other animal/plant species; fractions that are resistant to the antimicrobial in question
    - Prevalence of animal feed contaminated with resistant microorganisms
    - Prevalence of resistant microorganisms in soil or water, animal and human waste products

3.2. Post harvest factors affecting prevalence of hazard in food

- Initial level of contamination of the food product
    - Prevalence and level of resistant antimicrobial-resistant microorganisms and/or their resistance determinants present in/on the target at slaughter or time of crop harvest and proportion
    - Prevalence of antimicrobial resistant microorganisms and resistance determinants present in retail food
    - Food matrix factors (food product formulation)
- Food processing factors
    - Factors affecting the frequency and level of resistant microorganism persistence/contamination

- 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)
- Points for cross-contamination
- Packaging
- Probable use of additives and preservatives (due to their activities or impacts on growth or numbers of microorganisms)
- Starter cultures (type and number of microorganisms) used as ingredients
- Distribution and storage
- Catering and food services

- Consumer behaviors
  - Storage, cooking, and handling
  - Overall per capita consumption
  - Patterns of consumption and socio-economic, cultural, ethnic, and regional differences
- Microbial factors
  - Capacity of food-derived resistant microorganisms to transfer resistance to human commensal and/or pathogenic microorganisms
  - Growth and survival characteristics of resistant microorganisms
  - Microbial ecology in food: survival capacity and redistribution of microorganism in the food chain

3.3. Transfer of hazard

- Transmission of resistance determinants/resistant microorganisms among animals, food, feed, environment, and humans
- Occurrence and probability of resistance gene transfer from resistant microorganisms to human commensals/pathogens
- Potential human exposure from direct contact to primary production environments
- Potential human to human transmission of resistant organisms

3.4. Exposure to hazard

- Quantity of various food commodities consumed
- Point of food consumption (home, commercial establishment, or informal establishment)
- Human demographics data
- Socio-cultural etiquettes and susceptibility in relation to food consumption habits; consumption of a particular food commodity could be qualitatively classified as low, medium, or high
- Practices associated with food handling and processing

4. Hazard Characterization

4.1. Resistant microorganisms and resistance determinants

- Description of microorganism including pathogenicity
- Resistance occurrence
- Epidemiological patterns

- Resistance genotype and phenotype, including cross-resistance and co-resistance
- Transferability (mobile elements) and persistence
- Pathogenicity, virulence, and their linkage to resistance
- Food matrix related factors that can influence the survival capacity of the microorganisms while passing through the gastrointestinal tract

4.2. Antimicrobial

- Human use data
- Importance in human medicine

4.3. Human host and adverse health effects

- Host factors and susceptible population
- Nature of the infection, disease
- Diagnostic aspects
- Epidemiological pattern (outbreak or endemic)
- Treatment with antimicrobial therapy and hospitalization
- Drug selection for infections
- The overall antimicrobial drug importance ranking
- Severity of disease and additional consequences
- Persistence of hazards in humans

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

5. Risk Characterization

5.1. Factors in risk estimation

- Number of people falling ill and the proportion of that number with resistant strains of microorganisms
- Effects on sensitive subpopulations
- Increased severity or duration of infectious disease 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)
- Importance of pathology caused by the target microorganisms
- Existence or absence of therapeutic alternatives; absence of alternative antimicrobial and alternatives with potential
- Alternatives available in case of resistance, and potential impact of switching to alternative antimicrobial; absence of alternative antimicrobials or potential impact of switching to alternative antimicrobial (e.g., alternatives with potential toxicity).
- Incidence of resistance
- Consequences to allow weighted summation of (e.g., disease and hospitalization) or some arbitrary scale of impact to allow weighted summation of different risk impacts

5.2. Evaluation of RMOs

- Comparison of public health burden before and after interventions

5.3. Sensitivity analysis

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

5.4. 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 2. EXAMPLES OF QUALITATIVE AMR-RISK ASSESSMENT

1. 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.

2. The following examples illustrate potential approaches that can be used to conduct a qualitative risk assessment; however, this should not be viewed as a recommended or accepted default approach 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 could 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 categorization of hazard characterization into qualitative statements or scores, with similar considerations as the exposure assessment into interpretation and implications; 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 than a "medium" in both).

3. 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

4. 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 (e.g., <1e-6)
- Moderate (1) – Some probability for exposure to occur (e.g., 1e-6 to 1e-4)
- High (2) – Significant probability for exposure to occur (e.g., >1e-4)

5. 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

6. The hazard characterization translates the outcomes of this step into qualitative statements that reflect the implications of exposure to a hazard. While the exposure assessment qualitatively captures the probability of being exposed, the hazard characterization qualitatively estimates the implications of being exposed. In microbiological risk assessment, the focus of the hazard characterization step is to translate the probability of exposure to the probability of disease; however, in AMR-risk assessments, the focus is likely to be the implications of exposure to resistant microorganisms that are over and above those of being exposed to susceptible organisms. To illustrate, the following categories are proposed:

- Negligible (0) – Probability of disease upon exposure is the same as for susceptible organisms and the outcomes as a result of disease is not different

- Mild (1) – Probability of disease upon exposure is the same as for susceptible organisms, but the outcomes following disease are more serious requiring hospitalization
- Moderate (2) – Probability of disease upon exposure is higher and outcomes following disease are more serious requiring hospitalization
- Severe (3) – Probability of disease 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

7. 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

8. 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

9. 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 resistant microorganism in a given food or feed commodity, animal species, or plant. The different ranking is defined below:

- Negligible – The probability of exposure to susceptible people is extremely low
- Low (Unlikely) – The probability of exposure to susceptible people is low but possible
- Medium (Likely/Probable) – The probability of exposure to susceptible people is likely

- High (Almost Certain) – The probability of exposure to susceptible people is certain or very high
- Not assessable – The probability of exposure to susceptible people cannot be assessed

Illustrative Hazard Characterization Scoring

10. The AMR-related adverse human health effects (i.e., risk endpoints) may be ranked qualitatively as below (modified after National Cancer Institute, 2006. Common terminology criteria for adverse events v3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). In this example, it is considered that adverse health effects associated with the microorganisms that are resistant to critically important antimicrobials in human medicine (FAO/WHO/OIE, 2008. http://www.fao.org/ag/agn/agns/files/Prepub_Report_CIA.pdf) will likely have a more severe consequence than those with microorganisms resistant to antimicrobials of other categories:

- 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 AMR
- Fatal – Directly or indirectly contributes to the death of the subject; treatment failure is likely expected due to the AMR

Illustrative Risk Characterization Scoring

11. 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.

Table 2. Integration of the Outputs of Hazard Characterization and Exposure Assessment into the Qualitative Risk Characterization

Exposure Assessment **Probability of Exposure**	**Hazard Characterization** **Severity of Adverse Health Effect**	**Qualitative Risk Characterization**
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

APPENDIX 3: SUGGESTED ENDPOINTS FOR MONITORING THE EFFECTIVENESS OF AMR RISK MANAGEMENT MEASURES

1. In order to monitor the effects of risk management measures and variations in AMR, possible endpoints include the following (note that these endpoints also apply to crops that are intended for human consumption):

- Prevalence of antimicrobial-resistant microorganisms and/or resistance determinants at farm level;
- Prevalence of antimicrobial-resistant microorganisms and/or resistance determinants in food products at retail level;
- Prevalence of antimicrobial-resistant microorganisms and/or resistance determinants in human clinical isolates from foodborne diseases;
- Selection and dissemination of new microorganism resistance patterns;
- Prevalence of foodborne pathogens on farms;
- Prevalence of foodborne pathogens in food;
- Incidence and prevalence of foodborne disease in humans;
- Number of (incidence) human infections attributable to foodborne antimicrobial-resistant microorganisms;
- Number of (incidence) 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 increased mortality) attributable to foodborne antimicrobial resistant microorganisms and/or determinants;
- Morbidity and mortality due to foodborne infection caused by antimicrobial resistant microorganisms in “vulnerable populations”;
- Level of awareness of antimicrobial resistance risk (e.g., producers, consumers, industry);
- Level of compliance with specific drug use restriction or compliance with prudent use guidelines;
- Trends in non-human use of antimicrobials, including critically-important antimicrobials; and
- Animal health impact.